# Macrocyclic Diterpenes Isolated from Tobacco. α- and β-3,8,13-Duvatriene-1,5-diols

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Two macrocyclic diterpenes, α- and β-3,8,13-duvatriene-1,5-diols, isolated from tobacco, are shown to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (II). These compounds provide two additional examples of the newly characterized naturally occurring diterpene series containing a fourteen-membered ring.

In the preceding paper relating to the constituents of tobacco,[1] we have reported the isolation and characterization of two novel macrocyclic diterpenes. These diterpenes, designated α-4,8,13-duvatriene-1,3-diol (α-I) and β-4,8,13-duvatriene-1,3-diol (β-I), were shown to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-4,8,13-cyclotetradecatriene-1,3-diol (I). Since this work was completed, cembrene, an unsaturated hydrocarbon isolated from *pinus albicaulis*, has been characterized as 14-isopropyl-3,7,11-trimethyl-1,3,6,10-cyclotetradecatetraene[2] (named as 12-isopropyl-1,5,9-trimethyl-1,4,8,13-cyclotetradecatetraene by the numbering system used in this paper). The structural similarities of cembrene and the diols isolated from tobacco are obvious. Cembrene and the tobacco diols possess the same locations of isopropyl and methyl groups on a cyclotetradecane ring and three double bonds are located in identical positions. Cembrene and the tobacco diols are the first examples of macrocyclic diterpenes and are the first terpenes reported to contain the 14-carbon ring system.



1            Cembrene
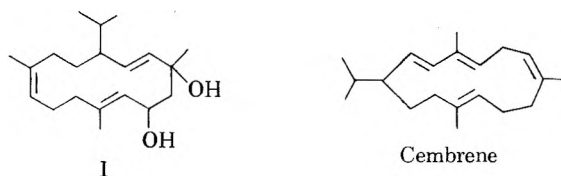
At this time we wish to describe the characterization of two additional diterpenes of related structure which we have isolated from tobacco. The new compounds, assigned the names α-3,8,13-duvatriene-1,5-diol[3a] (α-II)

and β-3,8,13-duvatriene-1,5-diol[3a] (β-II), are allylic isomers of the compounds of structure I and are demonstrated to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (II).



II
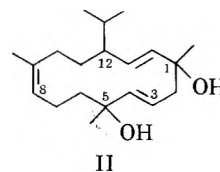
Because tobacco contains larger quantities of β-II than α-II, characterization studies were initiated upon the β-isomer.

Elemental analyses and active hydrogen determination showed that β-II, m.p. 150–152°, $[\alpha]^{25}D$ + 40°, possesses the formula $C_{20}H_{32}(OH)_2$. The mass spectrum is similar to that of α-I and β-I in showing the fragment of greatest mass at 288, corresponding to the loss of water from the formula $C_{20}H_{34}O_2$. The infrared absorption of β-II indicates that it is an allylic tertiary alcohol (3.0, 9.0 μ) containing a *trans* disubstituted olefinic linkage (10.25 μ). The n.m.r. spectrum[3b] shows the presence of an isopropyl group (6 protons, 9.15 p.p.m.), two $CH_3COH$ groups (6 protons, 8.61 and 8.65 p.p.m.), one $C(CH_3)=C$ group (3 protons, 8.50 p.p.m.), and five olefinic protons. Quantitative hydrogenation proved the presence of three double bonds and one ring. The absence of selective ultraviolet absorption by β-II shows that none of the double bonds are conjugated.

Catalytic hydrogenation of β-II using Adams' catalyst in ethyl alcohol yielded three products: a monohydroxyl compound, alcohol A; and two isomeric diols, alcohols B and C. The major product from hydrogenation, alcohol C, was stable to the oxidizing action of chromic oxide in pyridine or in acetic acid–water. The resulting conclusion that both hydroxyl groups are tertiary is in agreement with the n.m.r. spectra of β-II, alcohol B, and alcohol C, all of which show the presence

(1) D. L. Roberts and R. L. Rowland, *J. Org. Chem.*, **27**, 3989 (1962).

(2) W. G. Dauben, W. F. Thiessen, and P. R. Resnick, *J. Am. Chem. Soc.*, **84**, 2015 (1962).

(3) (a) The nomenclature used in this series of compounds is based on the name duvane previously assigned to the structure 12-isopropyl-1,5,9-trimethylcyclotetradecane. The α- and β-designations have no absolute stereochemical significance but the α- and β-compounds of the 3,8,13-duvatriene-1,5-diol structure are each related to the correspondingly designated compound of the 4,8,13-duvatriene-1,3-diol structure. (b) N.m.r. values are reported in τ units: G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

of two $CH_3COH$ groupings (six protons at 8.6–8.8 p.p.m.). Moreover, the formation of the monohydric alcohol, alcohol A, from hydrogenation of β-II, indicates that at least one of the hydroxyls of β-II is allylic.

Hydrogenation of β-II using Adams' catalyst in acetic acid gave, in addition to the three alcohols obtained with Adams' catalyst in ethyl acetate, a saturated hydrocarbon III in 7% yield. The same hydrocarbon was obtained in 90% yield by dehydration of the saturated monohydric alcohol A followed by catalytic hydrogenation. Since the product from dehydration of alcohol A should contain only one double bond, it was not susceptible to cyclization reactions and the saturated hydrocarbon III was anticipated to have the same carbon skeleton as that of β-II. Moreover, hydrocarbon III showed infrared absorption identical with that of the saturated hydrocarbon obtained by hydrogenolysis of β-4,8,13-duvatriene-1,3-diol (β-I). Since β-4,8,13-duvatriene-1,3-diol (β-I) has been shown to be 12-isopropyl - 1,5,9 - trimethyl - 4,8,13 - cyclotetradecatriene-1,3-diol (I),[1] hydrocarbon III is 12-isopropyl-1,5,9-trimethylcyclotetradecane, i.e., duvane. Accordingly, β-II must be an unsaturated diol with the carbon skeleton of III, containing a cyclotetradecane ring with isopropyl and methyl substitutions in the same positions as in the 4,8,13-duvatriene-1,3-diols (I).

III
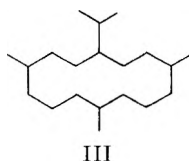
To complete the characterization of β-II except for stereochemical assignments, it is then necessary to assign the positions of the two hydroxyl groups and the three double bonds in the cyclotetradecane ring. From the n.m.r. spectrum of β-II and its hydrogenation products and from the absence of reaction of hexahydro-β-II (alcohol C) with oxidizing agents, the hydroxyl groups are located, along with two of the methyl groups, at the 1,5- or 1,9-positions. The n.m.r. spectrum of β-II requires that the third methyl group be attached to an olefinic double bond. The locations of the remaining two double bonds are limited in that at least one double bond is allylic to a hydroxyl and none of the double bonds are conjugated.

Surprisingly, although alcohol C (hexahydro-β-II) was not oxidized by chromic oxide, β-II was oxidized using a large excess of chromic oxide in pyridine. The major product (16–31% yield) was an oil with infrared, ultraviolet, and n.m.r. spectra identical with the spectra of β-4,8,13-duvatrien-1-ol-3-one (β-IV) obtained by oxidation of β-4,8,13-duvatriene-1,3-diol (β-I).[1] Catalytic hydrogenation of the β-4,8,13-duvatrien-1-ol-3-one (β-IV) obtained by oxidation of β-II yielded β-1-duvanol-3-one A and β-1-duvanol-3-one B (β-V), identical on the basis of infrared spectra, melting points, and mixture melting points with the β-1-duvanol-3-ones A
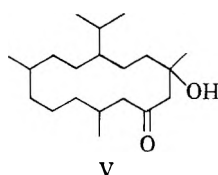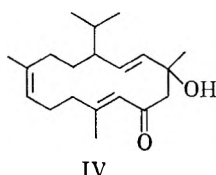
and B obtained from β-I by catalytic hydrogenation and subsequent oxidation.[1]

The conversion of β-II to β-4,8,13-duvatrien-1-ol-3-one (β-IV) allows structure assignment to β-II. Since β-II is a ditertiary alcohol, oxidation is proposed to have occurred via allylic rearrangement. Rearrangement of β-II to a secondary alcohol, either β-I or the alcohol which differs from β-I only in its configuration at the 3-position, and the subsequent oxidation of the secondary alcohol to ketone would account for the formation of β-IV. Accordingly, the structure, 12-isopropyl-1,5,9-trimethyl - 3,8,13 - cyclotetradecatriene - 1,5 - diol (II), is proposed for β-II.

Besides β-4,8,13-duvatrien-1-ol-3-one (β-IV), three other products were obtained from the oxidation of β-II. The structures of the other products, which are in agreement with structure II for β-3,8,13-duvatriene-1,5-diol, are discussed below.

An α,β-unsaturated ketone, obtained in 4–8% yield from chromic oxide–pyridine oxidation of β-II, is an isomer of β-4,8,13-duvatrien-1-ol-3-one and is designated as iso-β-4,8,13-duvatrien-1-ol-3-one. The infrared spectrum of iso-β-4,8,13-duvatrien-1-ol-3-one shows the presence of an α,β-unsaturated carbonyl group (6.01, 6.24 μ) and a trans disubstituted double bond (10.25 μ). The ultraviolet absorption, $\lambda_{max}$ 242 mμ, log ε 3.97, confirms the α,β-unsaturated ketone structure. The n.m.r. spectrum shows the presence of a hindered isopropyl group (9.17 p.p.m.), one methyl on a carbon bearing a hydroxyl group (8.76 p.p.m.), one methyl on an isolated double bond (8.51 p.p.m.), one methyl on a double bond in a conjugated system (8.24 p.p.m.), and four olefinic protons (5.15–4.0 p.p.m.). The only significant difference in the n.m.r. spectra of β-IV and the iso compound is related to the methyl group on the double bond in the conjugated system. The location of the peak for this methyl group at 8.24 p.p.m. in the iso compound and at 7.92 p.p.m. in β-IV indicates that the 4,5-double bond is cis in iso-β-4,8,13-duvatrien-1-ol-3-one and is trans in β-4,8,13-duvatrien-1-ol-3-one.[4]

A third product, obtained in 5–15% yield from the chromic oxide–pyridine oxidation of β-II, was shown from its elemental analyses and mass spectrum to correspond to a compound in which one oxygen atom has been added to either β-4,8,13-duvatrien-1-ol-3-one or iso-β-4,8,13-duvatrien-1-ol-3-one. The addition of oxygen to the α,β-unsaturated carbonyl system of IV is reasonable upon consideration of the isolation of α,β-oxido ketones from chromic oxide oxidation of allylic alcohols.[5] The α,β-oxido ketone structure for the third oxidation product is in agreement with its infrared spectrum (carbonyl absorption at 5.92 μ), the absence of selective absorption of ultraviolet light, and its n.m.r. spectrum. Identification of the third oxidation product was completed by its preparation from β-4,8,13-duvatrien-1-ol-3-one (β-IV) by reaction with alkaline

VI
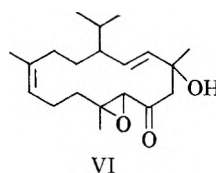
(4) L. M. Jackman and R. H. Wiley, J. Chem. Soc., 2886 (1960).

(5) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Company, New York, N. Y., 1949, p. 228.

IV

V

hydrogen peroxide. Accordingly, the third oxidation product is β-4,5-oxido-8,13-duvadien-1-ol-3-one (β-VI).

The fourth oxidation product, isolated in 2–8% yield, was shown by elemental and active hydrogen analyses to be $C_{20}H_{32}O(OH)_2$ and, accordingly, corresponds to β-II to which one oxygen atom has been added. Since the oxidation of β-II has been explained *via* rearrangement to a secondary alcohol, the oxide could be derived from either the tertiary alcohol (II) or secondary alcohol (I) structures. Structure VII, related to the tertiary alcohol II, is favored from consideration of the n.m.r. spectrum. The n.m.r. spectrum of this oxidation product shows two protons at 6.85–7.1 p.p.m.; the protons attached to an epoxide ring are reported to show absorption at 7.0–7.2 p.p.m.[6]



VII
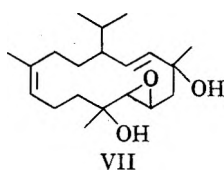
Although oxidative degradation of β-II gave poor yields of oxidation products, levulinic acid and 5-keto-2-isopropylhexanoic acid were identified in the acid fraction from the oxidation. Isolation of these acids is in agreement with structure II.

The α-isomer, α-II, was isolated from tobacco leaf in only trace amounts. α-II, m.p. 118–120°, $[\alpha]^{25}D$ + 100°, was shown from elemental and active hydrogen analyses to be a diol isomeric with β-II. The structural similarity of α-II and β-II is evident from the ultraviolet, mass, and n.m.r. spectra. The mass spectrum of α-II was very similar to that of β-II; however, α-II has the distinction of being the only isomer of this series (I and II) which showed a parent peak at mass 306. The n.m.r. spectrum of α-II is particularly instructive since it shows the presence of five olefinic protons, one methyl group at an olefinic double bond, two methyl groups of the type $CH_3C$—OH, and a hindered isopropyl group, with all methyl peaks in positions close to the positions observed in β-II.

The structure of α-II was determined from its oxidation product. The product obtained by chromic oxide–pyridine oxidation of α-II was identical with α-4,8,13-duvatrien-1-ol-3-one (α-IV) obtained by oxidation of α-4,8,13-duvatriene-1,3-diol (α-I).[1] Since α-II exhibits the n.m.r. spectrum of a ditertiary alcohol, the oxidation must have proceeded by allylic rearrangement similar to that postulated in oxidation of β-II. Therefore, α-II must be one of the diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (II). Since α-IV and β-IV are epimeric at position 1,[1] α-II and β-II must also differ in configuration at position 1.

The allylic relationship between the 4,8,13-duvatriene-1,3-diols (I) and the 3,8,13-duvatriene-1,5-diols (II) was further demonstrated by the rearrangement of the 1,3-diols to the 1,5-diols. These transformations of I to II were accomplished by slow chromatography on acidic alumina. The isomerizations of α-I to α-II and of β-I to β-II provide verification of the structures of α-II and β-II.

The conversion of α-I to α-II and of β-I to β-II raises the question whether α- and β-II are artifacts produced from α- and β-I during the isolation process. This

question is difficult to resolve for α-II since it was isolated from tobacco in minute quantity. However, α-II was isolated using procedures which did not cause isomerization of α-I. The isolation of β-II was accomplished by a variety of procedures involving a minimum of operational steps. Accordingly, we consider that β-II is not an artifact and that the allylic isomers of structures I and II are present in aged tobacco leaf. A similar occurrence of allylic isomers, phytol and isophytol, in jasmine has been noted by Demole and Lederer.[7]

## Experimental[8]

**Isolation of β-3,8,13-Duvatriene-1,5-diol (β-II).**—β-II has been isolated from aged flue-cured and burley tobaccos by several procedures. A simple isolation procedure was as follows: A methanol extract of tobacco was partitioned between 90% methanol and hexane. The material which partitioned into 90% methanol was purified by chromatography using silicic acid or Florisil. From the fractions eluted by hexane–ether mixtures, β-II crystallized after partial concentration and chilling to −27°. The recrystallized material corresponded to 0.0015% of the dry weight of the tobacco.

**Physical Properties of β-3,8,13-Duvatriene-1,5-diol (β-II).**—β-3,8,13-Duvatriene-1,5-diol melts at 150–152° after recrystallization from ether, $[\alpha]^{25}D$ = +40°. β-II shows no selective absorption of ultraviolet light. Infrared absorption occurs at 3.1, 9.0, and 10.25 μ. The n.m.r. spectrum shows 5 olefinic protons at 4.3–4.6 p.p.m. and methyl peaks at 9.16 (6), 8.61 (3), 8.65 (3), and 8.50 (3).

*Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.39; H, 11.19; active H (2), 0.66; O, 10.42; mol. wt., 306. Found: C, 78.25; H, 11.19; active H, 0.70; O, 10.96; mol. wt. (ebull.), 321; mass, 288 (306–18).

**Catalytic Hydrogenation of β-3,8,13-Duvatriene-1,5-diol (β-II).**—Quantitative hydrogenation using Adams' catalyst in ethyl acetate gave an equivalent weight of 99, corresponding to three double bonds in a molecular weight of 306. From reduction of 0.8 g. of β-II using Adams' catalyst (24 hr. at 3 atm.), three products were isolated by chromatographic separation followed by crystallization from hexane.

(a) Monohydric alcohol A, 190 mg., m.p. 80–82°, $[\alpha]^{27}D$ 0°.

*Anal.* Calcd. for $C_{20}H_{40}O$: C, 81.01; H, 13.60; active H (1), 0.34. Found: C, 80.96; H, 13.60; active H, 0.34.

(b) Dihydric alcohol B, 130 mg., m.p. 132–134°, $[\alpha]^{27}D$ +96°. N.m.r. spectrum: 8.78 (6) and 9.11 (9).

*Anal.* Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.89; mol. wt., 312. Found: C, 76.42; H, 12.80; mass, 294 (312–18).

(c) Dihydric alcohol C, 130 mg., m.p. 159–161°, $[\alpha]^{30}D$ +13°. N.m.r. spectrum: 8.82 (6) and 9.07–9.15 (9).

*Anal.* Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.89; mol. wt., 312. Found: C, 76.93; H, 12.88; mol. wt. (ebull.), 354; mass, 294 (312–18).

From the attempted reactions of alcohol C with chromium trioxide in pyridine or in acetic acid–water, alcohol C was recovered unchanged.

**Hydrogenolysis of β-3,8,13-Duvatriene-1,5-diol (β-II).**—Hydrogenolysis of 300 mg. of β-II, using Adams' catalyst in 50 ml. of ethyl acetate containing four drops of 70% perchloric acid, gave a 50% yield of a saturated hydrocarbon, $n^{26}D$ 1.4955, which appeared from its elemental analysis to be tricyclic.

*Anal.* Calcd. for $C_{20}H_{36}$: C, 86.87; H, 13.13. Found: C, 86.86; H, 13.03.

(6) C. Y. Hopkins and H. J. Bernstein, *Can. J. Chem.*, **37**, 775 (1959).

(7) E. Demole and E. Lederer, *Bull. soc. chim. France*, 1128 (1958).

(8) All melting points were determined using a Fisher–Johns melting point apparatus and are uncorrected. Elemental analyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colorado, and by the Spang Microanalytical Laboratory, Ann Arbor, Michigan. Active hydrogen was determined by the procedure of J. A. Giles, *Anal. Chem.*, **32**, 1716 (1960). Nuclear magnetic resonance (n.m.r.) spectra were run in deuterated chloroform solution using Varian Associates HR-60 instrument. The n.m.r. spectra are reported by τ value [G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)], with the number of hydrogens in parentheses. We are indebted to John J. Whalen and Johnnie L. Stewart for infrared spectra, to George W. Young for mass spectra, to Dr. A. H. Laurene for n.m.r. data, and to J. A. Giles and P. H. Ayers for the active hydrogen determinations.

The product from hydrogenation of 200 mg. of β-II using Adams' catalyst in glacial acetic acid (24 hr. at 3 atm.) was chromatographed with acid-washed alumina (Merck), giving 14 mg. of hydrocarbon III (with infrared absorption identical with that obtained by catalytic hydrogenation of dehydrated monohydric alcohol A), 60 mg. of monohydric alcohol A, and 130 mg. of a mixture of dihydric alcohols B and C.

**Conversion of Monohydric Alcohol A to 12-Isopropyl-1,5,9-trimethylcyclotetradecane (III).**—Alcohol A (60 mg.) and fused potassium acid sulfate (200 mg.) were heated under nitrogen at 180° for 10 min. The residue was extracted with three 10-ml. portions of ethyl acetate, and the ethyl acetate extracts were hydrogenated using Adams' catalyst. The hydrogenation product, 52 mg., showed infrared absorption identical with that of hydrocarbon III obtained in 7% yield by hydrogenation of β-II in acetic acid.

*Anal.* Calcd. for $C_{20}H_{40}$: C, 85.63; H, 14.37; mol. wt., 280. Found: C, 85.82; H, 14.29; mass, 280.

**Hydrogenolysis of β-4,8,13-Duvatriene-1,3-diol (β-I).**—The product from hydrogenation of 500 mg. of β-I using Adams' catalyst in glacial acetic acid (18 hr. at 3 atm.) was chromatographed using alumina (Merck). Besides the β-1,3-duvanediols A and B,[1] a saturated hydrocarbon (20 mg.) was isolated. The hydrocarbon showed infrared absorption identical with that of hydrocarbon III obtained from hydrogenolysis of β-II.

**Conversion of β-3,8,13-Duvatriene-1,5-diol (β-II) to β-1-Duvanol-3-ones A and B (β-V).**—The oxidation of 290 mg. of β-II with 1 g. of chromic oxide in 8 ml. of pyridine at room temperature for 40 hr., followed by chromatography on silicic acid, yielded 86 mg. of an oil, identified as β-4,8,13-duvatrien-1-ol-3-one (β-IV) by infrared absorption. Hydrogenation using Adams' catalyst in ethanol (24 hr. at 3 atm.) followed by chromatographic separation on silicic acid and crystallization from pentane gave 11 mg. of solid, m.p. 126–127.5°, no depression of melting point with β-1-duvanol-3-one A (β-V), and 41 mg. of solid, m.p. 99–100°, no depression of melting point with β-1-duvanol-3-one B (β-V). The infrared spectra were identical with those of the corresponding β-1-duvanol-3-ones prepared by chromic oxide–pyridine oxidation of β-1,3-duvanediols A and B.[1]

**Chromic Oxide–Pyridine Oxidation of β-3,8,13-Duvatriene-1,5-diol (β-II).**—For the oxidation of β-II using chromic oxide in pyridine, the reaction time was varied from 20 to 140 hr. In each case, four reaction products were isolated and β-II was recovered. The results from a typical run are as follows.

To a mixture prepared by addition of 6.0 g. of chromic oxide to 50 ml. of pyridine was added 1.9 g. of β-II. After 6 days, the mixture was diluted with 300 ml. of water and was extracted with 200 ml. of ether. The ethereal extract was washed with 100 ml. of water and with two 150-ml. portions of 2 N hydrochloric acid. The residue from concentration of the ethereal extract was separated by chromatography into five components, described in the order of elution from silicic acid.

(a) Iso-β-4,8,13-duvatrien-1-ol-3-one, 120 mg. Infrared absorption: 2.95, 6.01, 6.24, and 10.25 μ. Ultraviolet absorption: $\lambda_{max}^{EtOH}$ 242–243 mμ, log ε 3.97. N.m.r. spectrum: 9.17 (6), 8.76 (3), 8.51 (3), 8.24 (3), and 5.15–4.0 (4).

*Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.90; H, 10.60; mol. wt., 304. Found: C, 79.04; H, 10.63; mass, 304.

(b) β-4,8,13-Duvatrien-1-ol-3-one (β-IV), 310 mg. Infrared absorption identical with β-4,8,13-duvatrien-1-ol-3-one obtained by chromic oxide–pyridine oxidation of β-4,8,13-duvatriene-1,3-diol (β-I)[1]: 2.95, 6.04, 6.22, and 10.25 μ. Ultraviolet absorption: $\lambda_{max}^{EtOH}$ 244 mμ, log ε 4.27. The n.m.r. spectrum was identical with that of β-4,8,13-duvatrien-1-ol-3-one obtained by oxidation of β-I.[1]

(c) β-4,5-Oxido-8,13-duvadien-1-ol-3-one (β-VI), 100 mg., melting point after recrystallization from pentane at −27°, 122–124°. Infrared absorption: 2.90, 5.92, and 10.28 μ. Ultraviolet absorption: no selective absorption above 220 mμ. N.m.r. spectrum: 9.15 (6), 8.67 (3), 8.56 (3), 8.43 (3), 7.17 (2), 6.42 (1), and 5.45–4.7 (3).

*Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 75.00; H, 10.06; mol. wt., 320. Found: C, 75.36; H, 9.95; mass, 320.

(d) β-3,8,13-Duvatriene-1,5-diol (β-II), 50 mg., identified by its infrared spectrum and m.p., 150–152°.

(e) β-3,4-Oxido-8,13-duvadiene-1,5-diol (β-VII), 50 mg., melting point after recrystallization from pentane at −27°, 117–119°. Infrared absorption: 2.90, 6.0, 9.0, and 10.25 μ. Ultraviolet absorption: no selective absorption above 220 mμ.

N.m.r. spectrum: 9.14 (6), 8.93 (3), 8.60 (3), 8.50 (3), 7.0 (2), and 4.7 (3).

*Anal.* Calcd. for $C_{20}H_{34}O_3$: C, 74.48; H, 10.62; active H (2), 0.62; mol. wt., 322. Found: C, 74.49; H, 10.44; active H, 0.60; mass, 304 (322–18).

**Peroxide Oxidation of β-4,8,13-Duvatrien-1-ol-3-one (β-IV) to β-4,5-Oxido-8,13-duvadien-1-ol-3-one (β-VI).**—To a solution of 103 mg. of β-4,8,13-duvatrien-1-ol-3-one (β-IV) in 6 ml. of ethyl alcohol was added a solution prepared from 0.2 g. of hydrated sodium carbonate, 5 ml. of water, and 1 ml. of 30% hydrogen peroxide. After 10 min., 60 ml. of water was added. The mixture was extracted with two 100-ml. portions of ether. The ethereal extracts were washed with four 30-ml. portions of water. Chromatography of the residue from concentration of the ethereal extract gave 20 mg. of β-4,8,13-duvatrien-1-ol-3-one and 50 mg. of material showing the infrared absorption of crude β-4,5-oxido-8,13-duvadien-1-ol-3-one. Crystallization of the latter fraction from pentane at −27° yielded 14 mg. of solid, m.p. 120–122°, with infrared absorption identical with that of β-4,5-oxido-8,13-duvadien-1-ol-3-one isolated directly from chromic oxide–pyridine oxidation of β-3,8,13-duvatriene-1,5-diol.

**Oxidative Degradation of β-3,8,13-Duvatriene-1,5-diol (β-II).**—A solution of 2 g. of β-II in 200 ml. of pyridine was added with stirring to a mixture of 19 g. of sodium periodate, 0.2 g. of potassium permanganate, and 2 g. of potassium carbonate in 600 ml. of water. The permanganate color was dissipated rapidly. Potassium permanganate was added portionwise over a period of 4.5 days. After addition of 5.7 g. of potassium permanganate the permanganate color persisted for a period of 2.5 hr. The reaction mixture was filtered through Celite. The alkaline filtrate was extracted with two 350-ml. portions of ether. The aqueous solution was acidified with sulfuric acid to a pH of < 2 and the acidified solution was extracted with three 200-ml. portions of ether. Of the ethereal extracts from the acidified solution, 60% was allowed to react with diazomethane, yielding 560 mg. of mixed methyl esters. Chromatography on silicic acid gave 106 mg. of an oil showing infrared absorption indicative of methyl 5-keto-2-isopropylhexanoate and 91 mg. of an oil showing the infrared absorption of methyl levulinate.

Of the crude methyl 5-keto-2-isopropylhexanoate, 43 mg. was converted to the semicarbazone. After crystallization from pentane, 7 mg. of solid was obtained which showed infrared absorption similar to that of authentic methyl 5-keto-2-isopropylhexanoate semicarbazone. The product melted at 123–125° and a mixture with authentic semicarbazone melted at 124–127°.

The crude methyl levulinate isolated from the oxidation reaction was converted to the 2,4-dinitrophenylhydrazone derivative. After chromatography on silicic acid and crystallization from ethanol, 15 mg. of solid, m.p. 137–139°, with infrared absorption of methyl levulinate dinitrophenylhydrazone, was obtained.

**Isolation of α-3,8,13-Duvatriene-1,5-diol (α-II).**—The isolation of α-3,8,13-duvatriene-1,5-diol was accomplished by the procedure reported for isolation of the α- and β-4,8,13-duvatriene-1,3-diols (α- and β-I).[1] In the chromatographic separation using alumina, α-II was eluted after β-II but before α- and β-I.

**Physical Properties of α-3,8,13-Duvatriene-1,5-diol (α-II).**—α-II melts at 118–120° after recrystallization from hexane, $[\alpha]^{25}D$ +100°. α-II shows no ultraviolet absorption other than end absorption below 220 mμ. Infrared absorption occurs at 3.05, 8.8, 9.0, 9.25, and 10.2 μ. The n.m.r. spectrum shows peaks at 9.18 (6), 8.67 (6), 8.49 (3), 4.62 (3), and 4.37 (2).

*Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.39; H, 11.19; active H (2), 0.66; mol. wt., 306. Found: C, 78.40; H, 11.12; active H, 0.60; mass, 306.

**Chromic Oxide–Pyridine Oxidation of α-3,8,13-Duvatriene-1,5-diol (α-II).**—A mixture prepared by addition of 300 mg. of α-II to a suspension of 1.0 g. of chromic oxide in 15 ml. of pyridine was allowed to stand at room temperature for 4 days. After addition of 125 ml. of water, the mixture was extracted with ether. The residue from concentration of the dried ethereal extract was separated by chromatography using silicic acid into three fractions: (1) 54 mg. of α-4,8,13-duvatrien-1-ol-3-one (α-IV), m.p. 74–75°, mixture melting point with α-IV prepared by oxidation of α-I,[1] 73–74°, infrared absorption identical with that of α-IV prepared by oxidation of α-I; (2) 49 mg. of material which showed infrared absorption indicating a mixture of α-IV and another α,β-unsaturated keto alcohol; (3) 51 mg. of unreacted α-II.

Isomerization of 4,8,13-Duvatriene-1,3-diols (I) to 3,8,13-Duvatriene-1,5-diols (II).—A hexane solution of 216 mg. of α-I was added to a 20 × 75 mm. chromatographic column of acid-washed alumina (Merck). After α-I had been allowed to contact the adsorbent for 40 hr., elution was attempted using hexane–ether mixtures. Elution with ether yielded 20 mg. (9%) of material with infrared absorption identical with that of α-II. Starting material, α-I, 170 mg., was recovered by elution with ether containing 2% methanol.

Using the same procedure, β-I was converted to β-II in 20% yield.

# The Mitomycin Antibiotics. Synthetic Studies. I. Synthesis of Model Quinones

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Certain Bz(benz)-amino-substituted 2-hydroxy-1,4-naphthoquinones and 5-hydroxy-6-methyl-substituted indoloquinones, including a pyrrolo[1,2-a]indoloquinone, have been prepared. Their pertinence as ultraviolet models for mitomycin degradation products is discussed.

In the course of an investigation concerning the structure of the mitomycin group of antibiotics, Webb and collaborators isolated degradation products which were apparently amino-substituted 2-hydroxy-3-methyl-1,4-quinones.[1] In this paper we wish to report the synthesis of several naphtho- and indoloquinones prepared as ultraviolet models of these degradation products. One of the partial structures originally suggested for these products contained a 1,4-naphthoquinone nucleus and, therefore, we undertook the synthesis of the four possible Bz-amino-2-hydroxy-1,4-naphthoquinones. Although three of these compounds and a potential close precursor to the fourth had already been reported by Kehrmann and his collaborators,[2] it was desirable to devise more convenient pathways for the preparation of three of the compounds in view of the difficult and tedious procedures which the Kehrmann group had utilized. In particular, it appeared that the use of the Fremy's salt (potassium nitrosodisulfonate) procedure[3] for the conversion of phenolic compounds to quinones might lead to considerably shortened sequences.

The unknown 6-amino-2-hydroxy-1,4-naphthoquinone (II) was prepared by hydrolysis, according to the procedure of Thomson,[4] of the known[2a] 6-acetamido-4-anilino-1,2-naphthoquinone (I).



I → II
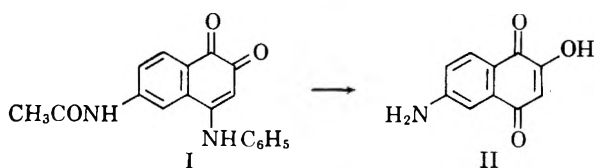
7-Amino-2-hydroxy-1,4-naphthoquinone (IX)[2b] was prepared as follows. 7-Amino-2-naphthol (III)[5] was converted to the N-acetyl derivative IV via O,N-di-

acetylation of the hydrochloride in aqueous solution, followed by de-O-acetylation in dilute alkali. The previously reported[5] acetylation in pyridine was found difficult to repeat. Oxidation of IV with Fremy's salt afforded an 89% yield of 7-acetamido-1,2-naphthoquinone (V). This conversion previously required three steps.[2d] Attempts to elaborate the 2-hydroxy-1,4-quinone system via Thiele acetylation of V followed by hydrolysis and oxidation of the tetraacetate VI were unpromising. The Thiele acetylation gave erratic results and the yield of VI was never better than 18%, although subsequent alkaline hydrolysis of VI followed by ferric chloride oxidation gave a 96% yield of the 7-acetamido derivative VII. A superior route was provided by the addition of aniline to V. The resulting 7-acetamido-4-anilino-1,2-naphthoquinone (VIII), formed in 40% yield by the procedure of Kehrmann and Wolff,[2d] then was hydrolyzed in sulfuric acid directly to the desired IX, obtained in 76% yield after partition chromatography. Compound IX could be N-acetylated to VII; VII could be hydrolyzed to IX.
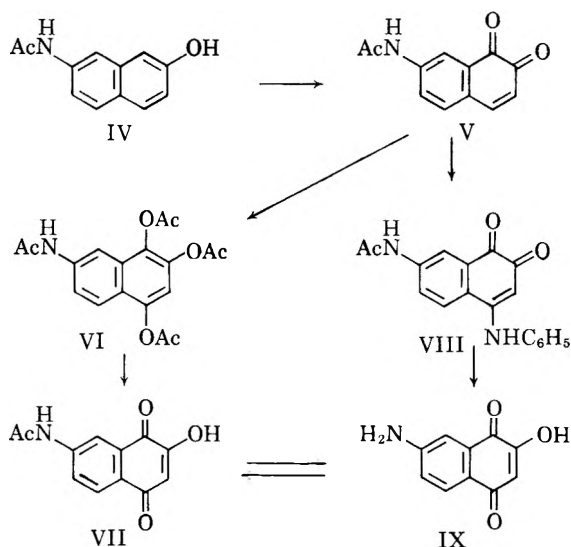


Preparation of 8-amino-2-hydroxy-1,4-naphthoquinone (XIII)[2e] was accomplished by similar procedures: Fremy's salt oxidation of 8-acetamido-2-naphthol (X), addition of aniline to the resulting 8-acetamido-1,2-

(1) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84**, 3185 (1962).

(2) (a) F. Kehrmann and M. Matis, *Ber.*, **31**, 2413 (1898); (b) F. Kehrmann and G. Steiner, *ibid.*, **33**, 3280 (1900); (c) F. Kehrmann and G. Steiner, *ibid.*, **33**, 3285 (1900); (d) F. Kehrmann and H. Wolff, *ibid.*, **33**, 1538 (1900); (e) F. Kehrmann and E. Misslin, *ibid.*, **34**, 1224 (1901); (f) F. Kehrmann and A. Denk, *ibid.*, **33**, 3295 (1900).

(3) (a) H. Teuber and G. Jellinek, *ibid.*, **85**, 95 (1952); (b) H. Teuber and G. Thaler, *ibid.*, **91**, 2253 (1958); (c) H. Teuber and G. Staiger, *ibid.*, **89**, 489 (1956).

(4) R. H. Thomson, *J. Org. Chem.*, **13**, 874 (1948).

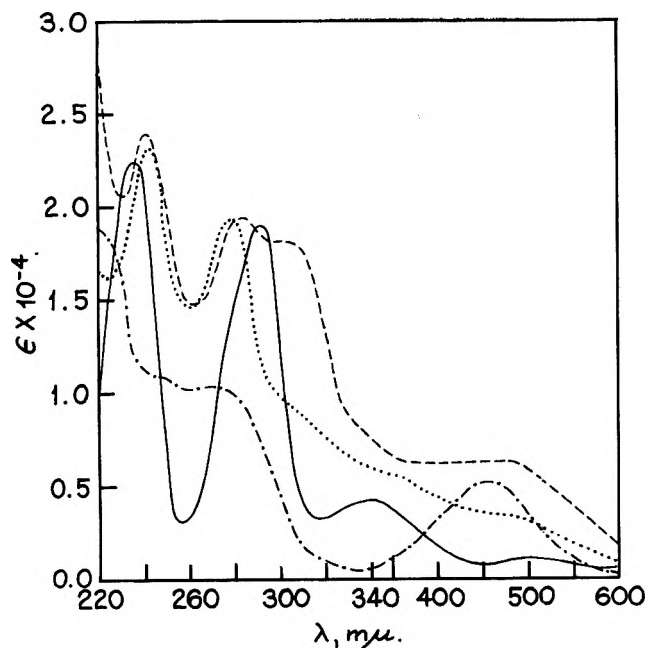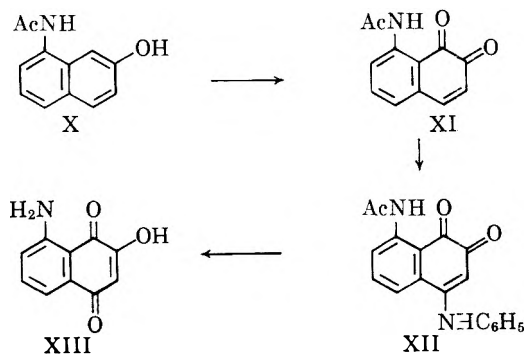(5) L. Raiford and W. Talbot, *J. Am. Chem. Soc.*, **49**, 559 (1927).

Fig. 1.—Ultraviolet absorption spectra in methanol: ———, 2-aminomitosene-1,7-diol; – – – –, 6-amino-2-hydroxy-1,4-naphthoquinone (II); . . . ., 7-amino-2-hydroxy-1,4-naphthoquinone (IX); — · —, 8-amino-2-hydroxy-1,4-naphthoquinone (XIII).

naphthoquinone (XI) and hydrolysis of the 4-anilino derivative XII to XIII.



We were unable to devise a successful alternate preparation for the known[2c] 5-amino-2-hydroxy-1,4-naphthoquinone XVII. In contrast to the facile Fremy's salt oxidation of the 7- and 8-acetamido-2-naphthols, this oxidation was unsuccessful with 5-acetamido-2-naphthol (XIV).[6] However, the desired *o*-quinone XV was obtained from XIV by the three-step procedure of Kehrmann and Denk.[2f] Addition of aniline to XV then afforded the 4-anilino-*c*-quinone XVI. Despite the successful hydrolysis of the other three acetamido-4-anilino-1,2-naphthoquinones, XVI could not be hydrolyzed to XVII.[7] Since at about this time the naphthoquinone hypothesis was abandoned,

(6) An interesting sidelight to the Fremy's salt oxidation studies was the observation that 5-amino-1-naphthol undergoes a facile selective oxidation of the phenolic ring to give 5-amino-1,4-naphthoquinone in high yield.



However, 8-amino-2-naphthol does not react with Fremy's salt under the same conditions.
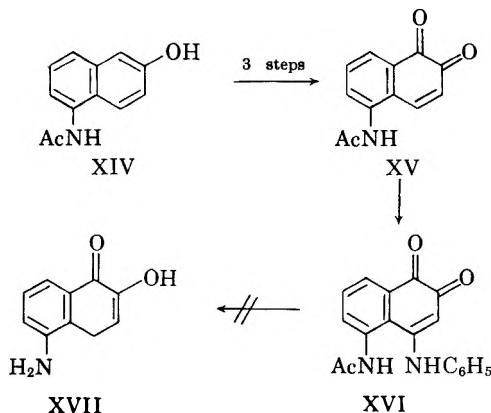


further attempts to prepare this particular naphthoquinone model were discontinued.

Comparison of the ultraviolet absorption spectra of the three Bz-amino-2-hydroxy-1,4-naphthoquinones with the spectra of the 2-hydroxy-1,4-quinone degradation product revealed no close similarity (Fig. 1); this observation in conjunction with other evidence led Webb and co-workers[1] to abandon the original postulation that the degradation products were naphthoquinones. Indoloquinone structures for the degradation products were then proposed[1] and the synthesis of appropriate model indoloquinones was undertaken. One pertinent indoloquinone had already been reported in the literature, namely, ethyl 5-hydroxy-2,6-dimethyl-4,8-dioxo-3-indolecarboxylate (XVIII) and we repeated the synthesis of this compound as described by Teuber and Thaler[3b] with some modification in the final step[8] (see Experimental section). Although XVIII was a reasonably good ultraviolet model for the hydroxy-*p*-quinone degradation products (Fig. 2 and 3), the carboxylate function of the former was obviously not present in the latter. An indoloquinone substituted only with alkyl groups seemed to be a more pertinent model. We, therefore, prepared 5,6,7,8-tetrahydro-3-hydroxy-2-methyl-1,4-carbazoledione (XX) from the known[3c] 5,6,7,8-tetrahydro-2-methyl-3,4-carbazoledione (XIX) by prolonged treatment with 0.1 *N* sodium hydroxide solution. The near identity of the ultraviolet absorption spectrum of XX with that of 2-amino-mitosene-1,7-diol[9] in acid (Fig. 2) and in alkali (Fig. 3)

(7) Since XVI is the only isomer that has the acetamido group in close proximity to the 4-anilino group, it is possible that this acetamido group either inhibits the hydrolysis or participates in the hydrolytic reaction forming alkali-insoluble products. Ring closures involving acetamido groups attached to *o*-quinone systems have been observed by Senoh and Witkop [*J. Am. Chem. Soc.*, **81**, 6222 (1959)]. Also, Sander reported that the
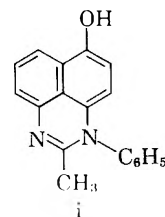


pyrimidine derivative i was formed by the stannous chloride–hydrochloric acid reduction of 5-acetamido-1,4-naphthoquinone-4-anil [*Ber.*, **58**, 824 (1925)].

(8) Considerable difficulty was encountered in repeating the elaboration of *o*-quinone to hydroxy-*p*-quinone in methanolic hydrochloric acid. The procedure that we finally utilized was derived from the observation of Mr. V. J. Kerr that prolonged aging in 0.1 *N* hydrochloric acid or 0.1 *N* sodium hydroxide produced the change in ultraviolet absorption characteristic of the desired elaboration.

(9) The trivial name "mitosene" has been proposed [ref. 1] for the structure 2,3-dihydro-9-hydroxymethyl-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione carbamate.

Fig. 2.—Ultraviolet absorption spectra in 0.1 $N$ hydrochloric acid: ———, 2-aminomitosene-1,7-diol; – – – –, 5,6,7,8-tetra-hydro-3-hydroxy-2-methyl-1,4-carbazoledione (XX); . . . ., ethyl 5-hydroxy-2,6-dimethyl-4,8-dioxo-3-indolecarboxylate (XVIII).

afforded significant support for the proposed indolo-quinone structure.[1]

Finally, a mitomycin A degradation product with an ultraviolet absorption spectrum significantly different from the above hydroxyindoloquinones (compare Fig. 3 with Fig. 4) was postulated by Webb and co-workers[1] to possess the 1-oxopyrrolo[1,2-a]indoloquinone struc-ture XXI. Therefore, we undertook the synthesis of the closely related model compound XXV from 2,3-di-hydro - 7 - methoxy - 6 - methyl - 1 - oxo - 1$H$ - pyrrolo-[1,2-a]indole (XXII).[10] Cleavage of the methoxy group in XXII was effected by treatment with alumi-num chloride in refluxing xylene and the resulting phenolic product XXIII was oxidized with Fremy's salt to the corresponding o-quinone XXIV. Prolonged treatment of XXIV with 0.1 $N$ hydrochloric acid fur-nished the hydroxy-p-quinone XXV. The ultraviolet absorption spectrum of the latter compound closely re-sembled that of the mitomycin A degradation product XXI (Fig. 4).[11]



Fig. 3.—Ultraviolet absorption spectra in 0.1 $N$ sodium hydrox-ide: ———, 2-aminomitosene-1,7-diol; – – – –, 5,6,7,8-tetrahydro-3-hydroxy-2-methyl-1,4-carbazoledione (XX); . . . ., ethyl 5-hydroxy-2,6-dimethyl-4,8-dioxo-3-indolecarboxylate (XVIII).

### Experimental

**General.**—Melting points are uncorrected. Ultraviolet spec-tra were determined in methanol using a Cary recording spectro-photometer. Infrared spectra were determined in potassium bromide disks on a Perkin–Elmer spectrophotometer (Model 21). Solutions were dried over magnesium sulfate.

**6-Amino-2-hydroxy-1,4-naphthoquinone** (II).—A solution of 0.52 g. of 6-acetamido-4-anilino-1,2-naphthoquinone (I)[2a] in 10 ml. of concentrated sulfuric acid was cautiously diluted with 20

ml. of water and the mixture was heated at mild reflux for 10 min. After cooling, the resulting brown solution was neutral-ized to pH 6 with 20% sodium hydroxide solution. The brown precipitate, which formed immediately, was collected and dried. The crude 6-amino-2-hydroxy-1,4-naphthoquinone (II) (0.32 g.) was purified by partition chromatography. It was dissolved in 20 ml. of the lower and 20 ml. of the upper phase of the system cyclohexane–dioxane–water (10:15:2) and mixed thoroughly with 40 g. of Celite[12] diatomaceous earth. This mixture was packed on a column which had been prepared from 250 g. of Celite diato-maceous earth and 125 ml. of the lower phase of the solvent sys-tem just described. The column (3.8 × 60 cm.) was eluted with the upper phase of the solvent system and the effluent was passed through a recording spectrophotometer which had been set at 300 m$\mu$. The ultraviolet absorbing material was contained in the

(10) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, to be published.

(11) The ultraviolet absorption spectra of hydroxy-p-quinones is nearly identical with those of the corresponding methoxy-p-quinones in acid and neutral solution. In dilute alkali the spectra of hydroxy-p-quinones undergo bathochromic shifts, but those of methoxy-p-quinones do not. In the present work only the neutral solution comparison was made since both XXI and XXV decompose in dilute alkali.
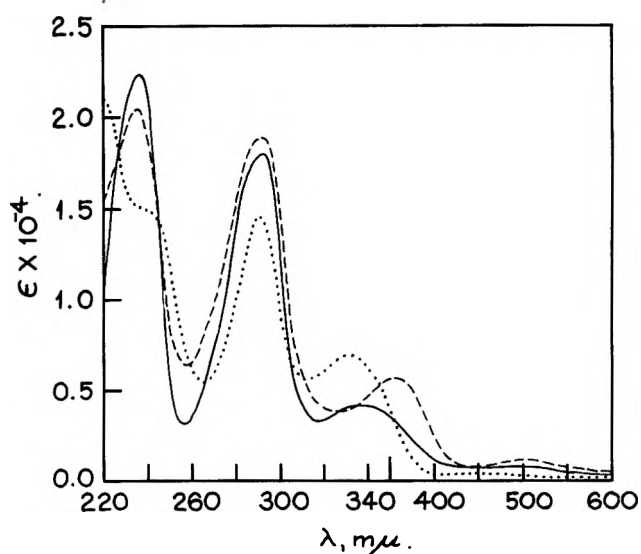
(12) Celite is the trademark of Johns-Manville Corporation for diatoma-ceous earth products.

Fig. 4.—Ultraviolet absorption spectra in methanol: ———, 7-hydroxymitosen-1-one (XXI); – – – –, 2,3-dihydro-7-hydroxy-6-methyl-1,5,8-trioxo-1H-pyrrolo[1,2-a]indole (XXV).

second hold-back volume (410 ml.). Concentration in vacuo afforded 0.25 g. (78%) of red-brown solid which did not melt below 320°; $\lambda_{max}$ 2.78, 2.86, 2.94, 6.06, 6.28 $\mu$; 242 ($\epsilon$ 24,000), 293 ($\epsilon$ 19,500), 309 ($\epsilon$ 18,500), 340 ($\epsilon$ 8,600), 465 ($\epsilon$ 6,500) m$\mu$; (see Fig. 1); p$K_a$ 5.10.

Anal. Calcd. for $C_{10}H_7NO_3$ (189.16): C, 63.49; H, 3.73; N, 7.41. Found: C, 63.44; 63.38; H, 4.40, 4.34; N, 7.25.

7-Acetamido-2-naphthol (IV).—A solution of 24.0 g. of 7-amino-2-naphthol (III)[5] in 280 ml. of water and 14 ml. of concentrated hydrochloric acid was treated with 24 ml. of acetic anhydride and a cold solution of 34.0 g. of sodium acetate and 0.50 g. of sodium hydrosulfite in 100 ml. of water. The precipitate of 7-acetamido-2-acetoxynaphthalene was collected on a filter, washed with water, and pressed dry. Without further purification, it was dissolved in a solution of 350 ml. of water and 56 ml. of 10% sodium hydroxide. A small amount of insoluble material was removed by filtration and the filtrate was acidified with 3 N hydrochloric acid. The white precipitate was collected, washed with water, and dried. This procedure afforded 23.3 g. (77%) of 7-acetamido-2-naphthol (IV), m.p. 227–232° (lit.,[5] m.p. 232°).

7-Acetamido-1,2-naphthoquinone (V).—An ice-cooled solution of 9.0 g. (0.045 mole) of 7-acetamido-2-naphthol (IV) in 200 ml. of methanol was added rapidly, with stirring, to an ice-cooled solution of 27.0 g. (0.10 mole) of Fremy's salt in 2 l. of water and 400 ml. of 0.167 M potassium dihydrogen phosphate. The brick-red quinone, which precipitated immediately, was collected, washed well with water, and dried. This procedure afforded 8.5 g. (88.5%) of 7-acetamido-1,2-naphthoquinone (V), m.p. 214–215°. Recrystallization from methanol raised the melting point to 223° (lit.,[2d] m.p. 224°); $\lambda_{max}$ 2.96, 6.02 $\mu$; 247 ($\epsilon$ 34,000), 272 ($\epsilon$ 19,500), 320 ($\epsilon$ 1,750), 335 ($\epsilon$ 1,950), 455 ($\epsilon$ 1,600) m$\mu$.

7-Acetamido-2-hydroxy-1,4-naphthoquinone (VII).—To a stirred, ice-cooled mixture of 20 ml. of acetic anhydride and 10 drops of concentrated sulfuric acid was added 1.0 g. of 7-acetamido-1,2-naphthoquinone (V). After 20 min., when a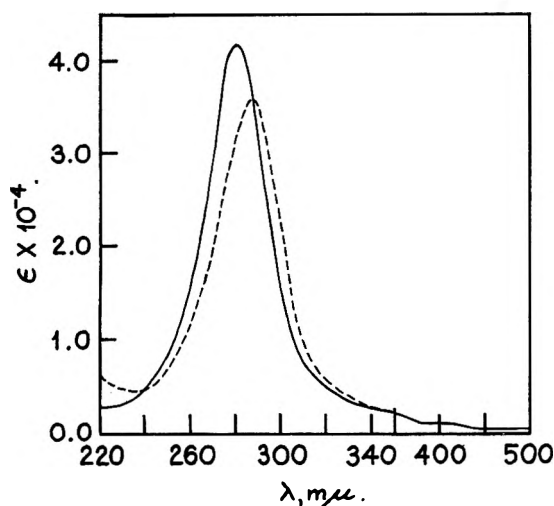ll of the quinone had dissolved, the resulting dark solution was poured into ice–water. The yellow oil that separated was extracted into 50 ml. of ethyl acetate. After successive washes with water, potassium bicarbonate solution (until the acetic acid was removed), and water, the extract was dried, filtered, and diluted with 50 ml. of ether. A white powder precipitated. It was washed with ether and dried; yield 0.29 g. (17.5%); m.p. 225–227°; $\lambda_{max}$ 3.03, 5.68, 6.02 $\mu$. Without further purification this 7-acetamido-1,2,4-triacetoxynaphthalene (VI) was dissolved in a solution of 0.34 g. of potassium hydroxide in 10 ml. of ethanol. The solution was kept under nitrogen for 10 min., then diluted with 25 ml. of water and acidified with 3 ml. of 3 N hydrochloric acid. A solution of 1.0 g. of ferric chloride in 15 ml. of water and 1 ml. of concentrated hydrochloric acid was added. The yellow precipitate of 7-acetamido-2-hydroxy-1,4-naphthoquinone (VII) was collected, washed with water, and dried. This procedure afforded 0.18 g. (17% over-all) of material with m.p. 239–240° dec.; $\lambda_{max}$ 2.78, 2.94, 5.95, 6.05 $u$; 233 ($\epsilon$ 12,500), 268 ($\epsilon$ 25,000), 292 ($\epsilon$ 13,000), 344 ($\epsilon$ 3,700), 410 ($\epsilon$ 1,400) m$\mu$.

Anal. Calcd. for $C_{12}H_9NO_4$ (231.20): C, 62.34; H, 3.92; N, 6.06. Found: C, 61.96; H, 4.27; N, 6.26.

7-Amino-2-hydroxy-1,4-naphthoquinone (IX).—This compound was prepared by the procedure utilized for 6-amino-2-hydroxy-1,4-naphthoquinone (II, see above). From 1.70 g. of 7-acetamido-4-anilino-1,2-naphthoquinone (VIII)[2d] there was obtained after partition chromatography of the hydrolysis product (contained in hold-back volumes 1.5–2.5, recording spectrophotometer set at 280 m$\mu$) an 0.80 g. (76%) yield of 7-amino-2-hydroxy-1,4-naphthoquinone (IX), red-brown solid, no melting below 320°; $\lambda_{max}$ 2.78, 2.86, 3.03, 6.06 $\mu$; 243 ($\epsilon$ 23,000), 281 ($\epsilon$ 19,000), 305 ($\epsilon$ 9,000), 360 ($\epsilon$ 6,000), 500 ($\epsilon$ 4,000) m$\mu$ (see Fig. 1).

Interconversion of 7-Amino-2-hydroxy-1,4-naphthoquinone (IX) and 7-Acetamido-2-hydroxy-1,4-naphthoquinone (VII).—To a stirred suspension of 50 mg. of 7-amino-2-hydroxy-1,4-naphthoquinone in 2 ml. of water containing three drops of concentrated hydrochloric acid was added a solution of 160 mg. of sodium acetate in a little water, followed by 0.15 ml. of acetic anhydride. The solid soon dissolved and then a yellow precipitate formed. After 12 hr., the mixture was filtered and the washed filter cake was dissolved in 3% sodium hydroxide solution. Upon acidification with 3 N hydrochloric acid, a yellow precipitate was formed. It had an infrared spectrum which was superimposable with that of 7-acetamido-2-hydroxy-1,4-naphthoquinone (VII) prepared via the tetraacetate (VI) (both samples were 0.375% in potassium bromide disks).

To a solution of 50 mg. of 7-acetamido-2-hydroxy-1,4-naphthoquinone (VII), prepared via the tetraacetate (VI) in 2 ml. of concentrated sulfuric acid was cautiously added 4 ml. of water. The resulting mixture was boiled 5 min., cooled, and diluted with 5 ml. of water. The brown solution was made slightly alkaline with 10% sodium hydroxide (dark red solution), then a few drops of dilute sulfuric acid were added to cause the precipitation of 7-amino-2-hydroxy-1,4-naphthoquinone (IX), which was collected, washed well with water, and dried. It had an infrared spectrum which was superimposable with that of the compound prepared via VIII (both samples were 0.375% potassium bromide disks).

8-Acetamido-1,2-naphthoquinone (XI).—To a suspension of 10 g. (0.05 mole) of 8-acetamido-2-naphthol (X) in a solution of 11.3 g. of potassium dihydrogen phosphate in 1000 ml. of ice-water was added 30 g. of Fremy's salt. The resulting suspension was stirred at 5° overnight. At the end of the reaction period, the brick-red product was collected on a filter, washed with water, and dried at 38° (125 mm.), yielding 5.9 g. (55%) of 8-acetamido-1,2-naphthoquinone. An additional 2.0 g. (18%) was obtained by extraction of the mother liquors with methylene chloride, desiccation of the extracts, and concentration to dryness. The product is soluble in most organic solvents, but darkens on standing in solutions; $\lambda_{max}$ 2.91, 6.09 $\mu$; 251 ($\epsilon$ 13,800), 440 ($\epsilon$ 3,200) m$\mu$. Although a satisfactory analysis could not be obtained for this compound, it was suitable for use in the preparation of subsequent compounds.

8-Amino-2-hydroxy-1,4-naphthoquinone (XIII).—To a suspension of 5.0 g. of 8-acetamido-1,2-naphthoquinone (XI) in 50 ml. of ethanol was added with stirring 5 ml. of aniline. Stirring was continued for 10 min., then 10.85 ml. of a solution 1.5 M in chromic anhydride and 4.5 M in sulfuric acid was added with stirring during about 20 min. with external cooling. Stirring was continued for an additional 10 min., then the product was collected on a filter, washed successively with 20 ml. of water, 20 ml. of ethanol, and 30 ml. of methylene chloride, and dried in a vacuum oven. The crude 8-acetamido-4-anilino-1,2-naphthoquinone (XII) weighed 7.7 g. Its insolubility in organic solvents precluded convenient purification by standard techniques. A satisfactory analysis could not be obtained and the material was used without further purification. It was converted to 8-amino-2-hydroxy-1,4-naphthoquinone (XIII) by the procedure utilized for 6-amino-2-hydroxy-1,4-naphthoquinone (II, see above). From 6.5 g. of XII was obtained after partition chromatography of the hydrolysis product [the second colored band (orange) that developed was collected] a 0.6 g. yield of 8-amino-2-hydroxy-1,4-naphthoquinone (XIII), m.p. 230–233° (lit.,[2e] m.p. 225°, sublimes with decomposition); $\lambda_{max}$ 2.94, 3.00, 6.16 $\mu$; 221 ($\epsilon$ 19,000) sh., 252 ($\epsilon$ 11,000) sh., 277 ($\epsilon$ 10,000), 480 ($\epsilon$ 5,100) m$\mu$ (see Fig. 1).

Anal. Calcd. for $C_{10}H_7NO_3$ (189.16): C, 63.5; H, 3.7; N, 7.4; $CH_3CO$, 0. Found: C, 63.9; 63.4, 63.8; H, 4.2, 4.2, 4.1; N, 7.3; $CH_3CO$, 0.6.

**5-Acetamido-4-anilino-1,2-naphthoquinone (XVI).**—Aniline (6 ml.) was added to a stirred suspension of 6.1 g. of 5-acetamido-1,2-naphthoquinone (XV) in 20 ml. of ethanol. The quinone dissolved on addition of the aniline and immediately a brown precipitate separated from the dark solution. This precipitate was collected on a filter, washed with 20 ml. of ethanol in several portions, and dried in a vacuum desiccator, yield 5.1 g. (72%), no melting below 320°; $\lambda_{max}$ 2.95, 5.95, 6.04 $\mu$; 260 ($\epsilon$ 19,000), 296 ($\epsilon$ 12,000), 410 ($\epsilon$ 4,900).

*Anal.* Calcd. for $C_{18}H_{14}N_2O_3$ (306.31): C, 70.6; H, 4.6; N, 9.2. Found: C, 70.8; H, 5.2; N, 8.9.

**Ethyl 5-Hydroxy-2,6-dimethyl-4,7-dioxo-3-indolecarboxylate (XVIII).**—This compound was prepared by a variation of the known method.[3b] A solution of 0.20 g. of 2,6-dimethyl-3-carbethoxy-4,5-indoloquinone[3b] in 1 l. of methanol was added to 9 l. of 0.1 N aqueous hydrochloric acid. After 7 days at 25°, the mixture was extracted with two 1-l. portions of ether. The extract was washed with water, dried, and concentrated to afford 0.21 g. of red solid, m.p. 215–235°. Recrystallization from benzene afforded 0.076 g. (36%) of red crystals, dec. at 250° (lit.,[3b] dec. at 250°); $\lambda_{max}$ 3.11, 5.88, 6.17 $\mu$; 220 ($\epsilon$ 21,000), 241 ($\epsilon$ 15,000), 291 ($\epsilon$ 14,500), 330 ($\epsilon$ 6,900), 450 ($\epsilon$ 540) m$\mu$ (see Fig. 2 and 3 for acid and alkali ultraviolet curves).

**5,6,7,8-Tetrahydro-3-hydroxy-2-methyl-1,4-carbazoledione (XX).**—A solution of 100 mg. of 5,6,7,8-tetrahydro-2-methyl-3,4-carbazoledione (XIX)[3c] in 1 l. of methanol was added to 9 l. of 0.1 N sodium hydroxide. After 18 hr. the resulting green solution had changed to blue. It was then acidified with 3 N hydrochloric acid until it turned pink and extracted with 2 l. of ether (in excess of the ether required to saturate the aqueous solution). The ether extract was washed with water, dried, and concentrated. The residue was recrystallized from acetone–benzene; copper-colored plates which did not melt below 330° were obtained. Yield 50 mg. (47%); $\lambda_{max}$ 2.96, 6.15 $\mu$; 232 ($\epsilon$ 19,000); 301 ($\epsilon$ 19,000); 360 ($\epsilon$ 4,400); 500 ($\epsilon$ 1,200) m$\mu$ (see Fig. 2 and 3 for acid and alkali ultraviolet curves).

*Anal.* Calcd. for $C_{13}H_{13}NO_3$ (231.24): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.44; H, 5.74; N, 6.26.

**2,3-Dihydro-7-hydroxy-6-methyl-1-oxo-1H-pyrrolo[1,2-a]-indole (XXIII).**—A mixture of 645 mg. (3 mmoles) of 2,3-dihydro-7-methoxy-6-methyl-1-oxo-1H-pyrrolo[1,2-a]indole (XXII),[9] 800 mg. (6 mmoles) of anhydrous aluminum chloride, and 20 ml. of xylene was stirred in a nitrogen atmosphere and heated at reflux temperature for 5 hr. It was cooled and decomposed with ice and dilute hydrochloric acid and extracted into ethyl acetate. The ethyl acetate solution was washed with water, dried, and concentrated. The glassy solid residue (536 mg.) was purified by partition chromatography (see above) on 850 g. of Celite diatomaceous earth with the system heptane–ethyl acetate–methanol–water (70:30:15:6). The recording spectrophotometer was set at 330 m$\mu$. The product was contained in hold-back volumes 3.5–5.0. Concentration of this effluent afforded 139 mg. (23%)

of 2,3-dihydro-7-hydroxy-6-methyl-1-oxo-1H-pyrrolo[1,2-a]indole (XXIII); orange powder, m.p. 255° dec.; $\lambda_{max}$ 3.05 (s), 5.95 (s) $\mu$; 332 ($\epsilon$ 20,000) m$\mu$.

*Anal.* Calcd. for $C_{12}H_{11}NO_2$ (201.22): C, 71.62; H, 5.51; N, 6.96. Found: C, 71.99, 71.70; H, 6.08, 5.82; N, 6.73.

**2,3-Dihydro-6-methyl-1,7,8-trioxo-1H-pyrrolo[1,2-a]indole (XXIV).**—To a solution of 268 mg. (1 mmole) of Fremy's salt in 20 ml. of 0.167 M potassium dihydrogen phosphate solution and 40 ml. of water was added a solution of 100 mg. (0.5 mmole) of 2,3-dihydro-7-hydroxy-6-methyl-1-oxo-1H-pyrrolo[1,2-a]indole (XXIII) in 25 ml. of acetone. The Fremy's salt was decolorized instantly and the dark red solution that formed was diluted with 65 ml. of water and extracted with 200 ml. of ethyl acetate. This extract was washed with brine, dried, and concentrated. The residue was purified by partition chromatography (see above) on 56 g. of Celite with the system heptane–ethyl acetate–methanol–water (50:50:15:6). The recording spectrophotometer was set at 300 m$\mu$. The product was contained in hold-back volumes 3.8–5.5. Concentration of the effluent afforded 30 mg. (28%) of 2,3-dihydro-6-methyl-1,7,8-trioxo-1H-pyrrolo[1,2-a]indole (XXIV), red prisms, dec. 230°; $\lambda_{max}$ 5.7 (s), 6.0 (s) $\mu$; 300 ($\epsilon$ 19,000), 510 ($\epsilon$ 750) m$\mu$.

*Anal.* Calcd. for $C_{12}H_9NO_3$ (215.20): C, 66.97; H, 4.22; N, 6.51. Found: C, 66.96; H, 4.62; N, 5.57.

**2,3-Dihydro-7-hydroxy-6-methyl-1,5,8-trioxo-1H-pyrrolo[1,2-a]indole (XXV).**—A solution of 15 mg. of 2,3-dihydro-6-methyl-1,7,8-trioxo-1H-pyrrolo[1,2-a]indole (XXIV) in 150 ml. of methanol was mixed with 1350 ml. of 0.1 N hydrochloric acid solution. The resulting pink solution was kept at 25° and its ultraviolet absorption spectrum was determined at intervals. After 10 days it had $\lambda_{max}$ 290 m$\mu$ and it was yellow. The solution was saturated with salt and extracted with 500 ml. of ether. This extract was dried and concentrated. Crystallization of the residue from acetone afforded 2.8 mg. (17%) of 2,3-dihydro-7-hydroxy-6-methyl-1,5,8-trioxo-1H-pyrrolo[1,2-a]indole (XXV), yellow needles; m.p. 265° dec.; $\lambda_{max}$ 3.05 (m), 5.8 (s), 6.0 (s), 6.10 (s) $\mu$; 289 ($\epsilon$ 19,000) m$\mu$ (see Fig. 4); violet solution in dilute alkali.

*Anal.* Calcd. for $C_{12}H_9NO_4$ (231.20): C, 62.34; H, 3.92. Found: C, 63.26; H, 4.44.

# Vinyl Proton Abstraction during Metalation of α-Olefins

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The acidic products obtained from metalation and subsequent carbonation of 1-dodecene are shown to vary with time. At short reaction times 2-tridecenoic acid, arising from metalation at the terminal vinylic position, predominates. At longer reaction times the major products are β,γ-unsaturated acids, due to metalation at the allylic position. The precursor of 2-tridecenoic acid, 1-sodio-1-dodecene, was shown to be stable to the metalation conditions. The variation of products with time is accounted for by competing metalation of 2-dodecene formed in an accompanying isomerization of starting material. No metalation is observed at the secondary vinylic position although 2-sodio-1-dodecene was found to be stable under the reaction conditions. These observations are discussed in terms of relative rates of proton removal at the terminal vinylic, the allylic, and the secondary vinylic positions.

Metalation of α-olefins generally has been considered to proceed through preferential reaction at the resonance stabilized allylic position.[1] Thus the acidic products obtained by stoichiometric metalation and carbonation,[2,3] as well as the base-catalyzed isomerization of olefins,[4] have been accounted for by reaction at this position. Benkeser's[5] recent work on the metalation of cumene and ethylbenzene discloses a kinetically favored proton abstraction at a ring position followed by equilibration to the thermodynamically favored α-isomer. That the benzenoid positions are not subject to appreciable resonance stabilization has been established previously.[6] In olefinic systems containing no allylic protons, such as 3,3-dimethyl-1-butene, and those in which allylic resonance stabilization is hindered, metalation with an alkylsodium compound removes vinylic protons.[7,8] However, by isolation of some straight chain α,β-unsaturated acid, following metalation and carbonation of α-olefins, Morton[2] has shown that proton abstraction at the terminal vinylic position does occur.

Since α-olefins contain both primary and secondary vinylic positions, neither of which would be expected to exhibit much resonance stabilization, as well as a potentially resonance stabilized allylic reaction site, a re-examination of this system under non-equilibrium conditions seemed worthwhile.

Metalating agents were prepared from the corresponding alkyl chlorides and metal dispersions using typical high speed stirring techniques.[2] Reactions were conducted at room temperature, with portions of the heterogeneous reaction mixture being removed at the time intervals reported in Table I. Carbonation was effected by pouring the reaction mixtures over excess solid carbon dioxide. Characterization of products was accomplished by a combination of infrared, nuclear magnetic resonance, and gas–liquid chromatographic (g.l.c.) studies. Details are given in the Experimental section. Table I gives typical data

## TABLE I

REACTION OF 1-DODECENE WITH PENTYLSODIUM[a]

| Time | Acids from 1-do-decene, % | Hexanoic acid, % | α-Vinyl-un-deca-noic, % | 3-Tri-decen-oic, %[b] | 2-Tri-decen-oic, %[b] | Recovered olefin composition, % 1-do-decene | 2-do-decene[c] |
|---|---|---|---|---|---|---|---|
| 5 min. | 75 | 25 | 26 | 9 | 65 | 82 | 17 |
| 15 min. | 50 | 50 | 31 | 12 | 52 | 57 | 42 |
| 20 min. | 52 | 48 | 38 | 17 | 44 | 37 | 63 |
| 2 hr. | 40 | 60 | 53 | 32 | 15 | 0 | 99 |

[a] The variations with time have been shown to be consistent in repeated runs, although the absolute values vary somewhat. [b] These are predominantly the *trans* isomers. [c] Approximately equal amounts of *cis* and *trans* isomers are present.

obtained from the reaction of a four molar excess of 1-dodecene with pentylsodium.

It is evident that the $C_{13}$ acid products can be accounted for by allyl carbanionic I and terminal vinyl carbanionic IV intermediates.[9]

$$C_9H_{19}C \colonequals C \colonequals CH_2 \xrightarrow{CO_2}$$
$$\overset{\ominus}{\phantom{.}} Na^{\oplus}$$
$$I$$

$$C_9H_{19}\overset{\underset{\displaystyle CH}{|}}{C}-\overset{O}{\overset{\|}{C}}OH + C_9H_{19}C=C-CH_2-\overset{O}{\overset{\|}{C}}OH \quad (1)$$
$$\underset{CH_2}{\overset{\|}{}} \quad II \qquad III$$

$$C_9H_{19}CH_2-C=C^{\ominus}Na^{\oplus} \xrightarrow{CO_2} C_9H_{19}CH_2C=C-\overset{O}{\overset{\|}{C}}OH \quad (2)$$
$$IV \qquad\qquad V$$
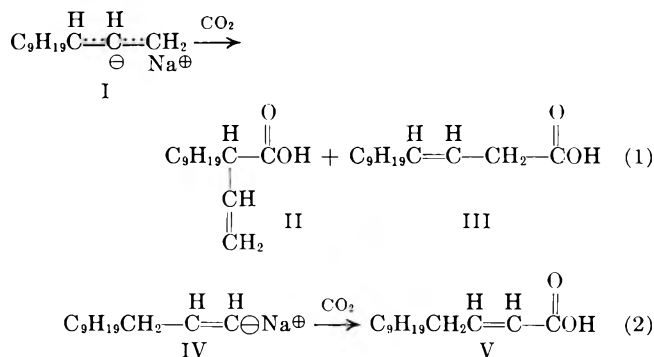
The g.l.c. data (see Experimental) show that little if any 2-carboxy-1-dodecene (VII), arising from proton abstraction at the secondary vinylic position, is realized. This can be rationalized on the familiar grounds that secondary positions yield higher energy anionic species than primary positions and that the higher energy requirement causes slower reaction. However, there is another possible explanation for the absence of this product. The secondary intermediate VI could be

(1) R. A. Benkeser, D. J. Foster, D. M. Sauve, and J. T. Nobis, *Chem. Rev.*, **57**, 867 (1957).

(2) A. A. Morton, F. D. Marsh, R. D. Coombs, A. L. Lyons, S. E. Penner, H. E. Ramsden V. B. Baker, E. L. Little, and R. L. Letsinger, *J. Am. Chem. Soc.*, **7** 3785 (1950).

(3) A. Lüttringhaus, G. Wagner, V. Sääf, E. Sweker, and G. Borth, *Ann.*, **557**, 66 (1945).

(4) W. O. Haag and H. Pines, *J. Am. Chem. Soc.*, **82**, 387 (1960).

(5) (a) R. A. Benkeser and T. V. Liston, *ibid.*, **82**, 3221 (1960); (b) R. A. Benkeser, A. E. Trevillyan, and J. Hooz, *ibid.*, **84**, 4971 (1962).

(6) G. E. Hall, R. Piccolini, and J. D. Roberts, *ibid.*, **77**, 4540 (1955).

(7) A. A. Morton and R. A. Finnegan, *J. Polymer Sci.*, **38**, 19 (1959).

(8) R. A. Finnegan and R. S. McNees, *Chem. Ind.* (London), **36**, 1450 (1961).

(9) The possibility that the α,β-unsaturated product arises from isomerization of III seems unlikely for several reasons. (1) More pronounced isomerization would be required at short times. While it is true, as a referee suggests, that more pentylsodium is present during carbonation at these times, consumption of pentylsodium produces another strong base (I) which could also cause isomerization during carbonation. (2) Since carbonation occurs preferentially at the internal position one might expect to observe isomerization of II. We have found no evidence for this process. (3) As reported later in the text, metalation of *trans*-2-dodecene to produce I followed by carbonation gives no detectable amount of α,β-unsaturated product under the same conditions used for 1-dodecene.

formed, but then undergo rapid conversion to the allyl isomer I and never be carbonated at the position of initial proton abstraction. We, therefore, generated 2-sodio-1-dodecene by another route and tested its stability to the metalation reaction conditions.

Two reaction paths can be visualized for the conversion of a secondary vinylorganosodium compound to a resonance stabilized allyl isomer. Either an intra- (reaction 3) or an intermolecular (reaction 4) process could give the postulated conversion. To determine

$$
\underset{\text{VI}}{C_9H_{19}CH_2\overset{\ominus}{\underset{}{C}}{=}\overset{Na^{\oplus}}{CH_2}} \longrightarrow \underset{\text{I}}{C_9H_{19}\overset{H}{\underset{}{C}}\cdots\overset{H}{\underset{\ominus\ Na^{\oplus}}{C}}\cdots CH_2} \tag{3}
$$

$$
\underset{\text{VI}}{C_9H_{19}CH_2\overset{\ominus}{\underset{}{C}}{=}CH_2} + C_9H_{19}CH_2{-}\overset{H}{\underset{}{C}}{=}CH_2 \longrightarrow
$$

$$
C_9H_{19}CH_2C{=}CH_2 + \underset{\text{I}}{C_9H_{19}\overset{H}{\underset{}{C}}\cdots\overset{H}{\underset{\ominus}{C}}\cdots CH_2} \tag{4}
$$
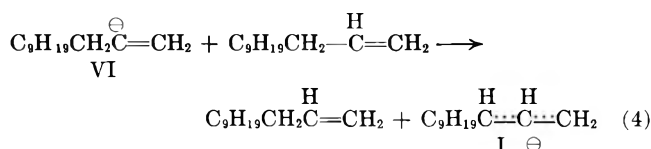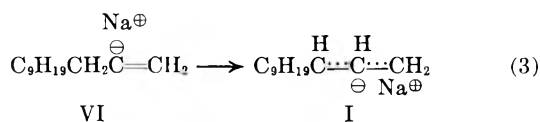
if the intramolecular process was important, 2-sodio-1-dodecene was formed (see Experimental) in octane and allowed to stir for four hours at room temperature. The reaction mixture was then carbonated and the acidic product shown to be exclusively 2-carboxy-1-dodecene (VII). Thus intramolecular proton transfer in this compound does not appear to be facile.

$$
\begin{array}{c} C_9H_{19}CH_2{-}C{=}CH_2 \\ | \\ C{=}O \\ | \\ OH \\ \text{VII} \end{array}
$$
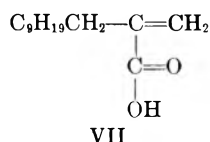
The possibility that intermediate VI was formed during olefin metalation, but underwent intermolecular reaction with excess olefin was tested similarly. The formation of 2-sodio-1-dodecene was repeated and a ten molar excess of 1-dodecene was added to the reaction mixture. After a two-hour stirring period the mixture was carbonated. The resulting $C_{13}$ acid product consisted of at least 50% VII. It thus appears that, if an organosodium intermediate were formed at the secondary vinylic position during metalation, it would possess sufficient stability to give rise to carbonation products at this position at short reaction times.

One is then left with the reasonable postulate that metalation at a secondary vinylic position is slow compared to reaction at either a terminal vinylic or at an allylic position. Support for this explanation is found in the potassium amide-catalyzed deuterium exchange of 1-propene in $ND_3$,[10] wherein the rate of exchange of the first five protons has been found to be quite rapid compared to the exchange of the sixth.

From Table I it is apparent that considerable variation in the composition of $C_{13}$ acid product occurs over the two-hour interval. The most striking observation is that the proportion of products attributable to an allyl intermediate, α-vinylundecanoic acid and 3-tridecenoic acid, increases at the expense of the proportion of product due to a vinyl intermediate, 2-tridecenoic acid. This leads to the conclusion that proton abstraction from the terminal vinylic position is

more rapid than from the allylic position in this reaction.

The demonstration that 2-sodio-1-dodecene is stable to the reaction conditions and that no 2-carboxyl-1-dodecene is realized on metalation and carbonation of 1-dodecene, coupled with the decrease in the ratio of α,β to β,γ-unsaturated acids, suggests that the relative rates of proton removal from different positions of α-olefins by alkylsodium metalating agents decrease in the order terminal vinylic > allylic > secondary vinylic.

To rationalize this order, one can speculate that the ground state energies of the bonds in question are an important factor. The allylic system would undoubtedly afford stabilization at any point along the reaction coördinate where C–H bond breaking had occurred to a significant extent. In other systems[11–13] studies on isotope effects indicate that the transition state for proton removal from carbon does involve considerable bond breaking. Nevertheless, the respective ground state hybridization of the terminal vinyl and allyl positions, $sp^2$ vs. $sp^3$, could account for a somewhat faster reaction at the nonresonance stabilized $sp^2$ position in our system.[14,15] That the state of hybridization is not an overriding factor is evident from the lack of reaction at the internal $sp^2$ position.

The increase with time in the amount of allyl-derived products as compared to the vinyl-derived acid, noted in Table I, suggests an explanation similar to that offered for alkylbenzene metalation,[5] i.e., that there is a kinetically favored formation of the nonresonance stabilized vinyl intermediate IV followed by conversion to the thermodynamically favored allyl isomer I. Since this would require a rather rapid disappearance of IV, we undertook an alternate synthesis of this intermediate to study its stability under metalation conditions.

Free radical addition of hydrogen bromide to 1-dodecyne[16] provided 1-bromo-1-dodecene. The product was found to be a mixture of cis and trans isomers in which cis predominates in a ratio of approximately 2 : 1.[17] Treatment of this mixture with n-butylsodium, under conditions essentially identical to the analogous reaction with 2-bromo-1-dodecene, gave not only the cis- and trans-α,β-unsaturated acids upon carbonation, but also a significant amount (44%) of 2-tridecynoic acid.[18] Reaction of the 1-bromo-1-dodecene mixture with sodium metal dispersed in octane provided the vinylorganosodium compounds[19] with only traces of

(11) (a) A. Streitseiser, Jr., W. C. Langworthy, and D. E. Van Sickle, J. Am. Chem. Soc., **84**, 251 (1962); (b) A. Streitwieser, Jr., and D. E. Van Sickle, ibid., **84**, 254 (1962).

(12) D. Bryce-Smith, V. Gold, and D. P. N. Satchell, J. Chem. Soc., 2743 (1954).

(13) (a) F. S. Yakushin, A. I. Shatenshtein, E. A. Yakolera, and Yu. G. Dubinski, Zh. Fiz. Khim., **33**, 2820 (1959); Kinetika i Kataliz, **1**, 489 (1960); (b) for a discussion of ref. 13a, see A. I. Shatenshtein, Tetrahedron, **18**, 95 (1962).

(14) S. I. Miller and W. G. Lee, J. Am. Chem. Soc., **81**, 6313 (1959).

(15) J. Hinze and H. Jaffe, ibid., **84**, 540 (1962).

(16) C. A. Young, R. R. Vogt, and J. A. Nieuwland, ibid., **58**, 1806 (1936).

(17) P. S. Skell and R. G. Allen, ibid., **80**, 5997 (1958).

(18) The reaction of 1-bromo-1-propene mixtures with butyllithium has been reported to give exclusively acetylenic derivatives [D. V. Curtin and J. W. Crump, ibid., **80**, 1922 (1958)]. The fact that 2-bromo-1-dodecene gives only metal interchange with n-butylsodium, while elimination competes with metal interchange in the case of 1-bromo-1-dodecene, supports the suggestion [S. J. Cristol and R. F. Helmreich, ibid., **77**, 5034 (1955)] that α-elimination is the preferred dehydrobromination reaction path.

(19) The question of geometric stability of these compounds is receiving further attention.

(10) A. I. Shatenshtein, L. N. Vasil'eva, N. M. Dykhno, and E. A. Izrailevich, Dokl. Akad. Nauk, SSSR, **85**, 381 (1952); Chem. Abstr., **46**, 9954 (1952).

acetylenic by-product, as determined by examination of the carbonation products obtained.

As in the case of 2-sodio-1-dodecene, two reaction paths can be visualized for the conversion of a terminal vinylorganosodium compound to an allyl intermediate. Thus, either an intra- (reaction 4) or an intermolecular (reaction 5) proton transfer could account for the observed decrease in the ratio of vinyl derived to allyl derived products with time.

Intramolecular

$$C_9H_{19}CH_2\text{—}\overset{H}{C}\text{=}\overset{H}{C}\ominus Na\oplus \longrightarrow C_9H_{19}\overset{H}{C}\text{---}\overset{H}{C}\text{---}CH_2 \quad (4)$$
$$\qquad\qquad\qquad\qquad\quad \underset{IV}{} \qquad\qquad\qquad \underset{\ominus\ Na\oplus}{} $$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad I$$

Intermolecular

$$C_9H_{19}CH_2\text{—}\overset{H}{C}\text{=}\overset{H}{C}\ominus Na\oplus + C_9H_{19}CH_2\text{—}\overset{H}{C}\text{=}CH_2 \rightleftharpoons$$
$$\qquad \underset{II}{} \qquad\qquad\qquad\qquad\qquad \underset{VIII}{}$$

$$C_9H_{19}CH_2C\text{=}CH_2 + C_9H_{19}\overset{H}{C}\text{---}\overset{H}{C}\text{---}CH_2 \quad (5)$$
$$\qquad \underset{VIII}{} \qquad\qquad\qquad\quad \underset{\ominus\ Na\oplus}{}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad I$$
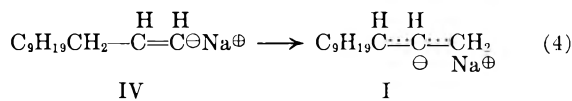
The feasibility of reaction path 4 was tested by preparing the vinylorganosodium mixture and stirring it at room temperature for four hours prior to carbonation. Even after this time interval there was no detectable amount of products arising from an allyl intermediate. It thus appears that this reaction path is not a contributing factor in the variation of acid isomers shown in Table I.

Similarly the possibility of intermolecular conversion was tested by the synthesis of 1-bromo-1-undecene and its conversion to the sodio derivative, followed by addition of a ten molar excess of 1-dodecene. If reaction path 5 is operative in the metalation sequence, one would expect a mixture of 1-sodio-1-undecene and 1-dodecene to give C$_{13}$ acid products upon carbonation, $i.e.$

$$C_9H_{19}CH_2\text{—}\overset{H}{C}\text{=}CH_2 + C_9H_{19}\overset{H}{\underset{Na\oplus}{C}}\text{=}\overset{H}{\underset{\ominus}{C}} \rightleftharpoons$$

$$C_9H_{19}\overset{H}{C}\text{=}CH_2 + C_9H_{19}\overset{H}{C}\text{---}\overset{H}{C}\text{---}CH_2 \quad (6)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad \underset{\ominus\ Na\oplus}{}$$

Repeated experiments, as described above, showed the presence of no detectable amounts of C$_{13}$ acid products upon carbonation of the reaction mixture after four hours of agitation.

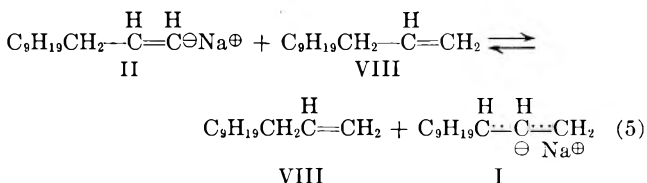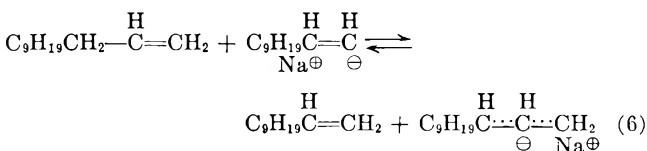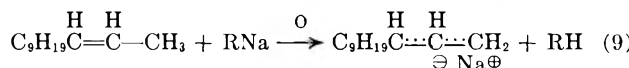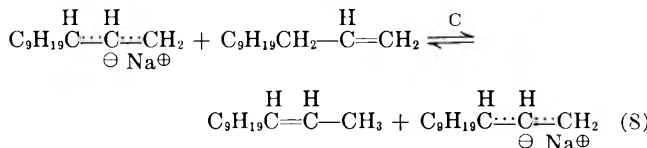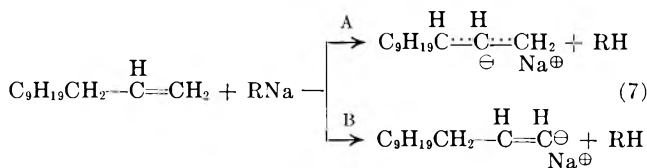These studies strongly indicate that vinylorganosodium intermediates are stable to the reaction conditions employed in metalation of α-olefins. Therefore, kinetic $vs.$ thermodynamic control is not an adequate explanation of the observed variation in acidic products.

The data included in Table I, however, suggest another explanation. It will be noted that as the reaction progresses the ratio of C$_{13}$ to C$_6$ acid in the product increases, indicating that proton abstraction from olefin by the saturated metalating agent continues. It will also be noted that the composition of the recovered olefin is undergoing a marked change. Thus the starting four molar excess of 1-dodecene has been converted essentially quantitatively to internal olefin during the two-hour interval. One can then reason that the increase in proportion of allylic products is due to competing proton abstraction from the 2-olefin in which there are no terminal vinylic protons to be abstracted.

Our metalation results may then be rationalized by the following scheme.

$$C_9H_{19}CH_2\text{---}\overset{H}{C}\text{=}CH_2 + RNa \longrightarrow$$

$$\overset{A}{\longrightarrow} C_9H_{19}\overset{H}{C}\text{---}\overset{H}{C}\text{---}CH_2 + RH$$
$$\qquad\qquad\qquad \underset{\ominus\quad Na\oplus}{}$$

$$\overset{B}{\longrightarrow} C_9H_{19}CH_2\text{---}\overset{H}{C}\text{=}\overset{H}{C}\ominus + RH \quad (7)$$
$$\qquad\qquad\qquad\qquad\qquad \underset{Na\oplus}{}$$

$$C_9H_{19}\overset{H}{C}\text{---}\overset{H}{C}\text{---}CH_2 + C_9H_{19}CH_2\text{—}\overset{H}{C}\text{=}CH_2 \overset{C}{\rightleftharpoons}$$
$$\underset{\ominus\ Na\oplus}{}$$

$$C_9H_{19}\overset{H}{C}\text{=}\overset{H}{C}\text{—}CH_3 + C_9H_{19}\overset{H}{C}\text{---}\overset{H}{C}\text{---}CH_2 \quad (8)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad \underset{\ominus\ Na\oplus}{}$$

$$C_9H_{19}\overset{H}{C}\text{=}\overset{H}{C}\text{—}CH_3 + RNa \overset{D}{\longrightarrow} C_9H_{19}\overset{H}{C}\text{---}\overset{H}{C}\text{---}CH_2 + RH \quad (9)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad \underset{\ominus\ Na\oplus}{}$$

The reactions involving saturated metalating agent (A, B, and D) are essentially irreversible. This is shown by the fact that although the reactions were conducted in a large excess of octane, no detectable amount of nonanoic acid was observed. There is no reason to believe that alkenylsodium compounds react with pentane, as required for the reverse reaction, and not with octane.

The isomerization of 1-dodecene is shown as occurring through proton abstraction by the saturated metalating agent to give an allyl intermediate (reaction A). A chain process involving this intermediate and starting olefin accounts for the production of 2-dodecene.[20]

The increase in proportion of product formed by carbonation of an allyl, as opposed to a vinyl, intermediate is thought to be due to a competition for reaction with saturated metalating agent between 1-dodecene and 2-dodecene, $i.e.$, reaction D begins to compete with reactions A and B. To demonstrate the feasibility of this proposal $trans$-2-dodecene was synthesized and subjected to metalation conditions identical to those used for 1-dodecene. The products obtained, at five minutes, half an hour, one hour, and two hours, were exclusively attributable to the allyl intermediate I, with no evidence of α,β-unsaturated product. Furthermore Shatenshtein's[21] studies on the rates of deuterium exchange of 1- and 2-pentenes indicate that these compounds undergo base-catalyzed reactions at similar rates.

It readily can be seen from Table I that at least a four molar excess of 1-dodecene has undergone isomerization during a time interval in which proton abstraction by the saturated metalating agent, pentylsodium, is still occurring. Surface coating of the heterogeneous pentylsodium by deposition of insoluble allyl and vinyl organosodium compounds most probably causes a decreased reactivity of the saturated compound. However, an equally important factor in the apparent rapid isomerization of 1-dodecene, as compared to formation C$_{13}$ organosodium compounds, could well be a more rapid rate of proton removal by the allyl intermediate.

This order of reactivity would be rather surprising since pentylsodium is undoubtedly more basic than the

(20) H. Pines, "Advances in Catalysis and Related Subjects," Vol. 12, Academic Press, New York, N. Y., 1960.

(21) A. I. Shatenshtein, L. N. Vasil'eva, and N. M. Dykhno, $Zh.$ $Fiz.$ $Khim.$, **28**, 193 (1954).

allyl intermediate[22] and even in cases of equal basicity resonance stabilized anions usually[23] undergo nucleophilic attack on hydrogen at a slower rate than their saturated counterparts.[24] However, Morton's[25] observations on the effectiveness of alkyl- *vs.* alkenylsodium compounds as catalysts for olefin isomerization are pertinent. These workers have reported that pentenyl- and octenylsodium are more effective catalysts than pentylsodium based on elapsed time for noticeable exothermic reaction and completeness of isomerization during a given interval.[26] One can conjecture that the degree of covalent bonding[27] in a carbon–sodium bond causes some localization of the negative charge in the resonance stabilized compounds, with concomitant increase in basicity. This argument, however, could only account for a basicity approaching that of a saturated anion. Unless some other factor is operative, an allyl intermediate, in which the negative charge is contained in a system possessing π character, would be expected to abstract protons from a common substrate at a slower rate than the saturated analog. This additional factor could be the "alpha effect" proposed recently by Edwards and Pearson.[28] These authors explain the inordinately rapid proton abstractions by anions containing an alpha hetero atom as a stabilizing effect which the adjacent electron pair exerts on the transition state. This explanation is clarified by considering proton abstraction in the limiting case. Thus the negative species is pictured as donating two electrons to a distant substrate, thereby developing positive charge during the transition state. One then can rationalize the apparent high reactivity of the allyl anionic system by this concept since a stabilizing effect[29] would be present in the transition state of the allyl anion (10) which would not be present in the saturated system (11).

$$R\text{—}\underset{\ominus}{C}\text{:·:}C\text{:·:}CH_2 \longrightarrow R\text{—}\underset{\oplus}{C}\text{:·:}C\text{:·:}CH_2 + 2\bar{e} \qquad (10)$$

$$RCH_2\ominus \longrightarrow RCH_2\oplus + 2e \qquad (11)$$
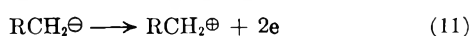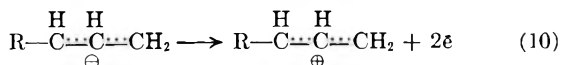
Although this effect may be a contributing factor, it certainly does not explain all the reported results.[26] Much more work is needed in this area before any definite conclusions can be drawn.

## Experimental

**Dodecene-1.**—This olefin was purchased from Matheson Coleman and Bell and was distilled from sodium metal prior to use.

**Metalating Agents.**—The alkylsodium metalating agents were prepared by the addition of the corresponding alkyl chloride to a previously prepared dispersion of sodium in *n*-octane at 0°.[2]

The high speed stirring apparatus used has been described.[30] Several runs of this preparation gave yields varying from 60 to 70% as measured by the acidic product formed upon carbonation.

**Metalation Reactions.**—Metalation was accomplished at room temperature by the addition of olefin to the alkylsodium–octane mixture with rapid stirring. Portions of the reaction mixture were removed at varying time intervals and poured over excess solid carbon dioxide. All operations were conducted under an atmosphere of dry nitrogen. The acidic and neutral fractions of the products were separated as usual.[2] Table I (see text) gives typical data obtained from repeated reactions of a four molar excess of 1-dodecene with *n*-pentylsodium.

Runs in which the total reaction mixture was carbonated after 18 hr. gave 40–50% yields. Distillation (b.p. 140–145° at 0.6 mm.) through an 8-in. Vigreux column failed to separate the $C_{13}$ acid isomers.

**Characterization of Acid Products.**—The skeletal arrangement of the acid products was established by esterification, hydrogenation, and g.l.c. comparison of the resultant saturated esters to alternately synthesized standards. Esterification was accomplished either by addition of diazomethane in ether[31] or by refluxing the acid in excess methanol with a catalytic amount of sulfuric acid. Hydrogenation was carried out in a Parr hydrogenator using 10% palladium on charcoal at 50 p.s.i. The g.l.c. standards were obtained as follows.

**Methyl Tridecanoate (IX).**—Tridecanoic acid was purchased from Matheson, Coleman and Bell and esterified using diazomethane in ether. Distillation through an 18-in. spinning band column gave the ester (b.p. 82–83° at 0.2 mm., $n^{28}$D 1.4320, lit.,[32] b.p. 71° at 0.1 mm. and b.p. 90.3° at 0.4 mm.) which was shown to be 99% pure by g.l.c.

**Methyl α-Methyldodecanoate (X).**—This ester was prepared by carbonation of the Grignard reagent obtained from 2-bromododecane followed by acidification and esterification. Distillation as above gave the ester (b.p. 65–66° at 0.1 mm., $n^{28}$D 1.4298) which was 99% pure by g.l.c. analysis.

*Anal.* Calcd. for $C_{14}H_{28}O_2$: C, 73.7; H, 12.3. Found: C, 74.2; H, 12.5.

**Methyl α-Ethylundecanoate.**—This ester was prepared by malonic ester condensations.[33] Distillation through an 18-in. spinning band gave the ester (b.p. 64–65° at 0.1 mm., $n^{28}$D 1.4295) which was 99% pure by g.l.c. analysis.

*Anal.* Calcd. for $C_{14}H_{28}O_2$: C, 73.7; H, 12.3. Found: C, 74.2; H, 12.5.

**Methyl α-Propyldecanoate (XII).**—This ester was also prepared by malonic ester condensations.[33] Distillation through the 18-in. spinning band column (b.p. 62–63° at 0.1 mm., $n^{28}$D 1.4288) gave the ester which was 98% pure by g.l.c. analysis.

*Anal.* Calcd. for $C_{14}H_{28}O_2$: C, 73.7; H, 12.3. Found: C, 73.5; H, 12.3.

Gas chromatographic analyses were performed on an Aerograph Model A-90-S using 10-ft., $^1/_4$-in. columns. A polyester (succinic acid–triethylene glycol) liquid phase supported on acid washed Chromosorb-W was used. During the course of this work the percentage of liquid phase varied from 15 to 25%. Each column was shown to separate the four standards before use in analysis. Their order of emergence was XII, XI, X, and IX.

Gas–liquid chromatography of the hydrogenated esters obtained from metalation and carbonation of 1-dodecene shows that at least 98% of the $C_{13}$ product is made up of methyl tridecanoate (IX) and methyl α-ethylundecanoate (XI). Comparison of the above chromatogram to that of methyl nonanoate shows that there is no detectable amount of this $C_9$ ester in the product. Apparently no metalation of the *n*-octane medium occurs.

The position of unsaturation and geometrical configuration of each unsaturated ester was established by g.l.c. collection of pure samples followed by a combination of hydrogenation, infrared, and nuclear magnetic resonance (n.m.r.) studies. Table II summarizes the hydrogenation and infrared data. Table III records the pertinent aspects of the n.m.r. spectra.

(22) The Brønsted relation (R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chap. X) would predict a faster rate for the stronger base.

(23) R. P. Bell, "Acid-Base Catalysis," Clarendon Press, Oxford, 1941, p. 92.

(24) R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).

(25) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **20**, 839 (1955).

(26) A referee reports that a later presentation of catalytic effectiveness (E. J. Lanpher, Symposia Preprints, Vol. 4, No. 4, p. B-5, Division of Petroleum Chemistry, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959) gives the order of sodium compounds as pentenyl > octenyl > pentyl = phenyl > butenyl > allyl > benzyl ≈ triphenylmethyl ≈ fluorenyl.

(27) E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 18.

(28) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

(29) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 148.

(30) "Sodium Dispersions," U. S. Industrial Chemicals Company, New York 16, N. Y., p. 18.

(31) F. G. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 165.

(32) K. S. Markley, "Fatty Acids," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 523.

(33) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1951, p. 467.

TABLE II

INFRARED AND HYDROGENATION STUDIES ON THE UNSATURATED
METHYL ESTERS OBTAINED FROM METALATION OF 1-DODECENE

| | After hydrogenation g.l.c. shows identity with | Infrared absorptions, $\mu^a$ | |
| | | C=C | C—H |
| --- | --- | --- | --- |
| Methyl α-vinylundecanoate | XI | 6.1 | 10.1 and 10.9 |
| 2-Carbomethoxy-1-dodecene | X | 6.15 | 10.65 |
| Methyl cis-2-tridecenoate | IX | 6.1 | 12.25 |
| Methyl trans-3-tridecenoate | IX | 6-6.1 | (sh) 10.3 |
| Methyl trans-2-tridecenoate | IX | 6.05 | 10.2 |

$^a$ See ref. 34.

The ratio of $C_6$ to $C_{13}$ acids at the varying time intervals was determined by esterification and comparison of peak areas by g.l.c. Areas were obtained by multiplying the peak height by the band width at half height.

**Characterization of Recovered Olefin.**—The composition of recovered olefins was determined similarly. However, since resolution of peaks was not complete, the ratio of 1-dodecene:2-dodecene was estimated from peak heights. This was shown to be in reasonable agreement with an alternate method in which periodate–permanganate oxidation of the double bond is followed by esterification and g.l.c. analysis of the resultant ester mixture. For example, a sample of the olefin recovered after 5 min. (see Table I) was found to be 80% 1-dodecene and 19% 2-dodecene by this method.[35]

**2-Bromo-1-dodecene.**—1,2-Dibromodecane (50 g., 0.15 mole) was added dropwise to sodamide (7.8 g., 0.2 mole) in 500 ml. of ammonia and stirred for 30 min. The ammonia was allowed to evaporate (overnight) and the residue was treated with a solution of 25 ml. of ethanol in 300 ml. of diethyl ether followed by 100 ml. of water. The organic layer was separated, dried with magnesium sulfate, and distilled through a 6-in. Vigreux column to yield 20 g. (53%) of a mixture of 1-bromo-1-dodecene and 2-bromo-1-dodecene. These compounds were separable on the g.l.c. columns described previously. The mixture was distilled through an 18-in. spinning band column to give 3.6 g. of chromatographically pure 2-bromo-1-dodecene. The product showed a strong infrared absorption at 11.2 $\mu$ and no absorption at 10.7 $\mu$, indicating isomeric purity.[34]

*Anal.* Calcd. for $C_{12}H_{23}Br$: C, 58.4; H, 9.13; Br, 32.2. Found: C, 58.6; H, 9.4; Br, 32.8.

**Reaction of 2-Bromo-1-dodecene with Butylsodium.**—A dispersion of sodium metal (4.6 g., 0.2 g.-atom) in 200 ml. of octane was prepared and n-butyl chloride (9.2 g., 0.1 mole) added dropwise at 0° with rapid stirring. The reaction mixture was allowed to stir for 30 min. after addition was complete. Then 2-bromo-1-dodecene (3.0 g., 0.012 mole) was added over a 5-min. interval. The mixture warmed to room temperature during the 4-hr. stirring period following addition. Carbonation was effected by pouring it over excess solid carbon dioxide. The acid products were isolated as described[2] and esterified by refluxing with a solution of 2 g. of sulfuric acid in 50 ml. of methanol for 1 hr. The esterification mixture was poured into 400 ml. of water and the organic layer extracted with ether. After drying with magnesium sulfate, the ether solvent was removed on a rotating evaporator yielding 2.1 g. (71%) of product. Gas–liquid chromatography showed the product to contain only one $C_{13}$ ester which was shown to be 2-carbomethoxy-1-dodecene (see Tables II and III).

**Reaction of 2-Sodio-1-dodecene with 1-Dodecene.**—The reaction of 2-bromo-1-dodecene with butylsodium was repeated to give 2-sodio-1-dodecene (0.013 mole), whereupon 1-dodecene (16.8 g., 0.1 mole) was added to the reaction mixture. Stirring was continued for 4 hr. before carbonation was effected by pouring the reaction mixture over excess solid carbon dioxide. Work-

up and esterification of the acid product gave a mixture of $C_{13}$ isomers of which 51% was 2-carbomethoxy-1-dodecene by g.l.c. analysis.

**Preparation of 1-Bromo-1-dodecene.**—The procedure of Young[16] was used with modifications. Dodecyne-1 (50 g., 0.3 mole) obtained from Farchan Chemical Co. was used as purchased. To the neat acetylene was added benzoyl peroxide (1 g.) and then dry hydrogen bromide was passed into the mixture at 0° until the original weight had increased by 23.8 g. The reaction mixture was washed successively with water and 10% sodium hydroxide solution, dried with magnesium sulfate, and distilled to yield 52.8 g. (71%) of a mixture of cis- and trans-1-bromo-1-dodecene. The product was characterized by g.l.c. and subsequent conversion to the sodium compounds followed by carbonation and esterification (see Tables II and III).

*Anal.* Calcd. for $C_{12}H_{23}Br$: C, 58.4; H, 9.13; Br, 32.2. Found: C, 58.9; H, 9.5; Br, 31.7. Infrared absorption at 10.7 $\mu$ and none at 11.2 $\mu$ indicated the 1-bromo product.

**Preparation of 1-Bromo-1-undecene.**—The same procedure as described for 1-bromododecene-1 was used to give a 76% yield of product.

*Anal.* Calcd. for $C_{11}H_{21}Br$: C, 56.7; H, 9.0; Br, 34.2. Found: C, 56.2; H, 8.9; Br, 35.1.

**Reaction of 1-Bromo-1-dodecene with Butylsodium.**—Butylsodium was prepared as previously described[2] from sodium metal (4.6 g., 0.2 g.-atom) and n-butyl chloride (9.2 g., 0.1 mole) in 200 ml. of octane. To this mixture was added 1-bromo-1-dodecene (5.0 g., 0.020 mole) dropwise with stirring. The resulting product was allowed to stand overnight prior to carbonation by pouring over excess solid carbon dioxide. The usual work-up provided 2.6 g. (61%) of acidic product. Esterification and g.l.c. separation of the resulting ester mixture shows that 44% of the acid product is methyl-2-tridecynoate. Infrared absorption at 4.5 $\mu$, hydrogenation to methyl tridecanoate, and an n.m.r. spectrum showing no vinylic protons established the identity of this product. The remaining 56% of acid product is accounted for by methyl cis- and trans-2-tridecenoate (see Tables II and III).

**Reaction of 1-Bromo-1-dodecene with Sodium Dispersion.**—A dispersion of sodium (6.9 g., 0.3 g.-atom) in 200 ml. of octane was prepared[2] and 1-bromo-1-dodecene (10.0 g., 0.04 mole) added dropwise at room temperature. Stirring was continued and a 50-ml. portion of the reaction mixture removed after 4 hr. This portion was poured over excess solid carbon dioxide to effect carbonation. The usual work-up and g.l.c. analysis showed three peaks in the approximate ratio of 2:1:0.1. Collection of pure samples by g.l.c. gave the data recorded in Table II and showed the mixture to consist of 2 parts methyl cis-2-tridecenoate, to 1 part methyl trans-2-tridecenoate, to 0.1 part methyl 2-tridecynoate. The remaining reaction mixture was allowed to stand for 24 hr. prior to carbonation. The acid mixture obtained was somewhat more complex in that peaks accounting for approximately 10% of the total $C_{13}$ ester mixture were observed at retention times corresponding to the allylic products, methyl α-vinylundecanoate and methyl-2-tridecenoate; however, 90% of the product is still accounted for by vinyl intermediates.

**Reaction of 1-Bromo-1-undecene with Sodium Dispersion.**—This reaction was run in an identical fashion to that of 1-bromo-1-dodecene and again an acidic product consisting of three compounds in a ratio of ca. 2:1:0.1 was realized. The infrared spectrum of this mixture (2.7 g., 32%) was identical to the previous mixture.

**Reaction of 1-Sodio-1-undecene with 1-Dodecene.**—1-Sodio-1-undecene (0.021 mole, maximum) was generated as in the foregoing examples and 1-dodecene (33.6 g., 0.2 mole) added to the reaction mixture. Stirring was continued for 4 hr. prior to carbonation with excess solid carbon dioxide. The acid mixture obtained was composed of the same isomers, by g.l.c. analysis, as found in the absence of added 1-dodecene. No evidence of metalation of the added 1-dodecene was obtained.
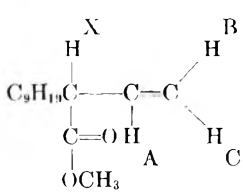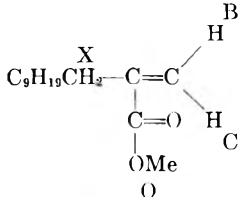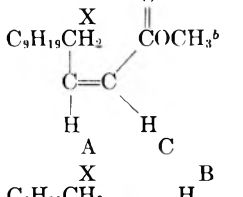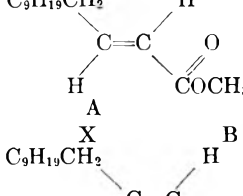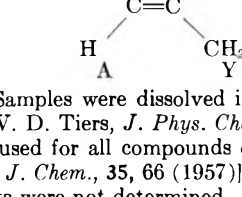
**Preparation of trans-2-Dodecene.**—The method of Hennion[36] was used. Undecyne-1 (62.0 g., 0.407 mole) was converted to the Grignard reagent by reaction with ethyl Grignard (0.407 mole) in tetrahydrofuran. Methyliodide (57.8 g., 0.407 mole) was added and the reaction mixture refluxed 8 hr. at which time

(34) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, pp. 45–51.

(35) We thank Dr. D. F. Kuemmel of these laboratories for performing the oxidative analyses.

(36) G. F. Hennion and T. F. Banigan, Jr., *J. Am. Chem. Soc.*, **68**, 1202 (1946).

TABLE III

N.M.R. CONSTANTS OF UNSATURATED METHYL ESTERS[a]



| | $\tau_Y$ | $\tau_X$ | $\tau_a$ | $\tau_b$ | $\tau_c$ | $|J_{AB}|$ | $|J_{AC}|$ | $|J_{BC}|$ | $|J_{AX}|$ | $|J_{BX}|$ | $|J_{CX}|$ | $|J_{BY}|$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) | .. | 7.09 | 4.2 | 4.9 | 4.9 | 17.0 | 9.0 | 2.0 | 8.0 | ~0 | ~0 | .. |
| (2) | .. | 7.75 | .. | 4.54 | 3.95 | .. | .. | 1.8 | ... | 1.5 | 0 | .. |
| (3) | .. | 7.38 | 3.89 | .. | 4.33 | .. | 11.0 | ... | 7.0 | ... | 1.5 | .. |
| (4) | .. | 7.85 | 3.18 | 4.32 | .. | 16.0 | .. | ... | 7.0 | 1.5 | ... | .. |
| (5) | 7.06 | 8.00 | 3.52 | 3.52 | .. | [d] | .. | ... | ~5[c] | [d] | ... | ~5[c] |

[a] Samples were dissolved in carbon tetrachloride solution using tetramethylsilane as an internal reference and adopting the τ scale [G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)]. The spectra were obtained on a Varian A-60 spectrometer. First-order analysis was used for all compounds except 1. In this case an ABXY approximation [H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can. J. Chem.*, **35**, 66 (1957)] was applied (H$_B$ = A, H$_C$ = B, H$_A$ = Y, H$_X$ = X). Consequently the signs of the spin coupling constants were not determined. [b] The values for these compounds are consistent with those reported [R. R. Fraser and D. E. McGreer, *Can. J. Chem.*, **39**, 505 (1961)] for methyl *cis*- and *trans*-crotonate. [c] These values are $\frac{1}{2} |J_{AX} + J_{BY}|$. [d] These values cannot be determined from the spectrum.

it was practically colorless. Dilute (*ca.* 5%) hydrochloric acid was added until all precipitated salts dissolved. The organic layer was washed several times with water, dried with magnesium sulfate, and distilled to give 59.3 g. (88%) b.p. 68–74° (0.2 mm.) of 2-dodecyne. The product shows no C—H stretch at 3.0 μ and a C≡C stretch at 4.7 μ; g.l.c. analysis shows the material to be 98% pure.

Reduction with sodium in liquid ammonia was used to produce *trans*-2-dodecene. Sodium (19.55 g., 0.85 g.-atom) was placed in 800 ml. of liquid ammonia in a three-necked flask equipped with stirrer and Dry Ice condenser. Dodecyne-2 (30.0 g., 0.18 mole) was added and the mixture was stirred overnight. The ammonia was allowed to evaporate and the residue hydrolyzed by the addition of 50 ml. of ethyl alcohol in 100 ml. of ether,

followed by enough water to dissolve all salts. The organic layer was separated, dried with magnesium sulfate, and distilled at aspirator vacuum (102–106°) to give 18.7 g. (62%) of pure olefin, as shown by g.l.c. analysis.

**Metalation of *trans*-2-Dodecene.**—Metalation and carbonation was carried out in the manner described previously. Portions of the reaction mixture were removed at 5 min., 0.5 hr., 1 hr., and 2 hr. Characterization of the acid products, by g.l.c. of the methyl esters, shows that at least 95% of the C$_{13}$ product is made up of α-vinylundecanoic acid and 3-tridecenoic acid in all cases and that no detectable amount of 2-tridecenoic acid is present in the product. Yields of the acidic product were not determined. The ratio of α-vinylundecanoic to 3-tridecenoic acid varied between 1.8 and 2.5.

# β-Condensation Reactions of Cyclic Amines with Benzaldehyde: Evidence for the Enamine Pathway

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The mechanism of condensation of benzaldehyde with piperidine to give 3,5-dibenzylpyridine (1) is discussed, and evidence is presented that N-benzyl-Δ²-tetrahydropyridine (4) is an intermediate. Reactions of benzaldehyde with 6-chloro-1,2,3,4-tetrahydroquinoline and with 1,2,3,4-tetrahydroisoquinoline have been shown to give 3-benzyl-6-chloroquinoline (16) and 4-benzylisoquinoline (17), respectively.
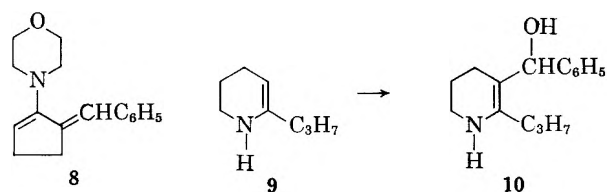
Seventy years ago Rügheimer reported that benzaldehyde condenses with N-benzoylpiperidine at high temperature to give 3,5-dibenzylpyridine (1).[2] This work was confirmed and extended recently by Poirer, Morin, McKim, and Bearse,[3] and by the present authors,[4] who found that the acetic acid-catalyzed reaction of piperidine and benzaldehyde in refluxing toluene gives the same product. From these results structures could be assigned to the unknown products of some similar reactions.[5,6] Piperidine or N-benzoylpiperidine has been shown to condense as well with *o*-, *m*-, and *p*-tolualdehyde,[7] *p*-cuminaldehyde,[8] *p*-dimethylamino-[3,6] and *p*-diethylaminobenzaldehyde,[6] anisaldehyde,[3] and 3- and 4-pyridinealdehyde.[3]

In the earlier paper we proposed that this transformation involves rearrangement of the initially formed Schiff cation (2) *via* a second Schiff cation (3) to the enamine (4) followed by condensation at the β-position
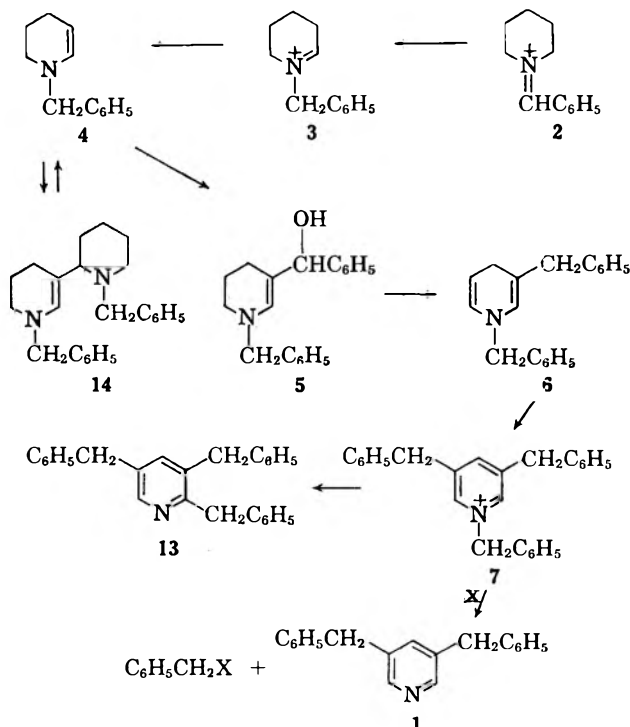
with benzaldehyde to give the adduct 5. Dehydration of 5 would give a second enamine (6) which on addition of benzaldehyde and loss of hydroxide would produce the 1,3,5-tribenzylpyridinium ion 7. Displacement by a suitable nucleophile such as acetate ion, water, or piperidine would then give 3,5-dibenzylpyridine.[9] We further suggested that Rügheimer's reaction proceeds by the same mechanism, except that water formed during the condensation is consumed in hydrolysis of N-benzoylpiperidine. We now report evidence in favor of the enamine pathway.

Addition of benzaldehyde to enamines and subsequent dehydration in the manner proposed finds support in the recent literature. Thus Birkofer, Kim, and Engels have prepared compounds such as 8 by reaction of cyclic ketones with benzaldehyde in refluxing benzene.[10] Although tetrahydropyridines have not been studied in this respect, it seems likely that the undefined 1:1 adduct of γ-coniceine (9) and benzaldehyde[11] is the 3-phenylhydroxymethyl derivative (10), similar to 5. From the reaction of N-benzoyl-





piperidine and *p*-cuminaldehyde Rügheimer and Herzfeld isolated, besides the dicuminylpyridine, 3-*p*-cuminylpyridine (11) and *p*-cymene.[8] The latter are most readily visualized as products of pyrolysis of the second enamine (12, corresponding to 6).
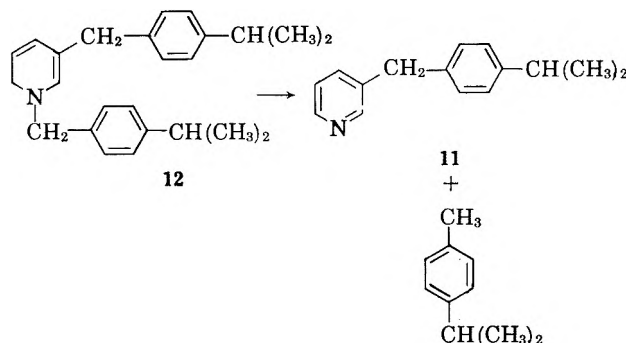


Concerning the last step of the reaction, decomposition of the pyridinium ion 7, Poirier, *et al.*, have shown

(1) Inquiries may be addressed to W. D. B. at Room 2-304, M.I.T.

(2)(a) L. Rügheimer, *Ber.*, **24**, 2186 (1891); (b) L. Rügheimer, *ibid.*, **25**, 2421 (1892); (c) L. Rügheimer, *Ann.*, **280**, 36 (1894); (d) L. Rügheimer and W. Kronthal, *ibid.*, **280**, 50, 51 (1894).

(3) R. H. Poirier, R. D. Morin, A. M. McKim, and A. E. Bearse, *J. Org. Chem.*, **26**, 4275 (1961).

(4) E. P. Burrows, R. F. Hutton, and W. D. Burrows, *ibid.*, **27**, 316 (1962).

(5) S. Skraup and K. Böhm, *Ber.*, **59**, 1015 (1926).

(6) E. D. Parker and A. Furst, *J. Org. Chem.*, **23**, 201 (1958).

(7) L. Rügheimer and K. Döring, *Ann.*, **280**, 74 (1894).

(8) L. Rügheimer and W. Herzfeld, *ibid.*, **280**, 60 (1894).

(9) Poirier, *et al.*, have outlined a similar pathway, but without specifically invoking enamine intermediates.

(10) L. Birkofer, S. M. Kim, and H. D. Engels, *Ber.*, **95**, 1495 (1962).

(11) J. von Braun and A. Steindorff, *ibid.*, **38**, 3094 (1905).

benzyl acetate to be present in the reaction mixture; however, stronger evidence that **7** is an intermediate is provided by Rügheimer's isolation (in low yield) of either 3,4,5- or 2,3,5-tribenzylpyridine (**13**),[2b] resulting most probably from Ladenburg rearrangement of the tribenzylpyridinium ion.[12]

Although every step in this mechanism is plausible, it seemed advisable to test at least one intermediate, the most accessible being N-benzyl-Δ²-tetrahydropyridine (**4**). Leonard and Hauck have shown that Δ²-tetrahydropyridines lacking a substituent in the 2-position undergo dimerization to tetrahydroanabasine derivatives.[13] We prepared N,N'-dibenzyl-Δ²-tetrahydroanabasine (**14**) according to their directions, anticipating that dimerization would be reversible under the β-condensation conditions. When the dimer was treated with benzaldehyde and acetic acid in refluxing toluene the product was indeed 3,5-dibenzylpyridine, in 16% yield.

There is, however, a serious objection to the first step of the piperidine reaction in which the Schiff cation **2** rearranges to **3**, for this is precisely the type of double bond migration shown not to occur in the closely related Sommelet reaction.[14] This introduces the possibility that the first step may be intermolecular hydride transfer from piperidine to the Schiff cation, producing N-benzylpiperidine and Δ¹-tetrahydropyridine (**15**). The latter could also give 3,5-dibenzylpyridine by a series of steps similar to those described above, although the Ladenburg product (**13**) would be more difficult to reconcile. The Sommelet-type mechanism would necessarily limit to 50% the yield of β-condensation product, but this, regrettably, is not disqualifying in any of the reactions we have studied.[15] Evidence eliminating this mechanism will be described later.
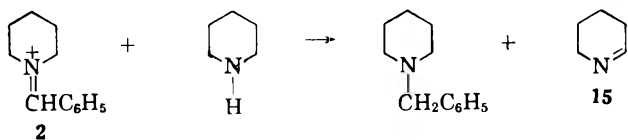


A number of other cyclic amines were treated with benzaldehyde. Neither 1,2,3,4-tetrahydroquinoline nor 6-methyl-1,2,3,4-tetrahydroquinoline gives a β-condensation product. In the former case the product is the same as that obtained by Einhorn from the zinc chloride-catalyzed reaction, probably 6,6'-benzalbis-tetrahydroquinoline (**16**).[16,17] In 6-chlorotetrahydroquinoline the aromatic ring is deactivated, and the β-condensation product, 3-benzyl-6-chloroquinoline (**17**), is formed in 20% yield. In 1,2,3,4-tetrahydroisoquinoline the problem of aromatic ring condensation is absent, and 4-benzylisoquinoline (**18**) is produced in

34% yield.[18] This being the cleanest reaction we encountered, it seemed best suited for testing the Sommelet-type mechanism, which requires that N-benzyl-1,2,3,4-tetrahydroisoquinoline (**19**) be formed in at least as great a yield as the isoquinoline. Infrared analysis of the reaction mixture showed that the N-benzyl derivative, if present at all, is produced in less than 3% yield. Since **19** was shown to be stable under the reaction conditions, the Sommelet mechanism may be discarded.
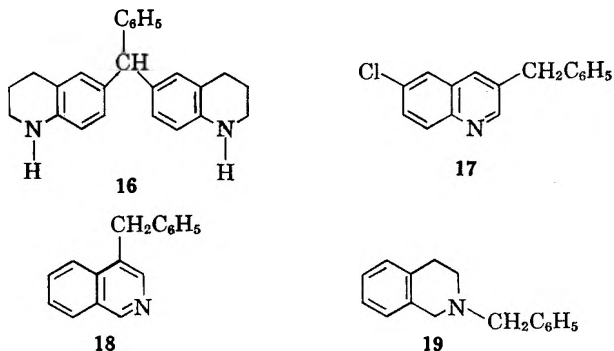


Providing, as it does access to the carbon skeleton of saturated amines, this reaction would appear to have important synthetic potential. At the onset of the work our sanguine expectation was that, within structural limitations, any aldehyde lacking a reactive α-hydrogen would undergo multiple alternate condensation with any amine, the most favorable prospects being those in which aromatic systems are created. We have not, however, succeeded in isolating pyridine derivatives from the reactions of pivalic or cinnamic aldehyde with piperidine, or from the reactions of benzaldehyde with 2-methyl- or 2,6-dimethylpiperidine, nor have we obtained a pyrrole from the condensation of benzaldehyde with pyrrolidine. In retrospect, these results are not inconsistent with the enamine mechanism, but they limit the preparative utility of β-condensation.

## Experimental

**3,5-Dibenzylpyridine from N,N'-Dibenzyl-Δ²-tetrahydroanabasine.**—The anabasine derivative was prepared in 38% yield by mercuric acetate oxidation of N-benzylpiperidine according to the directions of Leonard and Hauck,[13] except that solid sodium sulfide nonahydrate rather than hydrogen sulfide was used to precipitate the mercury salts after the reaction was complete. To 5.72 g. of the anabasine derivative in 100 ml. of dry toluene was added 7.5 g. of benzaldehyde and 3.0 ml. of glacial acetic acid. The solution was heated to reflux under a Dean–Stark trap. After 20 hr. about 1.5 ml. of aqueous phase had collected. The reaction mixture was cooled and the solvent was removed under reduced pressure, leaving 13.1 g. of dark, viscous oil. A 1.03-g. sample of the product was dissolved in benzene and chromatographed on 25 g. of Merck acid-washed alumina. Elution with ether (2–10% in benzene) yielded 0.106 g. of white crystalline material, m.p. 88–89° after recrystallization from ether. The infrared spectrum of this material (potassium bromide disk) was identical with that of 3,5-dibenzylpyridine,[4] and the mixture melting point with authentic material was undepressed.

**3-Benzyl-6-chloroquinoline.**—A solution of 8.18 g. of 6-chloroquinoline (Eastman White Label) in 200 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure using W-7 Raney nickel as catalyst. After 9 hr., 2430 ml. of

(12) H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 414.

(13) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(14) S. J. Angyal, *Org. Reactions*, **VIII**, 199 (1954). Dr. Hutton first called our attention to this point and suggested the alternative mechanism.

(15) Rügheimer reported a 70% yield of **1** from N-benzoylpiperidine.[2c] The yield of **1** claimed by Poirier, *et al.*, for the piperidine reaction is too high, being based on the wrong stoichiometry.

(16) A. Einhorn, *Ber.*, **19**, 1243 (1886).

(17) L. Rügheimer and W. Kronthal, *ibid.*, **28**, 1321 (1895), claimed that benzylquinolines were produced from N-benzoyltetrahydroquinoline and benzaldehyde, but provided no evidence in this or subsequent papers.

(18) For the similar condensation reactions of N-benzoyltetrahydroisoquinoline, cf. L. Rügheimer and B. Friling, *Ann.*, **326**, 261 (1903), and L. Rügheimer and E. Albrecht, *ibid.*, **326**, 297 (1903).

hydrogen had been taken up (2450 ml. corresponded to two molar equivalents of hydrogen), and further uptake was very slow. The catalyst was then separated and the filtrate was evaporated to dryness under reduced pressure, redissolved in acetone (25 ml.), and filtered to remove sodium hydroxide. Evaporation of the acetone gave 7.93 g. of crude crystalline 6-chloro-1,2,3,4-tetrahydroquinoline,[19] which was dissolved directly in 55 ml. of dry toluene. To this solution was added benzaldehyde (10.6 ml.) and glacial acetic acid (1 ml.), and the mixture was allowed to reflux 41 hr. under a Dean–Stark trap. The toluene was removed under reduced pressure and the residue was extracted with four 50-ml. portions of hot n-heptane. The heptane extracts yielded 9.56 g. of dark sirup, of which 1.03 g. was dissolved in benzene and chromatographed on 33 g. of Woelm alumina (activity I). From the later 1:10 ether–benzene fractions and the pure ether fractions 256 mg. of crude crystalline 3-benzyl-6-chloroquinoline was obtained. An analytical sample, recrystallized four times from ether, had m.p. 91.5–92°. The yield, based on the weight of 6-chlorotetrahydroquinoline, was 20%.

*Anal.* Calcd. for $C_{16}H_{12}NCl$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.90; H, 4.80; N, 5.57.[20]

The ultraviolet spectrum of the product [$\lambda_{max}$ 265–270 (unresolved multiplet), 296, 302, 309, 315, 323 m$\mu$, $\epsilon_{max}$ 4350, 3140, 2750, 4030, 3140, 5950] closely resembled that of 6-chloroquinoline [$\lambda_{max}$ 272 (broad), 292, 298, 306, 312, 319 m$\mu$, $\epsilon_{max}$ 4300, 2950, 2500, 3300, 2600, 4400].

**4-Benzylisoquinoline.**—A solution of 5.00 g. of 1,2,3,4-tetrahydroisoquinoline (Eastman White Label) and 1.5 ml. of acetic acid in 80 ml. of dry toluene was heated at reflux for 48 hr. under a Dean-Stark trap. About 2 ml. of aqueous phase collected. Removal of solvent under reduced pressure left 13.5 g. of thick red oil, which was extracted with five 50-ml. portions of hot heptane. The heptane extract was allowed to stand overnight, then decanted from precipitated gums and decolorized with charcoal. Evaporation under reduced pressure left 5.68 g. of yellow oil which partially crystallized. Crystalline material, washed with ether and recrystallized from acetone, had m.p. 119.5–120°. Authentic 4-benzylisoquinoline, prepared in 3.7% yield by a small-scale adaptation of the method of Avramoff

(19) J. von Braun, A. Petzold, and J. Seeman, *Ber.*, **55**, 3779 (1922).
(20) Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.
(21) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 4090 (1956).

and Sprinzak,[21] had m.p. 119.5–120° after three recrystallizations from acetone. A mixture melting point was undepressed, and the infrared spectra of the two samples potassium bromide disk) were superimposable.

The ultraviolet spectrum of 4-benzylisoquinoline had $\lambda_{max}$ 265 (sh), 274, 285, 298, 310, 318, 323 m$\mu$, $\epsilon_{max}$ 4480, 5130, 4270, 2070, 3910, 3870, 5480. A homogeneous sample of the decolorized reaction mixture exhibited the three longest wave length bands, from which it was determined that 4-benzylisoquinoline was produced in 34% yield from tetrahydroisoquinoline. About one third of the material was collected crystalline and ether-washed.

**N-Benzyl-1,2,3,4-tetrahydroisoquinoline** (3.87 g.), prepared from tetrahydroisoquinoline and benzyl chloride in pyridine solution, was treated with benzaldehyde (4 ml.) and acetic acid (1.5 ml.) in precisely the same manner as described above for tetrahydroisoquinoline. No water collected in the Dean–Stark trap, and recovery of the N-benzyl derivative was quantitative. The infrared spectrum of N-benzyltetrahydroisoquinoline (chloroform solution) exhibited a number of strong bands absent from the spectrum of 4-benzylisoquinoline. In particular, the band at 2800 cm.$^{-1}$ has intensity proportional to concentration. From this it was determined that N-benzyltetrahydroisoquinoline constituted no more than 6% of the noncrystalline portion of the decolorized reaction mixture of tetrahydroisoquinoline and benzaldehyde, and was thus formed in less than 3% yield in that reaction.

**1,2,3,4-Tetrahydroquinoline and Benzaldehyde.**—Treatment of tetrahydroquinoline with benzaldehyde under the conditions affording 4-benzylisoquinoline from tetrahydroisoquinoline gave only polymeric material. When the heating period was decreased to 15 hr. a small amount (less than 5% of the initial weight of tetrahydroquinoline) of crystalline material was isolated from the heptane extract. It was recrystallized from acetone and, on the basis of its melting point (151–152°) and infrared spectrum (N–H band at 3440 cm.$^{-1}$ in carbon tetrachloride solution) was assigned the same structure as Einhorn's compound[16] (6,6'-benzalbistetrahydroquinoline, m.p. 152–153°).

**Spectra.**—Ultraviolet spectra in 95% ethanol were determined using the Cary Model 14 recording spectrophotometer.

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# The Reaction of Chloroacetaldehyde with Cyanide Ion in Aqueous Medium

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When an aqueous solution of chloroacetaldehyde (I) is added to an excess of aqueous sodium cyanide at 0°, 2-chloro-1-cyanoethyl acetate (II) is obtained in 90% yield. A study of this reaction indicates that the cyanohydrin of I dehydrohalogenates to acetyl cyanide, which then acetylates the conjugate base of more cyanohydrin to yield II.

## Introduction

The reaction of an equimolar quantity of an aldehyde with cyanide ion in water normally will give the conjugate base of the corresponding aldehyde cyanohydrin. However, certain aldehydes have been shown to undergo reactions in the presence of cyanide ion which do not lead to cyanohydrins. The best known and most thoroughly studied example of what may be termed an atypical reaction of an aldehyde with cyanide ion is the benzoin condensation. In this reaction the cyanide ion sufficiently increases the acidity of the hydrogen of the —CHO group by converting the aldehyde to a mixture of cyanohydrin and its conjugate base so that this aldehydic hydrogen now alpha to a nitrile becomes easily removable in the presence of a base.[1] This appears to

be a crucial step in the formation of a benzoin from the corresponding aldehyde.

The rearrangement of $\beta$-formyl acrylic acid to succinic acid has also been shown to be cyanide ion-catalyzed.[2] The proposed mechanism as in the benzoin condensation again incorporates the ability of the cyanide ion to increase greatly the acidity of the hydrogen of the —CHO group.

The interesting cyanide ion-catalyzed decomposition of $\beta,\beta$-dicarbethoxypropionaldehyde into diethyl malonate and ethyl acetate is another example of a reaction whose mechanistic explanation depends on the increased acidity of the aldehydic hydrogen. In this latter case the anion formed fragments to give a more stable anion; the aldehyde is converted to an ester.

(1) For pertinent references see J. Hine, "Physical Organic Chemistry." McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 257.
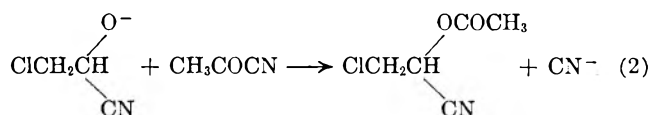
(2) V. Franzen and L. Fikentsher, *Ann.*, **623**, 68 (1959).

$$\begin{array}{c}
CO_2H \\ | \\ CH \\ \| \\ CH \\ | \\ CHO
\end{array}
\; + \; HCN \; \rightleftharpoons \;
\begin{array}{c}
CO_2H \\ | \\ CH \\ \| \\ CH \\ | \\ NC-\underset{H}{C}-OH
\end{array}
\; \overset{-H^+}{\rightleftharpoons}$$

$$\left[
\begin{array}{c}
CO_2H \\ | \\ CH \\ | \\ CH \\ | \\ {}^-:C-OH \\ | \\ CN
\end{array}
\leftrightarrow
\begin{array}{c}
CO_2H \\ | \\ {}^-:CH \\ \| \\ CH \\ | \\ C-OH \\ \| \\ CN
\end{array}
\leftrightarrow
\begin{array}{c}
O^- \\ | \\ C-OH \\ | \\ CH \\ \| \\ CH \\ | \\ C-OH \\ | \\ CN
\end{array}
\right]
\overset{+H^+}{\rightleftharpoons}$$

$$\begin{array}{c}
CO_2H \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ C=O \\ | \\ CN
\end{array}
\;\overset{H_2O}{\longrightarrow}\;
\begin{array}{c}
CO_2H \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ CO_2H
\end{array}
+ \; HCN$$

$$\begin{array}{c}
CO_2C_2H_5 \\ | \\ HC-CH_2-CHO \\ | \\ CO_2C_2H_5
\end{array}
\overset{HCN}{\rightleftharpoons}
\begin{array}{c}
CO_2C_2H_5 \quad OH \\ | \qquad\qquad | \\ HC-CH_2-CH \\ | \qquad\qquad \backslash \\ CO_2C_2H_5 \quad CN
\end{array}
\overset{B}{\rightleftharpoons}$$

$$\begin{array}{c}
CO_2C_2H_5 \quad OH \\ | \qquad\qquad | \\ HC-CH_2-C:^- \\ | \qquad\qquad \backslash \\ CO_2C_2H_5 \quad CN
\end{array}
+ \; HB^+ \longrightarrow$$

$$\begin{array}{c}
CO_2C_2H_5 \\ | \\ HC:^- \\ | \\ CO_2C_2H_5
\end{array}
+ \;
\begin{array}{c}
OH \\ | \\ CH_2=C \\ \backslash \\ CN
\end{array}
\overset{HB^+}{\underset{C_2H_5OH}{\longrightarrow}}$$

$$\begin{array}{c}
CO_2C_2H_5 \\ | \\ CH_2 \\ | \\ CO_2C_2H_5
\end{array}
+ \; CH_3-\overset{O}{\overset{\|}{C}}-OC_2H_5 + B + HCN$$

As early as 1873[3,4] it was observed that cyanide ion caused $\alpha$-chloroaldehydes to undergo unusual reactions. In aqueous solution these aldehydes were converted to acids containing one less chlorine atom in the alpha position by the action of cyanide ion. The most thoroughly studied reaction of this type is the cyanide ion-catalyzed transformation of chloral to dichloroacetic acid.[5] The mechanism generally accepted today was proposed, along with an alternate route, almost fifty years ago.[6] In 1931, Lapworth argued convincingly by analogies for the mechanism now favored.[7] Again, as in the previous examples, a necessary step in the postulated mechanism is the cyanide ion's ability to labilize the aldehydic hydrogen.

$$Cl_3CCHO \overset{HCN}{\rightleftharpoons}
\begin{array}{c}
OH \\ | \\ Cl_3C-C-H \\ | \\ CN
\end{array}
\overset{-HCl}{\longrightarrow}
\begin{array}{c}
OH \\ | \\ Cl_2C=C \\ \backslash \\ CN
\end{array}
\longrightarrow$$

$$\begin{array}{c}
O \\ \| \\ Cl_2CHC \\ \backslash \\ CN
\end{array}
\overset{H_2O}{\longrightarrow} Cl_2CHCO_2H + HCN$$

However, this mechanism has not been fully verified in spite of recent work projected toward this goal. Fodor and Katritzky[8] showed that, when chloral deuteriohydrate reacts with sodium cyanide in deuterium oxide, no CH is found in the product, dichloroacetic acid. This indicates that, if an epoxide intermediate is formed, it cannot rearrange to dichloroacetyl cyanide by an intramolecular hydride shift. However, an epoxide intermediate is not ruled out.

In 1958 another mechanism was proposed for this reaction but later experimentally refuted.[9,10]

We have now found another unusual aldehyde-cyanide ion reaction. When aqueous chloroacetaldehyde is added slowly to an aqueous solution of sodium cyanide at 0°, a 90% yield of 2-chloro-1-cyanoethyl acetate is isolated.[11] A mechanism for this reaction is proposed which is consistent with the experimental evidence to be presented.

### Results and Discussion

Addition of aqueous chloroacetaldehyde to an equimolar or preferably excess aqueous sodium cyanide solution, as in the preparation of a cyanohydrin, gives an unexpectedly vigorous exothermic uncontrollable reaction which finally leads to a black tarry mass. With proper temperature control, however, and slow addition of chloroacetaldehyde, the major product isolated is not acetic acid, as one might anticipate, but 2-chloro-1-cyanoethyl acetate (II) in 90% yield along with the cyanohydrin of I in 8% yield and a very small amount of acetic acid (<2%). Starting material I is thus roughly 100% accounted for. On a 0.10-molar scale the reaction can be completed in less than five minutes; the acetate begins to separate as a light yellow oil after about half of I has been added if the reaction temperature is kept at 0°. A sample of II prepared from the reaction of acetic anhydride with 3-chlorolactonitrile had an infrared spectrum, boiling point, refractive index, and n.m.r. spectrum identical with II prepared by the reaction studied.

Strong evidence in the literature supports the formation of a cyanohydrin as the initial step in this reaction. It is a fact well documented that the carbonyl-cyano-

$$ClCH_2CHO \overset{CN^-}{\rightleftharpoons}
\begin{array}{c}
O^- \\ | \\ ClCH_2CH \\ | \\ CN
\end{array}
\overset{H_2O}{\rightleftharpoons}
\begin{array}{c}
OH \\ | \\ ClCH_2CH \\ | \\ CN
\end{array}
\qquad (1)$$

$$\qquad\qquad\qquad\qquad III \qquad\qquad\qquad IV$$

hydrin equilibrium is a very rapid reaction for simple aldehydes, especially in the presence of base.[12] The pH of the aqueous cyanide ion solution is approximately

(3) O. Wallach, Ber., **6**, 114 (1873).

(4) F. D. Chattaway and H. Irving, J. Chem. Soc., 1038 (1929).

(5) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 181.

(6) A. Kötz and K. Otto, J. prakt. Chem., **88**, 531 (1913).

(7) W. Cocker, A. Lapworth, and A. T. Peters, J. Chem. Soc., 1382 (1931).

(8) G. Foder and A. R. Katritzky, Chem. Ind. (London), 1530 (1961).

(9) The suggestion was made (D. J. Cram and G. S. Hammond, "Organic Chemistry," J. Wiley and Sons, Inc., New York, N. Y., 1959, p. 255) that a necessary step may be incorporation of cyanide ion onto the product in the chloral transformation. A subsequent rebuttal was based on ¹⁴C experiments.¹⁰ However, it should be noted that the chloral transformation to dichloroacetic acid is published in "Organic Syntheses," ref. 5. Only a *catalytic amount* of cyanide ion is used.

(10) C. Rosenblum, C. Taverna, and N. L. Wendler, Chem. Ind. (London), 718 (1960).

(11) R. M. Nowak, U. S. Patent 2,915,549 (December 1, 1959).

(12) Some pertinent references discussing the rate of the carbonyl-cyanohydrin equilibrium are: A. Lapworth, J. Chem. Soc., 995 (1903); 2533 (1928); W. J. Jones, ibid., 1560 (1914); J. W. Baker and M. L. Hemming, ibid., 191 (1942).

12. Under these conditions chloroacetaldehyde cyanohydrin (IV) will form in a few seconds.

It was shown that IV can be formed easily and swiftly in 85% yield under nonbasic conditions by adding aqueous sodium cyanide to an equimolar solution of I and acetic acid in water. Here the pH of the solution never gets more basic than pH of 5.3. It was also shown that when IV was slowly added to an aqueous sodium cyanide solution at 0°, acetate II was formed in 90% yield. The reaction proceeded at an equivalent rate but much less exothermally than in the preparation of II from I. About 8% cyanohydrin was also reisolated. When IV reacted in ether at 20° with an equimolar quantity of triethylamine, dehydrohalogenation occurred smoothly over a sixty-minute interval, as evidence by the precipitation of triethylamine hydrochloride. Three products were isolated. They were α-acetoxyacrylonitrile (V) (66% yield), II (6% yield), and 1,1-dicyanoethyl acetate (VI) (12% yield). Compound V arises from dehydrochlorination of II formed during the reaction. This dehydrochlorination was studied under the same reaction conditions. An 80% yield of V was obtained from II at 30° within sixty minutes using triethylamine as base.[13] Both V and II were expected products. However, VI was the most interesting of the three products for its isolation is a strong indication that acetyl cyanide (VII) is present in the solution. It is well known that acetyl cyanide can be made to dimerize under the conditions used to yield VI.[14]

It is concluded from the above work that the reaction proceeds through the cyanohydrin and that another possible intermediate is VII.

The assumption that acetyl cyanide is an intermediate in the reaction was next tested. Bartlett has shown that VII solvolyzes rapidly in methanol.[14] In fact VII is almost as reactive an acylating agent as acetyl chloride or acetic anhydride. If VII is an intermediate in the reaction, path 2 should be a gen-

$$\underset{\underset{CN}{|}}{ClCH_2\overset{O^-}{\overset{/}{C}H}} + CH_3COCN \longrightarrow \underset{\underset{CN}{\setminus}}{ClCH_2\overset{OCOCH_3}{\overset{/}{C}H}} + CN^- \quad (2)$$

eral reaction for the formation of 1-cyanoalkyl acetates from aldehydes. This we have found to be true. This reaction was tried with acetaldehyde. An equimolar quantity of VII was added slowly to an aqueous solution of acetaldehyde and excess sodium cyanide. The same time and temperature interval as in the studied reaction to produce II was followed. A 92% yield of 1-cyanoethyl acetate (VIII) was isolated along with 5% cyanohydrin. The use of chloroacetaldehyde in this reaction gives no useful information regarding path 2 since I in the presence of sodium cyanide forms II without addition of VII.

If VII is an intermediate, as the above reaction strongly suggests, there are two logical paths to its formation. One possibility is through an epoxide intermediate.

$$\underset{\underset{CN}{|}}{ClCH_2\overset{O^-}{\overset{|}{C}H}} \longrightarrow \underset{\underset{CN}{|}}{\overset{O}{\overset{/\setminus}{CH_2\!-\!CH}}} + Cl^- \overset{B}{\longrightarrow} \underset{\underset{CN}{|}}{\overset{O}{\overset{/\setminus}{CH_2\!-\!C}}:^- \overset{BH^+}{\longrightarrow}}$$
$$\qquad\quad III \qquad\qquad IX$$

$$\underset{\underset{CN}{|}}{CH_2\!=\!C\overset{O^-}{|}} \overset{BH^+}{\longrightarrow} CH_3\!-\!COCN + B \quad (3)$$

To test this hypothesis glycidonitrile (IX) was prepared by the method of Payne.[15,16] Glycidonitrile then was added to an aqueous solution of sodium cyanide and acetaldehyde. If IX is an intermediate in the reaction, VIII should be formed. No VIII could be isolated. A small amount of IX was recovered on work-up along with a trace of an unidentified liquid. Even allowing the reaction to proceed twice as long as the chloroacetaldehyde cyanide reaction did not destroy all the IX. Glycidonitrile was next added to an aqueous sodium cyanide solution to determine whether under reaction conditions similar to that used to form II, acetic acid would form as would be anticipated if IX rearranged to VII. The reaction mixture was not analyzed for products. Instead Duclaux values were run on the acidified reaction mixture. Potentiometric titration of the distillate indicated that no acetic acid had been formed. Path 3 is therefore eliminated as the major source of VII.

A second possible path to VII is via dehydrohalogenation of IV followed by tautomerization. Support for this proposal was obtained by running the studied reaction in deuterium oxide.

$$\underset{\underset{CN}{|}}{ClCH_2\overset{OH}{\overset{|}{C}H}} \overset{B}{\longrightarrow} \underset{\underset{CN}{|}}{CH_2\!=\!C\overset{OH}{|}} \overset{BH^+ + Cl^-}{\longrightarrow} CH_3COCN \quad (4)$$
$$\qquad\qquad\qquad\qquad X$$
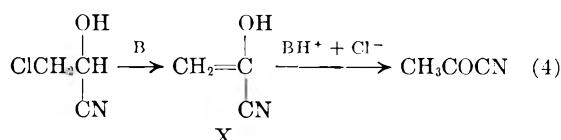
Due to the difficulty of preparing anhydrous I, a concentrated aqueous solution was used instead. When diluted with deuterium oxide, the solution contained 0.17, 0.30, and 1.2 moles of I, water, and deuterium oxide, respectively. This solution was added to a solution of 0.17 mole of sodium cyanide and 1.3 moles of deuterium oxide. Deuterium content in purified II was analyzed by mass spectrometry.

It was first shown by mass spectrometry that II does not exchange with deuterium oxide under the reaction conditions, so that any deuterium found in II must have entered before or during the reaction. Any exchange of starting material before dehydrohalogenation should fortunately show up in the chloromethyl group of II. The deuterium data in Table I show that only 9.6% of the chloromethyl groups contain deuterium, indicating that exchange of I before the formation of II was not rapid. However, 55% of the methyl groups of II were found to contain at least one deuterium.

It can be shown easily that while the deuterium found in the chloromethyl group is a statistical distribution based on simple exchange of ClCH₂— with solvent, the

(13) Heinrich Lange, U. S. Patent 2,266,771 (July 29, 1939).

(14) Bartlett states that acetyl cyanide is an active acetylating agent rapidly hydrolyzed by water. In methanol at room temperature the carbonyl absorption for the cyanide at 331 mμ is half gone in 40 sec. In water, hydrolysis is even faster. In a highly basic aqueous solution its hydrolysis must be exceedingly fast; see P. D. Bartlett and B. E. Tate, J. Am. Chem. Soc., 78, 5575 (1956).

(15) G. B. Payne, ibid., 81, 4901 (1959).

(16) We gratefully acknowledge a sample of glycidaldehyde supplied by G. B. Payne of the Shell Development Company, Emeryville, Calif. We also heartily agree with Dr. Payne when he points out the violent decomposition that glycidaldehyde oxime will undergo if left to stand at room temperature for much longer than 1 hr.

| Ion | Parts[b] | Ion | Parts[b] |
|---|---|---|---|
| $\overset{+}{ClCH_2CHCN}$ | 100 | $CH_3CO^+$ | 100 |
| $\overset{+}{ClCHDCHCN}$ | 10 | $CH_2DCO^+$ | 110 |
| $\overset{+}{ClCD_2CHCN}$ | 0.6 | $CHD_2CO^+$ | 13 |

[a] See ref. 17. [b] Each undeuterated moiety has been arbitrarily set equal to 100.

deuterium in the methyl group is far from that predicted by exchange with solvent.

The deuterium data are consistent with a mechanism shown by paths 1 followed by 4, then 2, with the following stimulations: dehydrohalogenation must be either a concerted mechanism or loss of chloride ion must at least be fast enough so as not to allow exchange of the aldehydic hydrogen (this means that the deuterium content found in the $\overset{+}{ClCH_2CHCN}$ moiety is also found in X before tautomerization); acetylation of III by VII must be rapid compared to exchange with solvent or enolization; and a deuterium isotope effect of 8.3 is encountered presumably at the tautomerization step.[18,19] This isotope effect is consistent with what is known about deuterium isotope effects at a carbon adjacent to a carbonyl in the presence of strong base.[20] Table II compares the observed values for deuterium distribution in the methyl group and the values predicted based on the proposed mechanism.

Table II

Observed and Predicted Deuterium Content in the Methyl Group

| Ion | Observed, %[a] | Predicted, % |
|---|---|---|
| $CH_3CO^+$ | 44.8 | 44.8 |
| $CH_2DCO^+$ | 49.4 | 50.1 |
| $CHD_2CO^+$ | 5.8 | 4.8 |
| $CD_3CO^+$ | [b] | ~0.3 |

[a] Calculations in this column are based on Table I. [b] A small peak at mass 46 could not be determined accurately due to the complexity of the cracking pattern, but is consistent with <0.5% $CD_3CO^+$.

To obtain the predicted values in Table II, enol X with a deuterium distribution identical to the $ClCH_2$- $\overset{+}{CHCN}$ moiety in Table I was calculated to pick up a ratio of hydrogen to deuterium such that the observed and predicted $CH_3CO^+$ moiety concentration in Table II coincided. The mono- and dideuterated moieties could then be compared with the observed results.

The good agreement between observed and predicted values in Table II strongly supports the postulated mechanism.

To add further support to a concerted E2 elimination of hydrogen chloride rather than a two-step E2 elimination. a solution of acetaldehyde was allowed to exchange in a solution of deuterium oxide and sodium cyanide under conditions similar to which I was converted to II.[21] However, the reaction time was five times as long. Then acetyl chloride was swiftly added as a method of efficiently and rapidly isolating acetaldehyde cyanohydrin (XI). Ether extraction and fractionation gave a 20% yield of 1-cyanoethyl acetate. It was determined by n.m.r. spectroscopy that, while the methyl group from the acetaldehyde had become highly deuterated, 100-$CD_3$, 66.2-$CHD_2$, and 15.8-$CH_2D$ for every 1.1-$CH_3$, neither the proton spectrum nor the deuterium spectrum gave the slightest indication that deuterium exchange had taken place at the aldehydic hydrogen. There was, as expected, no indication of exchange at the acetate methyl. This great difference in the rate of loss of proton from XI and from IV indicates that loss of hydrogen chloride from IV must follow a concerted E2 mechanism, that is, that carbanion formation cannot be the rate-determining step in loss of hydrogen chloride from IV. While XI would be expected to undergo exchange via a carbanion intermediate, if IV also passes through a carbanion intermediate the great acceleration in rate must be accounted for merely by the inductive effect of one β-chlorine atom. This is unreasonable, as Pearson has pointed out.[22] Rather, a proton is removed from IV with greater ease due to the simultaneous departure of the chloride ion and double bond formation.

## Experimental[23]

3-Chlorolactonitrile (IV).—To 588 g. (3.0 moles) of 40% aqueous chloroacetaldehyde was added slowly 183 g. (3.05 moles) of glacial acetic acid. To this solution was added, keeping the temperature between −10° and +5°, 147 g. (3.0 moles) of sodium cyanide dissolved in 500 ml. of water. Stirring was continued 1 hr. after addition was complete. The cyanohydrin (IV) then was extracted with ether. The ether solution was

(17) Mass spectrometry analysis of either the acetate or methyl ions might be expected to give the same results. This, however, was not the case. The $CH_3^+/CH_2D^+/CHD_2^+$ ratio was found to be 100/97/6.8, respectively. The discrepancy between the methyl and acetyl cations is assumed to be due to a deuterium isotope effect in the cleavage reaction during spectral analysis. The methyl cation should, therefore, be least accurate since the broken bond is closest to the methyl group. The ratio of peak heights of $CH_3CO^+$ to $CH_3^+$ is roughly 22 to 1 indicating $CH_3CO^+$ as the major cracking route. The acetyl cation was, therefore, accepted as giving the most reliable data.

(18) The temperature varied from −10 to 0° during the experiment and the ratio of water to deuterium oxide (determined by n.m.r.) was known only to an accuracy of ±5%.

(19) A maximum isotope effect for the O–H bond at 0° is 12.6. See K. Wiberg, Chem. Rev., 55, 713 (1955).

(20) Pocker found that $CD_3CHO$ reacted 7.4 times slower than acetaldehyde in an aldol condensation; see Y. Pocker, Chem. Ind. (London), 599 (1959).

(21) While it is logical to postulate a concerted E2 elimination, since the carbanion formed by proton loss can be resonance stabilized by —C≡N, a two-step E2 elimination appears as a possibility. Pertinent references to the study of two-step vs. one-step E2 eliminations can be found in E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1959, pp. 478–480.

(22) Weinstock, Bernardi, and Pearson have estimated that the inductive effect of a chlorine atom in the beta position of an ethyl ketone increases by roughly 15 times the rate of ionization of the chlorethyl over the ethyl ketone. Substitution of a —C≡N for the $\diagdown$C=O would not be expected to change this value greatly even though $\diagdown$C=O stabilizes the negative charge in the alpha position better than —C≡N; see J. Weinstock, J. L. Bernardi, and R. G. Pearson, J. Am. Chem. Soc., 80, 4961 (1958); R. G. Pearson and R. L. Dillon, ibid., 75, 2439 (1953).

(23) Melting points and boiling points are uncorrected. The infrared spectra were run on a Beckman-IR5 infrared spectrophotometer. A modified Westinghouse 90° sector type magnetic mass spectrometer with a heated inlet was used. Gas chromatography was run on a 3-ft. by 0.25-in. stainless steel column packed with 15% Dow polyglycol E-4000 (polyethylene glycol; 4000 molecular weight) on 42/60-mesh acid-washed Chromosorb. A high carrier gas rate at 151° was used. N.m.r. 30-Mc. spectra were run on a high resolution n.m.r. spectrometer described by E. B. Baker and L. W. Burd, Rev. Sci. Instr., 28, 313 (1957). N.m.r. 60- and 9.2-Mc. spectra were run on a high resolution n.m.r. spectrometer described by E. B. Baker and L. W. Burd, ibid., to be published. Line positions were measured with respect to a separate water sample by interchanging sample and reference.

dried, concentrated, and fractionated through a 12-in. Vigreux column to yield 225 g. (71%) of IV, b.p. 88–90° (2.5 mm.), $n^{35}D$ 1.4565. Infrared spectrum showed characteristic absorption at 3400 cm.$^{-1}$ and 2240 cm.$^{-1}$. N.m.r. spectrum at 30 Mc.: At a 20 volume % solution of IV in deuterium oxide, the —CH$_2$Cl protons are a slightly broadened doublet (splitting 5.0 ±0.1 c.p.s.) centered at −26.8 c.p.s. from the water reference. The CH proton is a pair of doublets (splittings of 4.8 and 5.2 c.p.s.) centered at +8.1 c.p.s. The unlike $\diagdown$CH—

CH$_2$— splittings indicate strongly hindered rotation about this C—C bond. The —OH proton is a single line at −1 c.p.s. due to fast exchange with deuterium oxide. On the neat sample $^{-}$OH exchange is much slower and OH/CH splitting of about 5 to 6 c.p.s. appears. The —OH proton lies at −1 c.p.s. and the CH at +8 c.p.s.

*Anal.* Calcd. for C$_3$H$_4$ClNO: C, 34.12; H, 3.79; Cl, 33.65; N, 13.27. Found: C, 34.42; H, 3.88; Cl, 33.54; N, 13.16.

**2-Chloro-1-cyanoethyl Acetate (II) from Chloroacetaldehyde and Sodium Cyanide.**—To a solution of 98 g. (1.95 moles) of sodium cyanide dissolved in 300 ml. of water was added slowly 389.5 g. (2.0 moles) of 39.3 ± 0.1% (aldehyde assay) aqueous chloroacetaldehyde. The temperature of the reactants was controlled between −10 and 0°. Addition time was 20 min. After an additional 5 min. of stirring, the solution was extracted with four 150-ml. portions of ether which were combined and dried over anhydrous sodium sulfate. After flashing the ether at 60° (20 mm.), 139 g. of a mixture of acetate (II) and cyanohydrin (IV) was obtained. N.m.r. indicated 8% cyanohydrin in the mixture while infrared with use of standards showed 7%. Fractionation gave a 90% yield of acetate (II), b.p. 65° (1 mm.), $n^{35}D$ 1.4355, along with 5–7% of IV. N.m.r. spectrum of pure I at 30 Mc.: CH$_3$CO (−76.0 ± 0.2 c.p.s.), CH$_2$ClCCNO (doublet centered at −25.5 ± 0.2 c.p.s., splitting 5.0 ± 0.2 c.p.s.) and CHCNO (triplet centered at +24.3 ± 0.2 c.p.s., splitting 4.9 ± 0.2 c.p.s.). The spectrum is in complete agreement with II.

*Anal.* Calcd. for C$_5$H$_6$ClNO$_2$ (II): C, 40.68; H, 4.06; Cl, 24.07; N, 9.50. Found: C, 40.76; H, 4.11; Cl, 24.24; N, 9.62.

The aqueous layer remaining after ether extraction was acidified to pH 3 and continuously extracted with ether for 20 hr. The infrared spectrum of the product after removal of the ether was identical with acetic acid with the exception of a strong bond at 3450 cm.$^{-1}$ indicating the presence of water. N.m.r. was used to determine that the 13.5 g. of solution was a mixture of water and acetic acid in a mole ratio of 1.5 to 1. There was no indication in the n.m.r. spectrum of a $\diagdown$CH$_2$. Neutral equivalent calculated for the above mixture: 87; found: 86. Material balance based on 1.95 moles of chloroacetaldehyde is 1.76 moles of II plus 0.08 to 0.09 mole of IV plus 0.12 mole of acetic acid for a total of 1.97 moles of I accounted for.

**2-Chloro-1-cyanoethyl Acetate (II) from 3-Chlorolactonitrile and Acetic Anhydride.**—A mixture of 20 g. of cyanohydrin (IV), excess acetic anhydride, and 5 drops of pyridine was allowed to stand for 24 hr. Fractionation gave 24 g. (86%) of II. The infrared spectrum, refractive index, and b.p. of II were identical with II prepared from I and sodium cyanide in aqueous solution.

**2-Chloro-1-cyanoethyl Acetate (II) Prepared in Deuterium Oxide.**—Anhydrous chloroacetaldehyde is not only difficult to obtain but also difficult to store due to a great tendency to trimerize and polymerize. To avoid the problem of preparing a pure sample of I a 40% aqueous solution of I was continuously extracted with ether. The ether was then dried over sodium sulfate and concentrated. A 71% aqueous solution of I was obtained. This solution was shown by n.m.r. to contain 0.17 mole of chloroacetaldehyde and 0.30 mole of water. To this was added 1.2 moles of deuterium oxide. The resultant solution was added to a solution 0.17 mole of sodium cyanide dissolved in 1.3 moles of deuterium oxide. The reaction was run as described above with the exception that addition took only 1 min. and the product was extracted with ether just 9 min. later. The 2-chloro-1-cyanoethyl acetate isolated by fractionation was shown to be at least 99.8% pure by gas chromatography. Mass spectrometric analysis of this sample is tabulated in Table I.

**Exchange of II in Deuterium Oxide–Sodium Cyanide Solution.**—A sample of pure II was stirred in a solution of sodium cyanide–deuterium oxide. The concentration of each material

approximated the concentration found in the preparation of II from I and cyanide. After 15 min. at 0° II was extracted with ether and fractionated. Infrared and refractive index indicated II had been recovered. Mass spectrometric analysis indicated that on the basis of 100 parts of CH$_3$C=O$^+$ and 100 parts of C$_3$H$_3$NCl$^+$ only 0.6 and 0.4 parts of CH$_2$DC=O$^+$ and C$_3$H$_2$DNCl$^+$, respectively, were found. Thus II does not significantly exchange under the conditions of the reaction.

**Glycidonitrile (IX).**—Prepared by the method of G. B. Payne, *J. Am. Chem. Soc.*, 81, 4901 (1959).

**α-Acetoxyacrylonitrile (V) *via* Dehydrohalogenation of 2-Chloro-1-cyanoethyl Acetate.**—To 295 g. (2.0 moles) of 2-chloro-1-cyanoethyl acetate in 2000 ml. of dry ether was added slowly 202 g. (2.0 moles) of triethyl amine diluted with 100 ml. of ether. The reaction temperature was kept below 30°. After addition, the solution which now contains a copious precipitate of amine hydrochloride was stirred an additional 6 hr. To the solution was added dilute aqueous hydrochloric acid to both dissolve the amine hydrochloride and neutralize any unreacted amine. Without a thorough acid wash the product will fractionate as an amber liquid instead of a colorless liquid. To the ether solution was added a pinch of *t*-butylcatechol as a polymerization inhibitor. The ether solution then was concentrated and fractionated through a 12-in. column packed with 0.25-in. Berl saddles to give 202 g. (91%) of V, b.p. 65° (12 mm.); $n^{35}D$ 1.4191. An 80% yield of V can be obtained if the reaction is run for only 1 hr. Identifying infrared absorption peaks are found at 2232, 1774, and 1636 cm.$^{-1}$. Other strong bands are found at 1370, 1190, 970, 923, 874, and 673 cm.$^{-1}$.

*Anal.* Calcd. for C$_5$H$_5$NO$_2$ (V); C, 54.05; H, 4.50; N, 12.61. Found: C, 54.28; H, 4.34; N, 12.39.

**Dehydrohalogenation of 3-Chlorolactonitrile (IV) with Triethylamine.**—To a stirred solution of 55 g. (0.55 mole) of triethylamine in 200 ml. of dry ether was added 53 g. (0.50 mole) of 3-chlorolactonitrile. After 15 min. the reaction became noticeably exothermic and a flocculant precipitate of amine hydrochloride began to form. The mixture was kept at 25° and stirred for a total of 1 hr. Water was added to dissolve the amine hydrochloride salts. The solution was acidified to pH 3 and extracted with ether. The ether was dried and then flashed to give 26 g. of a liquid which was examined by gas chromatography. Gas chromatography indicated 18.2 g. (66% of α-acetoxyacrylonitrile, 2.2 g. (6%) of II, and 4.2 g. (12%) of what was proved to be 1,1-dicyanoethyl acetate (VI). The over-all yield based on cyanohydrin was 84%. N.m.r. spectrum of VI at 30 Mc.: a sharp peak at −79 ± 0.5 c.p.s. and a broad peak at −83 ± 0.5 c.p.s.; m.p. 69.5–70.5° (69.4–70.2° reported by Bartlett[18]).

*Anal.* Calcd. for C$_6$H$_6$N$_2$O$_2$ (VI): C, 52.1; H, 4.35; N, 20.3. Found: C, 51.98; H, 4.21; N, 20.12.

**1-Cyanoethyl Acetate (VIII).**—To 200 ml. of water and 98 g. (2.0 moles) of sodium cyanide was added slowly 44 g. (1 mole) of acetaldehyde. Then, while the reaction temperature was kept at −10 to 0°, 94 g. (1.2 moles) of acetyl chloride was added dropwise with vigorous stirring. The addition reaction was very exothermic. After addition was complete stirring was continued for 2–3 min. To the solution was added 100 ml. of water to dissolve the sodium acetate. The product was extracted with ether and concentrated to give 113 g. (95% yield), $n^{35}D$ 1.3960 of crude product. Fractionation gave a 90% yield of VIII, b.p. 68° (8 mm.), $n^{36}D$ 1.3948. Infrared and n.m.r. spectra are consistent with VIII. If acetic anhydride is used instead of acetyl chloride, the yields are equally good. An excess of sodium cyanide is necessary for optimum yields. When equimolar cyanide and aldehyde was used, the yield of VIII was only about 55–65%.

*Anal.* Calcd. for C$_5$H$_7$NO$_2$ (VIII): C, 52.17; H. 4.35; N, 20.29. Found: C, 51.98; H, 4.21; N, 20.00.

**Exchange Reaction of Acetaldehyde in Deuterium Oxide–Sodium Cyanide.**—To a solution of 8.35 g. (0.17 mole) of sodium cyanide in 20 g. of deuterium oxide was added slowly at 0° 7.0 g. (0.16 mole) of acetaldehyde in 5 g. of deuterium oxide. The solution was kept between −10 and 0° for 25 min. Then 13.5 g. (0.2 mole) of acetyl chloride was added within a 2-min. interval. An oil formed almost immediately. The solution was twice extracted with ether. The combined ether fractions were concentrated and fractionated. A 20% yield of deuterated VIII was obtained. The major component was a high boiling residue probably arising from an aldol condensation. The infrared spectrum of this material was consistent with 1-cyano-3-acetoxybutyl

acetate. This material was not further identified. Purified VIII from the reaction was studied with n.m.r.

The proton spectrum shows a large sharp peak at $-180$ c.p.s.

$$\overset{O}{\underset{}{\parallel}}$$

due to nondeuterated $-O-C-CH_3$, a broad doublet at $-212$ c.p.s. due to partially deuterated $CH_3C$, and a broad triplet at

$$\underset{CN}{|}$$

$+13$ c.p.s. due to CH.

Spin decoupling at the D frequency of 9.211569 Mc. and high power sharpens both the $CH_3C$ and CH. The $CH_3$ is

$$\underset{CN}{|}$$

separable into three doublets corresponding to $CHD_2$, $CH_2D$, and $CH_3$. These are shifted 1 c.p.s. from each other due to a small isotopic effect on the chemical shift. Their relative areas, on a molar basis, should correspond to the amounts of each present.

The CH is split by the deuterated methyls into a seven line pattern corresponding to $1/8$ $CH_3$, $1/4$ $CH_2D$, $(1/2$ $CHD_2$ + $3/8$ $CH_3)$, $(CD_3$ + $1/2$ $CH_2D)$, $(1/2$ $CHD_2$ + $3/8$ $CH_3)$, $1/4$ $CH_2D$, and $1/3$ $CH_3$. The integral curve gives on a normalized basis: 100 $CD_3$, 66.2 $CHD_2$, 15.8 $CH_2D$, $\sim1.1$ $CH_3$. This corresponds well with the ratios 100 $CHD_2$, 47.7 $CH_2D$, 5.0 $CH_3$

in the $CH_3$ spectrum allowing for an apparent line shape assymetry.

The $CH_3$ spectrum shows no trace of a line near the center of the pattern which would be expected if there were any deuterium at the CH position.

The deuterium spectrum shows a large line due to the $CD_3$, $CHD_2$, and $CH_2D$ and a small line near the deuterium oxide reference point. In the proton spectrum the $CH_3$ and CH are separated by 225 c.p.s. or 3.74 p.p.m. Multiplying 3.74 p.p.m. by the deuterium frequency of 9.211 Mc. we obtain 34.5 c.p.s. for the $CD_3$ to CD separation which is not near the position of the small line found. It is concluded that there is no CD in VIII and that the small line is probably deuterium oxide impurity.

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# Pteridines. I. Synthesis of Some 6-Alkyl-7-aminopteridines from Nitrosopyrimidines

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Compounds with methylenes activated by acyl groups react with 4,6-diamino-5-nitroso-2-phenylpyrimidine in the presence of sodium cyanide with incorporation of cyanide, loss of acylate, and cyclization to form 6-substituted 7-aminopteridines. The principles involved in this process were modified to permit the synthesis of six 6-alkyl-7-aminopteridines.

The diuretic activity displayed by 4,7-diamino-2-phenyl-6-pteridinecarboxamide (I) and related compounds[2] prompted us to undertake the synthesis for biological screening of a series of compounds bearing alkyl groups in the 6-position (III). Although a number of 6-aryl-7-aminopteridines (IV) have been prepared through condensation of arylacetonitriles with appropriate 4-amino-5-nitrosopyrimidines,[3] compounds of type III have not been reported. While the methylene group of an arylacetonitrile is sufficiently acidic to form an anion and react with a 4-amino-5-nitrosopyrimidine in the presence of basic catalysts, the $\alpha$-methylene of a simple alkylnitrile cannot form an anion under similar conditions because it is a weaker acid than a 4-amino-5-nitrosopyrimidine. Reaction in the latter case therefore fails.

A solution to the problem of preparing compounds of type III came about in unexpected fashion. It was found that, although 4,6-diamino-5-nitroso-2-phenylpyrimidine (V) condenses with phenylacetaldehyde and phenylacetone in the presence of potassium acetate to give the pteridines VI and VII, the reactants condense in each case in the presence of sodium cyanide to give only the 7-aminopteridine (VIII). Compound VIII is also produced when V reacts with phenylacetonitrile in the presence of sodium cyanide.
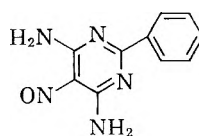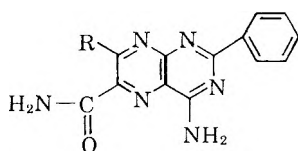


V
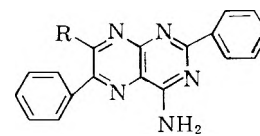
VI. R = H
VII. R = CH$_3$
VIII. R = NH$_2$



I. R = NH$_2$
II. R = phenyl

III. R = alkyl
IV. R = aryl

In similar fashion, benzoylacetamide reacts with V in the presence of potassium acetate to produce 4-amino - 2,7 - diphenyl - 6 - pteridinecarboxamide (II). With sodium cyanide as the condensing agent, the reactants yield I.

In the synthesis of VIII from phenylacetaldehyde or phenylacetone, and in the synthesis of I from benzoyl-acetamide, an acyl group is lost and a nitrile incorporated at appropriate stages in the process. Kröhnke[4]
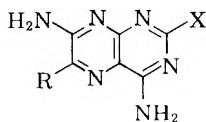
(1) Present address: Endo Laboratories, Richmond Hill 18, N. Y.

(2) (a) J. Weinstock, U. S. Patent 2,963,478 (1960); (b) E. C. Taylor, U. S. Patent 2,963,479 (1960); (c) E. C. Taylor and J. Weinstock, U. S. Patent 2,963,480 (1960); (d) J. Grannells and J. Weinstock, U. S. Patent 2,963,481 (1960); (e) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).

(3) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

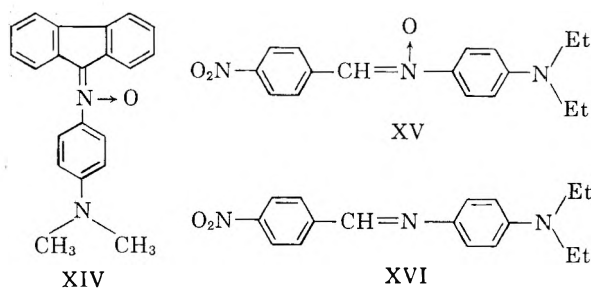(4) F. Kröhnke, *Chem. Ber.*, **80**, 298 (1947).

observed a related replacement of an acyl group by a nitrile some years ago.

The effect of catalyst on reaction course is noteworthy. In the acetate-catalyzed condensation of phenylacetone with V, for example, reaction proceeds through the hydroxylamine intermediate (IX). This intermediate loses water to form the anil (X) which, in turn, cyclizes to form VII.
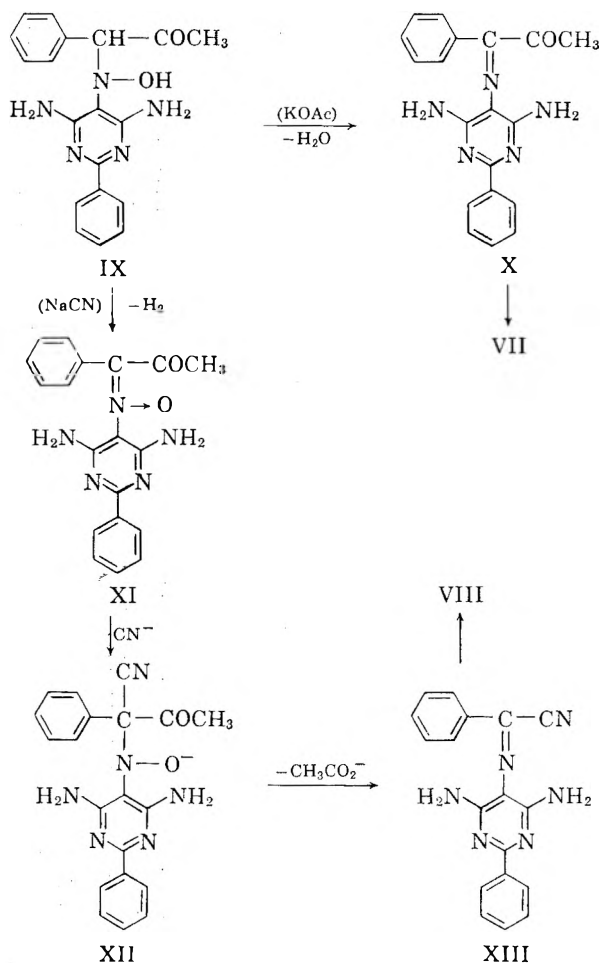


The cyanide-catalyzed reaction also proceeds through IX, but the latter, instead of dehydrating, becomes oxidized to the nitrone (XI). This then may add cyanide (XII), lose acetate to give the anil (XIII), and cyclize to produce VIII.

That hydroxylamines related to IX may undergo oxidation rather than dehydration is well known.[4-9] For example, fluorene condenses with p-nitrosodimethylaniline to give only the nitrone (XIV).[6]

(5) A. Schönberg and R. Michaelis, *J. Chem. Soc.*, 627 (1937).
(6) E. Bergmann, *ibid.*, 1628 (1937).
(7) F. Barrow and F. J. Thorneycroft, *ibid.*, 769 (1939).
(8) D. C. Dittmer and J. M. Kolyer, *J. Org. Chem.*, **27**, 56 (1962).
(9) F. Kröhnke, *Ber.*, **71**, 2583 (1938).

De Waal and Brink[10] have cited other instances where the nature of the product is dependent upon the condensing agent. They found that p-nitrobenzyl-γ-picolinium bromide reacted with p-nitrosodiethylaniline in the presence of sodium hydroxide at room temperature to produce the nitrone (XV), whereas the same reactants produced the anil (XVI) when the condensing agent was piperidine at 80°. Their work was complicated by the finding that the anil could be obtained, together with some p-nitrodiethylaniline, by heating the nitrone with p-nitrosodiethylaniline in the presence of piperidine. They regarded the nitrone as a possible intermediate in the formation of the anil.

It appears unlikely that nitrones are intermediates in the syntheses of II, VI, and VII for two reasons. (1) Compound II was obtained in 70% yield from V. This is higher than would have been predicted if one or more equivalents of nitrosopyrimidine had been consumed as oxidizing agent. (2) Numerous pteridine 5-oxides have been prepared in this laboratory in excellent yield through cyclization of nitrone intermediates in the presence of potassium acetate. The oxides are stable compounds and will be described in a subsequent paper.

The yield of VIII from phenylacetone is low partly because some of the nitrosopyrimidine is consumed as oxidizing agent. If one were to start with α-phenylacetoacetonitrile (XVII), the oxidation step would be omitted. Compound XVII would be expected to condense with V to form XII and ultimately to produce VIII in high yield. This is indeed the case and VIII was obtained from XVII in over 90% yield.



Compound XVII bears three activating groups on the same carbon atom. Replacement of phenyl by alkyl should give a molecule (XVIII) which is still sufficiently acidic to condense with an o-aminonitrosopyrimidine in the presence of alkali. If the reactions of compounds of type XVIII parallel those of XVII, 6-alkyl-7-aminopteridines (III) should result.

Four alkylnitriles were benzoylated with ethyl benzoate in the presence of sodium methoxide by the general procedure of Dorsch and McElvain.[11] Upon reaction with V in aqueous ethanol in the presence of sodium cyanide, each produced a 6-alkyl-7-aminopteridine (XIX–XXII).
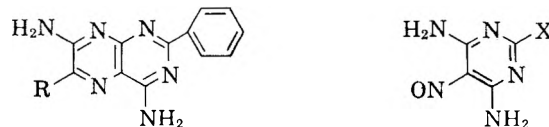


XIX. R = methyl  XXI. R = cyclohexyl  XXIII. X = SCH₃
XX. R = ethyl    XXII. R = benzyl     XXIV. X = H

Ethyl α-methylcyanoacetate used in place of α-methylbenzoylacetonitrile in reaction with V also yielded XIX. The reaction proceeded more slowly, however, and with inferior yield.

(10) H. L. de Waal and C. v. d. M. Brink, *Chem. Ber.*, **89**, 636 (1956).
(11) J. B. Dorsch and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 2960 (1932).

Table I

Ultraviolet Spectra
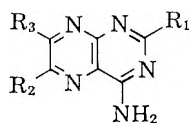


| Compound | R₁ | R₂ | R₃ | $\lambda_{max}$, m$\mu$ (log $\epsilon$) | pH |
|---|---|---|---|---|---|
| II | Phenyl | Carboxamide | Phenyl | 276 (4.42), 368 (4.34) | 1 |
| VI | Phenyl | Phenyl | Hydrogen | 238 (4.78), 287 (4.54), 372 (4.26) | 1 |
| VII | Phenyl | Phenyl | Methyl | 278 (4.45), 355 (4.23) | 1 |
| VIII | Phenyl | Phenyl | Amino | 240 (4.38), 266 (4.50), 370 (4.40) | 1 |
| | | | | 266 (4.47), 270 (4.38) | 13 |
| XIX | Phenyl | Methyl | Amino | 254 (4.42), 350 (4.31) | 1 |
| | | | | 243 (4.53), 346 (4.23) | 13 |
| XX | Phenyl | Ethyl | Amino | 241 (4.35), 254 (4.42), 350 (4.32) | 1 |
| | | | | 243 (4.55), 346 (4.24) | 13 |
| XXI | Phenyl | Cyclohexyl | Amino | 254 (4.43), 354 (4.35) | 1 |
| XXII | Phenyl | Benzyl | Amino | 255 (4.44), 354 (4.35) | 1 |
| XXV | Methylthio | Methyl | Amino | 255 (4.35), 347 (4.39), 363 (4.28) | 1 |
| | | | | 254 (4.58), 263 (4.37), 346 (4.25), 359 (s) (4.18) | 13 |
| XXVI | Methylthio | Methyl | Phenyl | 267 (4.31), 295 (4.00), 362 (4.31) | 1 |
| XXVII | Hydrogen | Methyl | Amino | 248 (4.20), 283 (3.61), 340 (4.21), 356 (s) (1.01) | 1 |
| | | | | 236 (s) (4.35), 259 (s) (4.05), 335 (4.08) | 13 |

The formation of the 6-alkyl-7-aminopteridines (XIX–XXII) from substituted benzoylacetonitriles, and the formation of XIII from XVII, required in each case that acylate rather than cyanate be eliminated at an appropriate stage in synthesis. In none of these reactions involving 4,6-diamino-5-nitroso-2-phenyl-pyrimidine (V) was there evidence of cyclization occurring through the carbonyl group with accompanying elimination of cyanate.

This remarkable specificity did not extend to the reactions of two other nitrosopyrimidines. When 4,6-diamino-2-methylthio-5-nitrosopyrimidine (XXIII) and 4,6-diamino-5-nitrosopyrimidine (XXIV) were used in place of V in reactions with α-methylbenzoylaceto-nitrile, mixtures were obtained. Single products could be made to predominate, however, through appropriate choice of solvent, catalyst, and reaction temperature.

Compound XXIII reacted with α-methylbenzoyl-acetonitrile in ethoxyethanol in the presence of potassium acetate to form 4,7-diamino-6-methyl-2-methyl-thiopteridine (XXV) and 4-amino-6-methyl-2-methyl-thio-7-phenylpteridine (XXVI) in a molar ratio of about eleven to one. On the other hand, when sodium cyanide in aqueous ethanol was used in the reaction, the same products were formed in about a one to one ratio.
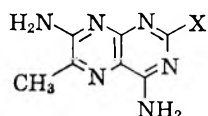


XXV. X = SCH₃
XXVII. X = H
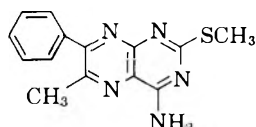
XXVI

The reaction of compound XXIV in ethoxyethanol in the presence of potassium acetate favored formation of 4,7-diamino-6-methylpteridine (XXVII) to a pteridine by-product by a molar factor of approximately five. In an aqueous alcoholic sodium cyanide medium only the by-product, the structure of which is currently under investigation, was isolated.

More information is needed before one can speculate significantly on the manner in which the 2-substituent on nitrosopyrimidines influences the course of pteridine formation. It must first be determined whether intermediates similar to XII, which are formed from nitrosopyrimidines and compounds of type XVII and XVIII, proceed to pteridines through loss of anion followed by cyclization of whether cyclization precedes loss of anion.

The role of solvent, catalyst, and reaction temperature also remains to be clarified. Cyanide catalyst is important in causing nitrone formation (XI) rather than anil formation (X), but the experiments with XXIII and XXIV show that it clearly does not determine the course of pteridine formation once intermediates of type XII are generated.

The ultraviolet spectra of new pteridines reported in this paper are recorded in Table I.

Several of the pteridines produced potent diuretic effects in the rat. The biological data will be reported elsewhere at a later date.

### Experimental

The *ultraviolet spectra* at pH 1 were determined in 4.5% aqueous formic acid. The spectra at pH 13 were determined by taking a 5 to 10-ml. aliquot of compound in 4.5% formic acid and bringing the volume to 100 ml. with 1 N aqueous sodium hydroxide. In those cases where the compound crystallized from alkaline solution, no values at pH 13 are recorded.

**4,7-Diamino-2-phenyl-6-pteridinecarboxamide (I).**—A mixture of 1.63 g. (0.01 mole) of benzoylacetamide, 1.0 g. (0.005 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 0.5 g. (0.01 mole) of sodium cyanide, 10 ml. of water, and 40 ml. of ethanol was heated under reflux for 3 hr. There was obtained 0.25 g. of yellow crystals, identical with an authentic sample of I.[22]

**4-Amino-2,7-diphenyl-6-pteridinecarboxamide (II).**—A mixture of 1.07 g. (0.005 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 1.63 g. (0.01 mole) of benzoylacetamide, 1.0 g. of potassium acetate and 50 ml. of ethanol was heated under reflux for 2 hr., during which time the nitroso compound dissolved and the product crystallized from solution in fine needles. The mixture was concentrated, cooled, and filtered to give 1.2 g. (70%) of almost colorless needles. After one recrystallization from ethanol, the compound melted at 322–324° dec.

*Anal.* Calcd. for C₁₉H₁₄N₆O: C, 66.66; H, 4.12; N, 24.55. Found: C, 66.69; H, 4.24; N, 24.67.

**4-Amino-2,6-diphenylpteridine (VI).**—A mixture of 6.45 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 5 g. of potassium acetate, 7.2 g. of phenylacetaldehyde, and 50 ml. of ethoxyethanol was heated under reflux for 30 min. The mixture was concentrated to half volume under reduced pressure and 10 ml. of water was added. A brown substance separated from the cooled solution. It was taken up in ethanol and the resulting solution was treated with charcoal, concentrated, and cooled. There was obtained 1.5 g. of orange crystals which, upon recrystallization from dimethylformamide, yielded 1.3 g. of orange plates, m.p., 288–289° dec.

*Anal.* Calcd. for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 72.23; H, 4.53; N, 23.16.

**4-Amino-7-methyl-2,6-diphenylpteridine (VII).**—A mixture of 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 3.3 g. of phenylacetone, 3.0 g. of potassium acetate and 50 ml. of *n*-butyl alcohol was heated under reflux for 4 hr. The mixture was cooled in an ice bath for 1 hr. and the yellow needles were filtered, washed with water and ethanol, and dried. The product weighed 1.3 g. (41.5% yield). For analysis a sample was recrystallized from 5:1 ethanol–ethoxyethanol, m.p. 288–290° dec.

*Anal.* Calcd. for $C_{19}H_{15}N_5$: C, 72.82; H, 4.82; N, 22.35. Found: C, 72.38; H, 5.13; N, 22.05.

**4,7-Diamino-2,6-diphenylpteridine (VIII). (A) From Phenylacetonitrile.**—A mixture of 1.17 g. of phenylacetonitrile, 0.5 g. of 4,6-diamino-5-nitroso-2-phenylpteridine, 0.25 g. of sodium cyanide and 30 ml. of 90% ethanol was boiled for 10 min. The green color rapidly disappeared and the yellow pteridine separated from solution. The product was collected and recrystallized from dimethylformamide to give 0.65 g. of VIII, m.p. over 320°.

*Anal.* Calcd. for $C_{18}H_{14}N_6$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.43; H, 4.60; N, 26.53.

**(B) From Phenylacetaldehyde.**—To a mixture of 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 2.4 g. of phenylacetaldehyde and 20 ml. of ethanol was added a solution of 1.0 g. of sodium cyanide in 5 ml. of water. The mixture was heated to boiling and the reactants went into solution. After standing at room temperature overnight, the 0.9 g. of yellow product that separated was washed thoroughly with water and recrystallized from dimethylformamide to yield 0.5 g. of VIII, identical with the product prepared by method A.

**(C) From Phenylacetone.**—Under conditions similar to those of method B 4 ml. of phenylacetone reacted with 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine to form 0.8 g. of VIII.

**(D) From α-Phenylacetoacetonitrile.**—To a boiling mixture of 1.1 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 1.6 g. of α-phenylacetoacetonitrile and 50 ml. of ethanol was added 0.5 g. of sodium cyanide in 5 ml. of water. The mixture was heated under reflux for 5.5 hr. Upon concentration and cooling there was obtained 1.45 g. (90.7%) of VIII, identical with an authentic sample prepared from phenylacetonitrile.

**4,7-Diamino-6-methyl-2-phenylpteridine (XIX). (A) From Reaction with α-Methylbenzoylacetonitrile.**—To a mixture of 21.5 g. (0.1 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 31.8 g. (0.2 mole) of α-methylbenzoylacetonitrile[11] in 200 ml. of ethanol was added a solution of 10 g. (0.2 mole) of sodium cyanide dissolved in 40 ml. of water. The mixture was heated for 18 hr. Upon concentration to about 60 ml. and cooling there was obtained 23 g. of crude pteridine. This was recrystallized from methanol to give 15.2 g. (60%) of pale yellow needles of XIX, m.p. 308–309° dec.

*Anal.* Calcd. for $C_{13}H_{12}N_6$: C, 61.89; H, 4.80; N, 33.31. Found: C, 62.05; H, 4.91; N, 33.33.

**(B) From Reaction with Ethyl α-Methylcyanoacetate.**—To a mixture of 2.15 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 2.6 g. of ethyl α-methylcyanoacetate and 30 ml. of ethanol was added a solution 1.0 g. of sodium cyanide in 10 ml. of water. The mixture was heated (24 hr.) until disappearance of green color. There was obtained 0.6 g. of XIX, identical with the sample obtained as described in method A.

**4,7-Diamino-6-ethyl-2-phenylpteridine (XX).**—To a mixture of 1.07 g. (0.005 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 1.7 g. (0.01 mole) of α-ethylbenzoylacetonitrile[11] in 35 ml. of ethanol was added a solution of 0.5 g. of sodium cyanide in 6 ml. of water. The mixture was heated under reflux for 8 hr. There was obtained 1.05 g. of yellow product, m.p. after recrystallization from dilute acetic acid, 276–280° dec.

*Anal.* Calcd. for $C_{14}H_{14}N_6$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.14; H, 5.46; N, 31.21.

**α-Cyclohexylbenzoylacetonitrile.**[12]—Cyclohexylacetonitrile was prepared from cyclohexylmethyl bromide by the general procedure described by Friedman and Shechter.[13] A solution of 55 g. of sodium cyanide in 400 ml. of dry dimethyl sulfoxide was heated to 60° and 177 g. of cyclohexylmethyl bromide was added at such a rate as to maintain the temperature at 60–65°. After the addition, the reaction mixture was heated to 85° for 3 hr. One liter of water was added and the oily layer was taken up in ether. The ethereal layer was dried over magnesium sulfate and distilled over phosphorus pentoxide to give 86.0 g. (70%) of cyclohexylacetonitrile, b.p. 83–86° (20 mm.), $n^{25}D$ 1.4577. Wallach[14] reported $n^{18}D$ 1.4575.

To a stirred mixture of 120 g. (0.8 mole) of ethyl benzoate and 43.2 g. (0.8 mole) of sodium methoxide heated at 80° was added 86 g. (0.88 mole) of cyclohexylacetonitrile over a period of 2 hr. The temperature of the heating bath was raised to 115–120° and heating was continued for 10 hr.

The thick mixture was cooled and diluted with ice and water at 0°. Ether was added and the mixture was stirred while sulfuric acid was added until the pH was brought to between 2 and 3. The mixture was extracted with several portions of ether and the combined ethereal extracts were washed with 5% sodium bicarbonate solution to remove benzoic acid. The ethereal solution was dried over magnesium sulfate and distilled. There was obtained 41 g. of pale yellow oil, b.p., 180–190°(1 mm.). The product solidified and, upon recrystallization from ether–hexane mixture, melted at 45–46°.

*Anal.* Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.53; H, 7.63.

**4,7-Diamino-6-cyclohexyl-2-phenylpteridine (XXI).**—A mixture of 7.4 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 15 g. of α-cyclohexylbenzoylacetonitrile, 3.5 g. of sodium cyanide, 60 ml. of water and 180 ml. of ethanol was heated under reflux for 20 hr. The green color remained and an additional 7 g. of α-cyclohexylacetonitrile was added and reflux maintained for an additional 16 hr. Upon cooling there was obtained 5.5 g. of yellow solid. Concentration yielded an additional 0.95 g. The two crops were combined and recrystallized from dilute acetic acid to give 5.4 g. of XXI, m.p. 338–340°.

*Anal.* Calcd. for $C_{18}H_{20}N_6$: C, 67.48; H, 6.29; N, 26.23. Found: C, 67.56; H, 6.49; N, 26.26.

**α-Benzylbenzoylacetonitrile.**[12]—This compound was prepared from hydrocinnamonitrile and ethyl benzoate by the same procedure used for the preparation of α-cyclohexylbenzoylacetonitrile. From 164 g. of hydrocinnamonitrile there was obtained 63 g. of product, b.p., 186–202° (0.5 mm.), m.p., upon recrystallization from methanol, 79–80°.

*Anal.* Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.81; H, 5.65.

**4,7-Diamino-6-benzyl-2-phenylpteridine (XXII).**—To a mixture of 12.9 g. (0.06 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 27.0 g. (0.12 mole) of α-benzylbenzoylacetonitrile and 225 ml. of ethanol was added a solution of 6 g. (0.12 mole) of sodium cyanide in 75 ml. of water. The resulting mixture was heated under reflux for 20 hr. The solvent was removed under reduced pressure and the residue was washed thoroughly with water and recrystallized from ethanol to yield 4.8 g. of XXII, m.p., 280–281° dec.

*Anal.* Calcd. for $C_{19}H_{16}N_6$: C, 69.49; H, 4.91; N, 25.59. Found: C, 69.27; H, 5.21; N, 26.53.

**4,7-Diamino-6-methyl-2-methylthiopteridine (XXV).**—A mixture of 1.85 g. of 4,6-diamino-2-methylthio-5-nitrosopyrimidine, 3.2 ml. of α-methylbenzoylacetonitrile, 3.0 g. of potassium acetate and 50 ml. of ethoxyethanol was heated under reflux for 2 hr. The brown solution was concentrated to 30 ml. and cooled. A yellow solid (1.0 g.) separated and was filtered. When the filtrate stood for 1 hr., 0.2 g. of a second compound separated which proved to be identical with XXVI described in the following experiment. The filtrate was then concentrated to about 15 ml. and diluted with 5 ml. of water. Upon standing overnight, an additional 0.8 g. of the first compound separated. The combined first and third crops (1.8 g.), upon recrystallization from ethanol, melted at 308–310° dec.

(12) We thank Mr. A. J. Villani of this laboratory for the preparation of this compound.

(13) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

(14) O. Wallach, *Ann.*, **359**, 311 (1908).

*Anal.* Calcd. for $C_8H_{10}N_6S$: C, 43.23; H, 4.53; N, 37.81. Found: C, 43.45; H, 4.57; N, 37.96.

**XXV and 4-Amino-6-methyl-2-methylthio-7-phenylpteridine (XXVI).**—A mixture of 14.8 g. (0.08 mole) of 4,6-diamino-2-methylthio-5-nitrosopyrimidine, 16 g. (0.1 mole) of α-methylbenzoylacetonitrile, 5.0 g. (0.1 mole) of sodium cyanide and 250 ml. of 75% ethanol was heated under reflux for 16 hr. There was obtained a first crop of 4.1 g. of pteridine and, after concentration, 3.9 g. of a second crop. The first crop was recrystallized from ethanol three times to give 2.5 g. of 4-amino-6-methyl-2-methylthio-7-phenylpteridine, m.p., 268–269°.

*Anal.* Calcd. for $C_{14}H_{13}N_5S$: C, 59.34; H, 4.62; N, 24.72; S, 11.32. Found: C, 59.40; H, 4.70; N, 24.91; S, 11.21.

The second crop was also recrystallized three times from ethanol to yield 2.6 g. of XXV, identical with the sample prepared by the method of the preceding experiment.

**4,7-Diamino-6-methylpteridine (XXVII).**—A mixture of 8.2 g. of 4,6-diamino-5-nitrosopyrimidine, 15 g. of α-methylbenzoylacetonitrile, 9.0 g. of potassium acetate, and 175 ml. of ethoxyethanol was heated under reflux for 1 hr. The dark brown solution was evaporated to dryness under reduced pressure and the residue was stirred with a little water and filtered. The brown precipitate was stirred at 60° with three 85-ml. portions of 5% hydrochloric acid. The acid solutions were combined, extracted with ether, and purified with charcoal. The resulting yellow solution was made basic with sodium hydroxide, cooled in the refrigerator for 4 hr., and filtered. There was obtained 5.2 g. of buff-colored product. For further purification, the product was dissolved in 60 ml. of warm 3% hydrochloric acid and cooled to give 4.1 g.

of beautiful, well formed needles of hydrochloride. The salt, on treatment with ammonia, yielded almost colorless needles of XXVII. The compound does not melt but turns black at about 330°.

*Anal.* Calcd. for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.70. Found: C, 47.85; H, 4.90; N, 47.89.

The brown gummy solid which was not dissolved by the extractions with hydrochloric acid was washed with ethanol and recrystallized from glacial acetic acid with the aid of charcoal. There was obtained 1.5 g. of well formed needles of by-product. For analysis, this product was recrystallized from ethanol with charcoal treatment. It formed colorless needles, m.p., 268–269° dec.

*Anal.* Found: C, 64.15; H, 3.88; N, 32.05.

**Reaction of XXIV with α-Methylbenzoylacetonitrile. The Cyanide-catalyzed Reaction.**—To 2.8 g. of 4,6-diamino-5-nitrosopyrimidine and 6.4 g. of α-methylbenzoylacetonitrile in 250 ml. of ethanol was added 2 g. of sodium cyanide in 8 ml. of water. The mixture was heated under reflux for 3 hr., concentrated to about 50 ml., cooled, and filtered. There was obtained 2.0 g. of crystals of a compound which, upon recrystallization from acetic acid, proved to be identical with the by-product in the aforementioned sodium acetate-catalyzed reaction.

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# Pteridines. II. Synthesis of 6-Substituted 7-Aminopteridines from Aldehydes

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2,4,5,6-Tetraminopyrimidine and 4,5,6-triamino-2-phenylpyrimidine react with aldehydes and hydrogen cyanide to form aminonitriles which may be cyclized with sodium methoxide and oxidized with hydrogen peroxide to 6-substituted-7-aminopteridines. α,β-Unsaturated aldehydes are reduced in the process; cinnamaldehyde and phenylpropargylaldehyde yield 6-phenethyl-7-amino- and 6-styryl-7-aminopteridines, respectively.

2,4,7-Triamino-6-phenylpteridine (I) (generically named triamterene), first reported from this laboratory to be a diuretic drug by Wiebelhaus, Weinstock, and co-workers[2] has proved to be an effective diuretic agent in man.[3,4]



I
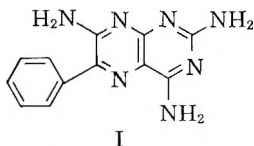
As part of an extensive program devoted to the preparation of related molecules for biological evaluation, the synthesis of 6-alkyl analogs was undertaken. The present paper reports the preparation of these and related compounds.

In the previous paper of this series,[5] the synthesis of a number of 6-alkyl-7-aminopteridines from nitrosopyrimidines was described. This synthetic method produced poor results when extended to comparatively

inactive nitrosopyrimidines such as 2,4,6-triamino-5-nitrosopyrimidines, and an alternate method, more generally applicable, was sought for the work of the present investigation.

Numerous 6-substituted 7-pteridinones have been synthesized through condensation of α-keto acids with 4,5-diaminopyrimidines. 7-Chloropteridines have occasionally been prepared from these pteridinones.[6,7] It was hoped that such compounds might serve as intermediates in the present study.

2,4-Diamino-6-phenyl-7-pteridinone[8–10] was converted into the corresponding chloro compound and thence into various 7-amino derivatives.[10] However, this route failed at the chlorination step in a number of related cases[10,11] and was clearly not of general applicability for the preparation of 6-substituted 7-aminopteridines.

It is well known that 2,4,5,6-tetraminopyrimidine (II) condenses with carbonyl compounds preferentially

(1) Present address: Endo Laboratories, Richmond Hill 18, N. Y.

(2) V. D. Wiebelhaus, J. Weinstock, F. T. Brennan, G. Sosnowski, and T. J. Larsen, *Fed. Proc.*, **20**, 409 (1961).

(3) A. P. Crosley, Jr., L. M. Ronquillo, W. H. Strickland, and F. Alexander, *Ann. Internal Med.*, **56**, 241 (1962).

(4) R. J. Donnelly, P. Turner, and G. S. C. Sowry, *Lancet*, **1**, 245 (1962).

(5) I. J. Pachter and P. E. Nemeth, Part I, *J. Org. Chem.*, **28**, 1187 (1963).

(6) J. H. Mowat, J. H. Boothe, B. L. Hutchings, E. L. R. Stokstad, C. W. Waller, R. B. Angier, J. Semb, D. B. Cosulich, and Y. SubbaRow, *J. Am. Chem. Soc.*, **70**, 14 (1948).

(7) A. Albert and F. Reich, *J. Chem. Soc.*, 127 (1961).

(8) A. G. Renfrew, P. C. Piatt, and L. H. Cretcher, *J. Org. Chem.*, **17**, 467 (1952).

(9) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

(10) I. J. Pachter and P. E. Nemeth, to be published.

(11) Dr. J. Weinstock, private communication.

TABLE I

2,4,6-TRIAMINO- AND 4,6-DIAMINO-2-PHENYL-5-($\alpha$-CYANOALKYLAMINO)-PYRIMIDINES



·$n$CH$_3$COOH

| Compound | R | R' | Yield,[a] % | n | M.p.,[f] °C. | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Amino | Methyl | 95 | 1 | 183–184 | 42.60 | 42.60 | 6.15 | 5.97 | 38.65 | 38.92 |
| 2 | Amino | Isopropyl | 120[b] | 2[c] | 143–145 | 45.74 | 45.60 | 6.79 | 6.70 | 28.72 | 28.48 |
| 3 | Amino | 3-Cyclohexenyl | 111[b] | 2[c] | 134–135 | 50.65 | 50.73 | 6.64 | 6.75 | 25.84 | 26.43 |
| 4 | Amino | Benzyl | 98[b] | 2[c] | 155–156 | 52.42 | 52.43 | 5.95 | 5.75 | 25.18 | 25.09 |
| 5 | Amino | $\beta$-Phenethyl | 78 | 2[c] | 160–162 | 53.89 | 53.60 | 6.25 | 6.59 | 24.30 | 24.29 |
| 6 | Amino | Phenyl | 103 | 1 | 169–170 | 53.32 | 53.59 | 5.43 | 5.66 | 31.10 | 31.04 |
| 7 | Amino | Styryl | 77 | 2[c] | 134–136 | 53.86 | 53.46 | 5.78 | 5.97 | 24.43 | 24.83 |
| 8 | Amino | Phenethynyl | 83[b] | .. | [d] | [d] | | [d] | | [d] | |
| 9 | Phenyl | Methyl | 95[e] | 0 | 212–213 | 61.40 | 60.98 | 5.55 | 5.78 | 33.05 | 33.16 |
| 10 | Phenyl | Phenyl | 97[e] | 0 | 217–219 | 69.07 | 69.15 | 5.49 | 5.75 | 25.44 | 25.27 |
| 11 | Phenyl | Phenyl | 89[e] | 0 | 201–203 | 68.34 | 68.31 | 5.10 | 4.75 | 26.57 | 26.64 |

[a] Crude yield based on assumption that products before recrystallization are monoacetate salts. [b] Cooled to −20° to ensure complete crystallization; contains extraneous salt. [c] Crystallized for analysis from methanolic acetic acid. [d] Cyclized during attempted purification. [e] Yield based on assumption that product is not a salt. [f] Melting point of analytical sample.

at the 5-amino group.[12] Condensation with aldehydes should, therefore, provide anils of type III which should, in turn, react with hydrogen cyanide to produce aminonitriles of type IV. If these aminonitriles, upon treatment with alkali, would undergo cyclization in preference to loss of hydrogen cyanide and regeneration of anils, a useful route to 6-substituted 7-aminodihydropteridines (V), and eventually to the desired pteridines (VI), would be at hand.
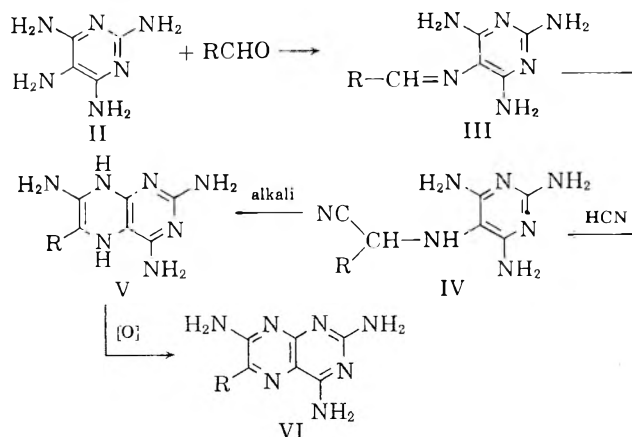


The literature contains two reports of work along these lines. Several years ago Blicke and Godt[13] successfully condensed 5,6-diamino-1,3-dimethyl-2,4-pyrimidinedione (VII) with formaldehyde and hydrogen cyanide, cyclized the intermediate with alkali and oxidized with hydrogen peroxide to obtain 7-amino-1,3-dimethyl-2,4-pteridinedione (VIII).

At about the same time, Polonovski[14] reported that 2,4,5-triamino-6-methylpyrimidine (IX) reacted with loss of ammonia during a related synthesis to produce 2-amino-7-hydroxy-4-methylpteridine (X).

In the present work, when, 2,4,5,6-tetraminopyrimidine (II) hydrochloride[15] was suspended in methanolic
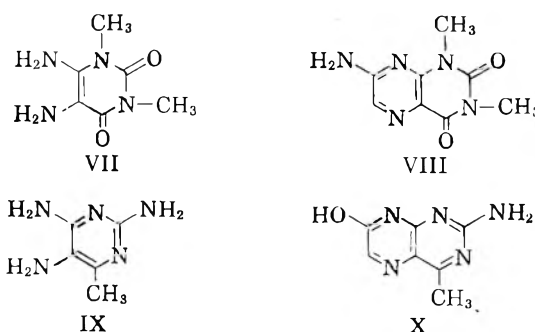


acetic acid, treated with aqueous sodium cyanide and then with various aldehydes, 2,4,6-triamino-5-($\alpha$-cyanoalkylamino)pyrimidines (IV) formed rapidly and crystallized from solution as acetate salts. Products were derived from eight aldehydes. The series included aliphatic, aromatic, $\alpha,\beta$-unsaturated and $\beta,\gamma$-unsaturated aldehydes. Crude yields of the products (Table I) were generally excellent. In each case, crystallization of product began at about room temperature when proper solvent conditions were worked out.

The products crystallized originally as monoacetate salts from the acetic acid–sodium acetate-containing reaction mixtures. Although they separated in high yield from solutions containing excess aldehyde and cyanide, they dissociated considerably into simpler components upon boiling with methanol. To minimize this retrograde process, samples were prepared for analysis in several cases in the presence of excess acetic acid. In these instances the analytical products were determined to be diacetate salts (Table I). When no acetic acid was added to the methanolic recrystallization solvent, products analyzing as monoacetate salts were obtained.

It was occasionally necessary to cool a reaction mixture to −20° to effect complete crystallization; in

(12) G. B. Elion, G. H. Hitchings, and P. B. Russell, J. Am. Chem. Soc., 72, 78 (1950).

(13) F. F. Blicke and H. C. Godt, Jr., ibid., 76, 2798 (1954).

(14) M. Polonovski, et al., in the "Ciba Foundation Symposium on Chemistry and Biology of Pteridines," Little, Brown and Company, Boston, Mass., 1954, p. 171.

(15) 2,4,5,6-Tetraminopyrimidine is commercially available as the sulfate salt.[16] This salt is very difficultly soluble in aqueous and alcoholic solutions and for the present work it was converted into the more readily soluble hydrochloride through treatment with barium chloride. The free base oxidizes rather readily to colored products and for this reason was not used.

(16) Aldrich Chemical Company, Milwaukee, Wis.

## TABLE II
### 2,4,7-TRIAMINO- AND 4,7-DIAMINO-2-PHENYL-6-SUBSTITUTED PTERIDINES
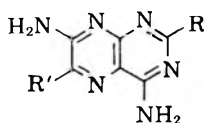


| Compound cyclized (Table I) | R | R' | Yield,[a] % | Over-all yield,[b] % | M.p., °C. | —Carbon, %— Calcd. | Found | — Hydrogen, % — Calcd. | Found | —Nitrogen, %— Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Amino | Methyl | 41 | 39 | >340 | 43.79 | 43.95 | 4.74 | 4.74 | 51.28 | 51.11 |
| 2 | Amino | Isopropyl | 28 | 34 | 343 | 49.30 | 49.38 | 5.98 | 6.28 | 44.72 | 44.61 |
| 3 | Amino | 3-Cyclo-hexenyl | 33 | 37 | >350 | 56.02 | 56.17 | 5.88 | 5.94 | 38.11 | 37.74 |
| 4 | Amino | Benzyl | 35 | 34 | 332 | 58.41 | 58.48 | 4.90 | 4.96 | 36.68 | 36.76 |
| 5 | Amino | β-Phenethyl | 54 | 42 | 296–298 | | d | | d | | d |
| 7 | Amino | β-Phenethyl | 60 | 46 | 296–298 | 59.77 | 59.88 | 5.37 | 5.51 | 34.85 | 34.86 |
| 6 | Amino | Phenyl | 33[c] | 34[c] | 320–322 | | d | | d | | d |
| 8 | Amino | Styryl | 45 | 37 | 345–347 | 60.20 | 60.17 | 4.69 | 4.96 | 35.11 | 34.86 |
| ..[c] | Amino | Styryl | ..[c] | 51[c] | 345 | | d | | d | | d |
| 9 | Phenyl | Methyl | 36 | 34 | 308–309 | | d | | d | | d |
| 10 | Phenyl | Benzyl | 34 | 33 | 280–281 | | d | | d | | d |
| 11 | Phenyl | Phenyl | 21[e] | 19[e] | >350 | | d | | d | | d |

[a] Yield based on crude aminonitrile (Table I).  [b] Yield based on quantity of original pyrimidine prepared as described in the Experimental section.  [c] Pteridine synthesized in one step in acid medium.  [d] Identified through comparison with previously analyzed sample.  [e] Cyclized to pteridine without use of peroxide.

such cases "yields" of crude products exceeded 100% due to co-crystallization of contaminating sodium salt.

Co-crystallization of extraneous salt could be avoided through use of hydrogen cyanide gas in place of sodium cyanide and acetic acid. In one experiment with 2,4,5,6-tetraminopyrimidine hydrochloride and benzaldehyde where this was done, the hydrochloride of the product (IV) (R = phenyl) was obtained in good yield. Since it was more convenient and less hazardous to generate hydrogen cyanide *in situ*, and since contaminating salt did not affect the results in the subsequent steps, the sodium cyanide–acetic acid procedure was used generally in this work.

Each nitrile cyclized when heated briefly under reflux with methanolic sodium methoxide. Except in the instances noted in the following discussion, the resulting hot methanolic solutions were diluted with aqueous hydrogen peroxide and in each case a crystalline light yellow pteridine (VI) separated from the solution within a few minutes. In Table II two columns of yields are listed. The first column indicates the yields of pteridines based upon the crude cyano compounds consumed. The second column, more significantly, lists the overall yields of the process based upon the polyaminopyrimidine employed in the first step. Generally, the over-all yields of pteridines ranged between 30 and 50%. The convenience of the synthesis deserves emphasis. The two stages of the process require minutes to carry out and in a few cases purified pteridines were prepared from pyrimidines within two hours.

It has been assumed in this work that the 5-amino group of a 4,5,6-triaminopyrimidine system condenses with aldehyde and cyanide and that the eventual product is a 6-substituted 7-aminopteridine. Others have felt,[17] however, that "the position of the amino group is not conclusively proved" in a pteridine prepared by a synthesis of this type.

To prove that the products are indeed 6-substituted 7-amino compounds, we undertook the preparation of the previously and unequivocally synthesized[5] 6-methyl- and 6-benzyl-7-aminopteridines XI and XII. 4,5,6-Triamino-2-phenylpyrimidine (XIII) rapidly formed aminonitriles in excellent yield when treated with acetaldehyde and phenylacetaldehyde in the presence of generated hydrogen cyanide. The aminonitriles cyclized in alkali and were oxidized to XI and XII. In each case the identity of the product was established through comparison with an authentic sample.[5]
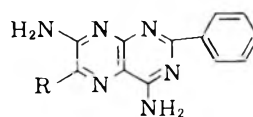


XI. R = methyl
XII. R = benzyl
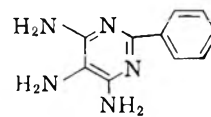
XIII

A dihydro derivative of triamterene (I) would be of interest from a biological standpoint. A synthesis starting with benzaldehyde, but with omission of the peroxide oxidation step, was therefore carried out in the hope that such a product might be obtained. The intermediate nitrile (compound 6, Table I) formed readily and was cyclized with sodium methoxide in a small volume of methanol. A new compound (XIV) was obtained. A small quantity of 2,4,6-triamino-5-benzylidenaminopyrimidine (XV), identical with a sample[18] prepared from benzaldehyde and 2,4,5,6-tetraminopyrimidine, was found in the mother liquor.

Compound XIV gave analytical values similar to those expected for a dihydro compound. Its ultraviolet spectrum (Fig. 1) was closely related to that of I. Instances have been reported previously where dihydropteridine spectra closely resemble those of pteridines.[19]

(17) T. S. Osdene and G. M. Timmis, *J. Chem. Soc.*, 2036 (1955).

(18) The author is grateful to Dr. J. Weinstock and Mr. J. L. Kirkpatrick for this sample.

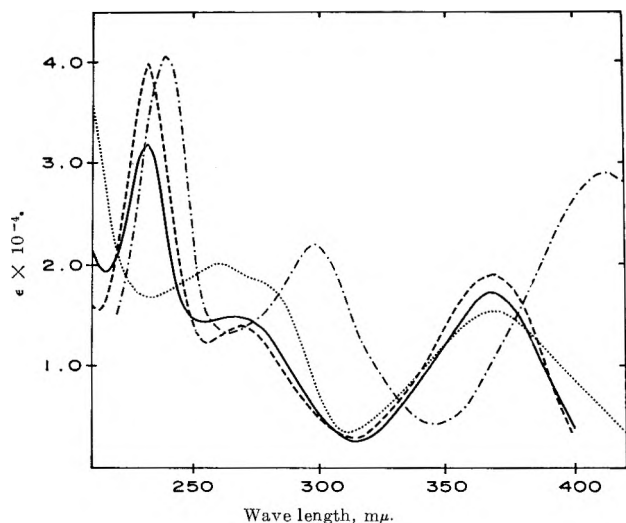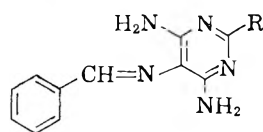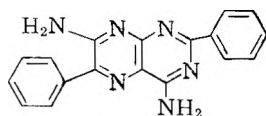(19) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 3877 (1952).

Fig. 1.—2,4,7-Triamino-6-phenylpteridine (I), – – – –; 2,4,6-triamino-5-benzylidenaminopyrimidine (XV), . . . . .; complex XIV (of I and XV), ———; 2,4,7-triamino-6-styrylpteridine, · – · –. Spectra in ethanol.



XV. R = amino
XVII. R = phenyl

XVI

There was evidence, however, which was not consistent with a dihydropteridine structure. For one thing, the yield of XIV was considerably higher than had been obtained for any of the pteridines of Table II. Secondly, the yield of I obtained from XIV after heating with dimethylformamide or diphenyl ether did not exceed 50%. Thirdly, when XIV was warmed with dilute acid and then made basic, I was obtained together with some *benzaldehyde*. Finally the ultraviolet spectrum of XV (Fig. 1) was found to be similar to those of both I and XIV. The data suggested the possibility that XIV was a molecular complex of I and XV. The analytical requirements for such a complex would agree closely with the values found for XIV.

To test this possibility, methanolic solutions of I and XIV were combined in the presence of sodium methoxide. Upon concentration to small volume, XIV crystallized from solution in good yield and its nature was thus revealed.

When nitrile 11 of Table I was treated in similar fashion, a mixture of XVI[5] and XVII was obtained. In this case the compounds did not form a complex and were readily separated.

These experiments indicate that dihydro-6-aryl-7-aminopteridines lack stability and oxidize readily to the corresponding pteridines.

An attempt was made to prepare 2,4,7-triamino-6-styrylpteridine (XXIV) from cinnamaldehyde and II. The aminonitrile (compound 7, Table I) formed in the expected manner. During the methoxide-catalyzed cyclization reaction, however, a product crystallized *before* addition of hydrogen peroxide. The product was unaffected by oxidizing agents. Its ultraviolet spectrum was similar to those of 2,4,7-triamino-6-alkylpteridines and clearly was not that of the more extensively conjugated styrylpteridine. It seemed prob-

able that an intermediate dihydropteridine (*e.g.*, XVIII) formed and then underwent isomerization to 2,4,7-triamino-6-(β-phenethyl)pteridine (XIX).

This was shown to be the case. When the nitrile XX, derived from β-phenylpropionaldehyde, was treated with methanolic sodium methoxide, a solution of XXI was obtained. Upon addition of hydrogen peroxide, the pteridine XIX crystallized and was found to be identical with the product of the cinnamaldehyde sequence.
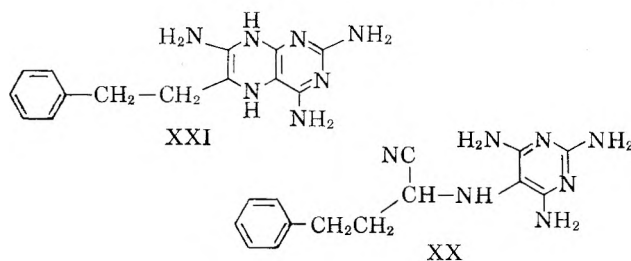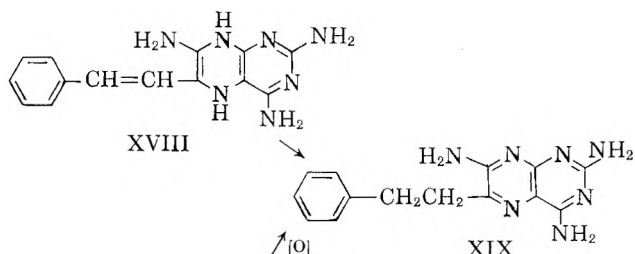


If cinnamaldehyde reacts to produce a 6-phenethylpteridine, phenylpropargylaldehyde might be expected to undergo related reactions to give a 6-styrylpteridine. The intermediate nitrile XXII derived from phenylpropargylaldehyde did indeed cyclize and undergo isomerization to yield the yellow styryl compound (XXIV) when treated with methanolic sodium methoxide. The ultraviolet spectrum of the product in ethanol (Fig. 1) displayed an absorption maximum at 414 mμ, which is in keeping with the assigned structure.

When recrystallization of XXII from boiling methanolic acetic acid was attempted, cyclization to the acetate salt of XXIV occurred. None of the other nitriles,
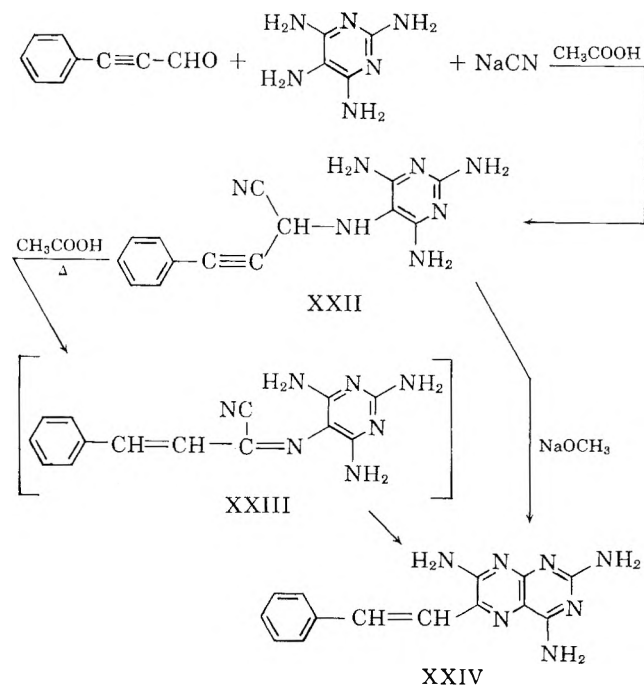
purified in this manner, underwent corresponding reactions. It is postulated that in the case of XXII, heating with acid causes rearrangement to the extended conjugated structure XXIII which then cyclizes readily to XXIV.

It was subsequently found that ten-minute reflux of a mixture of phenylpropargylaldehyde, 2,4,5,6-tetraminopyrimidine hydrochloride, methanolic acetic acid, and aqueous sodium cyanide produced the acetate salt of XXIV in 51% yield.

Further experiments along these lines are in progress and will be reported subsequently.

The ultraviolet maxima of the 2,4,7-triamino-6-substituted pteridines are recorded in Table III.

### TABLE III
### ULTRAVIOLET SPECTRA (AQUEOUS SOLUTIONS)



| R | $\lambda_{max}$, m$\mu$ (log $\epsilon$) | pH |
|---|---|---|
| Methyl | 255 (4.16), 278 (s) (3.65), 342 (4.29) | 1 |
| | 257 (4.16), 350 (4.15) | 13 |
| Isopropyl | 253 (4.18), 278 (s) (3.75), 342 (4.32) | 1 |
| | 258 (4.18), 280 (s) (3.76), 351 (4.18) | 13 |
| Cyclohexenyl | 253 (4.20), 279 (s) (3.76), 344 (4.33) | 1 |
| | 258 (4.21), 282 (s) (3.76), 349 (4.20) | 13 |
| Benzyl | 257 (4.23), 276 (s) (3.89), 344 (4.30) | 1 |
| | 260 (4.24), 282 (s) (3.88), 356 (4.19) | 13 |
| $\beta$-Phenethyl | 241 (4.26), 252 (s) (4.21), 280 (s) (3.76), 342 (4.29) | 1 |
| | 258 (4.20), 281 (s) (4.78), 354 (4.16) | 13 |
| Phenyl | 254 (s) (4.19), 288 (s) (3.85), 358 (4.33) | 1 |
| | 269 (4.13), 368 (4.27) | 13 |
| Styryl | 269 (4.33), 309 (4.22), 397 (4.43) | 1 |
| | 297 (4.30), 409 (4.42) | 13 |

The new compounds were tested for biological effects. The results will be discussed elsewhere at a later date.

### Experimental

The *ultraviolet spectra* of Table III at pH 1 were determined in 4.5% aqueous formic acid. The spectra at pH 13 were determined by taking a 5- to 10-ml. aliquot of compound in 4.5% formic acid and bringing the volume to 100 ml. with 1 *N* aqueous sodium hydroxide.

The *aldehydes* were obtained from commercial sources and were redistilled before use.

**2,4,5,6-Tetraminopyrimidine Hydrochloride.**—A 300-g. sample of 2,4,5,6-tetraminopyrimidine sulfate[16] was dissolved in a boiling mixture of 1500 ml. of water and 400 ml. of concentrated hydrochloric acid. The solution was treated with an equivalent amount of barium chloride in aqueous solution. Toward the end of the addition, the barium chloride was added dropwise until no further barium sulfate separated. The resulting mixture was filtered and concentrated to small volume under reduced pressure. Filtration and drying yield 252 g. of hydrochloride. Chlorine analyses by ionic titration and organic combustion showed that the product was an equal mixture of dihydrochloride and trihydrochloride. This material was used in the experiments described in this paper and yields are calculated based on this composition of the hydrochloride.

**Formation of Aminonitriles.**—The condensations of 2,4,5,6-tetraminopyrimidine hydrochloride and 4,5,6-triamino-2-phenylpyrimidine with aldehydes and hydrogen cyanide generally were carried out in similar fashion. Solvent conditions for proper crystallization of the rather labile reaction products were sometimes of critical importance and varied from case to case. Several reaction procedures are exemplified below and may be used,

together with the data of Table IV, to construct procedures for the other products listed in Table I which are not specifically exemplified in this section.

**2,4,6-Triamino-5-(α-cyanoethylamino)pyrimidine Acetate (Compound 1).**—A suspension of 9 g. of 2,4,5,6-tetraminopyrimidine hydrochloride in 50 ml. of methanol and 20 ml. of acetic acdi was heated to 50° and treated first with a solution of 5 g. of sodium cyanide in 20 ml. of water and then with a solution of 3 g. of acetaldehyde in 10 ml. of methanol. The solids dissolved and the resulting solution warmed spontaneously. Prisms soon began to crystallize. The mixture was allowed to stand at room temperature for 15 min. and then in the refrigerator for 2 hr. Upon filtration, there was obtained 11.6 g. of product.

**2,4,6-Triamino-5-(α-cyanoisobutylamino)pyrimidine Acetate (Compound 2).**—A mixture of 9 g. of 2,4,5,6-tetraminopyrimidine hydrochloride, 25 ml. of acetic acid and 40 ml. of methanol was heated to 50°. There was added 5 g. of sodium cyanide dissolved in 17 ml. of water followed by 5.5 g. of isobutyraldehyde in 10 ml. of methanol. The hot solution was filtered by suction to remove about 1 g. of insoluble solid and the filtrate was allowed to stand at room temperature for 1 hr. and then cooled to −20° overnight. Upon filtration there was obtained 13.4 g. of almost colorless needles.

**2,4,6-Triamino-5-(α-cyanobenzylamino)pyrimidine Hydrochloride. Formation with Gaseous Hydrogen Cyanide.**—A mixture of 5 g. of 2,4,5,6-tetraminopyrimidine monohydrochloride (obtained from the aforedescribed mixed hydrochlorides by treatment with aqueous ammonia), 6 g. of benzaldehyde and 10 ml. of acetic acid was heated until solution was achieved. A 75-ml. portion of hot ethanol was added and the mixture was heated to the boiling point. Heating was discontinued and a stream of hydrogen cyanide gas was passed into the solution for 10 min. The temperature fell to 65° and the product began to crystallize. The flask was stoppered and allowed to stand for 5 hr. Filtration yielded 6.0 g. of pure product, m.p. 197° dec.

The mother liquor was concentrated under reduced pressure and, on standing, yielded an additional 1.1 g. of product for a total yield of 7.1 g. of the hydrochloride. For analysis, a sample was recrystallized from ethanol.

*Anal.* Calcd. for $C_{12}H_{14}ClN_7$: C, 49.40; H, 4.84; N, 33.61. Found: C, 49.22; H, 4.72; N, 33.75.

**4,6-Diamino-5-(α-cyanobenzylamino)-2-phenylpyrimidine (Compound 6).**—A solution of 10 g. of 4,5,6-triamino-2-phenylpyrimidine in 75 ml. of methanol and 25 ml. of acetic acid was treated at room temperature with 5 g. of sodium cyanide in 25 ml. of water and 10 g. of benzaldehyde in 20 ml. of methanol. The solution became warm and within a minute began to deposit large crystals. The mixture was allowed to stand at room temperature overnight and was then filtered. The product was washed well with methanol and dried. It weighed 14.0 g. and melted at 201–203°. The melting point was unchanged upon recrystallization from dimethylformamide and methanol.

**Formation of Pteridines.**—The cyclization of aminonitriles was carried out in each case in methanolic sodium methoxide. The cyclization reaction time varied from 2 min. for compound 7 (Table I) to 20 min. for the difficultly soluble compound 10. Except in the cyclizations of compounds 6 and 11, it was found advantageous to add hydrogen peroxide to produce fully aromatic pteridines in best yield. The following examples are illustrative.

**4,7-Diamino-6-methyl-2-phenylpteridine (XI).**—To a solution of 5.0 g. of sodium methoxide in 80 ml. of methanol was added 5 g. of 4,6-diamino-5-(α-cyanoethylamino)-2-phenylpyrimidine. The mixture was heated under reflux for 10 min. during which time complete solution was obtained. The hot solution was diluted with 80 ml. of water and 10 ml. of 30% hydrogen peroxide. Upon standing, the product crystallized from solution. After 5 hr. at room temperature the mixture was filtered and 2.5 g. of crystals was obtained. Recrystallization from methanol yielded 1.8 g. of pure product, identical with a sample prepared by another procedure.[5]

**2,4,7-Triamino-6-phenylpteridine (I), 2,4,6-Triamino-5-benzylidenaminopyrimidine (XV), and Their Complex (XIV).**—A 5-g. sample of 2,4,6-triamino-5-(α-cyanobenzylamino)pyrimidine acetate and 2.5 g. of sodium methoxide were added to 40 ml. of methanol and the mixture was heated to boiling. The nitrile reacted and dissolved. After 10 min. of boiling, the solution was allowed to stand for 8 hr. There was obtained 3.6 g. of yellow elongated plates. The product, upon recrystallization from methanol yielded 3.0 g. of a complex of I and XV, m.p. 288–292°.

TABLE IV

CONDITIONS FOR AMINONITRILE PREPARATIONS

| Compound | Aldehyde, g. | 2,4,5,6-Tetramino-pyrimidine hydrochloride, g. | Methanol, ml. | Acetic acid, ml. | Sodium cyanide, g. | Water, ml. | Remarks |
|---|---|---|---|---|---|---|---|
| 1 | Acetaldehyde, 3 | 9 | 50 + 10 | 20 | 5 | 20 | b |
| 2 | Isobutyraldehyde, 5.5 | 9 | 40 + 10 | 25 | 5 | 17 | a |
| 3 | 3-Cyclohexene-1-aldehyde, 9.5 | 9 | 40 + 10 | 25 | 5 | 17 | a |
| 4 | Phenylacetaldehyde, 10 | 9 | 75 + 20 | 25 | 5 | 25 | b |
| 5 | $\beta$-Phenylpropionaldehyde, 9.5 | 9 | 40 + 10 | 35 | 5 | 22 | b |
| 6 | Benzaldehyde, 9 | 9 | 75 + 20 | 30 | 5 | 22 | b |
| 7 | Cinnamaldehyde, 10 | 9 | 75 + 20 | 60 | 5 | 25 | a |
| 8 | Phenylpropargylaldehyde, 10 | 9 | 45 + 10 | 45 | 5 | 20 | a |
| | | 4,5,6-Triamino-2-phenylpyrimidine, g. | | | | | |
| 9 | Acetaldehyde, 3 | 10 | 50 + 10 | 23 | 5 | 25 | b |
| 10 | Phenylacetaldehyde, 10 | 8.4 | 75 + 20 | 25 | 5 | 25 | c |
| 11 | Benzaldehyde, 10 | 10 | 75 + 10 | 25 | 5 | 25 | c |

[a] Cooled overnight at $-20°$.  [b] Cooled for 1 to 5 hr. at $7°$.  [c] Crystallized completely at room temperature.

*Anal.* Calcd. for $C_{23}H_{23}N_{13}$: C, 57.36; H, 4.82; N, 37.82. Found: C, 57.08; H, 4.86; N, 38.01.

From the alkaline methanolic filtrate a small quantity of a second yellow compound was obtained. It crystallized from ethanol in long solvated needles which, on drying *in vacuo*, melted at 159–161° and proved to be identical with a sample of 2,4,6-triamino-5-benzylidenaminopyrimidine (XV) prepared from 2,4,5,6-tetraminopyrimidine and benzaldehyde.[18]

*Anal.* Calcd. for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.79; H, 5.29; N, 36.92.

The complex (3 g.) was heated to boiling with 100 ml. of 1.5 N hydrochloric acid for 3 min. The mixture generated a strong odor of benzaldehyde and a pale yellow hydrochloride formed. The mixture was cooled, the hydrochloride collected, and dissolved in 250 ml. of hot water containing a few drops of hydrochloric acid. Addition of ammonia to the hot solution resulted in the crystallization of 1.3 g. of pure I, m.p. 320–322°.

**4,7-Diamino-2,6-diphenylpteridine (XVI)[5] and 4,6-Diamino-5-benzylidenamino-2-phenylpyrimidine (XVII).**—To a solution of 14 g. of sodium methoxide in 400 ml. of methanol was added 14 g. of 4,6-diamino-5-($\alpha$-cyanobenzylamino)-2-phenylpyrimidine. The mixture was boiled and stirred. Within 5 min., complete solution was achieved. Shortly thereafter the product began to crystallize. The mixture was stirred vigorously, concentrated to 150 ml. over a period of 30 min., cooled, and filtered. There was obtained 11.1 g. of yellow-orange solid.

The crude product was finely powdered and boiled, with stirring, with 400 ml. of methanol. It was then filtered and the hot methanolic filtrate was concentrated to yield 5.1 g. of XVII, which after one further crystallization from methanol, gave yellow-orange flat long prisms, m.p. 211–212°. The product was identical with a sample prepared from benzaldehyde and 4,5,6-triamino-2-phenylpyrimidine.

*Anal.* Calcd. for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23. Found: C, 70.54; H, 4.89.

The methanol-insoluble fraction weighed 4.6 g. Upon recrystallization from dimethylformamide there was obtained 2.9 g. of XVI, m.p. over 350°, identical by infrared spectral comparison with a previously prepared sample.[5]

**2,4,7-Triamino-6-$\beta$-phenethylpteridine (XIX). Method A.**—A 9.3-g. sample of finely divided 2,4,6-triamino-5-($\alpha$-cyanocinnamylamino)pyrimidine acetate was added to a solution of 9 g. of sodium methoxide in 200 ml. of methanol. The mixture was stirred and boiled for 2 min. The starting material rapidly dissolved and a yellow solid separated. It was collected, washed with methanol and dried to give 6.3 g. of product. Upon recrystallization from a large volume of ethanol with charcoal treat-

ment, there was obtained 4.55 g. of light yellow plates, m.p. 296–298° dec.

**Method B.**—A 2.5-g. sample of 2,4,6-triamino-5-($\alpha$-cyano-$\gamma$-phenylpropylamino)pyrimidine acetate was added to a solution of 2.5 g. of sodium methoxide in 35 ml. of methanol. The mixture was heated to boiling for 3 min. and was then diluted with 30 ml. of water and 4 ml. of 30% hydrogen peroxide. Within a minute, pale yellow crystals of pteridine began to separate from solution. After 1 hr. the product was collected by filtration, washed with methanol, and dried to give 1.1 g. of XIX, identical by infrared spectral comparison with the product of method A. There was no depression of melting point on admixture of the samples.

**2,4,7-Triamino-6-styrylpteridine (XXIV). Method A.**—To a solution of 6 g. of sodium methoxide in 125 ml. of methanol was added 6 g. of 2,4,6-triamino-5-($\alpha$-cyano-$\gamma$-phenylpropargylamino)pyrimidine. The mixture was boiled for 3 min., cooled, and filtered. A yellow insoluble pteridine was obtained in 2.2 g. yield. It formed large solvated prisms from dimethylformamide. Upon recrystallization from ethanol it melted at 345–347° dec.

**Method B.**—A mixture of 2.5 g. of 2,4,5,6-tetraminopyrimidine hydrochloride, 12 ml. of methanol, and 12 ml. of acetic acid was diluted successively with solutions of 1.5 g. of sodium cyanide in 6 ml. of water and 2.5 g. of phenylpropargylaldehyde in 3 ml. of methanol. The resulting mixture was boiled and stirred for 10 min. An orange solution formed from which a bright yellow solid crystallized. The mixture was cooled to room temperature and filtered. The product was washed with methanol, then thoroughly with water, then with methanol again, and dried. It weighed 1.9 g. and was identical by infrared spectrum with an acetate salt prepared from the product of method A. The acetate of XXIV was dissolved in boiling 5% acetic acid and the solution was filtered to remove traces of insoluble brown material and then diluted with excess aqueous ammonia and boiled for 2 min. The light yellow prisms that crystallized from the hot aqueous solution weighed 1.35 g. and were identical with the product of method A.

# Pteridines. III. Synthesis of Some Ketones, Carbinols, and N-Oxides

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*Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania*

4-Amino-5-nitrosopyrimidines condense with benzoylacetonitrile, phenacylpyridinium bromide, and acetonyl-pyridinium chloride in the presence of sodium cyanide to produce 7-amino-6-pteridyl ketones. Reduction of the products with sodium borohydride yields the corresponding carbinols. 7-Substituted pteridine 5-oxides are produced when 4-amino-5-nitrosopyrimidines condense with the aforementioned pyridinium salts in the presence of potassium acetate. The use of α-cyanobenzylpyridinium salts in related reactions results in the formation of 7-amino-6-phenylpteridine 5-oxides.

Many of the pteridines that produce diuresis in animals can be grouped into classes represented by structures I[2] and II.[3] Previous papers in the present series[4,5] dealt with the synthesis for biological evaluation of 6-alkyl and 6-aralkyl compounds in these classes. In pursuit of further information on the relationship of structure to diuretic activity, we have now undertaken the chemically interrelated syntheses of some 6-ketones, 6-carbinols, and 5-oxides of pteridines of classes I and II.
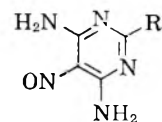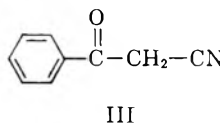


I

II
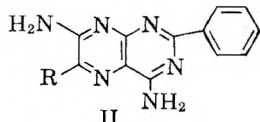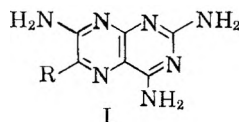
Although alkyl-substituted 6-pteridyl ketones were among the first pteridine derivatives to be reported,[6] they have not received recent attention and 7-amino-6-pteridyl ketones, required in the present investigation, have not been reported.

β-Ketonitriles, such as III, may be expected to condense with 4-amino-5-nitrosopyrimidines (IV) in the presence of alkaline catalysts to form pteridines of type V or VI, depending upon whether the cyclization involves nitrile or ketone. It was found that in ethanol in the presence of sodium methoxide or, preferably, sodium cyanide as the alkaline catalyst, pyrimidines IVa and IVb reacted with III to produce only the 6-pteridyl ketones Va and Vb.[7] The less reactive 2,4,6-triamino-5-nitrosopyrimidine did not condense with III in appreciable yield under the same conditions.
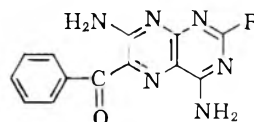
Kröhnke[8] has shown that phenacylpyridinium salts (VIIa) and acetonylpyridinium salts (VIIb) condense with nitrosobenzene derivatives the presence of cyanide to give the same products as do β-ketonitriles.

The pyridinium salts were useful in the present work. Compound VIIa reacted with IVa, IVc, and IVd to produce pteridines Va, Vc, and Vd. In the reaction of VIIa with IVa, compound VIa was isolated as a minor by-product; from none of the other reactions described in this paper was a 6-pteridinecarbonitrile isolated.[7]
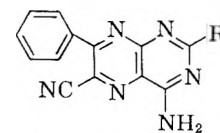


III

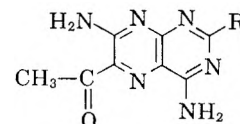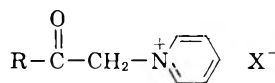IVa, b, c and d



Va, b, c and d           VIa

a. R = phenyl.   b. R = hydrogen.   c. R = methylthio. d. R = methyl.

Compound VIIb reacted readily with IVa, IVb, and IVc, to produce the methyl ketones VIIIa, VIIIb, and VIIIc.
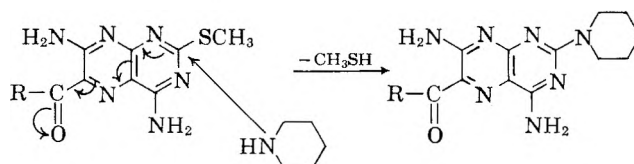


VIIa. R = phenyl        VIIIa. R = phenyl
     X = bromide            b. R = hydrogen
b. R = methyl           c. R = methylthio
     X = chloride

4,6-Diamino-2-piperidino-5-nitrosopyrimidine and 2,4,6-triamino-5-nitrosopyrimidine did not react satisfactorily with either VIIa or VIIb.

It was found possible to replace the 2-methylthio groups of Vc and VIIIc with piperidine under reflux and thus obtained derivatives (Ve and VIIId) with basic groups at positions 2, 4, and 7. In these reactions, the 6-carbonyls serve as activating groups. 4,7-Diamino-6-methyl-2-methylthiopteridine,[4] a related compound in which the activating effect is lacking, fails to react at an appreciable rate under the same conditions.



Vc. R = phenyl           Ve. R = phenyl
VIIIc. R = methyl        VIIId. R = methyl

Pure products were not obtained from the reactions of Vc and VIIIc with ammonia.

Triamino-5-nitrosopyrimidines react well under alkaline conditions only with strongly nucleophilic anions such as those derived from phenylacetonitrile and cyanoacetamide. The reactions generally require elevated temperatures. These nitrosopyrimidines are

(1) Present address: Endo Laboratories, Richmond Hill 18, N. Y.

(2) V. D. Wiebelhaus, J. Weinstock, F. T. Brennan, G. Sosnowsky, and T. J. Larsen, *Fed. Proc.*, **20**, 409 (1961).

(3) (a) E. C. Taylor and J. Weinstock, U. S. Patent 2,963,480 (1960); (b) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).

(4) I. J. Pachter and P. E. Nemeth, Part I, *J. Org. Chem.*, **28**, 1187 (1963).

(5) I. J. Pachter, Part II, *ibid.*, **28**, 1191 (1963).

(6) F. Sachs and G. Meyerheim, *Ber.*, **41**, 3957 (1908).

(7) As we shall describe elsewhere, VIa is the major product when brominated benzoylacetonitrile reacts with 4,5,6-triamino-2-phenylpyrimidine (XX).

(8) F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).

less reactive as a consequence of resonance interactions involving the nitroso and three amino groups.

In an attempt to render the molecules more reactive, they were subjected to acetylation. It was expected that competing interactions of amino and acetyl groups would decrease interactions of amino and nitroso groups and hence serve to activate the latter.

2,4,6-Triamino-5-nitrosopyrimidine reacted with acetic anhydride in acetic acid under mild conditions to produce a blue diacetyl compound. More prolonged reaction at higher temperature gave a green triacetyl derivative. 4,6 - Diamino - 5 - nitroso - 2 - piperidinopyrimidine reacted readily to form a green diacetyl compound.

The nature of the acetylated products is presently not certain. One possible structure for the diacetyl compounds is IX. Another is X[9]; infrared absorption data in the 5.5–6.1-$\mu$ region (Table I) are not inconsistent with ester formulations.
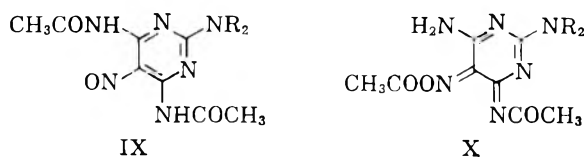


IX

X

TABLE I
INFRARED ABSORPTION MAXIMA (NUJOL)

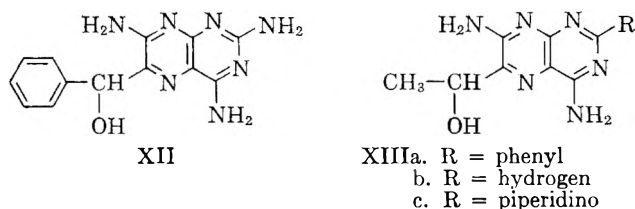| 5-Nitrosopyrimidine | Wavelength, $\mu$ |
|---|---|
| 2,4,6-Triamino- | 5.93, 6.02 (s), 6.05 (s), 6.08 |
| Diacetylated 2,4,6-triamino- | 5.68, 5.84, 5.93 |
| Triacetylated 2,4,6-triamino- | 5.69, 5.79, 5.90 |
| 4,6-Diamino-2-piperidino- | 6.02 (s), 6.08 |
| Diacetylated 4,6-diamino-2-piperidino- | 5.78, 5.85 |

Diacetylated 2,4,6-triamino-5-nitrosopyrimidine reacted rapidly when heated with benzoylacetonitrile (III) in the presence of aqueous ethanolic sodium cyanide to produce a yellow pteridine. The product, a monoacetyl derivative, gave phenyl 2,4,7-triamino-6-pteridyl ketone (Vf) in good yield when treated with cold aqueous sodium hydroxide.



Vf

XI
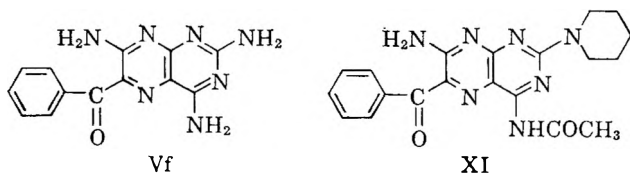
Similarly, diacetylated 4,6-diamino-5-nitroso-2-piperidinopyrimidine produced a pteridine to which structure XI is assigned. Upon brief alkaline hydrolysis the product gave Ve, identical with the compound previously derived from Vc.

Sodium borohydride in methanol reduced the ketones to the corresponding carbinols (XII and XIII). Four carbinols were prepared in this manner.



XII

XIIIa. R = phenyl
b. R = hydrogen
c. R = piperidino

Pteridine syntheses from pyridinium salts are not limited to the preparation of pteridyl ketones. The salt XIV reacted with IVa in the presence of sodium cyanide to produce 4,7-diamino-2-phenyl-6-pteridinecarboxamide (XV).



XIV

XV
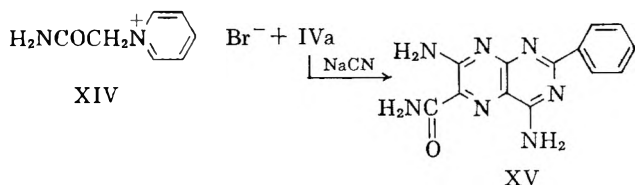
In the syntheses of pteridines from pyridinium salts, hydroxylamines (XVI) and nitrones (XVII)[8] are probable intermediates.



XVI

XVII
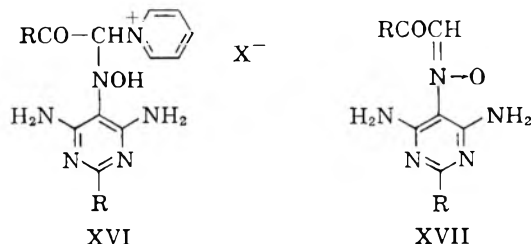
In the absence of cyanide, the nitrones might be expected to cyclize to the corresponding pteridine 5-oxides. Authentic pteridine N-oxides have thus far not been reported in the literature.

When VIIa and VIIb were condensed with IVa in the presence of potassium acetate in place of sodium cyanide, the N-oxides XVIIIa and XVIIIb were produced. Compound VIIb reacted with IVb in similar fashion to produce XVIIIc.

Upon hydrogenation of XVIIIa and XVIIIb with Raney nickel as catalyst, the pteridines XIXa and XIXb were produced. These were identical with the products derived from the reactions of phenylglyoxal and methylglyoxal with 4,5,6-triamino-2-phenylpyrimidine (XX). More prolonged hydrogenation of the N-oxides XVIIIb and XVIIIc or the pteridine XIXb yielded the 5,6,7,8-tetrahydro compounds XXIb and



XVIIIa, b, and c

XIXa, and b

RCOCHO +

XX

XXIb and c
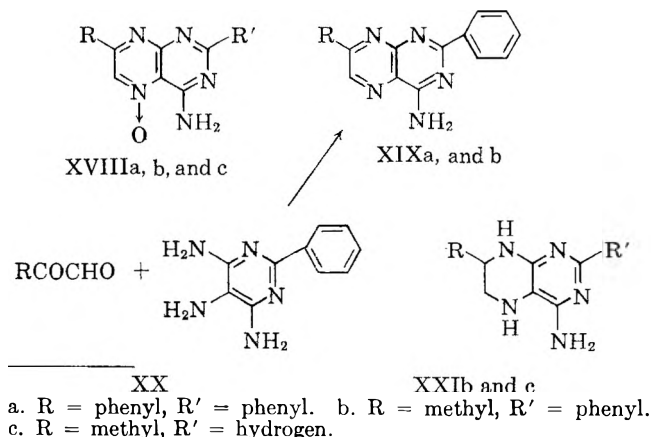
a. R = phenyl, R' = phenyl. b. R = methyl, R' = phenyl.
c. R = methyl, R' = hydrogen.

(9) E. C. Taylor, C. W. Jefford, and C. C. Cheng, J. Am. Chem. Soc., 83, 1261 (1961), reported that 4,6-diamino-2-dimethylamino-5-nitrosopyrimidine and related molecules underwent rearrangement to substituted 4-cyano-s-triazines when heated under reflux with acetic anhydride. They suggested that oximino esters related to X are intermediates in the process.

XXIc. Compound XIXa was resistant to further hydrogenation under the same conditions.

α-Cyanobenzyl benzenesulfonate (XXII), derived from benzaldehyde, benzenesulfonyl chloride and sodium cyanide,[10] was converted into the pyridinium compound XXIII. Without purification, the latter was treated with nitrosopyrimidines IVa and IVd in the presence of alkali to produce the N-oxides XXVa and XXVb in good yield.



XXVa and b        XXIVa and b
a. R = phenyl.   b. R = methylthio.
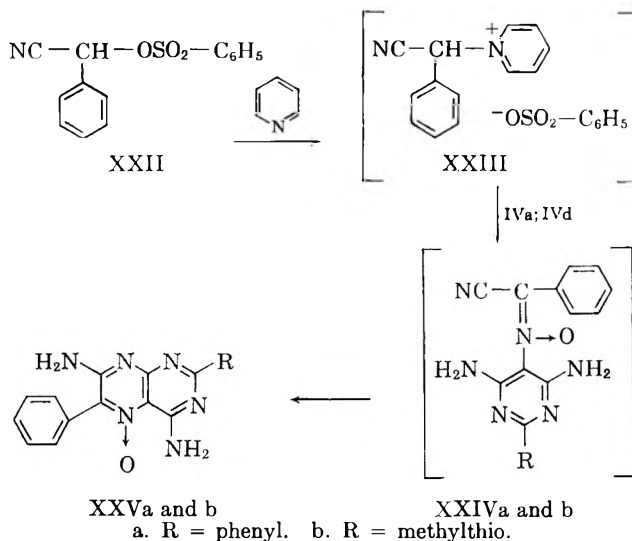
In the preparation of XXVa and XXVb, sodium cyanide was found to be a most effective alkaline catalyst. Apparently, intermediates of type XXIV cyclize to N-oxides rapidly and show little, if any, tendency to add cyanide and lose cyanate.[4]

Compound XXVb did not react at an appreciable rate with refluxing piperidine. This is not surprising, for the net effect of an oxide at N-5 on nucleophilic displacement should be marked activation of C-6 but only limited activation of C-2, C-4, and C-7.[11]
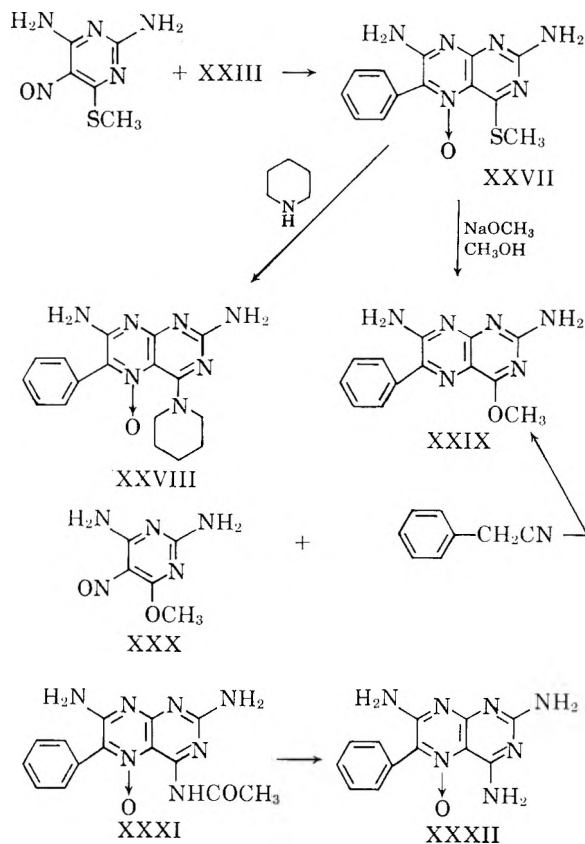
2,6 - Diamino - 4 - methylthio - 5 - nitrosopyrimidine (XXVI) reacted with XXIII to produce 2,7-diamino-4-methylthio-6-phenylpteridine 5-oxide (XXVII). 4-Methylthio groups undergo displacement more readily than the 2-isomers; compound XXVII was converted into XXVIII with piperidine at reflux. When XXVII was boiled with sodium methoxide in methanol, displacement accompanied by N-oxide reduction occurred. Compound XXIX was produced. It was identical with the product of the reaction[12] of 2,4-diamino-6-methylthio-5-nitrosopyrimidine (XXX) with phenylacetonitrile. Methoxide in methanol is not a general reducing agent, for neither XVIIIa nor XXXII (vide infra) was altered under conditions which produced XXIX.

2,4,6-Triamino-5-nitrospyrimidine reacted with difficulty with XXIII just as it had with III, VIIa, and VIIb. Its blue diacetyl derivative reacted readily, however, and an acetylated pteridine was produced. This derivative underwent deacetylation upon treatment with alkali, or even upon brief boiling with methanol, to produce 2,4,7-triamino-6-phenylpteridine 5-oxide (XXXII). The very facile loss of the acetyl group suggests that the initial product had structure

(10) R. M. Dodson and H. W. Turner, J. Am. Chem. Soc., 73, 4517 (1951).

(11) I. J. Pachter and M. C. Kloetzel, ibid., 74, 971 (1952).

(12) This reaction was carried out by Dr. Blaine Sutton and Miss Alice Sheppard of these laboratories.



XXXI and that the oxide function participated in the solvolysis.

The ultraviolet absorption maxima of selected pteridines prepared during the course of this work are listed in Table II.

Several of the compounds produced potent diuretic effects in experimental animals. The biological data will be reported elsewhere at a later date.

## Experimental

The *ultraviolet spectra* of Table II at pH 1 were determined in 4.5% aqueous formic acid. The spectra at pH 13 were determined by taking a 5- to 10-ml. aliquot of compound in 4.5% formic acid and bringing the volume to 100 ml. with 1 N aqueous sodium hydroxide. In those cases where the compound crystallized from alkaline solution, no values at pH 13 are recorded.

For analyses, the pteridines were dried *in vacuo* at 150°.

Phenyl 4,7-Diamino-2-phenyl-6-pteridyl Ketone (Va).—To a mixture of 12.5 g. (0.058 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 12.5 g. (0.086 mole) of benzoylacetonitrile and 150 ml. of ethanol was added a solution of 9.0 g. of sodium cyanide in 50 ml. of water. The resulting mixture was heated under reflux with stirring for 1.5 hr. and then cooled. The yellow crystalline product (16.1 g.) was collected. Upon recrystallization from dimethylformamide and then from dioxane it melted at 327–328° dec.

*Anal.* Calcd. for $C_{19}H_{14}N_6O$: C, 66.66; H, 4.12; N, 24.54. Found: C, 66.63; H, 4.20; N, 24.84.

Va and 4-Amino-2,7-diphenyl-6-pteridinecarbonitrile (VIa).— To 1.4 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine (IVa) in in 15 ml. of ethanol was added 1.4 g. of phenacylpyridinium bromide in 15 ml. of 50% ethanol and 0.5 g. of sodium cyanide in 2 ml. of water. The mixture was boiled for 15 min., cooled, and filtered to yield 1.2 g. of Va, identical with the product of the reaction of III and IVa.

The aqueous alcoholic filtrate was concentrated by boiling on a steam bath for 30 min. On cooling there was obtained 0.3 g. of a second compound (VIa), identical with a sample[7] to be described in a subsequent publication.

Phenyl 4,7-Diamino-6-pteridyl Ketone (Vb).—To a mixture of 7.0 g. (0.05 mole) of 4,6-diamino-5-nitrosopyrimidine, 10.15 g.

TABLE II

ULTRAVIOLET SPECTRA

| Compound | $\lambda_{max}$ m$\mu$ (log $\epsilon$) | pH |
|---|---|---|
| Vb | 280 (4.39), 386 (4.05) | 1 |
| | 256 (s) (4.26), 280 (4.11), 358 (3.89), 389 (3.90) | 13 |
| Vd | 279 (4.36), 384 (4.08) | 1 |
| | 252 (s) (4.23), 283 (4.18), 393 (4.06) | 13 |
| Ve | 287 (4.26), 394 (4.45) | 1 |
| Vf | 280 (4.30), 386 (4.27) | 1 |
| | 247 (4.48), 290 (4.19), 402 (4.39) | 13 |
| VIIIa | 277 (4.53), 394 (4.22) | 1 |
| VIIIb | 275 (4.46), 382 (4.07) | 1 |
| | 248 (4.21), 272 (s) (4.05) | 13 |
| VIIIc | 277 (4.46), 391 (4.33) | 1 |
| | 250 (4.47), 382 (4.27), 397 (4.30) | 13 |
| VIIId | 278 (4.24), 387 (4.45) | 1 |
| | 247 (4.58), 292 (4.21), 409 (4.52) | 13 |
| XII | 256 (4.22), 281 (s) (3.77), 345 (4.32) | 1 |
| | 260 (4.20), 284 (s) (3.74), 356 (4.21) | 13 |
| XIIIa | 258 (4.42), 354 (4.31) | 1 |
| | 246 (4.54), 350 (4.23) | 13 |
| XIIIb | 252 (4.18), 285 (3.60), 344 (4.16) | 1 |
| | 240 (4.33), 262 (s) (4.04), 338 (4.05) | 13 |
| XIIIc | 262 (4.18), 350 (4.37), 365 (s) (4.31) | 1 |
| | 267 (4.34), 293 (s) (3.97), 371 (4.20) | 13 |
| XVIIIa | 276 (4.41), 292 (s) (4.32), 330 (4.09), 368 (s) (4.21), 382 (4.27) | 1 |
| XVIIIb | 282 (4.38), 313 (4.15), 342 (4.01), 358 (3.99) | 1 |
| XVIIIc | 284 (3.81), 340 (3.95), 354 (3.97) | 1 |
| | 254 (4.10), 285 (3.88), 354 (3.84) | 13 |
| XIXa | 254 (4.33), 278 (s) (4.22), 312 (4.01), 361 (4.35), 373 (4.35) | 1 |
| XIXb | 271 (4.25), 301 (4.15), 320 (4.15), 333 (4.16), 346 (s) (4.08) | 1 |
| | 269 (4.41), 342 (3.97) | 13 |
| XXVa | 258 (4.50), 366 (4.28) | 1 |
| XXVb | 269 (4.40), 309 (3.76), 365 (4.27) | 1 |
| | 245 (4.46), 277 (4.38), 370 (4.18) | 13 |
| XXVIII | 252 (4.21), 380 (4.18) | 1 |
| | 244 (s) (4.35), 277 (4.19), 391 (4.10) | 13 |
| XXIX | 286 (3.85), 354 (4.40) | 1 |
| | 274 (3.99), 362 (4.33) | 13 |
| XXXII | 246 (4.42), 296 (3.70), 362 (4.25) | 1 |
| | 240 (4.61), 267 (4.39), 374 (4.20) | 13 |

(0.07 mole) of benzoylacetonitrile, and 250 ml. of ethanol was added a solution of 3.5 g. of sodium cyanide in 20 ml. of water. The resulting mixture was heated under reflux for 1 hr., concentrated, and cooled. There was obtained 7.90 g. of yellow plates. Upon recrystallization from ethanol the product melted at 291–293°.

*Anal.* Calcd. for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.79; N, 31.56. Found: C, 58.66; H, 3.81; N, 31.53.

**Phenyl 4,7-Diamino-2-methylthio-6-pteridyl Ketone (Vc).**—To 5.49 g. of 4,6-diamino-2-methylthio-5-nitrosopyrimidine and 10.7 g. of phenacylpyridinium bromide in 100 ml. of 80% ethanol was added a solution of 5.0 g. of sodium cyanide in 20 ml. of water. The mixture was heated under reflux for 20 min., cooled, and filtered. The yellow product was washed copiously with water[13] and dried to give 7.9 g. of crude Vc. Upon two recrystallizations from dimethylformamide there was obtained 4.5 g. of Vc, m.p. 335° dec.

*Anal.* Calcd. for $C_{14}H_{12}N_6OS$: C, 53.83; H, 3.87; N, 26.91. Found: C, 53.54; H, 3.93; N, 27.40.

**Phenyl 4,7-Diamino-2-methyl-6-pteridyl Ketone (Vd).**—This compound was prepared from 4,6-diamino-2-methyl-5-nitroso-pyrimidine (1.0 g.) and phenacylpyridinium bromide (2.0 g.) by a procedure similar to that used for the synthesis of Vc. There

(13) Failure to remove traces of sodium cyanide results in the formation of dark red impurities upon subsequent recrystallization from dimethylformamide.

was obtained 1.1 g. of yellow product from dimethylformamide, m.p. 307° dec.

*Anal.* Calcd. for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 59.87; H, 4.24; N, 29.85.

**Methyl 4,7-Diamino-2-phenyl-6-pteridyl Ketone (VIIIa).**—To 21.5 g. (0.1 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 20.6 g. (0.12 mole) of acetonylpyridinium chloride and 200 ml. of ethanol was added 7.5 g. (0.15 mole) of sodium cyanide in 50 ml. of water. The resulting mixture was heated under reflux with stirring until the green color of the nitrosopyrimidine was no longer apparent (80 min.). The mixture was cooled, filtered, and the product was washed thoroughly with hot water,[13] and dried. There was obtained 26.6 g. of yellow VIIIa.

For analysis, a sample was recrystallized from dimethylformamide and then from aqueous acetic acid. It then melted at 306–310° dec.

*Anal.* Calcd. for $C_{14}H_{12}N_6O$: C, 59.99; H, 4.32; N, 29.99. Found: C, 60.10; H, 4.23; N, 29.81.

**Phenylhydrazone of VIIIa.**—A solution of 0.7 g. of VIIIa, 1.0 g. of phenylhydrazine and 75 ml. of acetic acid was heated under reflux for 10 min. It was diluted with 50 ml. of water and cooled. The product was collected and washed with ethanol. The resulting 0.65 g. of yellow solid was recrystallized first from acetic acid and then from ethanol to give beautiful yellow needles, m.p. 306–308°.

*Anal.* Calcd. for $C_{20}H_{18}N_8$: C, 64.85; H, 4.90; N, 30.25. Found: C, 64.48; H, 4.73; N, 30.21.

**Methyl 4,7-Diamino-6-pteridyl Ketone (VIIIb).**—To a boiling mixture of 1.4 g. of 4,6-diamino-5-nitrosopyrimidine, 2.5 g. of acetonylpyridinium chloride and 100 ml. of ethanol was added a solution of 0.75 g. of sodium cyanide in 10 ml. of water. The mixture was stirred under reflux for 30 min., cooled, and filtered. The product (1.6 g.) was dissolved in water containing a few milliliters of acetic acid, treated with charcoal, and precipitated with ammonia. The 1.5 g. of long yellow needles thus obtained melted over 340°.

*Anal.* Calcd. for $C_8H_8N_6O$: C, 47.06; H, 3.95; H, 41.16. Found: C, 47.10; H, 4.09; N, 41.35.

**Methyl 4,7-Diamino-2-methylthio-6-pteridyl Ketone (VIIIc).**—A mixture of 6.0 g. of finely powdered 4,6-diamino-2-methylthio-5-nitrosopyrimidine, 5.0 g. of sodium cyanide, 7.5 g. of acetonyl-pyridinium chloride and 200 ml. of 80% ethanol was heated under reflux for 1.5 hr. The yellow product that formed was filtered, washed well with water,[13] and dried. It weighed 6.1 g. It became light orange in color upon recrystallization from dimethyl-formamide. It became black when heated over 280°.

*Anal.* Calcd. for $C_9H_{10}N_6OS$: C, 43.19; H, 4.03; N, 33.58. Found: C, 43.37; H, 4.03; N, 33.87.

**Phenyl 4,7-Diamino-2-piperidino-6-pteridyl Ketone (Ve).**—A mixture of 5.0 g. of phenyl 4,7-diamino-2-methylthio-6-pteridyl ketone (Vc) and 150 ml. of piperidine was heated under reflux for 26 hr. It was then evaporated to dryness under reduced pressure. The residue was washed with ethanol and dried to give 4.2 g. of yellow product. For analysis a sample was recrystallized from methanol. It melted at 300–301° dec.

*Anal.* Calcd. for $C_{18}H_{19}N_7O$: C, 61.88; H, 5.48; N, 28.06. Found: C, 61.91; H, 5.40; N, 28.31.

**Methyl 4,7-Diamino-2-piperidino-6-pteridyl Ketone (VIIId).**—A 1.0-g. sample of methyl 4,7-diamino-2-methylthio-6-pteridyl ketone (VIIIc) and 50 ml. of piperidine was heated under reflux for 24 hr. Excess piperidine was removed under reduced pressure and the product was recrystallized from ethanol with the aid of charcoal to obtain 0.76 g. of orange needles, m.p. 293–298° dec.

*Anal.* Calcd. for $C_{13}H_{17}N_7O$: C, 54.34; H, 5.96; N, 34.13. Found: C, 54.66; H, 6.07; N, 34.44.

**Diacetylated 2,4,6-Triamino-5-nitrosopyrimidine.**—A mixture of 10 g. of 2,4,6-triamino-5-nitrosopyrimidine, 50 ml. of acetic anhydride and 100 ml. of acetic acid was heated on a hot plate slowly with stirring. The starting material dissolved, the solution turned blue, and the blue compound began to crystallize from solution. The mixture was then quickly cooled in an ice bath to prevent further acetylation. The product was filtered, washed with ethanol, and dried. It weighed 13 g. and melted at 199–200° dec.

*Anal.* Calcd. for $C_8H_{10}N_6O_3$: C, 40.33; H, 4.23; N, 35.28. Found: C, 40.59; H, 4.56; N, 35.38.

**Triacetylated 2,4,6-Triamino-5-nitrosopyrimidine.**—A mixture of 5.0 g. of 2,4,6-triamino-5-nitrosopyrimidine, 50 ml. of acetic anhydride and 150 ml. of acetic acid was boiled gently with stir-

ring for 10 min. until the color of the solution turned from blue to green. The solution was cooled to 0° and scratched. There was obtained 4.2 g. of light green crystals. Upon concentration of the filtrate under reduced pressure, an additional 2.2 g. of green product was obtained. The compound was recrystallized from ethanol to give green needles, m.p. 214° dec.

*Anal.* Calcd. for $C_{10}H_{12}N_6O_4$: C, 42.86; H, 4.32; N, 29.99. Found: C, 42.71; H, 4.46; N, 30.10.

**Diacetylated 4,6-Diamino-5-nitroso-2-piperidinopyrimidine.**—A 2.0-g. sample of 4,6-diamino-5-nitroso-2-piperidinopyrimidine was heated at 50° with a mixture of 8 ml. of acetic anhydride and 16 ml. of acetic acid for 15 min. Three milliliters of water was added. The mixture was cooled in an ice bath for 1 hr. and filtered to yield 2.55 g. of green needles, m.p. upon recrystallization from ethanol, 185–186°.

*Anal.* Calcd. for $C_{13}H_{18}N_6O_3$: C, 50.97; H, 5.92; N, 27.44. Found: C, 51.45; H, 5.99; N, 27.48.

**Phenyl 2,4,7-Triamino-6-pteridyl Ketone (Vf).**—A mixture of 20 g. of benzoylacetonitrile and 24 g. of diacetylated 2,4,6-triamino-5-nitrosopyrimidine in 350 ml. of absolute ethanol was brought to boiling and 14 g. of potassium acetate in 150 ml. of absolute ethanol was added. The mixture was stirred under reflux until no blue starting material was visible (30 min.). It was cooled and filtered. A small sample of the yellow product thus obtained was washed with water, recrystallized once from ethanol, and analyzed. The analytical results, although disagreeing by 0.7, 0.2 and 0.8% with the theoretical values for carbon, hydrogen and nitrogen, respectively, indicated that the product was predominantly a monoacetyl derivative. The remainder of the yellow granular compound was stirred at room temperature with 350 ml. of 1.5% sodium hydroxide for 2 hr., during which time it dissolved and a new product crystallized from solution. The new product (Vf) was dissolved in hot dilute acetic acid, treated with charcoal and then with excess ammonia. There was obtained 19.6 g. of Vf. For analysis, a sample was dissolved once again in dilute acetic acid and reprecipitated with ammonia. It melted at 338–339° dec.

*Anal.* Calcd. for $C_{13}H_{11}N_7O$: C, 55.51; H, 3.94; N, 34.86. Found: C, 55.75; H, 4.09; N, 34.95.

**Phenyl 4,7-Diamino-2-piperidino-6-pteridyl Ketone (Ve) from Diacetylated 4,6-Diamino-5-nitroso-2-piperidinopyrimidine.**—A mixture of 1.02 g. of diacetylated 4,6-diamino-5-nitroso-2-piperidinopyrimidine and 1.0 g. of benzoylacetonitrile was heated under reflux with 25 ml. of absolute ethanol for 5 min. It was then treated with 0.6 g. of potassium acetate in 5 ml. of absolute ethanol. Heating under reflux was continued (about 10 min.) until the color of the mixture turned from blue-green to bright yellow. The mixture was then cooled to 20° and a solution of 0.5 g. of sodium hydroxide in 5 ml. of water was added. The yellow compound dissolved and glittering yellow plates separated. The mixture was allowed to stand at room temperature for 30 min. and the product was collected, washed with water until the washings were neutral, and dried to yield 1.1 g. of Ve, m.p. 300–302° dec., identical with the product prepared from Vc and piperidine.

**4,7-Diamino-2-phenyl-6-pteridinecarboxamide (XV).**—A mixture of 0.9 g. of the pyridinium salt of bromoacetamide, 0.3 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 0.1 g. of sodium cyanide dissolved in 4 ml. of water, and 12 ml. of ethanol was heated on a steam bath. Reaction proceeded to completion in less than a minute. There was obtained 0.35 g. of yellow crystals, identical with a sample of XV prepared from cyanoacetamide.[2]

**α-Phenyl-2,4,7-triamino-6-pteridylcarbinol (XII).**—A 9.0-g. sample of phenyl 2,4,7-triamino-6-pteridyl ketone (Vf) was boiled with 500 ml. of methanol for 10 min. and cooled to 50°. Over a 15-min. period, 6 g. of sodium borohydride in 100 ml. of methanol was added. The reaction temperature was kept between 50 and 55°. The mixture was filtered to remove 0.8 g. of insoluble material, neutralized with acetic acid, and evaporated to dryness under reduced pressure. The residue was thoroughly washed with water and dried to give 7 g. of crude product. A test showed that a small quantity of phenolic pteridine was present. The product was dissolved in dilute acetic acid and then made quickly alkaline with 5% sodium hydroxide. The finely divided precipitate that separated was stirred for 30 min. at room temperature with two 100-ml. portions of 1% sodium hydroxide. It was then recrystallized from dimethylformamide and finally dissolved in hot dilute acetic acid and reprecipitated

from the hot solution with ammonia. There was obtained 3.1 g. of yellow prisms which turn black at about 275°.

*Anal.* Calcd. for $C_{13}H_{13}N_7O$: C, 55.12; H, 4.63; N, 34.61. Found: C, 55.16; H, 4.75; N, 34.75.

**1-(4,7-Diamino-2-phenyl-6-pteridyl)ethanol (XIIIa).**—A mixture of 5.0 g. of methyl 4,7-diamino-2-phenyl-6-pteridyl ketone (VIIIa) and 150 ml. of methanol was treated with a solution of 5.0 g. of sodium borohydride in 50 ml. of methanol at such a rate that the reaction temperature did not exceed 50°. After 25 min., the solution was clarified by filtration, neutralized with acetic acid, and evaporated to dryness under reduced pressure. The residue was thoroughly washed with water and dried to give 4.5 g. of pale yellow plates. After recrystallization from methanol, the m.p. was 274–276° dec.

*Anal.* Calcd. for $C_{14}H_{14}N_6O$: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.58; H, 4.92; N, 29.69.

**1-(4,7-Diamino-6-pteridyl)ethanol (XIIIb).**—By a procedure similar to that used for the preparation of XIIIa, 1.0 g. of methyl 4,7-diamino-6-pteridyl ketone (VIIIb) was converted into 0.8 g. of XIIIb. The product formed off-white needles from methanol, m.p. 248–250° dec.

*Anal.* Calcd. for $C_8H_{10}N_6O$: C, 46.60; H, 4.89; N, 40.76. Found: C, 46.67; H, 5.20; N, 40.74.

**1-(4,7-Diamino-2-piperidino-6-pteridyl)ethanol (XIIIc).**—By a procedure similar to that used for the preparation of XIIIa, 4.0 g. of methyl 4,7-diamino-2-piperidino-6-pteridyl ketone (VIIId) was converted into 3.5 g. of XIIIc. The yellow product, m.p. 226–227°, was recrystallized for analysis from methanol.

*Anal.* Calcd. for $C_{13}H_{19}N_7O$: C, 53.96; H, 6.62; N, 33.89. Found: C, 53.99; H, 6.81; N, 33.54.

**4-Amino-2,7-diphenylpteridine 5-Oxide (XVIIIa).**—To a hot solution of 2.15 g. (0.01 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine and 1.96 g. (0.02 mole) of potassium acetate in 250 ml. of ethanol was added 3.98 g. (0.014 mole) of phenacylpyridinium bromide in 20 ml. of water. The resulting mixture was boiled for 1 hr., cooled, and filtered. The yellow product was recrystallized from dimethylformamide to give 2.3 g. of needles, m.p. 258–260°.

*Anal.* Calcd. for $C_{18}H_3N_5O$: C, 68.56; H, 4.16; N, 22.11. Found: C, 68.45; H, 4.22; N, 22.13.

**Reduction of 4-Amino-2,7-diphenylpteridine 5-Oxide (XVIIIa). Synthesis of XIXa.**—A mixture of 1.0 g. of XVIIIa, 200 ml. of ethanol, and a half teaspoonful of Raney nickel was shaken with hydrogen at 50 p.s.i. for 10 hr. The nickel was removed and the solution concentrated to give 0.8 g. of needles of XIXa, m.p., 252–253°, identical with a sample prepared from phenylglyoxal and 4,5,6-triamino-2-phenylpyrimidine.

*Anal.* Calcd. for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 71.94; H, 4.66; N, 23.86.

**4-Amino-2,7-diphenylpteridine (XIXa).**—To 6.0 g. (0.03 mole) of 4,5,6-triamino-2-phenylpyrimidine in 100 ml. of ethanol was added 6.16 g. (0.04 mole) of phenylgyoxal hydrate in 20 ml. of ethanol, and 3.92 g. (0.04 mole) of potassium acetate and 4.6 ml. (0.08 mole) of acetic acid in 10 ml. of water. The mixture was heated on a steam bath for 30 min., cooled, and filtered. The yellow product thus obtained weighed 8.6 g. It was recrystallized from dimethylformamide to give 7.1 g. of prisms, m.p. 252–253°.

**4-Amino-7-methyl-2-phenylpteridine 5-Oxide (XVIIIb).**—To a boiling mixture of 21.5 g. of 4,6-diamino-5-nitroso-2-phenylpyrimidine, 20.0 g. of potassium acetate and 1 l. of ethanol was added a solution of 25.6 g. of acetonylpyridinium chloride in 100 ml. of water. The resulting mixture was boiled for 1 hr. during which time the green nitroso compound disappeared and a golden yellow product (22.7 g.) separated. It was recrystallized from dimethylformamide to give 19.0 g. of well formed crystals, m.p. 287° dec.

*Anal.* Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.43; H, 4.72; N, 27.61.

**Reduction of 4-Amino-7-methyl-2-phenylpteridine 5-Oxide (XVIIIb). Synthesis of XIXb and XXIb.**—A mixture of 2.0 g. of 4-amino-7-methyl-2-phenylpteridine 5-oxide (XVIIIb), one-half teaspoonful of Raney nickel, and 200 ml. of ethanol was shaken under 50 p.s.i. of hydrogen for 30 min. The nickel was removed and the solution was evaporated to dryness. Upon treatment of the residue with dilute acetic acid, all but 150 mg. of yellow needles dissolved. The needles, upon recrystallization from ethanol, melted at 269–270° and proved to be identical with a sample of XIXb prepared from methylglyoxal and 4,5,6-triamino-2-phenylpyrimidine.

The yellow acetic acid solution was made basic with ammonia and a colorless solid (1.4 g.) separated. Upon recrystallization from methanol, colorless prisms of XXIb, m.p. 174–176°, were obtained.

When 1.8 g. of XVIIIb was similarly hydrogenated for 1.5 hr., 1.6 g. of XXIb was obtained as the only product.

*Anal.* Calcd. for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.03. Found: C, 64.77; H, 6.33; N, 29.28.

**4-Amino-7-methyl-2-phenylpteridine (XIXb).**—To a solution of 30.2 g. of 4,5,6-triamino-2-phenylpyrimidine, 72 g. of 30% methylglyoxal in water and 500 ml. of ethanol was added a solution of 29.4 g. of potassium acetate and 34 ml. of acetic acid in 100 ml. of water. Upon heating on a steam bath, yellow crystals rapidly formed. After 30 min. the mixture was cooled and filtered to yield 31.7 g. of XIXb. The product was dissolved in dilute hydrochloric acid, treated with charcoal, and then precipitated with 10% sodium hydroxide. Upon recrystallization from dimethylformamide there was obtained 18.7 g. of pale yellow needles, m.p. 269–271 dec.

*Anal.* Calcd. for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 66.04; H, 4.81; N, 29.67.

**Reduction of XIXb.**—Hydrogenation of 18.6 g. of XIXb with Raney nickel in 500 ml. of ethanol under 50-p.s.i. pressure yielded 16.7 g. of crude XXIb which, upon recrystallization from methanol, gave 13.0 g. of prisms, m.p. 174–176°.

**4-Amino-7-methylpteridine 5-Oxide (XVIIIc).**—A mixture of 1.39 g. (0.01 mole) of 4,6-diamino-5-nitrosopyrimidine, 1.96 g. (0.02 mole) of potassium acetate, and 250 ml. of ethanol was heated to boiling and diluted with 2.56 g. (0.015 mole) of acetonylpyridinium chloride in 20 ml. of water. The resulting mixture was boiled for 1.5 hr. Upon concentration and cooling there was obtained 2.0 g. of crude product which, upon recrystallization from ethanol with the aid of charcoal, yielded 1.0 g. of yellow prisms, m.p. 250–251.

*Anal.* Calcd. for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53. Found: C, 47.72; H, 4.25; N, 39.86.

**Reduction of 4-Amino-7-methylpteridine 5-Oxide (XVIIIc). Synthesis of XXIc.**—A 3.4-g. sample of XVIIIc was hydrogenated in 200 ml. of ethanol at 50 p.s.i. for 8 hr. with 1 teaspoonful of Raney nickel as catalyst. Removal of the catalyst and evaporation of the solvent left a noncrystalline residue which was converted to a solid hydrochloride with ethereal hydrogen chloride. Recrystallization of the product from methanol gave 1.5 g. of pale yellow prisms of the dihydrochloride of XXIc, m.p. 243–245° dec.

*Anal.* Calcd. for $C_7H_{13}Cl_2N_5$: C, 35.31; H, 5.50; N, 29.41. Found: C, 35.85; H, 5.63; N, 29.00.

**4,7-Diamino-2,6-diphenylpteridine 5-oxide (XXVa).**—To 4.3 g. (0.02 mole) of 4,6-diamino-5-nitroso-2-phenylpyrimidine in 250 ml. of acetone was added a solution of 7.4 g. (0.027 mole) of α-cyanobenzyl benzenesulfonate, 8 ml. of pyridine and 15 ml. of acetone which had been boiled previously for 5 min. To the resulting green solution was added 2.0 g. (0.04 mole) of sodium cyanide in 20 ml. of water. A deep red color developed instantly. The solution was heated to 40° for 5 min. and then allowed to stand at room temperature for 1 hr. The solid was collected, washed with water and ethanol and dried to give 6.5 g. of crude product. Recrystallization from dimethylformamide yielded 5.6 g. of fine pale yellow needles, m.p. over 350°.

*Anal.* Calcd. for $C_{18}H_{14}N_6O$: C, 65.44; H, 4.27; N, 25.44. Found: C, 65.21; H, 4.28; N, 25.73.

**4,7-Diamino-2-methylthio-6-phenylpteridine 5-Oxide (XXVb).**—A 3.7-g. (0.02 mole) sample of finely powdered 4,6-diamino-2-methylthio-5-nitrosopyrimidine was converted into XXVb by a procedure similar to that used for the preparation of XXVa. There was obtained 4.6 g. of product which was recrystallized from dimethylformamide to give 3.8 g. of pale yellow needles, m.p. 351° dec.

*Anal.* Calcd. for $C_{13}H_{12}N_6OS$: C, 51.99; H, 4.03; N, 27.98. Found: C, 51.91; H, 4.03; N, 28.26.

**2,7-Diamino-4-methylthio-6-phenylpteridine 5-Oxide (XXVII).**—The procedure used for the preparation of XXVa was modified to accommodate the lack of solubility of 2,6-diamino-4-methylthio-5-nitrosopyrimidine in pure acetone. A 3.7-g. (0.02 mole) sample of the nitrosopyrimidine was dissolved in 40 ml. of dimethyl sulfoxide. The resulting blue solution was diluted in rapid succession with 250 ml. of boiling acetone, with a solution of 8.0 g. of α-cyanobenzyl benzenesulfonate, 8 ml. of pyridine, and

15 ml. of acetone which had been boiled previously for 5 min., and finally with a solution of 2.0 g. of sodium cyanide in 20 ml. of water. Yellow prisms soon separated from the intensely colored solution. After 2 hr. the product was collected, washed with water and ethanol, and dried. The 3.5 g. of yellow compound thus obtained was dissolved in 50 ml. of dimethylformamide. Upon dilution with an equal volume of methanol, the solution deposited 2.8 g. of analytically pure prisms of XXVII, m.p. 306–308° dec.

*Anal.* Calcd. for $C_{13}H_{12}N_6OS$: C, 51.99; H, 4.03; N, 27.98. Found: C, 52.06; H, 4.24; N, 27.97.

**2,7-Diamino-6-phenyl-4-piperidinopteridine 5-Oxide (XXVIII).**—A 2.45 g. sample of 2,7-diamino-4-methylthio-6-phenylpteridine 5-oxide (XXVII) was heated under reflux for 16 hr. with 100 ml. of piperidine. Removal of excess piperidine and recrystallization of the residual product from ethanol gave 1.8 g. of yellow needles of XXVIII, m.p. 265° dec.

*Anal.* Calcd. for $C_{17}H_{19}N_7O$: C, 60.52; H, 5.68; N, 29.06. Found: C, 60.69; H, 5.56; N, 29.09.

**Reaction of XXVII with Methanolic Sodium Methoxide. Synthesis of XXIX.**—A 1.0-g. sample of XXVII was heated under reflux for 7.5 hr. with 1.0 g. of sodium methoxide in 150 ml. of methanol. The resulting clear solution was allowed to stand at room temperature for 16 hr. Yellow plates (0.6 g.) of XXIX, m.p., 256° dec., separated. Elemental analysis showed that the N-oxide function was no longer present. The product was found to be identical with a sample of XXIX prepared from 2,4-diamino-6-methoxy-5-nitrosopyrimidine and phenylacetonitrile.

**2,7-Diamino-4-methoxy-6-phenylpteridine (XXIX).**[12]—To a solution of 11 g. of 2,4-diamino-6-methoxy-5-nitrosopyrimidine in a mixture of 750 ml. of dry dimethylformamide and 250 ml. of methanol was added with stirring 3.2 g. of sodium methoxide and 7.6 g. of phenylacetonitrile. The reaction mixture was heated under reflux for 1.5 hr. The solvent was removed under reduced pressure and the residue was stirred with water, collected, and slurried twice with 5% hydrochloric acid. The crude hydrochloride was dissolved in water, treated with charcoal, filtered, and made basic with sodium hydroxide. The product was collected and recrystallized first from butanol and then from methanol to give 1.6 g. of yellow needles of XXIX, m.p. 258° dec.

*Anal.* Calcd. for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.51; N, 31.33. Found: C, 58.14; H, 4.52; N, 31.22.

**2,4,7-Triamino-6-phenylpteridine 5-Oxide (XXXII).**—A 10.0-g. sample of diacetylated 2,4,6-triamino-5-nitrosopyridine was dissolved in 120 ml. of dimethyl sulfoxide. The resulting solution was diluted in rapid succession with 400 ml. of boiling acetone, with a solution of 16.6 g. of α-cyanobenzyl benzenesulfonate, 16.6 ml. of pyridine, and 50 ml. of acetone which had been boiled previously for 5 min., and finally with a solution of 4.1 g. of sodium cyanide in 40 ml. of water. Yellow crystals soon separated from the intensely colored solution. The product was filtered, washed with water and ethanol and dried to give 6.8 g. of bright yellow solid (XXXI).

A 5.0-g. sample of the yellow acetylated derivative was suspended in 100 ml. of boiling stirred methanol. A solution of 5 g. of sodium methoxide in 75 ml. of methanol was added and the resulting mixture was boiled with stirring for 5 min. The mixture was then diluted with an equal volume of water and cooled. The product (XXXII) was collected, slurried with 15 ml. of acetic acid, and heated with 200 ml. of water until solution was achieved. The yellow solution was clarified by filtration and, while still hot, diluted with excess concentrated aqueous ammonia. Beautiful yellow plates (3.55 g.) crystallized, m.p. 340° dec.

It was subsequently found that XXXII could be obtained from XXXI upon boiling with methanol alone.

*Anal.* Calcd. for $C_{12}H_{11}N_7O$: C, 53.53; H, 4.12; N, 36.41. Found: C, 53.77; H, 4.39; N, 36.33.

# Pteridines. IV. Synthesis of 2,4,6-Triamino-7-phenylpteridine and Related Compounds through the Hofmann Reaction

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6- and 7-Pteridinecarboxamides were prepared and subjected to the Hofmann hypobromite reaction to obtain the corresponding amino compounds. A synthesis of 7-phenyl-6-pteridinecarbonitriles is described. 2,4-Diamino-6-phenylpteridine was synthesized and shown to be different from the compound previously assigned that structure.

2,4,7-Triamino-6-phenylpteridine (I) is an effective diuretic agent in man.[2] As part of a program devoted to the synthesis of compounds for comparative biological evaluation, the preparation of 2,4,6-triamino-7-phenylpteridine (II) and related substances was undertaken.



I        II
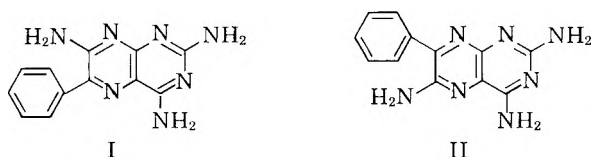
Although 2,4-diamino-6-phenyl-7(8H)-pteridinone[3,4] was converted into the corresponding chloro compound and thence into various 7-amino derivatives[4] of I, no useful product could be isolated when chlorination of the isomeric 2,4-diamino-7-phenyl-6(5H)-pteridinone[3b] was attempted under the same conditions.

As an alternate approach, the preparation of 6-pteridinecarboxamides followed by Hofmann hypobromite conversion into 6-aminopteridines appeared attractive.

We found previously that 4,6-diamino-5-nitroso-2-phenylpyrimidine (III) reacted with benzoylacetamide (V) in the presence of potassium acetate to produce 4-amino-2,7-diphenyl-6-pteridinecarboxamide (VI).[5] When the analogous reaction was attempted with the less reactive 2,4,6-triaminopyrimidine (IV), no significant yield of product was obtained.
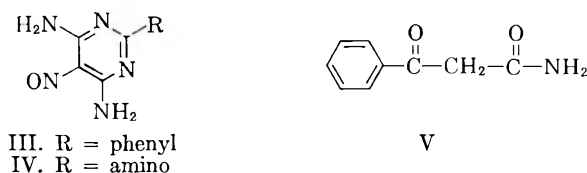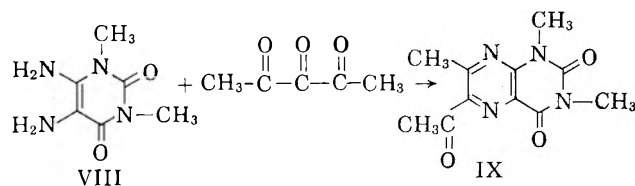


III. R = phenyl
IV. R = amino

V
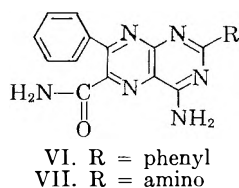


VI. R = phenyl
VII. R = amino

Sachs and Meyerheim[6] found that 5,6-diamino-1,3-dimethyl-2,4-pyrimidinedione (VIII) reacted with 2,3,4-pentanetrione to produce a single pteridine (IX). It was hoped that substances such as VI and VII might be produced by an analogous route.



VIII        IX

Upon treatment of benzoylacetamide with nitrous acid, the isonitroso compound X was produced. The latter reacted with excess nitrous acid to produce XI (or its solvated equivalent).[7] This product was not isolated, but was permitted to condense in solution with o-phenylenediamine (XII), 4,5,6-triamino-2-phenylpyrimidine (XIII) and 2,4,5,6-tetraminopyrimidine (XIV) to produce XV, VI and VII, respectively. Compound VI, prepared by this route, was identical with the product derived from III and V.



XI        X

XII

XV        VI; VII

XIII, R = phenyl
XIV, R = amino
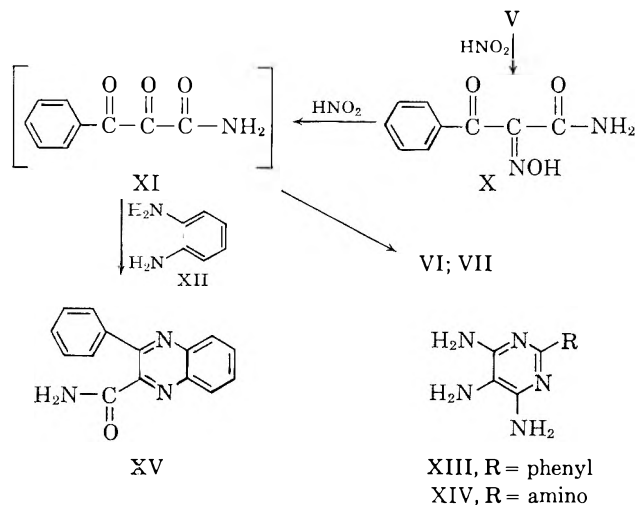
When it was found, in connection with subsequent work,[8] that IV could be activated for condensation reactions through diacetylation with acetic anhydride, the diacetyl compound and V were heated with ethanolic potassium acetate. A yellow pteridine formed readily. This intermediate acetylated product was hydrolyzed with cold alkali to give VII in good yield.

(1) Present address: Endo Laboratories, Richmond Hill 18, N. Y.

(2) A. P. Crosley, Jr., L. M. Ronquillo, W. H. Strickland, and F. Alexander, *Ann. Intern. Med.*, **56**, 241 (1962).

(3)(a) A. G. Renfrew, P. C. Piatt, and L. H. Cretcher, *J. Org. Chem.*, **17**, 467 (1952); (b) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).

(4) I. J. Pachter and P. E. Nemeth, to be published.

(5) I. J. Pachter and P. E. Nemeth, Part I, *J. Org. Chem.*, **28**, 1187 (1963).

(6) F. Sachs and G. Meyerheim, *Ber.*, **41**, 3957 (1908).

(7) F. Kröhnke, *Chem. Ber.*, **80**, 298 (1947), used a different process to make compounds related to XI.

(8) I. J. Pachter, P. E. Nemeth, and A. J. Villani, Part III, *J. Org. Chem.*, **28**, 1197 (1963).

The preparation of VII by this route constitutes a proof of structure.

3-Phenyl-2-quinoxalinecarboxamide (XI) reacted with aqueous potassium hypobromite to produce the known 2-amino-3-phenylquinoxaline[9] in excellent yield.

4-Amino-2,7-diphenyl-6-pteridinecarboxamide (VI) and 2,4-diamino-7-phenyl-6-pteridinecarboxamide (VII) are much less soluble than XV in aqueous potassium hypobromite. The Hofmann reactions were therefore carried out in dimethylformamide solution and the products XVI and II were obtained.



XVI                    XVII
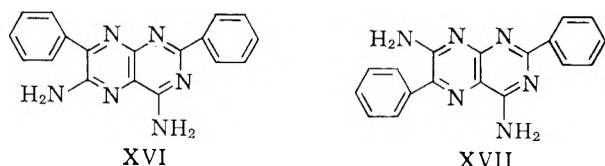
The ultraviolet spectra (Table I) of the 6-amino-7-phenylpteridines (XVI and II) were found to show absorption at much longer wave lengths than do those of the 7-amino-6-phenyl isomers (XVII and I).[3b,5,10] This is in accord with the results of previous investigations.[3b,11]

The hypobromite reaction in dimethylformamide was also used to convert 4,7-diamino-2-phenyl-6-pteridine-carboxamide (XVIII)[12] into 8-amino-2,3-dihydro-6-phenyl-1H-2-imidazo[4,5-g]pteridinone (XIX).



XVIII                    XIX
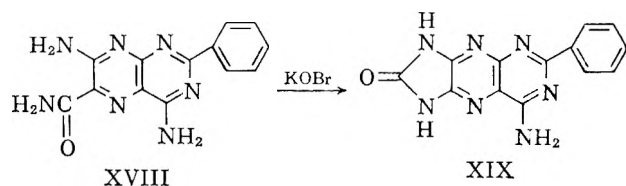
King and Spensley[13] reported that phenylglyoxal reacts with 2,4,5,6-tetraminopyrimidine (XIV) to give 2,4-diamino-7-phenylpteridine (XX), but that ω,ω-dichloroacetophenone reacts with XIV to give the isomeric compound XXI.

It was of interest to us to see whether halogen derivatives of V would react correspondingly with XIII and XIV to give products isomeric with VI and VII.



XX                    XXI
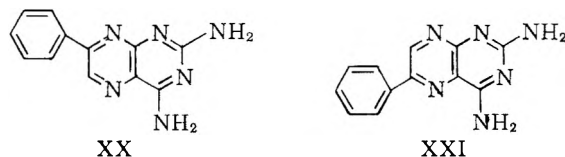
Compound V reacted with one and two moles of bromine to yield crystalline monobromo- and dibromobenzoylacetamide. Each reacted with XIII to give VI and with XIV to give VII. In the reactions of mono-bromobenzoylacetamide, air probably served as the oxidizing agent.

The lack of correspondence of our results with those of King and Spensley caused us to question and reinvestigate the previous work. It was reported that XX melted at 285–286°, that XXI melted at 290–291°

(9) F. Kröhnke and H. Leister, Chem. Ber., 91, 1479 (1958).
(10) I. J. Pachter, Part II, J. Org. Chem., 28, 1191 (1963).
(11) G. B. Elion, G. H. Hitchings, and P. B. Russell, J. Am. Chem. Soc., 72, 78 (1950).
(12) T. S. Osdene and E. C. Taylor, U. S. Patent 2,975,180 (1961).
(13) F. E. King and P. C. Spensley, J. Chem. Soc., 2144 (1952).

dec., and that a mixture of the two melted at 277°. It was further reported that ω-nitroacetophenone, XIV, and sodium dithionite yielded a product, probably a mixture, m.p. 280–281°, which did not show melting point depression on admixture with either XX or XXI.

In our hands, ω,ω-dichloroacetophenone reacted with XIV to give a product, m.p. 299–300° dec. Phenylglyoxal reacted with XIV to give a product, m.p. 300–301° dec. The infrared and ultraviolet spectra of the products were identical. Upon admixture there was no depression of melting point. Both reactions yielded XX.

The isomeric compound (XXI) was prepared unequivocally through condensation of diacetylated 2,4,6-triamino-5-nitrosopyrimidine[8] with phenylacetaldehyde in ethanolic potassium acetate followed by hydrolysis of the intermediate acetylated product. Compound XXI melted at 340° dec. and depressed the melting point of XX upon admixture.

In the reactions of α,β-dioxohydrocinnamamide (XI), the central carbonyl is most reactive. If the iso-nitroso compound (X) were to react to form a pteridine, the benzoyl carbonyl would be expected to react first. This proved to be the case and XXIV was produced when X reacted with XIII. The structure of the product was proved through its conversion in a Hofmann reaction to the previously prepared compound XVII.[5]



X + XIII ⟶                    KOBr ⟶ XVII

XXIV
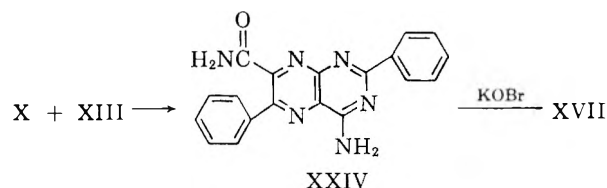
Monobrominated α-benzoylacetonitrile (XXV) reacted with XIII and XIV to produce the corresponding 6-pteridinecarbonitriles (XXVI and XXVII). In previous work[8] it was shown that cyclization occurred predominantly through the nitrile rather than through the ketone when benzoylacetonitrile and related compounds reacted with nitrosopyrimidines such as III. 6-Pteridyl ketones (e.g., XXVIII) were the products. In one reaction of III, compound XXVI was isolated as a minor by-product.[8] The formation of XXVI from III serves as proof for the structure assigned to the product of the reaction of XXV with XIII.



XXV                    XXVI, R = phenyl
                       XXVII, R = amino
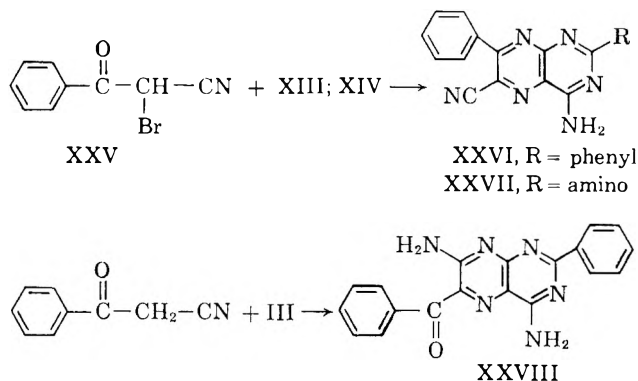


XXVIII

The structure of compound XXVII was also proved when, upon hydrolysis, it yielded the amide VII.

It is tempting to suggest that the relative reactivities of the nitrile and ketone groups in the syntheses of

XXVI and XXVIII are determined by reaction pH and that cyclization proceeds through nitrile in alkali and through ketone in near neutral or acid solution. There are most certainly other important factors involved in such reactions, for at times mixtures are produced[5] and occasionally a single product is obtained, the nature of which is at complete variance with the foregoing suggestions. For example, it has been found that when benzoylacetonitrile condenses with triazine in the presence of alkaline catalyst, ring closure to form the final product proceeds through the ketone and not through the nitrile.[14]

Kröhnke[7] reported that o-phenylenediamine reacts with benzoyl(p-dimethylaminophenylimino)acetonitrile in acetic acid to give 3-phenyl-2-quinoxazoline-carbonitrile. Although we could repeat this synthesis in excellent yield, we were unable to carry out analogous reactions with XIII or XIV to produce pteridines. Neither acid nor alkaline conditions proved useful.

The ultraviolet absorption maxima of new pteridines are recorded in Table I.

TABLE I

ULTRAVIOLET SPECTRA

| Compound | λmax, mμ (log ε) | pH |
|---|---|---|
| II | 262 (4.31), 404 (4.08) | 1 |
| | 269 (4.33), 416 (4.00) | 13 |
| VII | 254 (4.26), 354 (4.28) | 1 |
| | 272 (4.39), 381 (4.08) | 13 |
| XVI | 281 (4.39), 402 (4.26) | 1 |
| XIX | 250 (4.21), 268 (4.24), 350 (4.34), 366 (4.26) | 1 |
| | 271 (4.43), 308 (4.10), 382 (4.31), 399 (s) (4.20) | 13 |
| XX[a] | 256 (s) (4.03), 280 (3.87), 357 (4.35), 366 (s) (4.33) | 1 |
| | 238 (4.30), 266 (4.29), 306 (s) (3.78), 382 (4.10) | 13 |
| XXI | 266 (4.50), 365 (4.13) | 1 |
| | 276 (4.46), 302 (s) (4.18), 389 (4.06) | 13 |
| XXIV | 290 (4.40), 370 (4.20) | 1 |
| | 287 (4.42), 370 (4.12) | 13 |
| XXVI | 278 (4.30), 376 (4.22) | 1 |
| XXVII | 254 (4.40), 364 (4.31) | 1 |

[a] Prepared previously by King and Spensley.[13]

## Experimental

The *ultraviolet spectra* at pH 1 were determined in 4.5% aqueous formic acid. The spectra at pH 13 were determined by taking a 5- to 10-ml. aliquot of compound in 4.5% formic acid and bringing the volume to 100 ml. with 1 N aqueous sodium hydroxide. In those cases where the compound crystallized from alkaline solution, no values at pH 13 are recorded.

α-Isonitrosobenzoylacetamide (X).—A solution of 2.3 g. of sodium nitrite in 4 ml. of water was added dropwise with stirring to a solution of 5.0 g. of benzoylacetamide in 16 ml. of acetic acid. The reaction mixture was kept at 10–15° during the addition and then for an additional 30-min. period, during which time the product began to crystallize. The mixture was diluted with 30 ml. of cold water, cooled at 5° for 3 hr., and filtered. The product was recrystallized from ethanol to give 5.0 g. of X, m.p. 148–149°.

*Anal.* Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.93; H, 4.27; N, 14.40.

3-Phenyl-2-quinoxalinecarboxamide (XV).—To a solution of 5.0 g. of isonitrosobenzoylacetamide (X) in 16 ml. of acetic acid was added a solution of 6.9 g. of sodium nitrite in 15 ml. of water at such a rate that the reaction temperature did not exceed 15°. The mixture was allowed to stand at room temperature for 16 hr. and was then treated with 3.3 g. of o-phenylenediamine in 5 ml.

of acetic acid. The resulting solution was heated on a steam bath for 10 min., made basic with aqueous ammonia, and cooled. Colorless needles crystallized. The product was collected and recrystallized from ethanol to give 2.3 g. of XV, m.p. 200–201°.

*Anal.* Calcd. for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.18; H, 4.13; N, 16.57.

4-Amino-2,7-diphenyl-6-pteridinecarboxamide (VI). Method A.—To a solution of 0.5 g. of α-isonitrosobenzoylacetamide (X) in 10 ml. of acetic acid was added 0.69 g. of sodium nitrite in 3 ml. of water. The solution was stirred during the addition and the temperature was kept at 10–15°. It was then allowed to stand at 25° for 16 hr. A 0.5-g. sample of 4,5,6-triamino-2-phenylpyrimidine (XIII) was added and the resulting mixture was heated on a steam bath for 15 min., diluted with 10 ml. of water, and cooled. The pale yellow needles which crystallized weighed 0.55 g. Upon recrystallization from ethanol the product melted at 325° dec. and was found to be identical with a sample of VI prepared previously.[5]

Method B.—A mixture of 4.0 g. of 4,5,6-triamino-2-phenylpyrimidine, 5.0 g. of α-bromobenzoylacetamide and 150 ml. of water was heated under reflux for 1 hr. The yellow needles which separated were collected and recrystallized from ethanol to give 2.9 g. of VI, m.p. 320–322° dec., identical with a sample prepared previously.[5]

When a similar reaction was carried out with α,α-dibromobenzoylacetamide in place of α-bromobenzoylacetamide, the same product (VI) resulted.

2,4-Diamino-7-phenyl-6-pteridinecarboxamide (VII). Method A.—To a solution of 5.0 g. of α-isonitrosobenzoylacetamide (X) in 50 ml. of acetic acid was added a solution of 7.0 g. of sodium nitrite in 15 ml. of water at such a rate that the temperature was maintained at 10 to 15°. The mixture remained in the cold bath for 2 hr. and then stood at room temperature for 2 hr. It was heated on a steam bath and 3.5 g. of 2,4,5,6-tetramino-pyrimidine was added. Heating was continued for 30 min. The resulting solution was cooled and made basic with aqueous ammonia to precipitate an orange-yellow product (4.1 g.). Treatment with 5% hydrochloric acid yielded an insoluble salt which was collected and treated with aqueous ammonia. The reliberated base was recrystallized from dimethylformamide and finally boiled for 10 min. with water. The product analyzed as a hydrate of VII, m.p 318°.

*Anal.* Calcd. for $C_{13}H_{13}N_7O$: C, 52.11; H, 4.39; N, 32.76. Found: C, 52.11; H, 4.33; N, 32.68.

Method B.—A mixture of 1.2 g. of benzoylacetamide and 1.2 g. of diacetylated 2,4,6-triamino-5-nitrosopyrimidine[8] was heated under reflux for 5 min. with 30 ml. of absolute ethanol. Potassium acetate (1.0 g.) in a minimum volume of hot absolute ethanol was added and heating under reflux was continued for 30 min. The mixture was cooled and filtered and the product was stirred for 2.5 hr. with 25 ml. of 2% aqueous sodium hydroxide. During this time the pale yellow acetylated pteridine dissolved and a deeper yellow compound separated in 1.2 g. yield. Upon a single recrystallization from ethanol there was obtained 1.0 g. of the monohydrate of VII, identical with the product prepared by method A.

Method C.—A mixture of 5.6 g. of 2,4,5,6-tetraminopyrimidine, 9.6 g. of α-bromobenzoylacetamide and 250 ml. of water was heated under reflux for 6 hr. The hot solution was filtered to remove a small amount of insoluble reddish material and the filtrate was made basic with ammonia. The product (5.8 g.) separated. It was purified by converting it into a hydrochloride salt with 5% hydrochloric acid, reliberating the free base with ammonia, recrystallizing from dimethylformamide, and finally boiling with water for 10 min. The product was identical with the hydrate of VII prepared by method A.

The same product was obtained when α,α-dibromobenzoylacetamide was used in place of α-bromobenzoylacetamide in a related reaction.

2-Amino-3-phenylquinoxaline.—To a cold mixture of 1.6 g. of bromine and 15 ml. of water was added, with stirring, a cold solution of 3.4 g. of potassium hydroxide in 30 ml. of water. The resulting solution was stirred into a suspension of 2.1 g. of 3-phenyl-2-quinoxalinecarboxamide (XV) in 5 ml. of water. The resulting mixture was allowed to stand for 1 hr. at 25°. It was then heated on a steam bath for 2 hr. and cooled. There was obtained 1.9 g. of product which, upon recrystallization from 2:1 methanol–ethyl acetate, melted at 160°.

*Anal.* Calcd. for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.13; H, 5.09; N, 19.00.

(14) K. R. Huffman, F. C. Schaefer, and G. A. Peters, *J. Org. Chem.*, 27, 551 (1962).

The product was identical with a sample prepared by the method of Kröhnke and Leister[9] who reported m.p. 163°.

**4,6-Diamino-2,7-diphenylpteridine (XVI).**—To a cold stirred mixture of 2.8 g. of bromine and 30 ml. of water was slowly added a cold solution of 5.04 g. of potassium hydroxide in 25 ml. of water. The resulting hypobromite solution was cooled to 10° and added in one portion to 5.1 g. of 4-amino-2,7-diphenyl-6-pteridinecarboxamide (VI) in 50 ml. of dimethylformamide. The resulting solution turned dark immediately and the temperature rose spontaneously to 45°. It was allowed to stand for 1 hr. and was then heated on a steam bath for 1.5 hr. A solution 5 g. of potassium hydroxide in 25 ml. of water was added and heating was continued for another hour. Upon cooling, the brownish yellow product (4.1 g.) was collected and purified by twice dissolving it in dilute acetic acid, decolorizing with charcoal, and reprecipitating with aqueous ammonia. The yield of virtually pure product was 3.1 g. For analysis it was recrystallized once from dimethylformamide and once from ethanol to give 1.5 g. of needles of XVI, m.p. 280–281°.

*Anal.* Calcd. for $C_{18}H_{14}N_6$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.59; H, 4.44; N, 26.52.

**2,4,6-Triamino-7-phenylpteridine (II).**—A hypobromite solution prepared by adding a solution of 1.7 g. of potassium hydroxide in 12 ml. of water to a mixture of 0.8 g. of bromine and 8 ml. of cold water was added to a solution of 1.4 g. of 2,4-diamino-7-phenyl-6-pteridinecarboxamide (VII) in 6 ml. of dimethylformamide. The mixture was heated to 50°, allowed to stand for 2 hr., and then heated on a steam bath for 1 hr. A solution of 5 g. of potassium hydroxide in 5 ml. of water was added slowly and heating was then continued for another hour. The yellow product (0.75 g.) which separated was collected and recrystallized by dissolving in dimethylformamide, adding a little water, and cooling. The compound (II) melted at 320° dec.

*Anal.* Calcd. for $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.72. Found: C, 56.80; H, 4.70; N, 39.09.

**8-Amino-2,3-dihydro-6-phenyl-1H-2-imidazo[4,5-g]pteridinone (XIX).**—A solution of potassium hypobromite was prepared by adding a cold solution of 16.8 g. of potassium hydroxide in 140 ml. of water to a mixture of 8.0 g. of bromine in 90 ml. of water. It was added to a solution of 14.0 g. of 4,7-diamino-2-phenyl-6-pteridinecarboxamide (XVIII) in 70 ml. of warm dimethylformamide. The resulting mixture was heated on a steam bath for 3.5 hr. and filtered to remove 3.8 g. of unchanged XVIII. The solution was acidified with acetic acid and the product was collected, dissolved in dilute aqueous sodium hydroxide, clarified with charcoal, and reprecipitated with acetic acid. There was obtained 9.25 g. of XIX. The product, upon recrystallization from dimethylformamide formed a solvate, m.p. over 350°.

*Anal.* Calcd. for $C_{15}H_{16}N_8O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.93; H, 4.48; N, 32.14.

Upon boiling with water for 15 min., the unsolvated product, m.p. over 350°, was obtained.

*Anal.* Calcd. for $C_{13}H_9N_7O$: C, 55.91; H, 3.25; N, 35.11. Found: C, 55.77; H, 3.20; N, 34.91.

**α-Bromobenzoylacetamide.**—A solution of 32.0 g. (0.2 mole) of bromine in 50 ml. of chloroform was added dropwise with stirring to a solution of 32.6 g (0.2 mole) of benzoylacetamide in 450 ml. of chloroform. The reaction mixture was maintained at 10–15°. Stirring was continued for 20 min. after the bromine addition. The solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol to yield 41.5 g. of colorless crystals. Upon a second recrystallization from ethyl acetate, the product melted at 124–125°.

*Anal.* Calcd. for $C_9H_8BrNO_2$: C, 44.65; H, 3.33; N, 5.79. Found: C, 44.94; H, 3.26; N, 5.82.

**α,α-Dibromobenzoylacetamide.**—A solution of 3.2 g. of bromine in 20 ml. of chloroform was added dropwise to a stirred solution of 4.85 g. of α-bromobenzoylacetamide in 100 ml. of chloroform. The mixture was kept at 15–20° during the addition. When half the bromine had been added, the product began to crystallize. After completion of the addition, the mixture was stirred for 20 min. and concentrated *in vacuo* to half volume. The product was filtered, washed with chloroform, and dried to give 5.75 g., m.p. 174°. Upon recrystallization from ethanol, needles, m.p. 178–179°, were obtained.

*Anal.* Calcd. for $C_9H_7Br_2NO_2$: C, 33.68; H, 2.20; N, 4.36. Found: C, 33.42; H, 2.15; N, 4.49.

**2,4-Diamino-6-phenylpteridine (XXI).**—A mixture of 4.8 g. of diacetylated 2,4,6-triamino-5-nitrosopyrimidine, 5.2 g. of phenyl

acetaldehyde, 2.0 g. of potassium acetate and 125 ml. of ethanol was heated under reflux for 2.5 hr. It was cooled to room temperature and a solution of 2.0 g. of sodium hydroxide in 75 ml. of water was added. Upon brief warming, the yellow acetylated reaction product dissolved and crystals of XXI slowly separated. After 3 hr. the compound was filtered. The filtrate was neutralized with acetic acid and concentrated *in vacuo* to obtain a second crop. The yield of crude product was 4.3 g. It was dissolved in dilute acetic acid, treated with charcoal, reprecipitated with ammonia, recrystallized from dimethylformamide, and finally boiled with water. There was obtained 3.1 g. of XXI, m.p. 340° dec.

*Anal.* Calcd. for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.41; H, 4.45; N, 35.02.

**4-Amino-2,6-diphenyl-7-pteridinecarboxamide (XXIV) and 4,7-Diamino-2,6-diphenylpteridine (XVII).**—A mixture of 2.0 g. of α-isonitrosobenzoylacetamide (X) and 2.1 g. of 4,5,6-triamino-2-phenylpyrimidine (XIII) was heated under reflux with 100 ml. of water for 24 hr. There was obtained 1.4 g. of yellow pteridine. Upon standing for a day, a second crop of 0.7 g. was obtained. The two fractions had different infrared spectra. Upon recrystallization of each from dimethylformamide, however, each yielded the same compound (XXIV), m.p. 308–309°.

*Anal.* Calcd. for $C_{19}H_{14}N_6O$: C, 66.66; H, 4.12; N, 24.55. Found: C, 66.68; H, 4.08; N, 24.82.

When a sample of XXIV was treated with potassium hypobromite in a reaction analogous to that used for the conversion of VI into XVI, the previously described[5] 4,7-diamino-2,6-diphenylpteridine (XVII) was produced.

**4-Amino-2,7-diphenyl-6-pteridinecarbonitrile (XXVI).**—A solution of 6.0 g. of bromine in 25 ml. of chloroform was added dropwise to a stirred solution of 5.45 g. of benzoylacetonitrile in 25 ml. of chloroform. Stirring was continued for 45 min. after the addition while a stream of air was blown over the surface of the solution. The residual liquid was diluted with 50 ml. of methanol and 4.1 g. of 4,5,6-triamino-2-phenylpyrimidine (XII) was added. From the resulting solution, the reaction product was permitted to crystallize over a period of 1 hr. The yellow needles were collected and recrystallized from dimethylformamide to give 3.0 g. of XXVI, m.p. 306–307°.

*Anal.* Calcd. for $C_{19}H_{12}N_6$: C, 70.36; H, 3.73; N, 25.91. Found: C, 70.75; H, 3.82; N, 26.04.

The product was identical by infrared spectral comparison and mixed melting point with a sample of XXVI derived[8] from 4,6-diamino-5-nitroso-2-phenylpyrimidine (III).

**2,4-Diamino-7-phenyl-6-pteridinecarbonitrile (XXVII).**—To a solution of 3.7 g. of benzoylacetonitrile in 30 ml. of chloroform maintained at 10 to 15° was added a solution of 4.0 g. of bromine in 20 ml. of chloroform. After the addition, the solution was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the residual oil was dissolved in 25 ml. of ethanol. The ethanolic solution was added to a hot solution made by heating to boiling 3.2 g. of 2,4,5,6-tetraminopyrimidine dihydrochloride, 6.0 g. of potassium acetate, and 20 ml. of water. Upon admixture a brown solution resulted. The product formed rapidly and separated. The mixture was permitted to stand at room temperature for 2 hr. The yellow product (2.8 g.) was collected and dissolved in dimethylformamide. The resulting solution was diluted with ethanol and 2.15 g. of needles of XXVII, m.p. 328–330° dec., crystallized.

*Anal.* Calcd. for $C_{13}H_9N_7$: C, 59.31; H, 3.45; N, 37.25. Found: C, 59.13; H, 3.59; N, 37.55.

**Hydrolysis of 2,4-Diamino-7-phenyl-6-pteridinecarbonitrile (XXVII). Synthesis of VII.**—A 0.25-g. sample of 2,4-diamino-7-phenyl-6-pteridinecarbonitrile (XXVII) was heated on a steam bath for 15 min. with 2 ml. of concentrated sulfuric acid. The resulting yellow solution was cooled and poured into 25 ml. of cold water. Pale yellow plates of the sulfate salt crystallized immediately. The mixture was made strongly basic with aqueous ammonia. The salt dissolved and a new product (VII) crystallized in 0.25 g. yield. The product was identical with a previously prepared sample.

# Synthetic Studies on C-19 Oxygenated Pregnanes

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Secondary and tertiary 6β-hydroxy-5α-pregnanes (IIIa-h) have been used as substrates to study the nature of products obtained on treatment with lead tetraacetate in an inert solvent. The effect of the presence of iodine in this reaction was also studied in some cases. 3β,20β-Diacetoxy-5α-chloro-6β,19-oxidopregnane (IVc) and 3β-acetoxy-5α-bromo-17α-methyl-6β,19-oxidopregnan-20-one (IVf) are converted *via* saponification and oxidation to 6β,19-oxidopregn-4-ene-3,20-dione (IXa) and 17α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXb), respectively. 6α-Methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc) was synthesized by the oxidation of 5α-bromo derivatives Xa and Xb. Oppenauer oxidation of 3β,19,20β-trihydroxy-6-methylpregn-5-ene (VId) gave 19-hydroxy-6α-methylprogesterone (VIIIb) which was converted to 6α-methyl-19-norprogesterone (XVII). 6-Methyl-19-norpregna-4,6-diene-3,20-dione (XXI) was synthesized by ring opening of the oxidoprogesterone (IXc) followed by oxidation and elimination of C-19. The nature and reactivity of the Δ⁵-3β,19-dihydroxy system are discussed.

Intramolecular attack by an electron deficient group (oxygen in particular) on a suitably located non-activated C-H bond has been advantageously utilized[1] in recent years to synthesize C-18 and/or C-19 substituted steroids. The potentiality of 19-hydroxy-Δ⁴-3-ketones to generate[2] 19-norsteroids of biological importance has been demonstrated recently.[2c]

An investigation was initiated to study the scope and limitations of the reactions of 6β-hydroxypregnanes[3] with lead tetraacetate and to explore the transformations of 6β,19-oxides obtained therefrom to produce 19-norsteroids.

Readily available[4] 3β-hydroxy-Δ⁵-steroids were used to synthesize the substrates required for this work. Pregnenolone was converted to 3β,20β-diacetoxypregn-5-ene (Ia)[5] in excellent yields using sodium borohydride, followed by acetylation. Conventional routes such as (i) Δ⁵-steroid → 6-nitro derivative[6] → 6-ketone, and (ii) Δ⁵-steroid → 5α-bromo-6β-ol[7] → bromo ketone → 6-ketone gave 3β,20β-diacetoxy-5α-pregnan-6-one (IIa) in very poor yields (<20%). The latter compound as well as the ketones IIb and c were prepared in good yields using the hydroboration–oxidation method already described.[8] Ketones IIa and b were smoothly converted to the corresponding alcohols IIIa and d with sodium borohydride.[9] The carbinols IIIb, e, and g were synthesized by treating the corresponding ketones IIa, b, and c with methylmagnesium bromide.

**Lead Tetraacetate Reaction.**—The alcohols IIIa-h were treated[10] with excess lead tetraacetate and iodine (molar ratio 1:1) to yield the corresponding 6β,19-oxides IVa-h in satisfactory yields. In all the cases

where comparative lead tetraacetate experiments were conducted, the yields of the 6β,19-oxides obtained when iodine was present were consistently superior to those obtained when iodine was excluded. Of particular interest are the results obtained with 3β,20β-diacetoxy-5α-pregnan-6β-ol (IIIa) and 3β,20β,diacetoxy-5α-chloropregnan-6β-ol (IIIc). Treatment of IIIa with lead tetraacetate in the absence of iodine gave a mixture of products from which 3β,20β-diacetoxy-5α-pregnan-6-one (IIa) was isolated by crystallization in 62% yield.[11] A chromatography of the residue obtained from the mother liquors afforded 3β,20β-diacetoxy-6β,19-oxido-5α-pregnane (IVa, ca. 6%). Treatment of IIIc with lead tetraacetate likewise yielded a mixture[12] of 3β,20β-diacetoxy-5α-chloropregnan-6-one (IId) and the corresponding oxide IVc. Attempts to separate these compounds either by crystallization or by column chromatography were unsuccessful. Treatment of the mixture with zinc and acetic acid gave, on crystallization of the crude product, ketone IIa as a major component. Chromatography of the residual material, followed by crystallization of the benzene–ether (19:1) eluate, yielded 3β,20β-diacetoxy-5α-chloro-6β,19-oxidopregnane (IVc). In contrast, when IIIa and c were treated with excess 1:1 molar lead tetraacetate–iodine, the oxides IVa and c were directly obtained by crystallization in 68 and 85% yields, respectively. The type of annulation described here can lead[10] to 19-iodinated or 19-hydroxy oxides. However, we were not able to isolate[13] any such derivatives.[14] The structures of the oxides IVa-h were established by their elemental analyses and by their infrared and nuclear magnetic resonance (n.m.r.) spectra.

Treatment of the diketal oxide (IVd) with sulfuric acid in acetone hydrolyzed the protective ketal groupings to give 6β,19-oxido-5α-pregnane-3,20-dione (Va). This compound was also obtained from IVa by saponification followed by oxidation with 8 N chromic acid

(1) (a) M. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961); (b) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); (c) M. Akhtar and D. H. R. Barton, *ibid.*, **84**, 1496 (1962).

(2) (a) G. Barber and M. Ehrenstein, *J. Org. Chem.*, **20**, 1253 (1955); (b) M. Hagiwara, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull. Japan*, **8**, 84 (1960); (c) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962).

(3) For references to similar studies in androstane series, see A. Bowers, *et al.*, *J. Org. Chem.*, **27**, 1862 (1962).

(4) Similar substrates are used in an anlogous study involving nitrite photolysis see ref. 1c.

(5) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951).

(6) C. E. Anagnostopoulos and L. F. Fieser, *ibid.*, **76**, 532 (1954).

(7) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

(8) J. F. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, **27**, 2938 (1962).

(9) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(10) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961).

(11) These results present a marked contrast to those obtained when 3β,17β-diacetoxyandrostan-6β-ol was treated with lead tetraacetate under similar conditions (see ref. 3 and 10).

(12) The presence of 3β,20β-diacetoxy-5α-chloropregnan-6-one in the mixture was established by thin-layer chromatography and by its optical rotation (*vide* Experimental).

(13) Although no C-19 iodinated steroids were isolated, in some cases, *e.g.*, IVa and f after the work-up, the crude product slowly liberated some more iodine overnight. This was noted by production of brown color, odor, and by subsequent decolorization by thiosulfate extraction.

(14) Formation of such derivatives may involve C-19 diiodo compounds as intermediates (see ref. 10). An examination of models reveal severe 1,3 diaxial interaction between the C-19 diiodomethyl group and the C-2, C-4, C-6, and C-11 axial substituents.

|  | R | R' | R'' | R''' |
|---|---|---|---|---|
| a | OAc, H | —CH(OAc)CH₃ | H | H |
| b | (ketal) | CH₃ (ketal) | H | H |
| c) | OAc, H | —COOCH₃ | CH₃ | H |
| d | OAc, H | —CH(OAc)CH₃ | H | Cl |
| e | OAc, H | —COOCH₃ | CH₃ | Br |



|  | R | R' | R'' | X | Y |
|---|---|---|---|---|---|
| a | OAc, H | —CH(OAc)CH₃ | H | H | H |
| b | OAc, H | —CH(OAc)CH₃ | H | CH₃ | H |
| c | OAc, H | —CH(OAc)CH₃ | H | H | Cl |
| d | (ketal) | CH₃ (ketal) | H | H | H |
| e | (ketal) | CH₃ (ketal) | H | CH₃ | H |
| f | OAc, H | —CO—CH₃ | CH₃ | H | Br |
| g | OAc, H | —COOCH₃ | CH₃ | CH₃ | H |
| h | OAc, H | —COOCH₃ | CH₃ | H | Br |

CHART 1
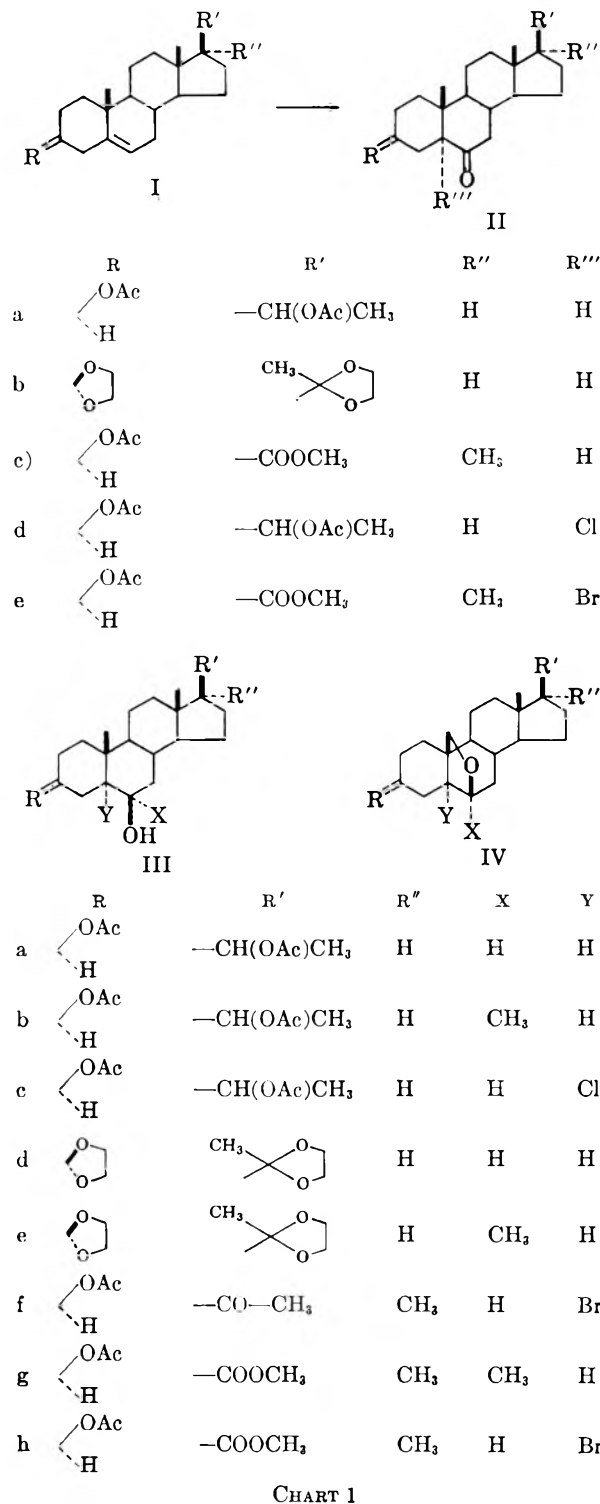
solution in acetone. 6α-Methyl-6β,19-oxido-5α-pregnane-3,20-dione (Vb) was similarly obtained from diketal oxide (IVe) and 3β,20β-diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb), respectively.

**Spectral Data.**—An examination of the infrared spectra of the oxides described above revealed the presence of a low intensity band in the 1499–1488-cm.⁻¹ region. This band was generally well separated[15] from the envelope of bands representing the C–H bending modes of the methylenes in the rest of the molecule. It appears after annulation of the 6β-alcohols to the 6β,19-oxides and is absent in the products where the

(15) This band is slightly shifted towards the lower frequency and hence was not completely resolved in compounds IXa, b, and c.

TABLE I

CHARACTERISTIC INFRARED BANDS OF 6β,19-OXIDO DERIVATIVES

| Compound no. | C-19 Methylene bending in cm.⁻¹ | Other band in cm.⁻¹ |
|---|---|---|
| IVa | 1492 | 850 |
| IVb | 1496 | 829 |
| IVc | 1497 | 853 |
| IVd | 1490 | 827 |
| IVe | 1492 | 831 |
| IVf | 1495 | 860 |
| IVg | 1488 | 828 |
| IVh | 1499 | 852 |
| Va | 1494 | 858 |
| Vb | 1492 | 826 |
| Xa | 1496 | 832 |
| Xb | 1497 | 830 |
| IXa | 1487 | 881 |
| IXb | 1487 | 880 |
| IXc | 1485 | 880 |

oxide ring is cleaved. The band may, therefore, be assigned to the C–H scissoring of the protons of the newly formed C-19 methylene. These bands together with another characteristic band in the 860–800-cm.⁻¹ region are listed in Table I.

Some observations on the n.m.r. spectra of the C-19 oxygenated compounds are worthy of mention. It is well established[16] that the nuclei of atoms of the same species bonded to a common carbon atom may behave as non-equivalent due to unsymmetrical electronic or steric environment. The n.m.r. spectra of the 6β,19-oxidoprogesterones (IXa, b, and c) exhibit a pair of doublets, having a pattern intermediate between A₂ and AB systems, ascribable to C-19 protons. Such a splitting of methylene protons α to the oxygen of a cyclic ether is not unprecedented.[17] The τ values for these signals are listed in Table II. The resonance signals of the C-19 protons of the oxides where the C-4 double bond is absent appears as a sharp singlet (A₂ system) in the region of 6.30 τ. In the case of the triacetates VIa and b, the signals due to C-19 protons appear as a pair of doublets (see Table II) of the type described above for oxidoprogesterones.

TABLE II

N.M.R. DATA FOR C-19 OXYGENATED DERIVATIVES IN CDCl₃[a]

| Compound no. | C-19 protons $(J)$[b] |
|---|---|
| IXa | 5.85 d (9.0) |
|  | 6.53 d (9.0) |
| IXb | 5.82 d (9.0) |
|  | 6.55 d (9.0) |
| IXc | 5.86 d (9.0) |
|  | 6.54 d (9.0) |
| IVa | 6.30 |
| IVb | 6.31 |
| IVc | 6.16 |
| VIa | 5.58 d (12.6) |
|  | 6.10 d (12.6) |
| VIb | 5.61 d (12.6) |
|  | 6.12 d (12.6) |

[a] Values are given in τ units relative to tetramethylsilane as reference. Singlets are unmarked, doublets are described by d. The values of doublets represent the center of the doublet. [b] In cycles per second.

(16) W. D. Phillips, J. Phys. Chem., 25, 949 (1955).

(17) L. F. Fieser, T. Goto, and B. K. Bhattacharyya, J. Am. Chem. Soc., 82, 1700 (1960).

IVa. R = H
b. R = CH₃

Va. R = H
b. R = CH₃

IVd. R = H
e. R = CH₃

VII

VIa. R = H, R' = COCH₃
b. R = CH₃, R' = COCH₃
c. R = R' = H
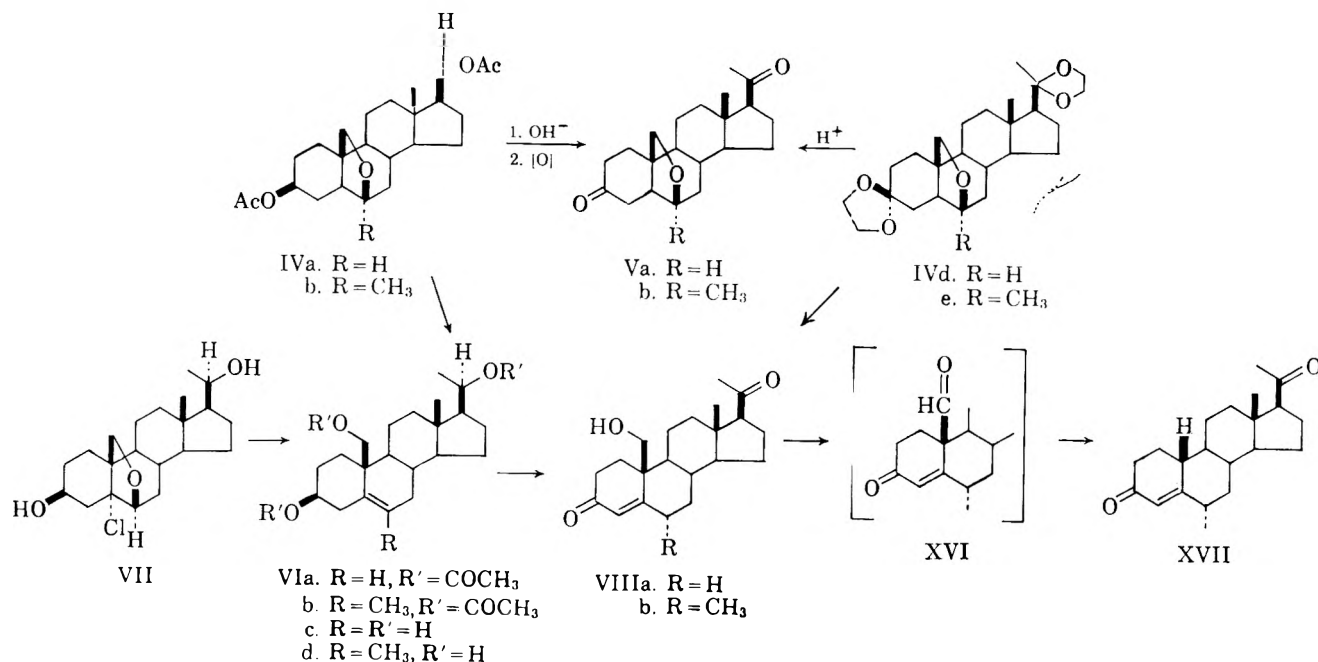d. R = CH₃, R' = H

VIIIa. R = H
b. R = CH₃

XVI

XVII

CHART 2

The appearance of "abnormal" ultraviolet spectra as a result of the interaction between non-adjacent chromophores has by now been amply exemplified.[18] These variations show up either as a charge transfer ($\pi \rightarrow \pi^*$) absorption band in some unsaturated ketones,[18c] or as intensified $n \rightarrow \pi^*$ absorption depending upon the value of the overlap integral between the olefinic $\pi$-orbitals and the p-orbitals of the carbonyl oxygen. We have observed the ultraviolet spectra of lactones XIIIa, b, and c. All three compounds exhibit an absorption band in the region of 230 m$\mu$. The appropriate $\lambda_{max}$ and $\epsilon$ values are listed in Table III. These lactones represent a novel class of chromophore exhibiting such $\pi \rightarrow \pi^*$ absorption. This absorption may be similar to that observed in some $\beta,\gamma$-unsaturated ketones not exhibiting intensification of $n \rightarrow \pi^*$ absorption.[18c] When the spectra of these compounds were recorded in alkaline medium, the absorption band disappeared and on treatment of the solution with acid the band reappeared. The above experiment clearly demonstrates that the absorption is associated with the stereoelectronic factors that are most favorable for $\pi \rightarrow \pi^*$ transition, due to the geometry of the system in the lactone form.

TABLE III

| Compound no. | Max (m$\mu$) | $\epsilon$ |
|---|---|---|
| XIIIa | 231 | 3350 |
| XIIIb | 228 | 1330 |
| XIIIc | 228 | 2410 |

**Cleavage of the Oxide Ring.**—The opening of the 6$\beta$,19-oxides described above was achieved (i) by acid catalysis in the cases where a C-5 hydrogen was present and (ii) by reductive cleavage in the cases where a halogen atom was attached to C-5. The latter method involved the use of lithium–liquid ammonia or

(18) (a) R. C. Cookson and N. S. Wariyar, J. Chem. Soc., 2302 (1956); (b) H. Labhart and G. Wagniere, Helv. Chim. Acta, 42, 2219 (1959); (c) S. Winstein, L. de Vries, and R. Orloski, J. Am. Chem. Soc., 83, 2020 (1961); R. C. Cookson and J. Hudec, J. Chem. Soc., 429 (1962).

of zinc and acetic acid. 3$\beta$,20$\beta$-Diacetoxy-6$\beta$,19-oxido-5$\alpha$-pregnane (IVa), when treated with a catalytic amount of $p$-toluenesulfonic acid in the presence of acetic acid and acetic anhydride, gave a mixture of products. An infrared spectrum of this mixture showed intense bands due to the acetate grouping (1720, 1250 cm.$^{-1}$), and absence of the 1492-cm.$^{-1}$ band present in the oxide. Saponification of the mixture, followed by chromatography of the crude alcohols, afforded 3$\beta$,19,20$\beta$-trihydroxypregn-5-ene (VIc) in ca. 27% yield. The structural assignment VIc follows from its n.m.r. spectrum (in deuterated methanol). The 6.07 $\tau$ signal attributed to the C-6 proton of the oxide IVa was absent, and a new singlet at 4.44 $\tau$ ascribable to the C-6 vinyl proton had appeared. Saponification of the oxide IVc gave 5$\alpha$-chloro-6$\beta$,19-oxido-pregnane-3$\beta$,20$\beta$-diol (VII). On treatment with lithium–liquid ammonia, diol VII afforded a triol in 59% yield. This triol was shown by mixture melting point, t.l.c.,[19] and by comparison of the n.m.r. spectra to be identical with compound VIc obtained above from IVa via acid catalysis. A triacetate obtained by acetylation showed an n.m.r. spectrum in complete agreement with the structure VIa.

An acid-catalyzed ring opening of 3$\beta$,20$\beta$-diacetoxy-6$\alpha$-methyl-6$\beta$,19-oxido-5$\alpha$-pregnane (IVb) proceeded smoothly to give a triacetate (VIb), which on saponification, afforded 3$\beta$,19,20$\beta$-trihydroxy-6-methylpregn-5-ene (VId) in excellent yield. N.m.r. spectra of the triol VId (in deuterated methanol) and the triacetate VIb both exhibited the signals attributable to vinyl methyl protons at 8.35 and 8.38 $\tau$, respectively. Acid-catalyzed cleavage of oxide IVd gave a crude product which was shown to contain an $\alpha,\beta$-unsaturated ketone by infrared and ultraviolet spectra ($\lambda_{max}$ 238 m$\mu$, $\epsilon_{max}$ 8380). Alkaline hydrolysis followed by careful chromatography resulted in isolation of 19-hydroxyprogesterone (VIIIa) in a very low yield. Compound VIIIa was also isolated from an Oppenauer oxidation of triol

(19) The abbreviation "t.l.c." throughout this article refers to "thin-layer chromatography."

XII. R = H or Br

Xa. R = $\langle$ OH, H $\rangle$, R' = CH₃
  b. R = O, R' = CH₃
  c. R = $\langle$ OH, H $\rangle$, R' = H

IXa. R = R' = H
  b. R = H, R' = CH₃
  c. R = CH₃, R' = H

IVa. R = Cl, R' = CH(OAc)CH₃, R'' = H,
  f. R = Br, R' = COCH₃, R'' = CH₃

XI

VIc. R = R' = H
  d. R = CH₃, R' = H

XV

XIIIa.   R = CH₃, R' = COCH₃
    b.   R = H, R' = COCH₃
    c.   R = H, R' = OCOCH₃
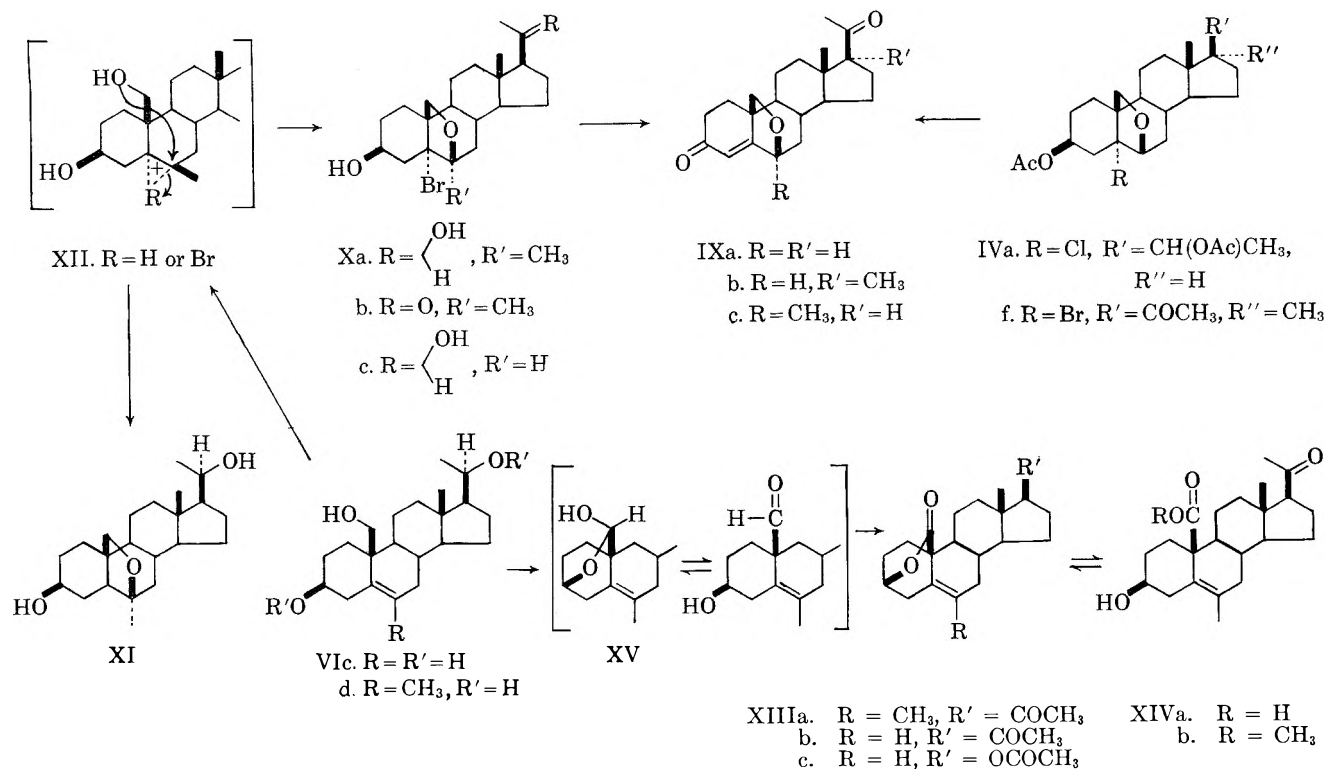
XIVa.   R = H
    b.   R = CH₃

CHART 3

VIc. The infrared spectra and the $R_f$ values by t.l.c. of the products obtained from both sources were identical.

6β,19-Oxidoprogesterone (IXa) and 6α-methyl-6β,19-oxidoprogesterone (IXc), when treated with zinc and acetic acid for varying periods of time and temperature, gave crude products whose infrared spectra indicated the cleavage of the oxide ring in varying degrees. When IXa was treated with zinc and acetic acid for thirty minutes at room temperature, essentially starting material was recovered together with a very small amount of hydroxylic material. The latter product had an $R_f$ value by t.l.c. identical with that of 19-hydroxyprogesterone (VIIIa). When the experiment was conducted at reflux temperature for 2.5 hours, a mixture of products was obtained which showed in its infrared spectrum a complete absence of bands in the O—H stretching region, and a band of 1735 cm.⁻¹ attributable to an acetate carbonyl. Saponification of the crude product gave an oil whose infrared spectrum showed strong O—H bands and absence of the acetate absorption. Treatment of 17α-methyl-6β,19-oxido-pregn-4-ene-3,20-dione (IXb) with zinc and acetic acid on a steam bath for twenty minutes yielded an oil which was shown to have hydroxyl and acetate groups from its infrared spectrum. The characteristic band at 1487 cm.⁻¹ (6β,19-oxide) in the starting material was absent.

**C-19 Substituted and C-19 Norprogesterones.**— The syntheses of 6β,19-oxidopregn-4-ene-3,20-dione (IXa) and the 17α-methyl derivative (IXb) were smoothly accomplished by saponification of the oxides IVc and f, respectively, followed by chromic acid oxidation.

The reaction of α-halo ketones with methylmagnesium bromide to give the corresponding dehalogenated ketones is well documented.[20] We found that 5α-halo-6-keto steroids likewise yielded 6-ketones in-

stead of the desired carbinol on treatment with methylmagnesium bromide. When triol VId reacted with N-bromoacetamide in t-butyl alcohol, a crystalline solid was obtained in 69% yield. An infrared spectrum showed bands at 3450, 3619 (bonded and nonbonded O—H stretching), 1695 (C-20 ketone) cm.⁻¹, and a band at 1497 cm.⁻¹ indicative of 6β,19-oxide. An elemental analysis indicated the presence of one atom of bromine. The structure of this product was readily discerned to be 3β-hydroxy-5α-bromo-6β,19-oxido-6α-methylpregnan-20-one (Xb). That the carbonyl group was located at C-20 rather than at C-3 was established as follows. Compound Xb was recovered unchanged on treatment with acid or with alkali. Mild acid treatment however, preceded by chromic acid oxidation gave 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc). The presence of a C-20 ketone in Xb was further confirmed by its n.m.r. spectrum (C-21 methyl, singlet at 7.94 τ). When a solution of bromine in acetic acid was added to a solution of the triols VIc or VId, they were quantitatively transformed to the diols Xc and Xa, respectively, characterized by their bromine analyses and by their infrared and n.m.r. spectra. Subsequent oxidation followed by acid-catalyzed dehydrobromination led to the corresponding oxidoprogesterones, IXa and c, respectively. Triol VId, when treated with methanolic hydrochloric acid, was quantitatively transformed into diol XI. Acetylation with pyridine and acetic anhydride afforded a diacetic identical in all respects with 3β,20β-diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb). Similar acid treatment of VIc was abortive and gave only unchanged starting material. All the cyclization reactions of Δ⁵-19-alcohols described above can be interpreted simply as being initiated by an electrophilic attack at the 5,6-double bond and terminated by an intramolecular nucleophilic

(20) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice Hall, New York, N. Y., 1954, p. 181.

ring closure by the C-19 oxygen on the intermediate cation (XII) thereby generating the products.

Oxidation of the triol VId with chromic acid in acetone at 0° resulted in isolation by crystallization[21] of a product in 32% yield. An infrared spectrum had a band at 1737 cm.$^{-1}$ suggesting the presence of a δ-lactone and one at 1698 (C-20 ketone) cm.$^{-1}$. An n.m.r. spectrum of this compound had a sharp singlet at 8.50 τ, characteristic of a vinyl methyl (at C-6) and an unresolved multiplet at 5.31 τ, ascribable to a proton on a carbon bearing an oxygen atom. Furthermore, it also exhibited sharp signals at 7.94 and 9.26 τ due to a C-21 methyl ketone and a C-18 angular methyl, respectively. We have assigned structure XIIIa to this lactone. This is further substantiated by the following experiments. Saponification of the lactone XIIIa yielded a carboxylic acid XIVa identified by its characteristic infrared spectrum. This acid was quantitatively transformed to its methyl ester XIVb whose infrared and n.m.r. spectra were in complete agreement with its assigned structure. The alcohol VIc on oxidation with chromic acid–acetone also yielded the corresponding lactone XIIIb.

The formation of lactones XIIIa and b under the above conditions of oxidation is particularly interesting. That the lactone results from the cyclization of the corresponding C-19 carboxylic acid during oxidation is highly improbable. The following arguments support this contention. In order to regenerate the lactone XIIIa from the acid XIVa, it was necessary to reflux the acid in methanolic hydrochloric acid for 2.5 to 3 hours. An analogous lactone XIIIc in the androstane series has been recently reported.[22] The lactonization in this case was effected by heating the corresponding C-19 acid with aqueous acetic acid in a sealed tube at 220–230° for two hours. Furthermore, lactone XIIIa was also isolated in low yields from a a pyridine–chromic acid oxidation of the triol VId. This reagent is known[24a] not to oxidize a primary alcohol to carboxylic acid. A mechanism for the genesis of the lactone XIIIa and b is readily envisaged by considering an equilibrium between the lactol XV and the corresponding aldehyde, followed by oxidation of XV.

Oppenauer oxidation of the triol VId yielded two crystalline products. One of these was shown by its infrared, ultraviolet, and n.m.r. spectra to be 19-hydroxy-6α-methylprogesterone (VIIIb). It was converted[2b] to 6α-methyl-19-norprogesterone (XVII) via aldehyde XVI. The second product of the Oppenauer oxidation showed in its infrared spectrum bands at 3420, 3622 (bonded and nonbonded O—H stretching), 1695 (C-20 ketone), and 1592 (aromatic C=C stretching) cm.$^{-1}$. The presence of the aromatic ring was confirmed by its characteristic ultraviolet spectrum ($\lambda_{max}$ 284 mμ, ε 1570). Acetylation of this compound afforded an acetate, the infrared spectrum of which showed no hydroxyl group and a new carbonyl band at 1755 (phenolic acetate) cm.$^{-1}$. Saponification of this acetate regenerated the phenol. An n.m.r. spectrum of this phenol showed signals at 9.44 and 7.87 τ attributable to C-18 and C-21 methyls, respectively, and a doublet at 8.8 τ ascribable to a C-6 methyl group.

The aromatic proton resonances appeared as a pair of doublets at 3.17 τ ($J_{ab}$ = 9 c.p.s.) characteristic of two protons located *ortho* to each other. Furthermore, the spectrum exhibited a sharp signal at 7.83 τ. This phenol had a correct analysis for $C_{22}H_{30}O_2$, suggesting the presence of a fourth methyl group. In the absence of the signal due to the third proton on the aromatic ring, we have assigned the 7.83 τ peak to a methyl group on the aromatic ring. The above spectral and analytical data can be accommodated by six structural possibilities (XVIII), *viz.*, where the aromatic *ortho* hydrogen atoms are attached to (i) C-1 and C-2, (ii) C-3 and C-4, or (iii) C-2 and C-3.



XVIII      XIXa. R = OH, R′ = CH₃
                     b. R = CH₃, R′ = OH
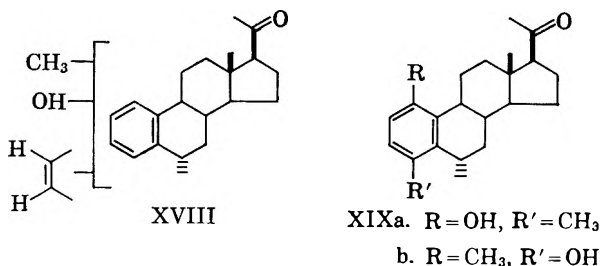
The 'Oppenauer phenol' was isolated in about 2–3% yield from the triol VId. The same phenol was also isolated in ca. 6% yield when 6α-methyl-19-hydroxypregn-4-ene-3,20-dione (VIIIb) was subjected to the same Oppenauer conditions as triol VId, thus indicating VIIIb as a progenitor of the 'Oppenauer phenol.' The 'Oppenauer phenol' is best formulated by the expressions XIXa or b. Its formation from VIIIb may be rationalized by considering a Lewis acid[23] catalyzed rearrangement. One possible pathway to such a rearrangement is shown below.
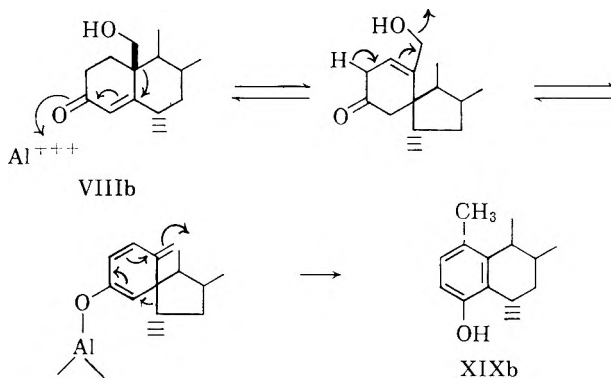


An acid-catalyzed (*p*-toluenesulfonic acid in presence of acetic acid and acetic anhydride) opening of 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc) yielded a 19-acetoxy compound which was saponified to give 6-methyl-19-hydroxypregna-4,6-diene-3,20-dione (XX).



IXc            XX            XXI
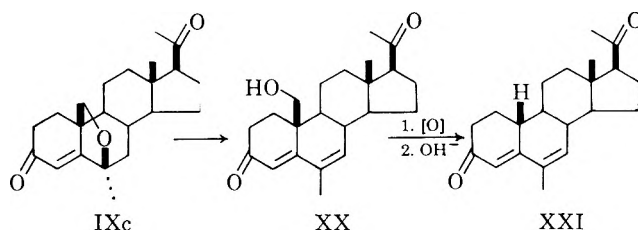
(21) Attempts to isolate, by chromatography, any crystalline material from the residue obtained from the mother liquor were unsuccessful.

(22) R. Gardi and C. Pedrali, *Gazz. chim. ital.*, **91**, 1420 (1961). We with to thank Dr. R. Gardi for supplying us with a sample of lactone XIIIc for spectral purposes.

(23) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950).

A pyridine–chromic acid oxidation followed by alkaline treatment of the crude product gave 6-methyl-19-norpregna-4,6-diene-3,20-dione (XXI).

Compounds IXa, b, and c were found inactive in Clauberg (subcutaneous and oral) assays.[24] They were also devoid of androgenic–anabolic activity. 6α-Methyl-19-norprogesterone (XVII) was found to be an active progestational agent, both orally and subcutaneously in preliminary tests.

## Experimental[25]

3β,20β-Diacetoxy-5α-pregnan-6β-ol (IIIa).—To a solution of ketone IIa (0.085 g.) in methanol (5 ml.) was added a solution of sodium borohydride (0.035 g.) in methanol (2 ml.). After stirring overnight at room temperature, acetic acid (2 ml.) was added to destroy the excess hydride. The solution was evaporated to dryness and the residue was taken up in chloroform. This solution was washed with sodium bicarbonate solution and water and then dried. The removal of solvent left a crystalline solid (0.078 g.), which after one crystallization from acetone–hexane, gave alcohol IIIa (0.050 g.), m.p. 165–167°. An analytical sample[26] had m.p. 173–174°; [α] +2°; ν 3650 (nonbonded O–H), 3500 (bonded O–H), 1725 (acetate carbonyl) cm.⁻¹.

*Anal.* Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.59. Found: C, 71.58; H, 9.80.

3,20-Diethylenedioxy-5α-pregnan-6β-ol (IIId).—To a refluxing solution of ketone IIb (0.58 g.) in methanol (30 ml.) was added a solution of sodium borohydride (0.24 g.) in methanol (6 ml.) over a period of 5 min. Refluxing was continued for 1 hr., the solution was cooled, and excess hydride was destroyed by acetone (2 ml.). After removing the solvents, the residue was taken up in chloroform and the latter solution was washed with sodium bicarbonate solution and water and then dried. Evaporation of the solvent left a white solid (0.56 g.), m.p. 193–196°. Crystallization from methanol (containing a trace of pyridine) afforded needles, m.p. 200–202°; [α] +3°; ν 3640 (nonbonded O–H), 3520 (bonded O–H) cm.⁻¹.

*Anal.* Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.59. Found: C, 71.61; H, 9.59.

6β-Hydroxy-5α-pregnane-3,20-dione.—A solution of alcohol IIId (0.40 g.) in methanol (20 ml.) containing a drop of perchloric acid was heated on a steam bath for 15 min. The solution was cooled, diluted with water, and extracted with ether. Working up in the usual way gave a white solid, m.p. 234–237°. An analytical sample obtained from acetone–hexane melted at 236–239°; [α] +84°; ν 3630 (nonbonded O–H), 3500 (bonded O–H), 1700 (carbonyl stretching) cm.⁻¹.

*Anal.* Calcd. for $C_{21}H_{32}O_3$ (332.47): C, 75.88; H, 9.70. Found: C, 75.67; H, 9.77.

3β,20β-Diacetoxy-6α-methyl-5α-pregnan-6β-ol (IIIb).—To a solution of ketone IIa (6.0 g.) in dry benzene (570 ml.) was added a solution[25] (180 ml.) of methylmagnesium bromide. The solvent was distilled until the vapor temperature reached 75°. The reaction mixture was refluxed for 2 hr., cooled, and ethyl acetate

(140 ml.) was added followed by 10% hydrochloric acid (187 ml.). After separating the layers, the aqueous layer was extracted with ethyl acetate; the combined extracts were washed with sodium bicarbonate solution and water and then dried. The crude product (6.5 g.) obtained after removal of the solvent was acetylated with pyridine (42 ml.) and acetic anhydride (23 ml.) at room temperature overnight. Working up in the usual manner and crystallization of the crude acetate from aqueous methanol gave IIIb (4.5 g.), m.p. 197–199°. Several recrystallizations from chloroform–methanol afforded an analytical sample, m.p. 199–200°; [α] +10°; ν 3630 (nonbonded O–H), 1722 (acetate carbonyl) cm.⁻¹.

*Anal.* Calcd. for $C_{26}H_{42}O_5$ (434.60): C, 71.85; H, 9.74. Found: C, 72.05; H, 9.91.

3,20-Diethylenedioxy-6α-methyl-5α-pregnan-6β-ol (IIIe).—Crude ketone[8] IIb (5.0 g., m.p. 163–166°) was dissolved in tetrahydrofuran (125 ml., freshly distilled over lithium aluminum hydride). A solution (25 ml.) of methylmagnesium bromide[25] was slowly added in an atmosphere of nitrogen, and the reaction mixture was stirred at room temperature overnight. Addition of a saturated ammonium chloride solution was followed by extraction of the mixture with ethyl acetate. The combined extracts were washed to neutrality and dried. Removal of the solvent and one crystallization of the residue from methanol gave colorless crystals (3.76 g.), m.p. 187–189°. Recrystallization from the same solvent afforded an analytical sample, m.p. 188–191°; [α] +10°; ν 3640 (nonbonded O–H), 3520 (bonded O–H), 1103 (C–3 ketal), 1052 (C–20 ketal) cm.⁻¹.

*Anal.* Calcd. for $C_{26}H_{42}O_5$ (434.60): C, 71.85; H, 9.74. Found: C, 71.73; H, 9.82.

6β-Hydroxy-6α-methyl-5α-pregnane-3,20-dione.—A solution of alcohol IIIe (0.21 g.) in acetone (15 ml.) containing a drop of concentrated sulfuric acid was refluxed for 1 hr. After cooling, the solution was diluted with water and extracted with ether. The combined ether extracts were washed free of acid, dried, and evaporated to dryness. An infrared spectrum of the crude product (0.18 g.) showed the presence of some Δ⁴-3-ketone (1660 cm.⁻¹). Elution with benzene from an alumina[25] column (9.0 g.) gave 6β-hydroxy-6α-methyl-5α-pregnane-3,20-dione (0.075 g.). Two crystallizations from acetone–hexane gave fluffy needles, m.p. 214–215°; [α] +78°; ν 3628 (nonbonded O–H), 3500 (bonded O–H), 1710–1697 (broad band, C–3 and C–20 ketone) cm.⁻¹.

*Anal.* Calcd. for $C_{22}H_{34}O_3$ (346.49): C, 76.26; H, 9.89. Found: C, 76.15; H, 9.69.

3β,20β-Diacetoxy-5α-chloropregnan-6β-ol (IIIc). A. From 5β,6β-Epoxide.—Dry hydrogen chloride gas was bubbled through a solution of 3β,20β-diacetoxy-5β,6β-epoxypregnane (5.0 g.) in chloroform (200 ml.) for 1 hr. Removal of the solvent, followed by crystallization of the residue from ethyl acetate–hexane, gave prisms (4.35 g.), m.p. 199–200°. An analytical sample had m.p. 203–204°; [α] −20°; ν 3630 (nonbonded O–H), 3480 (bonded O–H), 1720 (acetate carbonyl) cm.⁻¹.

*Anal.* Calcd. for $C_{25}H_{39}O_5Cl$ (455.02): C, 66.13; H, 8.65; Cl, 7.81. Found: C, 65.95; H, 8.79; Cl, 7.86.

B. From 3β,20β-Diacetoxypregn-5-ene (Ia).—To a solution of olefin Ia (50 g.) in ether (600 ml.) were added acetic acid (40 ml.) and a solution of calcium hypochlorite (50 g.) in water (3000 ml.). The reaction[27] mixture was stirred at 35° for 40 min. The organic layer was then separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with sodium bicarbonate solution and water and then dried. Removal of the solvent and crystallization of the residue from ethyl acetate–hexane gave crystalline chlorohydrin IIIc (20 g.), m.p. 193–196°.

3β-Acetoxy-5α-bromo-17α-methyl-17β-carbomethoxyandrostan-6β-ol (IIIh).—To a stirred solution of olefin[28] Ic (1.0 g.) in dioxane (20 ml.) and water (5 ml.) was added N-bromosuccinimide (0.7 g.) followed by 70% perchloric acid (0.2 ml.) in water (1.0 ml.). Stirring was continued at room temperature for 35 min. Sodium bicarbonate was added to decolorize the solution which was then poured into an excess of water. The resulting oily precipitate was extracted with ether, and the combined ether extracts were washed with sodium bicarbonate solution and water and then dried. Crystallization from acetone–hexane of the residue obtained on removal of the solvent gave colorless needles (0.46 g.), m.p. 164–166° dec. Two recrystallizations from chloroform–

(24) (a) We wish to thank Dr. C. Revesz of our laboratories for pharmacological testing. (b) J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

(25) All melting points are uncorrected. Unless otherwise mentioned the following holds. Rotations were determined in chloroform (∼1% solution) with a sodium lamp at room temperature. Infrared spectra were recorded in chloroform, on a Perkin-Elmer (Model 21) spectrophotometer equipped with sodium chloride optics. Ultraviolet spectra were taken in ethanol with a Beckman (Model DK) recording instrument. N.m.r. spectra were recorded on a Varian 60-Mc. spectrometer. Florisil (60–100 mesh, Floridin Co.), alumina (Woelm activity III), and silica gel (Davison grade 923, 100–200 mesh) were used for column chromatography. Silica gel G (acc. to Stahl, E. Merck Co., Germany) was used for thin- and thick-layer chromatography. Lead tetraacetate and calcium carbonate were dried over phosphorus pentoxide under vacuum for 48 hr. Petroleum ether refers to that fraction with b.p. 30–60°. Organic extracts were dried over anhydrous magnesium sulfate and the solvents were removed under vacuum. Acetone used for oxidation was distilled over potassium permanganate. Benzene and cyclohexane used for lead tetraacetate reactions were dried over sodium. Dry pyridine was used for acetylations. Grignard solution was 3 *M* in ethyl ether (Arapahoe Chemicals, Inc.).

The authors wish to thank Dr. G. Papineau-Couture and his associates for analytical and spectral data. Assistance from Dr. G. Myers and his group in large scale preparations is gratefully acknowledged.

(26) This alcohol was recently reported by D. H. R. Barton, *et al.*, *J. Am. Chem. Soc.*, **83**, 4076 (1961).

(27) S. Mori, *J. Chem. Soc. Japan*, **64**, 981 (1943).

(28) R. Deghenghi and R. Gaudry, *J. Am. Chem. Soc.*, **83**, 46, 68 (1961).

hexane yielded an analytical specimen, m.p. 171.5–172.5°; [α] −50°; ν 3635 (nonbonded O–H), 3520 (bonded O–H), 1722 (acetate carbonyl) cm.⁻¹.

*Anal.* Calcd. for $C_{24}H_{37}O_5Br$ (485.46): C, 59.39; H, 7.68; Br, 16.47. Found: C, 59.29; H, 7.77; Br, 16.59.

**3β-Acetoxy-5α-bromo-17α-methyl-17β-carbomethoxyandrostan-6-one (IIe).**—Crude bromohydrin IIIh (5.7 g.), obtained as above, was dissolved in acetone[25] (100 ml.) and the solution was cooled to 0°. An 8 N chromic acid[29] solution (2.5 ml.) was added and stirring was continued for 4 min. The reaction mixture was diluted with water and extracted with ether. Working up in the usual manner afforded a white solid (5.27 g.), m.p. 168–170° dec. Two crystallizations from acetone gave prisms, m.p. 183.5–184° dec.; [α] −149°.

*Anal.* Calcd. for $C_{24}H_{35}O_5Br$ (483.44): Br, 16.54. Found: Br, 16.73.

**3β-Acetoxy-17α-methyl-17β-carbomethoxy-5α-androstan-6-one (IIc).**—Bromo ketone IIe (32.0 g.), prepared as above, was dissolved in acetic acid (1040 ml.) and zinc dust (128 g.) was added. The reaction mixture was refluxed with vigorous stirring for 3 hr.. filtered while hot, and the residue washed with ether. The filtrate was evaporated and a solution of the residue in ether was washed free of acid and dried. Removal of the solvent, followed by crystallization of the residue from aqueous methanol, afforded needles (21.0 g.), m.p. 147–150°. This compound was identical in all respects with ketone IIc described before.[8]

**3β-Acetoxy-6α,17α-dimethyl-17β-carbomethoxy-5α-androstan-6β-ol (IIIg).**—To a solution of ketone IIc (3.7 g., m.p. 150–157°) in anhydrous benzene (150 ml.) was added a solution[25] (37 ml.) of methylmagnesium bromide. The resulting precipitate was dissolved by adding dry tetrahydrofuran (5 ml.). The reaction solution was stirred at room temperature overnight and excess Grignard reagent was destroyed with saturated ammonium chloride solution. After extracting the aqueous phase with ethyl acetate, the organic extracts were washed with water and dried. The removal of solvent yielded an oil (3.4 g.). This oil was acetylated in the usual manner with pyridine (26 ml.) and acetic anhydride (14 ml.). One crystallization of the crude acetate from aqueous methanol gave colorless crystals (2.8 g.), m.p. 165–175°. An analytical sample obtained by more recrystallizations from the same solvent had m.p. 178–180°; [α] −12.5°; ν 3635 (nonbonded O–H), 1720 (acetate carbonyl) cm.⁻¹.

*Anal.* Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.59. Found: C, 71.09; H, 9.55.

**3β-Acetoxy-5α-bromo-6β-hydroxy-17α-methylpregnan-20-one (IIIf).**—To a solution 17α-methylpregnenolone acetate[28] (11.0 g.) in dioxane (176 ml.) and water (6.6 ml.) was added N-bromosuccinimide (7.7 g.) followed by 72% perchloric acid (2.2 ml.) in water (11 ml.). The mixture was stirred at room temperature for 30 min., solid sodium bisulfite was added, and the mixture was diluted with ice–water. The usual work-up with ether gave a residue, which, after one crystallization from acetone–hexane, yielded bromohydrin IIIf (5.1 g.), m.p. 166–168°. Several crystallizations from the same solvents gave an analytical sample, m.p. 175–176°; [α] −49°; ν 3635 (nonbonded O–H), 3490 (bonded O–H), 1725 (acetate carbonyl), 1692 (C–20 carbonyl) cm.⁻¹.

*Anal.* Calcd. for $C_{24}H_{37}O_4Br$ (469.46): C, 61.40; H, 7.94. Found: C, 61.62; H, 8.04.

**Lead Tetraacetate Reaction. Method A (i).**—To a solution of steroid in dry benzene was added lead tetraacetate[25] and the mixture was refluxed with stirring for 18–48 hr. The mixture was then cooled and an excess of 20% aqueous potassium iodide was added. The liberated iodine was neutralized with sodium thiosulfate solution. After separating the layers, the aqueous layer was extracted with benzene. The combined organic liquor was washed with water and then dried. Evaporation of the solvent gave the crude product.

**Method A (ii).**—In the cases where ketals were used, the above method was modified by pretreatment of the lead tetraacetate with anhydrous[25] calcium carbonate in the manner described by Kalvoda and co-workers.[30] The reaction was carried out in dry cyclohexane at reflux temperature and was worked up as described in method A (i).

**Method B (i).**—In this procedure, method A (i) was modified by adding iodine to the solution of the steroid, followed by lead tetraacetate.

**Method B (ii).**—Same procedure as method A (ii), except that the reaction was conducted in the presence of iodine.

**Treatment of 3β,20β-Diacetoxy-5α-pregnan-6β-ol (IIIa) with Lead Tetraacetate. Method A (i).**—To a solution of alcohol IIIa (3.14 g.) in benzene (300 ml.) was added lead tetraacetate (12.6 g.) and the reaction mixture was refluxed for 17 hr. The crude product (2.7 g.) obtained after the work-up gave, on crystallization from hexane, ketone IIa (2.0 g.). The residue from the mother liquor was chromatographed on Florisil[25] (28 g.) in benzene. Elution with ether–benzene (1:19) gave a solid, which on crystallization from acetone–hexane, afforded 3β,20β-diacetoxy-6β,19-oxido-5α-pregnane (IVa, 0.19 g.), m.p. 134–140°. An analytical sample obtained by recyrstallization from aqueous methanol had m.p. 147–147.5°; [α] +19°; ν 1719 (acetate carbonyl), 1492 (C-19 methylene) cm.⁻¹.

*Anal.* Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.61; H, 9.22.

**Method B (i).**—The above experiment was repeated with alcohol IIIa (0.80 g.) in the presence of iodine (0.92 g.). Crystallization of the crude product from hexane gave stout plates (0.54 g., 68%), m.p. 151–153°. This material was shown to be identical in all respects with 3β,20β-diacetoxy-6β,19-oxido-5α-pregnane (IVa) obtained above. A chromatography on Florisil[25] of the residue from the mother liquor afforded 0.12 g. more of the oxide IVa, m.p. 122–126°, whose infrared spectrum was essentially identical to that of the standard.

**3,20-Diethylenedioxy-6β,19-oxido-5α-pregnane (IVd). Method A (ii).**—Alcohol IIId (1.0 g.) was added to a stirred suspension of calcium carbonate (1.33 g.) and lead tetraacetate (4.5 g.) in cyclohexane (135 ml.). The reaction mixture was refluxed for 50 hr. An infrared spectrum of the crude product (0.91 g.), m.p. 175–179°, showed it to be a mixture of starting material (absorption band in the O—H stretching region), C-6 ketone (weak band at 1703 cm.⁻¹), and 6β,19-oxide (inflection at 1495 cm.⁻¹). Attempts to purify this material by column chromatography were unsuccessful. An analytical sample of 3,20-diethylenedioxy-6β,19-oxido-5α-pregnane (IVd) was successfully obtained by thick-layer chromatography[31] on silica gel,[25] m.p. 201–202°; [α] +16°; ν 1490 (C-19 methylene) cm.⁻¹.

*Anal.* Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.73; H, 9.25.

**Method B (ii).**—The above experiment was repeated with diketal alcohol IIId (2.0 g.) in the presence of iodine (2.24 g.). The reaction mixture was refluxed for 64 hr. and was worked up as described above. One crystallization from methanol gave oxide IVd (1.48 g.), m.p. 199–201°. A second crop (0.19 g.), m.p. 188–192°, was obtained on concentration of the mother liquor.

**6β,19-Oxido-5α-pregnane-3,20-dione (Va). A. From Diketal IVd.**—Crude 3,20-diethylenedioxy-6β,19-oxido-5α-pregnane (IVd, 2.0 g.) obtained by method A (ii) was dissolved in acetone (120 ml.) containing sulfuric acid (3 drops). This solution was heated on a steam bath for 20 min., cooled, and then diluted with water. Extraction with ether followed by the usual work-up gave a white solid (1.72 g.). A portion (1.68 g.) was dissolved in benzene and chromatographed on alumina[25] (75 g.). Elution with benzene gave a crystalline solid "A" (0.88 g.). Further elution with 2% ether–benzene gave 0.43 g. of material shown to be 6β,19-oxido-5α-pregnane-3,20-dione (Va).[32] Two crystallizations from acetone–hexane gave needles (0.12 g.), m.p. 214–218°; ν 1705 (C-3 and C-20 carbonyls), 1494 (C-19 methylene) cm.⁻¹.

*Anal.* Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 76.45; H, 9.02.

The solid "A" eluted with benzene was shown by its infrared spectrum to be the C-3 monoketal. Further treatment of this material with acid gave the diketone Va.

**B. From Diacetate IVa.**—Diacetate IVa (0.16 g., m.p. 125–132°) was dissolved in methanol (2.0 ml.) and a solution of potassium hydroxide (0.1 g.) in methanol (1.4 ml.) was added to it. The reaction solution was refluxed for 5 hr., cooled, and worked up in the usual way to give the corresponding diol (0.13 g.). This material was taken up in acetone[25] (10 ml.) and cooled to

(29) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(30) J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailovic, K. Schaffner, and A. Wettstein, *Helv. Chim. Acta*, 44, 186 (1961).

(31) We wish to thank Dr. G. Schilling of our laboratories for purification of compounds IVd, IVe, VIIIb, and XIIIb by thick-layer chromatography.

(32) An alternative synthetic route diketone Va has been recently described (see ref. 3).

0°. To this stirred solution was added 8 N chromic acid[29] solution (0.6 ml.) and stirring was continued for 5 min. Methanol was added and working up in the usual manner gave diketone Va (0.114 g.), m.p. 208–216°. The identity of this product was confirmed by mixture melting point and comparison of infrared spectra.

3β,20β-Diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb). Method A (i).—To a solution of diacetate IIIb (1.0 g.) in benzene (60 ml.) was added lead tetraacetate (4.0 g.) and the suspension was refluxed for 48 hr. Crystallization of the crude product from acetone–hexane gave colorless plates (0.46 g.), m.p. 169–171°. Several recrystallizations afforded an analytical sample, m.p. 175–176°; [α] +18°; ν 1722 (acetate carbonyl), 1492 (C-19 methylene) cm.⁻¹.

Anal. Calcd. for C₂₆H₄₀O₅ (432.58): C, 72.19; H, 9.32. Found: C, 72.47; H, 9.23.

Method B (i).—To a solution of diacetate IIIb (4.7 g.) in benzene (284 ml.) were added iodine (5.3 g.) and lead tetraacetate (19.0 g.), and the reaction mixture was refluxed for 48 hr. Crystallization of the crude product from acetone–hexane gave oxide IVb (3.1 g., 72%), m.p. 171–173°.

3,20-Diethylenedioxy-6α-methyl-6β,19-oxido-5α-pregnane (IVe). Method A (ii).—Diketal alcohol IIIe (1.89 g.) was added to a suspension of calcium carbonate (2.6 g.) and lead tetraacetate (8.1 g.) in cyclohexane (250 ml.). The reaction mixture was refluxed for 40 hr. The crude product was purified by chromatography on alumina[25] (85 g.) in hexane. Elution with benzene–hexane (2:1) afforded a yellow sirup (0.58 g.) which was identified in infrared spectrum (characteristic band at 1492 cm.⁻¹) as oxide IVe. Further elution with ether–benzene of increasing polarity, followed by elution with pure ether, afforded a crystalline solid (0.73 g.) identified as unchanged starting alcohol (IIIe) by its infrared spectrum.

The crude oxide (IVe, 0.58 g.) obtained above was rechromatographed on alumina[25] (24 g.). Elution with benzene–hexane (2:1) followed by elution with benzene afforded a crystalline solid (0.22 g.). One crystallization from methanol gave needles, m.p. 138–141°. An analytical sample prepared by using thick-layer chromatography[31] had m.p. 138–140°; [α] −16°; ν 1492 (C-19 methylene) cm.⁻¹.

Anal. Calcd. for C₂₆H₄₀O₅ (432.60): C, 72.19; H, 9.32. Found: C, 71.88; H, 9.14.

Method B (ii).—Diketal alcohol IIIe (1.0 g.) and iodine (1.12 g.) were added to a suspension of calcium carbonate (1.3 g.) and lead tetraacetate (4.0 g.) in cyclohexane (120 ml.). The mixture was refluxed with stirring for 64 hr. and the crude product was purified by chromatography on alumina (40 g.). Elution with benzene–hexane (1:1), followed by benzene gave crystals (0.80 g.). One crystallization from hexane afforded needles (0.55 g.), m.p. 130–132°. An infrared spectrum of this solid was identical with that of oxide IVe obtained above.

6α-Methyl-6β,19-oxido-5α-pregnane-3,20-dione (Vb). A. From Diketal IVe.—The oxide IVe (0.23 g.) was dissolved in acetone (10 ml.) containing a drop of sulfuric acid. The solution was heated on a steam bath for 20 min., cooled, and diluted with water. Extraction with ether and working up in the usual way gave a white solid (0.18 g.). Two crystallizations from acetone gave needles, m.p. 211–212°; [α] +130°; ν 1702 (C-3 and C-20 carbonyls), 1492 (C-19 methylene) cm.⁻¹.

Anal. Calcd. for C₂₂H₃₂O₃ (344.48): C, 76.70; H, 9.36. Found: C, 76.72; H, 9.21.

B. From Diacetate IVb.—The diacetate IVb (0.43 g.) was dissolved in methanol (20 ml.) containing potassium hydroxide (0.54 g.) and the solution was refluxed for 5.5 hr. Solvent was subsequently distilled from the solution until crystals began to appear and then the reaction mixture was cooled. Filtration of this mixture afforded 6α-methyl-6β,19-oxido-5α-pregnane-3β,-20β-diol (0.37 g.), m.p. 224–226°.

This diol was dissolved in acetone[25] (90 ml.) and oxidized with 8 N chromic acid[29] solution (1.5 ml.). Working up in the usual way gave a crystalline solid (0.30 g.), m.p. 205–208°. This material was shown to be 6α-methyl-6β,19-oxido-5α-pregnane-3,20-dione (Vb) by a mixture melting point and by comparison of its infrared spectrum with that of an authentic sample of Vb.

3β,20β-Diacetoxy-5α-chloropregnan-6-one (IId).—To a cooled solution (0°) of chlorohydrin IIIc (0.50 g.) in acetone[25] (60 ml.) was added 8 N chromic acid[29] solution (1.0 ml.), and the reaction mixture was stirred for 5 min. Methanol was added to destroy excess chromic acid and the solvent was removed. The residue was dissolved in chloroform and the solution was washed with

sodium bicarbonate solution and water and then dried. Evaporation of the solvent afforded a crystalline material, which after one crystallization from acetone–hexane, gave a colorless solid (0.42 g.), m.p. 148–149°. An analytical sample from the same solvent had m.p. 149–150°; [α] −100°; ν 1720 (acetate and C-6 carbonyls) cm.⁻¹.

Anal. Calcd. for C₂₅H₃₇O₆Cl (453.0): C, 66.28; H, 8.23. Found: C, 66.13; H, 8.08.

Lead Tetraacetate Reaction with 3β,20β-Diacetoxy-5α-chloropregnan-6β-ol (IIIc). Method A (i).—Lead tetraacetate (7.0 g.) was added to a solution of diacetate IIIc (1.8 g.) in benzene (75 ml.) and the reaction mixture was refluxed with stirring for 19 hr. The crude product (1.8 g.) obtained was refluxed with zinc (7.0 g.) and acetic acid (130 ml.) for 3 hr. and then filtered. After evaporating the filtrate to dryness, the residue was taken up in ether and the solution was washed free of acid and then dried. Removal of the solvent and crystallization of the residue from acetone–hexane gave 3β,20β-diacetoxy-5α-pregnan-6-one[8] (IIa, 0.69 g.), m.p. 180–182°. The residue (0.85 g.) from the mother liquor was chromatographed[25] on a column of Florisil (34 g.). Elution with benzene–ether (19:1) gave a solid (0.48 g.), which on crystallization from acetone–hexane, afforded 3β,20β-diacetoxy-5α-chloro-6β,19-oxidopregnane (IVc, 0.22 g.), m.p. 153–155°. An analytical sample from acetone–hexane had m.p. 155–156°; [α] +24°; ν 1721 (acetate carbonyl), 1497 (C-19 methylene) cm.⁻¹.

Anal. Calcd. for C₂₅H₃₇O₆Cl (453.0): C, 66.28; H, 8.23; Cl, 7.82. Found: C, 66.36; H, 8.34; Cl, 7.92.

The crude product obtained from another reaction of diacetate IIIc (1.0 g.) with lead tetraacetate was chromatographed on Florisil (40 g.)[25] in benzene. The crystalline eluate obtained with ether–benzene (1:49) was crystallized from ether–hexane to give a solid (0.84 g.), m.p. 146–148°. The presence of chloro ketone IId and the oxide IVd in this mixture was established by comparison of the Rf values on a t.l.c.[19] with the authentic samples. The mixture was shown to contain 93.5% of chloro ketone IId and 6.5% of oxide IVc based on its optical rotation (−91.7°).

Method B (i).—To a solution of diacetate IIIc (15.0 g.) in benzene (490 ml.) were added lead tetraacetate (60.0 g.) and iodine (16.8 g.), and the reaction mixture was refluxed for 18 hr. Crystallization of the crude product from acetone–hexane gave oxide IVc (11.9 g., 85%), m.p. 151–153°.

5α-Chloro-6β,19-oxidopregnane-3β,20β-diol (VII).—Diacetate IVc (5.0 g.) was dissolved in methanol (147 ml.), and a solution of potassium hydroxide (6.0 g.) in 50% aqueous methanol (96 ml.) was added to it. The reaction solution was refluxed for 5.5 hr. and concentrated under a stream of nitrogen until the product began to crystallize. The mixture was cooled and filtered to give stout plates (3.5 g.), m.p. 252–254°. One more crystallization did not alter the melting point.

Anal. Calcd. for C₂₁H₃₃O₃Cl (368.93): Cl, 9.61. Found: Cl, 9.37.

6α,17α-Dimethyl-17β-carbomethoxy-6β,19-oxido-5α-androstan-3β-ol (IVg). Method B (i).—To a solution of alcohol IIIg (1.0 g.) in benzene (60 ml.) were added lead tetraacetate (4.0 g.) and iodine (1.12 g.), and the reaction mixture was refluxed for 48 hr. The crude product (1.06 g.), which failed to crystallize from solvents, was dissolved in methanol (10 ml.) and to this was added a solution of potassium hydroxide (0.48 g.) in 50% aqueous methanol (7.6 ml.). After keeping at room temperature overnight, the reaction mixture was diluted with water and extracted with ether. The usual work-up gave a crude product (0.80 g.), which after one crystallization from acetone–hexane, afforded colorless plates (0.62 g.), m.p. 158–160°. An analytical sample had m.p. 159–160°; [α] +2°; ν 3621 (nonbonded O–H), 3432 (bonded O–H), 1720 (ester carbonyl), 1494 (C-19 methylene) cm.⁻¹.

Anal. Calcd. for C₂₃H₃₆O₄ (376.52): C, 73.36; H, 9.64. Found: C, 73.00; H, 9.62.

3β-Acetoxy-5α-bromo-6β,19-oxido-17α-methylpregnan-20-one (IVf). Method B (i).—To a solution of alcohol IIIf (6.0 g.) in benzene (250 ml.) were added lead tetraacetate (24 g.) and iodine (6.72 g.), and the reaction mixture was refluxed for 18 hr. The usual work-up yielded a crude product (5.9 g.) which was chromatographed on a column of Florisil[25] (236 g.) in benzene. Elution with ether–benzene (1:19) followed by solvents of increasing polarity up to ether gave a semisolid (4.1 g.) which solidified over hexane, m.p. 145–158°. An analytical sample obtained by several crystallizations from acetone–hexane had m.p. 168–169°; [α] −1°; ν 1725 (acetate carbonyl), 1691 (C-20 ketone), 1498 (C-19 methylene) cm.⁻¹.

*Anal.* Calcd. for $C_{24}H_{35}O_4Br$ (467.42): C, 61.80; H, 7.35. Found: C, 61.93; H, 7.54.

**3β-Acetoxy-5α-bromo-17α-methyl-17β-carbomethoxy-6β,19-oxidoandrostane (IVh). Method B (i).**—Lead tetraacetate (8.0 g.) and iodine (2.24 g.) were added to a solution of bromohydrin IIIh (2.0 g.) in benzene (120 ml.), and the reaction mixture was refluxed for 19 hr. The crude product (1.95 g.) was crystallized from chloroform–methanol to yield colorless crystals (1.2 g.), m.p. 186–190°. An analytical sample from the same solvents had m.p. 213–214°; $[\alpha]$ −15°; $\nu$ 1499 (C-19 methylene) cm.⁻¹.

*Anal.* Calcd. for $C_{24}H_{35}O_5Br$ (483.42): C, 59.69; H, 7.29. Found: C, 59.97; H, 7.64.

**6β,19-Oxidopregn-4-ene-3,20-dione (IXa).[33]**—To a solution of diol VII (3.3 g.) in acetone,[25] cooled to 0°, was added an 8 *N* chromic acid[29] solution (15 ml.), and the mixture was stirred and allowed to reach room temperature. Excess chromic acid was destroyed with methanol then hydrochloric acid (0.5 ml.) was added and stirring was continued for 4 hr. at room temperature. The solvent was removed and the residue was dissolved in chloroform. The resulting solution was washed with sodium bicarbonate solution and water and then dried. Evaporation of the solvent gave an oily residue (2.96 g.) which crystallized to give oxidoprogesterone IXa (2.1 g.), m.p. 140–142°. An analytical sample, obtained by crystallization from hexane, had m.p. 142–143°; $[\alpha]$ −24°; $\nu$ 1699 (C-20 ketone), 1670 (C-3 ketone), 1487 (C-19 methylene) cm.⁻¹; $\lambda_{max}$ 239 m$\mu$ ($\epsilon$ 12,500).

*Anal.* Calcd. for $C_{21}H_{28}O_3$ (328.43): C, 76.79; H, 8.59. Found: C, 76.93; H, 8.65.

**6β,19-Oxido-17α-methylpregn-4-ene-3,20-dione (IXb).**—To a solution of acetate IVf (0.52 g., m.p. 161–163°) in methanol (8 ml.) was added a solution of potassium hydroxide (0.2 g.) in methanol (3.0 ml.). After standing overnight the crystalline precipitate (0.32 g., m.p. 219–221°) was collected by filtration. A second crop (0.13 g., m.p. 213–216°) was obtained by concentration of the filtrate.

The crude diol (both crops, 0.43 g.) obtained above was dissolved in acetone.[25] To the stirred solution, at 0°, was added 8 *N* chromic acid[29] solution (1.7 ml.), and the reaction mixture was allowed to reach room temperature. After destroying excess chromic acid with methanol the solution was evaporated almost to dryness. The residue was taken up in chloroform, and the solution was washed with aqueous sodium bicarbonate solution and water and then dried. Removal of the solvent gave an oily solid (0.35 g.), $\lambda_{max}$ 240 m$\mu$ ($\epsilon$ 12,300). One crystallization from acetone–hexane gave crystals (0.27 g.), m.p. 170–171°. An analytical sample from the same solvents had m.p. 170–171°; $[\alpha]$ −103°; $\nu$ 1687 (C-20 ketone), 1665 (C-3 ketone), 1620 (Δ⁴ C=C), 1487 (C-19 methylene) cm.⁻¹.

*Anal.* Calcd. for $C_{22}H_{30}O_3$ (342.46): C, 77.15; H, 8.83. Found: C, 77.43; H, 9.05.

**3β-Hydroxy-5α-bromo-6α-methyl-6β,19-oxidopregnan-20-one (Xb).**—To a solution of triol VId (0.55 g.) in *t*-butyl alcohol (25 ml.) was added a solution of N-bromoacetamide (0.76 g.) in water (9.0 ml.). After stirring at room temperature for 18 hr., the reaction solution was decolorized by adding sodium bisulfite. Dilution with water, extraction with ether, and working up in the usual manner gave a crude product (0.63 g.). One crystallization from acetone–hexane gave colorless crystals (0.47 g., 69%), m.p. 180–182°. Several recrystallizations from chloroform–hexane gave an analytical sample, m.p. 188–189°; $[\alpha]$ +39°; $\nu$ 3620 (nonbonded O–H), 3455 (bonded O–H), 1696 (C-20 ketone), 1497 (C-19 methylene) cm.⁻¹.

*Anal.* Calcd. for $C_{22}H_{33}O_3Br$ (425.40): C, 62.11; H, 7.88. Found: C, 61.91; H, 8.10.

**Acid Treatment of Xb.**—To a solution of alcohol Xb (0.266 g.) in methanol (3.0 ml.) was added 3 drops of hydrochloric acid and the solution was left at room temperature overnight. Removal of the solvent gave a residue (0.245 g.) which was identical in all respects with the starting material.

**Base Treatment of Xb.**—To a solution of Xb (0.060 g.) in methanol (5.0 ml.) was added a solution of potassium hydroxide (0.05 g.) in 50% aqueous methanol (1.0 ml.) and the reaction solution was refluxed for 1 hr. The solution was then neutralized with 10% hydrochloric acid, diluted with water, and extracted with ether. Working up in the usual way gave a solid (0.060 g.)

whose infrared spectrum was identical with that of the starting material.

**5α-Bromo-6α-methyl-6β,19-oxidopregnane-3β,20β-diol (Xa).**—To a solution of triol VId (3.5 g.) in methanol (70 ml.) was added dropwise a solution of bromine (1.9 g., 1.1 mole) in acetic acid (4.0 ml.). The solution was then diluted with water and the precipitate (4.2 g.) thus obtained was collected by filtration, m.p. 213–215°. Two crystallizations raised the melting point to 228–230°. An infrared spectrum (saturated solution) had bands at 3620 (nonbonded O–H), 1496 (C-19 methylene) cm.⁻¹. Analysis of this sample indicated the presence of one atom of bromine (calcd. 18.69; found 18.05).

**6α-Methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc). A. From Alcohol Xb.**—A solution of Xb (0.35 g.) in acetone[25] was cooled to 0° and to it 8 *N* chromic acid[29] solution (1.0 ml.) was added. The reaction mixture was allowed to reach room temperature and then methanol was added. After removal of the solvent the residue was taken up in ether and worked up as usual to give a tarry residue (0.28 g.) which was chromatographed on a column of Florisil[25] (12 g.) in benzene. Elution with ether–benzene (3:7 and 1:1) gave crystalline material which after one crystallization from acetone–hexane afforded 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc, 0.066 g.), m.p. 172–174°. An analytical specimen had m.p. 175–176°; $[\alpha]$ −101°; $\nu$ 1698 (C-20 ketone), 1666 (C-3 ketone), 1485 (C-19 methylene) cm.⁻¹; $\lambda_{max}$ 238 m$\mu$ ($\epsilon$ 13,600).

*Anal.* Calcd. for $C_{22}H_{30}O_3$ (342.46): C, 77.15; H, 8.83. Found: C, 77.09; H, 8.88.

**B. From Diol Xa.**—A solution of chromic anhydride (1.9 g.) in acetic acid (50 ml.) and water (2.0 ml.) was added to a solution of diol Xa (4.2 g., m.p. 213–215°) in acetic acid (100 ml.). The reaction solution was stirred for 2.5 hr. then diluted with water, and the solid (4.0 g.) which precipitated was collected by filtration. This solid was dissolved in methanol (90 ml.) containing 2 drops of concentrated hydrochloric acid. After standing overnight at room temperature, the solution was diluted with water, extracted with ethyl acetate, and worked up in the usual way. One crystallization of the crude product (2.8 g.) from acetone–hexane gave colorless prisms (2.2 g., 64% from triol VId), m.p. 173–175°. This compound was shown to be identical to 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc) in all respects.

**Acid Treatment of Triol VId.**—To a solution of triol VId (0.05 g.) in methanol (5.0 ml.) was added 3 drops of hydrochloric acid and this was heated for 1 hr. on a steam bath. The residue (0.05 g.) obtained on removal of the solvent was directly acetylated with pyridine and acetic anhydride and a crystalline solid (0.06 g.), m.p. 160–164°, was obtained on working up in the usual way. This diacetate was shown by comparison of its infrared spectrum and mixed melting point with an authentic sample to be identical with 3β,20β-diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb).

**3β,19,20β-Triacetoxypregn-5-ene (VIa).**—A solution of crude diol VII (3.0 g., m.p. 253–255°) in dry tetrahydrofuran (110 ml.) was added over 25 min. to a solution of lithium (3.0 g.) in liquid ammonia (450 ml.). The reaction solution was stirred for 10 min., saturated ammonium chloride solution (17 ml.) was carefully added, and then the ammonia was removed. Water was added gradually and the layers were subsequently separated. The aqueous layer was further extracted with tetrahydrofuran, and the combined organic liquor was worked up in the usual way to give the crude product (3.2 g.). This was acetylated with pyridine (58 ml.) and acetic anhydride (29 ml.) to yield the crude triacetate VIa (3.7 g.). One crystallization from aqueous methanol gave colorless needles (2.32 g.), m.p. 137–138.5°. An analytical sample from methanol had m.p. 143–144°; $[\alpha]$ −60°; $\nu$ 1722 (acetate carbonyl) cm.⁻¹.

*Anal.* Calcd. for $C_{27}H_{40}O_6$ (460.59): C, 70.40; H, 8.75. Found: C, 70.23; H, 9.00.

**Pregn-5-ene-3β,19,20β-triol (VIc). A. By Hydrolysis of Triacetate VIa.**—Triacetate VIa (2.3 g., m.p. 137–138.5°) was dissolved in methanol (69 ml.) and a solution of potassium hydroxide (2.97 g.) in 50% aqueous methanol (46 ml.) was added to it. The reaction solution was refluxed for 5.5 hr., and the solvent was removed until crystallization set in. After cooling, the triol VIc (1.6 g.), m.p. 225–230°, was collected by filtration. An infrared spectrum of this material (in Nujol) showed strong hydroxylic absorption and the absence of acetate bands.

**B. From Diacetate Oxide IVa.**—The oxide IVa (0.47 g.) was dissolved in acetic acid (3.0 ml.) and acetic anhydride (0.84 ml.) and *p*-toluenesulfonic acid (0.005 g.) was then added. The reaction solution was refluxed for 2 hr., diluted with methanol,

(33) Since completion of this work a modified route to compound VIIIb [K. Heusler, *et al.*, *Helv. Chim. Acta*, **45**, 2161 (1962)] and the synthesis of compound IXa [K. Heusler, *et al.*, *Experientia*, **18**, 464 (1962)] have appeared in the literature.

and the solvents removed under reduced pressure. The residue was taken up in ether, the solution was washed with sodium bicarbonate solution and water, and then dried. Removal of the solvent left an oily material (0.527 g.) which was hydrolyzed as described above. The crude triol VIc (0.21 g.) was subsequently purified by chromatography on Florisil (8.0 g.). Elution with methanol–chloroform (1:49) gave a solid which after one crystallization from chloroform–hexane yielded a material (0.11 g.) with m.p. 185–191°. T.l.c.[19] of this substance showed it to be mainly triol VIc. An n.m.r. spectrum of this sample was identical with that of the authentic triol VIc.

Oxidation of Triol VIc with Chromic Acid.—To a stirred solution of triol VIc (1.0 g.) in acetone[25] (45 ml.) at 10° was added an excess of 8 N chromic acid[29] solution. The cooling bath was removed and stirring was continued for 10 min. After methanol had been added to destroy excess oxidant the reaction mixture was diluted with water, extracted with ethyl acetate, and worked up in the usual way to give a yellow oil (0.75 g.). Two crystallizations from methanol gave lactone XIIIb (0.074 g.), m.p. 175–178°. Thick-layer chromatography[31] of the mother liquors afforded a further 0.053 g. of lactone XIIIb, m.p. 183–184°. An analytical sample from methanol had m.p. 183–184°; $[\alpha]$ +2°; $\nu$ 1736 (lactone carbonyl), 1697 (C-20 ketone) cm.$^{-1}$; $\lambda_{max}$ 228 m$\mu$ ($\epsilon$ 1330).

*Anal.* Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.83; H, 8.68.

5α-Bromo-6β,19-oxidopregnane-3β,20β-diol (Xc).—Bromine (1.46 g.) in acetic acid (13.5 ml.) was slowly added to a stirred solution of triol VIc (2.7 g.) in methanol (55 ml.) until a pale color persisted. Stirring was continued for 10 min. longer and dilution with water precipitated the crude product (2.85 g.), m.p. 205–216° dec. An analytical sample obtained after several crystallizations from methanol had m.p. 219–221° dec.; $[\alpha]$ −18°; $\nu$ 1497 (C-19 methylene) cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{33}O_3Br$ (413.39): C, 61.04; H, 8.04; Br, 19.32. Found: C, 60.93; H, 7.75; Br, 19.62.

Conversion of Diol Xc to 6β,19-Oxidoprogesterone (IXa).—Chromic anhydride (0.7 g.) was dissolved in acetic acid (16.0 ml.) and water (0.7 ml.) and this was added to a stirred solution of diol Xc (1.42 g.) in acetic acid (33.0 ml.). Stirring was continued at room temperature for 4 hr., and the solution was then poured into water. The solid (1.2 g.) which precipitated was collected by filtration, subsequently dissolved in methanol (25 ml.) containing concentrated hydrochloric acid (0.25 ml.), and left at room temperature overnight. Dilution with water, extraction with ether, and working up in the usual way gave a foam (0.7 g.). Crystallization from ether afforded crystals (0.17 g.), m.p. 136–138°; $[\alpha]$ −20°. This solid was shown by its ultraviolet and infrared spectra and by a mixture melting point to be 6β,19-oxidoprogesterone (IXa).

19-Hydroxypregn-4-ene-3,20-dione (VIIIa). A. From Diketal Oxide (IVd).—p-Toluenesulfonic acid (0.028 g.) was added to a solution of oxide IVd (0.28 g.) in acetic anhydride (28 ml.). The reaction solution was refluxed for 1.25 hr., cooled, and diluted with methanol. After removing the solvents under reduced pressure, the residue was taken up in ether and worked up in the usual way to give a brown sirup (0.425 g.), $\nu$ 1735 (acetate carbonyl), 1700 (C-20 ketone), 1665 (Δ⁴-3-ketone) cm.$^{-1}$; $\lambda_{max}$ 238 m$\mu$ ($\epsilon$ 8380).

The above product was dissolved in methanol (50 ml.) containing potassium hydroxide (1.0 g.) and the solution was refluxed for 45 min. The solution was concentrated under reduced pressure, diluted with water, and extracted with ether. Working up in the usual way gave an oil (0.215 g.) which was chromatographed on a column of Florisil (10.0 g.). Elution with methanol–ether (1:19) gave a solid (0.078 g.) which after two crystallizations from ether afforded 19-hydroxyprogesterone (VIIIa), m.p. 168–170°; $\nu$ 3640 (nonbonded O–H), 3460 (bonded O–H), 1700 (C-20 ketone), 1662 (Δ⁴-3-ketone) cm.$^{-1}$; $\lambda_{max}$ 243 m$\mu$ ($\epsilon$ 15,000). Reported[2a] m.p. 170–171°; $\lambda_{max}$ 242 m$\mu$ ($\epsilon$ 12,900).

B. From Triol VIc.—To a solution of triol VIc (0.50 g.) in dry toluene (40 ml.) and cyclohexanone (8.0 ml.) was added a solution of aluminum isopropoxide (0.8 g.) in dry toluene (10 ml.). The reaction mixture was refluxed for 4 hr., cooled, and washed with dilute hydrochloric acid, sodium bicarbonate solution, and water. The organic liquor was steam distilled and the residue was extracted with ether and worked up in the usual way. Chromatography of the crude product on a column of Florisil[25] (20 g.) gave, on elution with methanol–ether (1:19), a solid (0.088 g.) which after crystallization from acetone–ether had m.p.

150–155°; $\lambda_{max}$ 243 ($\epsilon$ 12,000). An infrared spectrum of this sample was essentially identical with that of VIIIa obtained by method A. T.l.c.[19] of this material with the product obtained by method A showed a major spot at the same $R_f$ value as that of the latter substance.

6-Methylpregn-5-ene-3β,19,20β-triol (VId).—To a solution of oxide IVb (18.5 g.) in acetic acid (500 ml. and acetic anhydride (250 ml.) was added p-toluenesulfonic acid (1.57 g.) and this was stirred at room temperature for 44 hr. The solution was then diluted with methanol and subsequently evaporated to dryness. The residue was taken up in ether and worked up in the usual way to give a sirup (20.6 g.) whose infrared spectrum indicated the absence of the characteristic oxide band (1496 cm.$^{-1}$). This sirup was dissolved in methanol (300 ml.), and a solution of potassium hydroxide (20 g.) in 50% aqueous methanol (240 ml.) was added to it. The solution was refluxed for 5 hr. and solvent was removed until crystallization set in. After cooling the mixture, the precipitated solid (13.15 g.), m.p. 202–204°, was collected by filtration. An analytical sample obtained from acetone–hexane had m.p. 203–204°; $\nu$ (saturated solution) 3630 (nonbonded O–H) cm.$^{-1}$.

*Anal.* Calcd. for $C_{22}H_{36}O_3$ (348.51): C, 75.81; H, 10.41. Found: C, 75.60; H, 10.20.

Reacetylation of triol VId (0.50 g.) with pyridine (4.0 ml.) and acetic anhydride (1.5 ml.) afforded a sirupy triacetate VIb whose infrared spectrum was identical with that of the triacetate obtained above by acid catalyzed cleavage of the oxide IVb. This sirup slowly crystallized over petroleum ether (b.p. 30–60°) and the crystals (0.40 g.), m.p. 102–105°, were collected by filtration. An n.m.r. spectrum of this solid was in complete agreement with the structure VIb.

Oxidation of Triol VId. A. With Chromic Acid.—To a solution of triol VId (0.80 g.) in acetone[25] (130 ml.) cooled to 0° was added 8 N chromic acid[29] solution (6.25 ml.). The reaction mixture was stirred and allowed to reach room temperature. Excess chromic acid was destroyed with methanol and the solvents were removed. The residue was taken up in chloroform and worked up in the usual way to give a sirup (0.70 g.), which crystallized from chloroform–methanol as colorless needles of lactone XIIIa (0.29 g.), m.p. 190–198°. An analytical specimen from the same solvents had m.p. 201–202°; $[\alpha]$ −70°; $\nu$ 1737 (lactone carbonyl), 1698 (C-20 ketone) cm.$^{-1}$; $\lambda_{max}$ 231 m$\mu$ ($\epsilon$ 3350).

*Anal.* Calcd. for $C_{22}H_{30}O_3$ (342.46): C, 77.15; H, 8.83. Found: C, 77.14; H, 8.71.

B. With Pyridine–Chromic Acid.—A pyridine–chromic acid complex was prepared from pyridine (10.0 ml.) and chromic acid (1.0 g.). To it was added a solution of triol VId (0.50 g.) in pyridine (10 ml.), and the reaction mixture was stirred at room temperature overnight. After filtering the reaction mixture the filtrate was diluted with water and extracted with benzene. The combined extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution, and water and then dried. Removal of solvent gave a brown oil (0.35 g.) whose infrared spectrum was essentially identical with that of lactone XIIIa. One crystallization from chloroform–methanol yielded a substance (0.15 g.), m.p. 189–196°, which was shown to be identical in all respects to the lactone XIIIa.

3β-Hydroxy-6-methylpregn-5-en-20-on-19-oic Acid (XIVa).—Lactone XIIIa (0.88 g.) was dissolved in a 0.1 N ethanolic sodium hydroxide solution (90 ml.) and refluxed for 2.5 hr. Ethanol was removed and the residue was taken up in water, cooled in an ice-water bath, and acidified with concentrated hydrochloric acid. The precipitated carboxylic acid XIVa (0.80 g.), m.p. 224–228°, was collected by filtration. An infrared spectrum (Nujol) showed the characteristic hydroxyl stretching band (3448 cm.$^{-1}$) of an acid and carbonyl bands at 1712 (carboxyl group) and 1684 (C-20 ketone) cm.$^{-1}$. The above material was repurified once through its sodium salt to give a crystalline solid (0.60 g.), m.p. 225–228°, and was used in the following experiment.

Methyl Ester of Carboxylic Acid XIVa.—To a solution of carboxylic acid XIVa (0.56 g.) in methanol, cooled to 0°, was added excess diazomethane solution in ether and the reaction solution was kept between 0–5° for 10 min. The solvents and excess diazomethane were removed under nitrogen atmosphere and the crude product crystallized from methanol to give colorless crystals of 3β-hydroxy-6-methylpregn-5-en-20-on-19-oic acid methyl ester (XIVb, 0.60 g.), m.p. 185–191°. Several crystallizations from the same solvent gave an analytical sample, m.p. 195–196°; $[\alpha]$ −60°; $\nu$ 3619 (nonbonded O–H), 3480 (bonded O–H), 1717 (ester carbonyl), 1700 (C-20 ketone) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 74.01; H, 9.38.

**6α-Methyl-19-hydroxypregn-4-ene-3,20-dione (VIIIb)[33].**—To a solution of triol VId (15.0 g.) in dry toluene (1200 ml.) and cyclohexanone (240 ml.) was added a solution of aluminum isopropoxide (24 g.) in dry toluene (50 ml.), and the reaction mixture was refluxed for 3.75 hr. After cooling the reaction mixture it was washed with dilute hydrochloric acid, sodium carbonate solution, and water. The organic solution was steam distilled and the residue was extracted with ether and worked up in the usual way. The crude product (16.0 g.) was chromatographed on a column[25] of Florisil (450 g.) in benzene. Elution with benzene–ether (9:1) gave, as a first fraction, an oil (1.1 g.) which crystallized slowly. Two recrystallizations from acetone–hexane gave colorless needles (0.31 g.) of a phenol (XIXa or b), m.p. 210–212°. An analytical sample from the same solvents had m.p. 219–220°; [α] +76.5°; ν 3625 (nonbonded O–H), 3420 (bonded O–H), 1696 (C-20 ketone), 1592 (aromatic C=C stretching) cm.⁻¹; $\lambda_{max}$ 284 mμ ($\epsilon$ 1570).

*Anal.* Calcd. for $C_{22}H_{30}O_2$ (326.46): C, 80.93; H, 9.26. Found: C, 81.20; H, 9.26.

Further elution with benzene–ether (1:1), ether, and ether–methanol (9:1) afforded a semisolid which, on trituration with ether, gave 6α-methyl-19-hydroxypregn-4-ene-3,20-dione (VIIIb, 2.65 g.), m.p. 178–180°; [α] +150°; ν 3640 (nonbonded O–H), 3440 (bonded O–H), 1696 (C-20 ketone), 1660 (Δ⁴-3-ketone) cm.⁻¹; $\lambda_{max}$ 242 mμ ($\epsilon$ 14,400).

*Anal.* Calcd. for $C_{22}H_{32}O_3$ (344.48): C, 76.70; H, 9.36. Found: C, 76.84; H, 9.03.

**6α-Methyl-19-norpregn-4-ene-3,20-dione (XVII).**—To a solution of chromic anhydride (2.1 g.) in pyridine (50 ml.) and water (25 ml.) was added a solution of alcohol VIIIb (1.0 g.) in pyridine (30 ml.), and the reaction solution was stirred at 60–65° for 1.5 hr. The solution was then poured into ice–water, extracted with ether, and worked up in the usual way to give a sirup (0.80 g.). An infrared spectrum of this material had an absorption band at 2730 (aldehydic C—H stretching) and another new band (shoulder) at 1717 (aldehyde carbonyl) cm.⁻¹.

The above material was dissolved in methanol (40 ml.) and poured into 4% aqueous sodium hydroxide solution (380 ml.), and this was stirred at 50–55° for 45 min. The reaction mixture was cooled, extracted with ether, and worked up in the usual way to give the crude product (0.69 g.). One crystallization from acetone–hexane gave a substance (0.35 g.) with m.p. 108–110°. An analytical specimen obtained by several recrystallizations from the same solvents had m.p. 113.5–114.5°; [α] +97°; ν 1700 (C-20 carbonyl), 1665 (Δ⁴-3-ketone) cm.⁻¹; $\lambda_{max}$ 241 mμ ($\epsilon$ 16,000).

*Anal.* Calcd. for $C_{21}H_{30}O_2$ (314.45): C, 80.21; H, 9.62. Found: C, 80.31; H, 9.49.

**6-Methyl-19-hydroxypregna-4,6-diene-3,20-dione (XX).**—A solution of 6α-methyl-6β,19-oxidoprogesterone (IXb, 2.7 g.) in acetic acid (80 ml.) and acetic anhydride (40 ml.) containing p-toluenesulfonic acid (0.26 g.) was stirred at room temperature for 40 hr. After dilution with methanol the solvents were removed and the residue was taken up in ether and worked up in the usual way to give a pale brown sirup (2.8 g.). An infrared spectrum showed bands at 1732 (acetate carbonyl), 1700–1660 (C-20 ketone and Δ⁴,⁶-3-ketone), 1627, 1585 (Δ⁴ and Δ⁶ double bonds) cm.⁻¹.

To a solution of the crude product obtained above in methanol (70 ml.) was added a solution of potassium carbonate (6.3 g.) in water (50 ml.) and this was kept at room temperature under nitrogen overnight. Dilution with water, extraction with ether, and working up in the usual way yielded a pale yellow sirup (2.32 g.). This was chromatographed on a column[25] of Florisil (80 g.) in benzene. Elution with benzene–ether (8:2 and 1:1) gave a colorless oil (1.5 g.) which crystallized over ether to give prisms (0.88 g.), m.p. 114–116°. An analytical sample from acetone–hexane had m.p. 116–117°; [α] +160°; ν 3640 (nonbonded O–H), 3465 (bonded O–H), 1697 (C-20 ketone), 1655 (Δ⁴,⁶-3-ketone), 1623 and 1581 (Δ⁴ and Δ⁶ double bonds) cm.⁻¹; $\lambda_{max}$ 290 mμ ($\epsilon$ 27,550).

*Anal.* Calcd. for $C_{22}H_{30}O_3$ (342.46): C, 77.15; H, 8.83. Found: C, 77.29; H, 8.84.

**6-Methyl-19-norpregna-4,6-diene-3,20-dione (XXI).**—A solution of alcohol XX (0.68 g., m.p. 114–116°) in pyridine (10 ml.) was added to a solution of chromic anhydride (1.5 g.) in water (16 ml.) and pyridine (33 ml.) and this was stirred at 74° (bath temperature) for 1.5 hr. The reaction solution was cooled and poured into 10% hydrochloric acid (208 ml.) containing crushed ice. Extraction with ether and working up in the usual way gave an oil (0.63 g.) whose infrared spectrum showed absorption at 2750 (aldehydic C—H stretching), and 1720 (shoulder, aldehyde carbonyl) cm.⁻¹.

The oil was dissolved in methanol (14 ml.) and added to a 4% sodium hydroxide solution (153 ml.). After stirring at 66° (bath temperature) for 1 hr., the crude product (0.30 g.) was isolated by extraction with chloroform and working up in the usual way. This material was chromatographed on a column of silica gel[25] (15 g.) in benzene. Elution with benzene–ether (9:1) gave a solid material (0.18 g.) which after two crystallizations from acetone–hexane afforded 0.083 g. of substance, m.p. 149–155°. An analytical sample from the same solvent pair had m.p. 155–156°; [α] +115°; ν 1697 (C-20 ketone), 1655–1650 (Δ⁴,⁶-3-ketone), 1622, 1581 (Δ⁴ and Δ⁶ double bonds) cm.⁻¹; $\lambda_{max}$ 289 mμ ($\epsilon$ 24,600).

*Anal.* Calcd. for $C_{21}H_{28}O_2$ (312.44): C, 80.73; H, 9.03. Found: C, 80.97; H, 8.88.

# Reactive Cleavage of *tert*-Alkyl Aromatic Hydrocarbons by Carbon Monoxide and Strong Acids

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The reaction of carbon monoxide with *tert*-alkyl aromatic hydrocarbons has been studied. High yields of α,α'-dialkyl substituted carboxylic acids are produced by cleavage and reaction of the *tert*-alkyl fragment with carbon monoxide.

The reaction of olefins with carbon monoxide and water to produce carboxylic acids has been studied extensively by Koch and co-workers.[4,5] The carbonylation goes readily at near room temperature under moderate carbon monoxide pressures in the presence of strong acid catalysts. Hydrolysis of the intermediate product–catalyst complex results in high yields of carboxylic acids. Friedman and Cotton[6] recently published a work on carbonylation using anhydrous hydrogen fluoride as catalyst. During the course of this study they showed that *tert*-butylbenzene undergoes reactive cleavage in the presence of hydrogen fluoride and carbon monoxide to produce moderate yields of benzene and trimethylacetic acid. The reactive cleavage of *tert*-alkyl aromatic hydrocarbons under carbonylation conditions using boron trifluoride monohydrate as catalyst has been studied in more detail in this laboratory. High yields of the aliphatic acids expected from addition of carbon monoxide to the tertiary carbonium ions resulting from alkyl group cleavage were produced.

When catalyst is used in molar excess, yields approach the theoretical. Results of carbonylation of selected *tert*-alkyl aromatic hydrocarbons using a boron trifluoride monohydrate/aromatic hydrocarbon ratio of 2 are shown in Table I. It is seen that even under these relatively mild conditions conversions are excellent and selectivities for the expected aliphatic

### TABLE I

#### CARBONYLATION OF *tert*-ALKYL AROMATIC HYDROCARBONS

Conditions: CO pressure      500 p.s.i.g.
         Temperature      25°
         Reaction time      2 hr.
         $BF_3 \cdot H_2O$/hydrocarbon      2.0 (*M*)

| Expt. no. | Hydrocarbon | Hydrocarbon converted, % | Yield of acid[a] | Yield of parent hydrocarbon[a] |
|---|---|---|---|---|
| 1 | 1,3-Dimethyl-5-*tert*-butyl-benzene | 93.0 | 89.5 | 98.4[b] |
| 2 | 1,3-Dimethyl-5-*tert*-pentyl-benzene | 72.2 | 97.5 | 99.7[b] |
| 3 | 1-Methyl-5-*tert*-pentyl-benzene | 74.9 | 97.9 | 99.7[c] |
| 4 | *tert*-Butylbenzene | 46.3 | 78.9 | 95.7[d] |

[a] Mole % on aromatic converted.    [b] *meta*-Xylene.    [c] Toluene.
[d] Benzene.

acids and the cleaved aromatic hydrocarbons are high. Of the *tert*-alkyl aromatic hydrocarbons studied, it is apparent that 1,3-dimethyl-5-*tert*-butylbenzene gives the highest conversions and that *tert*-pentyl aromatics were converted to a lesser extent than the *tert*-butyl homologs.

Lowering the catalyst to hydrocarbon ratio to one reduced conversions. This effect is shown in Table II. It is apparent that a molar excess of catalyst over hydrocarbon is required for high conversions. Since catalyst is tied up as a complex with the carbonylation product, the excess acid is likely necessary to cause cleavage to proceed to near completion; alkyl group cleavage is likely necessary before carbonylation can occur.

### TABLE II

#### CARBONYLATION OF 1,3-DIMETHYL-5-*tert*-BUTYLBENZENE

Conditions: CO pressure      500 p.s.i.g.
         Temperature      25°
         Reaction time      2 hr.

| Expt. no. | 1 | 5 | 6 |
|---|---|---|---|
| $BF_3 \cdot H_2O$/hydrocarbon (*M*) | 2.0 | 1.0 | 0.5 |
| Hydrocarbon converted | 93.0 | 58.6 | 30.0 |
| Yield of trimethylacetic acid[a] | 89.5 | 97.9 | 91.7 |
| Yield of *meta*-xylene[a] | 98.4 | 97.0 | 92.6 |

[a] Mole % on hydrocarbon reacting.

The high selectivity of the carbonylation of *tert*-alkyl aromatic hydrocarbons is believed to be due to the alkylation–dealkylation equilibrium as illustrated with
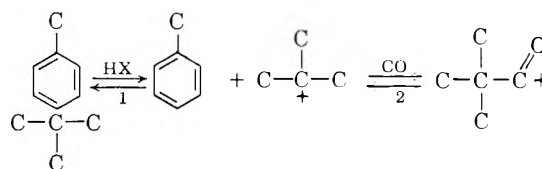


*tert*-butyltoluene. Since the equilibrium for reaction 1 lies far to the left under conditions employed in this study, it is apparent that *tert*-butyl ions are fed into the system only at the rate that they are consumed by the carbonylation reaction. Polymerization, which is a major side reaction in carbonylation of branched olefins, is not significant here since the carbonium ion concentration is regulated by the position of equilibrium 1. For this reason maintenance of a low olefin or *tert*-alkyl ion concentration results in high selectivities for acid formation.

To illustrate this, a series of runs was made in which carbonylation of a *tert*-alkyl aromatic, an isoölefin in presence of an aromatic, and an isoölefin alone were compared using a catalyst to alkyl group ratio of one. In Table III the yields of trimethylacetic acid produced

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(4) H. Koch, *Riv. Combust.*, **10**, 77 (1956); *Brennstoff-Chem.*, **36**, 321 (1956).

(5) H. Koch, U. S. Patent 2,831,877 (April 22, 1958); Belgian Patent 518,682 (March 4, 1955).

(6) B. S. Friedman and S. M. Cotton, *J. Org. Chem.*, **27**, 481 (1962).

TABLE III

EFFECT OF *tert*-BUTYL SOURCE

Conditions: CO pressure    500 p.s.i.g.
           Temperature       25°
           Time           2 hr.

| Expt. no. | 5 | 7 | 8 |
|---|---|---|---|
| Hydrocarbon charged (moles) | | | |
|    1,3-Dimethyl-5-*tert*-butylbenzene | 4.01 | ... | ... |
|    *meta*-Xylene | ... | 3.86 | ... |
|    2-Methylpropene | ... | 3.80 | 3.89 |
| BF$_3$·H$_2$O charged (moles) | 4.00 | 3.80 | 3.89 |
| *tert*-Butyl groups consumed | | | |
|    (mole %)[a] | 58.6 | 61.3 | 100.0 |
| Selectivity for trimethylacetic acid[b] | 97.9 | 49.7 | 36.5 |
| 1,3-Dimethyl-5-*tert*-butylbenzene | | | |
|    recovered[a] (mole %) | 41.4[c] | 11.6[d] | ... |

[a] That reacting to form products other than 1,3-dimethyl-5-*tert*-butylbenzene. [b] Calculated on *tert*-butyl groups reacting as in a. [c] Unchanged. [d] Formed by reaction.

by carbonylation of 1,3-dimethyl-5-*tert*-butylbenzene are compared with those produced by direct carbonylation of 2-methylpropene alone and in the presence of *meta*-xylene. In the case of the latter two runs the olefin was fed slowly into the reaction vessel containing the other reactants in order to minimize polymerization, whereas the 1,3-dimethyl-5-*tert*-butylbenzene was all charged at once. The *tert*-alkyl aromatic hydrocarbon gave higher yields of acid than either the olefin with *meta*-xylene or the olefin alone. In the latter cases the 2-methylpropene not going to acid was largely lost to polymer, while with 1,3-dimethyl-5-*tert*-butylbenzene the *tert*-butyl groups not converted to carboxylic acid were retained on the aromatic ring.

Several catalysts other than boron trifluoride monohydrate were tested for this reaction but were found to be ineffective. These included phosphoric acid, sulfuric acid, and methanesulfonic acid. Although anhydrous hydrogen fluoride was not tried, it would be expected to be an effective catalyst in light of the paper by Friedman and Cotton.

Carbonylation of isopropylbenzene was attempted using boron bifluoride monohydrate catalyst, under the conditions of Table I, but not even the odor of isobutyric acid was detectable. Friedman and Cotton were equally unsuccessful in carbonylation of isopropylbenzene in the presence of hydrofluoric acid. This is likely due to the failure of the isopropyl group to cleave under the conditions used.

Due to the specificity of this reaction for *tert*-alkyl groups, it may find utility not only as a method for synthesis of acids, but also as a degradative method of structure determination.

## Experimental

**Catalysts and Reactants.**—The boron trifluoride monohydrate catalyst was prepared by saturating deionized water with anhydrous boron trifluoride at about room temperature as previously described.[7] The carbon monoxide used was a commercial product of the Matheson Company.

1,3-Dimethyl-5-*tert*-butylbenzene was prepared by alkylating *meta*-xylene (95%) with technical grade (98%) diisobutylene (Petro-Tex Chemical Co.) at 30° using boron trifluoride monohydrate as catalyst. The alkylate product was separated by fractionation using a 1 in. × 4 ft. Podbielniak Hypercal column at a 20 to 1 reflux ratio. Analysis by gas chromatography indicated a purity of 98.9% 1,3-dimethyl-5-*tert*-butylbenzene with 0.7% *para*-*tert*-butylethylbenzene and 0.4% *tert*-butyl-*ortho*-xylene as the main impurities.

The *tert*-pentyl aromatics were prepared by alkylating the parent aromatic with 2-chloro-2-methylbutane using an aluminum chloride catalyst and fractionation as described above.

Pure grade (99 mole % minimum) isopropylbenzene and pure grade *tert*-butylbenzene from Phillips Petroleum Co. were used as received.

**Experimental Procedure.**—All experimental work was carried out in a 2-l. stainless steel autoclave. In each experiment 4 moles of *tert*-alkyl aromatic was charged and sufficient catalyst added to give the desired catalyst/hydrocarbon mole ratio. In a typical experiment 343 g. (4 moles) of catalyst and 649 g. (4 moles) of 1,3-dimethyl-5-*tert*-butylbenzene were charged to the reactor. Carbon monoxide was added to a total reactor pressure of 500 p.s.i.g. at 25° and stirring was started. At the end of the run the system was allowed to settle and the carbon monoxide was vented through a Dry Ice trap. The contents of the reactor were drained into a tared flask and weighed. Water (500 ml.) was added with stirring to the product–catalyst mixture with the temperature held below 25°. The aqueous phase, which contained no significant quantity of acid, was separated and discarded. The organic phase was made basic with 2 N sodium hydroxide. The phases were separated and the aqueous portion was extracted with 500 ml. of *para*-xylene, and then acidified with dilute hydrochloric acid until a pH of less than 2 was reached. The carboxylic acid, which formed a separate liquid layer, was separated by means of a separatory funnel. The aqueous layer was extracted with two 500-ml. portions of benzene and the extracts were added to the trimethylacetic acid product previously separated. The mixture was distilled to 125° overhead on a simple one-plate column. The purity of the product, in this example 97%, was determined by acid number.

Experiments in which isobutylene was carbonylated were made as described above with the isobutylene being charged at a constant rate throughout the run by means of a Ruska pump.

(7) R. J. Lee, H. M. Knight, and J. T. Kelly, *Ind. Eng. Chem.*, **50**, 1001 (1958).

# The Synthesis and N.m.r. Spectra of Some Tetracyanocyclopropanes[1]

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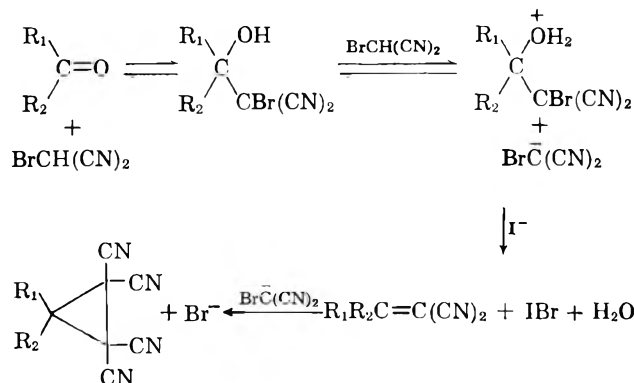
*Received November 9, 1962*

The scope of the condensation of carbonyl compounds with bromomalononitrile and iodide ion to produce tetracyanocyclopropanes (Wideqvist reaction) has been explored. The reaction is rapid and gives good yields with aldehydes. With methyl ketones the yield falls off as the other alkyl group is altered in order methyl > ethyl > isopropyl > *t*-butyl, the latter (pinacolone) giving no product. Bicyclopropyl derivatives can be made from cyclopropanecarboxaldehyde or methyl cyclopropyl ketone. 2-Pentanone gave 3,3-diethyl-1,1,2,2-tetracyanocyclopropane in modest yield; longer chain internal ketones (*i.e.*, di-*n*-amyl ketone) did not react. The reaction is general for preparing spiro compounds of the type

$$(CH_2)_{n-1} \diagup\hspace{-0.5em}\diagdown \begin{matrix} -CN \\ \diagup CN \\ \diagdown CN \\ -CN \end{matrix}$$
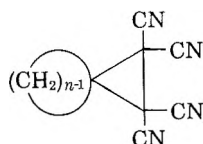
where $n = 4$–9, but fails for larger rings. The cyclopropane hydrogen in monoalkyl- or aryltetracyanocyclopropanes appears at abnormally low fields, and a possible rationalization is offered in terms of the anisotropy of the nitrile group.

## Introduction

The synthesis of tetracyanocyclopropanes from carbonyl compounds, bromomalononitrile, and iodide ion[2] is known[3] as the Wideqvist reaction. Although there are no mechanistic studies of the reaction, it is likely that it involves a series of equilibria such as those shown.[4] The reaction normally is carried out by add-

$$\begin{matrix} R_1 \\ \diagup \\ R_2 \end{matrix} C{=}O \;\rightleftharpoons\; \begin{matrix} R_1 \\ \diagup \\ R_2 \end{matrix} C \begin{matrix} OH \\ \diagdown CBr(CN)_2 \end{matrix} \;\xrightarrow{BrCH(CN)_2}\; \begin{matrix} R_1 \\ \diagup \\ R_2 \end{matrix} C \begin{matrix} \overset{+}{O}H_2 \\ \diagdown CBr(CN)_2 \end{matrix}$$

$$+ \\ BrCH(CN)_2 \qquad\qquad\qquad\qquad\qquad\qquad + \\ Br\bar{C}(CN)_2$$

$$\Big\downarrow I^-$$

$$\begin{matrix} R_1 \\ \diagup \\ R_2 \end{matrix}\diagup\hspace{-0.5em}\diagdown \begin{matrix} -CN \\ \diagup CN \\ \diagdown CN \\ -CN \end{matrix} + Br^- \xleftarrow{Br\bar{C}(CN)_2} R_1R_2C{=}C(CN)_2 + IBr + H_2O$$

ing aqueous potassium iodide to the aldehyde or ketone and bromomalononitrile at room temperature, using water, aqueous alcohol, or an excess of the carbonyl compound as solvent. Tetrahydrofuran was used as the solvent to prepare the parent member of the series ($R_1 = R_2 = H$).[5]

A summary of Wideqvist's investigations into the scope of the reaction is given in Table I. A number of his preparations were carried out under identical con-

ditions and give an indication of structural effects on the yield.

The present paper demonstrates with additional examples the generality of the Wideqvist reaction, and also points up some of its limitations. The n.m.r. spectra of Wideqvist products derived from aliphatic aldehydes confirm the presence of a cyclopropane ring, and the unusually low field at which these hydrogens appear, in relation to model acyclic compounds, is discussed.

## Results

A summary of tetracyanocyclopropanes prepared in the present work is given in Table II. The yields shown in the table are not necessarily optimum; a number of the preparations were carried out under identical, though not necessarily optimum, conditions, in order to compare the effect of structural changes on yield.

TABLE I

A SUMMARY OF PREVIOUS PREPARATIONS OF
TETRACYANOCYCLOPROPANES BY THE WIDEQVIST REACTION[a,b]

| $R_1$ | $R_2$ | Yield, % |
|-------|-------|----------|
| $CH_3$ | $CH_3$ | 70 |
| $CH_3$ | $CH_3CH_2$ | 68 |
| $CH_3$ | $C_6H_5CH_2$ | 39[c] |
| $CH_3$ | $n$-$C_6H_{13}$ | 30[c] |
| $CH_3$ | $C_6H_5$ | 14[c] |
| —(CH_2)_5— | | 92[c] |
| H | H | 68[a] |
| H | $CH_3$ | 70 |
| H | $C_6H_5$ | 80[c] |
| H | Furfuryl | 59[c] |

[a] All data are taken from ref. 2a except the formaldehyde product, for which see ref. 4. [b] The following compounds failed to give tetracyanocyclopropanes: methyl α-naphthyl ketone, mesityl oxide, acetol, benzophenone, α-hydroxyacetophenone, and quinone. [c] These reactions, as well as the unsuccessful ones in footnote b, were all carried out under similar conditions (1.5 g. of bromomalononitrile and 1 g. of carbonyl compound were dissolved in 10 ml. of alcohol and treated at room temperature with a solution of 3.5 g. of potassium iodide in 10 ml. of water. The product was filtered after a few minutes to a few hours, and recrystallized from aqueous acetone or alcohol).

(1) We are indebted to the donors of the Petroleum Research Fund, American Chemical Society, for financial support (grant 488-C).

(2) (a) S. Wideqvist, *Arkiv. Kemi, Mineral. Geol.*, **20B**, No. 4, 8 (1945); (b) L. Ramberg and S. Wideqvist, *ibid.*, **12A**, No. 22, 12 (1937).

(3) H. Hart and F. Freeman, *J. Am. Chem. Soc.*, in press.

(4) Bromomalononitrile is an acid with a p$K_a$ ~5 (R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953)), certainly strong enough for the protonation of the first condensation product. This mechanism, suggested by a referee, gains support from the observation that equimolar amounts of isopropylidene malononitrile and bromomalononitrile in aqueous ethanol gave a high yield of 3,3-dimethyl-1,1,2,2-tetracyanocyclopropane in a few minutes at room temperature (unpublished results with Yoon C. Kim).

(5) R. M. Scribner, G. N. Sausen, and W. W. Prichard, *J. Org. Chem.*, **25**, 1440 (1960). Wideqvist[2a] had failed to isolate a product using aqueous alcohol.

TABLE II

TETRACYANOCYCLOPROPANES PREPARED IN THE PRESENT WORK

| $R_1$ | $R_2$ | Yield, % | Method[a] | M.p., °C.[b] | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | $CH_3CH_2$ | 72.4 | A | 186–187[c] | $C_9H_6N$ | 63 52 | 3.55 | 32.93 | 63.34 | 3.61 | 32.80 |
| H | $CH_3CH_2CH_2$ | 75.9 | A | 130–131[d] | ... | . . | ... | ... | ... | ... | ... |
| H | $(CH_3)_2CH$ | 73.2 | A | 172.1–172.8 | $C_{10}H_8N_4$ | 65 20 | 4.38 | 30.42 | 65.48 | 3 99 | 30.70 |
| H | Cyclopropyl | 93.4 | B | 234–235 | $C_{10}H_6N_4$ | 65.93 | 3.32 | 30.76 | 65.79 | 3.38 | 30.87 |
| H | $p$-ClC$_6$H$_4$ | 84.0 | B | 240–241 | $C_{13}H_5N_4Cl$ | 61 80 | 1.99 | 22.17 | 61.87 | 2 04 | 22.00 |
| H | $m$-NO$_2$C$_6$H$_4$ | 77.2 | B | 245–246 | $C_{13}H_5N_5O_2$ | 59 32 | 1.91 | 26.61 | 59.43 | 2.04 | 26.70 |
| $CH_3$ | $CH_3CH_2CH_2$ | 39 | C | 167.5–168 | $C_{11}H_{10}N_4$ | 66 65 | 5.09 | 28.27 | 66.64 | 5.11 | 28.40 |
| $CH_3$ | $(CH_3)_2CH$ | 18.3 | C | 187–188 | $C_{11}H_{10}N_4$ | 66.65 | 5.09 | 28.27 | 66.84 | 5.27 | 28.25 |
| $CH_3$ | Cyclopropyl | 2.5[g] | C | 194–195[e] | $C_{11}H_8N_4$ | 67.33 | 4.10 | 28.55 | 67.48 | 4.06 | 28.38 |
| $CH_3CH_2$ | $CH_3CH_2$ | 21.2 | C | 167–168 | $C_{11}H_{10}N_4$ | 66.65 | 5.09 | 28.27 | 66.56 | 5.03 | 28.25 |
| —(CH$_2$)$_3$— | | 60.4 | B | 221–221.5[f] | $C_{10}H_6N_4$ | 65.93 | 3.32 | 30.76 | 65.78 | 3.30 | 30.68 |
| —(CH$_2$)$_4$— | | 76.3 | B | 239–240[e] | $C_{11}H_8N_4$ | 67.33 | 4.10 | 28.55 | 67.19 | 3.98 | 28.62 |
| —(CH$_2$)$_6$— | | 25 | D | 168–169 | $C_{13}H_{12}N_4$ | 69.62 | 5.40 | 24.98 | 69.42 | 5.48 | 25.00 |
| —(CH$_2$)$_7$— | | 4 | D | 172.5–173 | $C_{14}H_{14}N_4$ | 70.56 | 5.92 | 23.51 | 70.68 | 6.16 | 23.65 |
| —(CH$_2$)$_8$— | | 7 | D | 205–206 | $C_{15}H_{16}N_4$ | 71.40 | 6.39 | 22.21 | 71.47 | 6.42 | 22.25 |

[a] Method A: A solution of 7 g. of potassium iodide in 20 ml. of water was added, at room temperature, to 0.02 mole of carbonyl compound and 0.04 mole of bromomalononitrile in 5 ml. of ethanol, stirred for 30 min., and the product filtered and recrystallized. Method B: Same as A, except that 0.02 mole of bromomalononitrile and 20 ml. of ethanol were used. Method C: Same as B, but reaction time increased to 12 hr. Method D: 0.01 mole of carbonyl compound, 0.02 mole of bromomalononitrile, 10 ml. of ethanol, 7 g. of potassium iodide in 10 ml. of water, reaction time 24 hr. Compounds which failed to react by these procedures are discussed in the text. [b] All were recrystallized from 95% ethanol, unless otherwise indicated. [c] This compound was prepared previously by the action of bromine on propylidenebismalononitrile [R. P. Mariella and A. J. Roth, III, *J. Org. Chem.*, **22**, 1130 (1957)], who reported a m.p. of 197°. [d] Prepared previously by an alternate procedure (see footnote c), reported m.p. 131°. [e] Recrystallized from ethyl acetate. [f] Recrystallized from aqueous acetone. [g] This yield was raised to 14% using 0.02 mole of ketone, 0.04 mole of bromomalononitrile, 20 ml. of ethanol, and 8 ml. of saturated aqueous potassium iodide, allowing the mixture to stand for 12 hr., then diluting with water and filtering.

The position and multiplicity of the cyclopropyl hydrogen in the n.m.r. spectra of several tetracyanocyclopropanes prepared from aldehydes are given in Table III.

TABLE III

THE POSITION OF THE CYCLOPROPYL HYDROGEN IN THE N.M.R. SPECTRA OF SEVERAL TETRACYANOCYCLOPROPANES[a]
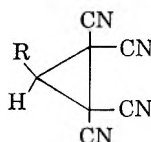


| R | $\tau$[b] | Description |
|---|---|---|
| H | 6.53 | Singlet |
| $CH_3$ | 6.49 | Quartet |
| $CH_3CH_2$ | 6.47 | Triplet |
| $CH_3CH_2CH_2$ | 6.45 | Triplet |
| $(CH_3)_2CH$ | 6.50 | Doublet |
| Cyclopropyl | 6.75 | Complex |
| $C_6H_5$ | 5.07 | Singlet |
| $p$-Cl-C$_6$H$_4$ | 5.10 | Singlet |
| $m$-NO$_2$-C$_6$H$_4$ | 4.77 | Singlet |

[a] Complete spectra are in the Ph.D. thesis of Fillmore Freeman, Michigan State University, 1962. [b] Measured in acetone-$d_6$ with tetramethylsilane as internal reference: see G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

## Discussion

**Scope of the Reaction.**—In general, the yields of tetracyanocyclopropanes seem to depend on the extent of condensation of the carbonyl compound with bromomalononitrile; *i.e.*, structural changes in the carbonyl component affect the yields in a manner predictable from other carbonyl addition reactions.[6] The entire equilibrium is not shifted to the production of tetra-

(6) See, for example, L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corporation, New York, N. Y., 1961, p. 417.

cyanocyclopropane because iodide ion also directly reduces the uncombined bromomalononitrile.

Aliphatic and aromatic aldehydes react almost instantaneously, the yields being high after short reaction times at room temperature. Glycidaldehyde was the only aldehyde tried which did not give an isolable crystalline product, failure here probably being due to the multiplicity of products which might arise from attack of bromomalononitrile anion on the epoxide ring. Notable is the facile synthesis of a bicyclopropyl derivative (I) from cyclopropanecarboxaldehyde.
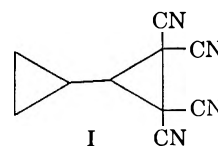


Ketones generally reacted more slowly than aldehydes. For a series of methyl ketones treated by an identical procedure (C, Table II), the yield decreased in order $CH_3$ (58.2%) > $CH_3CH_2$ (46.2%) > $CH_3CH_2CH_2$ (39%) > $(CH_3)_2CH$ (18.3%) > $(CH_3)_3C$ (0%). This fall-off may be rationalized in terms of electronic (inductive) or steric effects. That it is not entirely steric is shown by the poorer yield, under comparable conditions, from methyl cyclopropyl ketone (2.5%) than from methyl isopropyl ketone (18.3%). The carbonyl group in the latter is probably the more hindered sterically, but the partial positive charge on the carbonyl carbon is better dissipated by the cyclopropyl group, thus decreasing the reactivity of the ketone to addition reactions.[7] The poor yields with

(7) The effect is also apparent in a comparison of the relative rates of borohydride reduction of methyl isopropyl ketone [0.195; H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962)], and methyl cyclopropyl ketone (0.015; H. C. Brown, private communication). The reference compound is acetone (1.0).

methyl aryl ketones are also to be noted in this connection (Table I).

Cyclic ketones offer the possibility for producing spiro systems of the type II. Wideqvist[2a] had shown that good yields of II ($n = 6$) could be obtained from
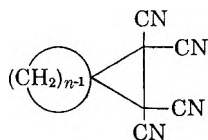


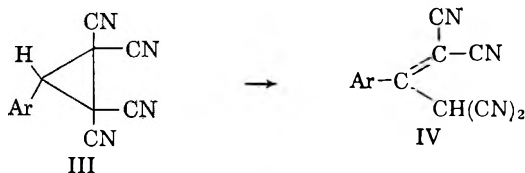cyclohexanone (92%, method B, Table II) and, as is seen from Table II, the reaction also goes extremely well for the smaller rings (II, $n = 4, 5$). This reaction constitutes perhaps as simple a synthesis of a spiro-[2.3] hexane as is known; despite the inherent strain in this ring system, the reaction must attain an appreciable driving force from the conversion of the $sp^2$ carbon of cyclobutanone to something which approaches $sp^3$ hybridization. The large difference often noted[8] between cyclopentanone and cyclohexanone in carbonyl addition reactions is not apparent from the present studies based on yield. There is a sharp drop in the yield of tetracyanocyclopropane from cycloheptanone, which falls off even further for cyclooctanone and cyclononanone. No product was obtained (method D, Table II) with larger rings (II, $n = 10$, 12, 15). The last of these might be expected to be comparable in reactivity to an acyclic internal ketone, such as di-$n$-amyl ketone, which also gave no Wideqvist product.

The reaction is not limited to methyl or cyclic ketones; 3-pentanone gave a yield (method C) only moderately less than 2-pentanone (see Table II). But many other internal ketones failed to react (*i.e.*, ethyl $n$-butyl ketone, diisopropyl ketone, dicyclopropyl ketone, benzophenone).

**The N.m.r. Spectra.**—The multiplicity of the cyclopropane hydrogen peaks in the n.m.r. spectra of tetracyanocyclopropanes prepared from aliphatic aldehydes clearly establishes their structures (quartet for R = $CH_3$, triplets for R = $CH_3CH_2$ or $CH_3CH_2CH_2$ and doublet for R = $(CH_3)_2CH$; see Table III). But the position of the aliphatic singlet in the n.m.r. of products from aromatic aldehydes does not exclude the alternate structure IV which conceivably could be obtained by a prototropic rearrangement of III. Indeed the methine proton in compounds analogous to IV (alkyli-



denebismalononitriles) appears[9] at 5.02–5.14 $\tau$, very close to the values for the last three compounds in Table III. Structure IV was unequivocally eliminated by comparison of the ultraviolet absorption spectrum of III (Ar = $C_6H_5$), which showed no absorption above 300 m$\mu$, with that of benzylidinemalononitrile, a model for IV, which had $\lambda_{max}$ 306 m$\mu$ ($\epsilon = 22,000$) in ethanol.

The cyclopropane hydrogen in these compounds ap-

pears at appreciably lower field (1–1.5 $\tau$ units) than one might anticipate by comparison with acyclic models. Cyclopropane hydrogens often appear at higher field than their acyclic analogs, the difference being generally about 1 $\tau$ unit (compare the cyclopropane methylenes at 9.78 $\tau$ with the methylene of propane, at 8.75 $\tau^{10-12}$). An explanation for the shielding of cyclopropane hydrogens has been given[12] in terms of a ring current, with the ring protons lying within the radius of the precessing electrons (contrary to aromatic protons which are deshielded because of their location outside the ring current). Since the electronegativity effects[13] of the nitrile groups on the resonance of the methylene protons in V and VI should be virtually identical, one might expect the methylene



of VI to appear at approximately 1 $\tau$ unit higher than for V, due to the cyclopropane ring. In fact, the methylene protons in VI (6.53 $\tau$) appear at *lower* field than those of V (6.90 $\tau^9$).[14] This must be the result of different geometries of the nitrile groups in V and VI with respect to the methylene protons. The rigid geometry of VI orients the nitriles in such a position that, due to the anisotropy of the carbon–nitrogen triple bond, the methylene protons will be deshielded.[15,16] This explanation may also account for the rather remarkable n.m.r. spectrum of cyclopropyl cyanide, recently reported[17] without comment. A methine hydrogen on the same carbon as a nitrile group should appear at about 7.2 $\tau$,[18] whereas in cyclopropyl cyanide all the protons show resonance between about 8.8 and 9.2 $\tau$,[17] in a relatively unstructured band. The nitrile group should shield the methine proton but deshield the methylene protons, the result being that, coupled with the shielding effect of the cyclopropane ring itself, all the protons appear lumped together.

### Experimental

The tetracyanocyclopropanes listed in Table II were prepared from the corresponding aldehydes or ketones by procedures described in the footnotes to the table. Melting points are uncorrected, yields are of recrystallized product, and all analyses were by Spang Microanalytical Laboratory, P.O. Box 1111, Ann Arbor, Michigan. The n.m.r. spectra (Table III) were run on a Varian Model A-60 instrument.

(8) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 238.

(9) H. Hart and F. Freeman, *Chem. Ind.* (London), 332 (1963).

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 52.

(11) For other examples, see J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, Inc., New York, N. Y., 1959, pp. 285, 289; also, M. C. Caserio, W. H. Graham, and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960), especially Fig. 3.

(12) K. B. Wiberg and B. J. Nist, *J. Am. Chem. Soc.*, **83**, 1226 (1961).

(13) B. P. Dailey and J. N. Shoolery, *ibid.*, **77**, 3977 (1955); A. A. Bothner-By and C. Naar-Colin, *ibid.*, **80**, 1728 (1958).

(14) The effect is general. In the second and third compounds in Table III, the cyclopropane hydrogen appears at 6.49 and 6.45 $\tau$; the corresponding protons in ethylidene- and propylidenebismalononitriles, the acyclic analogs, appear at 6.67 and 6.87 $\tau$, respectively.[9]

(15) See ref. 10, pp. 112–115, and particularly Fig. 7.4, for the regions of shielding and deshielding around a carbon–carbon triple bond.

(16) Attention has been called to the importance of the anisotropy of the nitrile group in interpreting the spectrum of acrylonitriles; G. S. Reddy, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.*, **83**, 1300 (1961).

(17) H. Weitkamp, U. Hasserodt, and F. Korte, *Ber.*, **95**, 2280 (1962).

(18) The average value for the methylene protons in $RCH_2CN$ is 7.35 ± 0.07$\tau$, from N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, 1962, Spectra 58, 69, 106, 127.

# Stereochemistry of Terpenes. IV. The Configuration of Some Amines[1]

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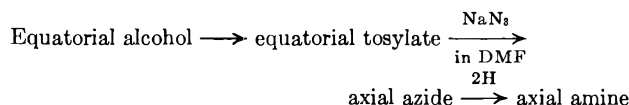
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A direct stereochemical correlation between menthol and menthylamine has been established through a sequence of stereospecific reactions on a menthanecarboxylic acid. The configuration of neoisomenthylamine and a new compound, neoisopinocamphylamine, has been determined by their preparation from isomenthol and isopinocampheol, respectively, by reactions of known stereochemistry.

The stereochemistry of isomeric menthylamines was assigned by Read[2] on the basis that the optical rotation of their derivatives fitted the principle of superposition and that there was a regular pattern in the behavior of the amines on treatment with nitrous acid.[3] Sodium and alcohol reduction of (−)-menthone and the corresponding oxime leads predominantly to (−)-menthol and (−)-menthylamine, respectively. Conformational analysis[4] predicts analogous stereochemistry (equatorial —OH and —NH₂) for (−)-menthol and (−)-menthylamine. Similar arguments can be advanced for the stereochemistry of isomenthol and isomenthylamine. We wish to report here data that correlate more directly the absolute configuration of some terpene alcohols and amines.

Carbonation of the Grignard reagent from (−)-menthyl chloride[5] (II) has been reported to give two epimeric acids (III and IV), one of which is a crystalline solid. We have carried out this Grignard reaction in tetrahydrofuran medium and analyzed the resulting mixture of acids by vapor phase chromatography of the corresponding methyl esters; the crystalline acid III and its epimer IV were obtained in the ratio of 2:1. Since the crystallization of III was a very slow process, the mixture of isomers was used in the next reaction. Treatment with methyllithium produced a mixture of methyl ketones V and VI with an epimer ratio of 3:1. Equilibration with base converted this mixture to V, the more stable isomer (acetyl side chain in the equa-

torial position). Hypobromite oxidation of V to menthanecarboxylic acid produced the isomer III exclusively. Since this oxidation proceeds without inversion, III and V must correspond to each other in configuration. Baeyer–Villiger oxidation of V followed by hydrolysis led to (−)-menthol. Schmidt reaction on III produced (−)-menthylamine. Since both the Baeyer–Villiger oxidation and the Schmidt reaction are known to proceed with retention of configuration, the absolute configuration of (−)-menthol (I), the carboxylic acid III, the methyl ketone V, and (−)-menthylamine (VII) must be as represented in col. 1.

We have recently described[6] a synthesis of axial amines by the following sequence.

$$\text{Equatorial alcohol} \longrightarrow \text{equatorial tosylate} \xrightarrow[\text{in DMF}]{\text{NaN}_3} \text{axial azide} \xrightarrow{\text{2H}} \text{axial amine}$$

The conversion of the tosylate to the azide is expected to proceed with Walden inversion[7] and this expectation was borne out by the preparation[6] of 3α-aminocholestane from 3β-cholestanol and (+)-neomenthylamine from (−)-menthol. Under similar reaction conditions we have prepared (+)-neoisomenthylamine from (+)-isomenthol (VIII). We can, therefore, write the absolute configuration IX for (+)-neoisomenthylamine.
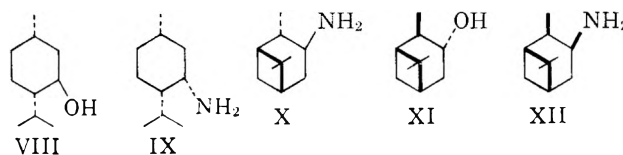


The only pinocamphylamine that appears to have been reported[8] so far was obtained by the reduction of pinocamphone oxime with sodium and alcohol. Conformation analysis predicts the stereostructure X for this isomer. We have prepared an amine via the tosylate and azide from (+)-isopinocampheol (XI).[9] The tosylate was found to be quite unstable and the poor yield (8%) of the amine obtained from this tosylate was obviously due to extensive decomposition prior to the formation of the azide. The n.m.r. spectrum of the N-acetyl derivative of this amine showed it to be homogeneous. In the light of the observations made in the menthol series, the absolute configuration XII can be assigned to this amine which should be called (+)-neoisopinocamphylamine in keeping with the general usage regarding terpene nomenclature.
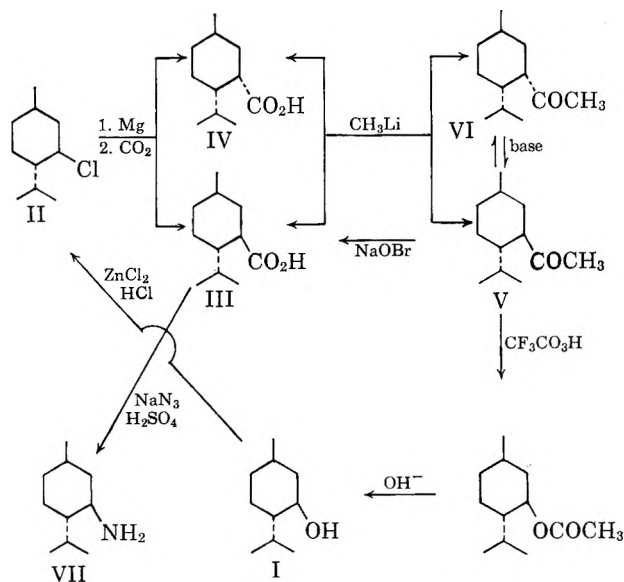
(1) Part III, A. K. Bose, *J. Org. Chem.*, **20**, 1010 (1955).

(2) J. Read and W. J. Grubb, *J. Chem. Soc.*, 313 (1934); N. L. McNiven and J. Read, *ibid.*, 153 (1952).

(3) Also see A. K. Bose, *Experientia*, **9**, 256 (1953); J. A. Mills, *J. Chem. Soc.*, 260 (1953).

(4) See, for example, H. S. Orloff, *Chem. Rev.*, **54**, 347 (1954).

(5) J. G. Smith and G. F. Wright, *J. Org. Chem.*, **17**, 1116 (1952).

(6) A. K. Bose, J. F. Kistner, and L. Farber, *ibid.*, **27**, 2925 (1962).

(7) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 178 (1950).

(8) O. Wallach and W. Rojahn, *Ann.*, **313**, 367 (1900); L. Ruzicka and S. Pontalti, *Helv. Chim. Acta*, **7**, 489 (1924).

(9) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959).

## Experimental

All melting points were taken in capillary tubes and were uncorrected. Microanalyses were prepared by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York, and Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim (Ruhr), West Germany. The optical rotatory dispersion studies were made with a Rudolph self-recording spectropolarimeter. Gas chromatographic studies were made with a Perkin–Elmer vapor fractometer using columns A (diisodecyl phthalate) and K (Carbowax 1500).

( − )-**Menthyl Chloride (II)**.—Following the method described by Smith and Wright,[5] ( − )-menthol was treated with the Lucas reagent to produce menthyl chloride, $n^{20}$D 1.4615. Vapor phase chromatography (v.p.c.) indicated the material to be homogeneous.

**p-Menthane-3-carboxylic Acids (III and IV)**.—( − )-Menthyl chloride (20 g.) in 10 ml. of tetrahydrofuran was added over 30 min. to 5 g. of magnesium turnings and 20 ml. of tetrahydrofuran under nitrogen. The Grignard reaction was best initiated by the addition of a few pieces of magnesium that were vigorously reacting with ethyl bromide and a crystal of iodine in a separate vessel. After refluxing for a further hour, the liquid phase of the solution mixture was siphoned onto 200 g. of solid carbon dioxide. Following acidification with dilute hydrochloric acid, the products were extracted with ether. The acid fraction was separated by washing the ether layer with 5% sodium hydroxide solution. Acidification of the aqueous layer and extraction with ether gave 16 g. of an acid, A. V.p.c. of the methyl ester prepared from a sample of this acid with diazomethane showed the presence of the epimers III and IV in the ratio of 68:32. The acid mixture, A, crystallized partially on long standing; filtration and washing with hexane gave the solid isomer III, m.p. 62–65°, $[\alpha]^{20}$D −46.5° (c, 1.46 in CHCl₃). The thiomorpholinamide derivative[10] of III, m.p. 111–113°, showed a negative Cotton effect.

**Menthyl Methyl Ketones (V and VI)**.—A solution of 6.5 g. of the acid mixture A (see above) in 50 ml. of ether was added dropwise with stirring under nitrogen to a solution of methyllithium prepared from 3 g. of lithium in 100 ml. of ether. After standing overnight the solution was poured into ice–water and the ether layer separated. Removal of the solvent after drying over magnesium sulfate gave 4.8 g. of crude ketone, vapor phase chromatography ("K" column) of which showed the presence of both epimers V and VI in about 3:1 ratio. The O.R.D. curve in methanol had a negative Cotton effect with the extremum at 320 mμ. Acidification of the aqueous layer gave 1.7 g. of unchanged acid.

**Equilibration of Methyl Menthyl Ketone Epimers V and VI**.—Four grams of the above epimer mixture was equilibrated by refluxing with 40 ml. of 2% methanolic sodium hydroxide solution. Addition of water and extraction with ether followed by drying and removal of the solvent gave the epimer V, b.p. 68–69° (2 mm). V.p.c. indicated less than 2% of the isomer VI. The O.R.D. curve in methanol of V had a positive Cotton effect with the extremum at 303 mμ, $[\alpha]^{23}$D −26.0° (c, 100), $[\alpha]^{25}$D 1.4557. The 2,4-dinitrophenylhydrazone of V had m.p. 136–137° (from isopropyl alcohol).

*Anal*. Calcd. for C₁₈H₂₆O₄N₄: C, 59.12; H, 7.18; N, 15.5. Found: C, 59.78; H, 7.29; N, 15.25.

**Hypobromite Oxidation of V**.—A solution of sodium hypobromite from 1.2 g. of sodium hydroxide, 200 mg. of bromine and 10 ml. of water was added dropwise to 240 mg. of V in 10 ml. dioxane at 0°, and stirred for 2 hr. After standing overnight, 200 mg. of sodium bisulphite was added and the solution refluxed for 2 hr. The reaction mixture was poured into water and the neutral fraction extracted with ether. Acidification of the aqueous layer gave 110 mg. of an acid. V.p.c. of the methyl ester prepared by the addition of diazomethane in ether showed a single peak which coincided with the peak observed for the ester of the crystalline acid III.

**Baeyer–Villiger Oxidation of V**.—Trifluoroacetic anhydride (14 ml.) was added dropwise to a suspension of 2 ml. of 90% hydrogen peroxide[11] in 20 ml. of methylene chloride at 0°, and the resulting solution added slowly to 2.4 g. of V in 50 ml. of methylene chloride at 0°. After 0.5 hr., 24 g. of anhydrous dibasic sodium phosphate was added and refluxed for 2 hr. The mixture was filtered, the solvent evaporated, and the product dis-

tilled at 150° (bath temp.) (2 mm.), yield 2.0 g. By coincidence of peaks by v.p.c., the product was shown to be ( − )-menthol acetate. Hydrolysis of 1.5 g. by refluxing in 5 ml. of 10% aqueous ethanolic potassium hydroxide for 2 hr. gave 1.1 g. of ( − )-menthol, isolated by addition of water and extraction with ether followed by drying and removal of solvent. Its comparison with ( − )-menthol using v.p.c. indicated that the two samples were identical. The 3,5-dinitrobenzoate had m.p. 152–153° [undepressed by admixture with an authentic sample of ( − )-menthol 3,5-dinitrobenzoate], $[\alpha]^{20}$D −79.3° (c, 1.6, CHCl₃).

( − )-**Menthylamine**.—One hundred and thirty milligrams of sodium azide was added in small portions to a stirred mixture of 166 mg. of the acid, 3 ml. of concentrated sulphuric acid, and 6 ml. of chloroform at 50–55°. After 0.5 hr. at this temperature, the mixture was diluted with ice–water and neutral materials removed by extraction with ether. Addition of excess sodium hydroxide solution liberated the free amine which was extracted into ether and dried over sodium hydroxide pellets. The solvent was removed, 2 ml. of acetic anhydride added, and the solution refluxed for 1 hr. Evaporation of the solvent under reduced pressure gave 109 mg. of N-acetyl ( − )-menthylamine which was recrystallized from benzene; m.p. 145–146°, $[\alpha]^{21}$D −84° (c, 0.8 in CHCl₃).

In a similar experiment 1 g. of III was converted to 0.8 g. of N-benzoyl-(−)-menthylamine, m.p. 157°, undepressed on admixture with an authentic sample.

( − )-**Neoisomenthylamine Hydrochloride**.—To 1.22 g. (3.9 mmoles) of ( + )-isomenthyl p-toluenesulfonate[12] dissolved in a mixture of 30 ml. of dimethylformamide and 4.5 ml. of water was added 1.29 g. (20 mmoles) of sodium azide. The temperature was kept at 85° with stirring for 9 hr. The reaction mixture then was poured into 30 ml. of a saturated aqueous sodium chloride solution diluted with 3 ml. of water. It was then extracted with ether and the combined ether extracts were washed with the saturated sodium chloride solution and dried over magnesium sulfate.

To a suspension of 0.3 g. (7.9 mmoles) of lithium aluminum hydride in 50 ml. of absolute ether there was added, over a period of 30 min., the dried ether extract from above. The mixture was stirred at room temperature for 1 hr. and then refluxed for 1 hr. more. The excess lithium aluminum hydride was destroyed with moist ether followed by water and the solid material was filtered off. The organic layer was washed twice with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Hydrogen chloride gas was passed into this ether solution and the mixture then was allowed to evaporate. After washing the resulting residue with hexane, 0.13 g. (17%) of white crystalline neoisomenthylamine hydrochloride was obtained.

Acetylation of neoisomenthylamine hydrochloride with acetic anhydride in a pyridine carbon tetrachloride solution yielded ( − )-N-acetylneoisomenthylamine, m.p. 99–100.5° (lit.,[13] 99–100°).

*Anal*. Calcd. for C₁₂H₂₃NO: N, 7.10. Found: N, 7.07.

**Neoisopinacocamphylamine Hydrochloride**.—To 6.17 g. (0.020 mole) of isopinocamphyl p-toluenesulfonate[14] dissolved in a mixture of 125 ml. of N,N-dimethylformamide and 21 ml. of water was added 6.50 g. (0.1 mole) of sodium azide. The mixture was stirred and kept at a temperature of 60° for 6 hr. The reaction mixture then was poured into water. It was extracted with ether and the combined ether extracts were washed with the saturated sodium chloride solution and dried over anhydrous magnesium sulfate.

To a suspension of 1.52 g. (0.04 mole) of lithium aluminum hydride in 50 ml. of absolute ether there was added, over a period of 30 min., the dried ether extract from above. The mixture was stirred at room temperature for 1 hr. and then refluxed for 1 hr. more. The excess lithium aluminum hydride was destroyed with moist ether followed by water and the solid material was filtered off. The organic layer was washed twice with a 3 N sodium hydroxide solution and dried over anhydrous magnesium sulfate. The solution was reduced in volume and to it was added a solution of hydrogen chloride gas in ether. The

(10) C. Djerassi and K. Undheim, *J. Am. Chem. Soc.*, **82**, 5755 (1960).
(11) W. D. Emmons and G. B. Lucas, *ibid.*, **77**, 2287 (1955).

(12) W. Hückel and H. Niggemeyer, *Ber.*, **72B**, 1354 (1939).
(13) J. L. Simonsen, "The Terpenes," Vol. I, 2nd ed., Cambridge University Press, Cambridge, England, 1953, p. 245.
(14) Reported as a liquid by H. Schmidt, *Ber.*, **77**, 544 (1944). Isopinocamphyl p-toluenesulfonate, which was prepared by treating ( + )-isopinocampheol with p-toluenesulfonyl chloride in pyridine, is an unstable crystalline material and was used immediately after preparation.

solid, white neoisopinocamphylamine hydrochloride, 0.31 g. (8.1%) was obtained.

Acetylation of neoisopinocamphylamine hydrochloride with acetic anhydride in the presence of sodium hydroxide solution gave (+)-N-acetylneoisopinocamphylamine, m.p. 148.5–149.5°, $[\alpha]^{26}D$ +50.8° (chloroform $c$, 1.51).

*Anal.* Calcd. for $C_{12}H_{21}ON$: C, 73.79; H, 10.84; N, 7.17. Found: C, 74.26; H, 10.87; N, 7.54.

# Alkylbenzenes. IX. Equilibration of the α- and β-Carbon Atoms in C14-Labeled n-Propylbenzenes by Lewis Acid Catalysts[1]

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Multiple treatments with fresh aluminum chloride of n-propylbenzene labeled in either the α- or β-position with C14 led to complete equilibration of the isotopic carbon between the α- and β-positions of the side chain of recovered n-propylbenzene; no appreciable amount of the isotope was found in the γ-position. The effectiveness of other Lewis acid catalysts for rearrangement of C14-labeled n-propylbenzene was tested; hydrogen bromide–aluminum bromide produced 44% rearrangement from the α- to the β-position in one treatment.

The aluminum chloride-induced rearrangement of n-propyl-β-C14-benzene was reported to result in the appearance of up to 31% of the C14 in the α-position of the normal side chain, while none was found in the γ-position.[3] Subsequently it was demonstrated that either isobutyl- or sec-butylbenzene is converted under the same conditions into a mixture containing a 2:1 proportion of isobutyl- and sec-butylbenzene, respectively.[4] In a sense, the butylbenzene isomers may be considered to be β- and α-methyl-labeled propylbenzenes, so that the similarity in the rearrangement reactions is obvious.
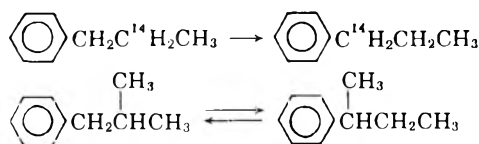


The 2:1 "equilibrium" proportion of isobutyl- and sec-butylbenzene produced from either of these butylbenzene isomers is probably a result of several factors; e.g., the relative thermodynamic stability of the two isomers[4,5] and their relative susceptibilities toward dealkylation and fragmentation reactions.[6]

However, α- and β-C14-labeled n-propylbenzene molecules are chemically identical, and one would expect that the isotopic rearrangement of n-propyl-β-C14-benzene should result in a 50:50 distribution of C14 between the α- and β-carbon atoms, since the γ-carbon atom is apparently not involved.[3] It occurred to us that a possible explanation of the observed incomplete rearrangement lay in deactivation of the catalyst by the di-, tri-, and polypropylbenzenes formed by dis-

proportionation reactions which are concurrent with the rearrangement. A simple experimental test of this theory appeared to be multiple treatments with fresh catalyst; i.e., α- or β-C14-labeled n-propylbenzene would be treated with catalyst, the monopropylbenzene separated from benzene, dipropylbenzene and higher disproportionation products, degraded, and radioassayed to determine the extent of isotopic rearrangement. This recovered, partially rearranged n-propylbenzene would then be subjected to treatment with fresh catalyst and the separation, degradation, and radioassay of recovered n-propylbenzene repeated. If the theory of catalyst deactivation were correct, repetition of these procedures should result in a 50:50 distribution of C14 between the α- and β-carbon atoms of the side chain.

This paper describes results of such experiments and of certain other related experiments.

## Discussion of Results

In previous papers we suggested two mechanisms for the rearrangement of n-propyl-β-C14-benzene to n-propyl-α-C14-benzene,[3,7] and Nenitzescu and coworkers[5] proposed a third which differed slightly from our second mechanism. Each of the steps in all of these mechanisms are assumed to be reversible, and hence we expected that an equal distribution of C14 between the α- and β-carbon atoms should be approached from starting material labeled in either position. To test the validity of these assumptions we synthesized both n-propyl-α-C14-benzene and n-propyl-β-C14-benzene.

Two syntheses of n-propyl-α-C14-benzene utilizing (a) sodium cyanide-C14 and (b) barium carbonate-C14 as sources of the isotopic label are outlined in Fig. 1. A method different from that used in the earlier work[3] was used for the synthesis of n-propyl-β-C14-benzene; it is outlined in Fig. 2.

**Multiple Rearrangements of n-Propyl-α-C14-benzene.**—Treatment of n-propyl-α-C14-benzene with aluminum chloride at 100° for 6.5 hours in three consecutive stages is outlined in Fig. 3. The procedure

(1) A preliminary report of some of the results described fully here was given in *Chem. Ind.* (London), 1557 (1958).

(2) Taken from the Ph.D. thesis of James E. Douglass, The University of Texas, 1959. Procter and Gamble Co. Fellow, 1957–1958; University of Kentucky, Lexington, Ky.

(3) (a) R. M. Roberts and S. G. Brandenberger, *Chem. Ind.* (London), 227 (1955); (b) R. M. Roberts and S. G. Brandenberger, *J. Am. Chem. Soc.* **79**, 5484 (1957).

(4) R. M. Roberts, Y. W. Han, C. H. Schmid, and D. A. Davis, *ibid.*, **81**, 640 (1959).

(5) C. D. Nenitzescu, I. Necsoiu, A. Glatz, and M. Zalman, *Chem. Ber.*, **92**, 10 (1959).

(6) These reactions will be the subject of a subsequent paper.

(7) J. E. Douglass and R. M. Roberts, *Chem. Ind.* (London), 926 (1959).

$$NaC^{14}N + CH_3CH_2Br \longrightarrow CH_3CH_2C^{14}N$$

$$\xrightarrow{H_2O, H_2SO_4} CH_3CH_2C^{14}O_2H$$

$$BaC^{14}O_3 \longrightarrow C^{14}O_2 \xrightarrow{C_2H_5MgBr} \xrightarrow{H_2O}{H_2SO_4} CH_3CH_2C^{14}O_2Na$$

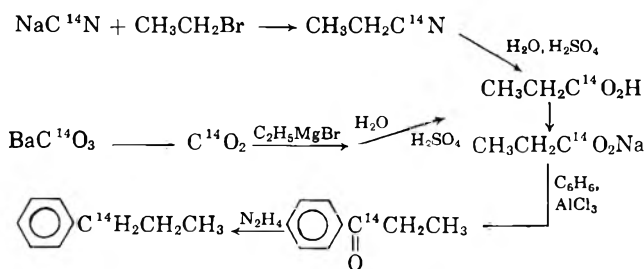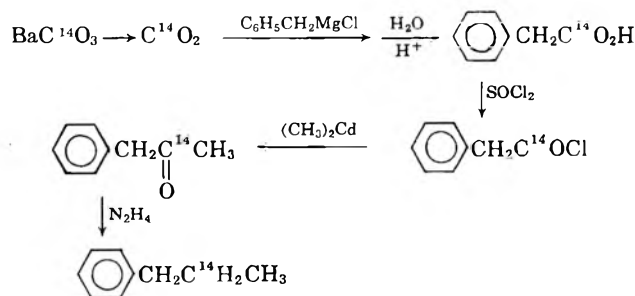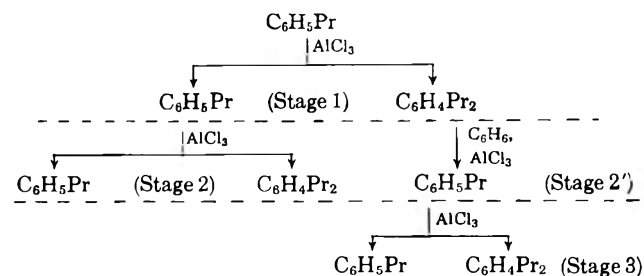$$\downarrow{C_6H_6, AlCl_3}$$

Figure 1

Figure 2

Figure 3

indicated by "stage 2'" was transalkylation of the dipropylbenzene fraction produced in stage 1, to conserve material. The propylbenzene recovered and the dipropylbenzene produced in each stage were degraded to benzoic and mixed phthalic acids by permanganate oxidation as described previously[3] and these acids were radioassayed to determine the amount of $C^{14}$ remaining in the $\alpha$-positions of the side chains. The extended degradation used in the previous work[3] was also applied to the propylbenzene recovered at each stage of this multiple rearrangement to confirm (by the benzaldehyde assay) the $\alpha$-$C^{14}$ content given by the simple oxidations, and to indicate individually the $C^{14}$ content of the $\beta$- and $\alpha$-carbon atoms (by the acetaldehyde and iodoform assays). The results are given in Table I. It can be seen that rearrangement of $C^{14}$ from the $\alpha$- to the $\beta$-carbon atom of the side chain did progress from $27 \pm 1\%$ in the first stage, to $43 \pm 1\%$ in the second stages, to $47 \pm 1\%$ in the third stage, and that no introduction of $C^{14}$ into the $\gamma$-position occurred.[8]

A second experiment was carried out in which water-activated aluminum chloride (mole ratio $AlCl_3:H_2O$

(8) After this work was completed, it was recognized that the experimental error in the radioassay of iodoform is unusually high owing to the extremely small carbon content of this compound (3.05%). Hence, although radioassays of iodoform showed no activity significantly above background, it is estimated that the iodoform could possibly have contained 2–3% of $C^{14}$. There is no actual evidence that it did, however, and the fact that the rearrangements of $C^{14}$ from both $\alpha$- and $\beta$-carbon atoms approached asymptotically a 50:50 distribution of the isotope between these two carbon atoms suggests that there was indeed no $C^{14}$ in the iodoform.

$= 1:0.25$) was used as catalyst. (Studies on the effect of water and other cocatalysts on the rearrangement are described in the latter part of this paper.) The starting material was $n$-propyl-$\alpha$-$C^{14}$-benzene (2.12 $\mu$c./mmole, determined by radioassay of benzoic acid from degradation). After heating at $100°$ for 6.5 hours with the catalyst, a sample of the $n$-propylbenzene recovered was degraded to benzoic acid, which was found to contain radioactivity of 1.42 $\mu$c./mmole, corresponding to 33.0% rearrangement of $C^{14}$ from the $\alpha$-position. The remainder of the recovered propylbenzene was heated with a fresh portion of water-activated catalyst and the propylbenzene fraction was again recovered by distillation. Degradation of a sample afforded benzoic acid having 1.11 $\mu$c./mmole, corresponding to 47.7% rearrangement of $C^{14}$ from the $\alpha$-position. Thus, the use of water-activated aluminum chloride accomplished the same degree of rearrangement in two stages as that produced in four stages by catalyst to which no water had been added deliberately.

TABLE I

THREE-STAGE REARRANGEMENT OF $n$-PROPYL-$\alpha$-$C^{14}$-BENZENE BY ALUMINUM CHLORIDE AT $100°$[a]

| Compound radioassayed | Molecular radioactivity, $\mu$c./mmole | | | Isotopic rearrangement, % |
|---|---|---|---|---|
| | $\alpha$-C | $\beta$-C | $\gamma$-C | |
| $n$-Pr-$\alpha$-$C^{14}$-benzene[b] | | | | |
| benzoic acid | 0.497 | 0 | 0 | ... |
| Stage 1 | | | | |
| Benzoic acid | 0.367 | ... | ... | 26.2 |
| Phthalic acids | 0.712 | ... | ... | 28.4 |
| Benzaldehyde | 0.362 | ... | ... | 27.2 |
| Acetaldehyde | ... | 0.129[c] | ... | 26.0 |
| Iodoform | ... | ... | 0[c] | ... |
| Stage 2 | | | | |
| Benzoic acid | 0.281 | ... | ... | 43.5 |
| Phthalic acids | 0.558 | ... | ... | 43.8 |
| Benzaldehyde | 0.284 | ... | ... | 42.8 |
| Acetaldehyde | ... | 0.206 | ... | 41.4 |
| Iodoform | ... | ... | 0 | ... |
| Stage 2' | | | | |
| Benzoic acid | 0.286 | ... | ... | 42.3 |
| Benzaldehyde | 0.284 | ... | ... | 42.9 |
| Acetaldehyde | ... | 0.214 | ... | 43.1 |
| Iodoform | ... | ... | 0 | ... |
| Stage 3 | | | | |
| Benzoic acid | 0.263 | ... | ... | 47.1 |
| Phthalic acids | 0.518 | ... | ... | 48.0 |
| Benzaldehyde | 0.265 | ... | ... | 46.6 |
| Acetaldehyde | ... | 0.227 | ... | 45.8 |
| Iodoform | ... | ... | 0 | ... |

[a] The degradation schemes are outlined in ref. 3b. [b] Starting material. [c] The acetaldehyde assayed actually included both $\beta$- and $\gamma$-C atoms, but since the iodoform derived from the acetaldehyde was always nonradioactive, the radioactivity of the acetaldehyde could be attributed to the $\beta$-C alone.

**Multiple Rearrangements of $n$-Propyl-$\beta$-$C^{14}$-benzene.**—A multistage experiment was also carried out using $n$-propyl-$\beta$-$C^{14}$-benzene as starting material. Unfortunately the first three stages of this experiment were, like the first experiment with $n$-propyl-$\alpha$-$C^{14}$ benzene, performed before the activating effect of a cocatalyst was recognized. It may be observed in Table II that the extent of rearrangement in the fourth

FOUR-STAGE REARRANGEMENT OF $n$-PROPYL-$\beta$-C$^{14}$-BENZENE
BY ALUMINUM CHLORIDE AT 100°

| Compound degraded | Molecular radioactivity, $\mu$c./mmole | Isotopic rearrangement, % |
|---|---|---|
| $n$-Pr-$\beta$-C$^{14}$-benzene (Starting material) | $\beta$-C$^{14}$, 0.622[a] | .. |
| $n$-Pr-$\alpha,\beta$-C$^{14}$-benzene | | |
| Stage 1 | $\alpha$-C$^{14}$, 0.109[b] | 17.6 |
| Stage 2 | $\alpha$-C$^{14}$, 0.179[b] | 28.8 |
| Stage 3 | $\alpha$-C$^{14}$, 0.226[b] | 36.4 |
| Stage 4[c] | $\alpha$-C$^{14}$, 0.281[b] | 45.2 |

[a] $p$-$n$-Propylbenzenesulfonamide assayed. [b] Benzoic acid assayed. [c] Water added to catalyst in molar ratio approximately AlCl$_3$/H$_2$O = 1:0.1.

stage, in which water was added to the aluminum chloride, was considerably greater than would have been expected on the basis of the results from the first three stages. If water-activated catalyst had been used in the first three stages, the final distribution of C$^{14}$ between the $\alpha$- and $\beta$-carbon atoms would undoubtedly have been very close to 50:50.

The results of these multiple catalyst treatments of $n$-propylbenzene labeled with C$^{14}$ in either the $\alpha$- or the $\beta$-position thus show that there is progressive equilibration of the $\alpha$- and $\beta$-, but not the $\gamma$-carbon atoms of the side chain and they support the theory that deactivation of the catalyst by disproportionation products is responsible for the incomplete rearrangements produced by single catalyst treatments.

The degree of rearrangement of $n$-propylbenzene to isopropylbenzene was determined in some of these experiments, by infrared spectrophotometry or by isotope dilution analysis. For example, after the first stage of the multiple rearrangements recorded in Table I, the propylbenzene fraction was found to contain 2.1% isopropylbenzene and, after the second stage, 4.6%. The distribution of the C$^{14}$ in this isopropylbenzene has been determined and is reported in the following paper.[9]

**Studies on Effects of Water and Other Cocatalysts.—** Having observed the activating effect of water on the aluminum chloride-induced rearrangement of $sec$-butyl- and isobutylbenzene,[4] we carried out a series of experiments designed to show if the propylbenzene rearrangement is similarly susceptible to cocatalysis by water. Experiments 1–9 in Table III indicate that it is. There was not a great difference in the extent of rearrangement produced by catalysts having mole ratios of H$_2$O/AlCl$_3$ from 0.067 to 0.500, but when the mole ratio was increased to 1.00, the activity of the catalyst toward rearrangement was greatly reduced. This is in contrast to experience with $sec$-butyl- and isobutylbenzene; catalysts having a H$_2$O/AlCl$_3$ mole ratio of 1.00 were found to give complete equilibration of the butylbenzenes.

An approximate measure of the rate of the rearrangement is given by experiments 6–8 and 3, in which treatments with catalyst having the optimum H$_2$O/AlCl$_3$ ratio were carried out for different time intervals at 100°. Experiment 9 was conducted at 80°. Since the equilibration of $sec$-butyl- and isobutylbenzene by water-activated aluminum chloride was found to be

complete within one hour at 100°, it can be seen that the $n$-propylbenzene rearrangement is much slower.

Comparison of experiments 3 and 10 shows that water-activated aluminum bromide is equally as effective as the chloride.

Several experiments were carried out in which aluminum bromide saturated with hydrogen bromide was used as catalyst. At room temperature for 6.5 hours, very little rearrangement occurred (experiment 11). One experiment in which the temperature was kept at 100° for 6.5 hours gave a black product from which no propylbenzene could be recovered. When the time was cut down to one hour, propylbenzene was recovered in about 7% yield; it had undergone the most extensive rearrangement effected in one stage (experiment 12).

EXTENT OF REARRANGEMENT OF C$^{14}$-LABELED $n$-PROPYL-
BENZENE INDUCED BY COMPLEX CATALYSTS[a,b]

| Expt. no. | C$^{14c}$ | Catalysts, mole ratios | Time, hr. | Rearrangement, % |
|---|---|---|---|---|
| | | H$_2$O/AlCl$_3$ | | |
| 1 | $\alpha$ | 0.067 | 6.5 | 36.4 |
| 2 | $\beta$ | .125 | 6.5 | 35.5 |
| 3 | $\alpha$ | .250 | 6.5 | 38.8 |
| 4 | $\alpha$ | .500 | 6.5 | 31.2 |
| 5 | $\beta$ | 1.00 | 6.5 | 11.4 |
| 6 | $\alpha$ | .250 | 0.5 | 4.27 |
| 7 | $\alpha$ | .250 | 1.5 | 13.5 |
| 8 | $\alpha$ | .250 | 4.5 | 31.6 |
| 9 | $\alpha$ | .250 | 6.5 | 9.22[b] |
| | | H$_2$O/AlBr$_3$ | | |
| 10 | $\alpha$ | 0.250 | 6.5 | 38.5 |
| | | HBr/AlBr$_3$ | | |
| 11 | $\beta$ | 0.500[d] | 6.5 | 1.25[b] |
| 12 | $\alpha$ | 0.500[d] | 1.0 | 44.3 |

[a] AlX$_3$/$n$-PrC$_6$H$_5$ mole ratio was 0.334 in all experiments except in no. 11, 0.458, and no. 12, 0.320. [b] Temperature was 100° in all experiments except no. 9, 80°, and no. 11, 25°. [c] Position of C$^{14}$ in starting material. [d] Reaction mixture was saturated with HBr.[9a]

## Experimental

**Radioassays** were made either by wet-combustion[10] to carbon dioxide which was collected in an ionization chamber and counted on a vibrating-reed electrometer[11] or by employment of a liquid scintillation spectrometer (Packard "Tri-carb"). For the scintillator solution, 2,5-diphenyloxazole and 1,4-di[2-(5-phenyloxazoyl)]benzene in toluene were used[12]; in the radioassay of acetophenone-C$^{14}$ semicarbazone it was necessary to add ethanol to the solution. Counting efficiency of the scintillometer was determined using a benzoic-1-C$^{14}$ acid standard (5620 d.p.m.) obtained from New England Nuclear Corp.[13]

**Sodium Propionate-1-C$^{14}$. A. From Sodium Cyanide-C$^{14}$.—** (See Fig. 1.) Sodium cyanide-C$^{14}$ (Tracerlab, Inc.[13]) (1.0 mmole, 1.0 mc.) was dissolved in 20 ml. water and "diluted" with 9.75 g. (199 mmoles) of ordinary sodium cyanide dissolved in 35 ml. of water. Treatment with aqueous alcoholic ethyl iodide in the manner described previously[3] resulted in 18.3 g. (93.5%) of dry sodium propionate-1-C$^{14}$.

**B. From Barium Carbonate-C$^{14}$.—**(See Fig. 1.) Carbonation of the Grignard reagent prepared from 210 mg. (8.8 mg.-atoms) of magnesium and 870 mg. (8.0 mmoles) of ethyl bromide was effected by modification to a small scale of the procedure de-

(9a) D. D. Eley and P. J. King, $J. Chem. Soc.$, 2517 (1952).

(10) D. D. Van Slyke and J. Folch, $J. Biol. Chem.$, **136**, 509 (1940); D. D. Van Slyke, J. Plazin, and J. R. Weisinger, $ibid.$, **191**, 299 (1951).

(11) O. K. Neville, $J. Am. Chem. Soc.$, **70**, 3501 (1948).

(12) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. D. Rogers, $Nucleonics$, **13**, No. 12, 38 (1955).

(13) On allocation from the U. S. Atomic Energy Commission.

(9) J. E. Douglass and R. M. Roberts, $J. Org. Chem.$, **28**, 1229 (1963).

scribed by Calvin, *et al.*,[14] using 26.23 mg. (0.133 mmole, 2.33 mc.) of barium carbonate-C[14] (Oak Ridge National Laboratory[13]) and 377.0 mg. (1.91 mmoles) of ordinary barium carbonate; 248 mg.[15] of sodium propionate-1-C[14] was obtained. The active material was diluted with ordinary sodium propionate before the next step.

**Propiophenone-1-C[14]** was prepared by acylation of benzene by sodium propionate-1-C[14] and excess aluminum chloride as described previously.[3b]

*n*-Propyl-$\alpha$-C[14]-benzene was obtained by reduction of propiophenone-1-C[14] using either the Clemmensen method[3b] or the Huang-Minlon modification of the Wolff–Kishner method.[16] The latter proved to be more reliable and simpler. The over-all radiochemical yields of the *n*-propyl-$\alpha$-C[14]-benzene by the two routes were 50% from sodium cyanide-C[14] and 32% from barium carbonate-C[14]. In view of a price differential of 1:9 in favor of barium carbonate-C[14], this is the reagent of choice in spite of the lower over-all yield.

The molecular radioactivity of the *n*-propyl-$\alpha$-C[14]-benzene was determined by oxidation to benzoic-7-C[14] acid[3b] or by conversion to the sulfonamide[17] and radioassay of these crystalline derivatives.

*n*-Propyl-$\beta$-C[14]-benzene was synthesized by the steps outlined in Fig. 2. The carbonation of the benzylmagnesium chloride was carried out in the same way as that of ethylmagnesium bromide (above), using about 1 g. of benzyl chloride in a typical run. A yield of about 82% of phenylacetic-1-C[14] acid was obtained. This was diluted with about 35 g. of phenylacetic acid and converted to the acyl chloride (93%) by the method of Truitt, *et al.*[18]; the excess thionyl chloride was removed to a cold trap under reduced pressure.[19]

Dimethylcadmium was prepared by Cason's method.[20,21] Good yields from its reaction with phenylacetyl-1-C[14] chloride were obtained only after considerable experimentation; details of the optimum conditions are given here. A suspension of dimethylcadmium (*ca.* 0.25 mole) in benzene (*ca.* 300 ml.) was cooled to 5° and a solution of phenylacetyl-1-C[14] chloride (0.24 mole) in dry benzene (75 ml.) was added to the stirred suspension over a period of 10 min. The mixture was then allowed to warm to room temperature with stirring during 2.5 hr. The reaction mixture was poured onto about 300 g. of cracked ice, followed by the addition of 100 ml. of 6 *N* hydrochloric acid. After stirring until all the ice had melted, the mixture was transferred to a separatory funnel and the two layers were separated. The aqueous layer was washed with two 100-ml. portions of water, 5% sodium bicarbonate solution, and water. It was then dried over anhydrous calcium chloride. Distillation afforded an 87% yield of 1-phenyl-2-propanone-2-C[14], b.p. 91–2° (10 mm.).

(14) M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert, and P. F. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 177.

(15) This was more than the theoretical amount of sodium propionate, due probably to incomplete drying or excess alkali. It caused no difficulty; the over-all result was equally satisfactory as the results from two other runs in which 94 and 97% yields of crude sodium propionate were obtained.

(16) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 246.

(18) P. Truitt, D. Mark, L. M. Long, and J. Jeans, *J. Am. Chem. Soc.*, **70**, 4214 (1948).

(19) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, p. 356.

(20) J. Cason and F. S. Prout, *J. Am. Chem. Soc.* **66**, 46 (1944).

(21) J. Cason, *ibid.*, **68**, 2078 (1946).

Wolff–Kischner[16] reduction of the ketone to *n*-propyl-$\beta$-C[14]-benzene was accomplished in 73% yield. An over-all radiochemical yield of 43% was obtained (from barium carbonate-C[14]).

For radioassay, the hydrocarbon was converted to the diacetamido derivative.[22]

**Multiple Rearrangements of C[14]-Labeled *n*-Propylbenzene.—** These were carried out as described previously,[3] using in all experiments a molar ratio of aluminum chloride/hydrocarbon of 0.3.

In the experiment of Table I, 60.3 g. of *n*-propyl-$\alpha$-C[14]-benzene was taken for the first-stage reaction; 19.8 g. of propylbenzene (2% isopropylbenzene, by infrared analysis) was recovered by distillation at 140–160°. The amount remaining for the second stage treatment (after samples had been taken for degradation) was 16.9 g., from which 4.3 g. of propylbenzene (5% isopropylbenzene) was recovered by distillation. The dipropylbenzene fraction from the first stage reaction, of which 7.1 g. remained after a sample had been taken for degradation, was transalkylated by treatment with 80 ml. of dry benzene and 3.6 g. of aluminum chloride at 100° for 4.5 hr. Decomposition with water followed by the usual work-up and distillation gave 6.422 g. of propylbenzene fraction. This was diluted with 8.712 g. of nonradioactive *n*-propylbenzene. After samples were taken for degradation, the remainder, 12.9 g. was treated with aluminum chloride (the third stage). The radioactivities reported in Table I are corrected for the dilution described above.

The details of the two-stage reaction of *n*-propyl-$\alpha$-C[14]-benzene with water-activated catalyst are given in the Experimental section of the following paper[9] as experiments 2.1 and 2.2.

The four-stage reaction of *n*-propyl-$\beta$-C[14]-benzene started with 96.2 g. of the hydrocarbon. The propylbenzene fraction recovered after the first stage of reaction was 37.4 g. After a sample was taken for degradation, 36.5 g. was subjected to reaction with aluminum chloride and 12.3 g. of propylbenzene fraction was recovered. For the third-stage treatment, 11.32 g. of this fraction was diluted with 22.54 g. of nonradioactive *n*-propylbenzene; 11.0 g. of propylbenzene fraction was recovered after the third treatment. The fourth and final reaction was carried out with 10.6 g. of hydrocarbon, from which 2.63 g. of propylbenzene fraction was recovered. The radioactivities in Table II are corrected for the dilution after stage two.

**Experiments with Complex Acids.—**Water was added to the hydrocarbon–aluminum halide mixtures in the proportions shown in Table III. The heterogeneous mixtures were stirred continuously for the times given in the table. The ratio of HBr/AlBr$_3$ is assumed from the finding of a complex of the approximate composition $(C_6H_6)_6 \cdot Al_2Br_6 \cdot HBr$.[9a] In our experiments, mixtures of *n*-propylbenzene and aluminum bromide were saturated with dry hydrogen bromide. Aluminum bromide was distilled directly into the reaction flask.

The molecular radioactivities of the starting materials were as follows: *n*-propyl-$\alpha$-C[14]-benzene, in experiments 10 and 12, 0.789 $\mu$c./mmole; in all others, 0.445 $\mu$c./mmole. *n*-Propyl-$\beta$-C[14]-benzene, in experiment 2, 2.29 $\mu$c./mmole; experiment 5, 0.580 $\mu$c./mmole; experiment 11, 0.622 $\mu$c./mmole.

Extent of isotopic rearrangement was determined in all experiments by degradation to benzoic acid.

(22) V. N. Ipatieff and L. Schmerling, *ibid.*, **59**, 1056 (1937).

# Alkylbenzenes. X. The Relationship Between the Distribution of Isotopic Carbon Found in Isopropylbenzene and *n*-Propylbenzene After Treatment of *n*-Propyl-α-C¹⁴-benzene with Aluminum Chloride[1]

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Using an isotope dilution technique, the distribution of $C^{14}$ in the small amount of isopropylbenzene produced from *n*-propyl-α-$C^{14}$-benzene by reaction with aluminum chloride has been determined. Consideration of the relationships found between the isotopic distribution in the two propylbenzene isomers has led to a better understanding of the mechanisms operative in these internal rearrangements of alkylbenzene side chains

## Introduction

In the preceding paper[3] we reported the progressive equilibration of $C^{14}$ between the α- and the β-positions in the side chain of *n*-propylbenzene effected by repeated treatment of *n*-propyl-α- or β-$C^{14}$-benzene with aluminum chloride. We have mentioned that isopropylbenzene is also produced in these reactions, but is found in only minor amounts,[3,4] presumably because of its greater susceptibility to dealkylation.[5]

Since it is possible to observe *partial* rearrangement of isotopic carbon from the α- to the β-position of the side chain (or *vice versa*), it seemed that determination of the distribution of the isotope in the isopropylbenzene produced concurrently might shed more light on the mechanism of these processes.[6] This was recognized to be a difficult task owing to the small amounts of isopropylbenzene remaining in the liquid reaction mixtures and the nearness of the boiling points of the isomeric propylbenzenes; however, a possible means of overcoming the difficulties appeared to be an isotope dilution technique.[7] This paper reports the successful application of this technique to the problem, and conclusions which have been drawn from the relationship found between the isotopic distributions in the propylbenzene isomers.

## Results and Discussion

The separation problem was solved satisfactorily by diluting the propylbenzene fraction recovered by distillation of the reaction mixture with a known amount of pure isopropylbenzene and redistilling the resulting mixture through a very efficient column. It was necessary to dilute the small amount of radioactive isopropylbenzene with an amount of pure nonradioactive isopropylbenzene large enough to give approximately equal weights of the two isomers in order to allow satisfactory fractionation. The radioactive isopropylbenzene thus obtained was shown to be at least 96% pure by infrared analysis.

The degradation of isopropylbenzene was accomplished by means of the two steps outlined in equations 1 and 2:



$$\text{(1)}$$



$$\text{(2)}$$
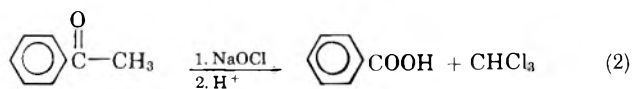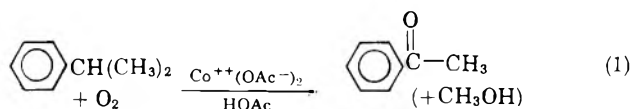
The autoxidation of cumene (isopropylbenzene) has been studied extensively, but usually for the purpose either of determining the kinetics of the reaction or of obtaining the hydroperoxide in good yield. The decomposition of cumyl hydroperoxide in the presence of certain transition metal ion catalysts is well known; *e.g.*, Kharasch, *et al.*,[8] obtained acetophenone in 70% yield by treating an aqueous suspension of the hydroperoxide with ferrous ammonium sulfate. However, since the isolation of the hydroperoxide from a small scale autoxidation mixture would be somewhat difficult, it was desirable to effect both the autoxidation of the isopropylbenzene and the decomposition of the resulting hydroperoxide without isolation of the latter. A glacial acetic acid solution of anhydrous cobalt(II) acetate proved to be most suitable.[9] The fate of the second β-methyl group is uncertain, although it most likely was converted into methanol, which perhaps underwent further oxidation. The procedure used for the hypochlorite oxidation of acetophenone to benzoic acid was patterned after that given by Newman and Holmes.[10]

Radioassay of the two degradation products, acetophenone (as semicarbazone) and benzoic acid, permitted calculation of the distribution of $C^{14}$ in the isopropyl side chain. The radioactivity data could also be used to calculate the percentage of isopropylbenzene in the total propylbenzene fraction, by using isotope dilution formulas. Details of these calculations are given in Experimental.

The degradation applied to disclose the isotopic distribution in *n*-propylbenzene was permanganate oxidation to benzoic acid, as in previous work.[4]

(1) A preliminary report of some of these results was given in *Chem. Ind* (London), 926 (1959).

(2) Taken from the Ph.D. thesis of J. E. D., The University of Texas, 1959; Procter and Gamble Co. Fellow, 1957–58. Present address, University of Kentucky, Lexington, Ky.

(3) R. M. Roberts and J. E. Douglass, Part IX, *J. Org. Chem.*, **28**, 1225 (1963).

(4) R. M. Roberts and S. G. Brandenberger, *J. Am. Chem. Soc.*, **79**, 5484 (1957).

(5) R. M. Roberts, paper presented at the Symposium on Carbonium Ions of the Organic Division, 139th National Meeting of the American Chemical Society, March 27, 1961, St. Louis, Mo.

(6) This was originally suggested by Professor C. D. Nenitzescu in a personal communication.

(7) We are indebted to Dr. S. G. Brandenberger for suggesting this approach.
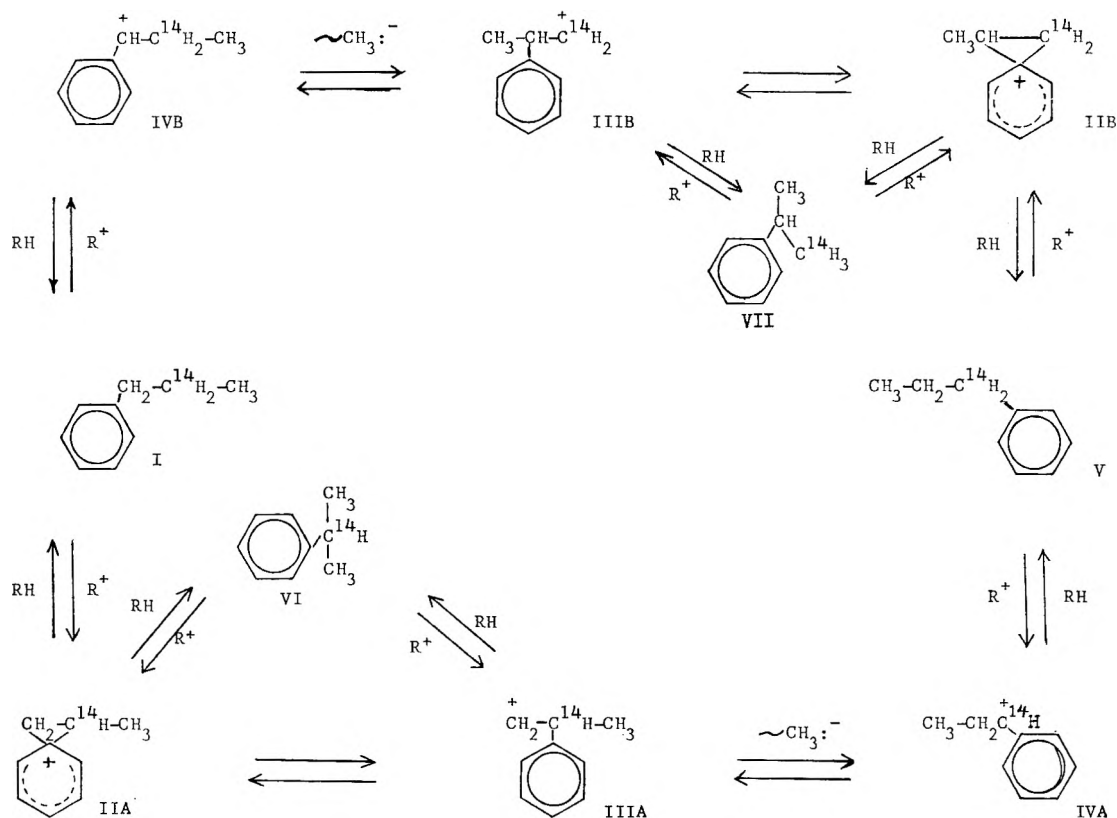
(8) M. S. Kharasch, A. Fono, and W. Nudenburg, *J. Org. Chem.*, **15**, 763 (1950).

(9) A. E. Woodward and R. B. Mesrobian, *J. Am. Chem. Soc.*, **75**, 6189 (1953).

(10) M. S. Newman and H. L. Holmes, *Org. Syn.*, **2**, 428 (1943).

Fig. 1.—Propylbenzene rearrangement mechanisms.

In the first experiment, $n$-propyl-$\alpha$-C$^{14}$-benzene was treated with water-activated aluminum chloride at 100°—conditions which previous experiments indicated should give about 30% isotopic rearrangement. Of the propylbenzene fraction recovered after the usual decomposition and distillation, a small sample was oxidized directly to benzoic acid, while the major part was diluted with pure (nonradioactive) isopropylbenzene and distilled through an efficient column in order to obtain a sample of radioactive isopropylbenzene. This material was then degraded to acetophenone and benzoic acid as described above. The results of the radioassays are given in Table I. The distribution of isotopic carbon calculated as described in the Experimental

TABLE I

RADIOACTIVITIES OF STARTING MATERIALS AND DEGRADATION PRODUCTS[a]

| Expt. | $n$-Pr-$\alpha$-C$^{14}$-Ph[b] | Benzoic acid[c] | Acetophenone[d] | Benzoic Acid[e] |
|---|---|---|---|---|
| 1 | 1.83 | 1.30 | 0.0565 | 0.0200 |
| 2.1 | 2.12 | 1.42 | 0.0610 | 0.0291 |
| 2.2[f] | ... | 1.11 | 0.0194 | 0.0128 |

[a] Radioactivities in microcuries per millimole ($\mu$c./mmole). [b] $n$-Propyl-$\alpha$-C$^{14}$-benzene assayed as sulforamide. [c] From $n$-propylbenzene. [d] As semicarbazone ($A_a$; cf. Experimental section). [e] From acetophenone ($A_b$; cf. Experimental section). [f] The propylbenzene fraction recovered from experiment 2.1 was treated with fresh AlCl$_3$ + H$_2$O.

TABLE II

DISTRIBUTION OF C$^{14}$ IN $n$-PROPYL- AND ISOPROPYLBENZENE

| | Percent C$^{14}$ in | | | |
|---|---|---|---|---|
| | $n$-PrC$_6$H$_5$ | | $i$-PrC$_6$H$_5$ | |
| Expt. | $\alpha$-C | $\beta$-C | $\alpha$-C | $\beta$-C's |
| 1 | 71 | 29 | 22 | 78 |
| 2.1 | 67 | 33 | 31 | 69 |
| 2.2 | 52 | 48 | 49 | 51 |

section is presented in Table II. The proportion of isopropylbenzene in the propylbenzene fraction before dilution calculated from the isotope dilution formula was 3.55%, which was in good agreement with the value from infrared analysis, 3.6%.

In a second experiment, a larger amount of $n$-propyl-$\alpha$-C$^{14}$-benzene was subjected to reaction so that enough propylbenzene could be recovered to allow a second treatment with fresh catalyst.[3] The results of the consecutive treatments with catalyst are tabulated under experiments 2.1 and 2.2 in Tables I and II. In experiments 1 and 2.1, the distribution of isotopic carbon between the $\alpha$- and $\beta$-positions of the side chains of $n$-propyl- and isopropylbenzene exhibited an inverse relationship. After two catalyst treatments (experiment 2.2), the isotopic carbon was almost equally distributed between the $\alpha$- and $\beta$-positions in both propylbenzene isomers. These results are not at variance with the mechanism which was first suggested for the isotopic rearrangement of $n$-propylbenzene,[4] but information accumulated since that time leads us to favor now a more orthodox mechanism which is outlined in Fig. 1.[11] This mechanism also allows a more plausible explanation of the presently reported results.

Since all of the steps outlined in Fig. 1 are expected to be reversible, conversion of $n$-propyl-$\alpha$-C$^{14}$-benzene (V) to $n$-propyl-$\beta$-C$^{14}$-benzene (I) may occur via either clockwise or counterclockwise routes. However, before equilibrium is reached, any isopropylbenzene

(11) The guiding principle in the formulation of the first mechanism was to account for the apparently insignificant amount of rearrangement to isopropylbenzene. We now know that there is more rearrangement to isopropylbenzene than is indicated by the amount of this isomer found in the liquid reaction mixture, owing to the greater susceptibility of isopropylbenzene to dealkylation[4]; thus there is no necessity of avoiding a mechanism which would be expected to lead to isopropylbenzene as well as to isotopically rearranged $n$-propylbenzene.

produced from V should have more of the isotopic carbon in the $\beta$-positions than in the $\alpha$-position, since there is a route to VII *via* IIB, but VI can not be produced without passing through the highest energy intermediate ions IIIA or IIIB. This expectation is realized in experiments 1 and 2.1. After equilibrium is reached (with respect to V and I) there is equal probability of formation of VII and VI, and this is the finding in experiment 2.2. For this reason we prefer the formulation of Fig. 1 to the somewhat similar scheme of Nenitzescu,[12] in which the primary carbonium ion is a common intermediate in the formation of both isopropylbenzene and isotopically rearranged *n*-propylbenzene. As a corollary, one may also cite this inverse relationship between isotopic distribution in *n*-propyl- and isopropylbenzene as evidence for the intervention of phenonium ions in these rearrangements.[13]

## Experimental

**Radioassays** were made by means of a liquid scintillation spectrometer (Packard "Tri-carb") as described in the preceding paper.[3]

*n*-Propyl-$\alpha$-$C^{14}$-benzene was synthesized from $BaC^{14}O_3$ as described in the preceding paper[3] and radioassayed in the form of its sulfonamide.

**Reaction of *n*-Propyl-$\alpha$-$C^{14}$-benzene with Aluminum Chloride–Water. Experiment 1.**—A mixture of 34.4 g. (0.286 mole) of *n*-propyl-$\alpha$-$C^{14}$-benzene, 12.7 g. (0.0952 mole) of anhydrous aluminum chloride and 0.145 g. (0.0081 mole) of water was heated with stirring at 100° for 6.5 hr. The mixture was decomposed with water, the organic layer was separated, dried, and distilled through a 45-cm. glass helices-packed column. A 10.4-g. propylbenzene fraction boiling at 148–160° was obtained; infrared analysis indicated it to contain 3.6% isopropylbenzene. Isotope dilution analysis (see below) gave 3.55% isopropylbenzene.

A 1.0-ml. portion of this fraction was oxidized to benzoic acid in the usual way[4] and recrystallized to constant melting point and radioactivity.

To the remainder of the propylbenzene fraction (8.955 g.) was added 5.941 g. of freshly distilled nonradioactive isopropylbenzene (b.p. 151–152°). The resulting mixture was distilled through a Podbielniak Series 3300 24-in. micro heli-grid column, rated at 100 plates under total reflux. A 4.7-ml. fraction, b.p. 151.3–152.0°, was shown by infrared analysis to be at least 96% isopropylbenzene.

**Autoxidation of Isopropylbenzene.**—A 50-ml. flask was equipped with a double-surface reflux condenser, to the top of which was attached a glass tube leading to an ice-cooled trap. Oxygen was introduced through a small side neck after having passed through a bubble-counting tube filled with silicone fluid. Glacial acetic acid used as solvent had added to it 1 ml. of acetic anhydride per 100 ml. of acetic acid to insure complete dryness. Anhydrous cobalt (II) acetate was prepared by heating the tetrahydrate in an oven at 110° for 8 hr.; it was finely ground and stored over magnesium sulfate in a desiccator.

To the reaction flask was added 16 ml. of the glacial acetic acid, 4.0 ml. of the isopropylbenzene fraction and 0.10 g. of anhydrous cobalt (II) acetate. The mixture was heated at 100 ± 1° with stirring (by means of a Teflon-covered magnet) for 24 hr., while a slow but steady stream of oxygen was passed into the flask. The contents of the flask and trap were then distilled, the acetic acid being removed at atmospheric pressure and acetophenone, 1.2 ml., at aspirator pressure.

The semicarbazone was prepared from a 0.6-ml. sample of the acetophenone by the standard procedure and the derivative was recrystallized to constant melting point and radioactivity.

A 0.5-ml. sample of the acetophenone was stirred with 50 ml. of a 5.25% solution of sodium hypochlorite (Clorox) at 60–70° for 45 min. Ethanol (1 ml.) was added and the mixture was stirred for another 10 min. in order to destroy any unchanged reagent. After cooling, the reaction mixture was washed with 10 ml. of ether to remove any unchanged acetophenone, the aqueous solution was evaporated on the steam cone to about one-half its original volume and then acidified to pH 1 with 6 $N$ hydrochloric acid. The crystals of benzoic acid which formed on cooling amounted to 336 mg. It was recrystallized and sublimed to constant melting point and radioactivity.

**Experiment 2.1**—A second experiment was carried out with 172 g. (1.44 moles) of *n*-propyl-$\alpha$-$C^{14}$-benzene, 63.7 g. (0.477 mole) of aluminum chloride and 2.16 g. (0.120 mole) of water as starting materials. The same conditions of reaction and procedures of work-up were used as in experiment 1. A 47.0-g. propylbenzene fraction was obtained by distillation. Isotope dilution analysis (see below) indicated 3.66% isopropylbenzene. A 1.0-ml. sample was oxidized to benzoic acid, which was purified and radioassayed as before. An 8.518-g. sample was diluted with 6.812 g. of isopropylbenzene. The mixture was fractionated using the Podbielniak column to give 6.0 ml. of radioactive isopropylbenzene, b.p. 150.2–151.6°. This was degraded to acetophenone and benzoic acid as before.

**Experiment 2.2**—The remainder of the propylbenzene fraction above, 37.7 g., 0.311 mole, was treated with 14.3 g. (0.107 mole) of aluminum chloride and 0.49 g. (0.027 mole) of water at 100° for 6.5 hr., with stirring. The products were distilled to yield 10.3 g. of propylbenzene fraction. A 1.0-ml. sample was degraded to benzoic acid. Another portion was diluted quantitatively with isopropylbenzene and the resulting mixture was distilled through the Podbielniak column. The radioactive isopropylbenzene obtained was degraded to acetophenone and benzoic acid as before.

The results of the radioassays are given in Table I. The values given are the average of at least two assays after constant activity was reached.

**Calculations.**—A. Distribution of $C^{14}$ in isopropyl-$\alpha,\beta$-$C^{14}$-benzene. Let

$A_a$ = molar radioactivity of acetophenone semicarbazone from degradation of isopropylbenzene (represents the amount of $C^{14}$ present in $\alpha$-position plus one-half that in $\beta$-positions of isopropylbenzene).

$A_b$ = molar radioactivity of benzoic acid from degradation of acetophenone (represents the amount of $C^{14}$ present in $\alpha$-position of isopropylbenzene).

Then $2(A_a - A_b)$ = amount of $C^{14}$ in $\beta$-positions and

$A_t$ = amount of $C^{14}$ in $\alpha$- plus $\beta$-positions
     = $A_b + 2(A_a - A_b)$
     = $2A_a - A_b$

Hence

$$\% \ C^{14} \text{ in } \alpha\text{-position} = \frac{A_b}{A_t} 100 = \frac{A_b}{2A_a - A_b} 100 \qquad (3)$$

$$\% \ C^{14} \text{ in } \beta\text{-positions} = \frac{2(A_a - A_b)}{A_t} 100 = \frac{2(A_a - A_b)}{2A_a - A_b} 100 \qquad (4)$$

B. Amount of isopropylbenzene in the total propylbenzene distillation fraction. Let

$A_0$ = molar radioactivity of undiluted isopropylbenzene
     = initial molar radioactivity of *n*-propyl-$\alpha$-$C^{14}$-benzene.

$W_0$ = weight of total propylbenzene fraction.

$W_i$ = weight of ordinary isopropylbenzene used as diluent.

$A_t$ = molar radioactivity of diluted isopropylbenzene =
     $2A_a - A_b$ (as above).

Then, the usual inverse isotope dilution formula may be derived to give

$$\% \text{ isopropylbenzene} = \frac{W_i}{W_0 \left( A_0/A_t - 1 \right)} 100 \qquad (5)$$

(12) C. D. Nenitzescu, I. Necsoiu, A. Glatz, and M. Zalman, *Chem. Ber.*, **92**, 10 (1959).

(13) A mechanism analogous to that of Fig. 1 can be written for the isobutylbenzene-*sec*-butylbenzene rearrangement.

# The Benzidine Rearrangement. V.[1]

## First-order Acid Dependence with 4,4'-Divinylhydrazobenzene

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4,4'-Divinylhydrazobenzene (I) has been prepared. The rates of the acid-catalyzed rearrangement of I in 95% ethanol at 0° and 25°, and in 75% t-butyl alcohol at 25° were determined. The rearrangement was followed by both the Bindschedler's Green titration method and spectrophotometrically. In each case the rearrangement was first-order in acid, over the range of acid concentrations 0.001 to 0.05 $M$. The rate of rearrangement of I is faster than that of hydrazobenzene. The product of rearrangement is neither the semidine nor the bis-$p$-aminophenylbutadiene. The product decomposes slowly with charring above 300°. is insoluble in ethanol, and has no unsaturation. The rearrangement is not accompanied by extensive disproportionation as is observed in the rearrangement of other di-$p$-substituted hydrazobenzenes. It is proposed that the product is a polymer that accompanies the o-benzidine type of rearrangement.

We have observed, with the rearrangement of 2,2'-hydrazonaphthalene, the connection between acid order and acid concentration which Banthorpe, Hughes, and Ingold[2] discovered in the rearrangement of 1-phenyl-2-β-naphthylhydrazine; that is, that the trend is from second-order at higher to first-order at lower acid concentrations.

The importance of rate data in interpreting the mechanism of the acid-catalyzed rearrangement of hydrazo compounds has been evident in the last few years. The rearrangement of hydrazobenzene was shown to be second order with respect to acid by Hammond and Shine.[3] Confirmation of second-order acid catalysis was provided by Carlin, Nelb, and Odioso[4] and by Croce and Gettler.[5]

In more recent years cases of rearrangement of substituted hydrazobenzenes have been disclosed in which a non-integral order of acid dependence was observed. These are o-hydrazotoluene,[6] 4-methyl-4'-chlorohydrazobenzene,[7] and 4-t-butyl-4'-chlorohydrazobenzene.[7] Since the variation in acid order with change in hydrazo structure must be capable of incorporation in a general mechanistic scheme for the benzidine rearrangement, and since, in one case,[7] the non-integral orders (1.58 and 1.51) were attributed to steric effects in the hydrazo compound, we were interested in investigating the kinetics of rearrangement of a number of pertinent hydrazo compounds.

Because of our prior interest in hydrazonaphthalenes[1] we chose to work with 2,2'-hydrazonaphthalene; while, because of the proposals concerning steric effects[7] we chose to work with some $p,p'$-disubstituted hydrazobenzenes.

The cases of 2,2'-hydrazonaphthalene and its isomers have now been reported by Banthorpe, Hughes, and Ingold,[2] in whose publications there are established cases of first-order and mixed-order acid dependence.

We have also worked with 2,2'-hydrazonaphthalene,[8] and have found that in acetone containing 25% water by volume, the rearrangement has an acid dependence that varies with acid concentration. The order in acid is close to 2 at acid concentrations of 0.01 to 0.02 $M$ and approaches 1 in the region of 0.005 $M$, the ionic strength being 0.02 in all cases.

Banthorpe, Hughes, and Ingold have observed an acid dependence of 1.15 with this case. The results with 2,2'-hydrazonaphthalene in our solvent and acid range, the details of which are available,[8] but which we shall omit in view of the prior publication,[2] confirm the observation, made by Banthorpe, Hughes, and Ingold with 1-phenyl-2-β-naphthylhydrazine, that it is at lower, rather than higher, acid concentrations that the trend to first-order acid dependence occurs.

We wish to report now our investigation of the acid-catalyzed rearrangement of 4,4'-divinylhydrazobenzene, I. This compound undergoes a transformation in acid solution by a process clearly first-order in acid.

## Kinetic Results

The rate of rearrangement of I was measured by the Bindschedler's Green technique[9] and also spectroscopically. The rate data from the titration method are given in Table I, while those from the spectroscopic method are given in Table II.

TABLE I

RATE CONSTANTS[a,b] FOR THE REARRANGEMENT OF 4,4'-DIVINYL-HYDRAZOBENZENE IN 95% ETHANOL AT 0°

[Hydrazo] = 2.5 × 10⁻³ $M$; ionic strength = 0.05.

| Run | [H⁺] × 10² | 10²k, min.⁻¹ |
|-----|-----------|--------------|
| 1 | 5.30 | 16.7 |
| 2[c] | 4.03 | 11.9 |
| 3[c] | 3.00 | 9.93 |
| 4[c] | 2.20 | 6.45 |
| 5 | 3.80 | 11.9 |
| 6 | 3.03 | 8.82 |
| 7 | 2.00 | 6.29 |
| 8 | 2.07 | 6.05 |
| 9 | 1.00 | 3.11 |
| 10 | 5.01 | 14.0 |
| 11 | 1.04 | 2.67 |

[a] Calculated by the method of least squares; H. Margenau and G. M. Murphy, "The Mathematics of Physics and Chemistry," D. Van Nostrand Co., Inc., Princeton, N. J., 6th printing, 1946, p. 502. [b] Bindschedler's Green method. [c] Lithium perchlorate used for maintaining ionic strength; in all other runs lithium chloride was used.

(1) For Part IV, see H. J. Shine, F.-T. Huang, and R. L. Snell, *J. Org. Chem.*, **26**, 380 (1961).

(2) D. V. Banthorpe, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2386–2444 (1962).

(3) G. S. Hammond and H. J. Shine, *J. Am. Chem. Soc.*, **72**, 220 (1950).

(4) R. B. Carlin, R. G. Nelb, and R. C. Odioso, *ibid.*, **73**, 1002 (1951).

(5) L. J. Croce and J. D. Gettler, *ibid.*, **75**, 874 (1953).

(6) R. B. Carlin and R. C. Odioso, *ibid.*, **76**, 100 (1954).

(7) M. J. S. Dewar and H. McNicholl, *Tetrahedron Letters*, **5**, 22 (1959).

(8) Unpublished work described in the M.S. degree thesis of S. J. Burdick, Texas Technological College, August, 1961.

(9) (a) M. J. S. Dewar, *J. Chem. Soc.*, 777 (1946); (b) H. J. Shine, R. L. Snell, and J. C. Trisler, *Anal. Chem.*, **30**, 383 (1958).

Rate Constants[a,b] for the Rearrangement of 4,4'-Divinyl-
hydrazobenzene at 25°

[Hydrazo] $= 5 \times 10^{-5}\ M$; ionic strength $= 0.05$.

| Solvent | $[H^+] \times 10^3$ | $10^2 k$, min.$^{-1}$ | $[H^+] \times 10^3$ | $10^2 k$, min.$^{-1}$ |
|---|---|---|---|---|
| 95% ethanol | 1.0 | 4.60 | 6.0 | 30.2 |
| | 1.0 | 4.54 | 6.0 | 30.4 |
| | 2.0 | 8.91 | 7.0 | 36.2 |
| | 2.0 | 9.03 | 7.0 | 34.1 |
| | 3.0 | 13.3 | 8.0 | 36.6 |
| | 3.0 | 13.8 | 8.0 | 39.6 |
| | 4.0 | 18.4 | 9.0 | 46.3 |
| | 4.0 | 18.8 | 9.0 | 45.8 |
| | 5.0 | 21.1 | 10.0 | 48.6 |
| | 5.0 | 22.8 | 10.0 | 48.8 |
| 75% t-butyl | 1.0 | 5.41 | 5.0 | 26.5 |
| alcohol | 1.0 | 5.55 | 5.0 | 26.2 |
| | 2.0 | 10.6 | 6.0 | 28.9 |
| | 2.0 | 10.6 | 6.0 | 30.4 |
| | 3.0 | 16.1 | 7.0 | 34.8 |
| | 3.0 | 16.0 | 7.0 | 34.3 |
| | 4.0 | 21.2 | 8.0 | 37.8 |
| | 4.0 | 21.5 | 8.0 | 38.9 |

[a] Calculated by the method of least squares.   [b] Spectroscopic
method.

The rate of rearrangement of I is faster than that of
hydrazobenzene. Comparison can be made with the
data reported by Carlin[4] for hydrazobenzene in 95%
ethanol. At 0.15° and in 0.102 $M$ acid the rate con-
stant for hydrazobenzene is 0.015 min.$^{-1}$, while the
rate constant obtained by us for the rearrangement of I
at 0° in 95% ethanol, which was only 0.053 $M$ in acid,
was eleven times larger, that is 0.167 min.$^{-1}$

Because of the rapid rate of rearrangement of I it was
not possible to go to ratios of acid to substrate concen-
tration higher than those in Table I and use the Bind-
schedler's Green method. We found that the disap-
pearance of I can be followed directly in the spectro-
photometer, so that, from runs with high acid to sub-
strate ratios, rates with half-lives of about one minute
could be followed easily. Fig. 1 shows a series of
traces obtained at time intervals with I dissolved in
acidic ethanol. The gradual disappearance of I is seen
at 287 m$\mu$, the $\lambda_{max}$ of this hydrazo compound.

The logarithms of the rate constants given in Tables
I and II were plotted against those of the acid concen-
trations. The data from ethanol solutions are plotted
in Fig. 2. The slopes of these plots were calculated by
the method of least squares and were: titration method
of following rates, 1.04; spectroscopic method (ethanol),
1.09; (t-butyl alcohol), 0.94.

Rate constants determined in conditions in which
only the initial hydrazo concentration was varied did
not differ sensibly from one and another.

## Product Analysis

The product was isolated from rearrangements in
both 95% ethanol and in wet ether. The product was
a pale yellow solid which did not melt below 300°.
Above this temperature blackening and decomposition
occurred slowly. It was not appreciably soluble in
ethanol and other common organic solvents. Elemen-
tal analysis agreed with the empirical formula of I.

The ultraviolet and infrared spectra of the product
were compared with those of known materials. Fig.
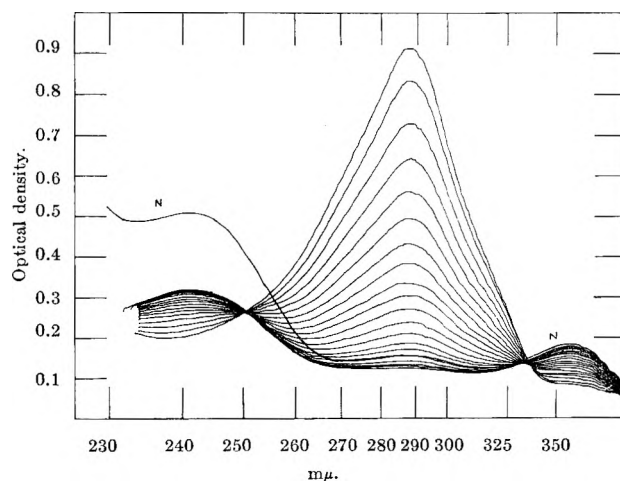1 shows that rearrangement in ethanol leads to a very



Fig. 1.—The change in the ultraviolet spectrum of 4,4'-
divinylhydrazobenzene in weakly acidic 95% ethanol. The traces
showing the decrease in absorption at 287 m$\mu$ were recorded at
5-min. intervals. The trace N was made after neutralizing the
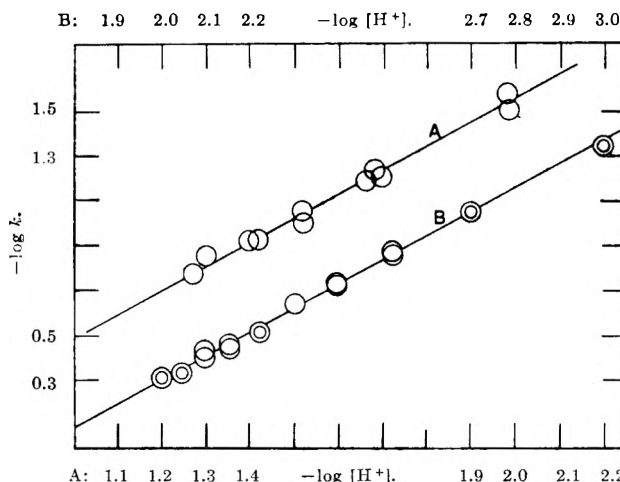acid.



Fig. 2.—Plots relating rate constants for the rearrangement of
4,4'-divinylhydrazobenzene in 95% ethanol to acid concentration.
A, titration method;  B, spectroscopic method.

simple spectrum. The ultraviolet spectrum of the iso-
lated product taken in acidic ethanol had a maximum
at 240 m$\mu$ and a broad shoulder at 290 m$\mu$. Neutrali-
zation of a rearrangement solution with sodium hy-
droxide gave a spectrum with increased absorption in the
240-m$\mu$ region and a weak absorption at 287 m$\mu$. The
spectrum indicating this is labeled N in Fig. 1.

The infrared spectrum varied very little from prepa-
ration to preparation even though some times the
product had a greenish tinge and had become hard and
resinous in appearance. The bands of the vinyl group
and substituted vinyl group bands near 900 and 1000
cm.$^{-1}$ were absent. $p$-Vinylaniline has two sharp
bands at 900 and 995 cm.$^{-1}$. Several 1,4-diphenylbuta-
dienes were examined and had sharp bands in the region
990–995 cm.$^{-1}$. In the product the aromatic region
was very simply represented by one large band centering
at 825 cm.$^{-1}$, indicative of 1,4 or 1,2,4-substitution. In
the shorter wave length region, the aromatic triplet be-
tween 2850 and 3000 cm.$^{-1}$ was clearly observed while
between 2900 and 3500 cm.$^{-1}$ the aromatic primary
amine was shown strongly. These characteristics are
shown in Fig. 3, in which the spectrum of polyvinylani-
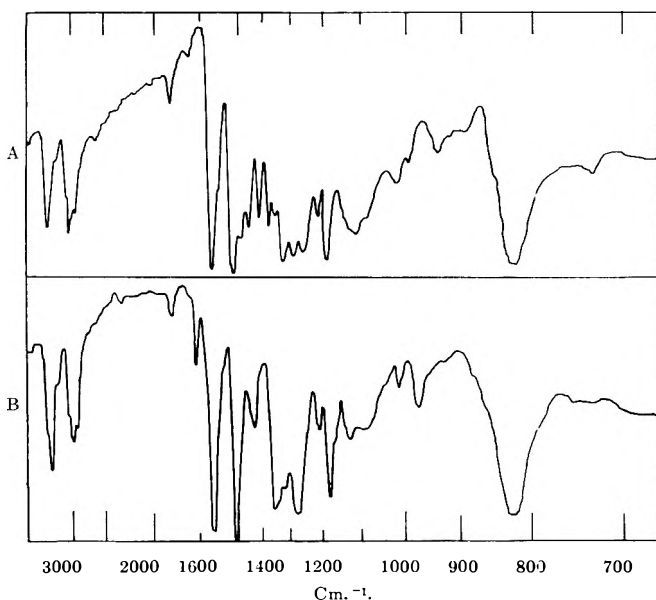line is included. The polyvinylaniline was made by

Fig. 3.—Infrared spectra: A, polyvinylaniline; B, the product of rearrangement of 4,4'-divinylhydrazobenzene.

the thermal polymerization of p-vinylaniline. Further analysis in the region 1100 to 1600 cm.$^{-1}$ is complicated by the overlapping of the aromatic and amino absorptions.

## Discussion

The coincidence of the kinetic orders in acid determined by the Bindschedler's Green and spectroscopic methods leaves us with no doubt that in each case we have measured the rate of disappearance of the hydrazo group. Since the amount of azostyrene present at the end of reaction was always very small the disappearance of the hydrazo group could not have resulted from either oxidation or disproportionation. The possibility of reduction[10] of the hydrazo compound to p-vinylaniline is also eliminated by our having carried out the reaction in wet ether and aqueous t-butyl alcohol and also failing to detect acetaldehyde in the ethanolic reaction medium. Thus, we conclude that the kinetics we have recorded are those of a true rearrangement, first-order in both hydrazo compound and in acid.

It is evident that I rearranges more rapidly than hydrazobenzene. We would anticipate that I is a weaker base than hydrazobenzene, and that the rate of attack of a second proton on the monoprotonated ion, which would lead to second-order acid kinetics, would be slower in the case of I than in that of hydrazobenzene. Thus, using the interpretation of rearrangement by two independent routes recently given,[7] we have followed in I the rate of rearrangement by a first-order process dominant because of the now less facile, compared with hydrazobenzene, attack of a second proton on the monoprotonated ion.

At the onset of this work we had anticipated that the product of rearrangement would be either the semidine or, less likely, 1,4-di(p-aminophenyl)-1,3-butadiene. It is our opinion now that neither of these is the product.

The melting point and solubility characteristics of the product make it evident that it is not simply the

semidine.[11] Further, it does not seem that the product has the semidine unit in it. The ultraviolet spectra of semidines are characterized by three well defined maxima, as shown by Carlin for the dimethyl case and as we have found in the diethyl and dichloro cases.[12] These maxima are in the regions 240, 280, and 300 m$\mu$. In acid solution the dimethylsemidine[13] absorbs strongly at 279 m$\mu$ and only moderately at 235 m$\mu$. In the last region absorption is not characterized by a maximum. This is clearly different from our product in acid solution.

The product, furthermore, is not a 1,4-diphenylbutadiene, a decision based on the absence of unsaturation bands in the infrared and the absence of the characteristic close trio of bands between 340–380 m$\mu$ in the ultraviolet spectrum of the product.

The product is, indeed, very much like polyvinylaniline, as seen in the infrared spectra, Fig. 3. p-Vinylaniline is consumed only very slowly in mildly acidic ethanol. The characteristic band at 275 m$\mu$ slowly disappears and after a week or more the spectrum is very much like that obtained by rearrangement of I. That is, the acidic solution of p-vinylaniline after two weeks has two broad bands at 345 and 242 m$\mu$. Addition of sodium hydroxide no longer gives the strong band at 275 m$\mu$, as happens when a fresh, acidic solution of the amine is treated this way, but gives a spectrum very similar to the one labeled N in Fig. 1; that is, a strong band at 238 m$\mu$, a weaker one at 287 m$\mu$, and lastly a very weak broad band at 345 m$\mu$. Unfortunately, we were able to retrieve only a gummy product from allowing p-vinylaniline to stand in acid for several weeks. The fact that the amine changes so slowly in this solution also stresses that p-vinylaniline is not the initial product in the rearrangement of I.

It is our proposal that the product is a polymer whose formation is initiated by the rearrangement that occurs intramolecularly. The rearrangement we choose is not the customary semidine type but the o-benzidine. We have noted earlier[1] that 1-phenyl-2-$\beta$-naphthylhydrazine forms the o-benzidine product both by thermal and acid-catalyzed rearrangement. The thermal rearrangements of this and other hydrazonaphthalenes may be Claisen type rearrangements, but the acid-catalyzed rearrangements are true benzidine rearrangements. Some of these, which lead to the o-benzidine products, rearrange by the first-order acid process.[2] It is our view in the present case that the process, which is first order in acid, leads to the o-benzidine product intermediate and that this intermediate is involved[1] in a way so far unknown, in initiating further reaction with available vinyl groups. Since p-vinylaniline is consumed only slowly in acidic ethanol solution, there is no reason to believe that either the semidine or the o-benzidine would be consumed at an appreciably dif-

(11) It is interesting to compare the properties of our product with those of 2,2'-divinylbenzidine reported by R. H. Wiley and N. R. Smith, *ibid.*, **70**, 2295 (1948), from the rearrangement of 3,3'-divinylhydrazobenzene. That is, the 2,2'-divinylbenzidine had m.p. 123°. Heating it to 135° gave an infusible insoluble polymer. Attempts to prepare 3,3'-divinylhydrazobenzene by reduction of m-nitrostyrene with zinc and hydrochloric acid gave a polymer. G. Komppa, Inaugural dissertation, Helsingfors, 1893 (we wish to thank the Librarian, University of Helsinki for a gift of a copy of this dissertation), reports the 2,2'-divinylbenzidine as being readily soluble in ether, benzene, and hot alcohol; and fairly soluble in cold alcohol.

(12) Unpublished work of J. T. Chamness.

(13) We wish to thank Professor Carlin for so kindly sending us this compound.

(10) R. B. Carlin and G. S. Wich, *J. Am. Chem. Soc.*, **80**, 4023 (1958).

ferent rate from $p$-vinylaniline if they were dissolved in weakly acidic ethanol. Similarly we think that I itself would not undergo a fast reaction at its vinyl groups in weakly acidic ethanol unless its hydrazo group was first involved in a rearrangement scission.

## Experimental[14]

**Materials.**—Ethanol was stock 95% and used without further treatment. The $t$-butyl alcohol was Eastman (White Label) and was allowed to crystallize, the supernatant liquid being discarded; this was done three times.

$p$-Nitrostyrene was made according to the method of Strassburg, Gregg, and Walling.[15]

**4,4'-Divinylazobenzene.**—A mixture of 90 ml. of ethanol, 15 ml. of 12 $N$ sodium hydroxide, and 7 g. of $p$-nitrostyrene was heated to boiling in a 250-ml., two-neck flask equipped with a reflux condenser. Zinc dust (25 g.) was added in small portions. Boiling was continued for 30 min. after the addition was complete, and the hot solution was filtered into a large volume of cold water. The precipitated red, gummy solid was filtered, dried, and sublimed at 120° and 2 mm. The sublimed solid was recrystallized several times from 95% ethanol to give 0.95 g. (17% yield), m.p. 138–138.5°.

*Anal.* Calcd. for $C_{16}H_{14}N_2$: C, 82.03; H, 6.02; N, 11.95. Found: C, 81.84; H, 6.18; N, 12.22.

The infrared spectrum showed a strong band at 997 cm.$^{-1}$ and a strong doublet at 906, 915 cm.$^{-1}$.

**4,4'-Divinylhydrazobenzene (I).**—The azo compound was reduced in acetone solution with zinc dust and aqueous ammonium chloride. The colorless acetone solution was filtered through sintered glass into a large volume of dilute aqueous ammonium hydroxide that had been de-gassed by stirring under a water aspirator vacuum for 30 min. The colorless I was filtered quickly, washed with water and dried in a vacuum desiccator. In all of the kinetic and product work the I used was prepared not more than 18 hr. prior to use. The product had a capillary melting point of 115°, determined by plunging into the melting point bath at various temperatures.

*Anal.* Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.85. Found: C, 81.01; H, 6.84; N, 11.99.

**1,4-Bis($p$-nitrophenyl)-1,3-butadiene.**—This compound was unknown when first made in our laboratory. Subsequently, it was reported by Buckles and Franklin,[16] via the decarboxylation of the corresponding pentadienoic acid. We used the simpler preparation via the Wittig reaction. To a solution of 11.6 g. of $p$-nitrophenyl triphenylphosphonium bromide (m.p. 275°)[17] and 5.0 g. of $p$-nitrocinnamaldehyde[18] (m.p. 139–140°, 2,4-dinitrophenylhydrazone m.p., 278–279°) in 137 ml. of absolute ethanol was added in small portions a solution of 0.2 g. of lithium metal in 103 ml. of absolute ethanol. After standing overnight at room temperature the solution was diluted with 100 ml. of water. The precipitate formed was filtered, washed with water, and dried. Recrystallization twice from $p$-xylene gave yellow-brown needles, m.p. 268–269°. Two more crystallizations from dimethylformamide gave m.p. 270–270.5° (lit.,[16] for the *trans–trans* isomer, 257.5–259°). Yield: 3.7 g. (44.3%).

*Anal.* Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.77, 64.92; H, 4.25, 4.09; N, 9.26, 9.71.

**1,4-Bis($p$-acetamidophenyl)-1,3-butadiene.**—One gram of the dinitro compound and 14 g. of zinc dust were boiled for 12 hr. with 120 ml. of acetic acid and 10 ml. of water. After cooling, the solution was decanted into 300 ml. of concentrated ammonium hydroxide. The light yellow solid was filtered, washed with ethanol, and dried giving 0.97 g. (90% yield). Crystallization from a mixture of dimethylformamide and methanol gave a colorless product, m.p. 356–357°.[19]

*Anal.* Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.75. Found: C, 75.03; H, 6.23; N, 8.72.

The ultraviolet spectrum of a chloroform solution showed a triplet of peaks at 341, 358, and 380 m$\mu$, and a small absorption at 278 m$\mu$.

The following 1,4-substituted butadienes were donated[20]: 1,4-diphenyl-, 1-$p$-nitrophenyl-4-phenyl-, and 1-$p$-acetamidophenyl-4-phenyl-1,3-butadiene.

$p$-**Vinylaniline.**—This was prepared by the aluminum amalgam reduction of $p$-nitrostyrene[21] in moist ether solution. Boiling of the reaction mixture was continued until a test sample was completely soluble in dilute hydrochloric acid. The amine was obtained by removing the ether under reduced pressure after filtering. The amine was not distilled and was stored at −10°. N-acetyl derivative, m.p. 139.5–140°; lit.,[21] 135–136°.

**Rate Work.**—Bindschedler's Green was prepared as earlier.[9b] Solutions containing approximately 3.2 g./l. were used. Commercial 20% aqueous titanium trichloride was diluted (7 ml./l.) and standardized with solutions of recrystallized potassium dichromate. Lithium chloride and lithium perchlorate were dried by heating and were stored in a desiccator. Alcoholic solutions of hydrogen chloride were made by bubbling the gas into 95% ethanol. The solutions were standardized prior to use. Rates of rearrangement were measured as described elsewhere.[3]

The spectroscopic procedure is illustrated with the following example. A solution of 8.8 mg. of I in 50 ml. of ethanol was diluted tenfold to $7.5 \times 10^{-5}$ $M$. Two ml. of this solution was pipetted into a ground-glass stoppered cell (Pyrocell Manufacturing Co., Westwood, N. J.). To this was added 1 ml. of an ethanol solution containing hydrogen chloride and lithium chloride. The stoppered cell was shaken while in the cell holder, inserted in the spectrophotometer previously set to read in transmission at 287 m$\mu$. Readings were taken at time intervals, converted to optical density and the logarithms were plotted against time. As an example, the acidic solution added last was made by diluting 3 ml. of 0.1 $M$ ethanolic hydrogen chloride to 50 ml. with ethanol and adding 0.3054 g. of lithium chloride. By using 1 ml. of this solution and 2 ml. of the I solution and assuming the volumes to be additive, the solution in the cell was $2 \times 10^{-3}$ $M$ in acid, $5 \times 10^{-5}$ $M$ in I and had an ionic strength of 0.05. In this case the rate data following were obtained.

| Time (min.): | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| % Trans.: | 10.7 | 12.5 | 14.8 | 17.5 | 20.2 | 23.5 | 26.4 | 29.4 | 31.8 |

A plot of log optical density against time gave a straight line whose calculated slope (ref. *a*, Table I) was $-3.87 \times 10^{-2}$, giving a rate constant of $8.91 \times 10^{-2}$ min.$^{-1}$.

The temperature of the cell compartment was maintained at 25° by pumping water from a temperature controlled bath through the coils of the cell compartment. The solutions used were brought to bath temperature prior to pipetting. A Beckman DK-2 instrument and a Beckman controlled-temperature cell compartment were used.

**Product Isolation.**—The following is one of the several preparations carried out. The I, 0.206 g., was dissolved in 100 ml. of 95% ethanol and 2 ml. of 1 $N$ ethanolic hydrogen chloride was added. Evaporation of the solvent with a jet of nitrogen was started 15 min. later. The solid residue obtained was dissolved in 1 $N$ hydrochloric acid and the solution was extracted several times with ether. The acid solution was poured onto 2 g. of sodium hydroxide pellets. A light yellow solid precipitated and this was filtered, washed with water, and dried, giving 0.200 g. (96.5%). Reprecipitation from dimethylformamide and drying 24 hr. at 70° and 1 mm. gave a light yellow solid.

*Anal.* Calcd. for: $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.85. Found: C, 80.96; H, 7.12; N, 11.77.

This solid was not soluble in ethanol, chloroform, benzene, diethylene glycol dimethyl ether, and water. It was soluble in dimethylformamide, dilute aqueous acid and dimethylsulfoxide.

A similar result was obtained when the rearrangement solution was not evaporated but was neutralized with ammonium hy-

(14) Analyses by Schwarzkopf Microanalytical Laboratories, Woodside 77, N. Y.

(15) R. W. Strassburg, R. A. Gregg, and C. Walling, *J. Am. Chem. Soc.*, **69**, 2141 (1947).

(16) W. E. Franklin, Ph.D. dissertation, State University of Iowa, February, 1960. University Microfilms, Inc., Ann Arbor, Mich.

(17) R. N. McDonald and T. W. Campbell, *J. Org. Chem.*, **24**, 1969 (1959).

(18) T. Nishimura, *J. Japan. Chem. Soc.*, **25**, 54 (1952).

(19) L. Katz, et al., U. S. Patent 2,852,556 (September 16, 1958), list this compound but do not give a melting point.

(20) We wish to thank Dr. Tod W. Campbell, E. I. du Pont de Nemours and Co., Wilmington, Del., for these compounds.

(21) J. H. Boyer and H. Alul, *J. Am. Chem. Soc.*, **81**, 2136 (1950).

droxide solution. Filtration of the flocculent precipitate was very tedious.

In two cases the azostyrene in the product was found to be 1.7% and 1.2% of the I used.

Infrared spectra were obtained with a Perkin–Elmer "Infra-cord," Model 137. All solids were run in potassium bromide pellets. *p*-Vinylaniline was run neat between sodium chloride plates.

# Organic Sulfur Compounds. I. Synthesis of *sec*-Mercaptoalkylamine Hydrochlorides[1a,b]
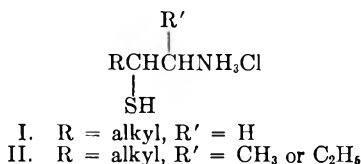
F. I. CARROLL, J. D. WHITE, AND MONROE E. WALL

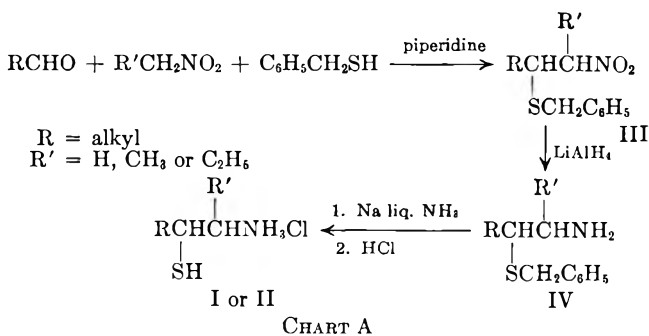*The Natural Products Laboratory, Research Triangle Institute, Durham, North Carolina*

Methods for the preparation of *sec*-mercaptoalkylamine hydrochlorides are presented. The scheme used for the preparation of these compounds involves the preparation of *sec*-benzylthionitroalkanes, followed by reduction of the nitro group with lithium aluminum hydride and reductive debenzylation with sodium in liquid ammonia to free the mercaptan. Several procedures for preparing the requisite *sec*-benzylthionitroalkanes involving isolation of nitroölefins followed by the addition of benzyl mercaptan or reaction of the latter with nitroölefins formed *in situ* are discussed.

The synthesis of mercaptoalkylamines is a subject of current interest because of the antiradiation activity of some of these compounds.[2,3] Although there are numerous reports of the synthesis of compounds in which the mercapto group is attached to a primary carbon atom, there is a paucity of data concerning the synthesis of mercaptoalkylamines bearing sulfur on secondary or tertiary carbon atoms. This paper describes the preparation of a group of new *sec*-mercaptoalkylamine hydrochlorides of type I or II shown below. In addition, improved procedures for preparing nitro-olefins and *sec*-benzylthionitroalkane precursors are described.

$$
\begin{array}{c}
R' \\
| \\
RCHCHNH_3Cl \\
| \\
SH
\end{array}
$$

I. R = alkyl, R′ = H
II. R = alkyl, R′ = CH₃ or C₂H₅

We initially planned to use the reaction scheme outlined in Chart A for the preparation of the *sec*-mercaptoalkylamine hydrochlorides.

$$
RCHO + R'CH_2NO_2 + C_6H_5CH_2SH \xrightarrow{\text{piperidine}} \begin{array}{c} R' \\ | \\ RCHCHNO_2 \\ | \\ SCH_2C_6H_5 \end{array}
$$

R = alkyl
R′ = H, CH₃ or C₂H₅

III $\xrightarrow{\text{LiAlH}_4}$ IV

$$
\begin{array}{c} R' \\ | \\ RCHCHNH_2 \\ | \\ SCH_2C_6H_5 \end{array} \quad \text{IV}
$$

$$
\begin{array}{c} R' \\ | \\ RCHCHNH_3Cl \\ | \\ SH \end{array} \xleftarrow[\text{2. HCl}]{\text{1. Na liq. NH}_3} \begin{array}{c} R' \\ | \\ RCHCHNH_2 \\ | \\ SCH_2C_6H_5 \end{array}
$$

I or II          IV

CHART A

Parham and Ramp[4] reported that nitromethane, propionaldehyde and benzyl mercaptan mixed in the absence of solvent and a catalytic amount of piperidine added, reacted exothermically to give 2-benzylthio-1-nitrobutane in nearly quantitative yield. These authors suggested that the 2-benzylthio-1-nitrobutane was apparently formed by the addition of benzyl mercaptan to 1-nitrobutene formed *in situ*. Our initial attempts to extend this method to longer chain aldehydes were unsatisfactory. The reaction products were impure and because of decomposition could not be distilled without undue losses. Therefore, we turned our attention to the route shown in Chart B.

$$
RCHO + R'CH_2NO_2 \xrightarrow{\overline{O}H} \begin{array}{c} R' \\ | \\ RCHCHNO_2 \\ | \\ OH \end{array} \quad V
$$
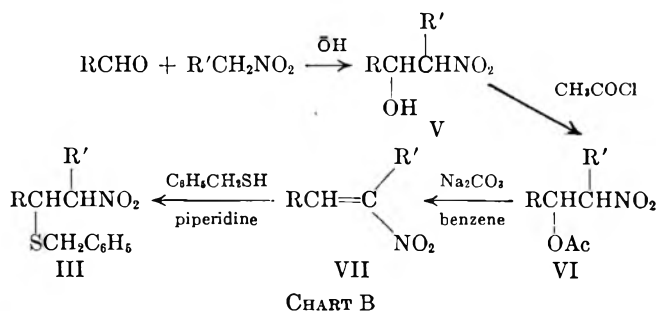
CHART B

Each of the four steps in Chart B is reported to occur in good yield. The major disadvantage was that several distillations were required. We overcame this difficulty, however, by preparing the desired nitroölefin from the appropriate aldehyde and nitroalkane without purification of either the nitro alcohol or the nitro acetate. The nitro alcohol was prepared by allowing the aldehyde and the nitroalkane to condense in the presence of aqueous alcoholic sodium hydroxide according to the method of Sprang and Degering.[5] The progress of the reaction was followed by the disappearance of the carbonyl band of the aldehyde and the appearance of a strong hydroxyl absorption at 3560–3600 cm.⁻¹. The nitro acetates could be obtained directly from the crude nitro alcohols. The simplest procedure was to add acetyl chloride directly to the

(1) (a) This investigation was supported by the Department of the Army and the U. S. Army Medical Research and Development Command, contract no. DA-49-193-MD-2164; (b) part of this material was presented at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(2) Proposed Anti-Radiation Drug Program, Part 2 and 3, Department of Radiobiology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center.

(3) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **26**, 3780 (1961).

(4) W. E. Parham and F. L. Ramp, *J. Am. Chem. Soc.*, **73**, 1293 (1951).

(5) C. A. Sprang and E. F. Degering, *ibid.*, **64**, 1063 (1942).

nitro alcohol without solvent. The completion of the reaction was determined by the disappearance of the hydroxyl absorption and the appearance of a strong carbonyl peak at 1725–1735 cm.$^{-1}$. The crude nitro acetate was converted to the desired nitroölefin using the method of Hass, Susie, and Heider[6] which uses a suspension of anhydrous sodium carbonate as the base in refluxing dry benzene. The progress of the reaction was readily determined by the disappearance of the acetate carbonyl absorption and the appearance of a strong carbon–carbon double bond peak at 1630–1640 cm.$^{-1}$. The relatively low boiling nitroölefins could be easily separated in high yield and good purity by one distillation (Table I). The desired sec-benzylthionitroalkanes (III) were prepared by the addition of benzyl mercaptan in benzene, catalyzed by piperidine, to the nitroölefin. Using this procedure the sec-benzylthionitroalkanes were prepared in high yield and excellent purity (Table II). The infrared spectra of these compounds show typical peaks at 3030, 3065, and 3085 cm.$^{-1}$ due to aromatic C—H stretching and strong bands at 1550 and 1360 cm.$^{-1}$ attributable to the nitro group. The crude sec-benzylthionitroalkane (III) (R′ = H; R = C$_3$H$_7$, C$_4$H$_9$, and C$_5$H$_{11}$) could be purified by distillation under reduced pressure.

However, III (R′ = H; R = C$_6$H$_{13}$, C$_7$H$_{15}$, and ⟨ ⟩—) and III (R = C$_3$H$_7$; R′ = CH$_3$, and C$_2$H$_5$) obtained in 93–100% yield decomposed on attempted distillation. These compounds as crude undistilled products were sufficiently pure to be reduced to the corresponding sec-benzylthioalkylamines which could be easily purified by distillation or conversion to the hydrochlorides followed by recrystallization.

<div align="center">

Table I

Nitroölefins

RCH=C(R′)NO$_2$

</div>

| R | R′ | % Yield from RCHO | B.p., °C. (mm.) | B.p., °C. (mm.) reported |
|---|---|---|---|---|
| n-C$_3$H$_7$ | H | 67.9 | 27–29 (0.1–0.15) | 69–70 (12)$^a$ |
| n-C$_4$H$_9$ | H | 42.4 | 44–47 (0.25–0.3) | 54–55 (1.5)$^b$ |
| n-C$_5$H$_{11}$ | H | 65.3 | 96–99 (0.08) | 57 (1)$^c$ |
| n-C$_6$H$_{13}$ | H | 49.2 | 73–74 (0.2) | 112 (9)$^a$ |
| n-C$_7$H$_{15}$$^d$ | H | 60.9 | 91–95 (0.2–0.3) | |
| ⟨ ⟩—$^e$ | H | 61.1 | 99–100 (0.1) | |
| n-C$_3$H$_7$ | CH$_3$ | 55.2 | 42–45 (0.05) | 53 (1)$^c$ |
| n-C$_3$H$_7$ | C$_2$H$_5$ | 38.9 | 61–65 (0.7–0.8) | 84.4 (10)$^f$ |

$^a$ E. Schmidt and G. Rutz, Ber., 61, 2142 (1928). $^b$ Ref. 12. $^c$ D. Nightingale and J. R. Janes, J. Am. Chem. Soc., 66, 352 (1944). $^d$ Anal. Calcd. for C$_9$H$_{17}$NO$_2$: C, 63.12; H, 10.01. Found: C, 63.07; H, 10.05. $n^{25}$D 1.4620; $d^{25}$ 0.9424. $^e$ Anal. Calcd. for C$_8$H$_{11}$NO$_2$: C, 62.73; H, 7.24. Found: C, 62.92; H, 7.25. $n^{25}$D 1.5195, $d^{25}$ 1.0721. $^f$ Ref. 6.

During the course of our investigation we found that the requisite benzylthionitroalkanes could be prepared by a route which eliminates the necessity for isolating the nitroölefin. We found that 2-benzylthio-1-nitrohexane and 3-benzylthio-2-nitroheptane could be obtained in good yield by refluxing the corresponding nitroacetate with benzyl mercaptan in a suspension of anhydrous sodium carbonate in benzene. See Chart C.

(6) H. B. Hass, A. G. Susie, and R. L. Heider, J. Org. Chem., 15, 8 (1950).

$$\underset{\overset{|}{OAc}}{\overset{\overset{R}{|}}{CH_3(CH_2)_3CHCHNO_2}} + C_6H_5CH_2SH \xrightarrow[\text{benzene, reflux}]{Na_2CO_3}$$

$$\underset{\overset{|}{SCH_2C_6H_5}}{\overset{\overset{R}{|}}{CH_3(CH_2)_3CHCHNO_2}}$$
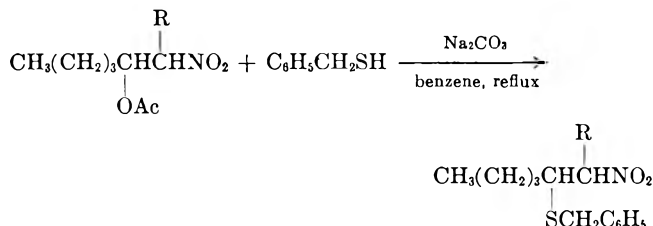
<div align="center">Chart C</div>

The 2-benzylthio-1-nitrohexane was distilled to afford an 82.6% yield of pure product. No attempt was made to distill the 3-benzylthio-2-nitroheptane. It was reduced directly to 3-benzylthio-2-heptylamine which was obtained in a 69% over-all yield from the starting nitroacetate.

Finally we turned our attention to a reinvestigation of the Parham and Ramp procedure. We found, by the simple modification of carrying out the reaction in benzene,[7] that the crude benzylthio-1-nitroalkane thus formed was now sufficiently pure to be directly reduced with lithium aluminum hydride to the corresponding crude amine. The latter could be then purified by distillation. In this manner, 2-benzylthio-1-hexylamine could be prepared in a 44% over-all yield from valeraldehyde. The compound was identical to the product obtained by lithium aluminum hydride reduction of the benzylthionitrohexane obtained by direct addition of benzyl mercaptan to pure 1-nitrohexene.

Although the Parham and Ramp method provides the simplest sequence for obtaining the 2-benzylthio-1-alkylamines, it cannot be used for the preparation of pure 2-benzylthio-1-nitroalkanes. If the latter are required, it is necessary to prepare them via the nitroölefin as outlined in Chart B or via the nitroacetate as outlined in Chart C.

The requisite sec-benzylthioalkylamines were best prepared by lithium aluminum hydride reduction of the corresponding nitro derivatives, using sodium potassium tartrate to decompose the alumino complex. One distillation afforded analytically pure amines in 58–84% yield. See Table III.

The sec-benzylthioalkylamines were converted to their hydrochlorides which were debenzylated with sodium in liquid ammonia to afford the desired sec-mercaptoalkylamine. The procedure used for the debenzylation was modified somewhat from that reported by Baddiley and Thain[8] (see Experimental section). The sec-mercaptoalkylamine hydrochlorides, which were obtained in 22–88% yield, showed –SH absorption at 2495–2550 cm.$^{-1}$ in the infrared and analyzed 98–100% pure by a N-ethylmaleimide sulfhydryl analysis.[9]

The sec-mercaptoalkylamines recorded in Table IV have been tested as possible anti-radiation agents by the Department of Radiobiology, Walter Reed Institute of Research, Walter Reed Army Medical Center, Washington, D. C. The compounds of general structure II were tested as a mixture of racemates. None of the compounds showed any protection to mice against ionizing radiation.

(7) The use of a Stark–Bidwell tube to collect the water formed provides a convenient method for following the course of the reaction.

(8) J. Baddiley and E. M. Thain, J. Chem. Soc., 800 (1952).

(9) N. M. Alexander, Anal. Chem., 30, 1 292 (1958).

TABLE II

2-BENZYLTHIO-1-NITROALKANES

RCHCH(R')NO₂
|
SCH₂C₆H₅

| R | R' | % Yield | $n^{25}$D | $d^{25}$ | B.p., °C. (mm.) | Molecular formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|
| n-C₃H₇ | H | 80.1 | 1.5404 | 1.0964 | 137 (0.1) | C₁₂H₁₇NO₂S | 60.22 | 60.40 | 7.16 | 7.15 |
| n-C₄H₉ | H | 81.3 | 1.5329 | 1.084 | 131–132 (0.15) | C₁₃H₁₉NO₂S | 61.62 | 61.81 | 7.56 | 7.55 |
| n-C₅H₁₁ | H | 91.9 | 1.5304 | 1.0619 | 135 (0.1) | C₁₄H₂₁NO₂S | 62.88 | 63.08 | 7.92 | 7.74 |

TABLE III

sec-BENZYLTHIOALKYLAMINES

RCHCH(R')NH₂
|
SCH₂C₆H₅

| R | R' | % Yield | $n^{25}$D | $d^{25}$ | B.p., °C. (mm.) | Molecular formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|
| n-C₃H₇ | H | 84.6 | 1.5468 | 1.0106 | 113 (0.05) | C₁₂H₁₉NS | 68.84 | 68.93 | 9.15 | 8.99 |
| n-C₄H₉ | II | 78.3 | 1.5404 | 0.9987 | 100 (0.1) | C₁₃H₂₁NS | 69.89 | 69.56 | 9.48 | 9.22 |
| n-C₅H₁₁ | H | 65 | 1.5350 | 0.9826 | 132 (0.1) | C₁₄H₂₃NS | 70.83 | 70.81 | 9.76 | 9.63 |
| n-C₆H₁₃ | H | 65ᵃ | 1.5303 | 0.9761 | 139 (0.06) | C₁₅H₂₅NS | 71.65 | 71.60 | 10.02 | 9.93 |
| n-C₇H₁₅ | H | 58.5ᵃ | 1.5265 | 0.9637 | 132 (0.09) | C₁₆H₂₇NS | 72.39 | 72.51 | 10.25 | 10.15 |
| ⬡– | H | 62.5ᵃ,ᵇ | | | 151–153ᶜ | C₁₆H₂₂NSClᵈ | 63.46 | 63.39 | 7.81 | 7.86 |
| n-C₃H₇ | CH₃ | 74ᵃ | 1.5381 | 0.9917 | 97–102 (0.05) | C₁₃H₂₁NS | 69.90 | 69.86 | 9.47 | 9.46 |
| n-C₃H₇ | C₂H₅ | 64.3ᵃ | 1.5338 | 0.9826 | 110–114 (0.05) | C₁₄H₂₃NS | 70.83 | 70.71 | 9.76 | 9.44 |

ᵃ Yields calculated from the crude 2-benzylthio-1-nitroalkanes. ᵇ Obtained as the hydrochlorides. ᶜ Melting point of the hydrochloride. ᵈ Analysis of the hydrochloride.

TABLE IV

sec-MERCAPTOALKYLAMINE HYDROCHLORIDES

RCHCH(R')NH₃Cl
|
SH

| R | R' | % Yield | M.p., °C. | % pure by SH analysis | Molecular formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found | Nitrogen, % Calcd. | Found | Sulfur, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n-C₃H₇ | H | 88.1 | a | 100 | C₅H₁₄NSCl | 38.57 | 38.92 | 9.06 | 9.02 | 9.00 | 8.70 | 20.60 | 20.72 |
| n-C₄H₉ ᵃ,ᵇ | H | 40 | a | 99.8 | C₆H₁₆NSCl | 42.46 | 42.46 | 9.50 | 9.34 | 8.25 | 8.00 | 18.89 | 18.65 |
| n-C₅H₁₁ | H | 59.2 | a | 99 | C₇H₁₈NSCl | 45.75 | 45.78 | 9.87 | 9.82 | 7.62 | 7.47 | 17.45 | 17.46 |
| n-C₆H₁₃ | H | 75 | a | 99.4 | C₈H₂₀NSCl | 48.58 | 48.85 | 10.19 | 10.05 | 7.08 | 6.94 | 16.21 | 16.06 |
| n-C₇H₁₅ | H | 49.9 | a | 100 | C₉H₂₂NSCl | 51.03 | 51.44 | 10.47 | 10.51 | 6.62 | 6.74 | 15.14 | 14.69 |
| ⬡– | H | 22 | a | 100 | C₈H₁₆NSCl | 49.59 | 49.40 | 8.33 | 8.22 | 7.23 | 7.14 | 16.55 | 16.26 |
| n-C₃H₇ | CH₃ | 57.5 | 136–138 | 99.4 | C₆H₁₆NSCl | 42.46 | 42.31 | 9.50 | 9.29 | 8.25 | 8.05 | 18.89 | 18.73 |
| n-C₃H₇ | C₂H₅ | 66.6 | 124–127 | 100 | C₇H₁₈NSCl | 45.75 | 45.62 | 9.87 | 9.67 | 7.62 | 7.47 | 17.45 | 17.25 |
| n-C₄H₉ | CH₃ | 55 | 143–147 | 100 | C₇H₁₈NSCl | 45.75 | 45.51 | 9.87 | 9.71 | 7.62 | 7.88 | 17.45 | 17.18 |

ᵃ These compounds had indefinite melting points. ᵇ Debenzylation done on free amine.

## Experimental[10]

**Preparation of the Nitroölefins via the Nitro Alcohol and Nitro Acetate.**—One mole each of the aldehyde and nitroalkane in ethanol were treated at 10° with 1 mole of sodium hydroxide according to the method of Sprang and Degering.[5] On acidification, an almost quantitative yield of the crude nitro alcohol was obtained. The infrared spectrum shows hydroxyl absorption at 3560–3600 cm.⁻¹ and typical nitro peaks at 1360 and 1550 cm.⁻¹. The nitro alcohol was converted to the nitro acetate by adding an excess of acetyl chloride directly to the crude nitro alcohol under anhydrous conditions. The excess acetyl chloride was removed at 50° under reduced pressure. The infrared spectrum showed absence of hydroxyl absorption and a strong acetate carbonyl peak at 1725–1735 cm.⁻¹. The nitroölefins were obtained from the crude nitro acetates using the method of Hass, Susie, and Heider[6] by refluxing 0.5 mole of anhydrous sodium carbonate with the crude nitro acetates dissolved in 400 ml. of benzene previously dried over calcium hydride. The nitroölefins obtained are recorded in Table I. The infrared spectra show absence of acetate peaks and contain a strong C=C peak at 1630–1640 cm.⁻¹.

**Preparation of sec-Benzylthionitroalkanes.**—To a mixture of 0.4 mole of benzyl mercaptan and 3 ml. of piperidine in 100 ml.

of benzene was added dropwise 0.4 mole of the nitroölefin in 75 ml. of benzene. The reaction mixture usually was left at room temperature from 2–15 hr. but essentially the same yield was obtained if the reaction was worked up immediately after the addition. The solution was washed with dilute hydrochloric acid, water and dried over magnesium sulfate. Removal of the benzene afforded 90–100% of the crude product. The crude products could be purified readily by one distillation through a 4-in. Vigreux column under reduced pressure. The infrared spectrum shows typical peaks at 3030, 3065, and 3085 cm.⁻¹ due to aromatic C–H absorption and strong bands at 1365 and 1550 cm.⁻¹ attributable to the nitro group. See Table II for analysis and yields. The higher molecular weight products decomposed on attempted distillation. These products were reduced in crude form to the sec-benzylthioalkylamines which could be purified by distillation or conversion to the hydrochloride followed by recrystallization.

**Preparation of the sec-Benzylthioalkylamines.**—A solution of 0.3 mole of the 2-benzylthio-1-nitroalkanes in 200 ml. of anhydrous ether (dried over sodium) was added dropwise to an ice-cooled stirred solution–suspension of 34.1 g. (0.9 $M$) of lithium aluminum hydride in 1600 ml. of anhydrous ether. The reaction was very exothermic, and the addition usually required 1 hr. or longer. The reaction mixture was refluxed for 1 hr. after the addition was completed. The excess lithium aluminum hydride was decomposed with water and 2 l. of 20% sodium potassium tartrate

solution was added. The reaction mixture was stirred until all the solids dissolved. The ether layer was decanted, and the aqueous layer was extracted three times with 150-ml. portions of ether. The ether layers were combined and dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure afforded an almost quantitative yield of the crude amines. One distillation through a 4-in. Vigreux column under reduced pressure afforded pure amines showing only one peak on a vapor phase chromatogram.[11] The yields and analysis are recorded in Table III. The infrared spectra shows N–H absorption at 3380 cm.$^{-1}$. The hydrochlorides of these amines were prepared by bubbling dry hydrogen chloride gas into an ethereal solution of the amine. Removal of the ether under vacuum afforded the crude amine hydrochloride in 98–100% yield. The crude products were used for the preparation of the sec-mercaptoalkylamine hydrochlorides.

**Preparation of 3-Acetoxy-2-nitroheptane.**—Nitroethane (150.2 g., 2 moles) was allowed to condense with n-valeraldehyde (172.3 g., 2 moles) at 10° using 2 moles of sodium hydroxide in aqueous alcohol as the base.[5] From the work-up 265.9 g. (82.4%) of crude product was obtained. The crude 3-hydroxy-2-nitroheptane was converted to the acetate using the procedure reported by Tindall.[12] 3-Hydroxy-2-nitroheptane (161.2 g., 1 mole) and concentrated sulfuric acid (0.98 g., 0.01 mole) were placed in a flask and acetic anhydride (102 g., 1 mole) was added; the temperature was kept at about 60°. The acetic acid was removed on a rotary evaporator, and the remaining liquid was distilled under reduced pressure to afford 157.9 g. (77%) of a liquid, b.p. 85–90° at 0.5 mm., $n^{25}$D 1.4353.

*Anal.* Calcd. for $C_9H_{17}NO_3$: C, 53.18; H, 8.43. Found: C, 53.11; H, 8.31.

**Preparation of 3-Benzylthio-2-heptylamine.**—A stirred mixture of 3-acetoxy-2-nitroheptane (101.6 g., 0.5 mole), benzyl mercaptan (62.1 g., 0.5 mole), sodium carbonate (26.5 g., 0.25 mole), and 400 ml. of benzene (dried over calcium hydride) was refluxed for 46 hr. The sodium acetate was filtered from the benzene and dissolved in water. The aqueous solution was extracted with benzene and after drying over magnesium sulfate was combined with the benzene filtrate. Removal of the benzene afforded 133 g. of crude 3-benzylthio-2-nitroheptane.

The reduction of the crude 3-benzylthio-2-nitroheptane was conducted in the manner described for the general reduction of sec-benzylthionitroalkanes using lithium aluminum hydride. A 69% yield of a colorless liquid, b.p. 108–115° at 0.07–0.08 mm., was obtained, $n^{25}$D 1.5321.

*Anal.* Calcd. for $C_{14}H_{23}NS$: C, 70.83; H, 9.76. Found: C, 70.61; H, 9.50.

**Preparation of 2-Acetoxy-1-nitrohexane.**—To a solution of 36.5 g. (0.249 mole) of crude 1-nitro-2-hexanol (prepared by the method of Sprang and Degering[5] in a 98.5% yield) in 100 ml. of chloroform was added 22 g. (0.28 mole) of acetyl chloride. The reaction mixture was left at room temperature for 2 hr. and then refluxed for 30 min. The reaction mixture was diluted with 100 ml. of chloroform, washed with water, and dried over magnesium sulfate. Removal of the chloroform afforded 43.1 g. of crude nitroacetate. Distillation under reduced pressure afforded 34.36 g. (74.3%) of liquid, b.p. 84–85 at 0.1 mm. Reported[13] b.p. 105 at 3 mm., $n^{25}$D 1.4385; reported[13] $n^{25}$D 1.4337.

**Preparation of 2-Benzylthio-1-nitrohexane** *via* **2-Acetoxy-1-nitrohexane.**—A mixture of 2-acetoxy-1-nitrohexane (18.9 g., 0.1 mole), benzyl mercaptan (12.4 g., 0.1 mole), sodium carbon-

ate (5.3 g., 0.05 mole), and benzene (25 ml.) was refluxed for 3 hr. The reaction mixture was worked up as described for the preparation of 3-benzylthio-2-nitroheptane to afford 26.2 g. of crude product. Distillation under reduced pressure yielded 20.9 g. (82.6%) of product, b.p. 140° at 0.1 mm., $n^{25}$D 1.5335 as compared to $n^{25}$D 1.5329 when prepared by the addition of benzyl mercaptan to 1-nitrohexene (Table II). The infrared spectra of the two compounds were superimposable, and both had the same retention time on a vapor phase chromatogram.[11]

**Preparation of 2-Benzylthio-1-hexylamine** *via* **2-Benzylthio-1-nitrohexane Obtained from the Parham and Ramp Procedure.[4]**—A mixture of 17.2 g. (0.2 mole) of n-valeraldehyde, 12.2 g. (0.2 mole) of nitromethane, 24.8 g. (0.2 mole) of benzyl mercaptan, 4 ml. of piperidine, and 75 ml. of benzene was refluxed for 20 hr. using a water separator. The product was taken up in benzene, washed with dilute acid, washed with water, and dried over magnesium sulfate. Removal of the benzene afforded 53 g. of crude product. An attempt was made to distil a small sample of the liquid at reduced pressure; however, the liquid decomposed on heating and no product could be forced over by heating the bath to 221°.

The remainder of the product was reduced to 2-benzylthio-1-hexylamine using the general procedure described for the reduction of sec-benzylthionitroalkanes with lithium aluminum hydride. A 42% yield of liquid, b.p. 114–116° at 0.07–0.10 mm., was obtained, $n^{25}$D 1.5404. When 2-benzylthio-1-hexylamine was obtained *via* 1-nitrohexene (Table III) the $n^{25}$D was 1.5404. The infrared spectra of these two compounds were identical, and both had the same retention time on a vapor phase chromatogram.[11]

**Preparation of sec-Mercaptoalkylamine Hydrochlorides.**—The above compounds were prepared according to the method of Baddiley and Thain[8] using the following modified procedure. The sec-benzylthioalkylamine hydrochloride[14] (0.1 mole) was placed in a 1-l. three-necked flask equipped with a stirrer, gas inlet tube, and Dry Ice condenser and the complete system was protected against moisture with a soda lime drying tube. Ammonia (300 ml.) was introduced into the flask and in the case of high molecular weight sec-benzylthioalkylamine hydrochlorides, 100 ml. of dry ether was added. Sodium metal in small pieces was added to the solution until a permanent blue color remained for 45 min. The sodium (0.20–0.22 g.-atom) was added while nitrogen was blown over the solution. The excess sodium was decomposed by adding a little ammonium chloride and the ammonia allowed to evaporate under nitrogen to a small volume. Anhydrous ether (200 ml.) was added, and the remainder of the ammonia was boiled out of the solution by heating the solution on a hot water bath. The stirred ether suspension was cooled, and 100 ml. of ether saturated with dry hydrogen chloride gas was added to the mixture and the contents were stirred rapidly for 2 hr. The solids were filtered, washed well with dry ether, transferred to a 1-l. flask, extracted three times with 200-ml. portions of isopropyl alcohol, and the total filtrate was concentrated under nitrogen. Ether was added and the solution allowed to crystallize in the ice box. The crude solids obtained were purified by recrystallization from an isopropyl alcohol and ether mixture or by vacuum sublimation. The products obtained showed —SH absorption at 2495–2550 cm.$^{-1}$ in the infrared and analyzed 99–100% pure by a N-ethylmaleimide sulfhydryl assay.[9] See Table IV for yields and elemental analysis.

(11) Vapor phase chromatograms were obtained on an F and M Model 300 vapor fractometer using a 24-in., 0.25-in. aluminum column packed with 60/80-mesh acid-washed Chromosorb P containing 5% Carbowax 20 M.
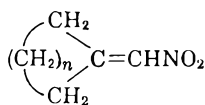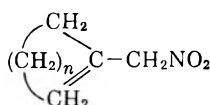
(12) J. B. Tindall, *Ind. Eng. Chem.*, **33**, 65 (1941).

(13) N. L. Drake and A. B. Ross, *J. Org. Chem.*, **23**, 717 (1958).

(14) In the case of 2-benzylthio-1-hexylamine the free amine was used in place of its hydrochloride. However, this led to a low yield, and the blue end point due to excess sodium was extremely difficult to detect.

# Organic Sulfur Compounds. II. Synthesis of *tert*-Mercaptoalkylamine Hydrochlorides[1a,b]

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A general method for the preparation of *tert*-mercaptoalkylamine hydrochlorides is presented. The method involves the preparation of a *tert*-benzylthionitroalkane by allowing a mixture of ketone, nitromethane, and benzyl mercaptan in benzene to react in the presence of piperidine followed by reduction of the nitro group with lithium aluminum hydride and reductive debenzylation with sodium in liquid ammonia. Other possible methods for the preparation of *tert*-benzylthionitroalkanes are discussed.

The previous article in this series[2] described the synthesis of a number of new *sec*-mercaptoalkylamine hydrochlorides. In this paper we will discuss the preparation of analogous *tert*-mercaptoalkylamine hydrochlorides both in the aliphatic and alicyclic series and some of the particular problems which occur in the synthesis of cyclic *exo*-nitroölefins and the corresponding cyclic *tert*-benzylthionitroalkanes. The general scheme used for the preparation of these *tert*-mercaptoalkylamine hydrochlorides is shown in Chart A.

$$\text{R—C(=O)—R' + C}_6\text{H}_5\text{CH}_2\text{SH} \xrightarrow[\text{benzene}]{\text{Piperidine}} \text{RR'CCH}_2\text{NO}_2 \text{ (SCH}_2\text{C}_6\text{H}_5\text{)}$$

I

(1) LiAlH$_4$ (2) HCl

RR'CCH$_2$NH$_3$Cl (SH) $\xleftarrow[\text{2. HCl}]{\text{1. Na, liq. NH}_3}$ RR'CCH$_2$NH$_3$Cl (SCH$_2$C$_6$H$_5$)

II

III. R = R' = CH$_3$—
IV. R = CH$_3$—, R' = C$_2$H$_5$
V. R,R' = (CH$_2$)$_n$; n = 3, 4, 5, and 6

CHART A

The crude *tert*-benzylthionitroalkanes (I) were reduced to the *tert*-benzylthioalkylamines (II) in good over-all yield. The debenzylation of II using the same procedure previously described[2] proceeded in high yield and afforded nice crystalline compounds of excellent purity.

The intermediates II [R, R' = (CH$_2$)$_4$] and [RR' = (CH$_2$)$_5$] were also prepared by the scheme outlined in Chart B.

$$\text{R—C(=O)—R'} \xrightarrow[\text{2. AcCl}]{\text{1. CH}_3\text{NO}_2\text{, CH}_3\text{ONa}} \text{RR'CCH}_2\text{NO}_2 \text{ (OAc)}$$

RR' = (CH$_2$)$_4$ or (CH$_2$)$_5$

1. Na$_2$CO$_3$, C$_6$H$_5$CH$_2$SH benzene
2. LiAlH$_4$

RR'CCH$_2$NH$_2$ (SCH$_2$C$_6$H$_5$)

CHART B

The products obtained by this procedure were identical to those obtained by the scheme outlined in Chart A.

In order to substantiate the structures of the *tert*-benzylthioalkylamines, methyl ethyl ketone and cyclohexanone were converted to II *via* the scheme shown in Chart C.

$$\text{RCR'(=O) + CH}_3\text{NO}_2 \xrightarrow{\text{CH}_3\text{ONa}} \text{RR'CCH}_2\text{NO}_2 \text{ (OH)} \xrightarrow[\text{2. Na}_2\text{CO}_3 \text{ benzene}]{\text{1. AcCl}} \text{RR'C=CHNO}_2$$

VI

R,R' = CH$_3$, C$_2$H$_5$ or (CH$_2$)$_5$

VII

1. C$_6$H$_5$CH$_2$SH piperidine
2. LiAlH$_4$

RR'CCH$_2$NH$_2$ (SCH$_2$C$_6$H$_5$)

II

CHART C

The *tert*-benzylthioalkylamines obtained by isolation of the nitroölefin followed by addition of benzyl mercaptan and reduction with lithium aluminum hydride were identical to the products obtained *via* the modified Parham and Ramp procedure, Chart A, or by the nitroacetate procedure, Chart B. 1-Aminomethylbenzylthiocyclohexane obtained *via* the modified Parham and Ramp procedure decomposed on attempted vacuum distillation and was isolated as the hydrochloride.

Several aspects of the reaction schemes given under Charts A, B, and C require further comment. In our previous paper[2] we have shown that the reaction of aldehydes with nitromethane to give nitro alcohols proceeds in good yield. In contrast, the reaction equilibrium in the case of the same reaction with simple aliphatic and alicyclic ketones lies on the side of the reactants. Thus, acetone gives about a 50% yield of the nitro alcohol, methyl ethyl ketone about 15% and diethyl ketone a negligible yield. Similarly, cyclohexanone gives a 47% yield of the nitro alcohol, whereas cyclopentanone and cycloheptanone gave very low yields. Hence, the procedure given under Chart C is of poor preparative significance. In addition, in the alicyclic series the *exo*-olefins VIII (n = 2 and 4) cannot be isolated. All elimination procedures tested have given the corresponding *endo*-olefins IX (n = 2 and 4.)[3,4]

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(2) F. I. Carroll, J. D. White, and Monroe E. Wall, Part I, *J. Org. Chem.*, **28**, 1236 (1963).

(3) H. B. Fraser and G. A. R. Kon, *J. Chem. Soc.*, 604 (1934).

(4) Z. Eckstein, A. Sacha, and T. Urbański, *Bull. Acad. Polon. Sci., Class III*, **5**, 213 (1957); *Chem. Abstr.*, **51**, 16318 (1957).

## TABLE I

### tert-BENZYLTHIOALKYLAMINES

$$RR'CCH_2NH_2$$
$$|$$
$$SCH_2C_6H_5$$

| RR' | % Yield[a] | $n^{25}D$ | $d^{25}$ | B.p. (mm.) or m.p., °C. | Molecular formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3$, $CH_3$ | 50[b] | | | 118–119[c] | $C_{11}H_{18}NSCl$[d] | 57.00 | 56.69 | 7.83 | 7.82 |
| $CH_3$, $C_2H_5$ | 76.5 | 1.5512 | 1.0148 | 110 (0.08) | $C_{12}H_{19}NS$ | 68.84 | 69.17 | 9.15 | 9.17 |
| $C_2H_5$, $C_2H_5$ | 46 | 1.5548 | 1.0158 | 109 (0.05) | $C_{13}H_{21}NS$ | 69.89 | 69.79 | 9.48 | 9.40 |
| $(CH_2)_3$ | 60.3 | 1.5699 | 1.0684 | 116–119 (0.07–0.05) | $C_{12}H_{17}NS$ | 69.51 | 69.49 | 8.27 | 8.14 |
| $(CH_2)_4$ | 52.7 | 1.5692 | 1.0698 | 126–130 (0.05–0.1) | $C_{13}H_{19}NS$ | 70.53 | 70.53 | 8.65 | 8.38 |
| $(CH_2)_5$ | 52.2[b] | | | 182–183 | $C_{14}H_{22}NSCl$[d] | 61.85 | 61.77 | 8.16 | 8.00 |
| $(CH_2)_6$ | 42.2[b] | | | 171–173 | $C_{15}H_{24}NSCl$[d] | 63.02 | 62.90 | 8.46 | 8.47 |

[a] Over-all yield from the ketone. [b] Isolated as the hydrochloride. [c] H. M. Crooks, Jr., "Penicillamine, Its Analogs and Homologs in the Chemistry of Penicillin," H. T. Clark, J. R. Johnson, and Sir R. Robinson, Princeton University Press, 1949, p. 649, reported m.p. 116–117°. [d] Analysis on amine hydrochloride.



VIII. $n = 2, 3$ and $4$    IX. $n = 2, 3$ and $4$

It has been reported[5] that acetic acid could be eliminated from 1-nitromethylcyclohexanol acetate with sodium carbonate to give the exo-olefin VIII ($n = 3$). When this experiment was performed in our laboratory, the exo-olefin VIII ($n = 3$) was formed. However, the main product obtained was the endo-olefin IX ($n = 3$). The condensation of nitromethane with cyclobutanone has not been reported.

The modified Parham–Ramp procedure adopted for the preparation of tert-benzylthioalkylamines[2] gives excellent yields, ranging from 42–76.5% (Table I). Several mechanisms can be formulated to account for the formation of the tert-benzylthioalkylnitroalkanes obtained via the Parham and Ramp[6] procedure. Our data, however, are most consistent with the mechanism originally proposed by the above authors who suggested that the reaction proceeds via the addition of benzyl mercaptan to a nitroolefin formed as an intermediate in the reaction.[7] Although as we have indicated, the equilibrium for the formation of nitro alcohols is unfavorable, the reaction can be driven forward because of the elimination of water giving the nitroolefin which is irreversibly trapped by immediate reaction with benzyl mercaptan. This is clearly shown in the case of methyl ethyl ketone which on base-catalyzed reaction with nitromethane affords a 15% yield of nitro alcohol but a 76% yield of benzylthioalkylamine when treated by the modified Parham–Ramp procedure. Similarly, diethyl ketone gives only a negligible yield of nitro alcohol but affords a 46% yield of benzylthioalkylamine via the modified Parham–Ramp procedure.

In the case of the alicyclic series as exemplified by cyclohexanone the results have particular mechanistic

significance. As shown in Chart D, 1-nitromethylbenzylthiocyclohexane (XII) can be prepared in three ways. Since XII decomposes on distillation, it is converted to XIII which can be purified easily. The most direct route to XII is via the Parham and Ramp reaction. The data indicates that this reaction involves formation of an intermediate nitroolefin, which in this case is the less stable exo-olefin VIII ($n = 3$). Olefin
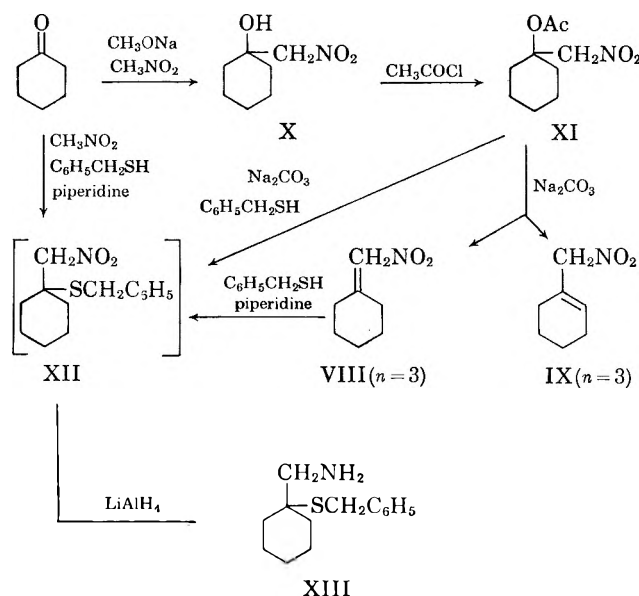


CHART D

VIII ($n = 3$) is readily converted to the endo-olefin IX ($n = 3$). However, IX ($n = 3$) does not react with benzyl mercaptan, whereas VIII ($n = 3$) in the presence of piperidine reacts rapidly under mild conditions to give XII. Treatment of the nitro acetate XI under the same conditions which yields the olefin mixture VIII ($n = 3$) and IX ($n = 3$) but in the presence of added benzyl mercaptan affords, after lithium aluminum hydride reduction, a high yield of XIII. This experiment indicates that the reactive exo-olefin VIII ($n = 3$) is indeed formed and is trapped by added benzyl mercaptan before it can isomerize to the endo form IX ($n = 3$). The data presented in conjunction with the previous results obtained by Parham and Ramp[7] indicate that the reaction of cyclohexanone with nitromethane and benzyl mercaptan in the presence of a base such as piperidine is probably a special case of the

(5) Z. Eckstein, T. Urbański, and H. Wojnowska, Roczniki Chem., 31, 1177 (1957); Chem. Abstr., 52, 9971 (1958).

(6) W. E. Parham and F. L. Ramp, J. Am. Chem. Soc., 73, 1293 (1951).

(7) When Parham and Ramp[6] allowed 2-nitropropane to react with formaldehyde and butyl mercaptan in the presence of piperidine, the only product isolated was 2-nitro-2-methylpropanol. The latter compound lacks an alpha hydrogen adjacent to the nitro group and hence cannot form a nitroolefin. Parham and Ramp suggested that the failure to isolate a β-nitro sulfide in this case indicated that their general reaction proceeds via a nitroolefin intermediate.

$$(CH_3)_2CHNO_2 + CH_2O + C_4H_9SH \xrightarrow{\text{piperidine}} (CH_3)_2CCH_2OH$$
$$\underset{NO_2}{|}$$

TABLE II

*tert*-MERCAPTOALKYLAMINE HYDROCHLORIDES

RR'CCH₂NH₃Cl

| | | | | | |
|---|---|---|---|---|---|

$$RR'CCH_2NH_3Cl$$
$$|$$
$$SH$$

| RR' | % Yield | M.p.,[a] °C. | % Pure by SH analysis | Molecular formula | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found | Nitrogen, % Calcd. | Found | Sulfur, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CH₃, CH₃ | 97 | 220–222[b] | 100 | C₄H₁₂NSCl | 33.91 | 33.92 | 8.54 | 8.49 | 9.89 | 9.76 | 22.64 | 22.38 |
| CH₃, C₂H₅ | 60.2 | 208–209 | 99.2 | C₅H₁₄NSCl | 38.57 | 38.65 | 9.06 | 8.96 | 9.00 | 8.90 | 20.60 | 20.68 |
| (CH₂)₃ | 92 | 227.5–228.5 | 100 | C₅H₁₂NSCl | 39.07 | 39.05 | 7.87 | 7.74 | 9.12 | 8.95 | 20.87 | 20.95 |
| (CH₂)₄ | 96.4 | 224.5–225.5 | 100 | C₆H₁₄NSCl | 42.97 | 43.19 | 8.41 | 8.22 | 8.35 | 8.10 | 19.12 | 19.15 |
| (CH₂)₅ | 55 | 194–196 | 100 | C₇H₁₆NSCl | 46.26 | 46.23 | 8.88 | 8.77 | 7.71 | 7.59 | 17.65 | 17.68 |
| (CH₂)₆ | 62 | 192–195 | 100 | C₈H₁₈NSCl | 49.08 | 49.03 | 9.27 | 9.39 | 7.17 | 7.03 | 16.38 | 16.35 |

[a] These m.p. values were done in a sealed capillary tube. The compounds sublimed without melting in an open capillary. [b] Reported m.p. 202–203°. See footnote c from Table I.

simpler reaction of 1-nitromethylcyclohexanol acetate (XI) described previously.

The purity of the *tert*-mercaptoalkylamine hydrochlorides was determined by a sulfhydryl analysis using the N-ethylmaleimide method reported by Alexander.[8] The success of this method depends on the reaction shown in Chart E. It was of some interest that the *tert*-mercaptoalkylamine hydrochlorides required thirty minutes to an hour to reach equilibrium, whereas equilibrium was obtained instantaneously in the case of all the *sec*-mercaptoalkylamine hydrochlorides.[2]



CHART E

Tests for the ability of the *tert*-mercaptoalkylamine hydrochlorides to protect mice against ionizing radiation have been carried out by the Department of Radiobiology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C. None of the compounds showed protection.

## Experimental[9]

**Preparation of *tert*-Benzylthioalkylamines *via* the *tert*-Benzylthionitroalkanes Obtained from the Modified Parham and Ramp Procedure.**—A mixture of ketone (0.2 mole), nitromethane (0.2 mole), benzylmercaptan (0.2 mole), piperidine (4 ml.), and 75 ml. of benzene (dried over calcium hydride) was refluxed under a water separator until water ceased coming off (12–15 hr.).[10] The reaction mixture was taken up in benzene, washed with dilute acid, washed with water, and then dried over magnesium sulfate. Removal of the benzene afforded an 87 to 100% yield of the product. The infrared spectra of these compounds showed no carbonyl peak and contained strong aromatic and nitro peaks.

The crude *tert*-benzylthionitroalkanes were reduced with lithium aluminum hydride using the method reported by Carroll, White, and Wall.[2] The amines (II) [R = R' = CH₃; R = CH₃, R' = C₂H₅; and R, R' = (CH₂)₃ and (CH₂)₄] were purified by distillation. The amines (II) [R, R' = (CH₂)₅ and (CH₂)₆] decomposed on attempted distillation. These amines were converted to their hydrochlorides by adding a cold saturated ethereal solution of hydrogen chloride to a cold ethereal solution of the amine and purified by recrystallization from isopropyl alcohol. The amine or amine hydrochlorides were obtained in 42.2 to 76.5% over-all yield from ketone.

**Preparation of 1-Nitromethylcyclohexanol Acetate.**—Sodium methoxide (12.5 g.) was added to a mixture of cyclohexanone (590 g., 6 moles) and nitromethane (122 g., 2 moles). After stirring in the deep freeze for 48 hr. the reaction mixture was neutralized with dilute hydrochloric acid, extracted with ether, washed with water, and dried over magnesium sulfate. Removal of the ether and excess cyclohexanone followed by distillation under reduced pressure afforded 150 g. (47.2%) of liquid, b.p. 81–85° at 0.1–0.15 mm.; reported[11] 93–95° at 2 mm., $n^{20}$D 1.4900; reported[11] $n^{20}$D 1.4875.

The 1-nitromethylcyclohexanol was converted to the acetate with acetyl chloride in chloroform. Distillation under reduced pressure afforded a 98% yield of 1-nitromethylcyclohexanol acetate, b.p. 98–101° at 0.2–0.25 mm.; reported[12] b.p. 116° at 1 mm., $n^{25}$D 1.4687; reported[12] $n^{20}$D 1.4669.

**Preparation of 1-Aminomethylbenzylthiocyclohexane *via* 1-Nitromethylcyclohexanol Acetate.**—A mixture of nitromethylcyclohexanol acetate (20.1 g., 0.1 mole), benzyl mercaptan (12.4 g., 0.1 mole), sodium carbonate (5.3 g., 0.05 mole), and 25 ml. of benzene was refluxed for 27 hr. The sodium acetate was filtered from the benzene and dissolved in water. The aqueous solution was extracted with benzene and after drying was combined with the benzene filtrate. Removal of the benzene afforded 23.7 g., 89.5% (crude yield) of product. The infrared spectrum of this liquid showed almost no acetate absorption at 1735 cm.⁻¹, and contained strong nitro peaks at 1545 and 1370 cm.⁻¹.

The crude 1-nitromethylbenzylthiocyclohexane was reduced to 1-aminomethylbenzylthiocyclohexane with lithium aluminum hydride.[2] Distillation under reduced pressure afforded 15.77 g. (74.8%) of pure product, b.p. 133–137° at 0.05 mm., $n^{25}$D 1.5700, $d^{25}$ 1.0683.

*Anal.* Calcd. for C₁₄H₂₁NS: C, 71.43; H, 8.99. Found: C, 71.36; H, 8.95.

A small sample of the amine was converted to the hydrochloride by adding a cold saturated ethereal solution of hydrogen chloride to a cold solution of the amine in ether. Recrystallization of the solid obtained from isopropyl alcohol afforded white crystals. M. p. 182–183°. A m.m.p. with the 1-aminomethylbenzylthiocyclohexane hydrochloride obtained *via* the modified Parham and Ramp procedure (Table I) was not depressed. The infrared spectra of the two compounds were identical.

**Preparation of 1-Nitromethylcyclopentanol Acetate.**—1-Nitromethylcyclopentanol was prepared using the same conditions as described for the preparation of 1-nitromethylcyclohexanol. From 168 g. (2 moles) of cyclopentanol and 122 g. (2 moles) of nitromethane 31.8 g. (10.8%) of product was obtained, b.p. 112–113° at 11 mm.; reported[13] 120–121° at 14 mm.

1-Nitromethylcyclopentanol was converted to 1-nitromethylcyclopentanol acetate with acetyl chloride in chloroform. Distillation under reduced pressure afforded a yield (50.8%) of liquid, b.p. 85° at 0.15 mm.; reported[14] b.p. 121–123° at 13 mm., $n^{25}$D 1.4622.

**Preparation of 1-Aminomethylbenzylthiocyclopentane *via* 1-Nitromethylcyclopentanol Acetate.**—1-Nitromethylbenzylthio-

(8) N. M. Alexander, *Anal. Chem.*, **30**, 1292 (1958).

(9) Boiling points and melting points are uncorrected. Elemental analyses are by Micro-Tech Laboratories, Skokie, Ill.

(10) In the case of diethyl ketone seven days reflux was required.

(11) T. F. Wood and R. J. Cadorin, *J. Am. Chem. Soc.*, **73**, 5504 (1951).

(12) W. Sobótka, Z. Eckstein, and T. Urbański, *Bull. Acad. Polon. Sci., Class III*, **5**, 653 (1957); *Chem. Abstr.*, **52**, 876 (1958).

(13) L. M. Kozlov, E. F. Fink, and G. B. Liorber, *Trudy Kazansk. Khim. Tekhnol. Inst.*, **23**, 148 (1957); *Chem. Abstr.*, **52**, 8933 (1958).

(14) L. M. Kozlov and B. G. Liorber, *Trudy Kazansk. Khim. Tekhnol. Inst.*, **26**, 48 (1959); *Chem. Abstr.*, **54**, 2448 (1960).

cyclopentane was prepared in the same manner as described for 1-nitromethylbenzylthiocyclohexane using 18.7 g. (0.1 mole) of 1-nitromethylcyclopentanol acetate, 12.4 g. (0.1 mole) of benzyl mercaptan, 5.3 g. (0.05 mole) of sodium carbonate, and 25 ml. of benzene. Removal of the benzene afforded 22.6 g. (89.6% crude yield) of sulfide. The infrared spectrum showed absence of acetate peaks and the expected aromatic and nitro peaks were present.

The crude 1-nitromethylbenzylthiocyclopentane was reduced with lithium aluminum[2] hydride to the desired 1-aminomethyl-benzylthiocyclopentane. Distillation of the crude liquid obtained afforded (63.2%) of pure amine, b.p. 129° at 0.1 mm., $n^{25}$D 1.5692, $d^{25}$ 1.0698. $n^{25}$D 1.5692 when obtained via the modified Parham and Ramp procedure (Table I).

**Preparation of Nitromethylene Cyclohexane.**—1-Nitromethyl-cyclohexanol, 142 g. (0.896 mole), was acetylated with excess acetyl chloride. After the addition the excess acetyl chloride was removed under reduced pressure. The crude nitro acetate which showed no hydroxyl absorption was refluxed with a suspension of anhydrous sodium carbonate, 47.5 g. (0.448 mole) in 400 ml. of benzene (dried over calcium hydride). The sodium acetate was filtered from the benzene. After drying over magnesium sulfate these extracts were added to the benzene filtrate and the benzene was removed under reduced pressure. The remaining liquid was distilled under reduced pressure through a 4-in. Vigreux column. The early fraction, 59 g., b.p. 53–58° at 0.07 mm., was 1-nitro-methylcyclohexene; reported[15] b.p. 98–102° at 12 mm. The later fraction, 25.6 g., b.p. 65–73° at 0.1 mm., was a mixture of 1-nitromethylcyclohexene and nitromethylenecyclohexene. Redistillation of the latter fraction through a 22-in. spinning band column afforded 15 g. of liquid that was mainly nitromethylene-cyclohexene, b.p. 105–106° at 12 mm.; reported[16] b.p. 108–110° at 12 mm., $n^{25}$D 1.5065; reported[15] $n^{25}$D 1.5079.

**Preparation of 1-Aminomethylbenzylthiocyclohexane via Nitro-methylenecyclohexane.**—To a solution of 10.1 g. (0.0815 mole) of benzyl mercaptan and 0.5 ml. of piperidine in 5 ml. of benzene was added 11.5 g. (0.0815 mole) of nitromethylenecyclohexane in 5 ml. of benzene. After standing at room temperature for 3 hr. the reaction mixture was diluted with benzene, washed with dilute hydrochloric acid, washed with water, and dried over magnesium sulfate. Removal of the benzene afforded 16.4 g. (76%) of crude product.

The 1-nitromethylbenzylthiocyclohexane, 16.4 g. (0.062 mole) was reduced with lithium aluminum hydride (7.05 g., 0.186 mole).[2] Distillation of the crude product afforded 3.28 g. (22.6%) of a colorless product, b.p. 133° at 0.08 mm., $n^{25}$D 1.5685. When 1-aminomethylbenzylthiocyclohexane was obtained via 1-nitro-methylcyclohexanol acetate the b.p. was 129° at 0.1 mm., $n^{25}$D 1.5692. The infrared spectra of the two compounds were identical.

A small portion of the 1-aminomethylbenzylthiocyclohexane was dissolved in cold ether and treated with a saturated ethereal solution of hydrogen chloride. The solid obtained was recrystallized from isopropyl alcohol to afford crystals, m.p. 182–183°. A mixture melting point with 1-aminomethyl-1-benzylthiocyclo-hexane hydrochloride obtained via the modified Parham and Ramp

procedure (Table I) was not depressed. The infrared spectra of the two compounds were identical.

**Preparation of 1-Nitro-2-methyl-2-butanol.**—A mixture of 2-butanone (2000 ml.), nitromethane (400 ml.) and sodium methoxide (60 g.) was allowed to stir at −20° for 4 days. The reaction mixture was neutralized to a Congo Red end point with 7% hydrochloric acid. The organic phase was decanted and the aqueous solution was extracted with ether. The ether extracts were mixed with the decanted organic layer and was washed with water. The ether solution was dried over magnesium sulfate and concentrated under vacuum. The remaining liquid was distilled under reduced pressure through a 4-in. Vigreux column. A 155.8-g. (15.8%) sample was collected; b.p. 112–115° at 23 mm.; reported[16] b.p. 96–97° at 18 mm. The infrared spectrum shows a strong hydroxyl peak at 3570 cm.$^{-1}$ and two strong nitro peaks at 1540 and 1385 cm.$^{-1}$.

**Preparation of 1-Nitro-2-methylbutene.**—In a 3-l. three-necked flask equipped with stirrer and dropping funnel and protected from moisture by a Drierite drying tube was placed (133.2 g., 1 mole) of 1-nitro-2-methyl-2-butanol. Acetyl chloride (85 g., 1.08 moles) was added dropwise at room temperature to the vigorously stirred nitro alcohol. The excess acetyl chloride was removed under reduced pressure. The infrared spectrum showed no –OH absorption and had a strong acetate peak at 1730 cm.$^{-1}$. Benzene (400 ml.) and anhydrous sodium carbonate (53 g., 0.5 moles) were added to the crude nitro acetate and the contents were refluxed for 24 hr. Work-up of the product as described by Hass, Susie, and Heider[17] afforded 105.6 g. of crude product. Distillation under reduced pressure through a 4-in. Vigreux column afforded 83.4 g. (72.5%) of 1-nitro-2-methylbutene, b.p. 41–43° at 0.08 mm.; reported[16] b.p. 62° at 11 mm. The infrared spectrum showed a strong C=C peak at 1635 cm.$^{-1}$ and the typical nitro peaks at 1510 and 1350 cm.$^{-1}$.

**Preparation of 2-Benzylthio-2-methyl-1-butylamine via 1-Nitro-2-methylbutene.**—This reaction was conducted in the same manner as described for the preparation of 1-aminomethylben-zylthiocyclohexane. The crude 2-benzylthio-2-methyl-1-butyl-amine was distilled under reduced pressure to afford a 76.5% yield of pure product from starting nitroölefin; b.p. 110° at 0.05 mm., $n^{25}$D 1.5530. $n^{25}$D was 1.5512 when prepared via the modified Parham and Ramp procedure. The infrared spectra of the two compounds were identical.

**Preparation of tert-Mercaptoalkylamine Hydrochlorides.**—The tert-mercaptoalkylamine hydrochlorides were prepared by the method of Carroll, White, and Wall.[2] The physical constants and elemental analysis are given in Table II.

The purity of the compounds were determined by a spectrophotometric assay for sulfhydryl groups using N-ethylmaleimide.[8] It was necessary to allow the tert-mercaptoalkylamine hydrochlorides to stand at room temperature from 30 min. to 1 hr. with the standard N-ethylmaleimide solution before equilibrium was obtained.

(15) G. D. Buckley and C. W. Scaife, British Patent, 595,282 (December 31, 1947); *Chem. Abstr.*, **42**, 3773 (1948).

(16) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947).

(17) H. B. Hass, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15** 8 (1950).

# The Chemistry of Fluorocarbon Sulfonic Acids.   I.   Preparation of Anhydrides and Sulfonyl Halides

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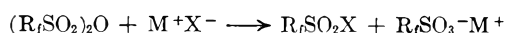
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The reaction of phosphorus pentachloride with cyclic fluorocarbon sulfonic acids leads first, with loss of hydrogen chloride, to a high melting solid, which decomposes upon strong heating to yield the sulfonic anhydride. The non-cyclic acids produce a mixture of anhydride and sulfonyl chloride. The higher-boiling sulfonic anhydrides are cleaved, above 200°, by metal salts such as sodium fluoride, zinc chloride, and aluminum chloride. Sulfonyl fluorides and chlorides may thus be prepared in good yield; however only half of the anhydride is available for conversion. A new and very powerful chlorodeoxygenation reagent, $PCl_5 \cdot 2ZnCl_2$, is introduced. It reacts directly with fluorocarbon sulfonate salts to produce the sulfonyl chlorides in high purity and in very high yields.

While the preparation and properties of perfluorinated sulfonic acids[1-6] and of their derivatives[2-7] have been reported, the reactions of these sulfonic acids have been set forth rather sketchily.[2-4,6] The object of the present paper is to describe several reactions of these acids having preparative significance.

The reaction of phosphorus pentachloride with the sulfonic acids is reported to yield the corresponding sulfonyl chlorides,[2,4,6] some anhydride also being noted.[2] Yields are variable for the *n*-perfluoroalkanesulfonyl chlorides, but are exceedingly small when the perfluoro cycloalkane sulfonic acids are so treated, the sulfonic anhydride instead being produced in high yield. The reaction proceeds in two definite stages, in the first of which hydrogen chloride is evolved and a fluffy white solid is formed. From the infusibility of this solid it may be suspected of being ionic, but the plausible structure $R_fSO_3^-PCl_4^+$ does not correspond to the stoichiometry since two sulfonate groups are involved. Perhaps the cation has the structure $R_fSO_2-OPCl_3^+$. When heated very strongly this solid is decomposed to yield the anhydride and phosphorus oxychloride.

There are certain synthetic advantages to be gained by use of the sulfonic anhydrides rather than the halides; these derive chiefly from their considerably higher boiling points which permit reactions to be effected at atmospheric pressure rather than in sealed vessels. The preparation of higher sulfonamides from strongly basic amines, such as piperidine, goes readily at room temperature; but weak amines, for example aniline and *p*-aminobenzoic acid, require much stronger heating. Such extreme conditions may result in decomposition of the nonfluorocarbon portion of the molecule; notably, in the case of *p*-aminobenzoic acid, reaction at 200° led to appreciable amounts of decarboxylation.

The cleavage of sulfonic anhydrides by metal salts, which may be represented by the following equation is of particular utility for the synthesis of fluorocarbon

$$(R_fSO_2)_2O + M^+X^- \longrightarrow R_fSO_2X + R_fSO_3^-M^+$$

sulfonyl fluorides; these compounds have hitherto only been obtained as endproducts of electrochemical fluorination.[1-5] For this purpose sodium fluoride was employed successfully; however, little or no yield of sulfonyl chloride resulted when potassium chloride was substituted in the reaction. Aluminum chloride and zinc chloride were effective, making it likely that the problem is one of effective contact. The perfluorocycloalkanesulfonyl chlorides were first isolated thus. A defect, for synthetic purposes, of all sulfonic anhydride reactions is that only one-half of the molecule can be used effectively, the rest being "downgraded" to sulfonate salt as shown in the preceding equation.

It has been noted that the fluorinated sulfonyl chlorides possess superior reactivity as compared to the sulfonyl fluorides which are produced by electrofluorination.[2,4] As yields of $CF_3SO_2F$ by the latter process are very high,[2-4] it is of particular interest to provide a convenient method for the production of sulfonyl chlorides, including $CF_3SO_2Cl$, from the sulfonyl fluorides by a route involving not too many steps. Previous syntheses[2,4-6] have required the free and substantially anhydrous fluorocarbon sulfonic acids which have been liberated from the sulfonate salts first formed in the alkaline hydrolysis of the sulfonyl fluorides. An obvious shortcut would be the direct utilization of the sulfonate salts, for example by reaction with thionyl chloride or phosphorus pentachloride after the fashion well known for ordinary organic sulfonic salts.[8] Unfortunately, the fluorocarbon sulfonates are unreactive up to the dissociation temperature of phosphorus pentachloride, *ca.* 162°. One might suspect that poor contact between reagents was responsible for the failure, but the addition of phosphorus oxychloride had no beneficial effect. A more vigorous chlorodeoxygenation reagent which is usable at higher temperatures is needed. The complex of phosphorus pentachloride with aluminum chloride is an ionic salt, $PCl_4^+ AlCl_4^-$.[9] Owing to its high melting point, 343°,[9] it failed to react with potassium perfluoro (4-ethylcyclohexane) sulfonate even upon strong heating. When the lower-melting sodium chloroaluminate was added to provide a liquid phase, some of the desired sulfonyl chloride was indeed produced.

(1) P. W. Trott and T. J. Brice, 126th National Meeting of the American Chemical Society, New York, N. Y., 1954; Abstracts, p. 42-M.

(2) T. J. Brice and P. W. Trott, U. S. Patent 2,732,398 (January 24, 1956).

(3) J. Burdon, L. Farazmand, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2574 (1957).

(4) T. Gramstad and R. N. Haszeldine, *ibid.*, 2640 (1957).

(5) T. Gramstad and R. N. Haszeldine, *ibid.*, 173 (1956).

(6) R. N. Haszeldine and J. M. Kidd, *ibid.*, 2901 (1955); 4228 (1954).

(7) H. A. Brown, 128th National Meeting of the American Chemical Society, Minneapolis, 1955; Abstracts, p. 29-M.

(8) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 821.

(9) Ya. A. Fialkov and Ya. B. Bur'yanov, *Dokl. Akad. Nauk, SSSR*, **92**, 585 (1953); *Chem. Abstr.*, **48**, 5708 (1954).

Table I

Physical Properties and Yields of Several Fluorocarbon Sulfonic Anhydrides and Sulfonyl Halides

| Compound | B.p., °C. | $n^{25}D$ | Infrared band position for $-SO_2X^a$, $\mu$ | Yield, % |
|---|---|---|---|---|
| $(4\text{-}CF_3\text{-}cyclo\text{-}C_6F_{10}SO_2)_2O$ | 267–269 | 1.3443 | 6.76, 6.83 13.50, 13.75$^b$ | 63$^c$ |
| $(4\text{-}C_2F_5\text{-}cyclo\text{-}C_6F_{10}SO_2)_2O$ | 207 (60 mm.) | 1.3489 | 6.75, 6.83 13.71 broad$^b$ | 95 |
| $4\text{-}CF_3\text{-}cyclo\text{-}C_6F_{10}SO_2F$ | 131–132 | 1.3172 | 6.78 | 80 |
| $CF_3SO_2Cl$ | 32 | 1.3315 | 6.98 | 94 |
| $n\text{-}C_8F_{17}SO_2Cl$ | 121 (100 mm.) 108 (60 mm.) | $(1.3278)^d$ m.p. 36.5–7.5° | 7.00 | 85$^e$ |
| $4\text{-}C_2F_5\text{-}cyclo\text{-}C_6F_{10}SO_2Cl$ | 118 (100 mm.) 105 (60 mm.) | 1.3518$^f$ | 7.01 | 53$^{c,g}$ |

$^a$ Only the structure-sensitive S=O asymmetric stretching frequency is listed.    $^b$ Very strong; presumably this is the S—O stretching frequency.    $^c$ Yield was no doubt higher, as there were substantial losses in handling.    $^d$ $d^{25}_4 = 1.861$; measured rapidly on the super cooled liquid.    $^e$ Also 7% of the anhydride.    $^f$ $d^{25}_4 = 1.914$.    $^g$ Also 17% of the anhydride.

A more suitable low-melting complex was sought, and it was found that phosphorus pentachloride dissolves readily in well-stirred molten zinc chloride until the composition reaches $PCl_5 \cdot 2ZnCl_2$. Further additions result merely in dissociation of the excess phosphorus pentachloride; heavy losses of this component may also occur if the mixture is not stirred during the preparation. The stoichiometric compound, $PCl_5 \cdot 2ZnCl_2$, has m.p. 190°, and begins to evolve phosphorus trichloride and chlorine at 250°; if excess zinc chloride is present this dissociation temperature is raised yet further. Curiously, this simple inorganic compound had not been reported in the literature at the time this work was carried out; since then it has been described,[10] but no reactions of it were presented.

When metal salts of the fluorocarbon sulfonic acids were treated with $PCl_5 \cdot 2ZnCl_2$, or with solutions of it in excess zinc chloride, the corresponding sulfonyl chlorides were produced in high yield, little or none of the anhydride being formed. This would appear to be the method of choice for such preparations, since the intermediate sulfonate salt can be stored conveniently until such time as the chloride is desired. The volatile by-product, phosphorus oxychloride, is removed by distillation, highly pure sulfonyl chlorides being thereby recovered.

A technical advantage is realized when the zinc salt of the sulfonic acid is used, since the resulting zinc chloride, unlike potassium chloride, does not cause the reaction mixture to become semisolid. For this purpose it is desirable to use calcium hydroxide for the original alkaline hydrolysis of the sulfonyl fluoride, since the resulting highly soluble calcium salt is readily freed of excess base by treatment with carbon dioxide followed by filtration, which also removes the calcium fluoride produced in the reaction. The readily soluble zinc sulfonate is then obtained by metathesis with zinc sulfate. Other metal salts may be prepared in like fashion.

Physical properties and yields for the sulfonyl halides and anhydrides prepared in this research are presented in Table I. Literature values, where available, were generally confirmed, though $n\text{-}C_8F_{17}SO_2Cl$ was shown to be a solid of m.p. 36.5–37.5°; Gramstad and Haszeldine, had reported it as a liquid but gave the wrong

refractive index. Presumably they did not have a sample of pure $n\text{-}C_8F_{17}SO_2Cl$.

## Experimental

**Materials.**—The fluorinated sulfonic acids and their salts, dried at 110°, were available in these laboratories, having been prepared by the described methods.[2–5] They were of good purity, this being further demonstrated by analytical data gathered on their derivatives, and reported below. The $PCl_5 \cdot 2ZnCl_2$ reagent, m.p. 190°, was prepared by adding phosphorus pentachloride to well-stirred molten zinc chloride in an open round bottomed flask, until a limiting gain in weight, corresponding exactly to the stoichiometric amount, was observed. The lower-melting solution of $PCl_5 \cdot 2ZnCl_2$ in 2 moles of zinc chloride was prepared similarly, except that only half the gain in weight was permitted; no significance should be attached to this exact composition as no freezing-point maximum is observed. For synthetic purposes the weight *gain* is the important quantity, as it corresponds to usable phosphorus pentachloride.

**Perfluoro(4-ethylcyclohexane)sulfonic Anhydride.**—In a 500-ml. distilling flask fitted with air condenser was placed 200 g. (0.433 mole) of perfluoro(4-ethylcyclohexane)sulfonic acid and 50.0 g. (0.240 mole) of phosphorus pentachloride. Upon warming of the well mixed reagents frothing occurred, copious quantities of hydrogen chloride being given off; the remaining material became a porous, snow white, and apparently infusible plaster-like solid. With strong heating to ca. 180° decomposition occurred, and on further heating for over 3 hr. to ca. 225° about 90% of the theoretical amount of phosphorus oxychloride distilled and was collected. Some of the excess phosphorus pentachloride remained in the flask, but otherwise the product was liquid. It was cooled to room temperature and washed repeatedly with water to remove phosphorus halides and unchanged sulfonic acid. The crude sulfonic anhydride, 192 g. (97.5%), had $n^{25}D = 1.3486$; after vacuum fractionation at 60 mm. there was recovered 187.1 g. (95%) the physical properties of which are listed in Table I.

*Anal.* Calcd. for $C_{16}F_{30}O_5S_2$: C, 21.20; F, 62.89. Found: C, 21.4; F, 63.4.

**Related Reactions.**—The reaction of 2.0 g. of perfluoro(4-ethylcyclohexane) sulfonic anhydride with 3 ml. of piperidine occurred at room temperature. The piperidide, 1.1 g. (95%), was recovered by dilution with water. It had m.p. 100–104° (recrystallized from ethanol).

*Anal.* Calcd. for $C_{13}H_{10}F_{15}NO_2S$: N, 2.65. Found: N, 2.69.

The anilide was prepared by heating the sulfonic anhydride with aniline to ca. 180°; the two immiscible phases suddenly coalesced and reacted. The product was dissolved in aqueous sodium carbonate, precipitated by acid, and recrystallized from concentrated aqueous acetic acid; it had m.p. 120–121°.

*Anal.* Calcd. for $C_{14}H_6F_{15}NO_2S$: C, 31.30; N, 2.61. Found: C, 31.4; N, 2.59. The 4-carboxyanilide was prepared similarly from 4-aminobenzoic acid, and had m.p. 234–235°.

*Anal.* Calcd. for $C_{15}H_6F_{15}NO_4S$: C, 30.99; N, 2.41. Found C, 31.1; N, 2.41. From this reaction there was also isolated some anilide, identified by melting point and mixture melting point with the authentic sample described previously.

The sulfonic anhydride did not react at elevated temperatures with potassium chloride. When the anhydride, 40 g. (0.044 mole), and aluminum chloride, 10 g. (0.075 mole), were strongly heated in a 100-ml. distilling flask, volatile products were collected which, upon fractional distillation, gave 12.8 g. (60%) of 4-$C_2F_5C_6F_{10}SO_2Cl$, b.p. 184°, $n^{25}D$ 1.3516. The same product was obtained in slightly better yield, ca. 75%, when an equivalent amount of freshly fused zinc chloride was substituted for the aluminum chloride. A limitation, despite the relatively good yields, is that half of the sulfonic anhydride molecule is unavailable in these reactions.

Perfluoro-(4-methylcyclohexane)sulfonic anhydride was made in exactly similar fashion, except that only half as much sulfonic acid had been employed. The excess phosphorus pentachloride was driven off with heating and clogged the apparatus; handling losses resulted and the yield (63%) was not truly representative. The sulfonic anhydride was isolated by fractional distillation. Despite the excess of phosphorus pentachloride used here, none of the corresponding sulfonyl chloride could be detected in any fraction by infrared spectroscopy.

*Anal.* Calcd. for $C_{14}F_{26}O_5S_2$: C, 20.86; F, 61.27. Found: C, 21.0; F, 61.0. The piperidide prepared as above, had m.p. 89-99° (isomer mixture).

*Anal.* Calcd. for $C_{12}H_{10}F_{13}NO_2S$: N, 2.92. Found: N, 2.80.

A similar reaction of perfluoro(n-octane)sulfonic anhydride[4] with piperidine yielded the piperidide, m.p. 77.5-78.5° (lit., m.p. 75-76.5°[2]; 77°[4]). The anhydride had been prepared from the acid by reaction with phosphorus pentachloride (mole ratio 2:1), about a 10% yield of sulfonyl chloride also having been produced.

**Perfluoro(4-methylcyclohexane)sulfonyl Fluoride.**—In a 25-ml. flask fitted with a 10-cm. fractionating column filled with $^1/_{16}$-in. "Helipak" (reg. t.m., Podbielniak Co.), was placed 20.8 g. (0.026 mole) of perfluoro(4-methylcyclohexane)sulfonic anhydride and 4.2 g. (0.10 mole) of sodium fluoride. The flask was slowly heated to 220° over a period of 10 hr. (more rapid heating should not be harmful), and refluxing volatile materials were taken off occasionally. The product, 8.5 g. (80%), boiled at 131-132° and had $n^{25}D$ 1.3172, in excellent agreement with reported data.[2]

*Anal.* Calcd. for $C_7F_{14}O_2S$: C, 20.30; F, 64.23. Found: C, 20.1; F, 64.2.

**Perfluoroöctanesulfonyl Chloride.**—Dried potassium perfluoroöctanesulfonate, 240 g. (0.45 mole) was heated with $PCl_5$·$2ZnCl_2$, 274 g. (0.57 mole of phosphorus pentachloride) and 156 g. of zinc chloride (1.14 moles) in a 1-l. distilling flask at 100 mm. until no more volatiles were collected. The distillate was fractionally distilled at reduced pressure and yielded, in two experiments, 201 g. (87%) and 192 g. (83%) of n-$C_8F_{17}SO_2Cl$, b.p. 121° (100 mm.), m.p. 36.5-7.5°.

*Anal.* Calcd. for $C_8ClF_{17}O_2S$: Cl, 6.84. Found: Cl, 6.95. Higher-boiling residues, ca. 6-8%, were shown by infrared analysis to be virtually pure perfluoroöctanesulfonic anhydride.

When instead $PCl_5$·$2ZnCl_2$ was used, the yield of sulfonyl chloride fell to 73-78%, much larger amounts of anhydride, ca. 18%, being recovered. The pasty, viscous condition of the reaction mixture may have been responsible for the lower yield, since less zinc chloride was present to establish a liquid phase; presumably some of the undissolved sulfonate salt reacted with sulfonyl chloride to give the anhydride.

**Perfluoro(4-ethylcyclohexane)sulfonyl Chloride.**—In a similar fashion 12.0 g. (0.024 mole) of dried potassium perfluoro(4-ethylcyclohexane)sulfonate reacted with 12.9 g. (0.027 mole) of $PCl_5$·$2ZnCl_2$. Upon fractional distillation there was obtained 5.1 g. (53%) of 4-$C_2F_5C_6F_{10}SO_2Cl$, b.p. 118° (100 mm.).

*Anal.* Calcd. for $C_8ClF_{15}O_2S$: C, 19.99; F, 59.30; Cl, 7.38. Found: C, 20.0; F, 59.4; Cl, 7.48. Difficulties were encountered in the mixing of the reagents which would have been alleviated by use of $PCl_5$·$4ZnCl_2$, and the 17% yield of anhydride might have been reduced appreciably also.

**Trifluoromethanesulfonyl Chloride.**—Dried zinc trifluoromethanesulfonate, 250 g. (0.69 mole), reacted with $PCl_5$·$2ZnCl_2$, 928 g. (1.93 moles), by heating to 260° for 8 hr. at atmospheric pressure in a stirred 2-l. distilling flask. Upon fractional distillation of the volatile products, 220.1 g. (94%) of highly pure $CF_3SO_2Cl$, b.p. 32°, $n^{25}D$ 1.3315, was obtained. When the potassium salt was used instead, the sulfonyl chloride was obtained in somewhat lower yield, 80-85%, but equal purity.

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# 3-Indoleacetic Acid

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The synthesis of indoleacetic acid in high yield by the reaction of indole with potassium glycolate at 250° is described. Selected methylated indoles also undergo this reaction as do salts of other α-hydroxy acids. The probable mechanism of the reaction is discussed.

3-Indoleacetic acid, its higher homologs, and their simple derivatives have been, over a period of the last twenty-five years, the subject of extensive investigation regarding their plant-growth regulating properties. A great many useful effects have been discovered, especially with the acetic and butyric acids, but the synthetic effort required to prepare these materials has precluded any practical agricultural applications. This communication describes a method by which indoleacetic acid may be readily prepared, namely by the direct reaction of indole with potassium glycolate.

Numerous examples of the reaction of simple primary and secondary alcohols with various indoles are known. For example, benzyl alcohol, hexahydrobenzyl alcohol, butanol, cyclohexanol, and others react with indole in the presence of a base and a nickel catalyst at 145-185° to give the corresponding 3-alkylated indoles.[1] At 210-220°, indole and alcohols react similarly in the presence of alkoxide and without a nickel catalyst, as do 2- and 7-methylindoles.[2,3] 2-Carboxyindole, however, reacts only with primary alcohols giving the 3-derivatives with concomitant loss of the carboxyl group.[2] Ethylene glycol and 2-ethoxyethanol gave 3-ethylindole under these conditions, while ethanolamine and N,N-diethylethanolamine gave no tryptamine derivatives or other characterizable products.[2] The reaction of other complex alcohols with indole apparently has not been reported.

Initial experiments in which indole and butyl glycolate were allowed to react together at 185° with a nickel catalyst, as described by Pratt and Botimer,[1] provided only traces of the desired ester. Further investigation led to heating indole with potassium

(1) E. F. Pratt and L. W. Botimer. *J. Am. Chem. Soc.*, **79**, 5248 (1957).

(2) R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, **1942**, 680.

(3) B. Oddo and C. Alberti, *Gazz. chim. ital.*, **63**, 236 (1933); *Chem. Abstr.*, **27**, 3933 (1933).
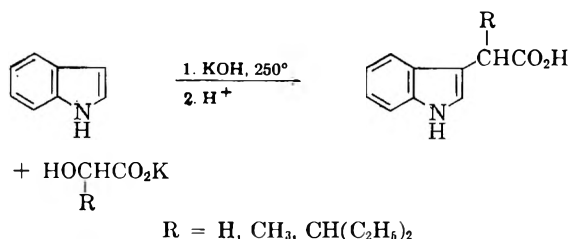
TABLE I

INDOLEACETIC ACIDS
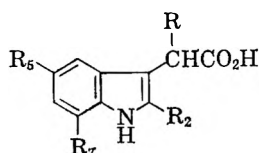


| R | R₂ | R₅ | R₇ | Yield, % | M.p., °C. | Conditions | | |
|---|---|---|---|---|---|---|---|---|
| H | H | H | H | 90 | 164–166 | 70% Glycolic acid[e] | 250° | 22 hr. |
| H | H | H | H | 54 | 164–166 | 18% Glycolic acid | 250° | 19 hr. |
| H | CH₃ | H | H | 87 | 197–199[a] | 16% Glycolic acid | 250° | 17 hr. |
| H | CH₃ | CH₃ | H | 43 | 169–171[b] | 22% Glycolic acid | 250° | 17 hr. |
| H | CH₃ | H | CH₃ | 29 | 164–166[c] | 7% Glycolic acid | 250° | 16 hr. |
| CH₃ | H | H | H | 80 | 105–110[d] | 85% Lactic acid | 250° | 21 hr. |
| CH(C₂H₅)₂ | H | H | H | 10 | 131–133 | See Experimental | | |

[a] Reported[6] 195–200°.    [b] Reported[7] 172–173°.    [c] Reported[8] 164–165°.    [d] Reported[7,9] 102°, 111–112°.    [e] Aqueous.

glycolate at 250° in the presence of potassium hydroxide which produced a 90% yield of indoleacetic acid, after dilution and acidification of the reaction mixture. Under similar conditions potassium lactate led to 2-(3′-indolyl)propionic acid in 80% yield, and potassium 2-hydroxy-3-ethylpentanoate the expected 2-(3′-indolyl)-3-ethylpentanoic acid in 10% yield. From the pentanoate there was also formed considerable amounts of 1-(3′-indolyl)-2-ethylbutane, the structure of which was established by synthesis from indole and 2-ethylbutanol. 2-Hydroxy-3-methylpropionic acid, as anticipated from mechanistic considerations (see below), failed to yield any of the corresponding indole derivative.



+ HOCHCO₂K
    |
    R

R = H, CH₃, CH(C₂H₅)₂

2-Methyl-, 2,5-dimethyl-, and 2,7-dimethylindole also reacted with potassium glycolate to yield the corresponding acetic acids (Table I). Only relatively small amounts of these starting indoles were available thus limiting the efficiency of agitation and resulting in low yields of the desired products. This difficulty was partially solved by the addition of sufficient water to the reaction vessel to allow proper mixing. However, control experiments with indole and potassium glycolate indicate that this procedure can, in itself, be detrimental to the yield of indole acid formed. 1,2-Dimethylindole, when treated with potassium glycolate, failed to give any of the 3-acetic acid; the 1,2-dimethylindole was recovered unchanged.

The formation of indoleacetic acids by the present method is only partially explained by either (A) the mechanism of Pratt and Botimer[1] for the 3-alkylation of indole or (B) that of Shoen and Becker[4] for the 9-alkylation of fluorene. The essential features of both mechanisms involve an initial oxidation of a small amount of the alcohol to an aldehyde or ketone which condenses at the nucleophilic site with loss of water to give an indolenine or fulvene intermediate. These intermediates are reduced by the alcohol or alkoxide

(4) K. L. Shoen and E. I. Becker, J. Am. Chem. Soc., 77, 6030 (1955).
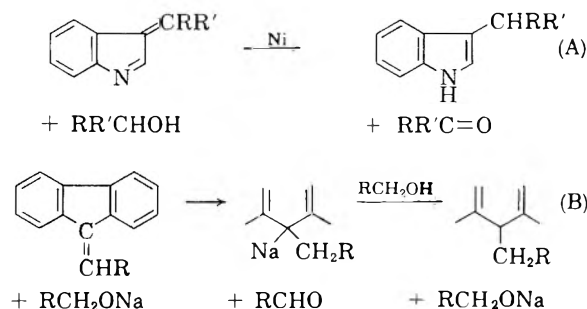


present, thereby regenerating the carbonyl function and producing product.

In order for the condensation of glycolic acid with indole to take place, it seems reasonable that the glycolate salt must be dehydrogenated to a glyoxalate intermediate. Reaction of this aldehyde with indole gives indolegycolic acid[5] which undergoes hydrogenolysis directly to product or dehydrates to an indolenine which is subsequently reduced.

$$HOCH_2CO_2K \rightleftharpoons \overset{O}{\overset{\|}{H}CCO_2K} + H_2$$
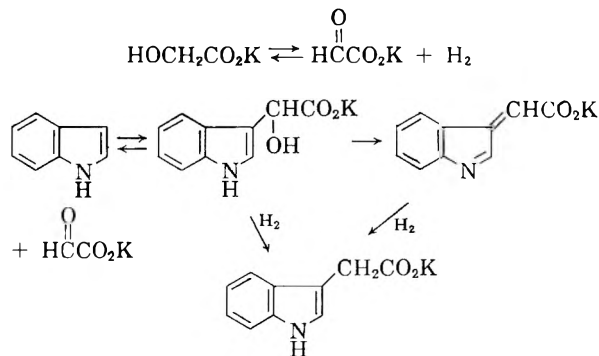


During the reaction at 250° the atmosphere of the reactor is abundant in hydrogen, and, if this hydrogen is released, the yield of indoleacetic acid is proportionately lowered. Also, the reaction cannot be successfully performed in an open system since at about 250° an exothermic reaction takes place with gas evolution and marked loss of product. These observations indicate that the reduction of indolenine or glycolate intermediates is a discrete step and is not affected by any direct interaction with potassium glycolate as in the previously described mechanisms.[1,4] Alternatively,

(5) J. B. Greenberg, A. W. Galston, K. N. F. Shaw, and M. D. Armstrong, Science, 125, 992 (1957).

(6) E. Fischer, Ann., 236, 149 (1886).

(7) F. Kögl and D. G. F. R. Kostermans, Z. physiol. chem., 235, 201 (1935).

(8) M. W. Bullock and J. J. Hand, J. Am. Chem. Soc., 78, 5852 (1956).

(9) H. Erdtmann and A. Jönsson, Acta Chem. Scand., 8, 119 (1954).

it is possible that dehydrogenation of glycolate occurs much more readily than does the reduction of the intermediates *via* reaction with glycolate. However, since the reaction is conducted in stainless steel equipment, it is likely that the metal surface catalyzes the reaction of hydrogen with the indolenine or indole glycolate. Conditions employing lower reaction temperatures (100–150°) in the presence of added Raney nickel, however, were ineffective in producing indoleacetic acid, although traces detectable by paper chromatography were formed at temperatures as low as 100°.

The fact that 1,2-dimethylindole is unreactive towards potassium glycolate and is recovered unchanged under the present reaction conditions is of interest. With this isomer, an indolenine cannot form and it is attractive to suggest that the reaction must proceed through reduction of this intermediate as opposed to hydrogenolysis of an indoleglycolate. However, the 1-substituent may, more simply, prevent the formation of an indole anion thus precluding the initial condensation of glyoxalate. This inertness does establish in the present case and in examples of other 3-alkylations[1–3] that the reaction does not involve 1-alkylation as part of the reaction sequence.

### Experimental[10]

**3-Indoleacetic Acid.**—A 3-l. stainless steel rocker autoclave was charged with 270 g. (4.1 moles) of 85% potassium hydroxide and 351 g. (3.0 moles) of indole followed by the gradual addition of 360 g. (3.3 moles) of 70% aqueous glycolic acid. The mixture was then heated at 250° under autogenous pressure for 14–22 hr., cooled to 90°, and 1 l. of water added to dissolve the crude potassium indoleacetate. Additional water was added to give a total volume of 3 l. and the solution extracted with ether to remove any neutral material present. The aqueous phase was acidified with concd. hydrochloric acid keeping the temperature 20–30° and finally cooling to 10°. The precipitated product was collected, washed with copious amounts of cold water, and dried. A 90% yield (475 g.) of light cream product was obtained, m.p. 163–165° dec. Crystallization of a sample from water (Darco) gave nearly colorless needles, m.p. 164–166° dec.; reported,[11] m.p. 165°.

(10) Melting points are corrected and boiling points are uncorrected. Infrared spectra were recorded by a Perkin-Elmer, Model 21, spectrophotometer.

(11) A. Ellinger, *Ber.*, **37**, 1801 (1904).

Indoleacetamide was prepared *via* the acid chloride by the method of Shaw and Woolley[12] and obtained as colorless needles after crystallization from water, m.p. 149–150°; reported[13] m.p. 150–151°.

**Methylated Indoleacetic Acids. General Procedure.**—For these preparations (Table I), 75- and 300-ml. stainless steel autoclaves were used in a Magne-Dash apparatus.[14] The reactions were conducted as described for the preparation of indoleacetic acid, except that, in cases where the quantity of starting indole was limited (5–10 g.), water was added in a quantity sufficient to give a level above the dash mechanism. Some of the indole always sublimed into the dash mechanism thereby resulting in decreased yields.

**Reaction of Indole with Potassium 2-Hydroxy-3-ethylpentanoate.**—In the manner described for the preparation of indoleacetic acid, 100 g. (0.85 mole) of indole, 75 g. (1.14 moles) of 85% potassium hydroxide, and 146 g. (1.0 mole) of 2-hydroxy-3-ethylpentanoic acid[15] were heated at 260° for 20 hr. The crude reaction mixture contained a considerable quantity of a neutral oil which was removed by extraction with ether. Acidification of the aqueous phase gave 22 g. (9.5%) of a red sticky solid. Several crystallizations from cyclohexane afforded pure (2-3'-indolyl)-3-ethylpentanoic acid as slightly reddish needles, m.p. 131–133°.

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.68; H, 7.59; N, 5.77.

Distillation of the ether extracts afforded 20 g. (20%) of indole, b.p. 118° (1.0 mm.), and 60 g. of a fraction, b.p. 136–150° (1.0 mm.), $n^{30}$D 1.5563–1.5570. Redistillation afforded 36 g. of nearly colorless 1-(3'-indolyl)-2-ethylbutane; a center fraction boiled at 124° (0.12 mm.), $n^{30}$D 1.5553. The infrared spectrum of this material was identical to the spectrum of an authentic sample as prepared below.

*Anal.* Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.83; H, 9.33; N, 6.79.

**1-(3'-Indolyl)-2-ethylbutane.**—A mixture of 60 g. (0.51 mole) of indole, 20 g. of 85% potassium hydroxide, and 500 ml. of 2-ethylbutanol was charged to a 3-l. stainless steel rocking autoclave and heated at 260° for 21 hr. The reactor was cooled and the contents washed out with ether. After washing the ether solution several times with water, it was distilled yielding 89 g. (87%) of product, b.p. 132–136° (0.6 mm.), $n^{30}$D 1.5513. A sample was redistilled, b.p. 161° (3.0 mm.), $n^{30}$D 1.5525, for examination of its infrared spectrum.

(12) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **203**, 979 (1953).

(13) R. Majima and T. Hoshino, *Ber.*, **58**, 2046 (1925).

(14) Autoclave Engineers, Erie, Pa.

(15) Geneously supplied by R. W. Kiefer of this laboratory.

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# Cotton Effects of α,β-Unsaturated Carboxylic Acids[1]

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*National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland*

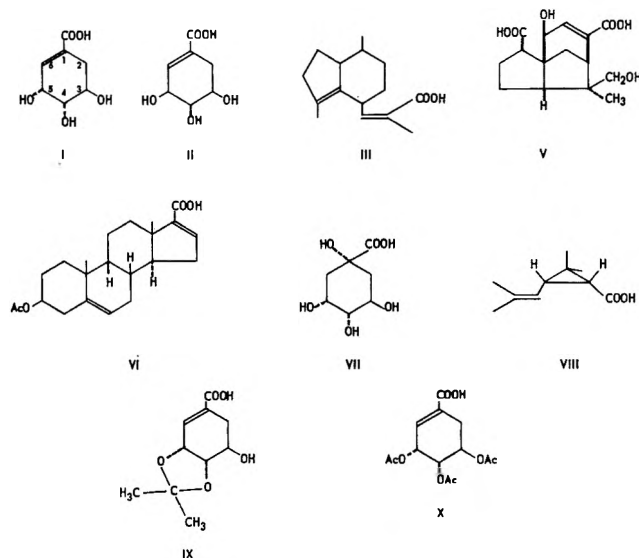Several α,β-unsaturated carboxylic acids show anomalous rotatory dispersion and circular dichroism at relatively long wave lengths (~250–270 mμ). This finding necessitates the assumption that hitherto undetected very weak bands exist in the absorption spectra of these compounds; one such band is actually observed in the vapor spectrum of β,β-dimethylacrylic acid. Similar Cotton effects are also given by the sodium salt of one of the acids, and by several α,β-unsaturated lactones. In the case of shikimic acid (I), the expected circular dichroism is found, but the corresponding anomalous rotatory dispersion is completely obscured by background effects.

Recently, the study of rotatory dispersion, which has been applied so successfully to ketonic compounds,[2]

(1) This paper is dedicated to the memory of our friend, Dr. Erich Mosettig.

(2) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

has been extended increasingly to substances having other chromophores. As a contribution to this field, we wish here to call attention to Cotton effects occurring at unexpectedly long wave lengths in the rotatory dispersion curves of α,β-unsaturated carboxylic acids having asymmetric carbon atoms adjacent to the chromo-
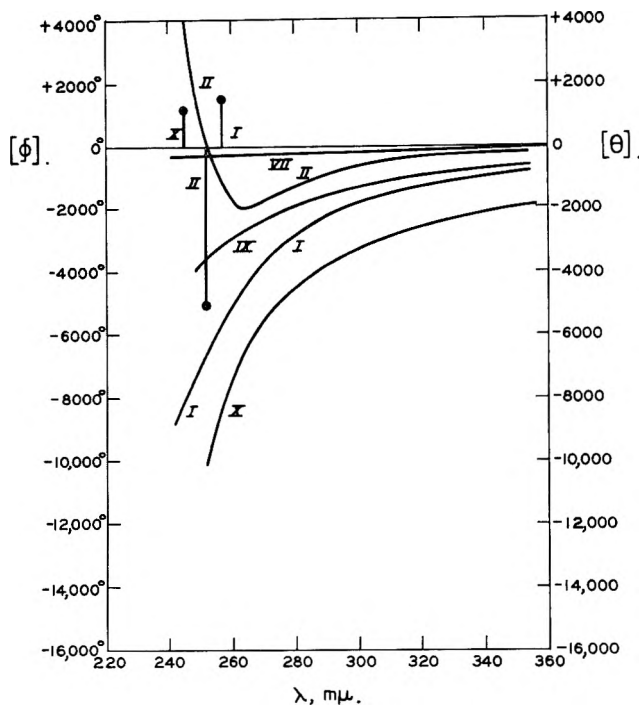
Fig. 1.—Optical rotatory dispersion of: I, water, $c = 0.048$ (246–240 m$\mu$: $c = 0.2$); II, water, $c = 0.5$; VII, water, $c = 0.5$; IX, ethanol, $c = 0.108$; X, methanol, $c = 0.144$. Maxima of circular dichroism indicated by vertical bars; circular dichroism expressed as molecular ellipticities, $\theta$.

phore, and to the existence of weak absorption bands causing these effects. The $\alpha,\beta$-unsaturated acids were investigated initially in the hope that it might be possible to reach the Cotton effects produced by the main absorption bands ($\sim$210–230 m$\mu$) of the compounds; such effects would be expected to occur below $\sim$240 m$\mu$ and hence might still be observable with available instruments (limit $\sim$230 m$\mu$). The substances investigated were: shikimic acid (I), 5-epi-shikimic acid (II),[3] valerenic acid (III),[4] valerenolic acid[4] [(IV), probably a hydroxy derivative of (III)], shellolic acid (V),[5] and 3$\beta$-acetoxyetia-5,16-choladienic acid (VI).[6]

All these acids except I (see below) showed anomalous rotatory dispersion (see Fig. 1, 2, and 3). Surprisingly, however, the Cotton effects occurred at much longer wave lengths ($\lambda \sim$ 250–280 m$\mu$) than had been anticipated; the difference between $\lambda_{max}$ and first extremum amounts to 40–60 m$\mu$, a fact which makes it very unlikely that the observed effects could be caused by the main absorption bands of the compounds. Where experimentally observable or indicated by extrapolation of the curves obtained, the crossing of the line of zero rotation occurred at $\sim$255–265 m$\mu$. It is thus necessary to assume that the absorption bands responsible for the Cotton effects are located in this spectral region.

More direct experimental evidence for the presence of these postulated bands was obtained by the finding that compounds I–VI (except III, which was not investigated) show circular dichroism in the expected range of wave lengths (244–260 m$\mu$) (see Fig. 1, 2, 3, and 4).

Little attention seems to have been paid to weak absorption bands occurring in the ultraviolet spectra of $\alpha,\beta$-unsaturated acids at wave lengths greater than that of the main peak; for instance, the detailed review of these spectra by Nielsen[7] does not mention such bands at all. The literature does, however, contain a few references which may be pertinent; see, e.g., the shoulder at $\sim$250 m$\mu$ observed in the spectrum of cro-

tonic acid in water,[8] and the bands above $\sim$250 m$\mu$ in the absorption spectra of several substituted acrylic acids in ethanol.[9a]

In our own work, careful investigation of the solution spectra of I–VI in water or ethanol, and of those of $\beta,\beta$-dimethylacrylic acid, an accessible and readily purified model compound, in water, hexane and cyclohexane failed to indicate the presence of any band in the pertinent region. With dimethylacrylic acid in the gas phase at 70°, however, a weak but distinct band with a maximum at 245 m$\mu$ was actually observed, thus giving final proof for the reality of the postulated bands in this area (Fig. 5). Under the same conditions, isovaleric acid, the saturated analog of dimethylacrylic acid, showed only relatively weak end-absorption without any indication of a band.[9b]

Our results thus seem to indicate that weak absorption bands at or above 250 m$\mu$ are typical of $\alpha,\beta$-unsaturated carboxylic acids; we tentatively ascribe them to $n \rightarrow \pi^*$ transitions of the conjugated carbonyl group, an interpretation which appears to be consistent with their location and low intensity.

The Cotton effects observed in our compounds, and the absorption bands causing them, are definitely connected with the presence of the chromophore C=C—COOH; thus quinic acid (VII), very closely related to II but lacking this chromophore, gives a plain negative

(3) I. I. Salamon, unpublished work.

(4) G. Büchi, T. L. Popper, and O. Stauffacher, *J. Am. Chem. Soc.*, **82**, 2962 (1960).

(5) P. Yates and G. F. Field, *ibid.*, **82**, 5764 (1960); R. C. Cookson, N. Lewin, and A. Morrison, *Tetrahedron*, **18**, 547 (1962).

(6) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **71**, 1487 (1938).

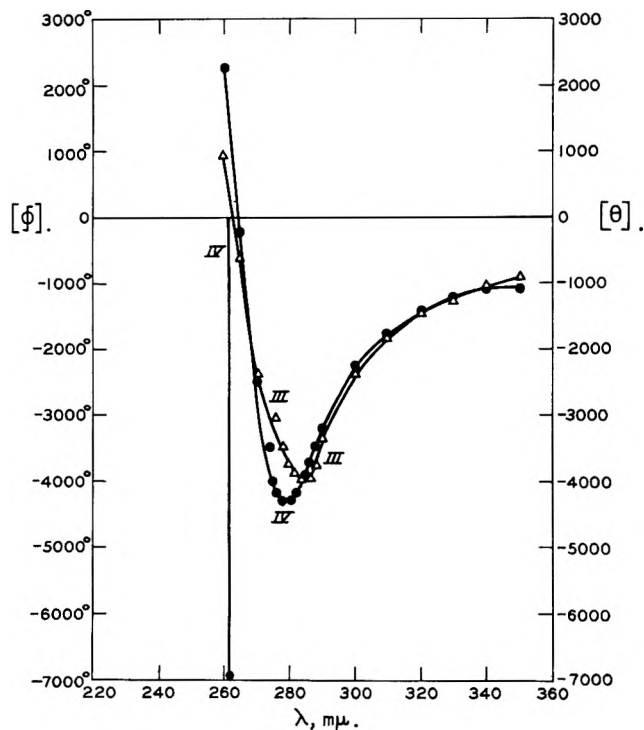(7) A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957).

(8) H. Mohler and H. Lohr, *Helv. Chim. Acta*, **21**, 485 (1938); G. O. Burr and E. S. Miller, *Chem. Rev.*, **29**, 419 (1941).

(9) (a) H. E. Ungnade and I. Ortega, *J. Am. Chem. Soc.*, **73**, 1564 (1951). (b) NOTE ADDED IN PROOF.—Our sample of $\beta,\beta$-dimethylacrylic acid (recrystallized from hexane and water) was free of impurities detectable by gasliquid chromatography (diethyleneglycol adipate on Gaschrom P, 131°). Our interpretation of the weak bands around 250 m$\mu$ as $n \rightarrow \pi^*$ transitions finds strong support by the proof (W. D. Closson, S. F. Brady, E. M. Kosower, and P. C. Huang, *J. Org. Chem.*, in press) that a weak band ($\lambda \sim$ 240 m$\mu$) of ethyl acrylate is indeed caused by such a transition. We are indebted to Professor Kosower for a preprint of this paper.

Fig. 2.—Optical rotatory dispersion of: III, methanol, $c = 0.1$ (270–260 m$\mu$: $c = 0.02$); IV, methanol, $c = 0.1$ (272–260 m$\mu$: $c = 0.02$).
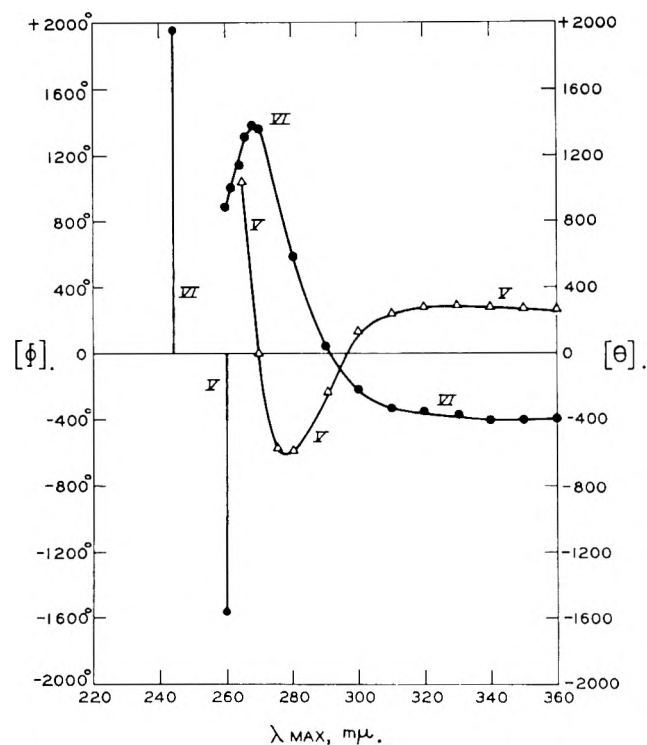


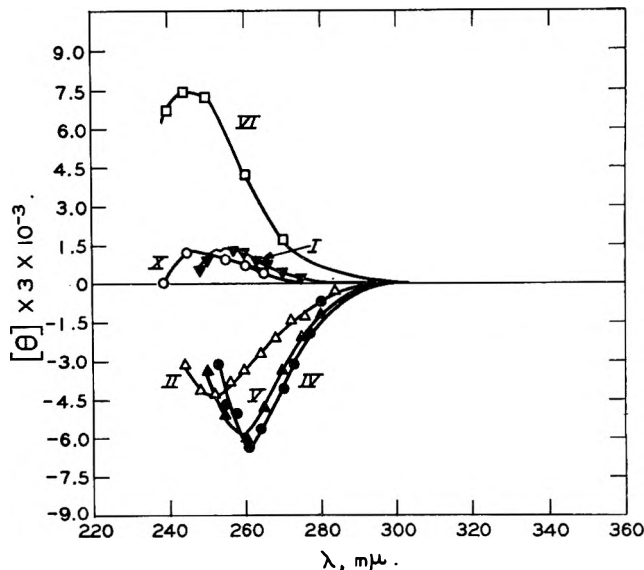Fig. 3.—Optical rotatory dispersion of: V, methanol, $c = 0.115$; VI, methanol, $c = 0.097$.



Fig. 4.—Circular dichroism of I, II, IV, V, VI, and X; all in ethanol.
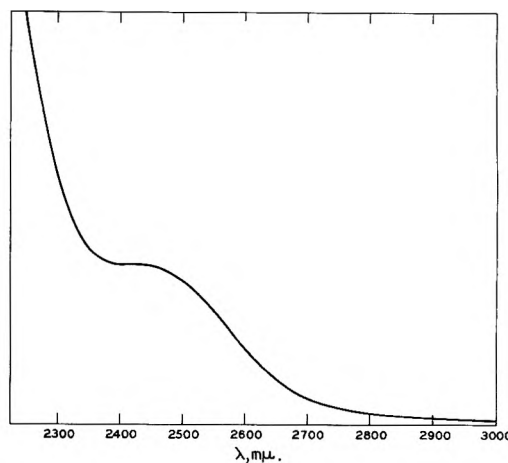


Fig. 5.—Absorption spectrum of $\beta,\beta$-dimethylacrylic acid; vapor at 70°, concentration unknown.

dispersion curve of low intensity without any anomaly down to ~240 m$\mu$ (see Fig. 1). Similarly, (+)-cis-chrysanthemumcarboxylic acid[10] (VIII) was investigated because it appeared possible that the grouping consisting of carboxyl, cyclopropane ring, and double bond might produce a Cotton effect analogous to the ones found with the $\alpha,\beta$-unsaturated acids. Compound VIII, however, gave a smooth curve without anomalies down to 240 m$\mu$, but the high molar rotation values indicate the proximity of a peak at shorter wave lengths ($[\Phi]_{253}$ +5000°; $[\Phi]_{244}$ +8600°, both at $c = 0.17$; $[\Phi]_{240}$ +14800°, $c = 0.034$).

Among the $\alpha,\beta$-unsaturated acids investigated, I and two of its derivatives, 4,5-isopropylidene-I (IX) and triacetyl-I (X), form an anomalous group. Since II is epimeric with I at the carbon atom which is adjacent to the chromophore, the remainder of the two molecules being identical, one would expect I to show a positive Cotton effect roughly antipodal to the negative one observed for II. Actually, I, IX, and X all give very similar *plain negative* dispersion curves (Fig. 1); no extremum could be reached with any concentration or path length investigated. This anomaly is made even more surprising by the fact that the levorotation of I is much more intense than that of II. It is necessary to ascribe the rotatory dispersion of I, IX, and X to an unusually strong background effect; this interpretation is shown to be correct by the finding that I does give the expected *positive* circular dichroism, antipodal to, but weaker than, the negative one of II (Fig. 1 and 4).

(10) L. Crombie and M. Elliott, "Progress in the Chemistry of Organic Natural Products," ed. by L. Zechmeister, Springer Verlag, Vienna, Vol. 19, 1961, p. 120, and literature quoted there.

In I, a weak positive Cotton effect thus appears to be completely hidden by an exceptionally large negative background. The reason for this anomaly is not apparent; the similar behavior of I, IX, and X shows that it cannot be ascribed to any simple conformational distortion of the double bond by, *e.g.*, formation of an additional ring through covalent (as in IX) or hydrogen bonds (as in I). In addition to this anomaly of their rotatory dispersions, I and its relatives are also anomalous in showing composite curves of circular dichroism (see Fig. 4), while those of the other acids investigated are simple. These facts indicate that the case of I is a complex one and that attempts at a more detailed interpretation should be postponed until more experimental material is available. It is remarkable, however, that the empirical rule of Bose and Chatterjee[11] correctly predicts that I should have a more negative $[\alpha]_D$ value than II.

The conjugated chromophore of I thus appears to behave entirely normally, but this fact could be detected only by study of the circular dichroism, not by that of optical rotatory dispersion, where the effect of this chromophore is completely obscured by background influences.[12]

The occurrence of Cotton effects in this area is not restricted to the free acids; their salts and esters seem to show the same behavior. Thus the sodium salt of V in aqueous solution gives a rotatory dispersion curve very similar to that of the free acid but shifted to greater negative rotations; though at 273 m$\mu$, $[\Phi]$ $-1900°$. Similarly, several $\alpha,\beta$-unsaturated lactones have been found to exhibit extrema in this area; *e.g.*, digitoxigenin,

$[\Phi]_{256}$ $+4600°$, $\alpha$-levantenolide,[13] $[\Phi]_{266}$ = $+5930°$, and $\beta$-levantenolide,[13] $[\Phi]_{266}$ = $-5940°$. The investigation is being extended to other compounds of this type.

It remains to be seen, when additional experimental material becomes available, whether the observation of such rotatory anomalies may be of value for the study of stereochemical problems, and what correlation exists between the direction of these Cotton effects and the configuration of the molecule.

(11) A. K. Bose and B. G. Chatterjee, *J. Org. Chem.*, **23**, 1425 (1958).

(12) *Cf.* C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.*, **84**, 4552 (1962).

(13) J. A. Giles and J. N. Schumacher, *Tetrahedron*, **14**, 246 (1961); **18**, 260 (1962).

(14) H. O. L. Fischer and G. Dangschat, *Helv. Chim. Acta*, **18**, 1206 (1935).

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# Preparation of *t*-Butyl Esters of Free Amino Acids[1]

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Most amino acids dissolve in dioxane–sulfuric acid mixtures and react with isobutene to form the *t*-butyl esters in 60–75% yield. The monobenzyl esters of aspartic and glutamic acid form benzyl-*t*-butyl esters, which can be hydrogenated to the mono *t*-butyl esters. $\beta$-*t*-Butyl L-aspartate and $\gamma$-*t*-butyl L-glutamate gave the N-carboxyanhydrides when treated with phosgene.

The *t*-butyl esters of amino acids are useful carboxyl-protecting groups in peptide synthesis because they are cleaved readily by acids. The esters have been prepared from N-acylated amino acids by reaction with isobutene,[2] or *t*-butyl acetate[3] and by conversion of the $\alpha$-chloro-*t*-butyl esters to the amino esters *via* the azide,[4] a process which yields racemic esters. Some amino esters have been prepared from the free amino acids by reaction with *t*-butyl acetate and perchloric acid.[5]

In a preliminary communication[6] we described a procedure for converting free amino acids to their *t*-butyl esters by reaction with isobutene in a mixture of dioxane and sulfuric acid. The yields reported at that time were around 45%. By using a more dilute reaction mixture, we have been able to raise the yields to 60–75% in many cases. The yield depends on the solubility of the amino acid in dioxane–sulfuric acid; L-phenylalanine is quite soluble and is converted rapidly to its *t*-butyl ester in 75% yield, while glycine is only slightly soluble and forms little ester. Diethylene glycol–sulfuric acid is also a satisfactory solvent for the reaction.

The four benzyl-*t*-butyl diesters of L-aspartic and L-glutamic acid were prepared from the monobenzyl esters. Hydrogenation of these provided the four

(1) This work was begun at the Lilly Research Laboratories, Indianapolis, and continued at the present address, supported in part by a research grant from the U. S. Public Health Service (GM-K3-17960). Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill. September, 1961.

(2) G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).

(3) E. Taschner, C. Wasielewski, and J. Biernat, *Ann.*, **646**, 119 (1961).

(4) A. Vollmar and M. Dunn, *J. Org. Chem.*, **25**, 387 (1960).

(5) E. Taschner, A. Chimiak, B. Bator, and T. Sokolowska, *Ann.*, **646**, 134 (1961).

(6) R. W. Roeske, *Chem. Ind.* (London), 1121 (1959).

mono-*t*-butyl esters. β-*t*-Butyl L-aspartate reacted with carbobenzoxy chloride to form an oily product which formed a crystalline salt with dicyclohexylamine, identical to that obtained by alkaline hydrolysis of carbobenzoxy-β-*t*-butyl α-benzyl L-aspartate.[7]

β-*t*-Butyl L-aspartate and γ-*t*-butyl L-glutamate reacted readily with phosgene to form the N-carboxyanhydrides. These ought to be useful intermediates in the preparation of poly-L-aspartic and poly-L-glutamic acid.

The hydroxyl group of tyrosine is not etherified extensively under our conditions; the reaction yields tyrosine-*t*-butyl ester in 45% yield. The ether-ester has been prepared from carbobenzoxy-L-tyrosine.[8]

Carbobenzoxy-*t*-butyl L-asparaginate (I) reacted readily with cold sodium hydroxide to form carbobenzoxy-α-amino-L-succinimide (II). This observation is surprising in view of the known resistance of t-butyl esters to alkaline hydrolysis and indicates that a β-*t*-butyl aspartate residue in a peptide chain will probably undergo cyclization to the succinimide derivative in base as the methyl ester does.
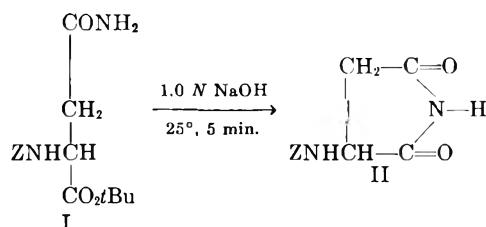


As an example of the use of *t*-butyl esters in peptide synthesis, L-cystinylbis-L-valine was prepared by coupling dicarbobenzoxy-L-cystinyl dichloride and *t*-butyl L-valinate. The four protecting groups were removed with hydrogen bromide in acetic acid, the solution of the dihydrobromide in water was adjusted to pH 4.9 with lithium hydroxide, and the free peptide was precipitated with ethanol.

All the *t*-butyl ester hydrochlorides have an infrared absorption band of medium strength in the 830 to 845-cm.$^{-1}$ region. Strong absorption in the 800–920-cm.$^{-1}$ region has been observed for the *t*-butoxy group in peroxides[9] and attributed[10] to skeletal vibration of the *t*-butoxy group.

### TABLE I

Amino Acid *t*-Butyl Ester Hydrochlorides, R·O-*t*-Bu·HCl[a]

| R | Yield, % | M.p., °C | $[\alpha]^{25}$D c = 2. EtOH | Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| α-Bz L-Asp[b] | 60 | 110–112 | −2.6° | 57.05 | 7.02 | 57.29 | 7.10 |
| β-Bz L-Asp | 73 | 115–117 | +23.3° | c | | | |
| α-Bz L-Glu | 67 | 124–126 | +13.8° | c | | | |
| γ-Bz L-Glu | 62 | 107–108 | +16.4° | 58.26 | 7.33 | 58.32 | 7.31 |
| ε-Z-L-Lys[d] | 65 | 147–149 | +13.6° | 57.97 | 7.84 | 57.93 | 7.94 |
| L-Pro | 27 | 110–112 | −30.5° | 52.04 | 8.73 | 52.29 | 8.79 |
| L-Ileu | 60 | 158–160 | +30.9° | c | | | |
| L-Leu | 62 | 166–167 | +12.4° | c | | | |
| ε-Tos-L-Lys[e] | 72 | 136–138 | +14.8° | c | | | |
| L-Phe | 75 | f | +44.2° | c | | | |
| L-Tyr | 45 | 143–145[g] | +24.4° | c | | | |
| L-Val | 65 | 147–149 | +20.5° | c | | | |

[a] See example 1 for procedure used. [b] Bz is benzyl. [c] Analysis reported in ref. 6. [d] Z is benzyloxycarbonyl. [e] Tos is *p*-toluenesulfonyl. [f] Decomposes without melting. [g] The free amino ester.

(7) R. Schwyzer and H. Dietrich, *Helv. Chim. Acta*, **44**, 2003 (1961).

(8) H. C. Beyerman and J. S. Bontekoe, *Rec. trav. chim.*, **81**, 691 (1962).

(9) A. Philpotts and W. Thain, *Anal. Chem.*, **24**, 638 (1952).

(10) H. Ory, *ibid.*, **32**, 509 (1960).

## Experimental[11]

Dioxane was distilled from calcium hydride or from sodium before use.

**1. β-Benzyl α-*t*-Butyl L-Aspartate Hydrochloride.**—Twenty-five milliliters of liquid isobutene was added to a solution of 3.0 g. (0.013 mole) of β-benzyl L-aspartate in a mixture of 25 ml. of dioxane and 2.5 ml. of concentrated sulfuric acid in a 500-ml. pressure bottle, and the mixture was shaken mechanically at room temperature for 4 hr.[12] The solution was poured immediately into a cold mixture of 200 ml. of ether and 125 ml. of 1 N sodium hydroxide, and the aqueous phase was washed well with ether. The ether solution was dried over sodium sulfate and evaporated under vacuum to about 5 ml. This was diluted with 25 ml. of ether. Addition of dry hydrogen chloride gave the crystalline hydrochloride.[13] After recrystallization from ethyl acetate, it weighed 3.0 g. (73%) and had m.p. 115–117°.

All of the esters listed in Table I except those of L-tyrosine and ε-tosyl L-lysine were prepared by this method. Acetone-ether and ethanol-ether were also used for recrystallization of the hydrochlorides.

***t*-Butyl L-Tyrosinate.**—Three grams of L-tyrosine was dissolved in a mixture of 25 ml. of dioxane and 6.0 g. of *p*-toluenesulfonic acid monohydrate or 2.5 ml. of concentrated sulfuric acid. Twenty-five milliliters of liquid isobutene was added slowly and the reaction mixture was shaken for 20 hr. The solution was added to a cold mixture of 100 ml. of ethyl acetate, 100 ml. of water and 5 ml. of 5 N sodium hydroxide, the pH was adjusted to 9.1, and the product extracted twice with ethyl acetate. Evaporation of the solvent left a crystalline residue of 1.8 g. (45%), m.p. 140–143°. The ester was recrystallized for analysis from ethyl acetate-petroleum ether, m.p. 143–145°. The p$K_a$' values in 66% dimethylformamide were 7.45 and 12.7.

***t*-Butyl ε-Tosyl-L-lysinate.**—This was prepared as in example 1 except that the aqueous phase was adjusted to pH 9.5 before extracting the product.

**2. β-*t*-Butyl L-Aspartate.**—A suspension of 5.93 g. (0.0188 mole) of α-benzyl β-*t*-butyl L-aspartate hydrochloride in 200 ml. of ether was treated with 20 ml. of 25% potassium carbonate solution and the liberated ester was immediately extracted into the ether and the aqueous solution washed again with 50 ml. of ether. The ether was dried over sodium sulfate and evaporated under vacuum. The oily residue was dissolved in a mixture of 125 ml. of 95% ethanol and 75 ml. of water, 0.2 g. of 5% palladium on charcoal was added, and the solution was shaken under 3 atm. of hydrogen for 1 hr. The catalyst was removed by filtration and the solution was evaporated under vacuum to 50 ml. When 400 ml. of acetone was added, a gel formed, which changed to a crystalline precipitate when the mixture was stirred. The yield of material of m.p. 194–195° dec. was 2.69 g. (76%).

The other mono *t*-butyl esters of aspartic and glutamic acid listed in Table II were prepared in a similar way.

**Carbobenzoxy-β-*t*-butyl L-Aspartate-dicyclohexylamine.**—A solution of 0.63 g. (0.0033 mole) of β-*t*-butyl L-aspartate in 3.3 ml. of 1.0 N sodium hydroxide was treated with two portions each of 0.28 ml. of carbobenzoxy chloride and 1.8 ml. of 1 N sodium hydroxide over a 10-min. period. The solution was stirred vigorously during this time and for another 45 min. at room temperature. It was washed with ether, adjusted to pH 3.2 with hydrochloric acid, and extracted with ether to yield 1.00 g. (93%) of the oily carbobenzoxy-β-*t*-butyl-L-aspartate. The dicyclohexylamine salt was prepared as described by Schwyzer[7]; m.p. 126–128°.

**3. β-*t*-Butyl L-Aspartate-N-carboxyanhydride.**—Phosgene gas was passed into a stirred suspension of 0.60 g. (0.0032 mole) of β-*t*-butyl L-aspartate in 25 ml. of dioxane at room temperature until the solid dissolved (about 10 min.). Stirring was continued for 2 hr. A stream of dry nitrogen was passed through the solution for 2 hr. and the solution was evaporated to dryness under vacuum. The white solid residue was stored *in vacuo* over potassium hydroxide overnight, then dissolved in 15 ml. of hot ethyl acetate, and filtered to remove a small amount of polymerized material. Petroleum ether was added until the solution

(11) Melting points are corrected. The analyses were done by Midwest Microlaboratories, Indianapolis, Ind.

(12) A Parr hydrogenation apparatus is satisfactory. About 15-p.s.i. pressure is developed during the reaction; the container is cooled to reduce the pressure before opening.

(13) Some of the hydrochlorides required addition of petroleum ether.

<div align="center">

TABLE II

MONO *t*-BUTYL ESTERS OF L-ASPARTIC AND L-GLUTAMIC ACID, R·O-*t*-Bu[a]

</div>

| R | Yield,[b] % | M.p., °C. | $[\alpha]^{25}$D | $R_f$[c] | Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| β-L-Asp | 76 | 198–199 dec. | +8.5° c, 1.3, H$_2$O | 0.63 | 50.78 | 7.99 | 50.77 | 8.49 |
| α-L-Asp | 71 | 178–179 dec. | +25.4° c, 1.1, H$_2$O | .66 | 50.78 | 7.99 | 50.79 | 7.83 |
| γ-L-Glu | 86 | 190–191 dec. | +17.3° c, 1.1, H$_2$O | .69 | 53.18 | 8.43 | 52.92 | 8.32 |
| α-L-Glu | 75 | 143–144 | +16.0° c, 1.0, H$_2$O | .71 | 53.18 | 8.43 | 53.10 | 8.43 |

[a] See example 2 for procedure used.    [b] From the benzyl *t*-butyl ester hydrochloride.    [c] In *n*-butyl alcohol–acetic acid–water 4:1:1.

was turbid and the product crystallized; 0.48 g. (70%). It melts with decomposition at 138–140°, if placed in the bath at 135°. $[\alpha]^{25}$D −35.6° (c, 2.0, EtOAc).

*Anal.* Calcd. for C$_9$H$_{13}$O$_5$N: C, 50.23; H, 6.09. Found: C 50.41; H, 6.02.

γ-*t*-Butyl L-Glutamate-*N*-Carboxyanhydride.—This was prepared from 0.602 g. (0.00296 mole) of γ-*t*-butyl L-glutamate as in example 3. It was recrystallized from ethyl acetate–petroleum ether; yield 0.54 g. (87%); m.p. 95–96°. $[\alpha]^{25}$D−19.0° (c, 2.0, EtOAc).

*Anal.* Calcd. for C$_{10}$H$_{15}$O$_5$N: C, 52.39; H, 6.60. Found: C, 52.89; H, 7.16.

Carbobenzoxy *t*-Butyl L-Asparaginate (I).—A solution of 3.0 g. of N-carbobenzoxy-L-asparagine, 25 ml. of dioxane and 2.5 ml. of concentrated sulfuric acid was treated with 25 ml. of liquid isobutene and the mixture was shaken for 4 hr. The solution was poured into a mixture of 100 ml. of ether and 250 ml. of 5% sodium bicarbonate, and extracted with ether (2 × 50 ml.). The ether solution was washed with 5% sodium bicarbonate, dried over sodium sulfate, and evaporated *in vacuo*. When the solid residue was recrystallized from ethyl acetate–petroleum ether, there was obtained 2.0 g. (55%) of material which melted at 105–106°. $[\alpha]^{25}$D-14.9° (c, 2.0, ethanol).

*Anal.* Calcd. for C$_{16}$H$_{22}$O$_5$N$_2$: C, 59.61; H, 6.88. Found: C, 59.77; H, 6.86.

Reaction of I with Sodium Hydroxide.—A solution of 1.61 g. (0.005 mole) of carbobenzoxy *t*-butyl L-asparaginate in 10 ml. of methanol and 5 ml. of water was treated with 5.0 ml. of 1.0 N sodium hydroxide, stirred for 3 min., acidified with 6 N hydrochloric acid, and evaporated to dryness under vacuum. The residue was dissolved in 25 ml. of ethyl acetate and 5 ml. of pH 7 buffer. The ethyl acetate was washed twice with pH 7 buffer, dried over sodium sulfate, and evaporated. The residue was recrystallized from ethyl acetate–petroleum ether to give II, 0.50 g. (40%), m.p. 78–82°. $[\alpha]^{25}$D −43° (c, 2.0, 95% ethanol). Electrometric titration indicated solvent of crystallization. A sample was dried at 60° for 24 hr. before analysis.

*Anal.* Calcd. for C$_{12}$H$_{12}$O$_4$N$_2$: C, 58.06; H, 4.87. Found: C, 58.35; H, 5.00.[14]

Di-*t*-butyl Dicarbobenzoxy-L-cystinylbis Valinate (III).—A mixture of 4.19 g. (0.02 mole) of *t*-butyl L-valinate hydrochloride in 75 ml. of chloroform and 25 ml. of aq. 25% potassium carbonate at 10° was stirred while the solid diacid chloride obtained from 5.0 g. (0.01 mole) of dicarbobenzoxycystine[15] was added. After the mixture was stirred for 30 min., the chloroform layer was washed with 5% sodium bicarbonate (3 × 100 ml.), 1 N hydrochloric acid (2 × 100 ml.), and 20 ml. of saturated sodium chloride solution, and dried over sodium sulfate. After evaporation of the solvent under vacuum, the solid residue was recrystallized from ethyl acetate–petroleum ether; yield 6.7 g. (82%), m.p. 172–174°. A sample recrystallized for analysis had m.p. 173–175°. $[\alpha]^{25}$D −80° (c, 1.0, dimethylformamide).

*Anal.* Calcd. for C$_{40}$H$_{58}$O$_{10}$N$_4$S$_2$: C, 58.70; H, 7.13; N, 6.83. Found: C, 58.27; H, 6.97; N, 6.88.

L-Cystinylbis-L-valine (IV).—A solution of 5.73 g. (0.007 mole) of the protected peptide III in 30 ml. of 2 M hydrogen bromide in acetic acid was allowed to stand at 25° for 1 hr., then heated at 100° for 1 min. The hydrobromide was precipitated by the addition of 200 ml. of ether, filtered, washed with ether, and allowed to stand *in vacuo* over potassium hydroxide overnight. It was dissolved in 50 ml. of water and washed with ether to remove benzyl bromide. The pH of the solution was adjusted to 4.9 by adding 13.5 ml. of 1 N lithium hydroxide and 400 ml. of ethanol was added. The precipitated peptide was filtered, washed well with ethanol, and dried. The yield was 2.8 g. (90%). $[\alpha]^{27}$D −22.7° (c, 0.81, 5 N HCl).

*Anal.* Calcd. for C$_{16}$H$_{30}$O$_6$N$_4$S$_2$.H$_2$O: C, 42.04; H, 7.07. Found: C, 41.99; H, 7.31.

The product gave one ninhydrin-positive spot on a paper chromatogram in *n*-butyl alcohol–acetic acid–water (4:1:5), $R_f$ 0.29.

(14) The physical properties agree with those found by E. Sondheimer and R. Holley. *J. Am. Chem. Soc.*, **76**, 2467 (1954).

(15) Prepared according to the procedure of V. du Vigneaud and G. Miller, *Biochem. Prep.*, **2**, 75 (1952), and used immediately.

# Synthesis of Unsaturated Fatty Acids. Positional Isomers of Linoleic Acid[1]

WALTER J. GENSLER AND JOHN J. BRUNO[2]

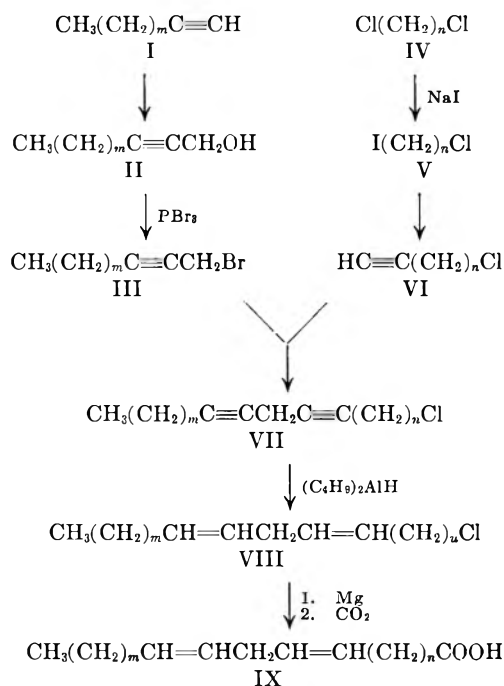*Chemistry Department of Boston University, Boston 15, Massachusetts*

Analogs of linoleic acid, an "essential fatty acid," have been synthesized. Coupling 1-bromo-2-alkynes with the Grignard derivative of appropriate chloroalkylacetylenes in the presence of cuprous chloride formed three 17-carbon compounds, 1-chloro-7,10-, 1-chloro-9,12-, and 1-chloro-10,13-heptadecadiyne. Diisobutylaluminum hydride reacted with these diynes to give adducts, which on protonation yielded 1-chloro-*cis,cis*-heptadecadienes. Adding another carbon atom by carbonating the Grignard reagents from the chloroheptadecadienes furnished the desired 18-carbon acids. In this way the following skipped (methylene-interrupted) unsaturated isomers of linoleic acid were obtained: *cis*-8,*cis*-11-octadecadienoic, *cis*-10,*cis*-13-octadecadienoic, and *cis*-11,*cis*-14-octadecadienoic acids. The acids were characterized by their melting points, indices of refraction, and the melting points of their tetrabromides. The 18-carbon compounds and their ozonolysis products were examined with the help of gas–liquid chromatography.

Only three of the approximately twenty octadecadienoic acids in the literature incorporate the methylene-interrupted or skipped unsaturated system. These acids, all biologically active,[3] are *cis*-9,*cis*-12-octadecadienoic, *cis*-8,*cis*-11-octadecadienoic,[4] and *cis*-6,*cis*-9-octadecadienoic acid.[5] Only the familiar *cis*-9,*cis*-12 isomer (linoleic acid) has been synthesized.[6] Since more information in this area is highly desirable, we undertook to synthesize and characterize three closely related isomers, the *cis*-8,*cis*-11-octadecadienoic, *cis*-10, *cis*-13-octadecadienoic, and *cis*-11,*cis*-14-octadecadienoic acids (IX). The present paper reports our results.

**Syntheses.**—The same general approach served for all the syntheses. Each proceeded through a 17-carbon diacetylenic intermediate VII, which was half-reduced to the diethylenic analog VIII and then extended to the final 18-carbon acid IX. The 17-carbon intermediates VII were prepared by combining 1-bromo-2-alkynes (III) with chloroalkynes (VI). These starting materials were reached by brominating 1-hydroxy-2-alkynes (II) with phosphorus tribromide and by alkylating sodium acetylide with chloralkyl iodides (V). Combination of the fragments III and VI was effected by adding cuprous chloride as catalyst[7,8] to a mixture of the bromide III and the Grignard derivative of chloroalkyne VI. With ether as solvent, the yield of coupling product VII was as high as or even higher than with tetrahydrofuran. However, tetrahydrofuran was preferred, since this solvent shortened the reaction time fifteenfold.[9]

We planned to arrive at the final dienoic acids by way of the corresponding 18-carbon diynoic acids, which should be available by carbonating the Grignard rea-

$$CH_3(CH_2)_mC{\equiv}CH \qquad Cl(CH_2)_nCl$$
$$I \qquad\qquad IV$$

$$\downarrow \qquad\qquad \downarrow NaI$$

$$CH_3(CH_2)_mC{\equiv}CCH_2OH \qquad I(CH_2)_nCl$$
$$II \qquad\qquad V$$

$$\downarrow PBr_3 \qquad\qquad \downarrow$$

$$CH_3(CH_2)_mC{\equiv}CCH_2Br \qquad HC{\equiv}C(CH_2)_nCl$$
$$III \qquad\qquad VI$$

$$CH_3(CH_2)_mC{\equiv}CCH_2C{\equiv}C(CH_2)_nCl$$
$$VII$$

$$\downarrow (C_4H_9)_2AlH$$

$$CH_3(CH_2)_mCH{=}CHCH_2CH{=}CH(CH_2)_uCl$$
$$VIII$$

$$\downarrow \begin{smallmatrix}1. & Mg\\2. & CO_2\end{smallmatrix}$$

$$CH_3(CH_2)_mCH{=}CHCH_2CH{=}CH(CH_2)_nCOOH$$
$$IX$$

gents derived from the 17-carbon diacetylenic chlorides VII. Actually, in one experiment, carbonation of the Grignard reagent from 1-chloro-9,12-heptadecadiyne (VII, $m = 4$, $n = 8$) gave the desired 10,13-octadecadiynoic acid (40–50%). But this experiment could not be repeated; thereafter all attempts to prepare the Grignard derivative failed. Although this remarkable inertness to magnesium[10] was not observed with 1-iodo-9,12-heptadecadiyne, the main process with the iodo compound was Wurtz coupling. Since replacing the halogen in chloro compounds VII or in 1-iodo-9,12-heptadecadiyne with a nitrile group was also unsatisfactory,[11] this approach was abandoned.

We then turned to the VII–VIII–IX sequence and so to the half-reduction of the triple bonds of chlorides

(1) Abstracted from the dissertation submitted by John J. Bruno to the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1960. The work was supported in part by research grant H 3773 from the National Heart Institute, U. S. Public Health Service.

(2) Present address: Sprague Electric Co., North Adams, Mass.

(3) *Cf.* H. J. Deuel, Jr., "The Lipids," Vol. III, Interscience Publishers, Inc., New York, N. Y., 1957.

(4) A. J. Fulco and J. F. Mead, *J. Biol. Chem.*, **235**, 3379 (1960).

(5) A. J. Fulco and J. F. Mead, *ibid.*, **234**, 1411 (1959); W. Stoffel and E. H. Ahrens, Jr., *J. Lipid Res.*, **1**, 139 (1960); J. F. Mead in K. Bloch's "Lipide Metabolism," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 41.

(6) The most recent synthesis is by M. de Gaudemaris and P. Arnaud, *Bull. soc. chim. France*, 315 (1962).

(7) *Cf.* W. J. Gensler and G. R. Thomas, *J. Am. Chem. Soc.*, **73**, 4601 (1951).

(8) *Cf.* W. J. Gensler and A. P. Mahadevan, *ibid.*, **77**, 3076 (1955).

(9) See among others S. N. Ege, R. Wolovsky, and W. J. Gensler, *ibid.*, **83**, 3080 (1961).

(10) Search of the literature revealed no examples of Grignard reagents prepared from chlorides containing acetylenic bonds. The unsuccessful attempts include trials with 1-chloro-6,9-pentadecadiyne [W. R. Taylor and F. M. Strong, *ibid.*, **72**, 4263 (1950)], 1-chloro-5-hexadecen-8-yne [L. Crombie and A. G. Jacklin, *J. Chem. Soc.*, 1632 (1957)], and 1-chloro-4,7,-10,13-nonadecatetrayne [A. I. Rachlin, N. Wasyliw, and M. W. Goldberg, *J. Org. Chem.*, **26**, 2688 (1961)]. Propargyl chlorides such as 1,4-dichloro-2-butyne [A. W. Johnson, *J. Chem. Soc.*, 1009 (1946)], 1-chloro-1,1-dialkyl-2-alkyne [K. N. Campbell and L. T. Eby, *J. Am. Chem. Soc.*, **62**, 1798 (1940)], and 1-chloro-2-heptyne (even with the entrainment method) [M. S. Newman and J. H. Wotiz, *ibid.*, **71**, 1292 (1949)] also fail to react.

(11) Sodium cyanide in alcohol gave tars, while cuprous cyanide in xylene [W. D. Celmer and I. A. Solomons, *ibid.*, **75**, 3430 (1953)] or in acetonitrile [B. C. L. Weedon, *J. Chem. Soc.*, 4168 (1954)] gave only starting material.

VII. Neither hydrogenation over a palladium-on-calcium carbonate catalyst[12,13] nor reduction with a zinc–copper alloy in alcohol[14] proved suitable. Diisobutylaluminum hydride,[15] on the other hand, reacted smoothly with the diynes to give the desired chlorodienes VIII. Whether necessary or not, we followed the practice of routinely reducing each diacetylene twice so as to eliminate the possibility of finding unchanged triple bonds in the dienes VIII. This method was used satisfactorily for all the VII to VIII conversions.

The last step, conversion of the 17-carbon chlorodienes VIII to the octadecadienoic acids IX, proceeded without difficulty. In sharp contrast to the reaction with chlorodiyne VII, a mixture of ethyl bromide[16] and chlorodiene VIII reacted smoothly with magnesium. Carbonation of the Grignard reagent with gaseous carbon dioxide gave analytically pure acids IX in yields of 50–60% or better.

The acids IX were converted to stearic acid by catalytic hydrogenation so that any question of the presence of a branched chain could be dismissed. Each unsaturated acid had the double bonds in the assigned positions, since ozonolysis of the methyl esters led to the expected mono- and dicarboxylic acid cleavage fragments.[17] The infrared absorptions curves of acids IX and their methyl esters gave no indication of trans-ethylenic materials; estimates based on the absorption at 10.3 μ limited the trans content to considerably less than 1%. The ultraviolet absorption at 233 mμ showed that conjugated unsaturation was present at a concentration lower than 1%.[18] Gas–liquid chromatographic analyses of the methyl esters, by indicating homogeneities of 98–99%,[19,20] were consistent with the results of the ultraviolet and infrared analyses.

## Discussion

With the exception of the 7,10 isomer, a series of skipped diunsaturated fatty acids from cis-6,cis-9-through cis-11,cis-14-octadecadienoic acid has now been reported. In vivo fatty acid transformations can occur by dehydrogenating unsaturated fatty acids between the point of unsaturation and the carboxyl group and by extending the chain at the carboxyl end.[4,5,21] Test of the generality of these processes by finding whether the new acids generate new families of skipped polyunsaturated acids is of considerable interest. The parent acids and their biosynthesized derivatives are also of importance in connection with essential fatty acid activity,[3,22] and even more so in the controversial

area of the relation between polyunsaturated acids, blood cholesterol, and atherosclerosis.[3,23]

With several of the diunsaturated acids IX at hand, comparison of some of their properties became possible. Table VII shows that the boiling points are closely bunched and that the indices of refraction are very similar. A clean separation of the acids by fractional distillation or a clear-cut distinction based on index of refraction appears unlikely. The melting points fall lower than those of the monounsaturated cis-octadecenoic acids.[24] The 8,11 acid has the lowest melting point, the 11,14 acid the highest. Our data are not precise enough to prove or disprove a generalization that the melting points go up as the unsaturation moves away from the carboxyl group or to show whether the zig-zag pattern observed for the melting points of the monounsaturated acids[24] has its counterpart in the diunsaturated acids IX.

Bromine added to acids IX to give crystalline tetrabromides, whose melting points differ by no more than 7° (Table VIII). The tetrabromo derivatives from adjacent members of the series show little depression in their mixture melting points. A tentative generalization may be drawn: only non-adjacent members of the series of tetrabromides will give appreciable depressions and ranges in their mixture melting points. Accordingly, caution is indicated before relying on the sharpness of melting point of a derived tetrabromo derivative as an indication of the absence of adjacent isomers.

None of the methyl esters of compounds IX showed more than one peak on gas–liquid chromatographic analysis. Table IX shows that the retention times on a 5-ft. silicone column all lie between 28.2 and 29.4 min. (230°). A 5-ft. polyester packing permitted the esters to pass through more rapidly, retention times of 15.5–19 min. (200°) being observed. Differences of 3–4 min. should permit at least partial separation. Unexpectedly, the order of retention time on the polyester column was not regular, although the shortest time was observed for the 8,11 isomer and the longest time for the 11,14 isomer. Better separation was obtained with longer packed columns and especially with long capillary columns.[20]

Homogeneity measures based on gas–liquid chromatography of the ozonolysis products indicated a 3–5.7% content of positional isomers in the methyl esters of acids IX. These measures accordingly were not in line with the abovementioned gas–liquid chromatography results nor with estimates based on ultraviolet and infrared absorption. Actually, by the same kind of cleavage analysis, the methyl ester of Hormel "high purity" linoleic acid furnished dimethyl azeleate with no less than 9.7% in homogeneity. We feel that assays based on ozonolysis products are better regarded as minimum, instead of true, measures of homogeneity.[25]

(12) H. Lindlar, Helv. Chim. Acta, 35, 446 (1952).

(13) The degree of selectivity and stereospecificity in catalytic half-hydrogenation of triple to double bonds can vary. [Cf. N. A. Dobson, G. Elinton, M. Krishnamurti, R. A. Raphael, and R. G. Willis, Tetrahedron, 16, 16 (1961).]

(14) B. S. Rabinowitz and F. S. Looney, J. Am. Chem. Soc., 75, 2652 (1953); A. J. Clarke and L. Crombie, Chem. Ind. (London), 143 (1957).

(15) G. Wilke and H. Müller, Chem. Ber., 89, 444 (1956); also Ann., 629, 222 (1960). Note that F. Bohlmann, E. Inhoffen, and J. Politt, ibid., 604, 207 (1957), using diethylaluminum hydride, failed to generate an ethylenic bond from an acetylenic bond, possibly because ether was used as solvent.

(16) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 38–45.

(17) J. G. Keppler, Rec. trav. chim., 76, 49 (1957).

(18) See R. T. Holman in "Methods of Biochemical Analysis," Vol. IV, D. Glick, ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 99.

(19) Personal communications from R. A. Landowne.

(20) R. A. Landowne and S. R. Lipsky, Biochim. Biophys. Acta, 46, 1 (1961).

(21) Cf. E. Klenk and H. Debuch, Ann. Rev. Biochem., 28, 39 (1939).

(22) Cf. H. J. Thomasson, Intern. Rev. Vitamin Research, 25, 62 (1953). Also note "Essential Fatty Acids," Proc. Intern. Conf. Biochem. Problems of Lipids, Oxford, 1957 [Chem. Abstr., 53, 17277 (1959)].

(23) Council Report, J. Am. Med. Assoc., 181, 411 (1962); J. Enselme, "Unsaturated Fatty Acids in Atherosclerosis," Pergamon Press, New York, N. Y., 1962.

(24) W. F. Huber, J. Am. Chem. Soc., 73, 2730 (1951).

(25) Other indications that the method of ozonolysis and analysis of the products is not free of complications have been found by Keppler,[17] R. R. Allen [J. Org. Chem., 21, 143 (1956)], F. L. Benton, A. A. Kiess, and H. J. Harwood [J. Am. Oil Chemists' Soc., 36, 457 (1959)], and E. Ucciani, J. Pasero, and M. Naudet [Bull. soc. chim. France, 1209 (1962)].

| m | Yield, % | B.p., °C. | $n^{24}$D | Calcd. C | H | Found C | H |
|---|---|---|---|---|---|---|---|
| 5$^a$ | 72 | 62–63 (2 mm.) | 1.4541 | C$_9$H$_{16}$O  77.10 | 11.50 | 77.. | 11.5 |
| 3$^{b,c}$ | 82 | 80–81 (9 mm.) | 1.4520 | | | | |
| 2$^c$ | 77 | 73–74 (15–16 mm.) | 1.4507$^d$ | C$_6$H$_{10}$O  73.40 | 10.27 | 73.2 | 10.3 |

$^a$ Ch. Moureu and H. Desmots, *Bull. soc. chim.*, [3] **27**, 360 (1902). $^b$ W. J. Gensler and G. R. Thomas, *J. Am. Chem. Soc.*, **73**, 4601 (1951). $^c$ M. S. Newman and J. H. Wotiz, *ibid.*, **71**, 1292 (1949). $^d$ At 26°.

TABLE II

1-BROMO-2-ALKYNES (III)

CH$_3$(CH$_2$)$_m$C≡CCH$_2$Br

| m | B.p., °C. | $n^{25}$D | Yield, % |
|---|---|---|---|
| 5$^a$ | 67–68 (2.5 mm.) | 1.4831 | 88 |
| 3$^b$ | 43–44 (4 mm.) | 1.4878 | 82 |
| 2$^c$ | 76–78 (35 mm.) | 1.4903 | 98 |

$^a$ *Anal.* Calcd. for C$_9$H$_{15}$Br: C, 53.20; H, 7.45; Br, 39.38. Found: C, 52.9; H, 7.3; Br, 39.7. $^b$ M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, **71**, 1292 (1949), report b.p. 104–105° (56 mm.); W. J. Gensler and G. R. Thomas, *ibid.*, **73**, 4601 (1951), report b.p. 76–80° (15 mm.) and $n$D 1.491; J. H. Wotiz, *ibid.*, **72**, 1639 (1950), reports b.p. 54° (4 mm.) and $n^{25}$D 1.4844. $^c$ M. S. Newman and J. H. Wotiz, *ibid.*, **71**, 1292 (1949), report b.p. 97–98° (80 mm.) and $n^{25}$D 1.4884; J. H. Wotiz, *ibid.*, **72**, 1639 (1950), reports b.p. 38° (4 mm.) and $n^{25}$D 1.4886.

## Experimental[26]

**1-Bromo-2-alkynes (III).**—Table I gives the results of combining appropriate acetylenic Grignard reagents with formaldehyde to form the intermediate propargyl alcohols (II).[27] Phosphorus tribromide with pyridine in catalytic quantities converted the propargyl alcohols (II) to 1-bromo-2-alkynes[28] (See Table II). One-mole quantities could be handled without difficulty.

**Chloroalkynes (VI).**—The chloroiodoalkanes (V) were prepared from the corresponding dichloroalkanes.[7,29] Table III summarizes the data. The directions used for alkylating sodium acetylide with the chloroiodoalkanes to give chloroalkynes VI are an adaption and modification of a procedure reported before for 9-chloro-1-nonyne.[30] The results in Table IV were obtained when sodium acetylide from 0.66 mole of sodamide was allowed to react with 0.26 mole of chloroiodoalkane in 100 ml. of ether plus 1.2 l. of liquid ammonia.

**1-Chloroheptadecadiynes (VII).**—The three diynes (VII) were obtained from the appropriate 1-bromo-2-alkyne (III) and chloroalkyne (VI) by following essentially the same procedure, which is given below for 1-chloro-7,10-heptadecadiyne (VII, m = 5, n = 6).

The reaction was carried out under dry nitrogen in a carefully dried three-necked flask equipped with dropping funnel and magnetic stirring bar. The tetrahydrofuran solvent was purified by treatment with potassium hydroxide and then distillation from lithium aluminum hydride. A solution of ethyl Grignard reagent was formed by dropping 20 ml. (23.0 g.; 0.211 mole) of dry ethyl bromide in 50 ml. of tetrahydrofuran into a stirred mixture of dry magnesium shavings (5.07 g.; 0.211 g.-atom; Dow sublimed metal) and 150 ml. of tetrahydrofuran. Bringing the mixture initially to a boil started the reaction, which then proceeded without external heating during the remainder of the addition. After another hour of boiling, the Grignard solution was treated with a solution of 29.25 g. (0.201 mole) of 8-chloro-1-octyne (VI, n = 6) in 50 ml. of tetrahydrofuran. The dropwise addition required 0.5 hr. The spontaneously boiling mixture

evolved a gas. The reaction mixture was boiled for an additional hour and then allowed to stand overnight under nitrogen.

Dry cuprous chloride (0.7 g.) was added, and the mixture was boiled for 1 hr. 1-Bromo-2-nonyne (III, m = 5; 40.8 g.; 0.201 mole) in 50 ml. of tetrahydrofuran was added to the stirred solution, which was then boiled for 2–4 hr. Approximately 88% of the initial Grignard content was consumed in the first hour, 94% after 2 hr.

The reaction mixture, containing a heavy, bright green precipitate, was poured over 500 g. of crushed ice plus 50 ml. of concentrated sulfuric acid. The aqueous layer was extracted with several 100-ml. portions of ether. The combined organic phases were washed with water until the washings were neutral to litmus and then dried with magnesium sulfate. Removal of solvent left the oily product, which was fractionated through a 5-cm. Vigreux column. The water-white 1-chloro-7,10-heptadecadiyne (VII) was distributed in ampoules, which were sealed without releasing the vacuum. In some preparations the distilled material contained small amounts of terminal acetylenic impurities as shown by a small absorption peak at 3.04 μ. Such impurities were readily precipitated by shaking the diyne (10 g.) with a saturated methanolic solution (50 ml.) of silver nitrate. Table V presents the data for the 1-chloroheptadecadiynes.

The infrared absorption spectra of the three compounds, taken as neat layers, were practically identical. The major absorption peaks occur at 4.35 (vw), 4.42 (vw), 4.48 (vw), 6.8 (s), 7.61 (s), 13.8, and 15.35 μ (s). No peaks were noted at 3 μ (acetylenic hydrogen) or at 5.1 μ (allenic unsaturation).

**1-Chloroheptadecadienes (VIII) by Diisobutylaluminum Hydride Reduction of 1-Chloroheptadecadiynes (VII).**—The reagent was prepared[31] by boiling 160 ml. of a 25% solution of triisobutylaluminum in heptane for 2–3 hr. Distillation afforded 27 ml. of colorless diisobutylaluminum hydride, b.p. 80–90° (0.05 mm.) The recommended precautions for handling organoaluminum compounds were observed.[15,32]

The reduction of 1-chloro-7,10-heptadecadiyne is given here as illustrative. The diyne (13.76 g.; 0.052 mole) was placed in a 300-ml. three-necked flask fitted with a mercury-sealed stirrer, a vertical condenser, and a dropping funnel. Dry, oxygen-free nitrogen, introduced through the top of the condenser under a slight positive pressure, blanketted the reagent and the reaction mixture at all times. Approximately 21 g. (0.15 mole) of diisobutylaluminum hydride was added over a period of 1 hr. to the stirred mixture at 0°. After residual reagent was rinsed into the flask with a small volume of dry heptane, stirring was continued at room temperature for 12–15 hr.

The condenser was replaced with a tube leading to a trap held at Dry Ice–acetone temperature. With the stirred reaction mixture in a bath at −5°, 60 ml. of a methanol–petroleum ether (b.p. 30–60°) solution (2:3) was carefully added in 1 hr. Then just enough ice-cold 20% sulfuric acid was slowly added to dissolve the precipitated aluminum methoxide. After the condensate in the trap was transferred to the acidified mixture with 50 ml. of ether, the aqueous layer was separated and extracted twice with ether. The combined organic layers were washed in succession with water, saturated sodium bicarbonate solution, and again with water until the washings were neutral to litmus. The solution was dried with magnesium sulfate and then warmed on the steam bath under water-pump vacuum to remove all solvent.

To eliminate all possibility of acetylenic impurities, the oil was treated routinely with a second portion of reagent in a repetition of the above procedure.

(26) Analyses were performed by Carol K. Fitz, Needham Heights, Mass.

(27) *Cf.* Taylor and Strong, *J. Am. Chem. Soc.*, **72**, 4263 (1950); Tchao Yin Lai, *Bull. soc. chim.*, [4] **53**, 682 (1933); R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950).

(28) M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, **71**, 1292 (1949). *Cf.* Taylor and Strong[27] as well as Tchao Yin Lai, ref. 27 and *Bull. soc. chim.*, [4] **53**, 1533 (1933).

(29) *Cf.* R. A. Raphael and F. Sondheimer.[27]

(30) W. J. Gensler and C. B. Abrahams, *J. Am. Chem. Soc.*, **80**, 4593 (1958).

(31) K. Ziegler, *Chem. Abstr.*, **51**, 15081 (1957) [British Patent 778,098 (1957)]; K. Ziegler, H. G. Geller, H. Lehmkuhl, W. Pfohl, and K. Zosel, *Ann.*, **629**, 1 (1960).

(32) *Cf.* "Handling and Properties of Triisobutylaluminum," Hercules Powder Co., Wilmington, Del.

## TABLE III

### CHLOROIODOALKANES (V)

### $I(CH_2)_nCl$

| n | B.p., °C. | $n^{25}D$ | | Calcd. | | | Found | | |
|---|-----------|-----------|---|---|---|---|---|---|---|
| | | | | C | H | I | C | H | I |
| $6^a$ | 55.5–57 (0.25 mm.) | 1.5176 | | | | | | | |
| $8^b$ | 85–89 (0.25 mm.) | 1.5089 | $C_8H_{16}ClI$ | 35.00 | 5.88 | 46.20 | 35.0 | 5.8 | 46.4 |
| $9^c$ | 96–98 (0.25 mm.) | 1.5066 | $C_9H_{18}ClI$ | 37.50 | 6.28 | 43.95 | 37.7 | 6.3 | 43.8 |

[a] W. J. Gensler and G. R. Thomas, *J. Am. Chem. Soc.*, **73**, 4601 (1951), report b.p. 112–116° (12 mm.) and $n^{25}D$ 1.5220; R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950), report b.p. 73–74° (0.7 mm.) and $n^{24}D$ 1.5248; W. F. Huber, *J. Am. Chem. Soc.*, **73**, 2730 (1951), reports b.p. 96–98° (6 mm.) and $n^{25}D$ 1.5214. [b] W. F. Huber, *ibid.*, **73**, 2730 (1951), b.p. 101–105° (2.5 mm.), and $n^{25}D$ 1.5113. [c] K. Ahmad, F. M. Bumpus, and F. M. Strong, *ibid.*, **70**, 3391 (1948), report b.p. 123–124° (2.8–2.9 mm.) and $n^{25}D$ 1.5060; W. F. Huber, *ibid.*, **73**, 2730 (1951), reports b.p. 123–126° (4 mm.) and $n^{25}D$ 1.5074.

## TABLE IV

### CHLOROALKYNES (VI)

### $HC{\equiv}C(CH_2)_nCl$

| n | Yield, % | B.p., °C. | $n^{25}D$ | | Calcd. | | | Found | | |
|---|----------|-----------|-----------|---|---|---|---|---|---|---|
| | | | | | C | H | Cl | C | H | Cl |
| $6^a$ | 77 | 40–42 (2.5 mm.) | 1.4507 | $C_8H_{13}Cl$ | 66.40 | 9.06 | 24.50 | 66.3 | 9.1 | 24.3 |
| 8 | 88 | 56–59 (2.5 mm.) | 1.4528 | $C_{10}H_{17}Cl$ | 69.60 | 9.93 | 20.55 | 69.6 | 9.8 | 21.4 |
| 9 | 80 | 57–58 (0.15–0.2 mm.) | 1.4538 | $C_{11}H_{19}Cl$ | 70.80 | 10.25 | | 70.9 | 10.5 | |

[a] R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950), report b.p. 73–76° (10 mm.) and $n^{12}D$ 1.4590; W. J. Gensler and G. R. Thomas, *J. Am. Chem. Soc.*, **73**, 4601 (1951), report b.p. 73–76° (11 mm.) and $n^{25}D$ 1.4548.

## TABLE V

### 1-CHLOROHEPTADECADIYNES (VII)

### $CH_3(CH_2)_mC{\equiv}CCH_2C{\equiv}C(CH_2)_nCl$

| m | n | B.p., °C. | $n^{25}D$ | Yield, % | | Found[c] | | |
|---|---|-----------|-----------|----------|---|---|---|---|
| | | | | | C | H | Cl | |
| 5 | 6 | 103–107 (0.5 × 10⁻³ mm.) | 1.4784 | 70 | 76.6 | 10.2 | 13.5 | |
| 3 | 8 | 106–109 (1 × 10⁻³ mm.) | 1.4779 | $68^b$ | 76.6 | 10.3 | 13.1 | |
| 2 | 9 | 101–111 (0.5 × 10⁻³ mm.) | 1.4780 | 62 | 76.7 | 10.3 | 13.2 | |

[a] Calcd. for $C_{17}H_{27}Cl$: C, 76.51; H, 10.20; Cl, 13.29. [b] With a 96-hr. reaction period in ether solvent, the yield was 81%.

The light yellow product (13.0 g.) dissolved in petroleum ether (b.p. 30–60°) was placed on a column of 130 g. of 28–200-mesh silica gel (Davison Chemical Co.). The first 250 ml. of eluate (petroleum ether solvent) contained 0.4 g. of a fatty solid which was discarded. The next 500 ml. of eluate (petroleum ether–ether solvent, 4:1) furnished 11.4 g. (82%) of pale yellow, solvent-free product. Distillation afforded colorless to faintly yellow 1-chloro-7,10-heptadecadiene (VIII), which was collected and stored *in vacuo* in sealed vials.

The 9,12 and 10,13 isomers were prepared in a similar way as colorless oils. The three isomers all showed very similar infrared absorption curves, with peaks evident at 3.32 (m), 6.05 (w), 7.15 (m), 7.26 (m), 7.64 (m), 7.8 (m), 10.3 (vw), 11.0 (m), 13.8 (s), and 15.3 (s) μ. The absorption curve of the 7,10 isomer was taken before as well as after distillation. The close similarity in the two curves suggested that the chromatographed material was practically pure, and that distillation (presumably with the other isomers as well), with its accompanying losses, may have been unnecessary.

Table VI presents the data.

## TABLE VI

### *cis,cis*-CHLOROHEPTADECADIENES (VIII)

### $CH_3(CH_2)_mCH{=}CHCH_2CH{=}CH(CH_2)_nCl$

| m | n | B.p., °C. | $n^{25}D$ | Yield, % | | Found[c] | | |
|---|---|-----------|-----------|---|---|---|---|---|
| | | | | a | b | C | H | Cl |
| 5 | 6 | 87–91 (1 × 10⁻⁴ mm.) | 1.4683 | 65 | 82 | | | |
| 3 | 8 | 87–89 (1 × 10⁻⁴ mm.) | 1.4678 | 83 | 94 | 75.8 | 11.6 | 12.7 |
| 2 | 9 | 75–77 (0.5 × 10⁻⁴ mm.) | 1.4678 | 70 | 87 | 75.3 | 11.5 | |

[a] After distillation. [b] Before distillation. [c] Calcd. for $C_{17}H_{31}Cl$: C, 75.37; H, 11.54; Cl, 13.09.

*cis,cis*-**Octadecadienoic Acids (IX).**—The appropriate 1-chloroheptadecadiene was converted to its Grignard reagent and then carbonated. The procedure, the same for the three acids, is given below for 8,11-octadecadienoic acid (IX, m = 5, n = 6).

A 250-ml. three-necked flask was fitted with a vertical condenser. Dry, oxygen-free nitrogen, which was supplied under a slight positive pressure through the top of the condenser, blanketted the reaction during the entire experiment. All glassware was carefully dried. Turnings of Dow sublimed magnesium (2.28 g. or 0.094 g.-atom) were dried briefly in the flask by brushing the flask with a soft flame. A mixture of 1-chloro-7,10-heptadecadiene (VIII, m = 5, n = 6) (5.00 g.; 0.0184 mole) and carefully dried ethyl bromide (6.05 g.; 0.0555 mole) was placed in a dropping funnel and was diluted with 45 ml. of ether distilled directly into the dropping funnel from lithium aluminum hydride. Approximately 80 ml. of ether, distilled directly into the flask, covered the magnesium. The ethereal halide solution was added to the boiling, magnetically stirred mixture over a period of 2 hr. After the addition, the mixture was boiled for 18 hr.

Gaseous carbon dioxide, after passing through a tower of concentrated sulfuric acid and then through an empty flask, was introduced into the cooled mixture through a tube reaching almost to the bottom of the flask. The inside temperature, initially −60°, climbed to −5° and then rapidly dropped to −60°. Solidification was noted.

Enough cold 10% sulfuric acid was added to dissolve the excess magnesium. The aqueous layer was separated and extracted with several portions of ether. The combined ether layers were shaken with several portions of water and then dried with magnesium sulfate. All material volatile below 50–60° (ca. 0.5 mm.) was removed, and the yellow residual oil (5.07 g.), diluted with an equal volume of light petroleum ether, was placed on a 2.5 × 33 cm. column of 28–200-mesh silica gel (100 g.). Passing 300 ml. of petroleum ether through the column removed 0.3 g. of material, which was discarded. The solvent was changed to petroleum ether–ether (4:1, v./v.), and 500 ml. was collected. Removal of solvent left 4.23 g. of 8,11-octadecadienoic acid, which was distilled through a 5-cm. vacuum-jacketed Vigreux column. The practically colorless main fraction was distributed in several small ampoules, which were sealed without breaking the vacuum.

Melting points were determined by observing 0.1–0.2 g. of sealed solidified material as it was allowed to warm slowly in a bath. The infrared absorption curves of the acids IX, taken with neat samples, were all very similar and corresponded closely to the curve for "high purity" linoleic acid (Hormel). All showed absorption peaks at 3.76 (m), 5.85 (s), 6.04 (w, sh), 7.17 (m), 7.26 (m), 7.8 (s), 8.1 (m), 10.7 (s), and 13.85 (s) μ. Ultraviolet absorption curves were determined with ca. 1.8 × 10⁻³ M methanolic solutions of the acids. The extinction at the 233 mμ maximum (log ε 2.2–2.5) served as a measure of the amount of conjugated impurities.[18] Neutralization equivalents were determined by titration of the acids in 95% alcohol under nitrogen with 0.05 N aqueous sodium hydroxide to a phenolphthalein end point. The values were slightly high (0.43–0.90%); but pure stearic acid by the same procedure also gave high results (0.18–

TABLE VII

cis,cis-OCTADECADIENOIC ACID (IX)

$$CH_3(CH_2)_mCH=CHCH_2CH=CH(CH_2)_nCOOH$$

| Isomer | m | n | B.p., °C. (10⁻⁴ mm.) | M.p., °C. (approx.) | $n^{25}D$ | Yield,[a] % | Conjugation, % | Found[b] C | Found[b] H | Neut.[c] equiv. | Iodine[d] no. |
|--------|---|---|------|------|------|------|------|------|------|------|------|
| $\Delta^{8,11}$ | 5 | 6 | 118–120 | −12.5 to −9.5 | 1.4663 | 58 | 0.62 | 77.1 | 11.5 | 283 | 185, 186 |
| $\Delta^{9,12}$ | 4 | 7 | | −5.1 to −5.4[e] | 1.4690[e] | | 0.45 | | | | 185, 185 184[f] |
| $\Delta^{10,13}$ | 3 | 8 | 121–128 | −9 to −6.5 | 1.4670 | 51 | 0.87 | 77.2 | 11.5 | 282 | 184 |
| $\Delta^{11,14}$ | 2 | 9 | 112–115 | 6.0 to 8.0 | 1.4664 | 60 | 0.73 | 77.3 | 11.5 | 282 | 185 |

[a] The figures refer to distilled material. The chromatographed acids were obtained in 20–30% higher yield. Much of the decreased yield of distilled material is due to mechanical losses. [b] Calcd. for $C_{13}H_{32}O_2$: C, 77.09; H, 11.50. [c] Molecular weight: 280.44. [d] Theoretical iodine number: 181. [e] Reported by B. Sreenivasan, J. B. Brown, E. P. Jones, V. L. Davidson, and J. Nowakowska, *J. Am. Oil Chemists' Soc.*, 39, 255 (1962). The index of refraction refers to 20°. Synthetic linoleic acid was reported recently with b.p. 115–120° (0.001 mm.), m.p. −5°, and $n^{22}D$ 1.4670 [M. de Gaudemaris and P. Arnaud, *Bull. soc. chim. France*, 315 (1962)]. [f] The Wijs iodine number of this Hormel "high purity" linoleic acid was found by the supplier to be 181, the theoretical value.

0.7%). Iodine numbers were obtained by the Kaufmann method.[33] Table VII summarizes the results.

**Hydrogenation of cis,cis-Octadecadienoic Acids (IX) to Stearic Acid.**—A mixture of the unsaturated acid (ca. 0.1 g.), platinum oxide (ca. 0.06 g.), and 95% alcohol (20 ml.) was magnetically stirred at room temperature in an atmosphere of hydrogen until absorption of hydrogen ceased. After filtration, the solution was concentrated under reduced pressures to a volume of 2–3 ml. Cooling the concentrated solution gave white crystals, which were collected and dried *in vacuo*. Stearic acid, melting within the range 68–70°, was obtained in better than 97% yield from each of the three acids IX. Mixtures of the hydrogenation stearic acids with authentic stearic acid (m.p. 69.5–70°) melted at 68–70°.

**Tetrabromostearic Acids from Skipped Octadecadienoic Acids (IX).**—Bromine was added dropwise to a stirred solution of 0.1–0.5 g. of unsaturated acid in 6–7 ml. of low boiling petroleum ether at temperatures held below 0°. When the yellow color persisted, the precipitated solids were collected and washed on the funnel with cold petroleum ether. The compounds were recrystallized two or three times from methylene chloride–pentane or methylene chloride–cyclohexane and then dried *in vacuo* at 56°. Table VIII summarizes the results. From the reported melting point of linoleic acid tetrabromide (m.p. 113.2–113.8°[34]; 115.4–115.5°[5]), we judge that the melting points in Table VIII might be slightly low.

TABLE VIII

TETRABROMO DERIVATIVES OF OCTADECADIENOIC ACIDS (IX)

$$CH_3(CH_2)_mCH-CHCH_2CH-CH(CH_2)_nCOOH$$
$$\quad\quad\quad\quad | \quad | \quad\quad | \quad |$$
$$\quad\quad\quad\quad Br \quad Br \quad\quad Br \quad Br$$

| Starting isomer | m | n | Yield, % | M.p.,[a] °C. | Found[b] C | Found[b] H | Found[b] Br |
|--------|---|---|------|------|------|------|------|
| $\Delta^{8,11}$ | 5 | 6 | 20 | 106–107 | 35.9 | 5.2 | |
| $\Delta^{9,12}$[c] | 4 | 7 | 35 | 111.5–112.5 | 36.3 | 5.1 | 53.3 |
| $\Delta^{10,13}$ | 3 | 8 | 22 | 111–111.5 | 36.1 | 5.1 | 53.4 |
| $\Delta^{11,14}$ | 2 | 9 | 26 | 112–112.5 | 36.2 | 5.2 | 53.5 |

[a] The mixture melting points are as follows: [8,11 + 9,12] 106–107°; [9,12 + 10,13] 107.5–112.5°; [9,12 + 11,14] 94–98.5°; [10,13 + 11,14] 108–111°. [b] Calcd. for $C_{18}H_{32}Br_4O_2$: C, 36.02; H, 5.38; Br, 53.26. [c] Hormel "high purity" linoleic acid.

**Methyl cis,cis-Octadecadienoates.**—The acids IX were esterified by treating 0.1–0.2 g. samples in 10–15 ml. of dry ether with distilled ethereal diazomethane until a yellow color persisted. An atmosphere of pure nitrogen was maintained in the flask. After filtration through thin layers of a filter aid (Celite), anhydrous magnesium sulfate, and activated charcoal, the solution was warmed in a stream of nitrogen to remove solvent. The residual colorless esters in several vials were exposed without delay to a 0.01-mm. vacuum. The vials, sealed without breaking the vacuum, were stored in the cold away from light.

Infrared absorption curves of the esters were taken with 0.04-

(33) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 736.

(34) H. M. Walborsky, R. H. Davis, and D. R. Howton, *J. Am. Chem. Soc.*, 73, 2590 (1951).

mm. thicknesses of the neat oils. All showed maxima at 3.33 (m), 3.49 (m), 6.05 (w), 7.15 (m), 7.26 (m), 7.34 (m), 7.58 (w), 8.05 (m), 8.36 (s), 8.55 (s), 9.85 (m), 10.1 (w), 10.98 (w), and 13.85 (m) μ. The minor differences in the 8–9- and 11–12.5-μ region offer little encouragement in the use of infrared to distinguish the several esters. Except for these differences, all the esters including methyl linoleate showed practically the same curves. The curves showed no characteristic *trans* double bond absorption at 10.3 μ. Since a distinct shoulder was observed here when a test mixture of methyl linoleate containing 1% of methyl *trans*-11-octadecenoate was scanned under the same conditions, the content of *trans* double bonds in the synthetic compounds was substantially less than 1%.

**Gas–Liquid Chromatographic Analysis of the Octadecadienoic Acids IX and Esters.**—Table IX gives the results of gas–liquid chromatography with the methyl octadecadienoates. Only one peak appeared for each ester. The retention times for the esters on a column with a polyester stationary phase show significant differences, but the trend of retention time with the position of the skipped unsaturation proved not to be regular.

TABLE IX

GAS–LIQUID CHROMATOGRAPHIC ANALYSIS[a] OF THE METHYL ESTERS OF OCTADECADIENOIC ACIDS (IX)

$$CH_3(CH_2)_mCH=CHCH_2CH=CH(CH_2)_nCOOCH_3$$
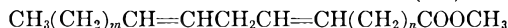
| Isomer | m | n | Silicone column Temp., °C. | Silicone column Retention time, min. | Polyester column Temp., °C. | Polyester column Retention time, min. |
|--------|---|---|------|------|------|------|
| $\Delta^{8,11}$ | 5 | 6 | 231 | 29.4 | 201 | 15.5 |
| $\Delta^{9,12}$[b] | 4 | 7 | 230 | 29.0 | 201 | 18.3 |
| $\Delta^{10,13}$ | 3 | 8 | 231 | 28.2 | 201 | 15.6 |
| $\Delta^{11,14}$ | 2 | 9 | 235 | 28.6 | 201 | 19.1 |

[a] An "Aerograph" unit with catherometer detector was used with two 5-ft. columns, one packed with silicone (sample size, 10 μl.) and the second with a polyester ("LAC-446"; sample size, 1–3 μl.). The carrier gas was helium at a constant flow rate (rotameter reading, 85.0 mm.). [b] Methyl ester of Hormel "high purity" linoleic acid.

Longer packed columns and, even better, capillary columns gave more effective separation. These results are fully documented elsewhere.[20] With the more efficient columns, the four methyl esters showed 98–99% homogeneity. The maximum single impurity was observed in the methyl linoleate.[19,20]

After approximately 6 months of storage at −5° *in vacuo* away from light, the acids themselves were examined. The analyses were performed at the Unilever Research Laboratory (Vlaardingen) through the courtesy of Dr. R. K. Beerthuis. A column (120 cm. long; 0.4-cm. diameter) packed with 10% Apiezon L on diatomaceous earth (Celite) was used. At a flow rate of 20 ml. per min. of argon and at a column temperature of 182° the retention times of the 18-carbon acids were just over 2 hr. The column gave only partial separation of the 8,11 isomer (with the shortest retention time) from the other acids. Homogeneity estimates were made as follows: for the 8,11-acid, ca. 94%; for the 10,13 acid, ca. 100%; for the 11,14 acid, ca. 96%. Whether the appearance of inhomogeneity in the 8,11 and 11,14 isomer is

TABLE X

GAS-LIQUID CHROMATOGRAPHIC ANALYSIS[a] OF THE OZONOLYSIS METHYL ESTERS DERIVED FROM OCTADECADIENOIC ACIDS

| Octadecadienoic acid IX | | | Column temperature, 100° | | | Column temperature, 190° | | | Impurity, % |
| Isomer | $m$ | $n$ | Reference methyl ester | | Cleavage ester | Reference methyl ester | | Cleavage ester | |
|---|---|---|---|---|---|---|---|---|---|
| $\Delta^{8,11}$ | 5 | 6 | Heptanoate | 4.28 | 4.32 | Octanedioate | 7.50 | 7.25 | 2.9 |
| $\Delta^{9,12b}$ | 4 | 7 | Hexanoate | 2.60 | 2.55 | Nonanedioate | 9.4 | 8.5[c] | 9.7 |
| $\Delta^{10,13}$ | 3 | 8 | Pentanoate | 1.6 | 1.6 | Decanedioate | 13.2 | 11.8[c] | 5.7 |
| $\Delta^{11,14}$ | 2 | 9 | Butanoate | 0.91 | 0.92 | Undecanedioate | 17.7 | 17.4 | 3.8 |
| | | | | | | Malonate | 1.4 | | |

[a] An "Aerograph" unit with a catherometer detector was used. Samples (2–3 μl.) were injected into a 5-ft. packed helical column containing a polyester stationary phase ("LAC-446"). Helium was used at a constant flow rate (rotameter reading, 85.0 mm.). [b] Methyl ester of Hormel "high purity" linoleic acid. [c] Column temperature: 195°.

due to deterioration on storage, or to partial isomerization of the acids[35] during the 2-hr. period on the column is not known.

**Cleavage Analysis of Skipped Unsaturated Acids IX.**—The procedure given below for the ozonolysis and analysis of methyl *cis*-10,*cis*-13-octadecadienoate was followed for all the methyl esters.

Ozonized oxygen was passed through a solution of 0.2 g. of the methyl ester of 10,13-octadecadienoic acid (IX, $m = 3$, $n = 8$) in 10 ml. of pure chloroform in a bath at −18°. The gas flow was interrupted when the emergent gases developed a brown color in an aqueous potassium iodide solution, and the reaction mixture was then allowed to stand at room temperature for 0.5 hr.

Solvent was removed at 30° by distillation *in vacuo*, and the residual oil was treated with a slurry of freshly prepared silver oxide (0.9 g.), 10 ml. of water, and 1.6 ml. of 10% aqueous sodium hydroxide in several portions. The mixture was stirred vigorously and heated at 90–95° during and for 1 hr. after the addition.[17] Hydrochloric acid (20%) was added to pH 2. The mixture was extracted several times with ether, and the combined extracts, after one rinsing with water, were dried with magnesium sulfate. Treatment of the solution with diazomethane, as described above for the preparation of the methyl octadecadienoates, esterified all

(35) The methyl esters of polyunsaturated acids suffer no significant change during gas–liquid chromatography at 197° with Apiezon M as the stationary phase [W. Stoffel, W. Insul, Jr., and E. H. Ahrens, Jr., *Chem. Abstr.*, **53**, 3973 (1959); *Proc. Soc. Exptl. Biol. Med.*, **99**, 238 (1958)].

free carboxylic acid groups. When volatile material was removed at steam temperatures under a moderately reduced pressure, 0.2 g. of residue consisting largely of methyl valerate and dimethyl sebacate remained. Yields ranging from 80–95% were obtained at this point. No dimethyl malonate was recovered.

Table X summarizes the results of gas–liquid chromatographic analysis of the mixture. One or more minor peaks revealed the presence of lower, homologous diesters. The diester tracings were used to obtain the percentage impurities listed in Table X. Whether the values obtained in this way in fact reflect the degree of inhomogeneity in the 18-carbon acids, or whether the values are artifacts or the consequence of the degradation of initially homogeneous cleavage products[25] was not determined.

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# *Yerba Buena.* II. The Identification of Micromerol as Ursolic Acid[1]

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It has been shown that micromerol is mainly ursolic acid, mixed, in some cases, with smaller amounts of oleanolic acid. The three-dimensional crystal structure of methylmicromerol bromoacetate (methyl ursolate bromoacetate) has been determined in the course of this study, providing an independent confirmation of the stereochemistry of the α-amyrin system.

Among the numerous products isolated by Power and Salway[2] from *yerba buena* (*Satureia douglassii*) were two colorless alcohols to which were assigned the formulas $C_{33}H_{52}O_3 \cdot 2H_2O$ and $C_{30}H_{46}O_4 \cdot 2H_2O$ and the names micromerol and micromeritol. Of these, micromerol was present in significantly greater quantities. Although the proposed formulas were not in agreement, the properties described for these compounds suggested strongly that they were triterpene carboxylic acids.

In the course of our isolation of xanthomicrol[1] we obtained by cooling the crude, concentrated ethereal extract of *yerba buena* a copious greenish white precipitate. This showed on thin-layer chromatography (t.l.c.)[3] two major components having the color reac-

tions of triterpenes.[4] The less polar material was present in considerably larger amounts and proved to be a colorless hydroxy acid, whose properties were in agreement with those reported for micromerol. Our sample and its derivatives, however, gave analyses compatible with the formula $C_{30}H_{48}O_3$, *i.e.*, a mono hydroxylated triterpene acid.

Methylation of micromerol with diazomethane gave a methyl ester which showed the same melting points for the hydrated and dried forms as reported by Powers. Since the ester appeared to be rather more easily crystallized and purified than micromerol itself, most of our material was isolated in this form by chromatography

(3) We wish to thank Mr. Erich Gauglitz, U. S. Bureau of Commercial Fisheries, Seattle, for first pointing out to us the striking advantages of this technique.

(4) C. R. Noller, R. A. Smith, G. H. Harris, and J. W. Walker, *J. Am. Chem. Soc.*, **64**, 3047 (1942).
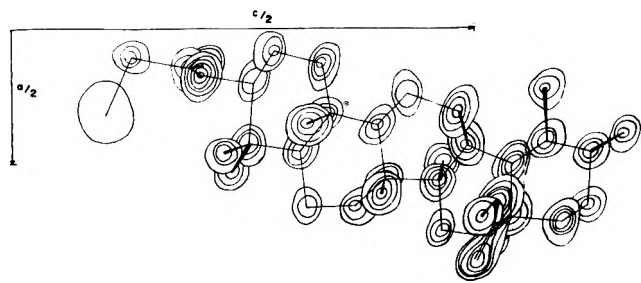
(1) Previous paper, G. H. Stout and V. F. Stout, *Tetrahedron*, **14**, 296 (1961).

(2) F. B. Power and A. H. Salway, *J. Am. Chem. Soc.*, **30**, 251 (1908).

Fig. 1.—Electron density projection on (010) of methylmicromerol bromoacetate. Contours at $1e/Å.^3$ starting at $2e/Å.^3$ except for bromine.
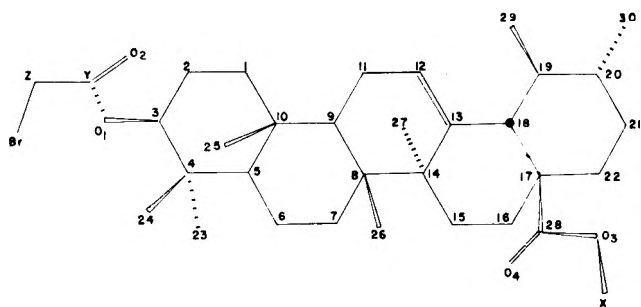


Fig. 2.—Numbering system and observed stereochemistry of methylmicromerol bromoacetate.

following methylation of the whole crude terpene fraction.

Consideration of the literature constants for micromerol[2,5a] had suggested that it was probably identical with ursolic acid[5b,6] (I), and a direct comparison between micromerol and ursolic acid appeared to substantiate this view. Further investigation, however, produced two striking anomalies. Acetylation of methylmicromerol gave a monoacetyl derivative (A) whose melting point of 203–206° was in marked disagreement with that reported for acetyl methyl ursolate[5b] (243–244°). Treatment of this acetate
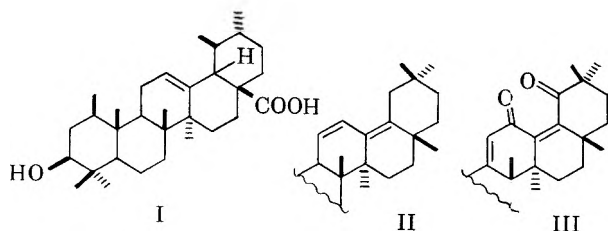


with selenium dioxide in refluxing acetic acid gave products whose ultraviolet spectra showed the chromophores II and III. The formation of a diene and a dienedione under these conditions is commonly used as proof that the compound oxidized belongs to the β-amyrin group of the triterpenes.[7] The problem was compounded when it was found that if micromerol was first acetylated and then methylated, a methyl acetate (B) melting 245–250° was obtained. Although the infrared and n.m.r. spectra of the two methyl acetates were nearly superimposable, and although both were homogeneous by t.l.c., all attempts to show

them to be dimorphic crystalline forms were fruitless. Mixed samples melted at intermediate temperatures, and seeding solutions of the low-melting form did not produce high-melting material.

In order to clarify the problem of the nature of the ring system involved, and to locate the substituents if we were dealing with a new β-amyrin derivative, methylmicromerol bromoacetate was prepared and subjected to three-dimensional X-ray analysis. This compound crystallizes in the space group $P2_12_12_1$ with four molecules to the unit cell and with dimensions, $a = 7.83$ Å., $b = 14.19$ Å., and $c = 27.11$ Å. The molecular weight found was 581 (calculated 592). Since the fine details of molecular structure were not in question, limited data were collected, consisting of 1113 reflections, of which 839 were observed and 274 unobserved. Almost all the reflections had $(\sin \theta)/\lambda$ less than 0.43 Å.$^{-1}$, so that the resolution was approximately 0.7 Å., ample to show discrete atoms but insufficient to provide good values for bond lengths.

The bromine atom was readily located from an unsharpened three-dimensional Patterson calculation, and starting with phases based on the bromine alone five cycles of Fourier and structure factor calculations revealed all of the atoms in the molecule. The Fourier calculations used for locating atoms included both $F_o$ syntheses and difference syntheses in which each difference ($|F_o| - |F_c|$) was weighted by the factor $|F_c|/|F_o|$ if $|F_c| < |F_o|$, corresponding approximately to the uncertaintiy in the phase information supplied by each calculated structure factor.[8] The resulting electron difference maps proved extremely useful in locating missing and badly misplaced atoms.

After all of the atoms had been found and the oxygen atoms assigned on chemical grounds and on their appearance on difference maps, refinement by block diagonal[9] and full matrix[10] least squares using an overall temperature factor gave a final residual index[11] value of $R = 16.1\%$. Fig. 1 shows a Fourier synthesis based on the final parameters, and Fig. 2 gives the numbering system of the heavy atoms, for which parameters are given in the Experimental section.

The structure indicated for micromerol by the X-ray analysis is that of an α-amyrin with a C-28 carboxyl group and a 3β hydroxyl, corresponding to the structure of ursolic acid. Although the standard deviation in bond lengths is 0.12 Å., $C_{12}$–$C_{13}$ is shorter than the remainder of the ring system bonds by an amount which is probably significant[12] and corresponds to the expected location of the double bond. Thus the original view that micromerol is ursolic acid is substantiated.

It should be noted that this determination represents the first published X-ray study of an α-amyrin and as such is an independent conformation of the structure proposed previously on the basis of degradation[13]

(5) (a) J. Simonsen and W. C. J. Ross, "The Terpenes," Vol. 4, Cambridge University Press, 1957, p. 437; (b) ibid., Vol. 5, p. 116ff.

(6) The existence of the solvated form, m.p. 115°, of methyl ursolate produced by crystallization from 95% ethanol is often ignored, but has been reported by F. B. Power and C. W. Moore, J. Chem. Soc., 97, 1099 (1910).

(7) C. Djerassi, C. H. Robinson, and D. B. Thomas, J. Am. Chem. Soc., 78. 5685 (1956).

(8) $F_o$ and $F_1$ are the observed and calculated structure factors, respectively.

(9) A modified version of UCLALSI, by P. K. Gantzel, R. A. Sparks, and K. N. Trueblood, University of California at Los Angeles, 1961.

(10) W. R. Busing and H. A. Levy, "A Crystallographic Least Squares Refinement Program for the IBM 704," Oak Ridge National Laboratories, 1959.

(11) $R = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$.

(12) D. W. J. Cruickshank, Acta Cryst., 2, 65 (1949).

(13) E. J. Corey and J. J. Ursprung, Chem. Ind. (London), 1387 (1954), J. Am. Chem. Soc., 78, 183 (1956); A. Melera, D. Arigoni, A. Eschenmoser, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, 39, 441 (1956).

and partial synthesis.[14] Although the ring system appears to be somewhat bowed, presumably from repulsion between the axial methyl groups, the stereochemistry found is in complete agreement with that shown in I.

In view of this conclusive evidence that micromerol is an α-amyrin, the selenium dioxide oxidation was studied further. It was found that when the low-melting methyl micromerol acetate was partially oxidized, the recovered material was high-melting and gave no melting point depression with authentic methyl acetylursolate. Furthermore, the dienedione produced was found to be identical with the dienedione from oleanolic acid. If crystallized micromerol was used as the starting material, the same, high-melting, methyl acetate was formed regardless of the order of methylation and acetylation.

Consequently, it may now be said that although micromerol is identical with ursolic acid, it may occur together with smaller amounts of a β-amyrin[15] which may be very difficult to remove and which may affect its properties to a striking degree. Pure methylmicromerol or methyl ursolate is very difficult to crystallize, but the impure form crystallizes readily. Apparently the β-amyrin component is concentrated during the isolation of the methyl esters from the crude methylated mixture and further during the purification of the acetylmethyl compound (A), as the melting point depression found corresponds to that produced by not less than 50% added oleanolic acid. T.l.c. is powerless to resolve the problem, as corresponding derivatives of the α- and β-amyrin series are not separated on the plates.

All of the material used for the studies described above was obtained from *yerba buena* gathered from one vacant lot near Seattle and probably representing a botanically homogeneous sample. A more recent collection made at a similar season but covering a considerably wider area around Deception Pass, Washington, has yielded only ursolic acid and not more than a trace of oleanolic acid; so the proportions of these two triterpenes are apparently rather variable within the species.

## Experimental[16]

**Isolation of Micromerol.**—Crude triterpene material was obtained by chilling the concentrated ethereal extract of defatted *yerba buena*.[1] The crude material (9.15 g., representing about 1850 g. of dry plant) was digested with a large amount of ethanol and filtered hot. On cooling, the filtrate deposited a fine precipitate which was recrystallized twice more from ethanol (charcoal) to give 1.49 g. of micromerol, m.p. 281–286° (cap., cor.) lit.,[2] 277°, $[\alpha]^{24}$D +40.5° (c, 0.347; abs. ethanol). A mixture melting point with authentic ursolic acid, m.p. 280–287° (cap., cor.), from bearberry (*Arctostaphylos uva-ursi*)[17] gave m.p. 281–285°, (cap., cor.).

*Anal.* Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.95; H, 10.61.

**Methylmicromerol (Impure).**—Crude terpene mixture (2.0 g.) was dissolved in ethanol (100 ml.) and treated at ice-bath temperature with an excess of diazomethane in ether. After 20 min.,

formic acid and water were added, and the solution was extracted with ether. The ethereal extract was washed with water, 5% sodium hydroxide, and water, dried, and evaporated to give a partially crystalline, greenish-white solid. This was chromatographed on Merck acid-washed alumina (80 g.), and crystalline methylmicromerol (1.26 g.) was obtained from the fractions eluted with benzene. Recrystallization from ethanol gave material, m.p. 110–115°, which after being dried in vacuum at 85° had m.p. 166–168°, lit.,[2] m.p. 167°. T.l.c. showed only one spot. $[\alpha]^{22}$D +67° (c, 0.400; CHCl₃).

*Anal.* Calcd. for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71; –OCH₃, 6.58. Found: C, 78.95; H, 10.55; –OCH₃, 7.37.

**Acetylmethylmicromerol.** (A-Impure).—Methylmicromerol (0.843 g.) prepared as above was treated with acetic anhydride (5 ml.) and pyridine (5 ml.) at room temperature for 18 hr. Water and ether were added, and the ethereal solution was washed with dil. hydrochloric acid, 10% sodium hydroxide, and water. Evaporation of the ether gave a white solid which was crystallized from methanol to give the low-melting form of acetylmethylmicromerol (0.536 g.), m.p. 203–206°, unchanged by recrystallization. $[\alpha]^{24}$D +74.3° (c, 0.635; CHCl₃).

*Anal.* Calcd. for $C_{33}H_{52}O_4$: C, 77.30; H, 10.22; —OCH₃, 5.66. Found: C, 76.97; H, 10.63; —OCH₃, 6.46.

**Acetylmicromerol.**—Crystallized micromerol (0.500 g.) was treated for 48 hr. at room temperature with pyridine (5 ml.) and acetic anhydride (5 ml.) The reaction was worked up as usual to give a white solid which crystallized from ethanol to give a monoacetate (0.379 g.), m.p. 290–293°, (cap., cor.).

*Anal.* Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11. Found: C, 76.85; H, 9.92.

Power and Salway[2] report an unstable acetate m.p. 188°. This is undoubtedly the mixed anhydride of acetylmicromerol and acetic acid.

**Methylacetylmicromerol (B-Pure).**—Acetylmicromerol (0.100 g.), was methylated in ethanol solution with an excess of diazomethane. Work-up in the usual manner and crystallization from ethanol gave product m.p. 245–250°. The melting point was not depressed by authentic acetylmethylursolate.

*Anal.* Calcd. for $C_{33}H_{52}O_4$: C, 77.30; H, 10.22. Found: C, 77.49; H, 10.19.

**Selenium Dioxide Oxidation of Acetylmethylmicromerol.**—Low melting acetylmethylmicromerol (A) (0.225 g.) in acetic acid (12.75 ml.) was refluxed with freshly sublimed selenium dioxide (0.128 g.), for 24 hr. The precipitated selenium was filtered off and the mixture of products was chromatographed on Davidson silica gel using 4:1 petroleum ether–ether containing 1% acetic acid as the eluent. The first crystalline fractions, m.p. 230–250°, were a mixture of two compounds partially separable by fractional crystallization. Two crystallizations from ethanol gave high-melting acetylmethylmicromerol (0.036 mg.) m.p. 245–250°, undepressed by admixture with form B above. The mother liquors showed an ultraviolet spectrum with $\lambda_{max}^{EtOH}$ 243, 252, 260 mμ, corresponding to the $\Delta^{11,13(18)}$-diene of oleanolic acid, but a pure sample was not obtained.

Continued elution of the column gave another crystalline compound (0.016 g.), m.p. 244–246°, $[\alpha]^{25}$D −152° (c, 0.36; CHCl₃), whose ultraviolet spectrum, $\lambda_{max}^{EtOH}$ 278 (ε 14,600), was that of a $\Delta^{9(11),13(18)}$-diene-12,19-dione. A mixture melting point with the dienedione prepared by selenium dioxide oxidation

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(14) E. J. Corey and E. W. Cantrall, *J. Am. Chem. Soc.*, **81**, 1745 (1959).

(15) This compound very probably is oleanolic acid, but since two asymmetric centers are lost in the formation of the oleanolic acid dienedione, it is conceivably a skeletal stereoisomer.

(16) Unless otherwise specified, melting points were taken on a Kofler hot stage and are uncorrected.

(17) C. E. Sando, *J. Biol. Chem.*, **90**, 477 (1931).

TABLE I

|  | x/a | y/b | z/c |  | x/a | y/b | z/c |
|---|---|---|---|---|---|---|---|
| Br | 0.3197 | 0.6960 | 0.1034 | C15 | 0.7636 | 0.5841 | 0.4899 |
| O1 | .1771 | .6684 | .2090 | C16 | .7899 | .5950 | .5497 |
| O2 | .1539 | .8267 | .2103 | C17 | .6970 | .5111 | .5684 |
| O3 | .6580 | .3408 | .5502 | C18 | .5092 | .5097 | .5637 |
| O4 | .8736 | .4027 | .5350 | C19 | .4171 | .6016 | .5933 |
| C1 | .1482 | .5740 | .3418 | C20 | .4552 | .5761 | .6499 |
| C2 | .0906 | .5918 | .2815 | C21 | .6704 | .5771 | .6559 |
| C3 | .1995 | .6599 | .2654 | C22 | .7327 | .4908 | .6265 |
| C4 | .4336 | .6402 | .2627 | C23 | .5233 | .7214 | .2461 |
| C5 | .4565 | .6167 | .3218 | C24 | .4661 | .5486 | .2343 |
| C6 | .6602 | .5986 | .3327 | C25 | .3566 | .4389 | .3299 |
| C7 | .6780 | .6148 | .3894 | C26 | .6212 | .4463 | .4171 |
| C8 | .5685 | .5465 | .4190 | C27 | .4985 | .6963 | .4806 |
| C9 | .3683 | .5689 | .4052 | C28 | .7245 | .4139 | .5540 |
| C10 | .3189 | .5442 | .3444 | C29 | .2141 | .5934 | .5900 |
| C11 | .2317 | .4990 | .4342 | C30 | .3947 | .6607 | .6826 |
| C12 | .3044 | .4853 | .4918 | Cx | .7153 | .2516 | .5328 |
| C13 | .4325 | .5275 | .5020 | Cy | .1535 | .7480 | .1944 |
| C14 | .5788 | .5992 | .4759 | Cz | .1162 | .7505 | .1338 |

of methyl acetyloleanolate showed no depression, and the infrared spectra were identical.

*Anal.* Calcd. for $C_{33}H_{46}O_6$: C, 73.57; H, 8.61. Found: C, 73.79; H, 8.63.

**Methylmicromerol Bromoacetate.**—Methylmicromerol (0.048 g.) in benzene (2.8 ml.) was treated with bromoacetyl bromide (0.1 ml.) and diethylaniline (0.2 ml.) at room temperature for 20 hr. Water and ether were added, and the ethereal solution was washed with water, dilute hydrochloric acid, and water. Evaporation of the ether left a reddish-brown oil which was chromatographed on Davidson silica gel to give a colorless oil which crystallized from pentane. Repeated crystallizations from pentane gave crystals suitable for X-ray studies, m.p. 146–150°.

*Anal.* Calcd. for $C_{33}H_{31}O_4Br$: C, 66.98; H, 8.68; Br, 13.50. Found: C, 67.10; H, 8.63; Br, 13.30.

X-Ray data were collected photometrically from Weissenberg photographs taken on a Nonius camera which was set to integrate in two directions.[18] Levels $h = 0$ to $h = 5$ were taken on a crystal rotating about the *a* axis. The final parameters relative to the conventional origin[19] are given in Table I. The final over-all temperature factor was B = 3.29 Å.²

(18) E. H. Wiebenga and D. W. Smits, *Acta Cryst.*, **3**, 265 (1950).

(19) "International Tables for X-Ray Crystallography," Vol. I, Kynoch Press, Birmingham, England, 1952, p. 105.

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# Organic Sulfur Compounds. IX.[1] Addition of Diethyldithiophosphoric Acid to Dienes

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O,O'-Diethyldithiophosphoric acid (phosphorodithioic acid O,O'-diethyl ester) was added by a radical mechanism to a variety of diolefins to study the factors determining the formation of the various isomeric monoadducts. Selective monoadditions of diethyldithiophosphoric acid to the unsubstituted olefinic bond in the bicycloheptene part of polycyclic diolefins (*endo*–dicyclopentadiene, Aldrin, 2,5-norbornadiene) could be readily carried out, probably in a *cis–exo* manner. On radical addition of diethyldithiophosphoric acid to 1,3-butadiene, 2,3-dimethyl-1,3-butadiene, isoprene, and 2,5-dimethyl-2,4-hexadiene, the thiophosphoryl-thiyl radical preferentially attacked the first carbon atom of the basic 1,3-butadiene skeleton in the first propagation step so as to give the more stable intermediate allylic radical. The latter in turn abstracted a hydrogen from the dithiophosphoric acid at the less highly substituted allylic carbon atom to yield the corresponding 1,4- and 1,2-monoadducts. Addition to piperylene, which proceeds *via* a radical intermediate having two secondary allylic carbon atoms, resulted in almost equal quantities of 1,2- and 1,4-adducts.

## I. Introduction

The addition of crude O,O'-dialkyldithiophosphoric acids (phosphorodithioic acid O,O'-dialkyl esters) to olefins is a much explored reaction[4] since many of the adducts are important oil additives[4-7] and insecticides.[7-11] Additions of crude dialkyldithiophosphoric acids, which are synthesized from alcohols and phosphorus pentasulfide,[12,13] to unsymmetrical olefins yield the normal addition products according to Markownikoff's rule.[4] This is probably the result of the presence of $P_4S_3$ in the crude acid. $P_4S_3$ could reduce the peroxide type catalysts of radical addition.[13]

Bacon and LeSuer[13] added purified O,O'-diethyldithiophosphoric acid (phosphorodithioic acid O,O'-diethyl ester, O,O'-diethylphosphorodithioate) to the monoölefins in an anti-Markownikoff manner. Radical type additions of dialkyldithiophosphoric acids to diolefins, however, remained unexamined. We became interested in the latter reaction in connection with our studies of thiol–diolefin addition reactions.[14-16] At first the reactivity, towards the addition of diethyldithiophosphoric acid, of different types of double bonds in various diolefins containing isolated double bonds was determined and compared to the corresponding thiol additions.[14] Then a study of dialkyldithiophosphoric acid-conjugated diene additions was undertaken to determine whether the "1,2-" or "1,4-mechanism" of these reactions is affected by the same factors as it was in the case of thiol–diene systems.[15,16]

Diethyldithiophosphoric acid was chosen as a reagent because it is readily available and easy to purify.[13] Some polycyclic diolefins—*endo*-dicyclopentadiene, Aldrin, and 2,5-norbornadiene—were selected for the study as diolefins containing isolated double bonds. Simple diolefins—1,3-butadiene, 2,3-dimethyl-1,3-butadiene, isoprene, piperylene, and 2,5-dimethyl-2,4-hexadiene—were used as conjugated diolefins.

## II. Results

It was found that purified diethyldithiophosphoric acid and other dialkyldithiophosphoric acids readily add at room temperature to most of the diolefins examined (Table I). The addition can be catalyzed by

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(4) G. R. Norman, W. M. LeSuer, and T. W. Mastin, *J. Am. Chem. Soc.*, **74**, 161 (1952); U. S. Patent 2,802,856 (1957).

(5) F. B. Augustine, U. S. Patent 2,561,773 (1951); 2,665,295 (1954); 2,528,732 (1950).

(6) C. W. Georgi, "Motor Oils and Engine Lubrication," Reinhold Publishing Corp., New York, N. Y., 1950, p. 167.

(7) R. R. Whetstone and C. A. May, U. S. Patent 2,767,206 (1956).

(8) G. A. Johnson, J. H. Fletcher, K. G. Nolan, and J. T. Cassaday, *J. Econ. Entomol.*, **45**, 279 (1952).

(9) G. Matolcsy and A. Oswald, *Magy. Kém. Folyoirat*, **60**, 348 (1954); *Novénytermelés*, **4**, 351 (1955).

(10) J. T. Cassaday, U. S. Patent 2,578,652 (1951).

(11) R. L. Metcalf, "Organic Insecticides," Interscience Publisher, Inc., New York, N. Y., 1955, pp. 251–315.

(12) T. W. Mastin, G. R. Norman, and E. A. Weilmuenster, *J. Am. Chem. Soc.*, **67**, 1662 (1945).

(13) W. E. Bacon and W. M. LeSuer, *ibid.*, **76**, 670 (1954).

(14) A. A. Oswald and F. Noel, *J. Org. Chem.*, **26**, 3948 (1961).

(15) A. A. Oswald, B. E. Hudson, Jr., G. Rodgers, and F. Noel, *ibid.*, **27**, 2439 (1962).

(16) A. A. Oswald, K. Griesbaum, W. A. Thaler, and B. E. Hudson, Jr., *J. Am. Chem. Soc.*, **84**, 3897 (1962).

### TABLE I
### ADDITION OF DIETHYLDITHIOPHOSPHORIC ACID TO DIOLEFINS[a]

| Name of diolefin used | Without added catalyst | In the presence of cumene hydroperoxide[c] | With ultraviolet irradiation[d] |
|---|---|---|---|
| | Diethyldithiophosphoric acid reacted, %[b] | | |
| Dicyclopentadiene | 64 | 67 | 76 |
| Aldrin | 28 | 42 | 63 |
| Norbornadiene | 99 | ..[e] | .. |
| 2,3-Dimethyl-1,3-butadiene | 91 | 93 | .. |
| Isoprene | 75 | 90 | .. |
| 2,5-Dimethyl-2,4-hexadiene | 47 | 61 | 57 |

[a] n-Heptane solutions (50 ml. each) containing diethyldithiophosphoric acid and a diolefin, both in 0.5 mole/l. concentration, were stirred for 3 hr. at room temperature in the presence of air. [b] Determined on the basis of the potentiometric titration of the acid left. [c] About 0.02 mole/l. of cumene hydroperoxide was added to the reaction mixture. [d] Round-bottom reaction flask of quartz was irradiated from 20-cm. distance during the reaction. [e] Very exothermic reaction occurred on the addition of the hydroperoxide.

peroxides or ultraviolet light. The distribution of the isomeric products of the catalyzed reactions are the same as those of the noncatalyzed reactions. These facts indicate that the reaction proceeds by a chain mechanism.

Most of the adducts were purified either by crystallization from ethanol or by distillation in vacuo (Table II). Simple vacuum fractionation did not result in a complete separation of the isomeric monoadducts. They could be separated, however, on a capillary gas chromatography (g.c.) column coated with a n-tridecyl polyethylene glycol ether. Identification of g.c. peaks was possible by semiquantitative determination of the isomers in the product mixtures by nuclear magnetic resonance spectroscopy (n.m.r., Table III). The n.m.r. spectra of diethyldithiophosphoric acid adducts generally resemble those of the corresponding thiol adducts.[14-16] There is one special characteristic of the dithiophosphoric acid adducts: the proton(s) on the α-carbon of the S-alkyl group of the O,O'-dialkyl-S-alkyl dithiophosphate products show an additional splitting of 15 c.p.s. due to electron coupling to the phosphorus nucleus ($I = 1/2$) through the thiolester bond. The O-ethyl groups of the phosphate ester products show a triplet for the methyl protons and a double quartet for the methylene protons. The methylene protons are split into the usual 7-c.p.s. triplet by the methyl protons; this triplet is then split by spin coupling to the phosphorus through the oxygen (10 c.p.s.).

The infrared spectra of the products were also studied (Table IV) but gave little help in structure determination because of the very strong absorption bands of the P—O—ethyl stretching vibration[17a] at about 9.8 μ and of an unassigned vibration at 10.4 μ obscured the out of plane hydrogen deformation vibrations of trans-disubstituted ethylenes[17b] and vinyl compounds.[17c] Another very strong band, probably due to the P=S stretching vibration,[17d] could interfere with possible out of plane hydrogen deformation vibrations of cis-disubstituted ethylenes.[17e]

(17) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, N. Y., 1959: (a) p. 317; (b) p. 45; (c) p. 49; (d) p. 322; (e) p. 48; (f) pp. 42–43; (g) pp. 35–42.

### TABLE II
### DIETHYLDITHIOPHOSPHORIC ACID–DIENE ADDUCTS

| Adduct no. | Starting diene | Adduct formula | Conversion at room temperature % | After hr. | With ultraviolet | Yield,[a] % | Isomers 1,2- | 1,4- | 4,1- | B.p.[b] °C (mm.) [M.p.] | Calc. C | Calc. H | Calc. P | Calc. S | Found C | Found H | Found P | Found S |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| II | endo-Dicyclopentadiene | C14H23O2PS2 | 90 | 3 | No | 85 | (One major component) | | | .... | 53.14 | 6.69 | 9.79 | 20.27 | 52.95 | 6.79 | 9.52 | 20.20 |
| IV | Aldrin | C16H19Cl6O2PS2 | 87 | 15 | No | 50 | | | | .... | 34.86 | 3.47 | 5.62 | 11.64 | 34.89 | 3.49 | 5.65 | 11.57 |
| VIII | 2,5-Norbornadiene[c] | C15H30P2S4O4[c] | 90 | 3 | No | 51 | | | | [89.5–90.5] | 38.78 | 6.51 | 13.33 | 27.61 | 38.74 | 6.53 | 13.40 | 27.56 |
| IX | 1,3-Butadiene | C8H17O2PS2 | 95 | 8 | Yes[d] | 45 | 6 | 94 | | [96.5–97.5] | 39.99 | 7.13 | 12.88 | 26.69 | 40.08 | 7.37 | 12.52 | 27.32 |
| X | 2,3-Dimethyl-1,3-butadiene | C10H21O2PS2 | 100 | 24 | Yes[d] | 77 | 4 | 96 | | 75–76 (1) | 44.76 | 7.88 | 11.54 | 23.90 | 44.62 | 7.74 | 11.37 | 24.44 |
| | Isoprene | C9H19O2PS2 | 100 | 24 | Yes[d] | 78 | .. | (90) | | 127–128 (2) | 42.50 | 7.52 | 12.17 | 25.22 | 42.34 | 7.45 | 11.90 | 25.40 |
| XI–XIII | Piperylene | C9H19O2PS2 | 98 | 10 | Yes[d] | 86 | (50) | (40) | (10) | 100–103 (0.5); 110–113 (1) | 42.50 | 7.52 | 12.17 | 25.22 | 42.60 | 7.67 | 12.26 | 25.43 |
| XIV | 2,5-Dimethyl-2,4-hexadiene | C12H25O2PS2 | 80 | 72 | Yes[d] | 86 | (85) | (15) | | 128–130 (1) | 48.63 | 8.50 | 10.44 | 21.64 | 48.25 | 8.44 | 10.17 | 21.55 |

[a] Based on conversion. [b] Uncorrected. [c] Diadduct. [d] Vycor reaction flask.

TABLE III

PARAMETERS OF NUCLEAR MAGNETIC RESONANCE SPECTRA OF DIETHYLDITHIOPHOSPHORIC ACID–DIENE ADDUCTS

$$\begin{array}{c}CH_3CH_2O\\ \diagdown\\ P-S-V-CX=CY-Z\\ \diagup \;\; \|\\ CH_3CH_2O \;\; S\end{array}$$

| Adduct no. | Starting diene | Adduct type | In general formula of adduct | | | | | Isomer by g.c. (n.m.r.) % | Chemical shifts of structural units, p.p.m., downfield from tetramethylsilane, internal reference s. singlet, d. doublet, q. doublet, q. quartet, m, multiplet (D double) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | X | Y | Z | V | | | $CH_3$— | $-CH_2-O-P(S)-S-V-$ | $-CX=$ | $=CY-$ | $-Z$ |
| VI | 1,3-Butadiene | 1,4 | H | H | $CH_3$ | $CH_2$ | 94 | t 1.30$^a$ | Dq 4.12$^{a,b}$ | m 4.9–6.1 | m 4.9–6.1 | d 1.67$^e$ |
| | 2,3-Dimethyl-1,3-butadiene | 1,4 | $CH_3$ | $CH_3$ | $CH_3$ | $CH_2$ | 96 | t 1.30$^a$ | Dq 4.13$^{a,b}$ | d 3.51$^d$ | s 1.65$^f$ | s 1.70$^f$ |
| VII | Isoprene | 1,4 | $CH_3$ | H | $CH_3$ | $CH_2$ | 82 | t 1.30$^a$ | Dq 4.12$^{a,b}$ | d 3.47$^d$ | s 1.71 | d 1.61$^a$ |
| | | 4,1 | H | $CH_3$ | $CH_3$ | $CH_2$ | 18 | | | | | |
| VIII | Piperylene | 1,4 | H | H | $CH_2$–$CH_3$ | $CH_2$ | (40) | t 1.32$^a$ | Dq 4.13$^{a,b}$ | Dd 3.46$^{c,d}$ | m 5.2–5.8 | m 1.75–2.2, t 0.97$^a$ |
| IX | | 1,2 | $CH_3$ | H | $CH_3$ | $CH_2$–$CH_2$ | (50) | t 1.32$^a$ | Dq 4.13$^{a,b}$ | Dt 2.87,$^{c,e}$ m 2.2–2.5 | m 5.2–5.8 | d 1.66$^e$ |
| X | | 4,1$^h$ | H | H | $CH_3$ | $CH(CH_3)$ | (10) | | | | | d 0.96$^a$ |
| XI | 2,5-Dimethyl-2,4-hexadiene | 1,4$^h$ | $CH_3$ | H | $C(CH_3)_2$ | $C(CH_3)_2$ | (15) | | | d 1.43 | | |
| | | 1,2 | H | H | $CH_3$ | $C(CH_3)_2$–$CH_2$ | (85) | t 1.32$^a$ | Dq 4.15$^{a,b}$ | s 1.44, d2.42$^a$ | t 5.25$^a$ | s 1.74$^i$ |

$^a$ $J = 7$ c.p.s.   $^b$ $J_{P-O-CH_2} = 10$ c.p.s.   $^c$ $J = 6$ c.p.s.   $^d$ $J_{P-S-CH_2} = 15$ c.p.s.   $^e$ $J_{CH-CH_2} = 5$ c.p.s.   $^f$ The specific assignment is arbitrary.   $^g$ Triplets are enhanced toward high field.   $^h$ Definite observation of n.m.r. signal is impossible because of the low concentration of the isomer.   $^i$ Due to the protons of the methyl group.

**Diolefins with Isolated Double Bonds. Dicyclopentadiene.** An equimolar amount of diethyldithiophosphoric acid spontaneously adds to *endo*-dicyclopentadiene[18] (I) at room temperature to yield a light yellow liquid adduct. When a mixture cf two moles of diethyldithiophosphoric acid and one mole of dicyclopentadiene reacted in the absence of a catalyst, one mole of the dithiophosphoric acid was recovered unchanged. This showed that normally only one double bond of the dicyclopentadiene takes part in the addition reaction to form S-5 or/and 6-(3a,4,5,6,7,7a-hexahydro-4,7-methano)indenyl O,O'-dialkyldithiophosphate (or phosphorodithioate), II.

Capillary g.c. indicated two major components. Comparison of the n.m.r. and infrared spectra (Tables III, IV) with those of dicyclopentadiene and of the 4-chlorobenzenethiol–dicyclopentadiene monoadduct indicated that in both cases addition of the thiol group to the bicycloheptene double bond had occurred. The triplet signal at 5.9 p.p.m. downfield from the tetramethylsilane internal reference, originating from vinylic hydrogens of the bicycloheptene part of the dicyclopentadiene molecule, was absent. The singlet signal of the vinylic hydrogens of the cyclopentenyl moiety at about 5.5 p.p.m., on the other hand, was retained in the adduct. The *endo* structure of the dicyclopentadiene ring system was probably preserved.
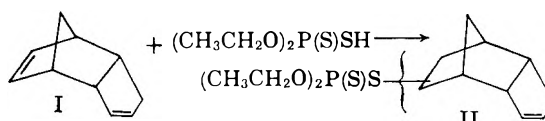


**Aldrin.**—An equimolar amount of diethyldithiophosphoric acid readily reacts with Aldrin (III), a widely used insecticide,[19] in a spontaneous, somewhat exothermic reaction to yield a crystalline adduct. The reaction can be catalyzed by a peroxide or ultraviolet light. A second molecule of diethyldithiophosphoric acid could not be added to the Aldrin molecule without catalysis.

N.m.r. spectra showed that the vinylic protons which gave signals at a low field (6.35 p.p.m.) in Aldrin were absent in both the diethyldithiophosphoric acid and the 4-chlorobenzenethiol adduct. Therefore, it was assumed that diethyldithiophosphoric acid, like thiols,[14,20] adds to Aldrin in a *cis–exo*-manner to yield *exo* - 2 - diethylthiophosphorylmercapto - *endo* - 5,6,7,-
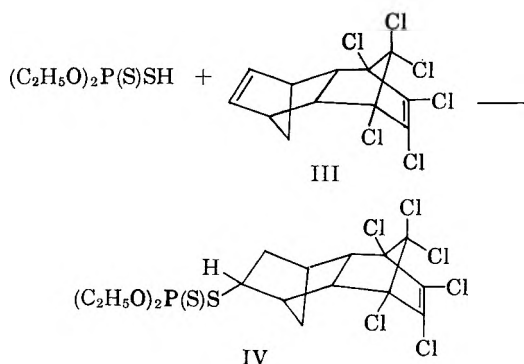
(18) A. Etart and P. Lambert, *Compt. rend.,* **112,** 945 (1891).

(19) C. W. Kearns, C. J. Weinman, and G. C. Decker, *J. Econ. Entomol.,* **42,** 127 (1949); R. E. Lidov, U. S. Patent 2,635,979.

(20) S. J. Cristol and R. P. Arganbright, *J. Am. Chem. Soc.,* **79,** 6039 (1957).

8,9,9 - hexachloro - *exo - endo* - 1,2,3,4,4a,5,8,8a - octa-hydro-1,4,5,8-dimethanonaphthalene, IV.

**Norbornadiene.**—The synthesis of a monoadduct of diethyldithiophosphoric acid and norbornadiene (V) has been described in a U. S. patent.[7] Monoaddition of 4-toluenethiol to norbornadiene by Cristol, Brindell, and Reeder[21] resulted in the formation of *exo*-5-norbornen-2-yl 4-tolyl sulfide and 3-nortricyclyl 4-tolyl sulfide in a 2:3 ratio.

We found that the synthesis of the diethyldithiophosphoric acid–norbornadiene monoadduct yields two major components in about 2:1 ratio.

On the addition of a second mole of diethyldithiophosphoric acid, the larger component gave a crystalline diadduct. This indicated that the main product of the monoaddition was probably O,O'-diethyl-S-*exo*-5-norbornen-2-yl dithiophosphate (phosphorodithioate) (VI) and the minor product was O,O'-diethyl-S-3-nortricyclyl dithiophosphate (VII).



VIII      VI      VII
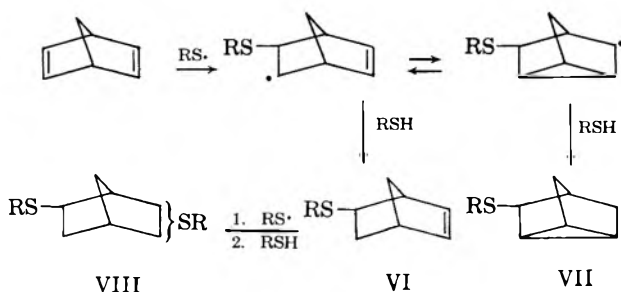
The sharp melting point of the diadduct obtained indicated a uniform compound (VIII). Elemental analyses (Table II), n.m.r., and infrared spectra (Table IV) of the compound supported the formation of a diadduct with a concurrent disappearance of unsaturation. The exact position of the addition of the second diethyldithiophosphorylthiyl radical could not be determined.

A similar crystalline diadduct of benzenethiol to norbornadiene was also obtained.

**Diolefins with Conjugated Double Bonds.**—On radical addition of various thiols to conjugated diolefins it was found that the adduct is derived from the intermediate allylic radical at the less highly substituted carbon atom.[15,16] It was of interest to determine whether the same rule holds for additions of dialkyl-dithiophosphoric acids.

**Butadiene.**—Addition of an equimolar amount of diethyldithiophosphoric acid to 1,3-butadiene could be catalyzed by ultraviolet irradiation. Capillary g.c. showed that the adduct was 95% one isomer.

The disubstituted ethylene structure of the adduct is clearly indicated by its n.m.r. spectrum (Table III). Two *trans*-vinyl protons show up as an incompletely resolved multiplet representing the MN portion of a $A_2MNX_3$ spin system.[22] The signal of the methylene protons on the carbon α to the sulfur is split into a double doublet with 6 c.p.s. coupling to the vinyl proton on the adjacent carbon, and 15 c.p.s. coupling to phosphorus through the sulfur. The methyl protons of the 2-butenyl group can be clearly recognized as a doublet at about 1.7 p.p.m.

(21) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Am. Chem. Soc.*, **80**, 635 (1958).

(22) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 242.

On the basis of g.c. and n.m.r. analyses, it is assumed that the addition of diethyldithiophosphoric acid to butadiene took place in an essentially 1,4-*trans* manner to yield O,O'-diethyl-S-2-buten-1-yl dithiophosphate (phosphorodithioate) (IX).
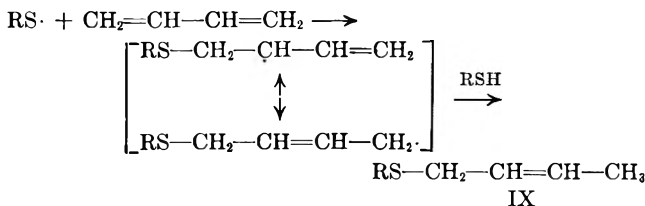


**Dimethylbutadiene.**—Capillary gas chromatography of the 1:1 adduct of diethyldithiophosphoric acid and 2,3-dimethyl-1,3-butadiene showed that the main isomer was formed in more than 96% yield. This was shown by n.m.r. to be the 1,4-adduct, O,O-diethyl-S-(2,3-dimethyl)buten-1-yl dithiophosphate (Table III). No vinylic protons resulting from 1,2-addition could be observed in the spectra. The virtual absence of 1,2-addition is also indicated by the doublet methylene signal which is split only by the phosphorus. The protons of the three methyl groups of the adduct show two signals, one of them of double intensity. The less intensive signal is probably due to the methyl group on the carbon α to the methylene, since that methyl group is situated differently from the other two methyl groups. The absence of a =C—H stretching band and the weak C=C stretching band[17f] (Table IV) in the infrared spectrum indicate that the 1,2-isomer is not present.

**Isoprene.**—Capillary gas chromatography (Table III) of the undistilled adduct of diethyldithiophosphoric acid and isoprene (2-methyl-1,3-butadiene) showed essentially two components present in about 1:4 ratio. N.m.r. analyses (Table II) indicated that the main component was the 1,4-adduct (X). The formation of this compound could be rationalized by the following mechanism.
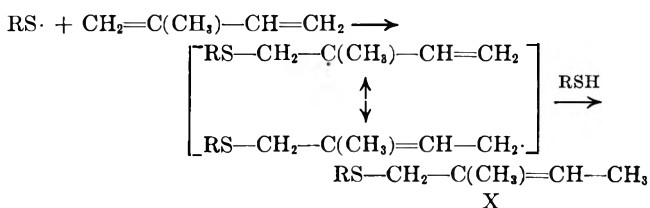


Methylene protons of the 1,4-adduct are represented by a doublet with a 15 c.p.s. coupling constant to phosphorus through sulfur. One methyl group signal appears as a singlet while the other is split into a doublet by the single vinyl proton. The presence of a possible "reverse," 4,1-adduct, in contrast to the reverse-adducts of thiol-isoprene additions,[16] could not be ascertained by n.m.r.

No terminal vinyl unsaturation corresponding to a 1,2- or 4,3-adduct could be observed in the n.m.r. spectrum. The infrared spectrum supports the proposed structures by excluding the presence of the 1,2- or 4,3-adducts. The absence of a distinct =C—H stretching band[17c] and the weak C=C stretching band[17f] indicate that these structural units (vinyl or unsaturated methylene group) are absent in the product.

N.m.r. indicated changes on the distillation *in vacuo* of the adduct which could not be interpreted.

## Table IV
### Infrared Absorption Spectra of Diethyldithiophosphoric Acid–Diene Adducts

| Adduct no. | Starting diene | Isomer type | =C—H | C=C | | | | | Characteristic Fingerprint region (including P–O–Et) |
|---|---|---|---|---|---|---|---|---|---|
| I | Dicyclopentadiene | Monoadduct | 3.30 s | 6.20 w | 8.04 i | | 8.60 s | | 9.10 s |
| II | Aldrin | exo-2- | | 6.23 s | 8.00 m | 8.48 s | 8.58 m | 8.71 w | 9.00 s |
| V | Norbornadiene | Diadduct | | | 8.10 m | 8.43 m | 8.58 s | 8.75 i | 9.10 s |
| VI | 1,3-Butadiene | 1,4- | 3.32 i | 6.00 m | 8.16 s | | 8.63 s | | 9.10 s |
| | 2,3-Dimethyl-1,3-butadiene | 1,4- | | 6.00 m | 8.12 m | 8.38 m | 8.60 s | | 9.10 s |
| VII | Isoprene | 1,4- | 3.29 i | 6.02 m | 8.10 m | 8.29 m | 8.62 s | | 9.13 s |
| VIII–IX | trans-Piperylene | 1,2- and 1,4- | 3.31 i | 6.01 w | 8.18 m | | 8.60 s | | 9.10 s |
| XI | 2,5-Dimethyl-2,4-hexadiene | 1,2- | 3.26 i | 6.00 m | 8.25 m | 8.38 m | 8.60 s | 8.92 s | 9.10 s |
| | (Diethyldithiophosphoric acid reference) | | 4.05 s[a] | | | | 8.60 s | | 9.10 s |

[a] Due to SH stretching.

**Piperylene.**—As a starting material for the addition, an equimolar amount of pure *trans*-piperylene (*trans*-1,3-pentadiene) was used. After the addition of 95% of the calculated amount of diethyldithiophosphoric acid, the unchanged piperylene was isomerized. Separation of the monoadducts by capillary g.c. showed two major peaks which are not completely separated and a small peak of much shorter retention time. Possible configurational isomers of the addition products were apparently not separated.

N.m.r. (Table III) indicated that the two major components of the product mixtures were the 1,2- and 1,4-adducts (XI and XII). The 1,4-isomer showed a double doublet similar to that of the 1,4-butadiene adduct for the methylene protons. The methyl protons of this isomer were split into a triplet by the adjacent methylene protons. The 1,2-isomer could be easily recognized from the doublet signal of the single methyl group of the pentenyl moiety. One of the two methyl doublets of the 4,1-adduct is almost obscured by the methyl triplets of the ethyloxy groups while the other virtually coincides with the methyl doublet of the 1,2-isomer. No significant amount of 4,3-adduct was formed since signals of terminal vinylic protons were absent from the infrared (Table IV) and n.m.r. spectra of the product.

The addition of diethyldithiophosphoric acid to piperylene apparently proceeds in the same manner as the addition of thiols. The diethylthiophosphorylmercapto radical preferentially adds to the first carbon atom of piperylene to yield the more stable allylic radical intermediate, having both of its reactive positions at a secondary carbon. Subsequent hydrogen abstraction from the dithiophosphoric acid then occurs at these carbons to yield the isomeric O,O'-diethyl-S-pentenyl dithiophosphates (phosphorodithioates), XI and XII.
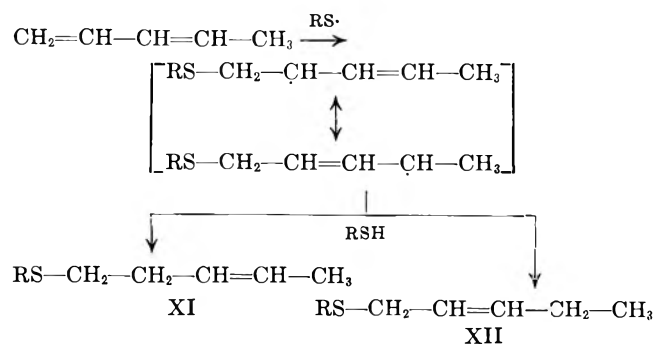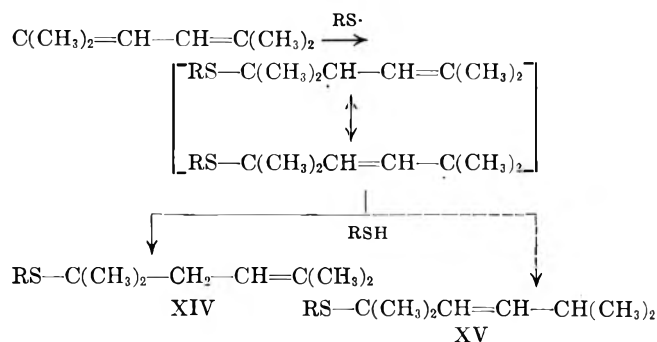
The small amount of 4,1-adduct (XIII) probably results from addition to carbon four of piperylene, followed by hydrogen abstraction at the primary carbon.

$$CH_3—CH=CH—CH=CH_2 \xrightarrow{RS\cdot}$$

$$\begin{bmatrix} RS—CH(CH_3)—\dot{C}H—CH=CH_2 \\ \updownarrow \\ RS—CH(CH_3)—CH=CH—CH_2\cdot \end{bmatrix} \xrightarrow{RSH}$$

$$RS—CH(CH_3)—CH=CH—CH_3$$
$$XIII$$
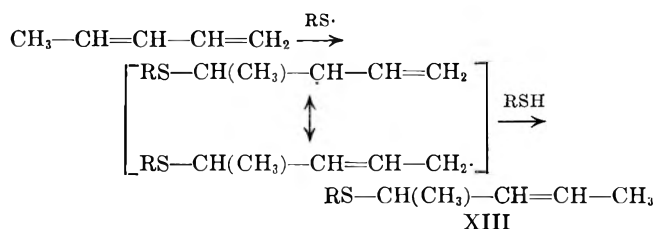
**Dimethylhexadiene.**—The addition of diethyldithiophosphoric acid to 2,5-dimethyl-2,4-hexadiene, like that of thiols, required ultraviolet light initiation and a longer reaction time. Gas chromatography of the product showed again a single major component.

Examination of the monoadduct by n.m.r. (Table III), in contrast to the other diene adducts examined, indicated that the main isomer was the 1,2-adduct (XIV). The spectrum showed a characteristic doublet at 2.42 p.p.m. for the methylene protons which are expected to be absent in the 1,4-adduct (XV). The vinyl proton resonance pattern also showed a characteristic triplet at 5.25 p.p.m. as a result of spin splitting by the adjacent methylene group. The isomeric dimethylhexenyl structures could be distinguished on the basis of the relative chemical shifts and splittings of their terminal methyl group signals. The two methyl groups on the unsaturated carbon atom of the 1,2-adduct produced separate singlet peaks as a result of their *cis* and *trans* locations with respect to the single vinyl proton. The signal of the corresponding methyl groups of the 1,4-adduct appears at a higher field and is split into a doublet by the single methine proton. The other signals of the 1,4-adduct cannot be observed in the spectrum because of the low concentration of this isomer. On the basis of the n.m.r. analysis it is con-

$$CH_2=CH—CH=CH—CH_3 \xrightarrow{RS\cdot}$$

$$\begin{bmatrix} RS—CH_2—\dot{C}H—CH=CH—CH_3 \\ \updownarrow \\ RS—CH_2—CH=CH—\dot{C}H—CH_3 \end{bmatrix}$$

$$\xrightarrow{RSH}$$

$$RS—CH_2—CH_2—CH=CH—CH_3 \qquad\qquad$$
$$XI \qquad\qquad RS—CH_2—CH=CH—CH_2—CH_3$$
$$XII$$

$$C(CH_3)_2=CH—CH=C(CH_3)_2 \xrightarrow{RS\cdot}$$

$$\begin{bmatrix} RS—C(CH_3)_2CH—CH=C(CH_3)_2 \\ \updownarrow \\ RS—C(CH_3)_2CH=CH—C(CH_3)_2 \end{bmatrix}$$

$$\xrightarrow{RSH}$$

$$RS—C(CH_3)_2—CH_2—CH=C(CH_3)_2 \qquad\qquad$$
$$XIV \qquad\qquad RS—C(CH_3)_2CH=CH—CH(CH_3)_2$$
$$XV$$

absorption peaks, microns, vs, very strong, m, medium, w, weak, i, inflection
above eight microns
stretching vibrations)        =C—H deformation region (including P—S stretching)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 9.60 vs | 9.80 vs | 10.45 vs | | 11.15 m | 11.87 i | 12.15 vs | | 13.55 s | 14.95 vs | 15.15 vs |
| 9.15 m | 9.27 m | 9.56 vs | 9.80 vs | 10.40 vs | 10.96 s | 11.21 m | 11.55 w | 12.03 s | 12.28 s | 14.48 m | 14.70 m | 15.15 vs |
| | | 9.56 vs | 9.80 vs | 10.40 vs | | 11.06 m | 11.58 w | 12.10 s | 12.30 s | | 14.88 vs | 15.10 vs |
| | | 9.60 vs | 9.85 vs | 10.45 vs | | | | 12.10 s | | | 14.90 vs | 15.15 vs |
| | | 9.60 vs | 9.80 vs | 10.45 vs | | 11.25 i | | 12.10 vs | | | 14.95 vs | 15.23 vs |
| | | 9.60 vs | 9.80 vs | 10.45 vs | | 11.15 i | 11.50 w | 12.20 vs | | | 14.95 vs | 15.23 vs |
| | | 9.60 vs | 9.80 vs | 10.45 vs | | | | 12.10 vs | 12.30 vs | | 14.85 vs | 15.20 vs |
| | | 9.60 vs | 9.80 vs | 10.45 vs | | | 11.70 m | 12.15 vs | 12.30 vs | | 14.95 vs | 15.20 vs |
| | | 9.60 vs | 9.80 vs | 10.50 vs | | | 11.85 vs | | | 13.00 vs | 14.95 vs | 15.15 vs |

cluded that the main addition product is the 1,2-isomer, O,O'-diethyl-S-2-(2,5-dimethyl-4-hexen)yl dithiophosphate, XIV. Its formation can be explained by the mechanism on p. 1266, bottom of col. 2.

## III. Discussion

Diethyldithiophosphoric acid and some other dialkyldithiophosphoric acids (e.g., O,O'-dialkylphosphorodithioates) can be readily and selectively added by a radical mechanism to nonconjugated diolefins having a reactive unsubstituted bicyclo[2.2.1]heptene group. The n.m.r. spectra of these monoadducts were very similar to those of the corresponding thiol monoadducts. Since the stereochemistry of the thiol adducts is known,[13,20,21,23] it is suggested that the additions of diethyldithiophosphoric acid, like thiol additions, occurred in a cis–exo manner without any inversion.



As expected two moles of diethyldithiophosphoric acid readily add to a mole of 2,5-norbornadiene, a diene which has both olefinic bonds in a bicycloheptene ring.

The course of radical additions of diethyldithiophosphoric acid to conjugated diolefins is apparently affected by the stability and the substitution of the intermediate allylic radical formed on radical addition to the diene. The thiophosphorylthiyl radical preferentially adds to the first carbon atom of unsymmetrically substituted butadienes so as to yield the more stable allylic radical. The latter than abstracts a hydrogen from the thiol predominantly at the less highly substituted of the two allylic positions.

The above course of the addition is similar to that of thiols examined earlier.[14,15] The hydrogen abstraction step of both reactions requires a significant activation energy.[24] Therefore, according to Hammond's correlation[25] the stability of the final product should make an important contribution to that of the transition state. Indeed the thermodynamically more stable olefinic product is formed in such reactions, i.e., the

allylic radical is considerably reorganized in the transition state and the product is derived from its less contributing resonance form.

## Experimental

**Materials.**—The diethyldithiophosphoric acid used was purified before use according to the method of Bacon and LeSuer.[13] Dimethyl- and diisopropyldithiophosphoric acids were purified by distillation in vacuo. Dicyclopentadiene of Enjay Chemical Co., bicyclo[2.2.1]2,5-heptadiene and 2,5-dimethyl-2,4-hexadiene of Matheson, 2,3-dimethyl-1,3-butadiene of Houdry Corp., and isoprene of Eastman were redistilled before use. Aldrin, a 95% pure experimental sample of Shell Chemical Corp., was recrystallized from n-heptane and then from methanol. The purified compound had a melting point of 101–102°. A commercial mixture of cis- and trans-piperylenes of Enjay was custom purified by Columbia Organic Chemicals Co. to yield 98% trans-piperylene, containing 2% cyclopentene but free from cis-piperylene. Benzenethiol was obtained from Matheson Co., Inc. and was distilled in vacuo under nitrogen before use. The cumene hydroperoxide catalyst used was from Hercules Powder Co. and had a hydroperoxide content of 81% according to the thiol method.[26] The n-heptane and ethanol solvents were 99%+ grade.

**Methods of Analyses.**—The n.m.r. spectra were recorded with a Varian Model A-60 proton resonance spectrometer. The liquid products were run as such, the solid compounds in carbon tetrachloride solution. Tetramethylsilane was used as an internal reference. The infrared spectra were obtained using a Baird, Model B, recording spectrophotometer. Purity of isoprene, 2,3-dimethyl-1,3-butadiene, piperylene and norbornadiene was checked by g.c. at room temperature using a Perkin–Elmer, Model D, vapor fractometer with a 2-m. "E" column (2,4-dimethylsulfolane). The other dienes and the monoadducts were separated at 150° by capillary g.c., on a Barber-Coleman IDS, Model 20, chromatograph using a 50-ft. column coated with a n-tridecyl polyethylene glycol ether obtained from 30 moles of ethylene oxide per mole of n-tridecyl alcohol. The progress of the addition reactions was determined by potentiometric titration of the diethyldithiophosphoric acid in the mixtures with silver nitrate using a silver-glass electrode pair. To detect any post-isomerization of the liquid adducts, they were analyzed before washing with aqueous sodium carbonate solution and before distillation in vacuo.

**Addition of Diethyldithiophosphoric Acid to endo-Dicyclopentadiene.**—Elemental analyses of the adducts are given in Table II. Characteristic infrared absorption peaks are recorded in Table IV.

For the removal of the unchanged diethyldithiophosphoric acid, the solution of the reaction mixture in 20 ml. of benzene was washed with 50 ml. of 5% aqueous sodium carbonate solution and then with 30 ml. of water. The organic phase was dried over anhydrous sodium sulfate and the benzene, unchanged dicyclopentadiene, and any other volatile component were removed by distillation. The remaining product (27 g., 85%) is

(23) N. Kharasch, ed., "Organic Sulfur Compounds I," Chap. 13 by G. Brindell and S. J. Cristol, "Additions of Thiols and Related Substances to Bridged Bicyclic Olefins," Pergamon Press, New York, N. Y., 1961, pp. 121–133.

(24) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 314.

(25) G. S. Hammond, J. Am. Chem. Soc., 77, 334 (1955).

(26) A. A. Oswald, F. Noel, and A. J. Stephenson, J. Org. Chem., 26, 3969 (1961).

a light yellow, mobile liquid of $n^{20}$D 1.5452, with a characteristic phosphate ester smell. Capillary g.c. analysis indicated that it contains two major components in two to three ratio.

*Saponification Value.* Calcd. for the monoadduct, $C_{14}H_{21}O_2PS_2$: 316. Found: 314.

In another experiment, 9.3 g. (0.05 mole) of diethyldithiophosphoric acid was added to 3.3 g. (0.025 mole) of dicyclopentadiene in the same manner. Three hours after the addition 48% of the dithiophosphoric acid had reacted. This percentage remained essentially unchanged during 3 days standing of the reaction mixture at room temperature. Work-up of the reaction mixture in a manner described above yielded the monoadduct.

Dimethyl- and diisopropyldithiophosphoric acid reacted with dicyclopentadiene in a similar manner to yield liquid monoadducts.

**Addition of Diethyldithiophosphoric Acid to Aldrin.**—To a solution of 18.2 g. (0.05 mole) of Aldrin (m.p. 101–102°) in 50 ml. of n-heptane, 9.3 g. (0.05 mole) of diethyldithiophosphoric acid was added. The reaction mixture was allowed to stand for 16 hr. A subsequent titration of a sample with potassium hydroxide in the presence of neutral red indicator showed that only 12.5% of the diethyldithiophosphroic acid remained unchanged. The diethyldithiophosphoric acid monoadduct of Aldrin crystallized from the solution on cooling. The crude crystals were recrystallized from ethanol to yield 13.8 g. (50%) of *exo*-2-diethylthiophosphorylmercapto - *endo* - 5,6,7,8,9,9 - hexachloro-*exo-endo*-1,2,3,4,4a,5,8 - dimethanonaphthalene, II, as colorless crystals of m.p. 89.5–90.5°.

A similar procedure starting with 7.9 g. (0.05 mole) of dimethyl dithiophosphoric acid and 18.2 g. (0.05 mole) of Aldrin yielded 14.3 g. (55%) of *exo*-2-dimethylthiophosphorylmercapto-*endo*-5,6,7,8,9,9-hexachloro-*exo-endo*-1,2,3,4,4a,5,8,8a-octahydro-1,4,-5,8-dimethanonaphthalene, m.p. 112–113.5°.

*Anal.* Calcd. for $C_{14}H_{15}Cl_6O_2PS_2$: C, 32.08; H, 2.88; Cl, 40.59; O, 6.11; P, 6.10; S, 12.24. Found: C, 32.18; H, 2.89; Cl, 40.80; O, 6.10; P, 5.94; S, 12.60.

**Addition of Diethyldithiophosphoric Acid to Norbornadiene.**—To 9.2 g. (0.1 mole) of norbornadiene, 37.4 g. (0.02 mole) of diethyldithiophosphoric acid was added in the manner described in the previous example. The spontaneous exothermic reaction was 90% completed in 3 hr. On further standing, partial crystallization of the mixture occurred. The crystals were filtered off and recrystallized from ethanol to yield 23.7 g. (51%) of the colorless diadduct, m.p. 97.5–99°.

In another experiment equimolar amounts of norbornadiene and diethyldithiophosphoric acid were reacted in the same manner. Titration of the reaction mixture indicated that practically all the diethyldithiophosphoric acid reacted within an hour. A slightly yellow liquid adduct of $n^{20}$D 1.5236 was obtained which according to g.c. consisted 70% of one and 30% of another isomer. G.c. analysis of the liquid part of the diaddition reaction showed the presence of the smaller component only.

**Addition of Benzenethiol to Norbornadiene.**—To 22 g. (0.2 mole) of benzenethiol, 9.2 g. (0.1 mole) of norbornadiene was

added in the manner described in the previous example. However, the sequence of addition was reversed to repress the formation of 3-nortricyclyl 4-tolyl sulfide by the excess of thiol present. After the completion of the addition, the mixture was heated to 70° and kept at that temperature for 1 hr. A subsequent thiol determination indicated that only 28% of the original thiol was still present unreacted in the reaction mixture.

On scratching and cooling, crystals were formed in the reaction mixture. To complete the crystallization, the mixture was kept and recrystallized from n-heptane. In this manner, 10.8 g. (24%) of bisphenylmercaptonorbornadiene, m.p. 122–123° was obtained as colorless, large rhombic crystals.

*Anal.* Calcd. for $C_{19}H_{20}S_2$: C, 73.03; H, 6.45; S, 20.52 Found: C, 72.92; H, 6.53; S, 20.36.

In another experiment, 9.2 g. (0.1 mole) of norbornadiene was added to 11 g. (0.1 mole) of benzenethiol with cooling at room temperature. Then the mixture was allowed to stand for 5 days. By that time, all the thiol had reacted. Analysis of the crude product by capillary g.c. showed four peaks of 1.5%, 34.4%, 6.9% and 57.2% intensity. G.c. analysis of the liquid part from the diaddition experiment showed the absence of the 34.4% peak.

**Addition of Diethyldithiophosphoric Acid to Conjugated Dienes.**—A mixture of 0.25 mole of a thiol and 0.25 mole of a diene reacted in a closed 100-ml. round-bottom flask with magnetic stirring at room temperature. In the case of 2,5-dimethyl-2,4-hexadiene ultraviolet irradiation of the reaction mixture was necessary to increase the reaction rate. Water cooling of the irradiated reaction mixtures was necessary to avoid any rise of the temperature. Relative rates of the additions were determined on the basis of the decrease of the diethyldithiophosphoric acid content. Some of the comparative rate data are shown in Tables I and II.

After an arbitrary length of time the reaction was discontinued and the mixture was worked up. The unchanged diethyldithiophosphoric acid was removed by washing with 5% aqueous sodium carbonate solution. If separation was difficult, the organic phase was diluted with ether or benzene. After the drying, the separated organic phase was fractionally distilled. The adducts were usually obtained at about 1 mm. as mobile, colorless or slightly yellow liquid distillates having a characteristic phosphate ester odor. Separation of the isomeric monoadducts by superfractionation was not attempted. Some of the physical and analytical data of the isomeric adduct mixtures are given in Table II. The various isomers were identified and semiquantitatively determined by n.m.r. (Table III). Quantitative determination of the isomers was accomplished by capillary g.c. (Table II).

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# Reactivity of Thiophosphates. I. Hydrolysis of Phosphorothioic Acid[1-3]

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The hydrolysis of phosphorothioic acid ($H_3PO_3S$) in aqueous solution at constant ionic strength has rate maxima at pH $\sim$3.0 and at pH $\sim$8.0 and the rate minima at pH $\sim$7.0 and at pH $\sim -0.30$. The reactivity of the dianion at pH 8 is unusual since the dianions of most simple organic phosphate esters are inert. In acid solutions stronger than 2 M a rate increase is observed which is interpreted as a salt effect on the rate of hydrolysis of the neutral acid.

Phosphorothioic acid, $H_3PO_3S$, is reported to decompose readily to hydrogen sulfide and phosphoric

acid although its anhydrous trisodium salt is stable.[5] This investigation was undertaken in order to compare quantitatively the rate of hydrolysis of phosphorothioic

(1) We are grateful to the National Institutes of Health for support of this work (grant A-1023).

(2) For experimental details, see O. B. Ramsay, Ph.D. thesis, University of Pennsylvania, 1960.

(3) Reported at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(4) Department of Chemistry, Syracuse University, Syracuse 10, N. Y.

(5) A. Wurtz, *Compt. rend.*, **24**, 288 (1847); R. Klement, *Z. anorg. allgem. Chem.*, **253**, 237 (1947); J. V. Karabinos, R. A. Paulson, and W. H. Smith, *J. Res. Natl. Bur. Std.*, **48**, 322 (1952); S. K. Yasuda and J. L. Lambert, *J. Am. Chem. Soc.*, **76**, 5356 (1954); F. Binkley, *J. Biol. Chem.*, **181**, 317 (1949).

acid with its thioalkyl analogs.[6,7] The lack of any nonpolar hydrocarbon fragment in this thiophosphate made it possible that the compound would show behavior different from that of the alkyl esters as the medium was altered. This report discusses the effect of the acidity of the medium on the rate of hydrolysis since this is an effect which has been extensively studied with other esters of phosphoric acid.[2,8]

**Ionization Constants.**—Values for $pK_2$ and $pK_3$ of phosphorothioic acid have been given as 5.6 and 10.2 at 25°.[9] A titration of a dilute solution of the trisodium salt at *ca.* 25° gave $pK_1 = 2.05$, $pK_2 = 5.6$, $pK_3 = 10.3$. The $pK$ values in solutions of 1 $M$ ionic strength were $pK_1 = 1.35$, $pK_2 = 4.95$, $pK_3 = 9.8$. A $pK_1$ of 1.26 can be calculated from Hammett parameters given by Kabachnik.[10] The $pK_1$ determined from a titration curve of the trisodium salt may be in error because of decomposition of the salt and because of the low concentrations of substrate used. The second and third ionization constants are greater than the corresponding constants for orthophosphoric acid.

**pH-Rate Profile.**[11]—A plot of the observed first-order rate constants against pH is shown in Fig. 1. The rate data are given in Table I. The rate constants for



Fig. 1.—pH-Rate profile for the hydrolysis of phosphorothioic acid at 1 $M$ ionic strength: O, experimental points; △, calculated points.

rate constants, a pH-rate profile can be constructed which agrees well with the observed profile. An equally good fit of the calculated curve to the observed can be obtained if $k_T = 0$ and $pK_3 = 10.3$. It is probable that $k_T$ is very small and that the $pK_3$ determination was in error.

**Hydrolysis in Neutral Acid Region.**—Phosphorothioic acid is reported to yield sulfur in the presence of oxidizing acids or air.[5] Yields of hydrogen sulfide were 79–86% in up to 5.4 $M$ perchloric acid. No visible sulfur was produced in the perchloric acid used, but considerable sulfur was produced in 9 $M$ sulfuric acid. Aqueous solutions of perchloric acid are reported not to be reduced by hydrogen sulfide.[12]

The rate of hydrolysis reaches a minimum around 2 $M$ hydrochloric or perchloric acid. At higher concentrations of acid the rate increases; increasing the concentration of neutral salt (lithium chloride) also increases the rate. The rate constant for the hydrolysis of the neutral acid is not proportional to the concentration of acid. The data on the hydrolysis in strong acid are given in Table II.

#### TABLE I
RATE CONSTANTS FOR HYDROLYSIS OF PHOSPHOROTHIOIC ACID AT 52.8° FROM pH 1–10.6 AT 1 $M$ IONIC STRENGTH

| pH | $10^5 k_{obsd}$, sec.$^{-1}$ | pH | $10^5 k_{obsd}$, sec.$^{-1}$ |
|---|---|---|---|
| 1.00 | 7.45 | 5.00 | 9.51 |
| 1.05 | 7.75 | 6.00 | 4.29 |
| 1.50 | 11.4 | 7.20 | 3.91 |
| 1.55 | 11.9 | 7.50 | 3.87 |
| 2.05 | 16.0 | 8.00 | 3.94 |
| 2.10 | 14.4 | 8.50 | 3.92 |
| 2.65 | 15.9 | 9.07 | 3.79 |
| 2.70 | 16.5 | 9.55 | 3.21 |
| 3.50 | 15.7 | 10.25 | 2.41 |
| 4.00 | 14.8 | 10.60 | 1.71 |

hydrolysis at 52.8° and at 1 $M$ ionic strength for the neutral acid ($k_N = 2.43 \times 10^{-5}$ sec.$^{-1}$), monoanion ($k_M = 16.7 \times 10^{-5}$ sec.$^{-1}$), dianion ($k_D = 3.81 \times 10^{-5}$ sec.$^{-1}$), and trianion ($k_T = 1.56 \times 10^{-5}$ sec. $^{-1}$) were calculated from the observed rate constants and the ionization constants (at 25°) by the method of least squares from

$$k_{obsd} = k_N \frac{C_N}{C_P} + k_M \frac{C_M}{C_P} + k_D \frac{C_D}{C_P} + k_T \frac{C_T}{C_P}$$

where $C_N$, $C_M$, $C_D$, and $C_T$ are concentrations of neutral acid, monoanion, dianion, and trianion, respectively, and $C_P = C_N + C_M + C_D + C_T$. From the calculated

(6) See Paper II, D. C. Dittmer, O. B. Ramsay, and R. E. Spalding, *J. Org. Chem.,* **28**, 1273 (1963).

(7) D. E. Koshland and E. B. Herr, *Biochem. Biophys. Acta,* **25**, 219 (1957).

(8) The hydrolysis of phosphate esters has been reviewed in "Phosphoric Esters and Related Compounds," Special Publication no. 8, The Chemical Society, London, 1957.

(9) P. D. Bartlett and C. G. Swain, *J. Am. Chem. Soc.,* **71**, 1406 (1949).

(10) M. I. Kabachnik, *Proc. Acad. Sci. USSR, Chem. Sect. (Eng. Transl.),* **110**, 577 (1956).

(11) Kinetic data cannot be used to distinguish between a reaction of water with a monoanion of phosphorothioic acid or of hydroxide ion with the neutral acid, nor can a reaction of water with a dianion be distinguished kinetically from a reaction of hydroxide ion with the monoanion. It may be noted, however, that hydroxide ion shows much greater nucleophilicity than does water toward phosphorus in triphenyl phosphate and trimethyl phosphate [R. F. Hudson and D. C. Harper, *J. Chem. Soc.,* 1356 (1958); P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *ibid.,* 2670 (1961)]. For the sake of organization, the discussion is arranged according to the major species present in each pH range.

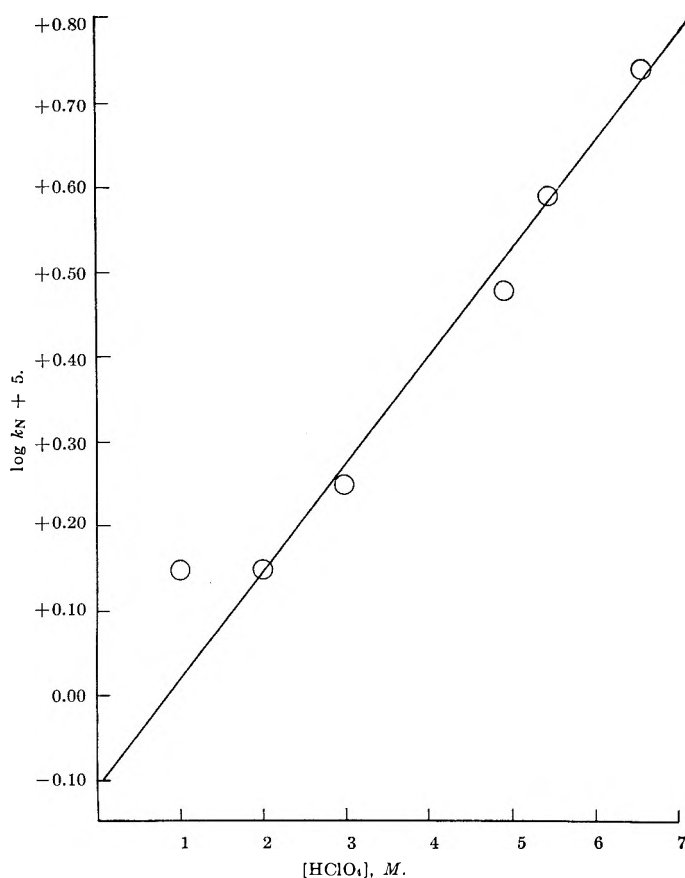(12) "Gmelins Handbuch der anorganischen Chemie," 8th ed., Vol. 3. Chlorine, Verlag Chemie, Berlin, 1927, p. 387.

Fig. 2.—Relationship of log $k_N$ to ionic strength.

TABLE II

RATE CONSTANTS FOR THE HYDROLYSIS OF PHOSPHOROTHIOIC
ACID AT 52.8° IN 1–6.86 $M$ ACID

| Acid concn., $M$ | $10^5 k_{obsd}$, sec.$^{-1}$ |
|---|---|
| 1.00 HClO$_4$ | 2.05 |
| 1.98 HClO$_4$ | 1.71 |
| 2.97 HClO$_4$ | 1.95 |
| 4.90 HClO$_4$ | 3.06 |
| 5.43 HClO$_4$ | 3.93 |
| 6.56 HClO$_4$ | 5.44 |
| 2.45 HCl | 1.84 |
| 3.93 HCl | 1.92 |
| 6.86 HCl | 2.76 |
| 2.31 HCl + 4.86 $M$ LiCl$^a$ | 5.97 |
| 2.31 HCl + 3.69 $M$ LiCl | 5.10 |
| 2.31 HCl + 2.69 $M$ LiCl | 4.33 |
| 3.33 HCl + 3.80 $M$ LiCl$^a$ | 5.06 |
| 4.76 HCl + 2.43 $M$ LiCl$^a$ | 4.00 |

$^a$ Ionic strength is constant at 7.1–7.2 $M$.

A plot of log $k_N$[13] against concentration (ionic strength) of perchloric acid (Fig. 2) is linear from 2–6.6 $M$ perchloric acid. An $H_0$ plot is linear also, but the slope is +0.24. The Hammett acidity function is related to the ionic strength.[14] A Bunnett plot[15]

(13) $k_N$ is defined as

$$\frac{k_{obsd} - k_M a_w \frac{C_M}{C_P}}{C_N/C_P}$$

where $a_w$ is the activity (relative humidity) of water and the other quantities are as defined earlier. At acidities greater than about 3.5 $M$, the term in $k_M$ becomes negligible. If it is assumed that the transition state of the monoanion contains a molecule of water, transition state theory requires that the $a_w$ term be included. The plot in Fig. 2 is not changed much by omitting $a_w$, but the points at low acidities show greater deviations from the line.

(14) I. I. Moiseev and R. M. Flid, *J. Appl. Chem. USSR (Eng. Transl.)*, **27**, 1047 (1954).

of (log $k_N$ + $H_0$) vs. log $a_{H_2O}$ is linear only from 5 $M$ upwards (slope = +4.1). Below 5 $M$ the slope increases greatly. A plot of $H_0$ vs. log $a_{H_2O}$ for these points also is linear above 5 $M$; and the linearity observed in the Bunnett plot is attributed to this, since $H_0$ is changing more rapidly with increasing acidity than is log $k_N$. A similar behavior in the plot of (log $k_N$ + $H_0$) vs. log $a_{H_2O}$ for the S-$n$-butyl ester of phosphorothioic acid has been observed,[6] although there was still some curvature at high acidities (a slope of about +4.5 could be obtained). A plot of (log $k_N$ − [HClO$_4$]) vs. log $a_{H_2O}$ has a maximum between 3 and 5 $M$. The plot of (log $k_N$ − [HClO$_4$]) for the S-$n$-butyl ester has no maximum and was similar in shape but shallower than the plot of (log $k_N$ + $H_0$); a crude slope of about +0.5 could be obtained from points beyond 5 $M$.

It may be thought that the increase in rate with increasing acidity is caused by the formation and hydrolysis of the conjugate acid of phosphorothioic acid. The conjugate acid of phosphoric acid was invoked to explain the increasing rate of its exchange with H$_2$$^{18}$O as the acidity of the medium was increased.[16] However, it is difficult to understand why S-$n$-butylphosphorothioic acid fails to show acid catalysis of its rate of hydrolysis.[2,6] Data in Table II show that hydrochloric acid affects the rate but slightly, less than does lithium chloride.

The conjugate acids of phosphoric acid[16] and its methyl ester[17] are reactive because on protonation the molecule obtains a better leaving group—water in the case of phosphoric acid, methanol in the case of methyl phosphate. Protonation of sulfur is less favored than protonation of oxygen, and the reactivity of the conjugate acids in the sulfur case and in the oxygen case would not be comparable since in the latter the leaving group has been provided by protonation. The conjugate acid of the sulfur compound (protonated on oxygen) may be reactive, but the results reported in this paper and in the paper on the hydrolysis of the S-$n$-butyl ester[6] indicate that it is not greatly reactive. The behavior of phosphorothioic acid and its S-$n$-butyl ester in acid medium may be attributed to salt effects on the rate of hydrolysis of the neutral acid. The lithium chloride data in Table II tend to support this interpretation.

It is conceivable that acid might catalyze the tautomerism of phosphorothioic acid; the conjugate acid may exist to a large extent in the thiono form which is less reactive than the neutral acid. The rate of hydrolysis of trialkylthionophosphates is less than the rate of hydrolysis of trialkylphosphates.[18] The addition of acid to aqueous solutions of phosphorothioic acid would have two effects: one to increase the rate of hydrolysis by a salt effect on the neutral acid, and two, to decrease the rate by formation of a less reac-

(15) J. F. Bunnett, *J. Am. Chem. Soc.*, **82**, 499 (1960); **83**, 4956, 4968, 4973, 4978 (1961).

(16) C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 1636 (1961).

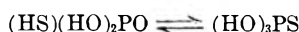(17) C. A. Bunton, D. R. Llewellyn, K. O. Oldham, and C. A. Vernon *ibid.*, 3574 (1958).

(18) D. F. Heath, *ibid.*, 3804 (1956).

tive conjugate acid. From this viewpoint, one can understand the greater effect of lithium chloride over hydrochloric acid in increasing the rate of hydrolysis.

If, despite these arguments, it is assumed that the rate increase with phosphorothioic acid is caused solely by the formation of the conjugate acid, a negative value of the equilibrium constant for the conversion of the conjugate acid to the neutral acid is obtained. The rate constant for the hydrolysis of the neutral acid used in this calculation was obtained from the pH-rate profile where its use gives good agreement with experiment.

Attempts to study the hydrolysis in perchloric acid–sodium perchlorate solutions of constant ionic strength were not successful because of the production of considerable sulfur even at low acidities. This could be caused by some impurity such as chlorate in the sodium perchlorate or to the increase in the oxidation potential of perchloric acid on addition of perchlorate ions.

The hydrolysis of the neutral acid may be complicated by the following equilibrium.

$$(HS)(HO)_2PO \rightleftharpoons (HO)_3PS$$

The reduced rate of hydrolysis of phosphorothioic acid as compared with its S-n-butyl ester[6] may be caused by such an equilibrium. A study of the phosphorus n.m.r. spectrum might reveal the extent to which the two species are present.

Hydrolysis may proceed (1) by a displacement (SN2) on phosphorus by water, (2) by way of metaphosphoric acid as an intermediate, or (3) through a pentacovalent intermediate which decomposes by rupture of the S–P bond. An investigation of the exchange of $H_2^{18}O$ and $H_2^{35}S$ with phosphorothioic acid may give an indication of the mechanism.

**Hydrolysis in Monoanion Region.**—The most reactive species in water appears to be the monoanion,[19] a not unexpected finding since the monoanions of monoesters of phosphoric acid are the most reactive of the possible species.[8]

The similarity of the first ionization constants of phosphorothioic acid and phosphoric acid may indicate that the monoanion of the former is produced principally by an ionization of the O–H bond rather than an S–H bond. The ionization constants of $(RO)_2PO_2H$ are greater than the constants of $(RO)_2-PS_2H$, and the ionization of O–H in $(RO)_2P(S)OH$ is reported to be greater than the ionization of S–H in $(RO)_2P(O)SH$; thus, the equilibrium (in water)

$$(RO)_2\overset{\overset{O}{\parallel}}{P}SH \rightleftharpoons (RO)_2\overset{\overset{S}{\parallel}}{P}OH$$ lies to the left.[20]

It is probable that both monoanions, $(HO)_2P(O)S^-$ and $H_2PSO_2O^-$, are present in solution and are interconvertible.

In the monoanion and neutral acid regions, phosphorothioic acid is considerably less reactive than the S-n-butyl ester.[2,6,7] This may be caused by the tautomeric equilibrium discussed above, or by an increased stability of the initial state of the phosphorothioic acid species (if it is assumed that the transition states for

the ester and the free acid are of the same stability) or by different mechanisms for the two compounds. Phosphorothioic acid may fit into the water structure better than the butyl ester. The additional hydrogen bonding from the sulfhydryl group to water might stabilize the initial state of phosphorothioic acid relative to that of the butyl ester whose butyl groups is not likely to be greatly solvated. Both compounds presumably are solvated by water at their oxygen atoms; it is this kind of specific solvation, an example of which is shown below, which has been suggested to facilitate the hydrolysis of the monoanions of phosphate esters.[8]



**Hydrolysis in the Dianion and Trianion Regions.**—In the dianion region, phosphorothioic acid shows considerable reactivity in contrast to S-n-butylphosphorothioate[2,6,7] and other phosphate esters.[8] This appears to be the first phosphate which shows any reactivity toward hydrolysis in the dianion region.[21] This hydrolytic reactivity of the dianion of phosphorothioic acid contrasts with the apparent lack of reactivity of the dianion of phosphoric acid to exchange with $H_2^{18}O$. The leaving group in the case of the phosphorothioate is $SH^-$ (or $S^{-2}$) which is expected to be a considerably better leaving group than $OH^-$ (or $O^{-2}$). Rates of alkaline hydrolysis of S-alkyl esters of phosphorothioic acid are considerably greater than their oxygen analogs.[22] A rate constant of $0.1 \times 10^{-6}$ sec.$^{-1}$ at 100° for exchange of the dianion of phosphoric acid with $H_2^{18}O$ would give a pH-rate profile nearly the same as the one obtained from the experimental data.[16] In the dianion of phosphorothioic acid, there still exists an hydroxyl group (or –SH) which, with a negatively charged oxygen, is held accountable for the great reactivity of monoanions of phosphate monoesters; an example of specific solvation by water follows.



Such specific hydration[8] positions a water molecule for attack on phosphorus, either to the rear of the semipolar P–O bond (sulfur equatorial in the transition state) or on the face of the phosphorus atom opposite sulfur (sulfur axial in transition state). The attack by an unshared pair of electrons in a $p$ or hybrid orbital on oxygen in the bound water could be accomplished by a rotation of the water molecule which brings the unshared pair of electrons, directed away from phosphorus, into position for attack. This rotation would stretch or weaken the hydrogen bonds and would rupture any hydrogen bond from external water to the

(19) Note the comment under ref. 11. The reaction of the neutral acid with hydroxide ion seemed unreasonable in the case of dibenzyl phosphate hydrolysis [J. Kumamoto and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2515 (1955)].

(20) M. I. Kabachnik, S. T. Joffe, and T. A. Mastryukova, *J. Gen. Chem. USSR (Eng. Transl.)*, **25**, 653 (1955).

(21) However, the monofluorophosphate ion is reported to be hydrolyzed rapidly in strongly alkaline solutions although it is stable in neutral or moderately alkaline solution [L. N. Devonshire and H. H. Rowley, *Inorg. Chem.*, **1**, 680 (1962)].

(22) R. F. Hudson and L. Keay, *J. Chem. Soc.*, 3269 (1956); E. M. Thain, *ibid.*, 4694 (1957).

unshared pair of electrons involved in the assault on phosphorus. The transition state for the attack of water may be either trigonal bipyramidal or tetragonal pyramidal, geometries which have been suggested for transition states for displacement reactions on phosphorus.[23]

Alternatively, the hydrogen bonding of water may be to sulfur to give an intermediate similar to one suggested for the hydrolysis of phosphate ester monoanions.[24]

Hydrolysis of the monoanion by hydroxide ion may be less likely because of repulsion between $OH^-$ and $H_2PSO_3^-$. In the dianion region, the S-$n$-butyl ester is quite unreactive.[2,6]

The trianion of phosphorothioic acid seems very stable since it is prepared by refluxing thiophosphoryl chloride with aqueous sodium hydroxide.[5] However, until a quantitative study of the hydrolysis of the trianion is made, its reactivity, although clearly less than the other anionic species, must remain in doubt.

## Experimental

Trisodium phosphorothioate was prepared as described elsewhere.[25] Analysis for inorganic phosphate, which is an impurity, indicated the salt was 97% pure.

**Determination of Products of Hydrolysis.**—To 40 ml. of 5.4 $M$ perchloric acid at 52.8° was added 0.886 g. (0.00492 mole) of trisodium phosphorothioate. The hydrogen sulfide produced was swept from the reaction flask by a stream of nitrogen and passed through a condenser and into a solution of 5% mercuric cyanide. The gas stream then was passed through a solution of 10% sodium hydroxide. After 1293 min., the mercuric sulfide was collected, washed with distilled water, and dried at 110° for 15 min. The yield of mercuric sulfide was 0.868 g. (0.00373 mole) corresponding, after correction for the amount of unhydrolyzed substrate, to 86%. Yields of mercuric sulfide from hydrolyses in 6.5 $M$ and 2.5 $M$ perchloric acid were 79% and 84%, respectively. These yields are undoubtedly lower limits. There was no visible evidence of sulfur.

When 1.042 g. (0.00579 mole) of trisodium phosphorothioate was heated with 50 ml. of 9 $M$ sulfuric acid on a steam-bath for 1 hr., 0.121 g. of mercuric sulfide and 0.157 g. of sulfur were produced. The total yield of mercuric sulfide plus sulfur corresponded to 94% hydrolysis.

**Determination of Dissociation Constants.**—A titration of an aqueous solution of trisodium phosphorothioate with perchloric acid gave the following p$K$ values: p$K_1$ = 2.05, p$K_2$ = 5.6, p$K_3$ = 10.3. The pH was determined by means of glass and calomel electrodes with a Beckman Model H-2 pH meter. The pH of a solution of equal concentrations of the neutral acid and monoanion was 1.35 at an ionic strength of 1 $M$ (NaCl–HClO$_4$). A sleeve-type calomel electrode was used in this determination. The pH values of solutions of 1 $M$ ionic strength (KCl–HCl) of equal concentrations of monoanion and dianion and of dianion and trianion were, respectively, 4.95 and 9.8. All determinations were at approximately 25°.

(23) P. C. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 1104 (1961); A. Bladé-Font, C. A. VanderWerf, and W. E. McEwen, *ibid.*, **82**, 2397 (1960); M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 227 (1959).

(24) W. W. Butcher and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2420 (1955).

(25) S. K. Yasuda and J. L. Lambert, *Inorg. Syn.*, **5**, 102 (1957).

**Kinetic Procedure.**—The rates of hydrolysis were followed by the rate of formation of inorganic phosphate which was determined by a colorimetric procedure similar to one described for the determination of phosphate in the presence of adenosine triphosphate.[26] Concentration of substrate in all kinetic runs was 1.27 × 10$^{-3}$ $M$.

All kinetic runs from pH 1–10.6 were adjusted to an ionic strength of 1 $M$ with potassium chloride. From pH 1–6, a phthalate buffer was used, from pH 7.2–8.5, a tris[27] buffer, and from pH 9.07–10.6, a borate buffer. In this work, no attempt was made to investigate general acid or base catalysis or specific buffer effects.

The molybdate reagent used in the phosphate determination was prepared by addition of 125 ml. of 10 $N$ sulfuric acid to a solution of 12.5 g. of ammonium molybdate and dilution to 500 ml. An acid–ethanol solution was prepared by addition of 10 ml. of concentrated sulfuric acid to 490 ml. of absolute ethanol. The 1-amino-2-naphthol-4-sulfonic acid reagent was prepared by addition of 0.5 g. of the sulfonic acid to 195 ml. of a 15% solution of sodium bisulfite solution followed by addition of 5 ml. of a 20% solution of sodium sulfite. If a homogeneous solution was not obtained after vigorous shaking, more sodium sulfite solution could be added; but excess sodium sulfite should be avoided. The pale yellow solution is stable for about a week in a refrigerator.

Aliquots (1.0 ml.) from the kinetic runs were added to 10 ml. of the molybdate solution in a 60-ml. separatory funnel, and 1 ml. of the aminonaphtholsulfonic acid reagent and 10 ml. of isobutyl alcohol were added. The aqueous layer was discarded after the contents of the funnel were shaken vigorously for 15 sec. The isobutyl alcohol layer was removed as completely as possible with a pipet, and 2 drops of the acid–ethanol solution were added. After 30 min. the optical density of the blue solution was read at 660 m$\mu$ on a Bausch and Lomb "Spectronic 20" spectrophotometer. An isobutyl alcohol extract of a molybdate solution which contains no phosphate can be used as a blank, but it was sufficient in most cases to use isobutyl alcohol itself since the difference in blanks was only 0.02–0.03 units of optical density. Infinity optical density readings were determined for each run since this reading was sensitive to the amount of sodium perchlorate and perchloric acid present. These readings were taken either after 10 half-lives or after oxidation of a sample with bromine water. Too acidic molybdate solutions (as, for example, would occur in the runs in strong acid) must be avoided or the analytical results will be erratic. The acidity may be adjusted by addition of sodium hydroxide solution. The concentration of phosphate in the aliquot is read from a standard plot of optical density versus concentration.

**Calculation of Rate Constants.**—The concentration of phosphate is linearly related to the optical density of the reduced phosphomolybdate complex. The rate constant is

$$k_{obs} = (2.303/t) \log \frac{D - D_0}{D - D_t}$$

where $D_0$, $D_t$, and $D$ are optical densities at zero time, time $t$, and at infinite time.

The values of $a_w$, the relative humidity of water, used in calculating the rate constants for the neutral acid used in Fig. 2, were the data of Robinson and Baker.[28] These data were obtained at 25° so that a small error was introduced on its use at 52.8°.

(26) B. B. Marsh, *Biochim. Biophys. Acta*, **32**, 357 (1959).

(27) Tris(hydroxymethyl)aminomethane.

(28) R. A. Robinson and O. J. Baker, *Trans. Proc. Roy. Soc. New Zealand*, **76**, 250 (1946).

# Reactivity of Thiophosphates. II. Hydrolysis of S-*n*-Butylphosphorothioate and S-(2-Aminoethyl)phosphorothioate[1-3]

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The hydrolysis of S-*n*-butylphosphorothioate ($n$-$C_4H_9SPO_3H_2$) in aqueous solution at constant ionic strength has a rate maximum at pH 3.25. As the acidity is increased to 10 $M$ perchloric acid and to 8 $M$ hydrochloric acid, the rate decreases. The rate decrease is interpreted as a salt effect on the hydrolysis of the neutral acid. At *ca.* pH 3.50, variation of the ionic strength or kind of buffer had very little effect on the rate. At pH 3.25 and 1 $M$ ionic strength, addition of Mn(II), Ni(II), Mg(II), and Zn(II) ions had little effect on the rate. Decreasing the ionic strength or dielectric constant of the solvent at pH 8 increases the rate. Added magnesium chloride decreased the rate at pH 8. These effects are interpreted as being caused primarily by variation of the second ionization constant and by complexing of the dianion with magnesium ion. S-(2-Aminoethyl)phosphorothioate is less reactive than the butyl ester from pH 1–7. It has a rate maximum between pH 2 and 3 and appears to have a second maximum between pH 8 and 9. It protects mice against the effects of radiation.

Monoesters of thiols and phosphoric acid have been suggested as models for intermediates in enzymic phosphate transfers.[5] The activity of several phosphate-transferring enzymes is dependent on the presence of sulfhydryl groups[6a] and S-phosphoryl derivatives have been suggested as intermediates in the formation of acetylcholine from acetate and adenosine triphosphate from adenosine diphosphate,[6b] in succinate activation,[6c] and in the enzymic reduction of amino acids.[6d]

Wieland and Lambert have shown that S-*n*-butylphosphorothioate is capable of transferring phosphate to acetic acid (yielding acetyl phosphate), to alcohols and to phenol,[7] and it has been shown more recently that S-*n*-butylphosphorothioate can yield pyrophosphate when treated with phosphoric acid.[8]

Walsh has found that S-*n*-propylphosphorothioate was hydrolyzed completely in seven minutes at 100° in 1 $N$ hydrochloric acid.[5] The hydrolysis of S-cysteinylphosphorothioate is reported to yield cysteine and phosphate in 1 $N$ sodium hydroxide and hydrogen sulfide, phosphoric acid, and ammonia in 1 $N$ perchloric acid.[9] The corresponding ester of coenzyme A was reported to be unstable in acidic and alkaline solutions.[10] After the work in this paper was completed, data on the hydrolysis of S-(2-aminoethyl)phosphorothioate were reported.[11] The single rate maximum was reported at pH 3.

While the work reported in this paper was in progress, Koshland and Herr reported briefly on the rate of hydrolysis of S-*n*-butylphosphorothioate.[12]

They reported a rate maximum for hydrolysis between pH 2 and 4 and a leveling off of the rate between 1 and 4 $N$ acid.

This paper reports the effects of various changes in the medium on the rate of hydrolysis of thiophosphate esters.

Kinetic data cannot be used to distinguish between a reaction of water with a monoanion of a phosphorothioate or of hydroxide ion with the neutral acid, nor can a reaction of water with a dianion be distinguished kinetically from a reaction of hydroxide ion with the monoanion. It may be noted, however, that hydroxide ion shows much greater reactivity than water toward phosphorus in triphenyl phosphate and trimethyl phosphate.[13] For the sake of organization, the discussion is arranged according to the major ionic species present in each pH range.

**pH–Rate Profiles.**—The profile for S-*n*-butylphosphorothioate shown in Fig. 1 agrees essentially with that of Koshland and Herr.[12] A profile calculated from values of the first and second ionization constants ($10^{-1}$ and $3.16 \times 10^{-6}$ at *ca.* 25°) of the S-*n*-butyl ester and values of the rate constants for hydrolysis of the neutral acid ($k_N = 2.92 \times 10^{-4}$ sec.$^{-1}$) and the monoanion ($k_M = 13.1 \times 10^{-4}$ sec.$^{-1}$) agrees well with the observed profile. The second ionization constant of the ester at 1 $M$ ionic strength was determined experimentally, but the first ionization constant was assumed in order to give the best fit of the calculated curve to the experimental curve. The rate constants, $k_N$ and $k_M$, were determined from experimental data by the method of least squares from the relationship,

$$k_{obs} = k_N \frac{C_N}{C_P} + k_M \frac{C_M}{C_P}$$

where $C_N$ = concentration of neutral acid, $C_M$ = concentration of monoanion, $C_P = C_N + C_M + C_D$, and $C_D$ = concentration of dianion.

The pH-rate profile for S-(2-aminoethyl)phosphorothioate is shown in Fig. 2. Determinations of the rate constants for this ester were less precise than for the *n*-butyl ester because of difficulty in determination

(1) We are grateful to the National Institutes of Health (grant A-1023) and the Walter Reed Army Institute of Research for support of this work.

(2) Taken in part from O. B. Ramsay, Ph.D. thesis, University of Pennsylvania, 1960.

(3) Reported in part at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April, 1958, and at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(4) Department of Chemistry, Syracuse University, Syracuse 10, N. Y.

(5) E. O'F. Walsh, *Nature*, **169**, 546 (1952).

(6) (a) E. S. G. Barron, *Advan. Enzymol.*, **11**, 243 (1951); L. Noda, *J. Biol. Chem.*, **232**, 237 (1958); (b) G. Feuer and M. Wollemann, *Acta Physiol. Acad. Sci. Hung.*, **7**, 343 (1955); *Chem. Abstr.*, **50**, 1097 (1956); (c) R. A. Smith, I. F. Franck, and I. C. Gunsalus, *Federation Proc.*, **16**, 251 (1957); (d) T. Stadtman, P. Elliott, and L. Tiemann, *J. Biol. Chem.*, **231**, 972 (1958).

(7) T. Wieland and R. Lambert, *Chem. Ber.*, **89**, 2476 (1956).

(8) D. C. Dittmer and V. B. Opshelor, *J. Org. Chem.*, **26**, 4706 (1961).

(9) F. Binkley, *J. Biol. Chem.*, **195**, 283 (1952).

(10) G. Feuer and M. Wollemann, *Acta Physiol. Acad. Sci. Hung.*, **10**, 1 (1956); *Chem. Abstr.*, **51**, 513 (1957).

(11) S. Akerfeldt, *Acta Chem. Scand.*, **14**, 1980 (1960).

(12) D. E. Koshland and E. B. Herr, Jr., *Biochim. Biophys. Acta*, **25**, 219 (1957); E. B. Herr, Jr., and D. E. Koshland, Abstracts of Papers, 131st National Meeting of the American Chemical Society, Miami, Fla. April, 1957, p. 44C.

(13) R. F. Hudson and D. C. Harper, *J. Chem. Soc.*, 1356 (1958); P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *ibid.*, 2670 (1961).
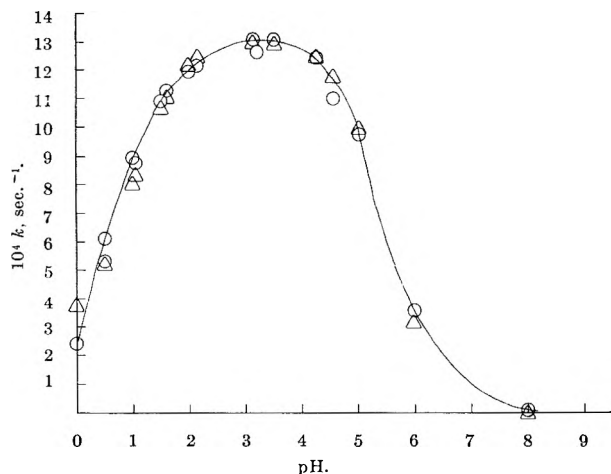
Fig. 1.—pH-Rate profile for the hydrolysis of S-n-butylphos-phorothioate at 37.1°, 1 $M$ ionic strength:  $\bigcirc$, observed;  $\triangle$, calculated.
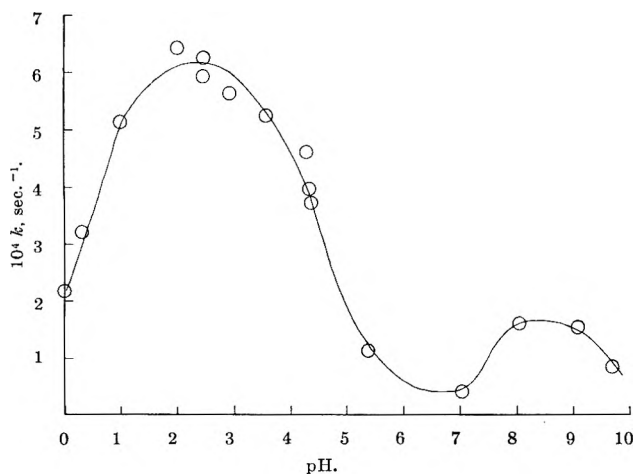


Fig. 2.—pH-Rate profile for hydrolysis of S-(2-aminoethyl)-phosphorothioate at 37°, 1 $M$ ionic strength.  All points except the ones at pH 0 and pH 9.70 were obtained by use of an arbitrary infinity point.

of the infinity point, but it appears that the aminoethyl ester is less reactive than the n-butyl ester over much of the pH range.  A second maximum appears at pH 8–9.

The general shapes of the curves in Fig. 1 and Fig. 2 are similar to those observed for other phosphate esters for which the monoanion is considered the most reactive species.[14a,b,15]

Rate data from pH 0.50 to pH 8.0 for S-n-butyl-phosphorothioate and from pH 0 to pH 9.7 for S-(2-aminoethyl)phosphorothioate are given in Tables I and II.

**Hydrolysis in the Neutral Acid Region.**—The apparent first ionization constant $(10^{-1})$ at $ca.$ 25° of S-n-butylphosphorothioate which gives the best fit of calculated to experimental curve in Fig. 1 is somewhat greater than $K_1$ for the corresponding oxygen ester $(1.3 \times 10^{-2})$[16] although the latter value is not at 1 $M$

(14) (a) A. Desjobert, *Bull. soc. chim. France*, 809 (1947); *Compt. rend.* **224**, 575 (1947); (b) C. A. Bunton, D. R. Llewellyn, K. O. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 3574, 3588 (1958).

(15) W. W. Butcher and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2420 (1955).

(16) W. D. Kumler and J. J. Eiler, *ibid.*, **65**, 2355 (1943).

### TABLE I

RATES OF HYDROLYSIS OF $1.64 \times 10^{-2}$ $M$ S-n-BUTYLPHOSPHORO-THIOATE AT 37.1° AND 1 $M$ IONIC STRENGTH (KCl)

| pH | Buffer | $10^4 k_{obsd}$, sec.$^{-1}$ |
|---|---|---|
| 0.50 | 0.1 $M$ Phosphate | 6.13 |
| 0.51 | .1 $M$ Phosphate | 5.33 |
| 1.00 | .1 $M$ Phosphate | 8.94 |
| 1.05 | .1 $M$ Phosphate | 8.77 |
| 1.50 | .1 $M$ Phosphate | 10.91 |
| 1.59 | .1 $M$ Phosphate | 11.26 |
| 2.00 | .1 $M$ Phosphate | 11.94 |
| 2.15 | .1 $M$ Phosphate | 12.15 |
| 3.15 | .1 $M$ Phthalate | 13.07 |
| 3.20 | .1 $M$ Phthalate | 12.60 |
| 3.50 | .1 $M$ Phosphate | 13.08 |
| 4.25 | .1 $M$ Phthalate | 12.40 |
| 4.55 | .1 $M$ Phthalate | 11.00 |
| 5.00 | .1 $M$ Phthalate | 9.75 |
| 6.00[a] | .1 $M$ Phosphate | 3.55 |
| 8.00[b] | .05 $M$ Tris[c] | 0.0933 |

[a] Ionic strength = 0.95 $W$.   [b] BuSPO$_3$Na$_2$ = $1.27 \times 10^{-3}$ $M$.   [c] Tris(hydroxymethyl)aminomethane.

### TABLE II

RATES OF HYDROLYSIS OF S-(2-AMINOETHYL)PHOSPHOROTHIOATE AT 37° AND 1 $M$ IONIC STRENGTH (KCl)

| pH | Substrate concn., $10^3$ $M$ | Buffer | $10^4 k$, sec.$^{-1}$ |
|---|---|---|---|
| 0 (1 $M$ HCl) | 1.25 | ... | 2.18 |
| 0.30 (0.5 $M$ HCl) | 1.25 | ... | 2.82 (3.21)[a] |
| 1.03 | 1.25 | 0.01 $M$ Phthalate | 4.62 (5.14) |
| 2.02 | 1.27 | .01 $M$ Phthalate | 5.85 (6.42) |
| 2.46 | 1.20 | .01 $M$ Phthalate | 4.72 (5.93) |
| 2.47 | 1.20 | .01 $M$ Phthalate | 4.62 (6.25) |
| 2.92 | 1.20 | .01 $M$ Phthalate | 4.62 (5.63) |
| 2.93 | 1.20 | .01 $M$ Phthalate | 4.81 (5.63) |
| 3.58 | 1.13 | .05 $M$ Phthalate | 4.62 (5.25) |
| 3.58 | 1.19 | .05 $M$ Phthalate | 3.85 (5.02) |
| 3.58 | 1.19 | .05 $M$ Phthalate | 4.62 (5.25) |
| 4.28 | 1.13 | .05 $M$ Phthalate | 3.98 (4.62) |
| 4.33 | 0.486 | .05 $M$ Phthalate | 3.50 (3.98) |
| 4.36 | 0.972 | .05 $M$ Phthalate | 3.39 (3.73) |
| 5.33 | 0.620 | .05 $M$ Phthalate | 1.02 |
| 5.37 | 1.24 | .05 $M$ Phthalate | 0.95 |
| 5.38 | 1.24 | .05 $M$ Phthalate | .96 (1.13) |
| 7.02 | 1.20 | .05 $M$ Tris[b] | .38 |
| 7.03 | 1.20 | .05 $M$ Phthalate | .35 (0.42) |
| 8.06 | 1.20 | .05 $M$ Tris[b] | 1.31 (1.60) |
| 9.08 | 1.20 | .05 $M$ Tris[b] | 0.99 (1.54) |
| 9.70 | 1.20 | .05 $M$ Borate | 0.86[c] |

[a] Values in parenthesis were obtained by using an arbitrary infinity point so that a plot of log $\dfrac{D - D_t}{D - D_0}$ against time gave the best straight line.  Values not in parenthesis were from data obtained in the first 50 or 60% of reaction.   [b] Tris(hydroxymethyl)aminomethane.   [c] Based on first 25% of reaction.  Rate plot deviated from first-order rate law.

ionic strength.  The first ionization constant was difficult to determine experimentally, but the second ionization constant $(3.16 \times 10^{-6})$ which was determined is greater than the second ionization constant $(1.45 \times 10^{-7})$ of the oxygen ester[16] which lends some support to the assumption of a greater acidity for the neutral thioester.  This greater acidity may be the result of a decreased electron density on phosphorus in the thioester.  Phosphorus n.m.r. spectra of phosphate
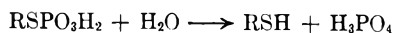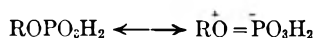
esters have indicated that replacement of oxygen by sulfur decreases the shielding at phosphorus.[17]

In contrast to the oxygen esters of phosphoric acid,[14b,18] there is no evidence of C–S cleavage in the hydrolysis of the thioester. In the hydrolysis in 3.6

$$RSPO_3H_2 + H_2O \longrightarrow RSH + H_3PO_4$$

$M$ sulfuric acid or in 6 $M$ hydrochloric acid, no hydrogen sulfide was produced as would be the case if phosphorothioic acid were formed.[19] In the sulfuric acid solution a 96% yield of $n$-butanethiol was isolated as its mercury derivative. Only sulfur–phosphorus cleavage has been reported for hydrolyses of tri(S-ethyl)phosphorotrithioate[20] and of di(S-isopropyl)methylphosphonodithioate.[21] Hydrolysis of S - (2 - aminoethyl)-phosphorothioate in 1 $M$ perchloric acid results in only sulfur–phosphorus cleavage.[22]

Resonance involving the electrons of the ether oxygen may predispose the oxygen ester to carbon–oxygen cleavage, whereas such resonance is absent in the sulfur derivatives.[23]

$$ROPO_2H_2 \longleftrightarrow R\overset{+}{O} = \overset{-}{P}O_3H_2$$

The rate of hydrolysis of S-$n$-butylphosphorothioate continues to decrease as the acidity increases, which contrasts with the behavior of oxygen esters[13–15] and with previous reported data on the hydrolysis of S-$n$-butylphosphorothioate which indicated a leveling-off of the observed rate in acidic solutions.[12] The rate data which are reported here in perchloric and in hydrochloric acids were obtained by the use of two different analytical methods (for inorganic phosphate and for unchanged ester) for following the reaction. The results obtained by each method were quite similar and are given in Table III. The analytical method for inorganic phosphate is sensitive to the acidity at which the determination is carried out and the acid concentration must be adjusted to ensure reproducible results.

The decreasing rate of hydrolysis of S-$n$-butylphosphorothioate with increasing acidity can be rationalized as being caused by salt effects of hydrochloric and perchloric acids.[24] Plots of the logarithm of the rate constant ($k_N$) of the neutral acid[25] against the concentration of hydrochloric or perchloric acid are linear from 2–10 $M$ acid concentration as shown in Fig. 3. The linearity is poorer at low acidities if the rate constant is not corrected for the amount of reaction
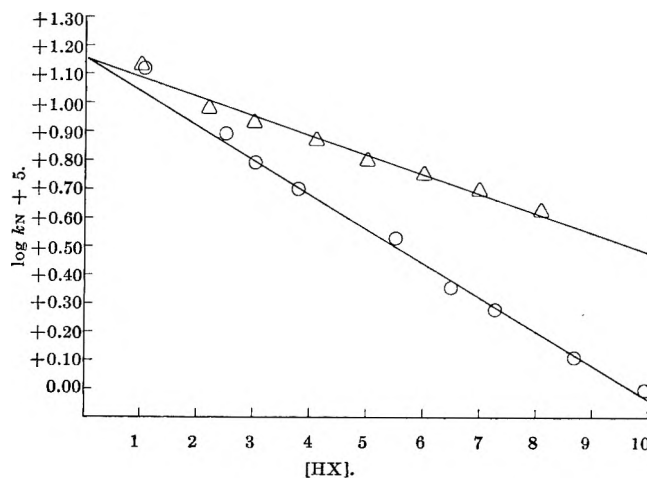
(17) J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *J. Am. Chem. Soc.*, **78**, 5715 (1956). This could be caused also by a neighbor-anisotropy effect. [J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 176.]

(18) C. A. Vernon in "Phosphoric Esters and Related Compounds," Special Publication no. 8, The Chemical Society, London, 1957, p. 17.

(19) D. C. Dittmer and O. B. Ramsay, *J. Org. Chem.*, **28**, 1268 (1963).

(20) E. Thain, *J. Chem. Soc.*, 4694 (1957).

(21) R. F. Hudson and L. Keay, *ibid.*, 3269 (1956).

(22) S. Akerfeldt, *Acta Chem. Scand.*, **13**, 1479 (1959).

(23) Delocalization of the electrons on the ether oxygen in phenylphosphate and in phosphonate esters has been discussed by H. R. Gersmann and J. A. A. Ketelaar, *Rec. trav. chim.*, **77**, 1018 (1958), and briefly by R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463 (1956).

(24) Salt–non-electrolyte interaction coefficients for sodium chloride and sodium perchlorate are considerably different [E. Grunwald and A. F. Butler, *J. Am. Chem. Soc.*, **82**, 5647 (1960)]. The differences in rates between hydrochloric and perchloric acids may be due in part to specific anion effects on the molar activity coefficients of the reacting species.

(25) A correction has been applied for the amount of reaction proceeding through the monoanion.
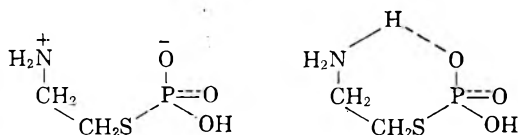
Fig. 3.—Relationship of log $k_N$ for S-$n$-butylphosphorothioate to ionic strength: O, HClO$_4$; △, HCl.

TABLE III

RATES OF HYDROLYSIS OF S-$n$-BUTYLPHOSPHOROTHIOATE IN ACID AT 37.1°

| Acid, $M$ | Substrate, $10^3\ M$ | Ionic strength, $M$ | $10^4 k_{obsd}$, sec.$^{-1}$ |
|---|---|---|---|
| 1.00 (HCl) | 4.97 | 1 | 2.40 |
| 1.00 (HCl) | 4.97 | 11 (LiCl) | 1.99 |
| 2.20 (HCl) | 16.4 | 2.20 | 1.44 |
| 2.80 (HCl) | 1.27 | 5 (KCl) | 1.31$^a$ |
| 3.00 (HCl) | 4.97 | 3 | 1.19 |
| 3.00 (HCl) | 4.97 | 11 (LiCl) | 0.939 |
| 4.11 (HCl) | 16.4 | 4.11 | .979 |
| 4.20 (HCl) | 1.27 | 5 (KCl) | .979$^a$ |
| 5.00 (HCl) | 4.97 | 5 | .808 |
| 5.00 (HCl) | 4.97 | 11 (LiCl) | .656 |
| 6.03 (HCl) | 16.4 | 6.03 | .700 |
| 7.00 (HCl) | 1.27 | 7 | .592$^a$ |
| 7.00 (HCl) | 4.97 | 7 | .607 |
| 7.00 (HCl) | 4.97 | 11 (LiCl) | .502 |
| 8.10 (HCl) | 16.4 | 8.10 | .510 |
| 1.06 (HClO$_4$) | 16.4 | 1.06 | 2.31 |
| 2.50 (HClO$_4$) | 1.27 | 2.50 | 1.19$^a$ |
| 2.51 (HClO$_4$) | 16.4 | 2.51 | 1.18 |
| 3.03 (HClO$_4$) | 16.4 | 3.03 | 0.940 |
| 3.81 (HClO$_4$) | 16.4 | 3.81 | .739 |
| 3.82 (HClO$_4$) | 1.27 | 3.82 | .750$^a$ |
| 5.52 (HClO$_4$) | 16.4 | 5.52 | .449 |
| 6.50 (HClO$_4$) | 16.4 | 6.50 | .310 |
| 7.29 (HClO$_4$) | 16.4 | 7.29 | .238 |
| 8.00 (HClO$_4$) | 1.27 | 8.00 | .210$^a$ |
| 8.69 (HClO$_4$) | 16.4 | 8.69 | .154 |
| 9.94 (HClO$_4$) | 16.4 | 9.94 | .105 |

$^a$ Rates followed by colorimetric analysis of inorganic phosphate. All other rates were followed by iodometric analysis of unchanged thioester.

proceeding through the monoanion. All data in Table III from 3–10 $M$ acid can be correlated by

$$\log k_{obsd} = -3.648 - 0.083[HCl] - 0.017[LiCl] - 0.132[HClO_4]$$

Plots of log $k_N$ or log $k_{obsd}$ against $-H_0$ have small slopes (ca. $-0.2$). Bunnett plots are not linear.[26]

The effects of ionic strength on the rate of reaction of neutral molecules has been discussed.[27]

In contrast to the decrease in rate for hydrolysis of S-$n$-butylphosphorothioate with increasing acidity, the

(26) J. F. Bunnett, *J. Am. Chem. Soc.*, **82**, 499 (1960).

(27) F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952); F. A. Long, W. F. McDevit, and F. B. Dunkle, *J. Phys. Colloid Chem.*, **55**, 813 (1951); F. A. Long, F. B. Dunkle, and W. F. McDevit, *ibid.*, **55**, 829 (1951).

rate of hydrolysis of phosphorothioic acid is increased.[19] This reversal of behavior could be caused by differences in the magnitudes and signs of the salt effects on the initial state, transition state or on both states of the neutral acids.

The lack of acid catalysis which distinguishes this sulfur ester from the oxygen esters is probably the result of sulfur being less basic to protons than the ether oxygen. The lack of C–S cleavage lends some support to this explanation.

Intervention of the conjugate acid of the substrate has been considered but an unusually low ionization constant $(4.5 \times 10^{-2})$ for it is required to fit the data to such an assumption.

**Hydrolysis in Monoanion Region.**—In the monoanion region, S-$n$-butylphosphorothioate and S-(2-aminoethyl)phosphorothioate are more reactive than the oxygen esters which in part may be because the P–S bond is weaker than a P–O bond. The mechanisms of hydrolysis of oxygen esters have been discussed[28] and there is no reason to propose any unique new mechanisms for the hydrolysis of thiophosphate esters. Possible mechanisms are discussed elsewhere.[2,19]

The somewhat lower reactivity of S-(2-aminoethyl)phosphorothioate as compared with S-$n$-butylphosphorothioate may be caused by an electrostatic effect of the $\beta$-ammonium group or by inter- or intramolecular hydrogen bonding.



**Effect of Metal Ions.**—The effects of Mg(II), Ni(II), and Mn(II) ions on the rate of hydrolysis of S-$n$-butylphosphorothioate at pH 3.5 and 1 $M$ ionic strength was negligible. Zn(II) ions caused an 18% decrease in the rate; a complex of zinc ions with the sulfur and the negative oxygen might decrease the rate by hindering proton transfer from water. Complexing of the ions with the buffer might decrease their catalytic effect.

At pH 8, Mg(II) ions significantly decrease the rate of hydrolysis of S-$n$-butylphosphorothioate with the decrease apparently proportional to the concentration of magnesium ions. The effect of Mg(II) ions seems likely to be an effect on the second ionization constant, since it is known that the apparent $pK_2$ of phosphoric acid is decreased by Mg(II) ions.[29] Magnesium and other divalent ions complex with the dianions of phosphoric acid and its esters.[30] Such complexing would decrease the concentration of the reactive monoanion (or neutral acid).

$$RSPO_3H^- \rightleftharpoons RSPO_3^- + H^+$$

$$RSPO_3^- + Mg^{++} \rightleftharpoons RSPO_3Mg$$

The data on metal-ion effects are given in Table IV. The effect of metal ions on the hydrolysis of S-(2-aminoethyl)phosphorothioate, which should be interesting, has not yet been investigated extensively but Hg(II) ions are reported to catalyze the hydrolysis.[22] Complexing of an amino group and a $\beta$-sulfur atom with a Cu(II) ion is effective in promoting an elimination reaction in S-alkyl cysteine derivatives.[31]

**Effect of Ionic Strength and Buffer Concentration.**—Increasing the ionic strength with potassium chloride at pH 8 decreased the rate of hydrolysis of S-$n$-butylphosphorothioate. The data are given in Table V.

### TABLE IV

RATES OF HYDROLYSIS OF S-$n$-BUTYLPHOSPHOROTHIOATE AT 37.6° IN THE PRESENCE OF METAL IONS

| pH | Substrate, $10^3$ M | Buffer, M | Ionic strength, M | Metal ion, M | $10^4$ $k_{obsd}$, sec.$^{-1}$ |
|---|---|---|---|---|---|
| 3.25 | 16.4 | 0.01 Phthalate | 1.0 (KCl) | 0.05 MnCl₂ | 12.0 |
| 3.25 | 16.4 | .01 Phthalate | 1.0 (KCl) | .05 NiCl₂ | 12.1 |
| 3.25 | 16.4 | .01 Phthalate | 1.0 (KCl) | .05 MgCl₂ | 12.2 |
| 3.25 | 16.4 | .01 Phthalate | 1.0 (KCl) | .05 ZnCl₂ | 10.0 |
| 8.00 | 1.27 | .05 Tris$^a$ | 0.50 (KCl) | ... | 0.126$^b$ |
| 8.00 | 1.27 | .05 Tris$^a$ | .50 (KCl) | .0196 MgCl₂ | .114$^b$ |
| 8.00 | 1.27 | .05 Tris$^a$ | .50 (KCl) | .0492 MgCl₂ | .0882$^b$ |
| 8.00 | 1.27 | .05 Tris$^a$ | .50 (KCl) | .0980 MgCl₂ | .0581$^b$ |

$^a$ Tris(hydroxymethyl)aminomethane. $^b$ Rates followed by analysis for inorganic phosphate. In the acid molybdate solution used in the analysis, magnesium acid phosphate is largely dissociated and magnesium ion does not interfere in the analysis. (Private communication from Dr. Robert Rutman, University of Pennsylvania.)

### TABLE V

EFFECT OF IONIC STRENGTH AND BUFFERS ON THE HYDROLYSIS OF S-$n$-BUTYLPHOSPHOROTHIOATE AT 37.1°

| pH | Substrate, $10^3$ M | Ionic strength, M$^c$ | Buffer, M | $10^4$ $k_{obsd}$, sec.$^{-1}$ |
|---|---|---|---|---|
| 8.00 | 1.27 | 0.03 | 0.05 Tris$^a$ | 0.206$^b$ |
| 8.00 | 1.27 | .10 | .05 Tris$^a$ | .186$^b$ |
| 8.00 | 1.27 | .20 | .05 Tris$^a$ | .151$^b$ |
| 8.00 | 1.27 | .30 | .05 Tris$^a$ | .135$^b$ |
| 8.00 | 1.27 | .50 | .05 Tris$^a$ | .127$^b$ |
| 8.00 | 1.27 | .75 | .05 Tris$^a$ | .110$^b$ |
| 8.00 | 1.27 | 1.00 | .05 Tris$^a$ | .0934$^b$ |
| 8.00 | 1.27 | 1.00 (Na₂SO₄) | .05 Tris$^a$ | .0961$^b$ |
| 3.50 | 16.4 | 0.19 | .20 Citrate | 12.1 |
| 3.50 | 16.4 | 1.00 | .20 Citrate | 12.8 |
| 3.15 | 16.4 | 1.00 | .10 Phthalate | 13.1 |
| 3.50 | 16.4 | 1.00 | .10 Phosphate | 13.1 |
| 3.25 | 16.4 | 0.13 | .10 Phthalate | 12.5 |
| 3.28 | 16.4 | .13 | .10 Phthalate 5 ml. dioxane per 50 ml. | 12.6 |
| 4.00 | 16.4 | 1.00 | 0.05 Phthalate | 12.6 |
| 3.50 | 1.27 | 1.00 | .05 Phthalate | 13.1$^b$ |
| 6.00 | 16.4 | 0.95 | .05 Phosphate | 3.73 |
| 6.00 | 16.4 | .95 | .10 Phosphate | 3.55 |
| 6.00 | 16.4 | .20 | .10 Phosphate | 3.19 |

$^a$ Tris(hydroxymethyl)aminomethane. $^b$ Rates followed by analysis for inorganic phosphate. $^c$ Potassium chloride added when necessary.

Increasing the ionic strength, besides affecting the rate constants, probably increases the concentration of

(28) "Phosphoric Esters and Related Compounds," Special Publication no. 8, The Chemical Society, London, 1957.

(29) I. Greenwald, J. Redish, and A. C. Kibrick, *J. Biol. Chem.*, **135**, 65 (1940).

(30) H. Tabor and A. B. Hastings, *ibid.*, **148**, 627 (1943); J. R. Van Wazer and C. F. Callis, *Chem. Rev.*, **58**, 1011 (1958).

(31) D. C. Dittmer and J. R. Schaeffer, *J. Am. Chem. Soc.*, **83**, 2475 (1961).

the dianion and decreases that of the monoanion.[32] The first and second ionization constants of phosphoric acid are increased as the ionic strength is increased.[33]

Variation of the buffer and ionic strength at pH 3.2–3.7 had little effect on the rate of hydrolysis of S-$n$-butylphosphorothioate. The data are given in Table V.

Earlier studies had indicated that pyridine and 2,6-lutidine were catalysts of the hydrolysis of S-$n$-butyl-phosphorothioate at pH 8, the stronger base being more efficient,[34] and such results might be interpreted as indicating proton removal in the transition state as was found for the solvolysis of tetrabenzylpyrophosphate.[35] However, experiments with imidazole, a stronger base than pyridine and 2,6-lutidine, indicated it was not the base strength of the latter two compounds that was important in determining the rates. Although the kinetic data for imidazole were not as precise as most of the other data, this base definitely showed no catalytic effect. The rate acceleration with pyridine and 2,6-lutidine could have been caused by a medium effect on a rate constant (perhaps the mono-anion is destabilized relative to the transition state) or the decrease in the dielectric constant of the medium could have altered the relative concentrations of the mono- and the dianion in favor of the monoanion. Dioxane caused a rate acceleration analogous to pyridine. Plots of log $k_{obsd}$ against $1/D$, where $D$ is the dielectric constant of the medium, are linear for pyridine[36] and dioxane but not for methanol. The latter, of course, can react with the ester.[7] The data are given in Table VI.

#### Table VI

EFFECT OF DIOXANE, PYRIDINE, METHANOL, AND IMIDAZOLE ON THE RATES OF HYDROLYSIS OF $1.27 \times 10^{-3}$ M. S-$n$-BUTYL-PHOSPHOROTHIOATE AT "pH 8.0," IONIC STRENGTH 0.10 M, AT 37.1° IN 0.05 M TRIS BUFFER

| Solute, vol. % | $10^4 k_{obsd}$, sec.$^{-1a}$ |
|---|---|
| 1.96 Dioxane | 0.197 |
| 3.29 Dioxane | .234 |
| 9.80 Dioxane | .325 |
| 1.96 Pyridine | .195 |
| 3.92 Pyridine | .229 |
| 9.80 Pyridine | .312 |
| 4.90 Methanol | .259 |
| 9.80 Methanol | .297 |
| 0.178$^b$ Imidazole | .0837 |
| 0.888$^b$ Imidazole | .0828 |

$^a$ Rates followed by analysis for inorganic phosphate. $^b$ Molar. These molar quantities are approximately equal to 1 and 5 vol. % calculated by assuming the density of imidazole was 1.1.

(32) One might speculate that, if esters of thiols and phosphoric acid are intermediates in phosphorylations in living systems, the permeability of the cell walls to ions and the transport of ions may play an important part in the regulation of phosphorylation reactions. Specific effects, such as observed for Mg(II) ions, may be especially important. It has been reported that the phosphorylation of adenosine diphosphate in rat brain mitochondria occurs in a hypotonic medium but not in an isotonic one [A. Fonyo and J. Somogy, *Acta Physiol. Acad. Sci. Hung.*, **18**, 191 (1960); *Chem. Abstr.*, **55**, 13492 (1961)]. Calcium ions inhibit oxidative phosphorylation [F. Aiello and R. Maggio, *Experientia*, **17**, 390 (1961)].

(33) J. W. H. Lugg, *Trans. Faraday Soc.*, **27**, 297 (1931); *J. Am. Chem. Soc.*, **53**, 2554 (1931).

(34) D. C. Dittmer and O. B. Ramsay, Abstracts of Papers, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April, 1958, p. 28 N.

(35) G. O. Dudek and F. H. Westheimer, *J. Am. Chem. Soc.*, **81**, 2641 (1959).

(36) A linear relationship of dielectric constant to weight per cent of pyridine was assumed.

**Reactivity in the Dianion Region.**—Data are insufficient to determine if the dianion of S-$n$-butylphosphorothioate has any reactivity at all but it is reported stable in alkali for four hours at 37°.[12] The slight increase in rate around pH 8–9 for S-(2-aminoethyl)phosphorothioate may be caused by a nucleophilic attack of the free amino group on phosphorus as has been suggested for the hydrolysis of diphenyl 2-aminoethyl phosphate,[37] or by an elimination reaction. The decrease in rate observed at pH 10 may not be real. There was difficulty in obtaining an experimental point at the pH of 9.70, and the rate constant was calculated on the basis of only 25% of reaction.

**Activation Energies and Entropies.**—The energies and entropies of activation for S-$n$-butylphosphorothioate at pH 3.2 and in 2.5 M perchloric acid are given in Table VII. The decrease in rate on going from pH 3.2

#### Table VII

ACTIVATION DATA FOR THE HYDROLYSIS OF S-$n$-BUTYLPHOS-PHOROTHIOATE

| pH | Buffer, M | Ionic strength | $T$, °C. | $10^5 k_{obsd}$, sec.$^{-1}$ | $E_a$, kcal./mole | $\Delta S$, e.u. |
|---|---|---|---|---|---|---|
| 3.35 | 0.10 Phthalate | 1.0 (KCl) | 14.9 | 6.60$^a$ | 23.85 | ... |
| 3.20 | .10 Phthalate | 1.0 | 25.2 | 27.3$^a$ | 23.85 | +3.08 |
| 3.20 | .10 Phthalate | 1.0 | 37.1 | 131$^a$ | 23.85 | ... |
| 2.50 M HClO$_4$ | ... | 2.50 | 25.2 | 3.14$^b$ | 21.64 | −8.62 |
| 2.50 M HClO$_4$ | ... | 2.50 | 37.1 | 11.9$^b$ | 21.64 | ... |
| 2.50 M HClO$_4$ | ... | 2.50 | 46.8 | 36.4$^b$ | 21.64 | ... |

$^a$ $1.64 \times 10^{-2}$ M substrate.    $^b$ $1.27 \times 10^{-3}$ M substrate.

to 2.5 M acid is the result of a decrease in entropy of activation. In 2.5 M perchloric acid, approximately 96% of the reaction proceeds through the neutral acid; and at pH 3.2, nearly 99% of the reaction proceeds through the monoanion (or the neutral acid and hydroxide ion).

The initial state of the monoanion[38] probably is strongly hydrogen bonded (water plus monoanion) and as these hydrogen bonds are broken or stretched in the transition state, the entropy increases. The initial state of the neutral acid may be less strongly hydrogen bonded and the transition state may be more polar and more highly solvated relative to the initial state. One might suppose that the energy to break up the hydrogen-bonded initial state of the monoanion is reflected in the higher energy of activation.

**Antiradiation Results.**[39]—Monosodium S-(2-aminoethyl)phosphorothioate gave "good" protection to mice when administered thirty minutes before irradiation. One hundred percent of the mice survived (30 days) a dose of 825 r. after administration of 400 mg. of the thiophosphate per kg. of mouse. Smaller doses of the compound gave much less protection, and larger doses were toxic. Disodium S-$n$-butylphosphorothioate gave only "slight" protection at levels of 1000. mg./kg.

(37) G. J. Durant, J. H. Turnbull, and W. Wilson, *Chem. Ind.* (London) 157 (1958).

(38) It is assumed that the reactive species is the monoanion.

(39) The testing was done at the Walter Reed Army Institute of Research, Washington 12, D. C., and these results were kindly communicated by Dr. David P. Jacobus.

## Experimental

Dioxane was purified by treatment with hydrochloric acid, potassium hydroxide, and sodium.[40] Pyridine, A.C.S. Analytical Reagent Grade, was distilled from calcium hydride, b.p. 114.5–115°. Other reagents were reagent grade and were used without further purification.

**Barium S-*n*-Butylphosphorothioate.**—The salt was prepared by the method of Wieland and Lambert.[7]

*Anal.* Calcd. for $C_4H_9O_3PSBa\cdot C_2H_5OH$: S, 1.752 mmoles. Found: S, 1.755 mmoles (iodometric analysis).

**Disodium S-*n*-Butylphosphorothioate.**—The disodium salt was prepared by trituration of the barium salt with an equivalent amount of sodium sulfate. The barium sulfate was removed by filtration and a large excess of isopropyl alcohol (ca. 20 vol.) was added to the filtrate. The gelatinous disodium salt was filtered and dried *in vacuo.* Several recrystallizations may be required to give a pure sample.

*Anal.* Calcd. for $C_4H_9O_3SPNa_2$: C, 22.43; H, 4.24; S, 14.97. Found: C, 22.17; H, 4.56; S, 14.76.

The disodium salt could be prepared also by passage of a solution of the barium salt through an ion-exchange column of Amberlite IR-120 (sodium form).

**Sodium S-(2-Aminoethyl)phosphorothioate.**—The monosodium salt was prepared by the same method as that used by Akerfeldt by reaction of trisodium phosphorothioate with 2-bromoethylammonium bromide in aqueous dimethylformamide.[22]

**Determination of Products of Acid Hydrolysis of S-*n*-Butylphosphorothioate.**—To 50 ml. of 3.6 *M* sulfuric acid was added 1.059 g. (0.00494 mole) of disodium S-*n*-butylphosphorothioate, and the mixture was heated on the steam bath for 3.5 hr. The butanethiol was trapped in 5% solution of mercuric cyanide. No mercuric sulfide was observed. The yield of the air-dried mercury salt of butanethiol was 0.9002 g. (96%), m.p. 80–82°. The derivative was recrystallized from ethanol, m.p. 84.5–85° (cor.). No depression of the melting point was observed with an authentic sample of the mercury salt.[41] The sulfuric acid solution was adjusted to pH 4 and refluxed overnight. No further precipitate was observed in the mercuric cyanide trap and the reaction solution gave a negligible titer with iodine.

No mercuric sulfide was observed when the hydrolysis was carried out in 6 *M* hydrochloric acid. A considerable amount of $C_4H_9SHgCl$ was produced along with $(C_4H_9S)_2Hg$.

**Determination of Dissociation Constants of S-*n*-Butylphosphorothioate.**—The disodium salt was titrated at ca. 25° with 0.60 *N* hydrochloric acid and the pH was read from a Beckman Model H-2 pH meter. A plot of pH *vs.* ml. of acid gave a curve with two sharp inflection points. From this curve, $pK_1 = 2.21$ and $pK_2 = 5.93$. The determination of the ionization constants by titration is subject to error because of the hydrolysis which occurs during the time for titration. It is also necessary to use inconveniently large samples for the determination of the $K_1$ of strong acids. Glass and calomel electrodes were used.

When 10 ml. of 0.10 *N* hydrochloric acid was added to a solution of 0.143 g. ($6.67 \times 10^{-4}$ mole) of $C_4H_9SPO_3Na_2$ and 2.021 g. (0.0271 mole) of potassium chloride in 15 ml. of water, the pH was 1.90. When 5.0 ml. of 0.10 *N* hydrochloric acid was added

to a solution of 0.214 g. (0.001 mole) of $C_4H_9SPO_3Na_2$ and 1.722 g. (0.0228 mole) of potassium chloride in 20 ml. of water, the pH was 5.50. Since these pH values are of half-neutralized acid and monoanion, they are equal to $pK_1$ and $pK_2$, respectively, but the determination of the $pK_1$ is subject to the limitations mentioned in the preceding paragraph.

**Kinetic Procedure.**—The rates of hydrolysis of S-*n*-butylphosphorothioate were followed either by determination of inorganic phosphate as described in the preceding paper[19] or by determination of unchanged ester. In the latter case, 5-ml. aliquots are removed from the reaction flask and drained into *ca.* 25 ml. of phosphate buffer at pH 8.5 to quench the reaction. The *n*-butanethiol is extracted with carbon tetrachloride (extraction is complete at this pH). For hydrolyses in strong acid solutions, it is necessary to add a calculated amount of sodium hydroxide solution to the buffer in order to neutralize the excess acid. After two extractions with carbon tetrachloride, the aqueous buffer solution was acidified to pH 1–2 with 6 *N* hydrochloric acid. The unchanged ester was determined by addition of 1.00 ml. of 0.050 *N* iodine solution and back titration with 0.050 *N* sodium thiosulfate.

Pyridine has a pronounced inhibitory effect upon the development of the phosphomolybdenum blue which is used to determine inorganic phosphate. Pyridine also causes the phosphomolybdate complex to become colloidal. These difficulties may be overcome by a change in the order of addition of reagents. After addition of 1 ml. of the reaction solution to the molybdate solution, 10 ml. of isobutyl alcohol is added and the mixture shaken in a separatory funnel for 10 sec. Then, 1 ml. of the reducing agent is added, and the mixture shaken for 10 sec. more. The usual procedure is then followed.[19] Optical densities resulting from this procedure are higher than expected; this is also the case for runs in dioxane, but the rate constants from runs in which the "normal" procedure was followed are not different from the rate constants from runs followed by the modified procedure.

The measurement of "pH" of pyridine solutions was best done by means of a sleeve-type calomel electrode (Beckman 4970–71); a fiber-type calomel electrode gave erratic results.

The hydrolysis of S-(2-aminoethyl)phosphorothioate was followed by analysis of inorganic phosphate since the thiol formed could not be extracted from the reaction mixture. Some difficulty was experienced in determination of some of the infinity points. Two sets of rate constants could be determined depending upon whether one uses half-lives determined from a plot of $\log (D_\infty - D_t)/(D_\infty - D_0)$ *vs.* time for the first 50–60% of reaction or a more arbitrary infinity point chosen to give a straight line through all of the observed points.

**Calculation of Rate Constants.**—Values of $k_{obsd}$ for the hydrolyses followed by the iodometric procedure were obtained by plotting $\log 10 (1 - z)$, where $z$ is the fraction reacted, *vs.* time, whence

$$k_{obsd} = \frac{0.693}{t_{1/2}}$$

where $t_{1/2}$ is the half-life. Runs in which phosphate was determined colorimetrically were treated as previously described.[19]

(40) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, 1955, p. 285.

(41) E. Wertheim, *J. Am. Chem. Soc.,* **51**, 3661 (1929).

# Fluorocarbon Nitro Alcohols and α-Hydroxycarboxylic Acids. The Reaction of Dinitrogen Tetroxide with 2H-Polyfluoro-1-alkenes

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Fluoroölefins possessing the structure —$CF_2CH=CF_2$ have been found to undergo reaction with dinitrogen tetroxide with formation (after hydrolysis) of the novel nitro alcohols —$CF_2CHOHCF_2NO_2$ and α-hydroxycarboxylic acids —$CF_2CHOHCOOH$. From $C_3F_7CH=CF_2$ and $C_3F_7CH_2CF_2CH=CF_2$ there were obtained $C_3F_7CHOHCF_2NO_2$ plus $C_3F_7CHOHCOOH$ and $C_3F_7CH_2CF_2CHOHCF_2NO_2$ plus $C_3F_7CH_2CF_2CHOHCOOH$, respectively. From 2H-pentafluoropropene there was obtained 2H-pentafluoro-1-nitro-2-propanol (which formed a stable addition compound with ethyl ether, $3CF_3CHOHCF_2NO_2 \cdot C_2H_5OC_2H_5$) as well as trifluorolactic acid.

The addition of dinitrogen tetroxide to hydrocarbon olefins which usually yields *vic* dinitroalkanes, nitronitrites (often hydrolyzed to nitro alcohols), and nitronitrates has been well investigated.[1,2]

The addition of dinitrogen tetroxide to the perhaloölefins has been reported to produce the dinitro adduct with tetrachloroethylene,[3,4] tetrabromoethylene,[3] tetrafluoroethylene,[5-8a,9] chlorotrifluoroethylene,[5,7,9] dichlorodifluoroethylene,[5,7] and hexafluoropropene.[8a] Bissel[9] also reported the production of 1-chloro-2-nitrotrifluoroethyl nitrite from chlorotrifluoroethylene, while Knunyants[8a] reported the formation of nitronitrites of the perfluoro-olefins, tetrafluoroethylene, hexafluoropropene, and octafluoroisobutylene, which on hydrolysis gave the nitrocarboxylic acid $NO_2CF_2COOH$, $CF_3CF(NO_2)COOH$, and $(CF_3)_2C(NO_2)COOH$, respectively. Due to the hydrolytic instability of —$CFOH$[8b] or —$CF_2OH$ groups, nitro alcohols are not obtained in these reactions.

The ready availability of highly fluorinated olefins of the type $R_fCH=CF_2$ and $R_f(CH_2CF_2)_nCH=CF_2$,[10] where $R_f$ = perfluoroalkyl, prompted us to study the reaction of these olefins with dinitrogen tetroxide in the hope of synthesizing fluorocarbon nitro alcohols, a new class of compounds.[11] It was indeed of much interest to find that the major product of the reaction (after hydrolysis) was the desired nitro alcohol and that the principal byproduct was the novel fluorocarbon α-hydroxy acids.

Thus, terminal olefins of the structure $R_fCH=CF_2$, where $R_f$ = $CF_3$, $C_3F_7$, or $C_3F_7CH_2CF_2$, have reacted with dinitrogen tetroxide[12] at temperatures of about 100° and in the presence of a halogenated solvent to produce $N_2O_4$ addition products that on hydrolysis yield the nitro alcohol $R_fCH_2OHCF_2NO_2$, derived from the nitronitrite,[13] $R_fCHONOCF_2NO_2$, and the α-hydroxy acid $R_fCHOHCOOH$, probably derived from the dinitrite, $R_fCHONOCF_2ONO$[13,14] and its unstable hydrolysis intermediate, *i.e.*, $R_fCHOHCF_2OH \xrightarrow{-HF} R_fCHOHCOF \xrightarrow{H_2O} R_fCHOHCOOH$.

In contrast to nitro alcohols possessing the —$CHOHCH_2NO_2$ group, the fluorocarbon nitro alcohols such as $C_3F_7CHOHCF_2NO_2$ are stable to both strong acid and base. Thus, 2H-nonafluoro-1-nitro-2-pentanol was stable to boiling concentrated sulfuric acid and hot 20% potassium hydroxide solution. These properties unequivocally eliminated the remote possibility that the structure had a nitrite group in place of the nitro group. The presence of a nitrite group was also ruled out by the infrared and ultraviolet spectra (see below). Incidentally, the intermediate nitronitrite could not have been the isomer resulting from reverse addition, *i.e.*, $R_fCHNO_2CF_2ONO$, because the nitro alcohol and not the nitro acid, *i.e.*, $R_fCHNO_2CF_2OH \rightarrow R_fCHNO_2COF \rightarrow R_fCHNO_2COOH$, was the hydrolysis product isolated.

The infrared spectrum of $C_3F_7CHOHCF_2NO_2$ showed OH stretching absorption at 2.88 $\mu$ and had bands at 6.25 and 7.42 $\mu$, corresponding to the asymmetric and symmetric $NO_2$ stretching vibrations for a —$CF_2NO_2$ group. The ultraviolet spectrum showed the characteristic nitro absorption at 283 m$\mu$.[15,16] The spectra of nitrites, *e.g.*, 2,2,2-trifluoroethyl nitrite, shows a strong band at 221 m$\mu$ and multiple weak absorption bands in the 315–380-m$\mu$ region of the ultraviolet and at 5.8 $\mu$ in the infrared.[15] On the other hand, the compound $ICH_2CF_2NO_2$ shows bands at 6.28 and 7.40 $\mu$ corresponding to the asymmetric and symmetric $NO_2$ stretching absorptions, while the isomer $ICF_2CH_2NO_2$ has corresponding peaks at 6.37 and 7.31 $\mu$[16]; $CF_3CH_2NO_2$

(1) H. Schechter and F. Conrad, *J. Am. Chem. Soc.*, **75**, 5610 (1953), and references therein.

(2) H. Schechter, J. J. Gardikes, and A. H. Pagono, *ibid.*, **81**, 5420 (1959), and references therein.

(3) H. Blitz, *Ber.*, **35**, 1528 (1902).

(4) W. L. Argo, E. M. James, and J. L. Donnelly, *J. Phys. Chem.*, **23**, 578 (1919).

(5) H. B. Haas and A. C. Whitaker, U.S. Patent 2,447,504.

(6) D. D. Coffman, M. S. Raasch, G. W. Ribgy, P. L. Barrick, and W. E. Hanford, *J. Org. Chem.*, **14**, 747 (1949).

(7) R. N. Haszeldine, *J. Chem. Soc.*, 2525 (1953).

(8) (a) I. L. Knunyants and A. V. Fokin, *Dokl. Akad. Nauk SSSR*, **111**, 1035 (1956); **112**, 67 (1957); (b) The first example of a perfluorinated α-fluoro alcohol, heptafluorocyclobutanol, reasonably stable in the absence of moisture, was reported by S. Andreades and D. C. England, *J. Am. Chem. Soc.*, **83**, 4670 (1961).

(9) E. R. Bissell, *J. Org. Chem.*, **26**, 5100 (1961).

(10) M. Hauptschein and R. E. Oesterling, *J. Am. Chem. Soc.*, **82**, 2868 (1960).
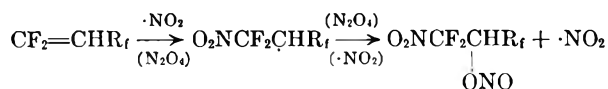
(11) D. J. Cook, O. R. Pierce, and E. T. McBee, *ibid.*, **76**, 83 (1954), prepared the first (and only) examples of aliphatic fluorine-containing nitro alcohols by condensation of nitroalkanes with fluoral and heptafluorobutyral hydrates. These compounds, *e.g.*, $C_3H_7CHOHCH_2NO_2$ and $C_3F_7CHOHCH(C_2H_5)NO_2$, contain hydrocarbon moieties alpha to the nitro group.

(12) Dinitrogen tetroxide is, of course, an equilibrium mixture with other nitrogen oxides, particularly nitrogen dioxide. The composition is dependent on temperature with the monomolecular form predominating at higher temperatures; J. L. Riebsomer, *Chem. Rev.*, **36**, 157 (1945).

(13) It should be understood that, due to the oxidative reaction conditions, the intermediates could also be nitronitrates and dinitrates, respectively.

(14) It is of interest to note that J. L. Reibsomer, *Chem. Rev.*, **36**, 197 (1945), indicated that there had been no instance in which it was shown clearly that the dinitrite is a product of the reaction of an olefin with dinitrogen tetroxide. On the other hand, a usual product, the dinitroalkane, was not isolated from the present reactions, although the lack of a quantitative accounting of products does not preclude the possibility that some dinitro compounds were formed.

(15) R. N. Haszeldine, *J. Chem. Soc.*, 2525 (1953); R. N. Haszeldine and B. J. H. Mattinson, *ibid.*, 4172 (1955).

(16) M. Hauptschein, R. E. Oesterling, M. Braid, E. A. Tyczkowski, and D. M. Gardner, *J. Org. Chem.*, **28**, 1281 (1963). Also, M. Hauptschein and R. E. Oesterling, unpublished work.

has corresponding bands at 6.34 and 7.33 $\mu$[16] (all infrared spectra are of liquid phase). Thus, all of the spectral data support the formulation of a —CF$_2$NO$_2$ compounds as distinct from any isomeric nitrite.

The nitro alcohols were also characterized as either the N-phenyl carbamate or the cyanurate. The compound tris(2H, 4H, 4H-undecafluoro-1-nitro-2-heptyl) cyanurate did not decompose at temperatures up to 340°.

2H-Pentafluoro-1-nitro-2-propanol was isolated as the stable etherate, 3CF$_3$CHOHCF$_2$NO$_2$·C$_2$H$_5$OC$_2$H$_5$. This nitro alcohol, like the perfluoro fatty acids,[17] is sufficiently acidic to form stable addition compounds with ethers in other than 1:1 molar ratios.

The formation of the nitronitrite addition compound probably proceeds by a homolytic process[2] involving attack of nitrogen dioxide (or dinitrogen tetroxide) at the terminal olefin carbon to form a nitroalkyl radical, which then chain transfers (homolytic exchange) with dinitrogen tetroxide or couples with a nitrogen dioxide radical.

$$CF_2{=}CHR_f \xrightarrow[\text{(N}_2\text{O}_4)]{\cdot NO_2} O_2NCF_2\dot{C}HR_f \xrightarrow[\text{(}\cdot NO_2)]{\text{(N}_2\text{O}_4)} O_2NCF_2CHR_f + \cdot NO_2$$
$$\underset{ONO}{|}$$

If the above mechanism is correct, we have in this case an example where the direction of attack of a ·NO$_2$ radical is opposite to that of a CF$_3$· radical.[18,19]

## Experimental

**Reaction of 2-H-Nonafluoro-1-pentene with Dinitrogen Tetroxide.**—A 46.4-g. portion (0.2 mole) of 2H-nonafluoro-1-pentene[10] was added to 100 ml. of 1,1,2-trichlorotrifluoroethane and the resulting solution was cooled to 0°. Into this solution there was condensed 27.6 g. (0.3 mole) of dinitrogen tetroxide and the mixture then was dried over phosphorus pentoxide at 0° for 2 to 3 hr. The solution was filtered into a 300-ml. stainless steel autoclave chilled to −10°, which then was sealed and heated at 100° for 16 hr. with agitation. The autoclave was cooled in an ice bath and the contents transferred to a 200-ml. Vigreux still. The excess dinitrogen tetroxide and trichlorotrifluoroethane solvent was distilled from the product leaving 40 g. of a yellow oil.

This crude product was stirred with 200 ml. of water and then with excess sodium carbonate. An immiscible pale yellow oil was separated, and the water layer was extracted twice with 40-ml. portions of ether. The ether extracts were combined with the separated oil, dried over anhydrous magnesium sulfate, and subsequently evaporated to provide 24 g. (40%) of 2H-nonafluoro-1-nitro-2-pentanol, CF$_3$CF$_2$CF$_2$CHOHCF$_2$NO$_2$. Distillation gave the pure nitro alcohol, b.p. 62° (44 mm.), $n^{25}$D 1.3240.

*Anal.* Calcd. for C$_5$F$_9$H$_2$NO$_3$: C, 20.35; H, 0.68; N, 4.75. Found: C, 20.56; H, 0.86; N, 4.99.

The infrared spectrum of the liquid showed the typical asymmetric and symmetric NO$_2$ stretching vibrations in compounds containing the —CF$_2$NO$_2$ group[15,16] at 6.25 and 7.42 $\mu$, respectively. A typical hydroxyl absorption band was present at 2.88 $\mu$. The ultraviolet spectrum in 95% ethanol showed the expected maximum at 283 m$\mu$.[15,16]

The N-phenyl carbamate derivative of 2H-nonafluoro-1-nitro-2-pentanol was prepared by refluxing for 30 min. 6 g. of the nitro alcohol dissolved in 20 ml. of carbon tetrachloride with 3.6 g. of phenyl isocyanate together with 3 drops of triethylamine.

On cooling, a heavy precipitate was formed, which after filtering and drying yielded 6.8 g. of a pale yellow solid. Recrystallization from a benzene–light petroleum ether solvent gave colorless needles of pure 2H-nonafluoro-1-nitro-2-amyl carbanilate, C$_3$F$_7$CH(O$_2$CNHC$_6$H$_5$)CF$_2$NO$_2$, m.p. 88–89°.

*Anal.* Calcd. for C$_{12}$F$_9$H$_7$N$_2$O$_4$: C, 34.79; H, 1.70; N, 6.76. Found: C, 34.65; H, 2.17; N, 6.57.

The alkaline (sodium carbonate) aqueous layer remaining after ether extraction of the nitro alcohol in the original reaction was acidified with dilute hydrochloric acid and extracted three times with 40-ml. portions of diethyl ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated to give 10 g. (20% yield) of a pale yellow oil which crystallized on standing overnight. Recrystallization from a benzene–light petroleum ether solvent gave colorless needles of pure 2H-pentafluoro-2-hydroxypentanoic acid, CF$_3$CF$_2$CF$_2$CHOHCOOH, m.p. 68–69°, the infrared spectrum of which showed the characteristic—OH and —COOH absorptions at 2.9 and 5.8 $\mu$, respectively.

*Anal.* Calcd. for C$_5$F$_7$H$_3$O$_3$: C, 24.60; H, 1.24; F, 54.49; neut. equiv., 244. Found: C, 24.38, 24.44; H, 1.43, 1.65; F, 54.90, 54.87; neut. equiv., 241, 246, 246.

**Reaction of 2H,4H,4H-Undecafluoro-1-heptene with Dinitrogen Tetroxide.**—A 50-g. portion (0.17 mole) of 2H,4H,4H-undecafluoro-1-heptene[10] was allowed to react with 23 g. (0.25 mole) of dinitrogen tetroxide in 100 ml. of trichlorotrifluoroethane at 100° for 15 hr. according to the previous procedure. There was obtained 61 g. of a crude liquid product that after hydrolysis in aqueous sodium carbonate gave 35 g. (58%) of the water insoluble nitro alcohol. Distillation gave the pure colorless oil, 2H,4H,4H-undecafluoro-1-nitro-2-heptanol, CF$_3$-CF$_2$CF$_2$CH$_2$CF$_2$CHOHCF$_2$NO$_2$, b.p. 72° (4 mm.), $n^{25}$D 1.3347.

*Anal.* Calcd. for C$_7$F$_{11}$H$_4$NO$_3$: C, 23.41; H, 1.12; N, 3.90. Found: C, 23.79; H, 1.20; N, 3.86.

The infrared spectrum of the liquid showed the typical asymmetric and symmetric NO$_2$ stretching vibrations in compounds containing the —CF$_2$NO$_2$ group at 6.25 and 7.39 $\mu$, respectively; an —OH band was at 2.86 $\mu$. The ultraviolet spectrum in 95% ethanol showed a maximum at 284 m$\mu$.

The aqueous alkaline layer from the above reaction was acidified with dilute hydrochloric acid and extracted with diethyl ether to give 10 g. (19%) of a pale yellow oil which crystallized on standing. Recrystallization from benzene–light petroleum ether gave colorless needles of pure 2H,4H,4H-nonafluoro-2-hydroxyheptanoic acid, C$_3$F$_7$CH$_2$CF$_2$CHOHCOOH, m.p. 82–83°, the infrared spectrum of which showed the characteristic —OH and —COOH absorptions at 2.88 and 5.8 $\mu$, respectively.

*Anal.* Calcd. for C$_7$F$_9$H$_5$O$_3$: C, 27.28; H, 1.63. Found: C, 27.00; H, 1.69.

**Reaction of 2H,4H,4H-Undecafluoro-1-nitro-2-heptanol with Cyanuric Chloride.**—A 7.2-g. sample of C$_3$F$_7$CH$_2$CF$_2$CHOHCF$_2$-NO$_2$ was converted to the sodium salt by treating with 0.6 g. of sodium hydride in 40 ml. of anhydrous diethyl ether. There was then added slowly 1.1 g. of cyanuric chloride (heat of reaction caused ether to reflux) and the mixture was then stirred for 1 hr. at room temperature. The reaction mixture was poured into an ice slush and the ether layer was separated, dried, and evaporated to give 7.5 g. of a dense yellow oil. Distillation *in vacuo* gave a pale yellow viscous oil, b.p. 175–185° (0.1 mm.). The infrared spectrum of the liquid is consistent with a tris-(polyfluoronitroalkyl)cyanurate having bands at 5.77, 6.05 sh, 6.20, 6.30 sh, 6.77, 6.99 sh, 7.18, and 12.24 $\mu$; cf., tris-2,2,2-trifluoroethyl cyanurate (Nujol mull) bands at 5.82, 6.27, 6.36, 6.86, 7.01, 7.19, and 12.41 $\mu$.[16]

These bands are generally associated with a triazine ring structure.[20] The strongest of these absorptions in the nitro-cyanurate derivative is at 6.2 $\mu$ enhanced, of course, by the intense NO$_2$ asymmetric stretching vibration. The spectrum of the nitroalkyl cyanurate showed no —OH absorption, as expected.

*Anal.* Calcd. for C$_{24}$F$_{33}$H$_9$N$_6$O$_9$: N, 7.29. Found: N, 7.27.

**Reaction of 2H-Pentafluoropropene with Dinitrogen Tetroxide.**—To a solution of 27.6 g. (0.3 mole) of dinitrogen tetroxide in 100 ml. of CF$_2$ClCFCl$_2$ in a 300-ml. stainless steel autoclave was added by vacuum transfer 26.4 g. (0.2 mole) of 2H-pentafluoropropene.[10,21] After heating at 90–100° for 17 hr. while

(17) M. Hauptschein and A. V. Grosse, *J. Am. Chem. Soc.*, **73**, 5139 (1951).

(18) R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, 3005 (1955). These authors noted, however, that the HBr adduct had the structure CF$_3$-CH$_2$CF$_2$Br, representing attack of a Br on the CF$_2$ group if the mechanism was free radical, which their experimental evidence suggested. They preferred to leave open the issue as to whether a bromine atom behaves differently from a trifluoromethyl radical in that instance.

(19) Although not isolated the formation of small amounts of R$_f$CHNO$_2$-COOH by hydrolysis of R$_f$CHNO$_2$CF$_2$ONO (which represents attack of ·NO$_2$ on the CH group) is not unequivocally eliminated.

(20) W. M. Padgett, II, and W. F. Hamner, *J. Am. Chem. Soc.*, **80**, 803 (1958).

(21) A. L. Henne and T. P. Waalkes, *ibid.*, **68**, 496 (1946).

shaking, the autoclave was cooled to room temperature; upon venting 2.5 g. of unchanged olefin was collected. The liquid product from the autoclave was stirred with 100 ml. of water and then made slightly alkaline with sodium bicarbonate. The water insoluble layer was separated, dried, and the solvent was removed by evaporation. The water layer was extracted three times with diethyl ether; the ether extract was dried and the ether removed by evaporation. The pale yellow oil residues were combined to provide 16 g. of a product that was vacuum distilled to give a colorless liquid, the constant boiling etherate of the nitro alcohol, $3CF_3CHOHCF_2NO_2 \cdot C_2H_5OC_2H_5$, b.p. 70° (100 mm.), $n^{29}D$ 1.335.

*Anal.* Calcd. for $C_{13}F_{15}H_{16}N_3O_{10}$: C, 23.7; H, 2.44; F, 43.2; N, 6.37; ethoxyl, 6.84. Found: C, 24.4; H, 2.78; F, 43.0; N, 6.35; ethoxyl, 6.92.

The infrared spectrum of this etherate showed strong bonded —OH in the 3-$\mu$ region, and a strong asymmetrical and symmetrical $NO_2$ stretching band at 6.25 and 7.33 $\mu$, respectively.

The N-phenyl carbamate derivative of 2H-pentafluoro-1-nitro-2-propanol was prepared by treating the etherate of this nitro alcohol with an equimolar amount of freshly distilled phenyl isocyanate and a small amount of triethylamine as a catalyst. The reaction mixture was warmed for a few minutes on a steam bath and then cooled in ice to solidify the product. Recrystallization from petroleum ether gave $C_6H_5NHCO_2CH(CF_3)CF_2NO_2$, white needles, m.p. 88–89°.

*Anal.* Calcd. for $C_{10}F_5H_7N_2O_4$: C, 38.24; H, 2.25; N, 8.92. Found: C, 38.05; H, 2.27; N, 8.38.

The aqueous alkaline layer remaining after ether extraction of the nitro alcohol was acidified with dilute hydrochloric acid and extracted three times with diethyl ether. This ether extract was dried over magnesium sulfate and evaporated to give 15 g. of a base soluble oil consisting mainly of a hydrate of 3,3,3-trifluoro-lactic acid, $CF_3CHOHCOOH$, b.p. 57° (123 mm.)

*Anal.* Calcd. for $CF_3CHOHCOOH$: F, 39.6; neut. equiv., 144; calcd. for $CF_3CHOHCOOH \cdot H_2O$: F, 35.2; neut. equiv., 162. Found: F, 36.15; neut. equiv., 154.

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# The Reaction of 1,1-Difluoroethylene with Mixtures of Dinitrogen Tetroxide and Iodine. Difluoroiodonitroethanes and 1,1-Difiuoro-1-alkoxynitroethanes

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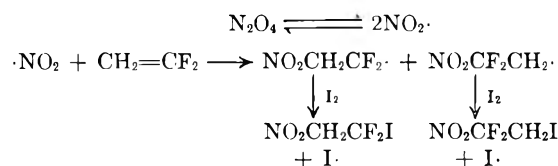*Research and Development Department, Pennsalt Chemicals Corporation, Philadelphia 18, Pennsylvania*

The reaction of 1,1-difluoroethylene with a mixture of dinitrogen tetroxide and iodine has been found to give the two novel isomeric adducts, 1,1-difluoro-1-iodo-2-nitroethane (predominantly) and 1,1-difluoro-2-iodo-1-nitroethane. The unusual facile reaction of the former isomer with alkanols to yield the novel fluoronitro ethers $ROCF_2CH_2NO_2$, where R = $CH_3$- or $CH_3CH_2$-, is described. 1,1,1-Trifluoro-2-nitroethane was produced in good yield by the reaction of anhydrous sodium fluoride in tetramethylene sulfone with 1,1-difluoro-1-iodo-2-nitroethane.

The reaction of olefins with mixtures of dinitrogen tetroxide and iodine has been reported to produce either $\beta$-iodoalkyl nitrates or $\beta$-nitroalkyl iodides, depending on the olefin used and on the reaction conditions.[1-3]

As part of our studies on the chemistry of the olefin 1,1-difluoroethylene,[4,5] we wished to investigate the synthesis and reactivity of the nitroiodides of 1,1-difluoroethylene. Of the theoretically possible adducts, $ICF_2CH_2NO_2$, $ICH_2CF_2NO_2$, $ICH_2CF_2ONO$ ($ICH_2COOH$ after hydrolysis), and $ICF_2CH_2ONO$ ($ICF_2CH_2OH$ after hydrolysis), the first three were obtained from the reaction of a mixture of dinitrogen tetroxide and excess iodine with 1,1-difluoroethylene using methylene chloride as the solvent.

The predominant nitroiodide isomer produced was 1,1-difluoro-1-iodo-2-nitroethane, whether the olefin was added to a mixture of dinitrogen tetroxide and iodine or whether dinitrogen tetroxide was added slowly to the other reactants. The latter procedure minimized the formation of iodonitrite (or iodonitrate), which after hydrolysis gave iodoacetic acid, *i.e.*, $ICH_2CF_2ONO \rightarrow [ICH_2CF_2OH] \rightarrow ICH_2COOH$. The mechanism of formation of the nitroiodides probably

involves the trapping of an intermediate $\beta$-nitroalkyl radical with iodine.

The nitro radical preferentially, but not exclusively, attacked the $CH_2$ group of 1,1-difluoroethylene to give predominantly $ICF_2CH_2NO_2$. This finding is similar to the attack of a perfluoralkyl radical, *e.g.*, $C_3F_7$· from $C_3F_7I$, on 1,1-difluoroethylene, which gave 95% of $C_3F_7CH_2CF_2I$ and only 5% of $C_3F_7CF_2CH_2I$.[6]

The main isomer $ICF_2CH_2NO_2$ was found to react readily with dry sodium fluoride in tetramethylene sulfone to give a good yield of 1,1,1-trifluoro-2-nitroethane, $CF_3CH_2NO_2$, demonstrating that the iodine atom was attached to the —$CF_2$ group. The infrared and ultraviolet spectra of both of these compounds were consistent with the presence of a —$CH_2NO_2$ group (see Experimental) and with a —$CF_2I$ group for the former, *i.e.*, $\lambda_{max}$ at 270 m$\mu$ in the ultraviolet.

The isomer 1,1-difluoro-1-iodo-2-nitroethane is unstable in basic aqueous solution, and has been found

$$N_2O_4 \rightleftharpoons 2NO_2\cdot$$
$$\cdot NO_2 + CH_2{=}CF_2 \longrightarrow NO_2CH_2CF_2\cdot + NO_2CF_2CH_2\cdot$$
$$\downarrow I_2 \qquad\qquad \downarrow I_2$$
$$NO_2CH_2CF_2I \qquad NO_2CF_2CH_2I$$
$$+ I\cdot \qquad\qquad + I\cdot$$

(1) G. B. Bachman and T. J. Logan, *J. Org. Chem.*, **21**, 1467 (1956).

(2) T. E. Stevens and W. D. Emmons. *J. Am. Chem. Soc.*, **80**, 338 (1958).

(3) G. B. Bachman, T. J. Logan, K. R. Hill, and N. W. Standish, *J. Org. Chem.*, **25**, 1312 (1960).

(4) M. Hauptschein, A. H. Fainberg, and M. Braid, *ibid.*, **23**, 322 (1958).

(5) M. Hauptschein, M. Braid, and F. E. Lawlor, *J. Am. Chem. Soc.*, **80**, 846 (1958).

(6) (a) M. Hauptschein and R. E. Oesterling, *ibid.*, **82**, 2868 (1960); (b) We favor this explanation for the principal mode of formation of the isomer 1,1-difluoro-2-iodo-1-nitroethane over alternative interpretations involving ionic species (*e.g.*, $NO_2^-$, $I^+$) or iodine atom attack.

to undergo facile reactions with alkanols such as ethanol and methanol.

$$ROH + ICF_2CH_2NO_2 \longrightarrow ROCF_2CH_2NO_2 + HI$$

It is believed likely that the reaction proceeds through the *in situ* formation of the very reactive nitroölefin.

$$ICF_2CH_2NO_2 \xrightarrow{-HI} [CF_2{=}CHNO_2]$$

$$[CF_2{=}CHNO_2] + ROH \longrightarrow ROCF_2CH_2NO_2$$
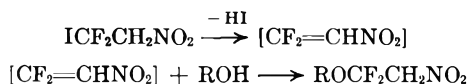
### Experimental

**The Reaction of 1,1-Difluoroethylene with a Mixture of Dinitrogen Tetroxide and Iodine.**—A stainless steel autoclave of 1400-ml. capacity was charged with 500 ml. of methylene chloride, 92 g. (1.0 mole) of dinitrogen tetroxide and 381 g. (1.5 moles) of iodine. The autoclave was connected to a cylinder of 1,1-difluoroethylene, and placed on a shaking apparatus. The olefin at a pressure of 250 p.s.i.g. was introduced into the autoclave at room temperature. Within 5–10 min. the pressure dropped to less than 100 p.s.i.g. The reactor was repressured with 1,1-difluoroethylene several times over a period of about 4 hr. until the pressure remained constant at 200 p.s.i.g. During this procedure, the reaction temperature remained at 25–30°; very little heat of reaction was observed. The autoclave was vented and the concents were filtered to remove unchanged iodine. The methylene chloride solution was washed with aqueous sodium bisulfite until all iodine color was removed, leaving a pale yellow solution. The solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed by distillation. The residue was distilled through a Vigreux column at 161 g. (68%)[7] of product having a boiling range of from 65 to 70° at 20 mm. was collected.

This product was shown by vapor–liquid chromatographic analysis to consist of the isomers 1,1-difluoro-1-iodo-2-nitroethane, $ICF_2CH_2NO_2$, and 1,1-difluoro-2-iodo-1-nitroethane, $ICH_2CF_2NO_2$, in about a 3:1 ratio.

*Anal.* Calcd. for $C_2F_2H_2INO_2$: C, 10.13; H, 0.85; N, 5.91. Found: C, 10.46; H, 0.87; N, 6.07.

Pure $ICH_2CF_2NO_2$, the first isomer component to be trapped by preparative chromatography, using a DC-200 column (10% substrate on Chromosorb) at 75°, boiled at about 50° (10 mm.). The mass spectrum showed a parent peak ($m/e$) of 237 (molecular weight), and peaks ($m/e$) for $C_2F_2H_2I$ (191), $C_2F_2H_2NO_2$ (110), and $C_2F_2H_2$ (64), corresponding to the loss of $NO_2$, I, or both $NO_2$ and I, respectively. The corresponding peaks for $NO_2$ (46) and for I (127) were also present, as well as many of the possible one carbon cleavage products and NO (30). The principal absorption bands (in microns) for the liquid in the infrared spectrum were at 3.27 m, 3.35 m, 3.40 m, 6.28 vvs, 7.09 s, 7.40 vs, 7.76 vs, 7.96 vs, 8.51 s, 8.88 vs, 9.36 vs, 10.15 vs, 11.82 vs, 13.47 vs, 14.55 s (s = strong, vs = very strong, vvs = very, very strong, m = medium). The peaks at 6.28 and 7.40 $\mu$ correspond to the asymmetric $NO_2$ and symmetric $NO_2$ stretching vibrations, respectively, of the $-CF_2NO_2$ group.[8] The ultraviolet spectrum of the isomer $ICH_2CF_2NO_2$ taken in isoöctane solution had a maximum absorption at 267 m$\mu$, corresponding to the $-CH_2I$ group in that compound.

Pure $ICF_2CH_2NO_2$, the second isomer component to be trapped out by preparative chromatography, and also obtained by fractional distillation, boiled at 61° (11 mm.) and at 30° (1 mm.), $n^{26}D$ 1.4750.

*Anal.* Calcd. for $C_2F_2H_2INO_2$: C, 10.13; H, 0.85; N, 5.91. Found: C, 10.13; H, 0.87; N, 5.97.

The mass spectrum of 1,1-difluoro-1-iodo-2-nitroethane showed a parent peak ($m/e$) of 237, as well as the other peaks noted for the isomer 1,1-difluoro-2-iodo-1-nitroethane, although in quite different relative intensities, as expected for isomers. It is of interest to note that the relative intensity of the $m/e$ peak at 110 representing loss of an iodine was much greater for $ICF_2CH_2NO_2$ than for the isomer $ICH_2CF_2NO_2$, whereas the reverse was true

(to a lesser extent) for the $m/e$ peak at 191 representing loss of a $NO_2$ group.

The infrared spectrum of $ICF_2CH_2NO_2$ (liquid) displayed the following principal absorption bands (in microns): 3.27 m, 3.36 m, 3.42 m, 6.37 vvs, 7.08 vs, 7.31 vs, 7.51 vs, 8.06 vs, 8.50 vs, 9.02 vs, 9.58 vs, 10.57 vs, 10.98 vs, 11.23 vs, 11.96 s, 13.17 s, 15+ s. The peaks at 6.37 and 7.31 $\mu$ correspond to the asymmetric $NO_2$ and symmetric $NO_2$ stretching vibrations, respectively of the $-CH_2NO_2$ group.

The ultraviolet spectrum of $ICF_2CH_2NO_2$ taken in isoöctane solution has an absorption maximum at 270 m$\mu$, corresponding to the $-CF_2I$ group.[9,10]

**Isolation of By-product Iodoacetic Acid.**—The aqueous bisulfite wash from the previous experiment was not examined. From a prior run, however, carried out in a 300-ml. autoclave, charged with 100 ml. of methylene chloride, 51 g. of dinitrogen tetroxide, 1.55 g. of iodine, and 64 g. of 1,1-difluoroethylene, which yielded 34 g. of crude nitroiodide adduct, mostly $ICF_2CH_2NO_2$, the bisulfite aqueous layer was extracted with diethyl ether and dried with anhydrous magnesium sulfate. After removal of the ether by distillation there was obtained 15 g. of iodoacetic acid, m.p. 80–81°, the infrared spectrum of which was identical to an authentic sample. An additional 16 g. of iodoacetic acid was found in the residue after vacuum distillation of the nitroiodide. (Note that since no significant residue containing iodoacetic acid was found after distillation of the nitroiodide of the previous reaction, it is probable that relatively small quantities of iodoacetic acid were present in the aqueous wash of that reaction.)

**Reaction of 1,1-Difluoroethylene with a Mixture of Dinitrogen Tetroxide and Iodine (Alternative Procedure).**—A 300-ml. stainless steel autoclave was charged with 155 g. (0.61 mole) of iodine crystals, 75 ml. of methylene chloride, and 64 g. (1.0 mole) of 1,1-difluoroethylene. A stainless steel cylinder was charged with 51 g. (0.55 mole) of dinitrogen tetroxide and 25 ml. of methylene chloride. The methylene chloride solution of dinitrogen tetroxide was pumped slowly into the autoclave over a period of about 16 hr. while shaking at room temperature. After venting of the autoclave and removal of about 68 g. of solid iodine, the methylene chloride solution was washed with water and then with an aqueous solution of sodium bisulfite. The solution was dried over anhydrous magnesium sulfate. The methylene chloride was removed by distillation to give 97 g. of a red liquid. Fractional distillation and infrared analysis showed it to consist mostly of the isomer $ICF_2CH_2NO_2$ and minor amounts of the reverse addition product $ICH_2CF_2NO_2$. There was recovered from this run only 3 g. of iodoacetic acid.

**Preparation of 1,1,1-Trifluoro-2-nitroethane from 1,1-Difluoro-1-iodo-2-nitroethane.**—A mixture of 25 ml. of dry tetramethylene sulfone, 9.3 g. (0.04 mole) of $ICF_2CH_2NO_2$ and 3 g. of dry sodium fluoride (0.07 mole) was stirred at 100° for 1.5 hr. The reaction mixture was then diluted with 200 ml. of water and steam distilled giving a pale yellow oil which was separated and dried over anhydrous magnesium sulfate. A yield of 3.5 g. (68%) of crude $CF_3CH_2NO_2$ was obtained which on distillation gave the pure colorless liquid, 1,1,1-trifluoro-2-nitroethane, b.p. 96°.[11]

*Anal.* Calcd. for $C_2F_3H_2NO_2$: N, 10.86. Found: N, 10.99.

The infrared spectrum (liquid) showed the characteristic asymmetric $NO_2$ vibration of 6.34 $\mu$ and the symmetric $NO_2$ vibration at 7.33 $\mu$. The ultraviolet spectrum of $CF_3CH_2NO_2$ taken in isoöctane had a maximum absorption of low intensity at 277 m$\mu$.

**The Reaction of 1,1-Difluoro-1-iodo-2-nitroethane with Ethanol.**—To 28 g. (0.61 mole) of absolute ethanol at room temperature there was slowly added while stirring 23 g. (0.097 mole) of $ICF_2CH_2NO_2$. The temperature rose during the addition to about 40°. Stirring was continued for an additional 4 hr. and the reaction product then was isolated by distillation of all volatile components boiling lower than 50° at 0.1 mm. and then treatment of the distillate with water. The water-insoluble parts were dried and redistilled affording 9.5 g. of the fluorinated nitro ether, 1,1-difluoro-1-ethoxy-2-nitroethane, $CH_3CH_2OCF_2CH_2NO_2$, b.p. 61° (20 mm.).

*Anal.* Calcd. for $C_4F_2H_7NO_3$: C, 30.97; H, 4.55; N, 9.03. Found: C, 30.40; H, 4.28; N, 8.93.

The infrared spectrum of $C_2H_5OCF_2CH_2NO_2$ (liquid) displayed the following absorption bands (in microns): 3.27 m, 3.35

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(7) Based on utilization of two nitro groups from each mole of dinitrogen tetroxide.

(8) The corresponding values for the asymmetric and symmetric $NO_2$ vibrations for the compounds $R_fCHOHCF_2NO_2$ were at 6.25–6.26 $\mu$ and at 7.39–7.42 $\mu$, respectively. See M. Hauptschein and R. E. Oesterling, *J. Org. Chem.*, **28**, 1279 (1963).

(9) R. N. Haszeldine, *J. Chem. Soc.*, 1764 (1953).

(10) M. Hauptschein, M. Braid, and A. H. Fainberg, *J. Am. Chem. Soc.*, **83**, 2495 (1961).

(11) E. T. McBee, H. B. Hass, and I. M. Robinson, *ibid.*, **72**, 3579 (1950).

ms, 3.42 m, 6.36 vvs, 7.04 s, 7.26 vs, 7.40 vs, 7.81 vs, 8.07 vs, 8.35 s, 8.72 s sh, 9.16 s, 9.38 s, 9.67 vs, 10.37 m, 10.97 ms, 11.30 s, 12.07 ms, 13.04 ms, 14.47 s. The peak at 6.36 $\mu$ corresponded to the asymmetric $NO_2$ stretching vibration in compounds containing the —$CH_2NO_2$ group.

On treatment of the nitro ether with a sodium hydroxide solution, much fluoride ion was liberated, a behavior similar to that for ethers of the type $ROCF_2CH_2Cl$.[12]

**The Reaction of 1,1-Difluoro-1-iodo-2-nitroethane with Methanol.**—$ICF_2CH_2NO_2$ (10.3 g.) was refluxed with 50 ml. of methanol for 4 hr. after which the excess methanol, as well as some methyl iodide and hydrogen iodide formed in the reaction, were boiled off at atmospheric pressure. The residue was dissolved in methylene chloride, washed with aqueous sodium bisulfite to remove iodine, dried over anhydrous magnesium sulfate, and distilled. The pure ether, 1,1-difluoro-1-methoxy-2-nitroethane, b.p. 57° (22 mm.), was obtained in 95% yield.

*Anal.* Calcd. for $C_3F_2H_5NO_3$: C, 25.54; H, 3.57; F, 26.93; N, 9.93. Found: C, 25.51; H, 3.41; F, 26.44; N, 9.84.

The infrared spectrum of $CH_3OCF_2CH_2NO_2$ (liquid) displayed the following absorption bands (in microns): 3.22 m, 3.32 ms,

3.46 m, 6.38 vvs, 6.89 s, 7.03 s, 7.22 s, 7.40 vs, 7.77 vs, 8.05 vs, 8.73 s, 8.90 s, 9.33 s, 9.71 s, 10.00 s, 10.97 vs, 12.02 s, 12.22 ms, 13.00 s, 14.46 s. The peak at 6.38 $\mu$ corresponds to the asymmetric $NO_2$ stretching vibration in compounds containing the —$CH_2NO_2$ group.

**Vapor–Liquid Partition Chromatography.**—A Perkin–Elmer, Model 154, vapor fractometer was used.

**Infrared Spectra.**—A Perkin–Elmer Infracord, Model 137, was used. The individual spectrograms were calibrated immediately after they were run using a polystyrene film as a standard. The absorption wave lengths are believed accurate to ±0.02 $\mu$.

**Ultraviolet Spectra.**—A Beckman ratio recording spectrophotometer, Model DK-2, was used. The wave length accuracy was checked by means of the mercury-in-quartz arc lamp.

**Mass Spectra.**—A Bendix Time-of-Flight spectrometer (Model 12) at an ionizing potential of 70 volts was used.

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(12) P. Tarrant and H. C. Brown, *J. Am. Chem. Soc.*, **73**, 1781 (1951).

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# The Synthesis of DL-*threo*- and -*erythro*-Amicetose 2,4-Dinitrophenylhydrazones[i]

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*Received November 21, 1962*

The DL-*erythro* (III) and -*threo* (IV) 2,4-dinitrophenylhydrazones of amicetose have been prepared from 1-nitro-4-hexene (VIII) which was synthesized from *trans*-4-hexen-1-ol (V). The structure proof of these isomers involved reaction with one mole of periodate. The natural isomer (I) was shown to be in the *erythro* series by an analysis of the rate of oxidation with periodate. Paper electrophoresis studies confirmed this result.

The antibiotic amicetin has been isolated from *Streptomyces plicatus*[3] and *Streptomyces vinaceus-drappus*.[4] Methanolysis of amicetin yielded, besides cytimidine,[5,6] a basic amino sugar, amosamine, and a neutral sugar amicetose isolated as its methyl glycoside in this laboratory.[7] Hydrolysis of the methyl glycoside of amicetose with 3 $N$ hydrochloric acid gave free amicetose which was characterized as a crystalline 2,4-dinitrophenylhydrazone (I), m.p. 152–153°. The structure was established[7] by periodate cleavage of the 2,4-dinitrophenylhydrazone (I), which consumed only one mole of reagent in fifteen minutes with no further significant uptake in three hours. Acetaldehyde was isolated as its 2,4-dinitrophenylhydrazone in 51% yield as the volatile reaction product. The nonvolatile residue gave succindialdehyde bis-2,4-dinitrophenylhydrazone (II) in quantitative yield.

In this paper the synthesis of the DL-*erythro* and -*threo* isomers (III and IV) of amicetose 2,4-dinitrophenylhydrazone is reported and evidence presented that shows natural amicetose 2,4-dinitrophenylhydrazone to be in the *erythro* series.

4-Hexen-1-ol (V) was prepared from 3-bromo-2-methyltetrahydropyrane by the procedure of Brandon, Derfer, and Boord[8] in 55% over-all yield. The infrared absorption spectrum of (V) showed a strong absorption at 10.38 $\mu$, characteristic of a *trans* double bond. The 3,5-dinitrobenzoate derivative (VI) was prepared from V in 41% yield and also showed a strong absorption at 10.38 $\mu$. Addition of phosphorus tribromide to a cooled ethereal solution of *trans*-4-hexen-1-ol (V) gave a 53% yield of 1-bromo-4-hexene (VII). Treatment of VII with sodium nitrite in dimethylformamide[9] at −10° converted it to 1-nitro-4-hexene (VIII) in 65% yield.



V. R = —OH
VI. R = $C_6H_3(NO_2)_2$—COO—
VII. R = —Br
VIII. R = —$NO_2$
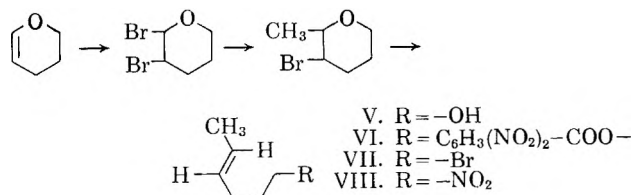
The reaction of 1-nitro-4-hexene (VIII) with silver acetate and iodine in acetic acid and water (1.5 moles)[10] gave the expected monoacetate of DL-1-nitro-4,5-

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(1) This investigation was made possible by research grants CY 3772 and A 769 from the National Institutes of Health, Public Health Service.

(2) Wellcome Trust Travel Grant Recipient, 1960.

(3) T. H. Haskell, A. Ryder, R. P. Frohardt, S. A. Fusari, T. L. Jakubowski, and Q. R. Bartz, *J. Am. Chem. Soc.*, **80**, 743 (1958).

(4) J. W. Hinman, E. L. Caron, and C. DeBoer, *ibid.*, **75**, 5864 (1953).

(5) E. H. Flynn, J. W. Hinman, E. L. Caron, and D. O. Woolf, *ibid.*, **75**, 5867 (1953).

(6) T. H. Haskell, *ibid.*, **80**, 747 (1958).

(7) C. L. Stevens, K. Nagarajan, and T. H. Haskell, *J. Org. Chem.*, **27**, 2001 (1962).

(8) R. C. Brandon, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **72**, 2120 (1950); L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707 (1950), prepared V from the corresponding chlorotetrahydropyrane and showed the product to be mostly the *trans* isomer.

(9) N. Kornblum, H. O. Larsen, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *ibid.*, **78**, 1497 (1956).

(10) R. B. Woodward and F. V. Brutcher, *ibid.*, **80**, 209 (1958); S. Winstein and R. E. Buckles, *ibid.*, **64**, 2780, 2787 (1942).

hexanediol (IX) in 38.5% yield. In addition, the diacetate X was isolated in 14.5% yield. The monoacetate IX readily dissolved in 2 N aqueous potassium hydroxide solution containing a trace of methanol. The resulting *aci* salt solution was added to an 8 N sulfuric acid solution containing 2,4-dinitrophenylhydrazine reagent. Extensive alumina chromatography of the Nef reaction[11] products afforded a solid 2,4-dinitrophenylhydrazone, m.p. 105–106°, in 11% yield. Since this was the only isomer isolated, it was considered to be the DL-*threo* isomer IV of amicetose arising from an attack by water molecules on the reaction intermediate shown below.[10]



IX. $R_1$ = Ac, $R_2$ = H
or $R_1$ = H, $R_2$ = Ac
X. $R_1$ = $R_2$ = Ac
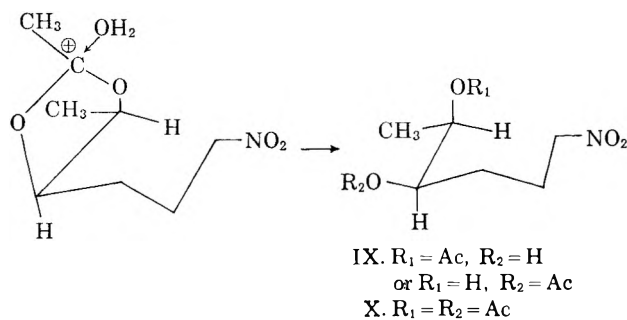
On paper chromatography the *threo* isomer IV ran as a single spot in several different systems. The $R_f$ values were identical to that of the natural isomer I. The ultraviolet and infrared spectra were very similar to those of natural isomer but the latter showed a slightly different pattern in the C—O stretching region (8.5 to 9.5 μ). The *threo* isomer IV was further characterized as its diacetate IVa, m.p. 124.5–125.5°. This DL-diacetate also strongly resembled the optically active natural isomer diacetate in its paper chromatographic behavior and in its infrared and ultraviolet absorption spectral properties. 1-Nitro-4,5-hexanediol diacetate (X) was likewise converted to the *aci* salt and then treated under the conditions of the Nef reaction to give the same steric isomer IV, which was isolated as its 2,4-dinitrophenylhydrazone in 9% yield. Thus, both the monoacetate and the diacetate from the original hydroxylation reaction had the same steric configuration. The diacetate undoubtedly arose from the monoacetate by acetylation with the solvent acetic acid, as shown by Lucas, Mitchell, and Garner.[12]

Synthesis of the DL-*erythro* isomer (III) was attempted by the reaction of 1-nitro-4-hexene (VIII) with dry silver acetate and iodine in benzene.[13] However, in the reaction, an inseparable mixture of the DL-*threo* (IV) and -*erythro* (III) isomers was obtained (probably due to the presence of some water in the system). Hence, an alternate approach was sought.

Epoxidation of 1-nitro-4-hexene (VIII) with peracetic acid in chloroform gave 1-nitro-4,5-epoxyhexane (XI). This compound formed a water soluble sodium *aci* salt on addition to an aqueous solution of 1 N sodium hydroxide containing a trace of methanol. This *aci* salt solution was added slowly to a well stirred aqueous 8 N sulfuric acid 2,4-dinitrophenylhydrazine solution at 0°. Chromatography of the Nef reaction products

over alumina gave a solid, m.p. 138°, in 3% yield, which had correct analysis for the DL-*erythro* isomer as would be expected from a *trans* opening of the epoxide by acid. Paper chromatography showed a single spot with an $R_f$ value identical with that of the natural isomer, and the ultraviolet and infrared absorption spectra closely resembled those of the natural isomer (I).

The structural identity of the DL-*erythro* (III) and -*threo* (IV)-isomers was proved by cleavage with sodium periodate. In each case one mole of periodate[14] was consumed. The periodate cleavate products were isolated as their 2,4-dinitrophenylhydrazones. Both the DL-*erythro* and -*threo* isomers gave succindialdehyde and acetaldehyde in good yields.
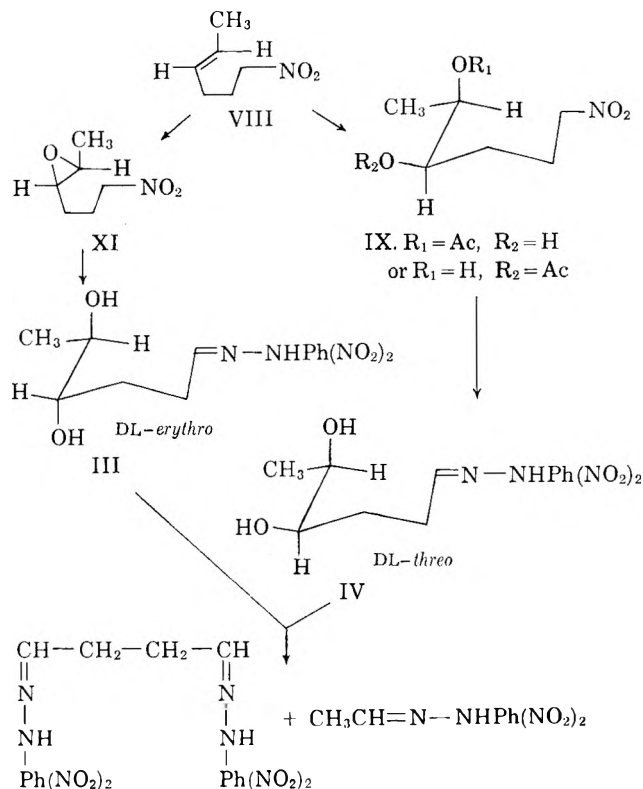


A comparative study of the rates of periodate uptake of the natural (I) and the DL-*threo* (IV) and -*erythro* (III) isomers was conducted in dilute solutions at 8°. The results (Table I) show that the DL-*threo* isomer (IV) consumed periodate more rapidly than either the DL-*erythro* (III) or natural (I) isomer, the latter two having identical rates within experimental error. This result indicated that the natural isomer was in the *erythro* series.

Confirmation of this result came from paper electrophoresis studies. Frahn and Mills[15] were able to separate *meso* and DL-*diols* by paper electrophoresis using a borate buffer. In the first run the three isomers (I, III, and IV), as their 2,4-dinitrophenylhydrazones, were dissolved in borax solution and then spotted as yellow zones on paper strips. However, on applying a potential each of the isomers was observed to move the same distance[16] within experimental error. In the

(11) W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

(12) H. J. Lucas, F. W. Mitchell, Jr., and H. K. Garner, *J. Am. Chem. Soc.*, **72**, 2138 (1950). Also see S. Winstein and R. E. Buckles, ref. 10.

(13) C. Prevost, *Compt. rend.*, **196**, 1129 (1933); **197**, 1661 (1933); and C. Prevost and Wiemann, *ibid.*, **204**, 700 (1937).

(14) Stevens, Nagarajan, and Haskell[7] have previously shown in a control experiment that acetone 2,4-dinitrophenylhydrazone consumed a negligible amount of periodate even after 24 hours.

(15) J. L. Frahn and J. A. Mills, *Chem. Ind.* (London), 578 (1956).

(16) Under the same experimental conditions heptaldehyde 2,4-dinitrophenylhydrazone did not move.

next run the three isomers (I, III, and IV) were dissolved in methanol and spotted as a yellow zone on paper strips. Paper electrophoresis was conducted in 0.083 *M* borax at a pH of 9.2 and a constant voltage of 380. Under these conditions, only the *threo* isomer (IV) was observed to migrate. This result was interpreted as evidence that the natural isomer (I) was in the *erythro* series. The results from the periodate and electrophoresis studies were not unexpected. Both reactions involve a *cis* cyclization between the diol group and either sodium periodate or sodium borate. In both cases a *cis* cyclization reaction of the *erythro* isomer (III) would involve methylalkyl chain eclipsing with an unfavorable conformation. A *cis* cyclization reaction of the *threo* isomer (IV) would involve a much less severe eclipsing (methyl and hydrogen) and was therefore expected to be favored. Thus, the *erythro* isomer (III) could be expected to consume periodate less rapidly and complex with borate and consequently migrate more slowly than the *threo* isomer (IV).



X = Periodate or Borate Complex

DL-*erythro*                    DL-*threo*
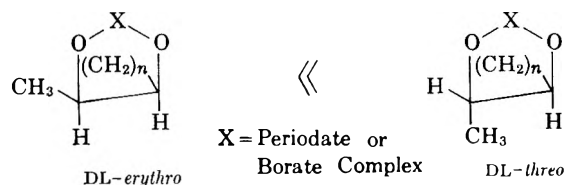
## Experimental

The 3,5-Dinitrobenzoate of *trans*-4-Hexen-1-ol.—A solution of 3,5-dinitrobenzoyl chloride (3.2 g., 13.8 mmoles) in dry benzene (10 ml.) was added at 0° to a solution of *trans*-4-hexen-1-ol (1.0 g., 10 mmoles), [prepared in 62% yield by the procedure of Brandon, Derfer, and Boord[8] from 3-bromo-2-methyltetrahydropyran (130.0 g., 0.72 mole) and sodium (32.5 g., 1.41 g.-atoms)], dry benzene (50 ml.), and pyridine (0.94 g.) and set aside at 25° for 12 hr. Pyridine hydrochloride was filtered and the benzene layer was washed consecutively with aqueous sodium carbonate and water. Evaporation of the solution after drying with anhydrous magnesium sulfate gave a pasty solid which was chromatographed in benzene over alumina to give the 3,5-dinitrobenzoate of *trans*-4-hexen-1-ol (1.2 g., 40.8%), m.p. 38.8–39.4° (recrystallized from methanol). It showed an infrared absorption

at 10.38 μ (image of C=C structure with H atoms).
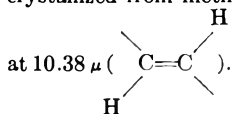
*Anal.* Calcd. for $C_{13}H_{14}N_2O_6$: C, 53.09; H, 4.80; N, 9.50 O, 32.63. Found: C, 53.25; H, 4.67; N, 9.46; O, 32.33.

1-Bromo-4-hexene.—Phosphorus tribromide (350.0 g., 1.3 moles) in dry ether (500 ml.) was added dropwise over a 2-hr. period to a solution of 4-hexen-1-ol (338.0 g., 3.38 moles) in dry ether (1 l.) and pyridine (30 ml.) in a bath cooled to −30°. The temperature was maintained at 20° for 24 hr. and then the reaction mixture was poured into ice–water (2 l.) and extracted with ether (5 × 100 ml.). The ether was washed with dilute aqueous sodium bicarbonate at 5°, water and then saturated aqueous sodium chloride. After drying the resulting solution over anhydrous magnesium sulfate, distillation gave an oil, 1-bromo-4-hexene (295.0 g., 53%), b.p. 63–65° (35 mm.), $n^{25}D$ 1.4652, infrared, 10.35 μ.

*Anal.* Calcd. for $C_6H_{11}Br$: C, 44.18; H, 6.81. Found: C, 44.08; H, 6.81.

1-Nitro-4-hexene.—To a vigorously stirred solution of sodium nitrite (10.5 g., 0.15 mole) in dry dimethylformamide (500 ml.) cooled to −10° was added 1-bromo-4-hexene (16.3 g., 0.1 mole). After the addition, the temperature was allowed to rise to 20°, and after 4 hr. the solution was poured into ice–water (500 ml.). After extraction with petroleum ether, the organic layer was washed successively with water and saturated aqueous sodium chloride and then dried over anhydrous magnesium sulfate. Distillation gave two fractions; the lower boiling one had b.p.

53–55° (32.0 mm.), $n^{25}D$ 1.4224, infrared, 6.2 μ, and amounted to 1.3 g. (probably a nitrite ester); and the higher boiling 1-nitro-4-hexene (7.5 g., 65%) which distilled as a colorless oil had b.p. 34–37° (1.2 mm.), $n^{25}D$ 1.4423, infrared (CCl₄), 6.45 μ (nitro) and 10.35 μ.

*Anal.* Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.49; H, 8.58; N, 11.09.

The Mono- and Diacetates of 1-Nitro-4,5-hexanediol.—To a well-stirred yellow complex of silver acetate (6.72 g., 0.04 mole) and iodine (5.20 g., 0.04 mole) in glacial acetic acid (240 ml.) maintained at 40° was added 1-nitro-4-hexene (2.58 g., 0.022 mole) in glacial acetic acid (10 ml.) and water (0.5 ml.). The mixture was stirred and heated under reflux for 16 hr., and the acetic acid was distilled *in vacuo* to yield a viscous oily residue. This oil was dissolved in benzene, filtered to remove insoluble inorganic material and after evaporation of the benzene gave a residual oil which on distillation afforded unchanged 1-nitro-4-hexene (0.31 g., 9.6%), b.p. 25° (0.05 mm.). The viscous residue was chromatographed over alumina to give on elution with petroleum ether DL-*threo*-1-nitro-4,5-hexanediol diacetate (0.9 g., 14.2%) as an oil, infrared, 5.75 μ (-OAc) and 6.45 μ (-nitro).

*Anal.* Calcd. for $C_{10}H_{17}NO_6$: C, 48.56; H, 6.93; N, 5.69; CH₃CO, 34.81. Found: C, 48.87; H, 6.87; N, 6.17; CH₃CO, 35.09.

Further elution of the original alumina column with benzene–ether (9:1) gave as a gum the monoacetate of DL-*threo*-nitro-4,5-hexanediol (1.44 g., 38.5%), infrared, 5.75 μ (-OAc) and 6.45 μ (nitro).

*Anal.* Calcd. for $C_8H_{15}NO_5$: C, 46.82; H, 7.40; N, 6.83; CH₃CO, 20.96. Found: C, 46.87; H, 7.10; N, 6.91; CH₃CO, 21.64.

1-Nitro-4,5-epoxyhexane.—To peracetic acid (3.5 g., 0.053 mole) in chloroform (233 ml.) cooled to 0° was added 1-nitro-4-hexene (5.4 g., 0.041 mole) in chloroform (10 ml.) and the mixture was set aside at 25° for 15 hr. After washing with aqueous sodium carbonate the chloroform layer was dried over anhydrous magnesium sulfate and concentrated to give 5.3 g. (82%) of an oil which was chromatographed over alumina. Elution with petroleum ether–ether (99:1) gave as an analytical sample a colorless oil, 1-nitro-4,5-epoxyhexane, b.p. 51–53° (0.1 mm.), $n^{25}D$ 1.4429, infrared, 6.45 μ (nitro).

*Anal.* Calcd. for $C_6H_{11}NO_3$: C, 49.63; H, 7.63; O, 33.06. Found: C, 49.53; H, 7.85; O, 33.05.

DL-*threo*-Amicetose 2,4-Dinitrophenylhydrazone.—DL-*threo*-1-Nitro-4,5-hexanediol monoacetate (1.44 g., 7 mmoles) was added slowly with stirring to a 2 *N* aqueous potassium hydroxide solution (15 ml.) containing methanol (1 ml.). The resultant solution was allowed to stand for 24 hr. and then added slowly with stirring to an aqueous 8 *N* sulfuric acid solution of 2,4-dinitrophenylhydrazine (1.8 g.) at −10°. The solution was allowed to stand for 1 hr. at −10°, diluted with water (1:1), extracted with chloroform, and the organic layer washed successively with water, with saturated sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of chloroform gave a red gum which was chromatographed over alumina. Elution with chloroform afforded various compounds not further investigated. Elution with chloroform–methanol (98:2) gave 235 mg. (11%) of 2,3,6-trideoxy-DL-*threo*-hexose 2,4-dinitrophenylhydrazone (DL-*threo*-amicetose 2,4-dinitrophenylhydrazone) as yellow plates crystallized from chloroform, m.p. 105–106°, infrared (KBr), 2.95 μ (OH weak), 3.05 μ (-NH), 6.15 μ (C=N). $\lambda_{max}^{EtOH}$ 226 mμ (ε 14,620) and 356 mμ (ε 20,980). On paper chromatography, the $R_f$ value was 0.79 in a system of methanol saturated with heptane.

*Anal.* Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.14; H, 5.16; N, 17.96; O, 30.76. Found: C, 46.06; H, 5.34; N, 17.93; O, 31.07.

Acetylation of the DL-*threo*-amicetose 2,4-dinitrophenylhydrazone (100 mg., 0.32 mmole) in acetic anhydride (2 ml.) and pyridine (2 ml.) at 40–45° for 16 hr. gave an orange gum after removal of the volatile reagents *in vacuo*. Chromatography over alumina gave on elution with pentane–ether (9:1) the diacetate of DL-*threo*-amicetose 2,4-dinitrophenylhydrazone (50 mg., 40%) which crystallized as yellow plates from ethanol, m.p. 127–127.5°, $\lambda_{max}^{EtOH}$ 226 mμ (ε 13,780) and 356 mμ (ε 20,490), infrared, 5.75, μ (-OAc).

*Anal.* Calcd. for $C_{16}H_{20}N_4O_8$: C, 48.49; H, 5.09; N, 14.33; O, 32.29. Found: C, 48.70; H, 5.26; N, 14.24; O, 32.33.

In a similar manner DL-*threo*-1-nitrohexanediol diacetate after formation of the *aci*-salt with aqueous potassium hydroxide

and subsequent Nef reaction with acidic 2,4-dinitrophenylhydrazine, gave a 9% yield of the DL-*threo*-amicetose 2,4-dinitrophenylhydrazone.

DL-*erythro*-**Amicetose 2,4-Dinitrophenylhydrazone.**—1-Nitro-4,5-epoxyhexane (4.7 g., 0.036 mole) was added slowly with stirring to 60 ml. of aqueous 1 N sodium hydroxide and the mixture was stirred for 2 hr. until it was homogeneous. This solution was added slowly with stirring over a period of 1 hr. to an aqueous solution of 2,4-dinitrophenylhydrazine in 9 N sulfuric acid (20 ml.) and methanol (50 ml.) cooled to 0°. The reaction mixture was maintained at 10° for 30 min., then diluted with an equal volume of water and set aside for a further 30 min. at 20°. After thorough extraction of the reaction mixture with chloroform, the extracts were washed with water, dried over anhydrous magnesium sulfate and the chloroform removed under reduced pressure to give a red gum which was chromatographed over alumina. On elution with chloroform various compounds were obtained which were not investigated further. Continued elution with chloroform–methanol (98:2) gave 2,3,6-trideoxy-DL-*erythro*-hexose 2,4-dinitrophenylhydrazone (DL-*erythro*-amicetose 2,4-dinitrophenylhydrazone). Recrystallization from chloroform gave 295 mg. (3%) of the pure isomer, m.p. 137.5–138°. Infrared (KBr), 2.96 μ (OH weak), 3.05 μ (-NH), 6.15 μ (C=N), $\lambda_{max}^{EtOH}$ 226 mμ (ε 13,700), 356 mμ (ε 20,000). Paper chromatography gave a spot with an $R_f$ value of 0.79 in a system of methanol saturated with heptane.

*Anal.* Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.14; H, 5.16; N, 17.96; O, 30.76. Found: C, 46.34; H, 5.40; N, 18.16; O, 30.95.

**Product Isolation from Periodiate Cleavage of DL-*threo*- and -*erythro*-Amicetose 2,4-Dinitrophenylhydrazones.**—A solution of DL-*threo*-amicetose 2,4-dinitrophenylhydrazone (100 mg., 0.32 mmole), dioxane (2 ml.), and water (8 ml.) was added to 0.2 N aqueous sodium periodate (10 ml.) contained in a Claisen flask and set aside for 3 hr. The reaction mixture, after dilution with water (30 ml.), was steam distilled and the volatile products were passed through a trap at 0° containing 2,4-dinitrophenylhydrazine in 3 N hydrochloric acid. An orange precipitate was obtained which was extracted into benzene, after which the benzene solution was dried and passed over an alumina column. Elution with benzene gave acetaldehyde 2,4-dinitrophenylhydrazone (35 mg., 43%) as yellow needles, m.p. 163–165° after crystallization from ethanol. With an authentic sample, the mixture m.p. was undepressed and the infrared spectra were superimposable. Paper chromatography in a system of methanol saturated with heptane showed an $R_f$ value of 0.82 for the compound.

Excess ethanolic 2,4-dinitrophenylhydrazine-2 N hydrochloric acid reagent was added to the solution remaining in the flask after steam distillation. The resulting orange precipitate was filtered and recrystallized from hot dimethylformamide to give orange needles of succindialdehyde bis-2,4-dinitrophenylhydrazone (100 mg., 68%), m.p. 273–275°(d), $\lambda_{max}^{DMF}$ 580 mμ (ε 37,540), 458 mμ (ε 19,610), and 377 mμ (ε 18,060). In the usual paper chromatographic system of methanol saturated with heptane, the derivative had an $R_f$ value of 0.0 as did an authentic sample. With this authentic sample the mixture melting point was undepressed and the infrared spectra were superimposable.

In a similar manner the DL-*erythro*-2,4-dinitrophenylhydrazone was cleaved with sodium periodate to give both acetaldehyde identified as its 2,4-dinitrophenylhydrazone by m.p., infrared spectrum and paper chromatography and succindialdehyde bis-

2,4-dinitrophenylhydrazone in 53%, identified in the same way.

Natural amicetose 2,4-dinitrophenylhydrazone has already been shown by Stevens, Nagarajan, and Haskell[7] to give, on cleavage with sodium periodate, both acetaldehyde 2,4-dinitrophenylhydrazone in 51% yield and succindialdehyde bis-2,4-dinitrophenylhydrazone quantitatively.

**The Rate of Periodate Cleavage.**—In a typical determination a sample (4.5 to 8.5 mg., 0.015 to 0.026 mmole) was dissolved in dioxane (5 ml.) and made up to a volume of 25 ml. in a graduate flask with water (15 ml.) and 0.02 N aqueous sodium periodate (5 ml., 0.05 mmole). The reaction mixture was allowed to stand at 8° and periodically an aliquot (2 ml.) was withdrawn by pipette and quenched by the addition of an aqueous solution of sodium bicarbonate and 0.01 N sodium arsenite (10 ml.). Then a few grains of potassium iodide were added and the solution was allowed to stand for a minimum period of 10 min. The solution was titrated with 0.01 N iodine to the first permanent blue color using starch as an indicator. Under the conditions of the experiment, it was necessary to back titrate and titrate again several times until a reproducible end point was obtained. In this manner the rates of oxidation of the 2,4-dinitrophenylhydrazones of DL-*threo*-, DL-*erythro*-, and natural amicetose were measured and compared (see Table I). A blank was run under identical conditions.

TABLE I

THE RATE OF PERIODATE CLEAVAGE AT 8 ± 2°

| Time, min. | Moles of periodate consumed | | |
| | DL-*threo* (8.20 mg.) | DL-*erythro* (4.5 mg.) | Natural (8.14 mg.) |
|---|---|---|---|
| 7 | 0.70 | 0.10 | 0.20 |
| 18 | .70 | . . . | .25 |
| 23 | . . . | .26 | . . . |
| 63 | . . . | . . . | .72 |
| 93 | .71 | .63 | . . . |
| 190 | . . . | . . . | .91 |
| 218 | .79 | . . . | . . . |
| 240 | . . . | .78 | . . . |

**Paper Electrophoresis Studies.**—A methanolic solution of each of the 2,4-dinitrophenylhydrazones indicated in Table II was introduced onto a paper strip (Spinco no. 300-846, S and S 2043 A. gl.) as a narrow band and placed in a Beckman Spinco Model R paper electrophoresis system. A comparison was made using 0.083 M borax with a pH 9.2, at a constant voltage of 380 v. and a current of about 10–12 ma. After 2 hr. and 10 min., the strips were removed and dried. The migrations of the products are shown below in Table II.

TABLE II

| 2,4-Dinitrophenylhydrazone | Migration (cm.) |
|---|---|
| (a) Natural-amicetose | −0.1 |
| (b) DL-*erythro*-amicetose | −0.1 |
| (c) DL-*threo* amicetose | +2.3 |
| (d) Heptaldehyde | −0.05 |

# Cyclizations of Dialdehydes with Nitromethane. IX.[1] Nitrogenous Heptulosans

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The synthesis of three 2,7-anhydro-4-nitro-4-deoxy-β-D-heptulopyranoses and of the corresponding 4-amino sugars by way of the nitromethane method is described. The products are presumed to bear their nitrogen functions in equatorial positions, *i.e.*, to possess any three of the *ido*, *gulo*, *altro*, and *allo* configurations.

In contrast to the vast amount of knowledge that has accumulated in the field of nitrogenous five- and six-carbon sugars, little is known about their seven-carbon homologs. In fact, we are not aware of any that occur in nature, and only three 2-acetamido-2-deoxy-aldoheptoses[2] and a number of 1-nitro-1-deoxyheptitols[3] have been synthesized. In this paper we wish to report on the synthesis of some members of a new group of nitrogen derivatives in the seven-carbon sugar family. They are 4-nitro- and 4-amino-4-deoxyheptulosans. Their synthesis was accomplished by applying the nitromethane cyclization, which has been described in preceding papers of this series, to the dialdehyde I that is readily obtainable from sedoheptulosan.[4]

When the dialdehyde I was condensed in *methanolic* solution with one molecular equivalent of nitromethane in the presence of one molecular equivalent of sodium methoxide, solid *aci*-nitro sodium salts were obtained, in various fractions comprising three stereoisomers, in nearly quantitative total yield. On the basis of earlier experiences with this method[5] we assigned to the products structure II (2,7-anhydro-4-*aci*-nitro-4-deoxy-β-D-heptulopyranose sodium salts). The least soluble of them, salt IIa, crystallized directly out of the reaction solution and amounted to 14% of the total salts formed.
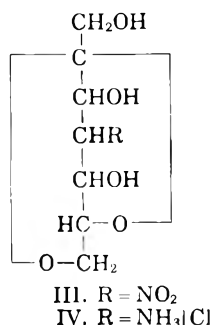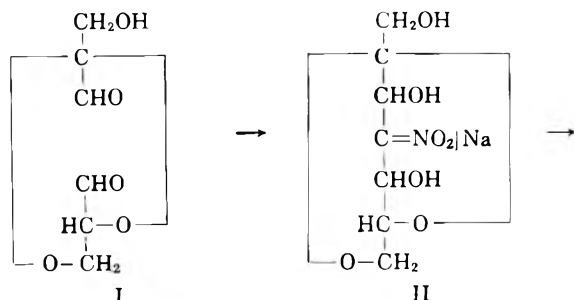
The mother liquor upon prolonged standing deposited, in similar yield, a second salt, IIb, which differed from the first in the infrared spectrum as well as, most strikingly, in its rotatory behavior in water. Whereas IIa exhibits a virtually constant levorotation ($[\alpha]$D −51° → −50°), a fresh solution of IIb is strongly dextrorotatory, with the initial value of $[\alpha]$D +115° decreasing rapidly, turning negative and reaching a final value of −92° after several hours. A third isomer, IIc, was recognized to exist in the mother liquor of the condensation solution although it could not be isolated directly from the latter. It was obtained in solid form when the free crystalline nitrodeoxyheptulosan IIIc described below was reconverted into the sodium salt. This salt IIc shows a mutarotation of $[\alpha]$D −138.5° → −73°, which is opposite in sense to that of IIb. As was established earlier,[1] mutarotations of *aci*-nitro glycoside salts are indicative of spontaneous epimerizations taking place at carbon atoms adjacent to the nitro groupings.

Roughly 70% of the *aci*-nitro salts formed in the nearly quantitative condensation reaction did not crystallize spontaneously. However, by means of simple general techniques the total condensation products could be obtained in solid state. Thus, the remainder of the products after the collection of most of the crystallizable IIa was worked up giving fractions of material whose aqueous solutions were all levorotatory and exhibited considerable mutarotations. These salt fractions were not stereochemically homogeneous but could nevertheless be utilized for further preparative work. For the sake of convenient reference they are herein given a common designation, salt IIm.

By deionization with cation exchange resin the salts II were converted into free 2,7-anhydro-4-nitro-4-deoxy-β-D-heptulopyranoses (III). Thus, we have obtained three beautifully crystalline isomers, IIIa, IIIb and IIIc (method A).

Alternatively, the nitroheptulosans IIIb and IIIc could be prepared directly, without the isolation of *aci*-nitro salts, by conducting the nitromethane condensation of the dialdehyde in *aqueous* solution in the presence of one equivalent of sodium hydroxide followed by deionization (method B). The latter method is the preferred one for the preparation of IIIc.



I



II



III. R = NO₂
IV. R = NH₃|Cl
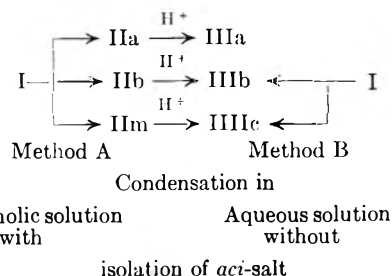
(1) Paper VIII in this series: H. H. Baer. *J. Am. Chem. Soc.*, **84**, 83 (1962).

(2) R. Kuhn and G. Baschang, *Ann.*, **636**, 164 (1960).

(3) J. C. Sowden and R. Schaffer, *J. Am. Chem. Soc.*, **73**, 4662 (1951); J. C. Sowden and H. O. L. Fischer, *ibid.*, **68**, 1511 (1946); J. C. Sowden and D. R. Strohbach, *ibid.*, **82**, 954 (1960).

(4) J. W. Pratt, N. K. Richtmyer, and C. S. Hudson, *ibid.*, **74**, 2200 (1952).

(5) See ref. 1, and the preceding papers I–VII.



$$
\text{I} \begin{cases} \xrightarrow{\text{H}^+} \text{IIa} \xrightarrow{} \text{IIIa} \\ \xrightarrow{\text{H}^+} \text{IIb} \xrightarrow{} \text{IIIb} \leftarrow\!\!\!\!\leftarrow \text{I} \\ \xrightarrow{\text{H}^+} \text{IIm} \xrightarrow{} \text{IIIc} \leftarrow\!\!\!\!\leftarrow \end{cases}
$$

Method A         Method B

Condensation in

Methanolic solution      Aqueous solution
with                without

isolation of *aci*-salt

The characteristic physical data of the nitrodeoxy-heptulosans are given in Table I, and their ways of formation are indicated in the preceding scheme (p. 1287).

TABLE I

PHYSICAL CONSTANTS OF THREE ISOMERIC
NITRODEOXYHEPTULOSANS III

| Compound | M.p., °C. | $[\alpha]^{23}$D in H$_2$O | $R_f{}^a$ |
|---|---|---|---|
| IIIa | 176 | $-60°$ | |
| IIIb | 203 | $+69°$ | 0.58 |
| IIIc | 159 | $-176.5°$ | 0.52 |

$^a$ See Experimental.

Catalytic hydrogenation of the nitrodeoxyheptulosans III readily afforded the corresponding 2,7-anhydro-4-amino-4-deoxy-$\beta$-D-heptulopyranoses which were isolated as their crystalline hydrochlorides IV. The constants of the new amino sugars are given in Table II. They were produced immediately in chromatographically pure state when the pure, uniform nitro compounds were hydrogenated. However one need not always employ, in the preparation of the amines, homogeneous crystalline nitro compounds; rather, sirupy mixtures may be used since the amine hydrochlorides crystallize without difficulty. Thus, the product obtained upon acidification of the heterogeneous salt IIm, followed by hydrogenation, represented a mixture of amino sugars from which pure IVc could be crystallized in fair yield. Similarly, sirups remaining after the collection of all the nitro products which crystallized in the experiments of method B have been hydrogenated and have furnished crystalline mixtures of amino sugars.

TABLE II

SPECIFIC ROTATIONS AND $R_{gm}$-VALUES OF THREE ISOMERIC
AMINODEOXYHEPTULOSAN HYDROCHLORIDES IV

| Compound | $[\alpha]^{23}$D in H$_2$O | $R_{glucosamine}{}^a$ |
|---|---|---|
| IVa | $-55°$ | 1.04 |
| IVb | $+39°$ | 1.30 |
| IVc | $-126°$ | 1.00 |

$^a$ See Experimental.

The configurations of our new sugar derivatives have not been established as yet. However, Richardson and Fischer,[6] having investigated the course of the nitromethane condensation with the homologous dialdehyde from levoglucosan, adduced experimental proof that in all their nitro sugars the NO$_2$ group had adopted an equatorial position, and they suggested for a reason the large steric interference which an axial NO$_2$ would encounter from the anhydride bridge. It is therefore very likely that our products III (and hence IV, too) also carry equatorially linked nitrogen atoms, i.e., that they possess any three of the gulo, altro, allo and ido configurations.

A comparison of the molecular rotations of the pair of homologs, 1,6-anhydro-$\beta$-D-gulopyranose (M$_D$ $+8165$)[7] and 2,7-anhydro-$\beta$-D-guloheptulopyranose (M$_D$ $+7620$),[8] suggests that the corresponding 3-amino-3-deoxygulosan hydrochloride (M$_D$ $+9100$)[6] has its homolog in IVb (M$_D$ $+8900$). A comparison of

1,6-anhydro-$\beta$-D-altropyranose (M$_D$ $-34,800$)[9] with 2,7-anhydro-$\beta$-D-altroheptulopyranose (sedoheptulosan, M$_D$ $-28,000$)[4] might allow the conclusion that 3-amino-3-deoxyaltrosan hydrochloride (M$_D$ $-34,100$)[6,10] and IVc (M$_D$ $-28,800$) are homologs. A similar tentative assignment for IVa cannot be made at present for lack of pertinent data.

## Experimental

The melting points were determined in an aluminum block. The optical rotations were measured in 2-dm. tubes in carbon dioxide-free water; c, approximately 1 unless otherwise stated. Evaporations were done in vacuo at 35–40° (bath temperature).

**Paper Chromatography.**—The descending technique on Whatman no. 1 paper was used. The nitro compounds were irrigated with 1-butanol–acetic acid–water (4:1:5 v./v., upper layer, with the lower layer in the bottom of the tank) and made visible by spraying with $N$ aqueous sodium hydroxide–methanol–butanol (1:2:7, v./v.) and inspection under an ultraviolet lamp. The amino derivatives were chromatographed with the Fischer–Dörfel[11] solvent system and detected with a ninhydrin spray, glucosamine hydrochloride being used as a speed standard. The $R_{gm}$-values given refer to a freshly set up solvent system; in older tanks the values tend to become somewhat lower.

**Dialdehyde (I) from Sedoheptulosan.**—Crystalline sedoheptulosan hydrate[4] (10.5 g., 0.05 mole) was added, in the course of 10 min., to an ice-cooled solution of 21.4 g. of sodium metaperiodate (0.1 mole) in 250 ml. of water. The reaction mixture then was allowed to assume room temperature and to stand in the dark for 4 hr., during which period 45 ml. of a $M$ sodium bicarbonate solution (90% of 1 molar equiv.) was gradually added. Thereafter the solution was concentrated to beginning crystallization, mixed with two volumes of ethanol, chilled, and filtered. The inorganic filter residue was washed with ethanol and the filtrate further concentrated. This procedure was repeated, usually three to four times, until no more crystalline material could be removed. Finally a colorless sirup of I resulted that was deemed sufficiently free of salts (sodium iodate and formate) when it dissolved clearly in three volumes of cold methanol.

**2,7-Anhydro-4-aci-nitro-4-deoxy-$\beta$-D-heptulopyranose Sodium Salts (II).**—The sirupy dialdehyde obtained above was dissolved in 100 ml. of methanol. The solution was chilled in ice-water, 2.7 ml. of nitromethane (1 molar equiv.) was added, and then 36.5 ml. of a chilled sodium methoxide solution (containing 3 g. of sodium per 100 ml.) was dropped in with swirling in the course of 10 min. The reaction mixture was then kept overnight in the refrigerator.

The first crop of crystals which had slowly appeared was collected and washed with ice-cold methanol. The yield of the desiccator-dried, yellowish-white product was 1.65 g. Salt IIa. $[\alpha]^{23}$D $-50.8° \rightarrow -49.8°$ (final after 26 hr.). Vapor phase chromatography of a solution in water indicated the presence of methanol of crystallization.

*Anal.* Calcd. for C$_7$H$_{10}$O$_7$NNa·CH$_3$OH (275.2): N, 5.09; Na, 8.37. Found: N, 5.64; Na, 8.35.

A second crop of IIa separated from the mother liquor that was kept at 4°, and was collected after 3 days; 0.53 g., $[\alpha]^{23}$D $-52.3° \rightarrow -50.8°$. The infrared spectra of the first and second crops were identical.

When after removal of the crystalline IIa the mother liquor was placed in the refrigerator again, another crop of crystals was deposited in the course of several days. It was salt IIb which after washing with cold methanol weighed 1.9 g. (desiccator-dried); $[\alpha]^{23}$D $+115.0°$ (3 min.) $\rightarrow -92.0°$ (final, 16 hr.). Vapor phase chromatography (Perkin–Elmer fractometer, Model 154, W-column) indicated the presence in the crystals of methanol of crystallization.

*Anal.* Calcd. for C$_7$H$_{10}$O$_7$NNa·½CH$_3$OH (259.2): C, 34.80; H, 4.65; Na, 8.90. Found: C, 35.22; H, 4.99; Na, 8.96.

(6) Part VI of this series, *J. Am. Chem. Soc.*, **83**, 1132 (1961).

(7) L. C. Stewart and N. K. Richtmyer, *ibid.*, **77**, 1021 (1955).

(8) By reversal of the sign of rotation of the known enantiomorph; L. C. Stewart, N. K. Richtmyer, and C. S. Hudson, *ibid.*, **74**, 2206 (1952).

(9) N. K. Richtmyer and C. S. Hudson, *ibid.*, **61**, 214 (1939).

(10) L. F. Wiggins, *J. Chem. Soc.*, 18 (1947).

(11) Pyridine–ethyl acetate–water–acetic acid (5:5:3:1, v./v.), with pyridine–ethyl acetate–water (6:40:11, v./v.) in the bottom of the tank; F. G. Fischer and H. Dörfel, *Z. physiol. Chem.*, **301**, 224 (1955).

The infrared spectrum of IIb differed markedly from that of IIa, especially in the regions of 1550–1570, 1325–1350, 1130, and 900–700 cm.$^{-1}$.

In a number of otherwise identical experiments we did not wait for the slow formation of a second crop of IIa nor for the crystallization of IIb. Rather, the reaction solution upon collection of the first crop of IIa (*i.e.*, about 17 hr. after the start of the nitromethane condensation) was immediately worked up to give mixed salt fractions of generally similar however varying size and composition. These fractions are referred to as salt IIm. The following description is typical.

The combined filtrate and washings obtained upon collection of the first crop of crystals (IIa) was evaporated to dryness and the solid residue triturated with approximately 50 ml. of a mixture of methanol and ethanol (2:1). Insoluble matter was filtered off and washed with the same solvents. Its dry weight was 4.64 g.; $[\alpha]^{23}$D −51.9° → −76.2° (final). From the filtrate another crop was precipitated by the addition of excess ethanol; 2.07 g., $[\alpha]$D −69.2° → −82.0° (final). The filtrate from this precipitate was brought to dryness and the residue of evaporation then triturated with a little ethanol. The major part remained undissolved and was isolated and washed with ethanol; 3.05 g., $[\alpha]^{23}$D −14.8° → −65.7° (final). The ethanolic extract and washings were finally evaporated yielding 0.47 g. of a solid, $[\alpha]^{23}$D +2° → −22.4° (final). The combined yield of these fractions IIm was 10.23 g. When added to the 1.65 g. of previously separated IIa the total yield in sodium salts II was 97% based upon the starting sedoheptulosan hydrate. The sodium contents of the fractions of IIm from this and similar experiments were found to be 8.4, 8.1, 8.4, 8.6, 8.5, 8.5, 8.7, 8.0%.

**2,7-Anhydro-4-nitro-4-deoxy-β-D-heptulopyranoses (III). A. From the Sodium Salts (II).**—One part of a salt II was generally dissolved in 50 parts of ice-cold water and at once stirred for 10 min. with a cation-exchange resin (22 ml. of Amberlite IR-120 [H$^+$] per gram of II). The resin was filtered off, washed exhaustively with water, and the filtrate evaporated to dryness, finally with the addition of two consecutive portions of ethanol. Colorless crystalline residues of III were thus obtained.

**Nitrodeoxyheptulosan IIIa.**—The product obtained from 1.60 g. of salt IIa was triturated with a little ethyl acetate and after short standing at 0° collected on a Büchner funnel and washed with cold ethyl acetate. The yield of crude IIIa was 640 mg., with m.p. 167° dec. and $[\alpha]^{23}$D −55.8°. Another 32 mg. crystallized from the mother liquor upon storage at 4°. Two recrystallizations from boiling ethanol with the addition of a few drops of water gave beautiful needles that melted at 173.5° and showed $[\alpha]^{23}$D −60°. The highest melting point observed was 176°.[12]

*Anal.* Calcd. for C$_7$H$_{11}$O$_7$N (221.2): C, 38.01; H, 5.01; N, 6.33. Found: C, 38.67; H, 5.28; N, 6.52.

**Nitrodeoxyheptulosan IIIb.**—The product obtained from 1.50 g. of salt IIIb was triturated with a small amount of ice-cold ethanol. After 1.5 hr., 990 mg. of platelets showing $[\alpha]^{23}$D +67.9° and m.p. 202° dec. were isolated; from the filtrate additional crops amounting to 164 mg. and melting at 197–199° were obtained. Total yield, 85%. The product was proved by its infrared spectrum and $R_f$ value to be identical with IIIb described under B.

All the inhomogeneous fractions of salt IIm were deionized in the same manner and invariably yielded crystalline dextrorotatory IIIb amounting to 10–20% of the products of deionization, while the bulk of these products consisted of strongly levorotatory sirups. Although it was possible to obtain from the sirups impure crystals of **nitrodeoxyheptulosan IIIc** amounting to 14–22% (m.p. 143–145°, $[\alpha]^{23}$D −125°; −137.5°), it was more satisfactory for the preparation of this isomer to use method B. The sirups, however, could be utilized in hydrogenation experiments whereby they afforded crystalline aminodeoxyheptulosan IVc as described later.

(12) Material with virtually the same rotation but with m.p. 176° was obtained in separate experiments. In general it was difficult to raise the melting point of samples of IIIa by recrystallization because of the instability of the compound in hydroxylic solvents. Thus, the material invariably gave streaking spots on paper chromatograms, and crystals recovered from aqueous optical rotation solutions melted 8–10° lower than before. When a sample was refluxed in propanol for 2 hr., a complete transformation resulted as demonstrated by hydrogenation followed by paper chromatography, which showed predominantly a new amine ($R_{gm}$ 1.20) and no IVa ($R_{gm}$ 1.04). In the preparation of IIIa from IIa the mother liquor was similarly shown to contain a product giving rise to the unknown amine ($R_{gm}$ 1.20).

**B. By Nitromethane Condensation in Aqueous Solution.**—Sirupy dialdehyde I (0.05 mole) was dissolved in 50 ml. of water containing 3 drops of phenolphthalein indicator. The solution was carefully adjusted with N sodium hydroxide to the point of a slight pink coloration remaining for at least 1 min.; about 4 ml. of the base was required. Under swirling in an ice bath 2.7 ml. of nitromethane was now added at once and 50 ml. of N sodium hydroxide was dropped in over a period of 10 min. The stoppered reaction vessel was allowed to stand at room temperature for 17 hr. The slightly yellow solution was then chilled again with ice, stirred vigorously with 70 ml. of Amberlite IR-120 (H$^+$) for 15 min., filtered, and, after exhaustive washing with water of the resin, decolorized with activated charcoal. The colorless solution afforded a sirupy mixture of nitrodeoxyheptulosans III by evaporation and dehydration with ethanol.

**Nitrodeoxyheptulosan IIIb.**—The above sirupy residue was dissolved in 20 ml. of warm ethyl acetate with the addition of a small amount of ethanol. Upon keeping the solution overnight at 4° crystallization occurred and 1.62 g. of crude IIIb was isolated and washed with ethyl acetate. After three recrystallizations from ethanol the melting point and rotation of the colorless platelets were constant; m.p. 203.5°, $[\alpha]^{23}$D +69.5°; $R_f$ 0.58.

*Anal.* Calcd. for C$_7$H$_{11}$O$_7$N (221.2): C, 38.01; H, 5.01; N, 6.33. Found: C, 38.72; H, 5.20; N, 6.52.

Further crops of IIIb were obtained pursuant to the isolation of IIIc described in the next paragraph.

**Nitrodeoxyheptulosan IIIc.**—After the isolation of the above crude IIIb the ethyl acetate mother liquor upon addition of excess ether furnished an amorphous precipitate which was filtered off, washed with ether, and dried. It weighed 3.3 g. and showed $[\alpha]$D −125.5°. This product was dissolved in warm ethyl acetate containing a little methanol and placed in an open beaker. Evaporation in the air gave, after 2 days, a crystal-containing sirup from which by trituration with ethanol 1.22 g. of crystalline IIIc, m.p. 153°, $[\alpha]^{23}$D −175.0°, could be isolated. Recrystallization from ethanol afforded 0.88 g. of the pure IIIc in oblong prisms of m.p. 159° and $[\alpha]^{23}$D −176.5°; $R_f$ 0.52.

*Anal.* Calcd. for C$_7$H$_{11}$O$_7$N (221.2): C, 38.01; H, 5.01; N, 6.33. Found: C, 38.51; H, 5.24; N, 6.26.

The mother liquor of the ether precipitate was allowed to evaporate in the air to give a crystal-containing sirup. Trituration with ethyl acetate and methyl acetate furnished 710 mg. of crystals with a m.p. of 146° and $[\alpha]^{23}$D −94°. Additional crops (160 mg. of m.p. 147° and $[\alpha]^{23}$D −158°, and 560 mg. of m.p. 149° and $[\alpha]^{23}$D −78.5°, respectively) were obtained from the filtrate which had been kept in the refrigerator for several days. These crystalline fractions obviously were mixtures of isomers, with relatively small proportions of the dextrorotatory IIIb being present. A total of 200 mg. of the latter (which is the least soluble) was obtained from these fractions, in fairly but not entirely pure state, by recrystallization from ethanol.

When no additional crystalline material could be obtained from the main mother liquor, the latter was evaporated to a sirup whose dry weight was 1.99 g.; $[\alpha]^{23}$D −60.3°. The sirup was hydrogenated taking up 3 moles of hydrogen and yielding a sirupy mixture of amine hydrochlorides. Chromatography suggested the presence of the three amino sugars IV described in a following paragraph. Part of the sirup crystallized giving a preparation (640 mg., $[\alpha]$D −78.6°) which still showed three spots on paper.

**Reconversion of IIIc into Its Sodium Salt IIc.**—To an ice-cold solution of 93 mg. of nitroheptulosan IIIc in 4 ml. of methanol-ethanol (1:1) 1 molar equiv. of sodium methoxide in methanol was added. The white precipitate of IIc that occurred immediately was isolated and washed with ethanol by centrifugation and was dried in a desiccator. The infrared spectrum was similar to spectra given by IIm fractions but was clearly distinct from those of IIa and IIb. $[\alpha]^{23}$D −138.5° (1 min.) → −73° (16 hr., final; c, 0.5).

**2,7-Anhydro-4-amino-4-deoxy-β-D-heptulopyranose Hydrochlorides (IV).**—The catalytic hydrogenations of the nitrodeoxyheptulosans III were performed as described in earlier work.[13] A 10% excess over the calculated amount of 1 equiv. of hydrochloric acid was provided, the starting acid concentration being approximately 0.05 N. The hydrogen uptake (3 molar equiv.) was usually complete and ceased after 1 to 1.5 hr. if the vessel was agitated vigorously. Evaporation of the hydrogenated

(13) H. H. Baer and H. O. L. Fischer, *J. Am. Chem. Soc.*, **82**, 3709 (1960); H. H. Baer, *Ber.*, **93**, 2865 (1960); *cf.* also ref. 1.

solutions followed by codistillation with ethanol led to the aminodeoxyheptulosans IV.

**Aminodeoxyheptulosan IVa.**—A 200-mg. sample of nitroheptulosan IIIa (m.p. 173.5) was hydrogenated furnishing a crystalline product, $[\alpha]^{23}$D $-46.7°$ (c, 0.5), which was revealed by paper chromatography to be not uniform. Besides the main spot of $R_{gm}$ 1.03–1.04 there was a weaker spot of $R_{gm}$ 1.20.[14] Recrystallization from the minimum amount of water and a tenfold excess of glacial acetic acid afforded 107 mg. of short prismatic columns which were chromatographically pure IVa; $R_{gm}$ 1.03, $[\alpha]^{23}$D $-54.7°$.

*Anal.* Calcd. for C$_7$H$_{14}$O$_5$NCl (227.7): C, 36.93; H, 6.20; N, 6.15. Found: C, 37.03; H, 6.28; N, 5.94.

**Aminodeoxyheptulosan IVb.**—Nitrodeoxyheptulosan IIIb (130 mg.) upon hydrogenation yielded 110 mg. of elongated needle-like prisms with square, sometimes sloping, end faces. The product, IVb, was immediately chromatographically uniform ($R_{gm}$ 1.30) and analytically pure; $[\alpha]^{23}$D $+39.0°$, unchanged upon recrystallization from water–acetic acid.

*Anal.* Calcd. for C$_7$H$_{14}$O$_5$NCl (227.7): C, 36.93; H, 6.20; N, 6.15; Cl, 15.57. Found: C, 37.12; H, 6.35; N, 6.00; Cl, 15.48.

In another run 280 mg. of IVa showing $[\alpha]^{23}$D $+37.5$ was obtained from 315 mg. of IIIa.

**Aminodeoxyheptulosan IVc.**—Crystalline nitrodeoxyheptulosan IIIc (442 mg.) was hydrogenated to give 410 mg. of chromatographically uniform IVc ($R_{gm}$ 1.00); $[\alpha]^{23}$D $-124.0°$. Recrystallization from water–acetic acid gave fine needles (rapid crystallization) or rectangular prisms and platelets (slow crystallization in the air); $[\alpha]^{23}$D $-126°$.

*Anal.* Calcd. for C$_7$H$_{14}$O$_5$NCl (227.7): C, 36.93; H, 6.20; N, 6.15; Cl, 15.57. Found: C, 36.86; H, 6.23; N, 5.91; Cl, 15.71.

In another run 220 mg. of IVc showing $[\alpha]^{23}$D $-123.5°$ was obtained from 221 mg. of IIIc.

Aminodeoxyheptulosan IVc was also obtained by the hydrogenation of levorotatory, sirupy nitrodeoxyheptulosan mixtures which originated in deionization of salt IIm (previously described). Thus, 3.76 g. of a sirup ($[\alpha]^{23}$D $-90.5°$) was hydrogenated and furnished a slightly yellowish, partly crystalline product which on the chromatogram showed spots of equal strength corresponding to IVb and IVc, and an unidentified faint spot of $R_{gm}$ 1.60. Recrystallization from water–glacial acetic acid afforded 705 mg. of colorless crystals of IVc containing but a trace of IVb; $[\alpha]^{23}$D $-122.0°$. The mother liquor of the re-

crystallization gave another 160 mg. of crystals being mainly IVc ($[\alpha]^{23}$D $-114°$), as well as various mixed fractions. Similarly, a nitrodeoxyheptulosan sirup (1.3 g.) stemming from the deionization of another fraction of the salts IIm was hydrogenated to a partly crystalline amine mixture ($[\alpha]$D $-93°$) whose chromatographic pattern was the same as that just described. By recrystallization from water–glacial acetic acid, 390 mg. of rather pure IVc ($[\alpha]^{23}$D $-121.5°$) was obtained. The mother liquor contained both IVc and IVb; 50 mg. of the former was deposited after 3 days. The infrared spectra of the preparations of IVc obtained *via* the sirupy nitrodeoxyheptulosan mixtures were identical with that of IVc from crystalline IIIc.

**The Behavior of the *aci*-Nitro Salt IIb in Aqueous Solution.**—Two 120-mg. samples of one preparation of the salt IIb were treated as follows.

Sample (a) was introduced into an ice-cold solution of 5.5 ml. 0.1 N hydrochloric acid and 50 ml. of water. After 5 min., 5 ml. of Amberlite IR-120 (H$^+$) was added and the mixture was shaken for 10 min. in order to remove sodium ion. Upon filtration, the acid solution was immediately hydrogenated. Chromatographic inspection of the total residue of evaporation obtained after the hydrogenation indicated the presence of only *one* amine, namely IVb. It crystallized readily.

Sample (b) was dissolved in 30 ml. of carbon dioxide-free water at 23° and allowed to reach a constant specific rotation of $-92°$. After 18 hr. the solution was deionized with 5 ml. of Amberlite IR-120 (H$^+$), acidified with 5.5 ml. of 0.1 N hydrochloric acid and hydrogenated. Chromatography of the product revealed that it contained at least *two* amines, giving spots of about equal strength at $R_{gm}$ 1.27 and $R_{gm}$ 1.01.

Another sample of IIb was allowed to mutarotate in aqueous solution to the final $[\alpha]$D-value. By careful evaporation the solute was recovered. Its infrared spectrum was now clearly distinct from that of the starting salt IIb. It was also different from the spectrum of IIa, but it resembled closely those given by the non-uniform salts IIm.

(14) The occurrence of that spot obviously is connected with the instability of IIIa and the difficulty of preparing it in entirely pure state (*cf.* ref. 12). It might be possible to obtain IVa in better yield and purity by directly hydrogenating an acidified solution of IIa, *i.e.*, without isolating the intermediate nitro compound, IIIa.

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# Direct Epoxidation of o-Chlorobenzylidenemalononitrile with Hypochlorite Ion

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Hypochlorite ion is a nucleophile toward the electronegatively substituted olefin, o-chlorobenzylidenemalononitrile. The product formed with stoichiometric amounts of the reactants is the epoxide (II).

The hydrogen peroxide epoxidation of olefins activated by electron-withdrawing groups such as carbonyl and nitrile is well known.[1–4] The active reagent species is the perhydroxyl anion, which is an extraordinarily powerful nucleophile, as noted by Edwards and Pearson.[5] It would appear that hypochlorite ion,

another potent nucleophile,[5] has not found use in direct epoxidation,[6] with the possible exception of a single patent[9] on the epoxidation of acrolein and alkyl-sub-

(1) C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, 665 (1949).

(2) E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921); G. B. Payne, *J. Am. Chem. Soc.*, **81**, 4901 (1959); G. B. Payne, *J. Org. Chem.*, **24**, 2048 (1959); H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959).

(3) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961).

(4) G. B. Payne, *ibid.*, **26**, 663 (1961).

(5) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

(6) In fact, mesityl oxide, which is epoxidized[1] by perhydroxyl ion at pH 11–13, reacts with hypochlorous acid at pH 4.5 to 10 to give the chlorohydrin,[7] and under very alkaline conditions to give 3,3-dimethylacrylic acid through a haloform reaction.[8]

(7) J. Colonge and L. Cumet, *Bull. soc. chim. France*, [5] **14**, 838 (1947).

(8) L. I. Smith, W. W. Prichard, and L. J. Spillane, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 302.

(9) G. W. Hearne, D. S. LaFrance, and H. de V. Finch, U. S. Patent 2,887,498 (1959).

stituted acroleins, in which instance the role of the anion was not made clear. Both hydrogen peroxide and hypochlorous acid are commonly employed as electrophilic reagents, but are ineffective in this capacity toward electronegatively substituted carbon-carbon double bonds. It now appears that *both* these electrophilic reagents (not uniquely hydrogen peroxide) can be converted to reagents which are nucleophilic toward olefins of suitable structure by the simple expedient of raising the pH from the usual acidic conditions in which these reagents are used. In a sense, the electronegative substituents provide an advantage, in that they make possible the conversion of olefin to epoxide in a single step instead of the two steps required for the chlorohydrin route.

The present study concerned itself with the reaction of hypochlorite with o-chlorobenzylidenemalononitrile (I), a compound known[10] to react with nucleophilic reagents such as cyanide and bisulfite. By contrast, it was demonstrated early in the present work that I does not react with the electrophilic reagent chlorine (in carbon tetrachloride). Depending on reaction conditions, epoxidized o-chlorobenzylidenemalononitrile (II), the two isomers (III) resulting from hydrolysis of one or the other nitrile group of II to amide, and an acid or mixture of acids (IV) resulting from hydrolysis of the amide to carboxyl were obtained on treating I with hypochlorite. Possible mechanisms for the chlorine-mediated conversion of nitrile to amide to carboxyl have been presented in a previous publication,[11] and the present work offers additional evidence of the susceptibility of electronegatively substituted nitriles to nucleophilic attack by hypochlorite, as postulated there. Thus, when previously prepared compound II was kept at pH 8, it was recovered intact in the absence, but not in the presence, of hypochlorite.



I

II

III

IV

a. (m.p. 138–140°)
b. (m.p. 189–190.5°)
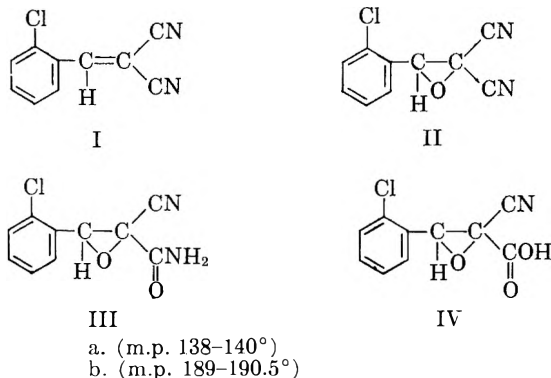
A few experiments were carried out on the kinetics of the hypochlorite epoxidation reaction (summarized in Table I). According to these experiments, the second order rate constant at 25° is approximately $2.2 \times 10^4$ $M^{-1}$ sec.$^{-1}$ (assuming[12] $K_a = 4 \times 10^{-8}$). In the first experiment, a high concentration of sodium chloride was added, which, it may be calculated, should have converted about half the HOCl to Cl$_2$, at least a thousandfold more Cl$_2$ than could have been present in the sixth experiment; that this hardly affected the value of $k_{obsd}$ leads one to dismiss any possible role for Cl$_2$ as a reactive species. For comparison purposes, a single

(10) B. B. Corson and R. W. Stoughton. *J. Am. Chem. Soc.*, **50**, 2825 (1928).

(11) D. H. Rosenblatt and G. H. Broome, *J. Org. Chem.*, **26**, 2116 (1961).

(12) N. G. Lordi and J. Epstein, *J. Am. Chem. Soc.*, **80**, 509 (1958).

experiment was carried out to determine the reactivity of I with perhydroxyl ion, whence the second-order rate constant of $4 \times 10^5$ $M^{-1}$ (assuming[13] $K_a = 2.24 \times 10^{-12}$); and II was synthesized by the perhydroxyl method, some III being produced at the same time, to demonstrate the parallelism.

The kinetic experiments (on disappearance of the olefin bond of I) are of greatest significance in the choice among the possible reaction mechanisms below.
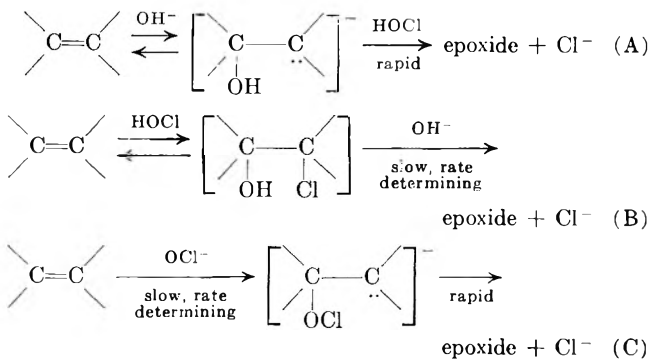
KINETICS OF EPOXIDATION OF o-CHLOROBENZYLIDENEMALONO-NITRILE WITH A LARGE EXCESS OF HYPOCHLOROUS ACID (IN WATER CONTAINING 1% ACETONITRILE) AT AMBIENT TEMPERATURE (APPROXIMATELY 25°)

| pH | $10^4$ [HOCl] | Ionic strength | $10^3$ $k_{obsd}$, sec.$^{-1}$ | $k_2'$,$^a$ $M^{-1}$ sec.$^{-1}$ | $10^8 K_a{}^b$ | $10^{-4} k_2$, $M^{-1}$ sec.$^{-1}$ |
|------|-------|--------|------|-------|-------|-------|
| 3.24 | 6.98 | 1.0$^c$ | 2.22 | 3.18 | ... | ... |
| 3.30 | 4.33 | 0.105 | 1.28 | 2.95 | 8.56 | 1.73 |
| 3.30 | 10.83 | 0.105 | 4.33 | 4.00 | 8.56 | 2.34 |
| 3.30 | 21.66 | 0.105 | 8.30 | 3.83 | 8.56 | 2.24 |
| 3.30 | 43.32 | 0.105 | 16.1 | 3.72 | 8.56 | 2.18 |
| 3.57 | 6.98 | 0.005 | 2.98 | 4.27 | 4.72 | 2.44 |
| 3.89 | 9.06 | 0.015 | 10.2 | 11.25 | 5.33 | 2.72 |
| 3.98 | 6.98 | 0.015 | 8.12 | 11.63 | 5.33 | 2.29 |
| 4.02 | 6.98 | 0.015 | 6.90 | 9.89 | 5.33 | 1.77 |

$^a$ $k_2' = k_{obsd}/[\text{HOCl}]$. $^b$ log $K_a = $ log $K_{thermodynamic} + 1.02$ (ionic strength)$^{1/2}$. $^c$ 1 $M$ in sodium chloride.

Mechanism A would imply linear rate dependence on hydroxyl ion concentration, as is indeed the case. This part of the reaction would have to be formulated as a reversible equilibrium lying far to the left because the disappearance rate of the double bond of o-chlorobenzylidenemalonitrile, in the absence of the nucleophile, is negligible within the pH range covered in Table I. This mechanism would also imply, however, independence of hypochlorous acid concentration at constant pH; this is controverted by the data for pH 3.30. Mechanism B would permit a concentration dependence on both hypochlorous acid and hydroxyl ion. This involves the unlikely elimination of hypochlorous acid in the reverse step of the equilibrium, which would have to be quite rapid in order for the equilibrium to lie substantially to the left, as it must to satisfy the concentration dependence requirements derived from a consideration of the steady state approximation.[14] Thus, mechanism C is left; it satisfies the experimental data, and is analogous to the well-studied perhydroxyl reaction.[1–5]

(13) W. C. Schumb, C. N. Satterfield, and R. L. Wentworth, "Hydrogen Peroxide," Reinhold Publishing Co., New York, N. Y., 1955, p. 393.

(14) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 195.

The formation of II, III and IV is probably sequential. The mechanism for concurrent epoxidation of the olefinic linkage and hydrolysis of nitrile to amide, demonstrated in the reaction of $\alpha,\beta$-unsaturated nitriles with hydrogen peroxide[3,4] can find no analogy where hypochlorite is the reagent. This is borne out by the failure to isolate III or IV when a stoichiometric amount of hypochlorite is used.

Hypochlorite ion, as shown above, is a weaker nucleophile towards o-chlorobenzylidenemalononitrile than perhydroxyl ion. Below pH 10, however, hypochlorous acid is more reactive than hydrogen peroxide because it is so much more highly ionized. By extension, it is evident that olefins sufficiently reactive toward hypochlorite could be epoxidized by this reagent under less alkaline conditions than those required for hydrogen peroxide; avoidance of alkaline conditions might be an important consideration. For less reactive olefins, however, perhydroxyl might be the only nucleophilic reagent, albeit only at very high pH. Another difference in the use of hypochlorite, as opposed to perhydroxyl, is peculiar to $\alpha,\beta$-unsaturated nitriles. It lies in the fact that the dominant reaction of perhydroxyl ion with these compounds involves attack at the nitrile group first, followed by intramolecular epoxidation,[3,4] so that an epoxyamide is obtained in a single step, and often very little product of simple epoxidation. The epoxyamide can also be obtained with hypochlorite (e.g., III), but most likely by a step subsequent to epoxidation.

## Experimental

**Failure of o-Chlorobenzylidenemalononitrile (I) to React in a Short Time, at Ambient Temperature, with Chlorine in Carbon Tetrachloride.**—A carbon tetrachloride solution containing 0.05 M chlorine and 0.05 M o-chlorobenzylidenemalononitrile[10] was permitted to stand 10 min. A sample of the mixture was then diluted 3:2500 with the solvent and its absorption spectrum measured[15] in the vicinity of the 300 m$\mu$ maximum (absorptivity = 1.03). A blank solution, similar in all respects except for the absence of chlorine, exhibited a nearly identical spectrum.

**Reaction of I (M.p. 96°) with Hypochlorite. A. In Stoichiometric Proportion.**—Both partially neutralized chlorine water and hypochlorous acid[12] were used successfully in this preparation. An early preparation of the epoxide (II), using partially neutralized chlorine water, gave a product which, after repeated recrystallization from petroleum ether, sintered at 53.0–53.2° and melted at 53.2–53.5°, with the following analyses.

*Anal.* Calcd. for $C_{10}H_5ON_2Cl$: C, 58.69; H, 2.46; O, 7.84; N, 13.69. Found: C, 58.9; H, 2.6; O, 8.2; N, 13.5.

The following procedure incorporates a somewhat improved technique for isolation: Aqueous hypochlorous acid[12] (234 ml., 0.141 M) and 1 N sodium hydroxide (47 ml.) were added concurrently to a solution of 5.66 g. of I in 270 ml. of acetonitrile,[16] at such a rate that the solution was maintained in the vicinity of pH 7 with the help of a pH meter.[17] When reaction was complete, as evidenced by constancy of pH, a little sodium chloride was added and the mixture was extracted twice with ether (250 and 125 ml.). The combined ether extract was concentrated to remove all ether and steam distilled.[18] The oil collected in the distillate was recrystallized from petroleum ether (b.p. 30–60°) to give 2.2 g. of II, m.p. 51–52°.

**B. With a Mole Ratio of Hypochlorite to I of 1.8:1.**—Chlorine water was adjusted to pH 7 with sodium hydroxide to give a 0.121 M hypochlorite solution (by titration). When 225 ml. of

this solution was added to a solution of 2.39 g. of I in 100 ml. of acetonitrile, the pH dropped quickly to about 3 and was adjusted to 7 with 14 ml. of 1 N sodium hydroxide. Solvent was removed on the rotating evaporator and the residue was washed well with ether, the ether containing mostly IIIa and the washed residue containing largely IIIb and sodium chloride. The crude IIIa (0.75 g.) left on evaporation of the ether washings was purified by fractional precipitation from benzene with petroleum ether, appearing as the more soluble fraction. Further recrystallizations of this crude IIIa from chloroform–carbon tetrachloride produced 0.08 g. of a mixture of slender needle-like and diamond-shaped transparent crystals, which became opaque on standing or heating, indicating that solvent was included; m.p. 138–140°.

*Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: C, 53.90; H, 3.17; O, 14.4. Found: C, 53.89; H, 3.2; O, 13.8.

The residue containing IIIb was washed with water and recrystallized several times from benzene to give 0.6 g. of pure IIIb, m.p. 189–190.5°.

*Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: C, 53.90; H, 3.17; O, 14.4. Found: C, 54.2; H, 3.2; O, 13.9.

The isomers IIIa and IIIb had very similar infrared spectra.

**C. With a Mole Ratio of Hypochlorite to I of 4.3:1.**—In this experiment, the attempt was made to permit I to react, in the neighborhood of pH 7, with as much hypochlorite as it would consume. Chlorine water, brought to pH 7, was therefore added periodically to a solution of 1.07 g. of I in 105 ml. of acetonitrile, with continual pH adjustment (no higher than pH 7.8) with 1 N sodium hydroxide, until the hypochlorite to olefin ratio had reached 4.3:1 (the total volume of added aqueous solutions being 330 ml.). After standing overnight, the mixture was evaporated to dryness at reduced pressure, and the residue taken up in a small volume of water and acidified with concentrated sulfuric acid to give a precipitate of IV, which was isolated and washed with cold water (0.458 g.). On recrystallization from chloroform–petroleum ether, the substance melted at 166.5–167° on a melting point block; the melting point is sometimes lower, evidently depending on conditions and age of the sample. The $pK_a$ is about 2.4, close to that of cyanoacetic acid.[19]

*Anal.* Calcd. for $C_{10}H_6O_3NCl$: C, 53.7; H, 2.7; N, 6.3. Found: C, 53.5; H, 2.9; N, 6.3.

**Preparation of II with Hydrogen Peroxide.**—A mixture of 3 ml. of 30% hydrogen peroxide, 65 ml. of water and 1 ml. of 1 M potassium nitrate was found to be 0.524 M in peroxide by titration. A 20-ml. aliquot of this was added to a solution of 1.92 g. of I in 50 ml. of acetonitrile and the mixture was brought to pH 7.6 with 8 ml. of 0.03 N sodium hydroxide. After about 15 min., the mixture was concentrated in the rotating evaporator until a second phase appeared. Then ether and 2 N sodium chloride were added, and the mixture was shaken and separated. The ether layer was evaporated to an oil, which was extracted with several portions of hot petroleum ether (b.p. 30–60°); the petroleum ether extract, on chilling, deposited 0.79 g. of crude II; while the residue from extraction, 0.39 g., contained mostly impure IIIb, m.p 176–185°. On recrystallization of crude II from petroleum ether, nearly pure material, m.p. 49–50°, was obtained. Recrystallization of IIIb from benzene gave material of m.p. 190–191°; a small amount of IIIa was isolated from the mother liquors.

**Kinetic Experiments.**—Reaction mixtures for kinetic studies contained 0.1 M acetate buffer adjusted to pH with sodium hydroxide and $5 \times 10^{-5}$ M I, introduced in acetonitrile (so that the reaction mixtures also contained 1% by volume of acetonitrile). The absorptivity (A) at 300 m$\mu$ was measured[15] as a function of time after introduction of the epoxidizing agent, and the half-lives, $t_{1/2}$, obtained from plots of log (A − A∞) against time; $k_{obsd} = 0.693/t_{1/2}$; the apparent second-order rate constant $k_2' = k_{obsd}/[\text{oxidant}]$; the true second-order rate constant, $k_2 = ([H^+] + K_a) k_2'/K_a$. Data for hypochlorite are shown in Table 1. A single experiment conducted similarly with $1.1 \times 10^{-3}$ M hydrogen peroxide in phosphate buffer gave $k_2' = 18.1$ M$^{-1}$ sec.$^{-1}$, or taking $K_a$ as $2.24 \times 10^{-12}$ for hydrogen peroxide,[13] $k_2 = 4.3 \times 10^5$.

**Disappearance of II in the Presence of Hypochlorous Acid.**—

(15) Cells of 1-cm. light path, in a Beckman Model DU spectrophotometer modified for recording by Process and Instruments, Inc., were used.
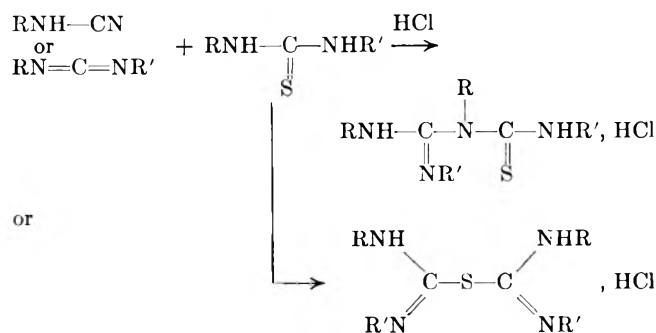
(16) This solvent appeared to be relatively inert to the oxidizing reagent under conditions employed here.

(17) A Beckman Model G pH meter was used with glass and calomel electrodes.

(18) Glycidonitrile is similarly quite steam volatile.

(19) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," 3rd ed., Vol. 1, Oxford University Press, New York, N. Y., 1953, p. 624.

A mixture of 0.9 g. of II, 50 ml. of acetonitrile and 40 ml. of 0.17 $M$ hypochlorous acid was adjusted to pH 8 with 7 ml. of 1 $N$ sodium hydroxide. At the end of an hour the mixture was acidified to pH 4.7 and extracted with ether. About 32% of starting material was recovered after evaporating off the ether layer. When a similar amount of II was kept for an hour at pH 8 in a mixture of 50 ml. of acetonitrile plus 50 ml. of water, the starting material was almost completely recovered.

# Interaction of 2-Chlorobenzothiazole with Aromatic Thiocarbamides. I. Formation of Guanylthiocarbamides and Sulfides

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Interaction of 2-chlorobenzothiazole has been investigated with arylthiocarbamides. Hydrochlorides of the related substituted guanylthiocarbamides are obtained. 1,3-Diphenylthiocarbamide, however, gave bis(N,N'-diphenylguanyl) sulfide hydrochloride.

The interaction, mostly in alcoholic medium, of 2-chlorobenzothiazole with thiocarbamides has been investigated by Watt[1] and Scott and Watt.[2] Thiocarbamide and its monosubstituted derivatives were found to give mercaptobenzothiazole, benzothiazolyl sulfide and cyanamide corresponding to the thiocarbamide used, as the main products. Based on these facts a reaction mechanism which involved initial formation of S-2-benzothiazolylisothiouronium chloride as an intermediate stage was proposed, although this last could not be isolated in any of the cases studied. From disubstituted thiocarbamides even on prolonged action no products were obtained except in the case of N,N'-o-phenylenethiocarbamide (thiobenzimidazolone) where a gray solid believed to be an addition product was isolated. With trisubstituted thiocarbamides no reaction was observed.

In connection with our work[3] on 2-substituted benzothiazole derivatives the interaction of thiocarbamides and 2-chlorobenzothiazole was reinvestigated. In view of the extreme lability of the S-R link in isothiocarbamides where R was an acyl or an electronegative group in general, it was felt that the reaction conditions employed by the above workers were unconducive for the isolation of the addition or other more reactive products. In the present study, therefore, the reactions were carried out at the ordinary room temperature or at about 40–50° mostly without any solvent or with actone as solvent.

The reaction was investigated with (i) 1-phenyl-, (ii) 1-(p-tolyl)-, (iii) 1-(o-tolyl)-, (iv) 1-(2,6-dimethylphenyl)-, (v) 1-phenyl-3-methyl-, (vi) 1-phenyl-3-ethyl-, (vii) 1-(p-tolyl)-3-methyl-, (viii) 1-phenyl-3,3-dimethyl-, and (ix) 1,3-diphenylthiocarbamides.

The products were colorless in all cases except the last one, *viz.*, (ix) where it had a lemon-yellow color. All were hydrochlorides, of unstable bases which could not be isolated in pure condition, except in the case of (v), (vi), (vii), and (viii) where they were found to be identical with the products obtained by the oxidation of the related thiocarbamides[4] with bromine in alcoholic medium and have been assigned structure Ia through Id, respectively.



Ia from v, where R = H, R' = CH₃, Ar = Ar' = C₆H₅
Ib from vi, where R = H, R' = C₂H₅, Ar = Ar' = C₆H₅
Ic from vii, where R = H, R' = CH₃, Ar = Ar' = CH₃C₆H₄
Id from viii, where R = R' = CH₃, Ar = Ar' = C₆H₅

As judged from their decomposition products and other behavior there does not appear any doubt that the colorless products from other thiocarbamides also possessed similar structures. In the case of 1-phenyl- and 1-(p-tolyl)thiocarbamides, the products were found different from II, the 1-arylguanyl-3-arylthiocarbamides[5,6]



where Ar = phenyl or p-(tolyl) group. That they were identical with III was confirmed by their almost quantitative and easy decomposition to diarylguanidine and thiocyanic acid, respectively.

The yellow product obtained from 1,3-diphenylthiocarbamide was proved by its identical behavior to be the hydrochloride (IV) corresponding to the hydrobromide of bis(N,N'-diphenylguanyl) sulfide described by Suresh.[7] The infrared absorption spectra of IV



and of bis(N,N'-diphenylguanyl) sulfide hydrobromide prove unequivocally their identical sulfide structures.

There is evidence suggesting that in the case of the above reactions the initial product is an S-(2-benzothiazolyl)isothiouronium chloride[8] as envisaged by Watt[1] and as shown by Suresh and D'Souza[9] in the case of reaction with p-toluenesulfonyl chloride and by

(1) G. Watt, *J. Org. Chem.*, **4**, 436 (1939).

(2) W. Scott and G. Watt, *ibid.*, **2**, 148 (1937).

(3) C. P. Joshua, *J. Indian Chem. Soc.*, **37**, 621 (1960); **38**, 155, 979 (1961).

(4) P. K. Srivastava, unpublished work.

(5) S. N. Dixit, *J. Indian Chem. Soc.*, **37**, 153 (1960).

(6) K. S. Suresh, *J. Sci. Res. Banaras Hindu Univ.*, IX (2), 92 (1958–1959).

(7) K. S. Suresh, *J. Indian Chem. Soc.*, **37**, 483 (1960).

(8) R. H. Sahasrabudhey, C. P. Joshua, and S. N. Pandey, *Proc. Indian Sci. Congr.*, Part III, Abstracts, 102 (1961).

(9) K. S. Suresh and M. S. A. D'Souza, *J. Vikram Univ.*, 3 (3), 10 (1959).

Pandeya and Joshua[10] in the reaction of N-alkylthiocarbamides with 2-chlorobenzothiazole. This, being unstable, decomposes into mercaptobenzothiazole, hydrochloric acid and the related cyanamide. It is likely that one of the following reactions then takes place.

$$
\begin{array}{c}
\text{RNH—CN} \\
\text{or} \quad + \text{RNH—C—NHR'} \longrightarrow \\
\text{RN=C=NR'} \qquad \overset{\|}{\text{S}}
\end{array}
$$

$$
\begin{array}{c}
\qquad\qquad\qquad \text{R} \\
\text{RNH—C—N—C—NHR', HCl} \\
\overset{\|}{\text{NR'}} \quad \overset{\|}{\text{S}}
\end{array}
$$

or

$$
\begin{array}{c}
\text{RNH} \qquad\qquad \text{NHR} \\
\longrightarrow \quad \underset{\text{R'N}}{\overset{}{\text{C—S—C}}} \quad , \text{HCl} \\
\text{R'N} \qquad\qquad \text{NR'}
\end{array}
$$

where R is an aryl group and R' an alkyl or hydrogen.

The reaction affords a method for the preparation of guanylthiocarbamides carrying more than one substituent in the formamidino grouping and also with a substituent on the nitrogen to which the formamidino group was attached.

### Experimental

The required aromatic thiocarbamides were obtained by the usual methods; viz., (1) isomerization of the related amine thiocyanates obtained in solution by mixing aqueous solutions of amine hydrochloride and ammonium thiocyanate and (2) by the reaction of an aryl or alkyl isothiocyanate with an appropriate amine.

2-Chlorobenzothiazole was prepared by the reaction of 2-mercaptobenzothiazole with thionyl chloride.

**Interaction of 2-Chlorobenzothiazole with 1-Arylthiocarbamides. Formation of 1-(Arylguanyl)-1-arylthiocarbamide Hydrochlorides.** —The interaction of 2-chlorobenzothiazole with 1-arylthiocarbamides was carried out in acetone. A typical set of details pertaining to the reaction of 1-phenylthiocarbamide is as follows.

A clear solution of doubly crystallized 1-phenylthiocarbamide (10 g.) in acetone (50 ml.) was mixed with 2-chlorobenzothiazole (4.5 ml.) and kept aside for some time. Within 10 min. the reaction mixture warmed up and a clot-like precipitate was formed which on standing for some time granulated as a white microcrystalline powder. The solid was filtered, washed with warm acetone and then finally with ether (yield 9.5 g., m.p. 158°). The product was extremely soluble in water and ethanol and could not be crystallized from these solvents. From aqueous solution (which was acidic) a picrate (m.p. 142°) was obtained on addition of picric acid.

The 1-(p-tolyl)-, 1-(o-tolyl)-, and 1-(2,6-dimethylphenyl)thiocarbamides also reacted in a similar manner. The reaction can be facilitated by warming the mixture on a water bath at about 40–50° and by adding a drop of concentrated hydrochloric acid. The products obtained were slightly hygroscopic and decomposed gradually on keeping if moisture was not excluded.

Evaporation of the acetone mother liquors and washings left a sticky mass which, when treated with alkali, largely dissolved and was reprecipitated when acidified. On crystallization from ethanol, needle shaped crystals, m.p. 178°, identified as 2-mercaptobenzothiazole by undepressed mixture melting point with an authentic sample, were obtained.

(i) 1-(Phenylguanyl)-1-phenylthiocarbamide hydrochloride (product from 1-phenylthiocarbamide), m.p. 158°. Picrate m.p. 142°.

*Anal.* Calcd. for $C_{14}H_{14}N_4S\cdot HCl$: equiv. wt., 306.5; C, 54.81; H, 4.89; N, 18.27; S, 10.44; Cl, 11.58. Found: equiv. wt., 311.5; C, 54.98; H, 4.89; N, 18.83; S, 10.82; Cl, 11.82.

(ii) 1-(p-Tolylguanyl)-1-p-tolylthiocarbamide hydrochloride (product from 1-(p-tolyl)thiocarbamide), m.p. 146°. Picrate, m.p. 145°.

(10) S. N. Pandeya and C. P. Joshua, *J. Vikram Univ.*, 1962, in press.

*Anal.* Calcd. for $C_{16}H_{18}N_4S\cdot HCl$: N, 16.7. Found: N, 16.82

(iii) 1-(o-Tolylguanyl)-1-o-tolylthiacarbamide hydrochloride (product from 1-(o-tolyl) (thiocarbamide), m.p. 156°. Picrate m.p. 152°

*Anal.* Calcd. for $C_{16}H_{20}N_4SO\cdot HCl$: equiv. wt., 352.5; C, 54.56; H, 5.67; N, 15.88. Found: equiv. wt., 349.2; C, 54.90; N, 15.82.

(iv) 1-(2,6-Dimethylphenylguanyl) 1-(2,6-dimethylphenyl)-thiocarbamide hydrochloride [product from 1-(2,6-dimethylphenyl)-thiocarbamide], m.p. 157°. Picrate, m.p. 136°.

*Anal.* Calcd. for $C_{18}H_{22}N_4S\cdot HCl$: equiv. wt., 362.5; C, 59.58; H, 6.34; N, 15.44. Found: equiv. wt., 365.8; C, 60.81; H, 6.74; N, 15.56.

**Behavior of 1-(Phenylguanyl) 1-Phenylthiocarbamide Hydrochloride with Water, Acid, and Alkali.** —Aqueous solutions of 1-(phenylguanyl)-1-phenylthiocarbamide hydrochloride decomposed gradually on standing; the decomposition was rapid when heated; phenylthiocarbamide (m.p. 154°), phenylcarbamide (m.p. 147°), and hydrochloric acid were formed. When heated under reflux with concentrated hydrochloric acid and steam distilled, a few drops of an oily substance smelling of mustard oil separated. (This was identified as phenyl isothiocyanate by its reaction with aniline, when 1,3-diphenylthiocarbamide was obtained.) The warm residual solution deposited needle-shaped crystals which were identified as phenylthiocarbamide (m.p. 154°); the filtrate, on cooling and standing, deposited more crystals. They were a mixture of phenylthiocarbamide and phenylcarbamide which could be separated by fractional crystallization from water.

Addition of a very dilute solution of alkali to an aqueous solution of 1-(phenylguanyl)-1-phenylthiocarbamide hydrochloride afforded a white fluffy precipitate which could be isolated without much decomposition when the solution was still slightly acidic. This was the free base (m.p. 85°). It decomposed gradually on keeping and could not be crystallized. When warmed with a moderately strong solution of alkali, 1-(phenylguanyl)-1-phenylthiocarbamide decomposed. The solid product and the filtrate were examined. Phenylcyanamide, phenylthiocarbamide, diphenylguanidine, and thiocyanic acid were identified as follows:

When the ice-cooled alkaline filtrate was made just acidic to litmus, phenylcyanamide hydrate[11] precipitated as a white creamy mass. It was found soluble in excess of acid and gave a silver salt. When boiled with dilute hydrochloric acid it formed phenylcarbamide, m.p. 147°, identified by comparison with an authentic sample. The alkaline filtrate, on acidification and treatment with a few drops of very dilute ferric chloride solution, gave a very deep red color which could be extracted with ether indicating the presence of thiocyanic acid. Extraction of the alkali-insoluble residue with cold, dilute acid and reprecipitation with alkali yielded diphenylguanidine, m.p. 147°. It did not show any depression in melting point when mixed with an authentic sample. The residue which was insoluble in both dilute acid as well as alkali could be crystallized from hot water and was found to be phenylthiocarbamide.

**Decomposition of 1-(Phenylguanyl)-1-phenylthiocarbamide Hydrochloride with Ammonium Hydrogen Sulfide.** —An ethanolic solution of ammonia saturated with hydrogen sulfide was mixed with a solution of 5 g. of the hydrochloride of 1-(phenylguanyl)-1-phenylthiocarbamide, and hydrogen sulfide gas passed through the solution for about 10 min. The resulting solution, after evaporation of alcohol, was treated with strong ammonia. Shining white crystals were collected and crystallized from boiling water (yield 3 g.). They were soluble in very dilute acid and were identified as diphenylguanidine (m.p. 147°). The ammoniacal sulfide mother liquors gave a deep red color, indicating thiocyanic acid, when acidified and treated with ferric chloride.

**Interaction of 2-Chlorobenzothiazole with 1-Phenyl-3-methylthiocarbamide. Formation of 1-(N-Phenyl-N'-methylguanyl)-1-phenyl - 3 - methylthiocarbamide Hycrochloride.** — 1-Phenyl-3-methylthiocarbamide (10 g.) was triturated with 2-chlorobenzothiazole (4.2 ml.) in a china dish. The reaction mixture warmed up and became a pasty, pale yellow mass. On treatment with warm, dry acetone and ether a white crystalline solid (about 9 g.) was obtained, m.p. 162°. It was acidic to litmus.

*Anal.* Calcd. for $C_{16}H_{18}N_4S\cdot HCl$: equiv. wt., 334.5. Found: equiv. wt., 335.5.

(11) R. Sahasrabudhey and H. Krall, *J. Indian Chem. Soc.*, **19**, 343 (1942).

It formed a picrate, m.p. 155°, and on treatment with dilute alkali gave a free base, m.p. 83°, which was found identical with the base obtained by Srivastava[4] by the bromine oxidation of 1-phenyl-3-methylthiocarbamide.

*Anal.* Calcd. for $C_{16}H_{18}N_4S$: C, 64.20; H, 6.30; N, 18.72. Found: C, 64.18; H, 6.15; N, 18.84.

An aqueous solution of the hydrochloride decomposed when heated under reflux for about 1 hr. On steam distillation a few drops of an oily liquid smelling of mustard oil and identified as phenyl isothiocyanate were obtained. The residual solution on cooling gave a crystalline solid from which 1-methyl-3-phenyl-thiocarbamide, m.p. 114°, and 1-methyl-3-phenylcarbamide, m.p. 147°, were separated by fractional crystallization from water. Methylamine was evolved when the acidic filtrate was treated with strong alkali, and some unchanged base, m.p. 83°, precipitated.

Reaction with strong hydrochloric acid also afforded the same products. When the hydrochloride of the above guanylthio-carbamide or the free base was decomposed with ammoniacal hydrogen sulfide, N,N'-diphenyl-N''-methylguanidine, m.p. 109°, was obtained. These observations are in agreement with those made earlier.[4]

**Interaction of 2-Chlorobenzothiazole with 1-(p-Tolyl)-3-methyl-thiocarbamide. Formation of 1-(N-p-Tolyl-N'-methylguanyl)-1-p-tolyl-3-methylthiocarbamide Hydrochloride.**—The reaction was carried out as above using the reactants in the same proportion. A white, crystalline, acidic solid, m.p. 113° was obtained. With aqueous picric acid it afforded a picrate, m.p. 140°, and on treatment with dilute alkali precipitated the free base, m.p 72°.

*Anal.* Calcd. for $C_{18}H_{22}N_4S$: C, 66.25; H, 6.74; N, 17.17; equiv. wt. (hydrochloride), 362.5. Found: C, 66.31; H, 6.93; N, 16.90; equiv. wt. (hydrochloride), 365.3.

Analogous to the behavior of the above compounds on reaction with hydrochloric acid, it afforded 1-(p-tolyl)-3-methylthiocar-bamide, m.p. 126°, 1-(p-tolyl)-3-methylcarbamide, m.p. 178°, p-tolylisothiocyanate and methylamine.

**Interaction of 2-Chlorobenzothiazole with 1-Phenyl-3-ethylthio-carbamide. Formation of 1-(N-Phenyl-N'-ethylguanyl)-1-phenyl-3-ethylthiocarbamide Hydrochloride.**—The reaction was carried out as above using the reactants in the same proportion. A white, crystalline, acidic solid, m.p. 158° was obtained. With aqueous picric acid it afforded a picrate, m.p. 136°, and on treatment with dilute alkali precipitated the free base, m.p. 85°, which decomposed gradually on keeping.

*Anal.* Calcd. for $C_{18}H_{22}N_4S \cdot HCl$: equiv. wt., 362.5. Found: equiv. wt., 370.3.

*Anal.* Calcd. for $C_{18}H_{22}N_4S$: N, 17.17; S, 9.81. Found: N, 17.21; S, 9.92.

**Interaction of 1-Phenyl-3,3-dimethylthiocarbamide and 2-Chlorobenzothiazole. Formation of 1-(N,N-Dimethyl-N'-phenyl-guanyl)-1-phenyl-3,3-dimethylthiocarbamide Hydrochloride.**—Finely powdered 1-phenyl-3,3-dimethylthiocarbamide (10 g.) and 2-chlorobenzothiazole (4.2 ml.) were triturated in a china

dish and allowed to stand after adding a droplet of concentrated hydrochloric acid. The reaction mixture warmed up within a few minutes, and a yellowish sticky mass was obtained. Washing with warm, dry acetone and ether yielded a product, m.p. 105° (about 9 g.).

*Anal.* Calcd. for $C_{18}H_{22}N_4S \cdot HCl$: equiv. wt., 362.5. Found: equiv. wt., 364.5.

It afforded a picrate m.p. 139°. On treatment with alkali the free base, m.p. 118°, was obtained which was found identical with the product obtained by Srivastava[4] from the bromine oxidation of 1-phenyl-3,3-dimethyl-thiocarbamide.

*Anal.* Calcd. for $C_{18}H_{22}N_4S$: C, 66.25; H, 6.74; N, 17.17. Found: C, 65.78; H, 6.65; N, 17.46.

On prolonged heating with strong hydrochloric acid, like other derivatives of this type (*vide supra*), it decomposed into 1-phenyl-3,3-dimethylthiocarbamide, m.p. 134°, 1-phenyl-3,3-dimethyl-carbamide, m.p. 131°, phenyl isothiocyanate, and dimethyl-amine.

**Interaction of 2-Chlorobenzothiazole with 1,3-Diphenylthio-carbamide. Formation of bis(N,N'-Diphenylguanyl)sulfide Hydrochloride.**—Finely powdered, doubly crystallized 1,3-diphenylthiocarbamide (10 g.) and 2-chlorobenzothiazole (4 ml.) were thoroughly mixed in a china dish, and a drop of concentrated hydrochloric acid was added to facilitate the reaction. Within a few minutes the reaction mixture warmed up, and a yellow sticky product was obtained. On washing with dry, warm, acetone a pale yellow microcrystalline powder (about 9 g.) separated, m.p. 155° (dec.). It was found to be acidic to litmus.

*Anal.* Calcd. for $C_{26}H_{22}N_4S \cdot HCL$: equiv. wt., 458.5; C, 68.04; H, 5.01; N, 12.21. Found: equiv. wt., 454.0; C, 68.14; H, 5.88; N, 12.27.

The product decomposed at once on contact with water giving phenyl isothiocyanate and triphenylguanidine hydrochloride, m.p. 248°, which on treatment with base gave free triphenyl-guanidine, m.p. 145°. Its identity with the free base of the hydrobromide formed by the oxidation of 1,3-diphenylthio-carbamide with bromine in ethanol[7] was established by a comparison of infrared spectra. The following absorption characteristics were noted.

Above derivative (hydrochloride): 3290 m, 2800 s, 2100 m, 1630 s, 1570 s, 1494 s, 1440 s, 1338 s, 1260 m, 1200 m, 1176 m, 1036 w, 1026 m, 908 s, 833 m, 745 s, 735 s, 690 s, 638 m.

Suresh's[7] compound (hydrobromide): 3320 m, 2800 s, 2090 m, 1630 s, 1570 s, 1494 s, 1440 s, 1336 s, 1260 m, 1200 m, 1176 m, 1036 w, 1025 m, 908 s, 835 m, 745 s, 735 s, 690 s, 638 m.

# The Effect of Solvent upon the N.m.r. Spectra of N-Methylamides. I. Solvent-Solute Complex Formation between Amides and Aromatic Solvents

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The effect of aromatic solvents such as pyridine, collidine, and benzene upon the chemical shift of protons in systems possessing internal hindered rotation has been studied. It was found that progressive dilution of a carbon tetrachloride solution of N-methylcyclohexylacetamide with pyridine shifted the two N-methyl peaks unequally with respect to each other leading to gradual coalescence and crossover with a change in sign of their chemical shifts. This behavior is discussed in terms of specific complex formation between the amide and pyridine. Similar solvent dependency studies using N-methylsulfonamido, N-methylsulfinamido, and N-methylnitrosoamino derivatives also are described.

Nuclear magnetic resonance has proved to be a very valuable method for the study of hindered internal rotation in systems in which the rate of interconversion between two rotational conformers is sufficiently slow to allow a chemical shift difference between signals arising from the two rotamers.[1] Several N-methylamides[2,3] show a doublet methyl resonance attributable to such a chemical shift difference between the methyl groups at each rotational site.[3] Gutowsky and Holm[3] have determined the barrier height $Ea$ for rotation about the CO—N bond for a number of amides. This measurement is based upon the variation with temperature of the signals arising from the resonance absorption due to each rotational isomer. Typical values of $Ea$ are $7 \pm 3$ kcal. for N,N-dimethylformamide and $12 \pm 2$ kcal. for N,N-dimethylacetamide. The origin of the potential energy barrier is due to resonance conjugation between the p-orbital on nitrogen and the p-orbital of the carbonyl $\pi$-electron system resulting in the two planar dipolar forms A and C.
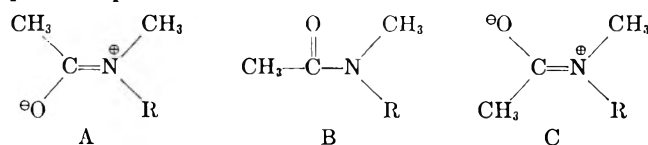


The effect of solvent on this process may be separated into a direct effect on the barrier height changing its value and leading to a different rate of interconversion or, secondly, a molecular association between solvent and solute leading to an alteration of the proton chemical shifts of the rotamers. One would predict a solvent effect upon the barrier height since the ground state A is polar relative to the nonpolar transition state for rotation B. Such solvent dependency has been demonstrated by Rogers and Woodbrey.[4] The second type of solvent effect is due to the specific contribution of aromatic solvents to the reaction field of the solute, $\delta_\epsilon$,[5] and possible solute solvent complex formation $\delta_c$.[6-8] These latter solvent effects lead to a difference in the chemical shift from the pure substance due to the

secondary magnetic field generated by the ring current of the solvent.[5]

## Results and Discussion

**Solvent Effects on the Amide Group.**—N-Methylcyclohexylacetamide (I) was chosen as a model compound for these studies because both N-methyl and C-methyl groups appear as sharply resolved doublets at room temperature when measured as a pure liquid (Fig. 1) and in 20% carbon tetrachloride solution. At elevated temperatures (55°) both methyl groups are singlets in agreement with the concept of a relatively large barrier to internal rotation about the N—C—O bond.[9] Cooling to room temperature leads to a restoration of the doublet pattern. The spectrum at room temperature is a superposition of the bands due to rotamers Ia and Ib. In contrast to a symmetrical case such as N,N-dimethylformamide, Ia and Ib correspond to different structures. Each has a different energy and the composition at room temperature should contain unequal amounts of each isomer depending upon
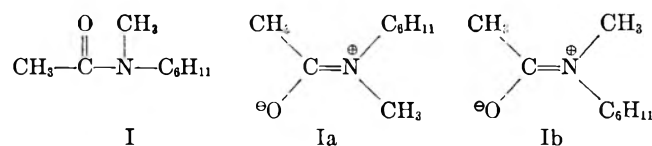


their relative stabilities. The high and low field component of each doublet may be distinguished by the dissimilar shapes but assignment of their actual position in A or B cannot be made. For this discussion the taller peak in each doublet is designated as $\alpha$ and the shorter as $\beta$. The band position of the methylenes and methine of the cyclohexane ring and the N-methyl and C-methyl are based upon abundant analogy and supported by the integrated ratios. Dilution of a 30% carbon tetrachloride solution with pyridine to solutions of mole fraction of 83.50, 67.23, and 53.10 (in amide and pyridine) causes a progressive downfield shift of the $\alpha$ C—CH₃ by $\Delta\delta = 0.08$, the $\beta$ C—CH₃ by $\Delta\delta = 0.09$, and the $\alpha$ N—CH₃ by $\Delta\delta = 0.04$, and the $\beta$ N—CH₃ by $\Delta\delta = 0.13$ (Table I). The spectra of the amide-pyridine-carbon tetrachloride solution $N_1$, 83.50, 67.23, and 53.10 are shown in Fig. 1, 2, 3, and 4, respectively. At the concentrations of amide mole fraction of 53.10 and 45.90 the $\alpha$- and $\beta$-N-methyl bonds coalesce to a sharp singlet absorption at $\delta = 2.80$. As dilution with pyridine is continued the $\beta$ N-methyl peak moves from

(1) J. A. Pople, W. G. Schneider, and H. J. Berstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1958, p. 365.

(2) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955).

(3) H. S. Gutowsky and C. H. Holm, *J. Am. Chem. Soc.*, **25**, 1228 (1956). In this discussion the terms singlet and doublet refer to multiplicity resulting from hindered internal rotation and not spin-spin coupling.

(4) J. C. Woodbrey and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 13 (1962).

(5) A. D. Buckingham, T. P. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, **32**, 1227 (1960).

(6) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960).

(7) (a) J. V. Hatton and R. E. Richards, *ibid.*, **5**, 139 (1960); (b) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(8) J. V. Hatton and W. G. Schneider, *Can. J. Chem.*, **40**, 1285 (1962).

(9) The temperature required for averaging the N-methyl shifts in N,N-dimethylformamide in dilute methylcyclohexane is 99° (ref. 8).

Table I

Proton Shifts ($\delta$) for N-Methylcyclohexylacetamide (I) in Various Solutions[a–d]

| Spectrum | Mole fraction I in 30% carbon tetrachloride solution | Solvent | N—CH₃ | | | | C—CH₃ | | | | —CH₂— |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $\alpha$ | $\Delta\alpha$ | $\beta$ | $\Delta\beta$ | $\alpha$ | $\Delta\alpha$ | $\beta$ | $\Delta\beta$ | |
| 1 | 100 | | 2.79 | | 2.66 | | 1.94 | | 1.99 | | 1.50 |
| 2 | 83.50 | Pyridine | 2.83 | 0.04 | 2.77 | 0.11 | 2.01 | 0.07 | 2.06 | 0.07 | 1.55 |
| 3 | 67.23 | Pyridine | 2.83 | .04 | 2.79(sh) | .13 | 2.02 | .08 | 2.08 | .09 | 1.55 |
| 4 | 53.10 | Pyridine | 2.80 | .01 | 2.80 | .14 | 2.02 | .08 | 2.08 | .09 | 1.55 |
| 5 | 45.90 | Pyridine | 2.80 | .01 | 2.80 | .14 | 2.02 | .08 | 2.08 | .09 | 1.55 |
| 6 | 33.75 | Pyridine | 2.73 | − .06 | 2.81 | .15 | 2.04 | .10 | 2.10 | .11 | 1.55 |
| 7 | 19.61 | Pyridine | 2.70 | − .09 | 2.81 | .15 | 1.99 | .05 | 2.08 | .09 | 1.55 |
| 8 | 6.95 | Pyridine | 2.67 | − .13 | 2.79 | .13 | 2.00 | .06 | 2.09 | .10 | 1.55 |
| 9 | 34.10 | Benzene | 2.41 | − .38 | 2.68 | .02 | 1.80 | − .14 | 1.90 | − .09 | 1.40 |
| 10 | 61.10 | s-Collidine | 2.80 | .01 | 2.78 | .12 | 2.04 | .10 | 2.00 | .01 | 1.55 |
| 11 | 19.00 | Piperidine | 2.80 | .01 | 2.80 | .14 | 2.00 | .06 | 2.00 | .01 | 1.50 |
| 12 | 10.00 | Ethanol | 2.82 | .03 | 2.73 | .07 | 2.00 | .06 | 2.05 | .06 | 1.60 |
| 13 | 30.00 | Piperidine | 2.81 | .02 | 2.81 | .15 | 2.00 | .06 | 2.00 | .01 | 1.49 |

[a] Chemical shifts $\delta = 10^6 \dfrac{H - H_{ref}}{H_{ref}}$ are relative to tetramethylsilane as internal standard at $\nu = 60.0$ Mc. [b] $\Delta\alpha$ and $\Delta\beta$ refer to the shifts of the $\alpha$ and $\beta$ components of the N-methyl and C-methyl doublets relative to their positions in the N-methylcyclohexylacetamide in 30% carbon tetrachloride solution. [c] All spectra were determined at room temperature. [d] The methine proton and solvent bands are not included in this table.

under the singlet peak and appears at a new downfield position with a concomitant high field shift of the $\alpha$ N—CH₃ peak. This reversed order of appearance persists as additional pyridine is added. Although the $\alpha$- and $\beta$-C-methyl peaks are shifted to lower field upon dilution with pyridine, no coalescence and crossover is observed. Benzene as solvent leads to uniform shifts of all bands to higher fields with the $\alpha$ N—CH₃ being shifted past the $\beta$-peak by $\Delta\delta = -0.38$. The spectrum of the amide in ethanol is similar to the spectrum of the pure amide in carbon tetrachloride. In 30% carbon tetrachloride solution of I in collidine, the doublet character of the methyl groups is retained but the spacings between the doublet peaks are decreased. Using piperidine as solvent the C-methyl peak appears as a sharp singlet. These results are summarized in Table I. Fig. 5 represents the spectrum of I in 30% carbon tetrachloride solution with benzene and corresponds to spectrum 9 in Table I.

A complete explanation of these solvent effects must account for (a) the direction of the line shifts observed in adding pyridine to a dilute solution of the amide in carbon tetrachloride, (b) the fact that the $\alpha$ and $\beta$ components of the methyl doublets are shifted unequally relative to one another and in the case of the N-methyl groups, the observed coalescence and crossover pattern, and finally (c) the concentration dependency of the chemical shifts. These three points may be considered in terms of an amide–pyridine complex present according to the following equilibrium.[10]

amide + pyridine ⇌ amide–pyridine
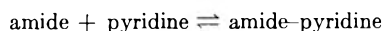
It is proposed that the complex formed in this system has a definite structure based upon electrostatic attraction between the amide group and the pyridine. It has been suggested that "disk-shaped" aromatic solvents such as benzene solvate polar molecules by occupying a plane parallel to the plane of the solute.[6,7a] The effect

of this arrangement is quite generally highfield shifts due to the secondary magnetic field of the benzene. Johnson and Bovey[7b] have derived a method for calculation of the diamagnetic or paramagnetic shift $\delta$ for a proton in any position relative to the benzene ring,
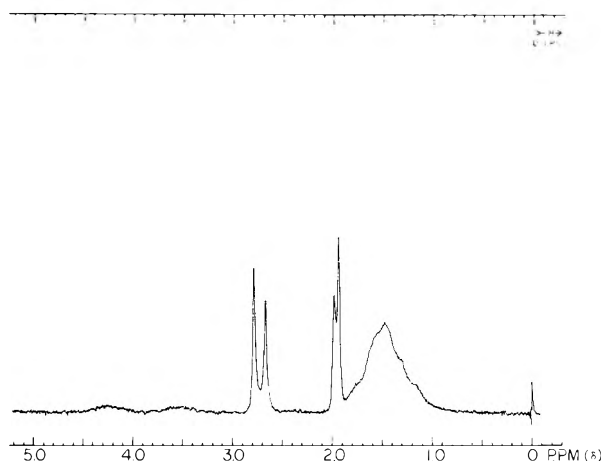


Fig. 1.—N-Methylcyclohexylacetamide (I) in 30% carbon tetrachloride solution measured relative to tetramethylsilane.
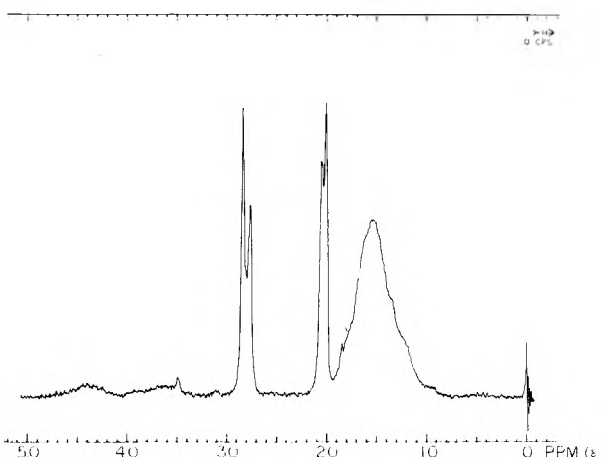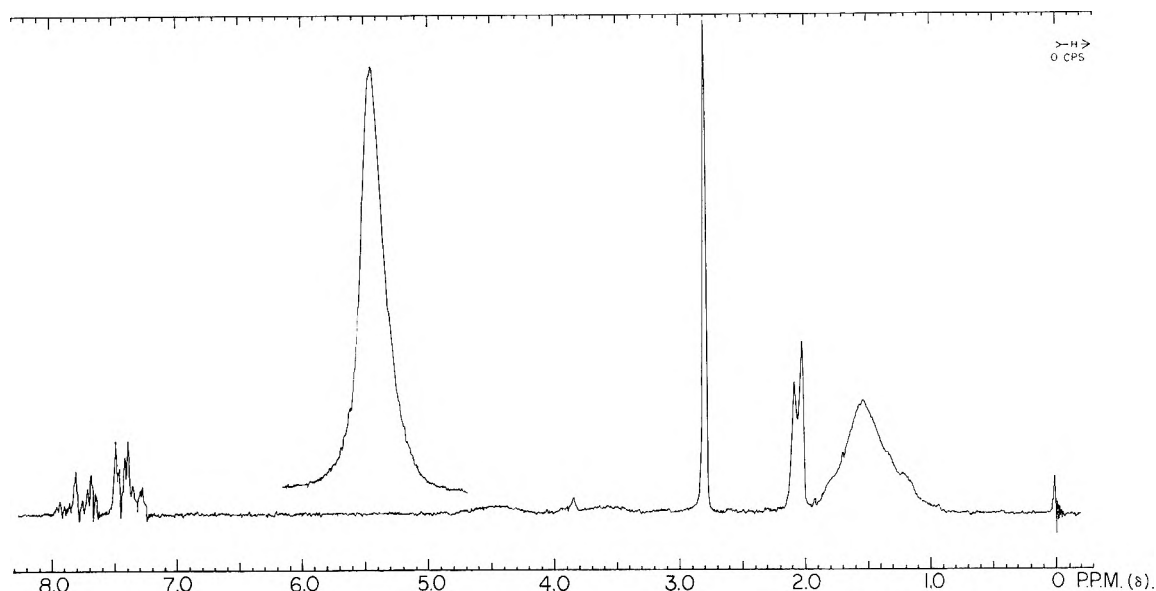


Fig. 2.—N-Methylcyclohexylacetamide (I) and pyridine of mole fraction $N_I$ 83.50 in 30% carbon tetrachloride solution relative to tetramethylsilane.

(10) In dilute carbon tetrachloride solution the amide is considered to be non-associated relative to the dimeric dipolar form proposed for the pure amide (ref. 4).

Fig. 3.—N-Methylcyclohexylacetamide (I) and pyridine of mole fraction $N_I$ 53.10 in 30% carbon tetrachloride solution relative to tetramethylsilane. The N-methyl peak is repeated at a sweep width of 50 c.p.s.
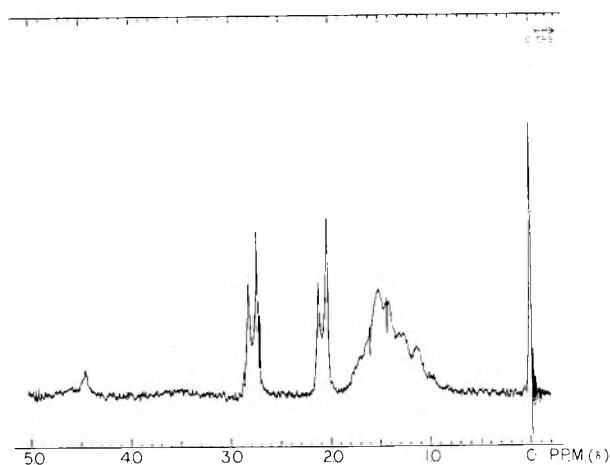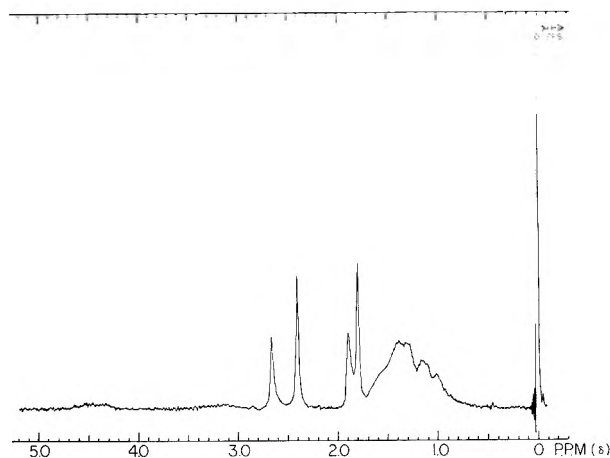


Fig. 4.—N-Methylcyclohexylacetamide (I) and pyridine of mole fraction $N_I$ 33.75 in 30% carbon tetrachloride solution relative to tetramethylsilane.



Fig. 5.—N-Methylcyclohexylacetamide (I) and benzene of mole fraction $N_I$ 34.10 in 30% carbon tetrachloride solution relative to tetramethylsilane.

if a free electron model is assumed for the aromatic. The effect is maximal when the aromatic solvent and solute are close; the diagmagnetic shifts decrease inversely with the third power of the separation R of the solute and center of the aromatic ring. This is the behavior observed in the present study with benzene namely, highfield shifts (Table I).

Pyridine, unlike benzene, does not have a symmetrical electronic structure and probably is attracted to a specific site in the amide group. The lone pair on the nitrogen of the pyridine might be partially bonded to the carbonyl group of the amide in the complex structure. This could result in an approximately perpendicular orientation of the pyridine with respect to the average plane of the amide group. Contrasted with the parallel planes model for a symmetrical aromatic, the result of the perpendicular arrangement would be the observed lowfield shifts. This is due to the greatest magnetic susceptibility being direct along the axis of the pyridine ring and the amide carbonyl resulting in enhancement of the external field. These two structural models for the amide–benzene (II) and amide–pyridine (II) are shown below.
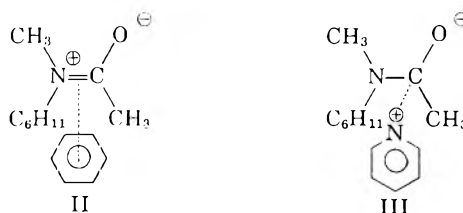


Also, it is clear that since $\alpha$ and $\beta$ conformations of the N-methyl group occupy different positions relative to the pyridine molecule, they would experience different shielding. It is reasonable that in changing the concentration and, therefore, the proportion of the complex, the resonance line due to one rotational state ($\alpha$ N—CH$_3$) might be shifted by a larger amount relative to the other ($\beta$ N—CH$_3$). Since the relative shifts of the resonance lines is dependent upon the equilibrium concentration of the amide–pyridine complex, by decreasing the mole fraction of amide we favor complex formation and observe a constant variation of the spectrum with concentration.

**Solvent Effects upon the Sulfonamido, Sulfinamido, and Nitrosamino Groups.**—Similarly hindered internal rotation in the related sulfinamides would require

delocalization of the electron pair on nitrogen into the 3d orbital of the sulfinyl group (IV and IVa).
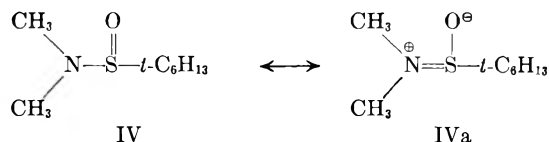


This system bears a formal relationship to the α-sulfinyl carbanion in which some question exists concerning stabilization of the anion by doubly bonded structures implying p-3d delocalization.[11]

The appearance of a doublet N-methyl resonance in the spectrum of N,N-dimethyl-*tert*-hexylsulfinamide (IV) at room temperature indicates the existence of IVa.  In dilute carbon tetrachloride solution the spacing of the N-methyl decreases to a broad singlet peak. N,N-Dimethyl-*p*-toluenesulfinamide (V) shows a sharp singlet N-methyl peak presumably due to resonance conjugation of the sulfur atom with the aromatic ring resulting in a decrease of the S—N double bond character.  N-Methylcyclohexylmethanesulfonamide (VI) possesses two different methyl groups, namely, the N-methyl and S-methyl.  Since rotation about the N—S bond leads to two equivalent rotational isomers, the N-methyl groups should appear as singlets.  In dilute carbon tetrachloride solution both the N-methyl group and S-methyl group occur at δ = 2.69.  In pyridine solution, however, they are resolved appearing at δ = 2.71 and δ = 2.87.  This result may be interpreted in terms of amide–pyridine complex formation leading to an unequal change in their chemical shifts. N-Methylcyclohexylnitrosamine (VII) might be expected to exhibit hindered rotation about the N—N bond leading to a doubling of the N-methyl resonance. In dilute carbon tetrachloride solution the N-methyl resonance appears as a sharp singlet at δ = 2.82.  In dilute pyridine this band, occurring at δ = 2.93, is broadened and less symmetrical than in carbon tetrachloride solution.  The change in the chemical shift of the N-methyl group in VII from δ = 2.92 in the pure liquid to δ = 2.82 in 20% carbon tetrachloride is probably due to dissociation of the polar nitrosamine by dilution.  These results are summarized in Table II.

It may be concluded that pyridine forms a unique complex with polar molecules based upon electrostatic attraction.  The effect of the complex formation is very specific changes in the chemical shifts of groups within the polar molecule.  The magnitude and direction of the change in chemical shifts from a suitable model may be explained satisfactorily in terms of the preferred orientation of the pyridine with respect to the polar molecule.  Future work is aimed at a quantitative study of complex formation in the amide–pyridine system.

### Experimental

A Varian Associate high-resolution A-60 instrument operating at 60.0 Mc. was employed.  A sweep width of 500 c.p.s. was used,

(11) F. G. Bordwell and P. J. Bouton, *J. Am. Chem. Soc.*, **79**, 717 (1957).

### TABLE II

CHEMICAL SHIFTS (δ) OF N,N-DIMETHYL-*t*-HEXYLSULFINAMIDE (VI), N,N-DIMETHYL-*p*-TOLUENESULFINAMIDE (VIII), N-METHYLCYCLOHEXYLMETHANESULFONAMIDE, (IX) AND N-METHYLCYCLOHEXYLNITROSAMINE (X) IN VARIOUS SOLVENTS[a]

| Spectrum | Compound | Solvent | Concn., % | $NCH_3$ | $S—CH_3$ |
|---|---|---|---|---|---|
| 14 | IV | . . . | . . | 2.64[b] | . . |
| 15 | IV | Carbon tetrachloride | 20 | 2.65 | . . |
| 16 | V | Carbon tetrachloride | 20 | 2.60 | . . |
| 17 | VI | Carbon tetrachloride | 20 | 2.69 | 2.69 |
| 18 | VI | Pyridine | 30 | 2.71 | 2.87 |
| 19 | VII | . . . | | 2.92 | |
| 20 | VII | Carbon tetrachloride | 20 | 2.82 | |
| 21 | VII | Pyridine | 30 | 2.93 | |

[a] Chemical shifts δ are measured relative to tetramethylsilane. [b] Broad doublet.

and spectra were repeated to assure constancy of the band positions which are considered accurate to within 0.01 p.p.m.  The symmetry of singlet peaks was checked by using an expanded scale of 50 c.p.s.  The resonance absorption positions were checked also by using a sweep width of 50 c.p.s.  Precision drawn tubes (8 in. × 0.20 in.) were used.  All solvents were reagent grade quality and were dried and doubly distilled prior to use. Solutions were prepared by weighing solvent and solute to the nearest milligram.

N-Methylcyclohexylacetamide (I) was prepared by treatment of N-methylcyclohexylamine with acetic anhydride according to the method of Skita,[11] b.p. 140° (13 mm.).  It was shown to be a pure substance by v.p.c. and had an infrared and n.m.r. spectrum consonant with the expected structure.  N-Methylcyclohexylnitrosamine (X) was prepared according to Skita[11] and had b.p. 121° (12 mm.).  The infrared and n.m.r. spectra were consistent with the expected structure.

**N,N-Dimethyl-*p*-tolenesulfinamide (VIII).**—Dimethylamine, 4.5 g. (0.10 mole), was dissolved in 50 ml. of ether.  To this solution cooled to 0° was added *p*-toluenesulfinyl chloride[12] (3.49 g., 0.02 mole) in 50 ml. of ether.  The dimethylamine hydrochloride which formed immediately was filtered and the ether solution concentrated to dryness yielding a crystalline residue.  Recrystallization from hexane yielded 5.2 g., m.p. 54–55°.

*Anal.*  Calcd. for $C_9H_{13}NSO$: C, 58.87; H, 7.16; N, 7.64. Found: C, 59.07; H, 7.15; N, 7.47.

**N-Methylcyclohexylmethanesulfonamide (IX).**—N-Methylcyclohexylamine, 5 g. (0.0443 mole), was dissolved in 20 ml. of pyridine, and 10 g. (0.114 mole) of methanesulfonyl chloride was added.  After standing at room temperature overnight, ice was added and the resulting crystalline produce was collected, washed with water, and recrystallized from ethanol yielding 1.8 g., m.p. 65–66°.

*Anal.*  Calcd. for $C_8H_{17}NSO_2$: C, 50.23; H, 8.94; N, 7.32. Found: C, 50.20; H, 8.90; N, 7.58.

**N,N-Dimethyl-*t*-hexanesulfinamide (VI),** b.p. 69–70° (0.35 mm.), $n^{20}D$ 1.4724, was supplied by Phillips Petroleum Co.[13]  It was distilled prior to examination and v.p.c. analysis revealed impurities to the extent of 5%.

(12) F. Kurzer, *Org. Syn.*, **34**, 93 (1954).
(13) We wish to thank Dr. J. E. Mahan for supplying us with a sample of this material.

# Polymerization by Oxidative Coupling. V. Catalytic Specificity in the Copper–Amine-catalyzed Oxidation of 2,6-Dimethylphenol[1a]

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A study was made of the influence of certain reaction variables on the relative rates of carbon–oxygen and carbon–carbon coupling in the oxidation of 2,6-dimethylphenol in the presence of homogeneous catalysts derived from copper(I) chloride and pyridine, in solution under oxygen (one atmosphere). With all other conditions held constant, the relative coupling rates are little affected by variation of the 2,6-dimethylphenol or copper(I) chloride concentrations. However, C–O coupling is markedly favored relative to C–C coupling by an increase of the ligand ratio [molar ratio of pyridine to copper(I) chloride] at constant copper(I) chloride concentration, or an increase of the catalyst concentration at constant ligand ratio. Increasing temperature or use of the sterically hindered ligands quinoline or 2,6-lutidine favors C–C coupling, but there is little effect of solvent dielectric constant in the range 2.3–7.5. An explanation of catalytic specificity in this system is advanced, which involves catalytic activity by two copper–amine complexes, differing in coördination number with respect to the ligand. It is proposed that the complex with the lower coördination number catalyzes predominantly C–C coupling, while that with the higher coördination number is specific for C–O coupling.

Previous papers in this series have been concerned with the scope of the oxidative coupling of 2,6-disubstituted phenols in the presence of copper–amine catalysts,[2,3] and with the problem of over-all mechanistic type in the polymerization *via* carbon–oxygen coupling.[4] It was demonstrated[3] that in a series of 2,6-dialkyl substituted phenols, two different types of product tend to form, depending on the bulk of the substituents R and R' (equation 1).



$$(1)$$
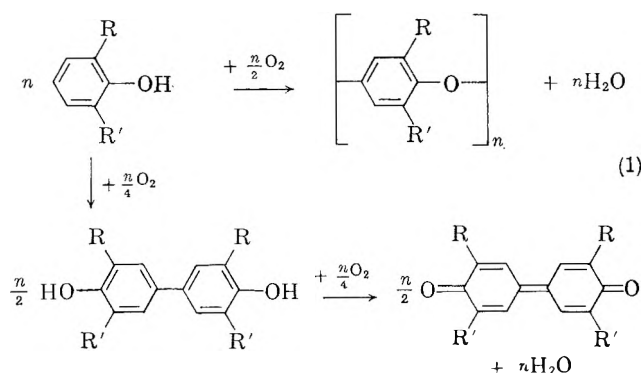
With larger groups, such as *t*-butyl, carbon–carbon coupling predominates and tetrasubstituted diphenoquinones are produced *via* intermediate dihydroxydiphenyl derivatives. On the other hand, with smaller substituents, such as methyl, a facile carbon–oxygen coupling can occur, resulting in poly(2,6-dialkyl-1,4-phenylene ethers) of high molecular weight. It will be shown in the present paper that C–O and C–C coupling can be competitive reactions even in the oxidation of 2,6-dimethylphenol, and that their relative rates are very sensitive to certain reaction conditions. It is believed that an examination of the dependence of the relative coupling rates on the conditions is desirable, not only from the point of view of synthetic utility, but also because this system is a novel example of transition metal coördination catalysis in homogeneous solution.[5] Further, as a phenol oxidation with

a catalytic system involving a copper–nitrogen coördinate linkage, a study of this system might help to clarify the mechanism of the action of certain important enzymes of the oxidase type.[6,7] Indeed, it recently has been reported[8] that an enzyme of this type converts 2,6-dimethylphenol into 3,5,3',5'-tetramethyldiphenoquinone in 30% yield. The oxidation of phenol itself in methanol solution using a morpholine–copper(II) acetate catalyst has already been very well studied.[9] We believe that the study of 2,6-dimethylphenol in the present system can shed considerable further light on the subject, owing to the relative simplicity of the reaction sequence and products, and the high degree of specificity that can be achieved.

## Experimental

Copper(I) chloride, pyridine, and 2,6-dimethylphenol were purified as described previously.[4] Quinoline (Eastman Synthetic), 2,6-lutidine, chlorobenzene, and o-dichlorobenzene (all Matheson Coleman and Bell) were fractionally redistilled, retaining constant-boiling middle fractions. Gas chromatographic analysis of the o-dichlorobenzene indicated that a considerable amount of the *meta* isomer was still present after such treatment. Benzene (Mallinckrodt AR) was used without further purification.

All oxidation experiments reported here were carried out in closed systems in stirred constant-temperature water baths, permitting quantitative measurement of the rate and extent of oxygen absorption. The reaction vessel was constructed from a 60/50 standard taper ground glass joint. The female half was rounded into a vessel of 40–80-ml. liquid capacity, and fitted with a 10/30 female joint at the side to receive a small self-contained dropping funnel. The male half was fashioned into a vessel head, with two 10/30 female joints to receive gas inlet or exit tubes and a port at the center to accommodate the shaft of a Vibro-Mixer stirrer. The latter was connected to the port with short overlapping sleeves of vinyl tubing, making a gas-tight but flexible seal. Volume changes in the system were measured and atmospheric pressure maintained with a 100-ml. capacity gas

(1) (a) Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961; (b) Chemistry Department, Cornell University; (c) Capacitor Department, General Electric Company, Hudson Falls, N. Y.

(2) A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Am. Chem. Soc.*, **81**, 6335 (1959).

(3) A. S. Hay, *J. Polymer Sci.*, **58**, 581 (1962).

(4) G. F. Endres and Jack Kiwatek, *ibid.*, **58**, 593 (1962).

(5) Abstracts of Papers, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, Division of Inorganic Chemistry, Symposium on Homogeneous Catalysis and the Reactions of Coördinated Ligands.

(6) W. D. McElroy and B. Glass, ed., "Copper Metabolism," Johns Hopkins Press, Baltimore, Md., 1950.

(7) C. R. Dawson and W. B. Tarpley, in "The Enzymes," Vol. II, Academic Press, New York, N. Y., 1951, Chap. 57.

(8) S. M. Bocks, B. R. Brown, and A. H. Todd, *Proc. Chem. Soc.*, 117 (1962).

(9) W. Brackman and E. Havinga, *Rec. trav. chim.*, **74**, 937, 1021, 1070, 1100, 1107 (1955).

buret and reservoir filled with dibutyl phthalate, and a U-tube manometer open at one end to the atmosphere.

The usual procedure was to add the copper(I) chloride, pyridine (as a solution aliquot if the quantity was too small for accurate pipette measurement), and anhydrous magnesium sulfate to the solvent in the vessel (30-ml. solution volume), with the 2,6-dimethylphenol in 10 ml. of solvent in the funnel. After flushing the system with oxygen, the catalyst solution was "preoxidized" by agitation under oxygen for 20–45 min. (longer times are required at the lower ligand ratios). At zero time the monomer solution was run in quickly, with continued vigorous agitation, and the monomer solution was run in quickly, with continued vigorous agitation, and the absorption of oxygen at atmospheric pressure was recorded as a function of time. Reaction was continued in each case until absorption of oxygen had ceased or become very slow.

The products were worked up as follows. Under conditions where no tetramethyldiphenoquinone was detectable, the reaction mixture was poured into four volumes of methanol containing an excess of concentrated hydrochloric acid relative to the copper salt, a procedure which deactivates the catalyst. The precipitated polymer was filtered off, washed with methanol, and resuspended in 5% (vol.) concentrated hydrochloric acid in methanol. After refiltration and rewashing, the polymer was dried superficially under vacuum, redissolved in chloroform, and reprecipitated in 1% (vol.) concentrated hydrochloric acid in methanol. The work-up was completed with a final filtration on a tared sintered glass funnel, washing and drying under vacuum at 65°. Where tetramethyldiphenoquinone was detected, the reaction mixture was chilled and filtered directly. The vessel and residue were washed with a little chloroform, and the residue was air-dried and resuspended in dilute aqueous hydrochloric acid (to dissolve magnesium sulfate and any residual copper salts). The finely crystalline red product was filtered onto a tared funnel, washed with distilled water, and dried under vacuum at room temperature. The first filtrate was added to four volumes of 1% lithium chloride in methanol, and the precipitated polymer filtered onto a tared funnel, washed with methanol, and dried under vacuum at room temperature. Hydrochloric acid was not normally used in the work-up of such polymers since it sometimes led to a darkening of the color of the suspension, and the reprecipitation was omitted in order to minimize solubility losses of these low polymers. It was found that the infrared spectra of polymers worked up in this way were not significantly changed after reprecipitation in methanol containing hydrochloric acid.

Intrinsic viscosities were measured in Ubbelohde dilution viscometers in chloroform solution at 25°, using the customary extrapolation of several values of the reduced viscosity to zero concentration.

Infrared spectra were recorded with a Beckman IR-7 grating instrument, as differential spectra of 1.5% solutions (wt./vol.) in carbon disulfide in 0.5-mm cells, or as potassium bromide disks.

## Results and Discussion

The particular system chosen for study was the oxidation of 2,6-dimethylphenol in solution under oxygen gas at atmospheric pressure, using as catalysts complexes derived from copper(I) chloride and pyridine or certain derivatives. Data concerning the effects on the relative rates of carbon–oxygen and carbon–carbon coupling were obtained for the following variables: (1) concentrations of phenol, copper salt and amine ligand, (2) temperature, (3) dielectric constant of the medium, and (4) steric hindrance in the ligand. Although pyridine can be used as both ligand and solvent for the reaction, it was necessary in the examination of these variables to introduce another solvent. In most of this work o-dichlorobenzene was used, since it is inert as far as coördination with copper ions is concerned, and a reasonably good solvent for both the catalytic complexes and the C–O coupled polymeric products. It was soon found that one of the most critical and interesting variables is the ligand ratio,

or stoichiometric molar ratio of amine ligand to copper salt. When attempts were made to extend the study into the region of low ligand ratios, where the concentration of amine is relatively low, difficulties were encountered with auto-retardation effects, and frequently complete reaction could not be observed in a reasonable period of time. An example of this is shown in Fig. 1, for an oxidation of 2,6-dimethylphenol at
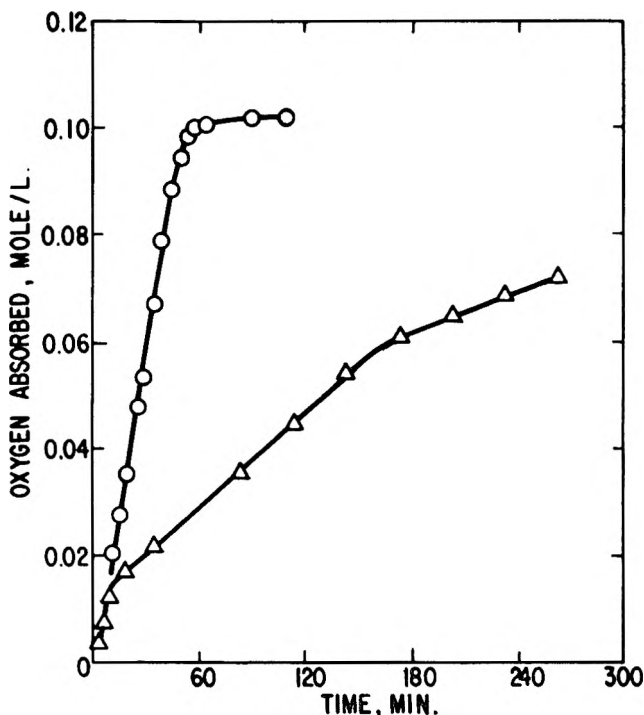


Fig. 1.—Oxidation of 2,6-dimethylphenol (0.2 M) in the presence of 0.01 M copper chloride and 0.02 M pyridine, in o-dichlorobenzene at 30°: O, magnesium sulfate, 0.2 mole/l.; △, without magnesium sulfate.

ligand ratio 2.0. It was also frequently observed that separation of another liquid phase or a solid copper salt accompanies autoretardation, suggesting that the effect is due to interference with catalysis by the water formed as reaction product (equation 1). This is confirmed by the fact that the effect can be eliminated by suspending anhydrous magnesium sulfate or other inert drying agent in the reaction mixture (Fig. 1), and this procedure was followed in all experiments at low ratios reported here. At relatively high ligand ratios autoretardation effects have not been observed and a drying agent is unnecessary.

The effects of ligand ratio (or varying pyridine concentration at fixed copper salt concentration) are summarized in Table I, for values ranging from 0.67 to 2,420. The lower limit represents the minimum ligand ratio required for complete oxidation of copper(I) chloride in inert solvent (to be described in a following publication), while the upper corresponds to pyridine at 0.005 M copper salt. Plots of oxygen absorption vs. time for the experiments of Table I are of varying form, and the reaction kinetics are quite complex. Accordingly, the maximum slope of the plot in each case, given as $R_{max}$ in the tables, is used as a measure of overall reaction rate. The data for per cent oxygen absorption in the tables are calculated on the basis of the stoichiometry of equation 1, and represent reaction times at which absorption has either ceased or become

relatively very slow. Over a wide range of ligand ratios the final oxygen absorptions are close to the ideal 100%, but at both low and high ratios an excess is observed which is greater than the experimental uncertainty. The fractional yields of C–O and C–C coupled products (methanol-insoluble polymer and tetramethyldiphenoquinone, respectively) are based on the dry weights of the isolated products, and the weight of 2,6-dimethylphenol originally present. The total yields are seen to be less than quantitative, and this is believed to be due primarily to loss of methanol-soluble low polymer fractions in the workup, and the mechanical losses involved in isolating a few hundred milligrams of material in pure condition. The fractional yield of C–C coupled product is the most reliable measure of relative coupling rates, since the poorly soluble tetramethyldiphenoquinone is filtered directly from the reaction mixture, and losses should be relatively constant. The data are believed to be sufficiently accurate to serve as qualitative measures of the relative coupling rates.[10]

### TABLE I
#### EFFECTS OF VARYING PYRIDINE CONCENTRATION[a]

| Pyridine $M$ | Ligand ratio, N/Cu | $R_{max}$ $\times 10^3$, mole l.$^{-1}$ min.$^{-1}$ | Oxygen absorbed, % | Fractional yields $f_{C-O}$ | $f_{C-C}$ | Intrinsic viscosity decil. g.$^{-1}$ |
|---|---|---|---|---|---|---|
| 0.0033 | 0.67 | 0.091 | 107 | 0.072 | 0.56 | c |
| .0050 | 1.0 | .206 | 105 | .16 | .49 | c |
| .0100 | 2.0 | .662 | 96.5 | .40 | .34 | 0.086 |
| .0150 | 3.0 | 1.26 | 100 | .51 | .26 | .097 |
| .050 | 10 | 5.20 | 99 | .75 | .10 | .17 |
| .50 | 100 | 11.4 | 98.5 | .86 | 0 | .49 |
| 2.79 | 558 | 7.70 | 99 | .82 | 0 | .725 |
| 9.00 | 1800 | 1.30 | 108 | .785 | 0 | .71 |
| 9.00 | 1800 | 1.33 | 111 | .79 | 0 | .76 |
| 12.1[b] | 2420 | 0.666 | 109 | .80 | 0 | .94 |

[a] Conditions: 2,6-Dimethylphenol 0.2 $M$; copper(I) chloride 0.005 $M$; o-dichlorobenzene solvent; 30°. At ligand ratios 0.2 to 100, anhydrous magnesium sulfate was also present at 0.2 mole/l. [b] Pyridine solvent. [c] Insufficient sample for determination.

From the fractional yield data of Table I, and their graphical representation in part in Fig. 2, it is evident
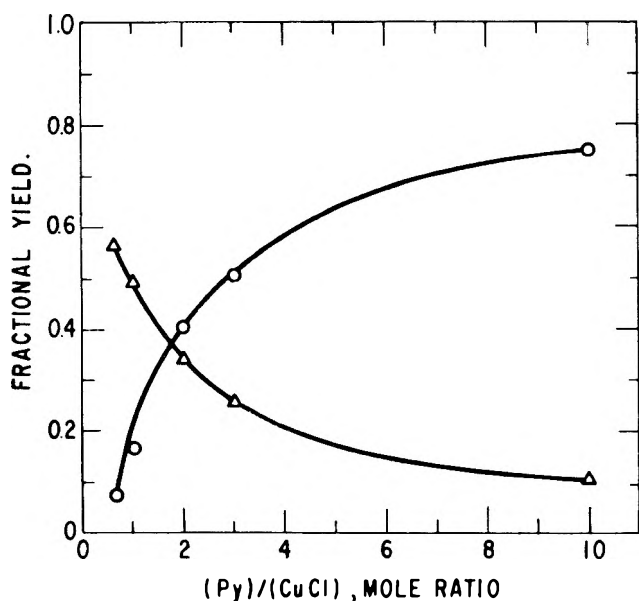


Fig. 2.—Dependence of fraction yields on the ligand ratio (Table I). $\bigcirc, f$, ; $\triangle, f_{C-C}$.

that the relative rates of C–O and C–C coupling are profoundly affected by the ligand ratio. Also affected are the maximum rate of oxygen absorption and the intrinsic viscosity of the C–O coupled polymer, as shown in Fig. 3 and 4. (The latter figures are plotted on a semilog scale for the sake of clarity.) At the lowest ligand ratio (0.67) a rather slow reaction leads predominantly to C–C coupling. Increasing the ligand ratio favors C–O coupling at the expense of C–C, so that C–O coupling is dominant at ligand ratio 10 and C–C coupled products are no longer isolated at ligand ratio 100. The over-all rate rises to a maximum in the region of ligand ratio 100, falling off as pyridine becomes the major part of the reaction mixture.[11] The intrinsic viscosity data indicate that the polymers formed along with the C–C coupled product at low ligand ratio are of low degree of polymerization. Increasing ligand ratio causes a rise which levels off at about ratio 500, with a further increase when pyridine is the solvent.[12]

Unlike the low polymers formed in the intermediate stages of oxidation of 2,6-dimethylphenol at high ligand ratio,[4] those formed on complete oxidation at low ligand ratio exhibit no absorption in the hydroxyl region of the infrared spectrum. Evidently a molecular termination reaction has occurred in the latter cases. Since C–C coupling takes place simultaneously under these conditions, the possibility emerges that the tetramethyldiphenoquinone or the intermediate dihydroxydiphenyl (equation 1) is functioning as a molecular terminating agent in the C–O coupling polymerization. To test this possibility, 2,6-dimethylphenol was oxidized under conditions favorable for high polymerization, with the dihydroxydiphenyl derivative present as an additive from the start. The experiment of Table I at ligand ratio 558 was repeated with 0.05 $M$ 3,5,3',5'-tetramethyl-4,4'-dihydroxydiphenyl added with the 2,6-dimethylphenol. The final oxygen absorption was 98% (based on phenol plus diol) with $R_{max} = 8.44 \times 10^{-3}$ mole l.$^{-1}$ min.$^{-1}$. An 81% yield of polymer (based on 2,6-dimethylphenol) of intrinsic viscosity 0.86 and an 85% yield of tetramethyldiphenoquinone (based on diol) were recovered. Thus, the oxidations of 2,6-dimethylphenol and its dihydroxydiphenyl derivative appear to have occurred independently, and there is no decrease of the intrinsic viscosity of the polymeric product.

A further important effect on the relative coupling rates is evident in Table II and Fig. 5, where the catalyst concentration is varied at a constant ligand ratio of 1.0 or 2.0. Higher concentrations result in increased over-all rates and favor C–O coupling, with a change-over from mainly C–C to mainly C–O coupling observed in a tenfold variation at ligand ratio 1.0. On the other

(10) In principle, the fractional yields can be combined with the over-all rate data in the calculation of the "partial rates" of the competing processes, and this was done in a preliminary communication.[1] However, such partial rates can be compared meaningfully under varying conditions only if that step in the reaction sequence which determines the relative coupling rates is also the rate determining step in oxygen absorption. Since this has not been demonstrated, partial rates are not employed in the present paper.

(11) This is probably not a gross medium effect, since the dielectric constants of pyridine and o-dichlorobenzene are similar. It is noteworthy that the slow reaction in pyridine is accompanied by a small amount of C–C coupling. The tetramethyldiphenolquinone is not formed in sufficient quantity to separate from the reaction mixture, but it can be observed as a hydrophobic red precipitate if the solution is diluted with water.

(12) This latter effect may be related to the fact that in pyridine solvent a precipitate of polymer and some catalyst separates from the reaction mixture toward the end of the reaction.

hand, variation of the copper(I) chloride concentration at a constant pyridine concentration (0.05 $M$) causes the over-all rate to pass through a maximum, but has little effect on the relative coupling rates, except where the concentration of the copper salt approaches that of the ligand (Table III and Fig. 6). These results can be accounted for as a near balance between two opposing effects, i.e., increasing catalyst concentration and decreasing ligand ratio. The data of Table IV and Fig. 7 show little dependence of the relative coupling rates on the initial concentration of 2,6-dimethylphenol over a sixfold range, at a constant catalyst ligand ratio (3.0).

### TABLE II

EFFECTS OF VARYING CATALYST CONCENTRATION AT CONSTANT LIGAND RATIOS[a]

| CuCl $M$ | Ligand ratio, N/Cu | $R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$ | Oxygen absorbed, % | Fractional yields | | Intrinsic viscosity decil. g.$^{-1}$ |
|---|---|---|---|---|---|---|
| | | | | $f_{C-O}$ | $f_{C-C}$ | |
| 0.005 | 1.0 | 0.206 | 105 | 0.16 | 0.49 | $b$ |
| .010 | 1.0 | .535 | 102 | .305 | .40 | 0.096 |
| .050 | 1.0 | 3.27 | 101 | .465 | .18 | .16 |
| .005 | 2.0 | 0.662 | 96.5 | .40 | .34 | .086 |
| .010 | 2.0 | 2.1 | 102 | .54 | .23 | .16 |

[a] Conditions: 2,6-Dimethylphenol 0.2 $M$; anhydrous magnesium sulfate, 0.2 mole/l.; o-dichlorobenzene solvent; 30°. [b] Insufficient sample for determination.

### TABLE III

EFFECTS OF VARYING COPPER(I) CHLORIDE CONCENTRATION[a]

| CuCl, $M$ | $R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$ | Oxygen absorbed, % | Fractional yields | | Intrinsic viscosity decil. g.$^{-1}$ |
|---|---|---|---|---|---|
| | | | $f_{C-O}$ | $f_{C-C}$ | |
| 0.005 | 5.20 | 99 | 0.75 | 0.10 | 0.17 |
| .010 | 7.35 | 99 | .75 | .12 | .21 |
| .020 | 8.25 | 100 | .73 | .15 | .20 |
| .040 | 5.71 | 100 | .66 | .19 | .15 |
| .050 | 3.27 | 101 | .465 | .18 | .16 |

[a] Conditions: 2,6-Dimethylphenol 0.2 $M$; pyridine 0.05 $M$; anhydrous magnesium sulfate, 0.2 mole/l.; o-dichlorobenzene solvent; 30°.

### TABLE IV

EFFECTS OF VARYING INITIAL 2,6-DIMETHYLPHENOL CONCENTRATION[a]

| 2,6-Dimethyl phenol, $M$ | $R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$ | Oxygen absorbed, % | Fractional yields | | Intrinsic viscosity, decil. g.$^{-1}$ |
|---|---|---|---|---|---|
| | | | $f_{C-O}$ | $f_{C-C}$ | |
| 0.10 | 0.99 | 102 | 0.47 | 0.18 | 0.092 |
| .20 | 1.26 | 100 | .51 | .26 | .097 |
| .40 | 2.21 | 103.5 | .565 | .27 | .098 |
| .60 | 3.05 | 108 | .58 | .29 | .12 |

[a] Conditions: Copper(I) chloride 0.005 $M$; pyridine 0.015 $M$; anhydrous magnesium sulfate; o-dichlorobenzene solvent; 30°.

Table V summarizes data for an increase of temperature from 30° to 60°, with ligand ratio 1.0 at two catalyst concentrations. The higher temperature is seen to favor C–C coupling at the expense of C–O, leading to a change-over from C–O to C–C domination at 0.05 $M$ catalyst. However, in the absence of knowledge of the temperature dependence of oxygen solubility in o-dichlorobenzene and the effect of oxygen concentration on the relative coupling rates, it is not certain that this observation is purely a temperature effect.

The solvent could conceivably affect the structure of the catalyst or the active complex in the present system
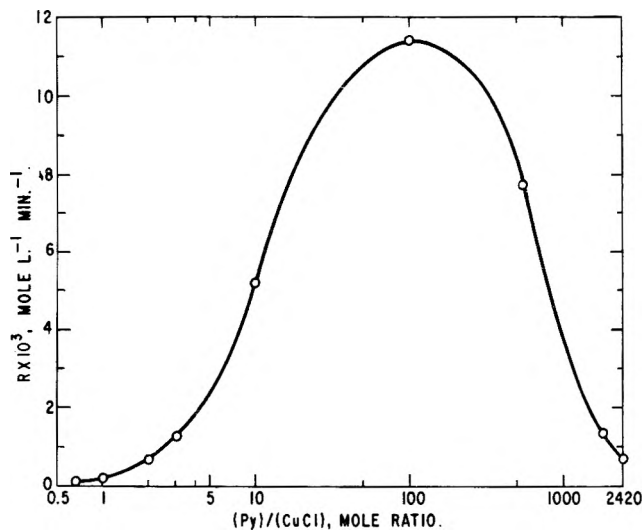


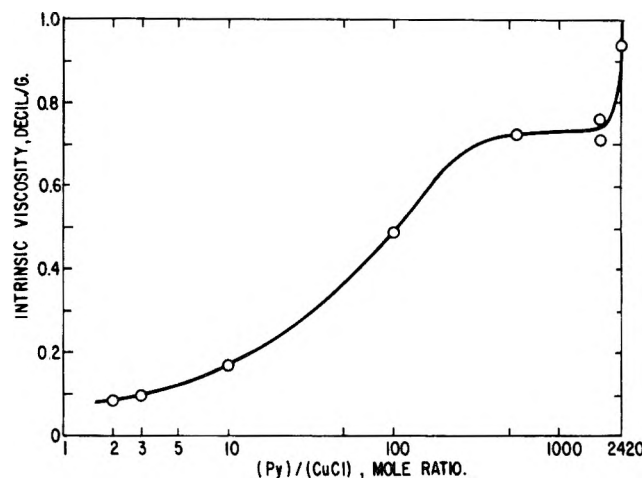Fig. 3.—Dependence of maximum rate of oxygen absorption on the ligand ratio (Table I).



Fig. 4.—Dependence of intrinsic viscosity of C–O coupled polymeric products on the ligand ratio (Table I).
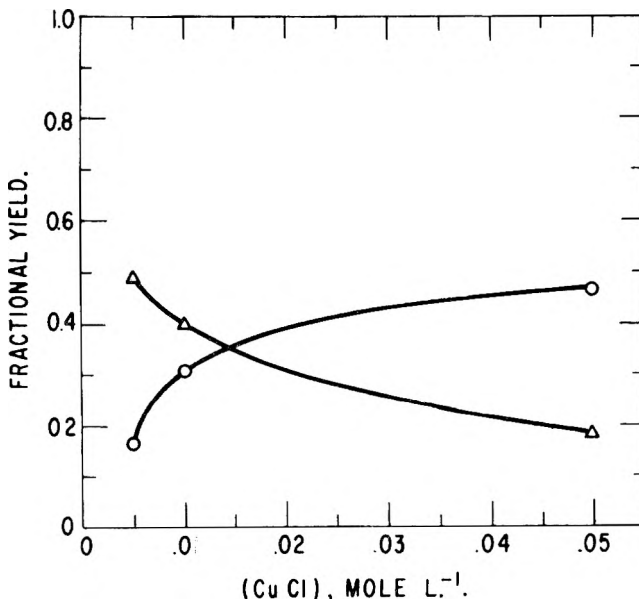


Fig. 5.—Fractional yields as functions of copper chloride concentration, at constant ligand ratio (1.0) (Table II): O, $f_{C-O}$; △, $f_{C-C}$.

in at least two ways: (1) the more active solvents could function as ligands and coördinate with copper ions in the inner sphere, or (2) solvents of relatively weak
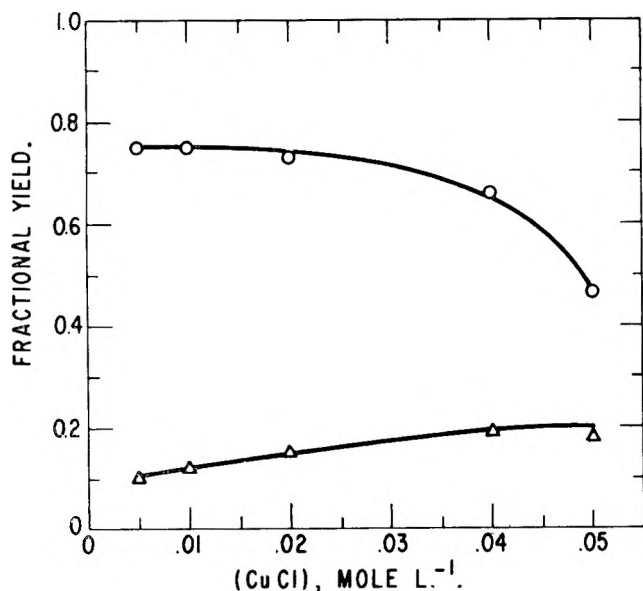
Fig. 6.—Fractional yields as functions of copper chloride concentration, at constant pyridine concentration (0.05 M) (Table III): O, $f_{C-O}$; $\triangle$, $f_{C-C}$.
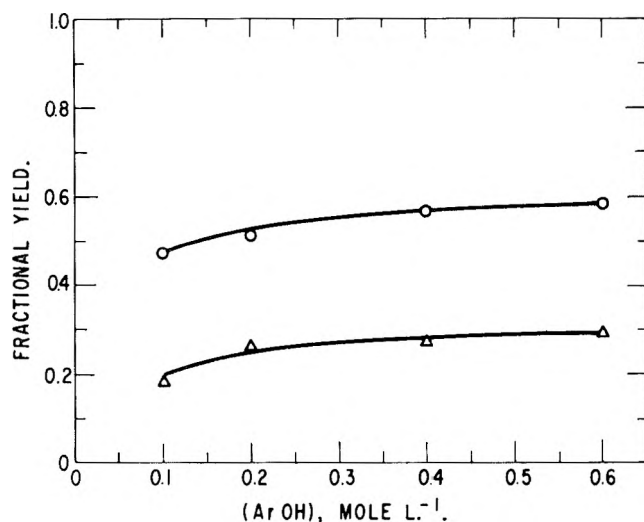


Fig. 7.—Fractional yields as functions of initial 2,6-dimethylphenol concentration, at constant ligand ratio (3.0) (Table IV): O, $f_{C-O}$; $\triangle$, $f_{C-C}$.

### TABLE V
#### EFFECTS OF VARYING TEMPERATURE[a]

| CuCl, M | Temp., °C. | $R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$ | Oxygen absorbed, % | Fractional yields $f_{C-O}$ | $f_{C-C}$ |
|---|---|---|---|---|---|
| 0.005 | 30 | 0.206 | 105 | 0.16 | 0.49 |
| .005 | 60 | .870 | 102 | .01 | .75 |
| .05 | 30 | 3.27 | 101 | .465 | .18 |
| .05 | 60 | 7.20 | 86 | .11 | .63 |

[a] Conditions: 2,6-Dimethylphenol 0.2 M; ligand ratio 1.0; anhydrous magnesium sulfate, 0.2 mole/l.; o-dichlorobenzene solvent.

coördinating power could still play an important role through solvation of the complexes as a whole, the solvents of higher dielectric constant promoting ionic dissociation or ion-pair formation. The first effect seemed too broad in scope for the present investigation, but an attempt was made to assess the importance of the second. The series of solvents benzene, chlorobenzene, o-dichlorobenzene offers a moderate range of dielectric constant (2.3–7.5) without strong coördinat-

ing ability, and oxidations were carried out in these solvents at ligand ratio 3.0. The results (Table VI) indicate little effect on the relative coupling rates under these conditions.

### TABLE VI
#### EFFECTS OF VARYING SOLVENT DIELECTRIC CONSTANT[a]

| Solvent | Dielectric constant | $R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$ | Oxygen absorbed, % | Fractional yields $f_{C-O}$ | $f_{C-C}$ | Intrinsic viscosity decil. g.$^{-1}$ |
|---|---|---|---|---|---|---|
| Benzene | 2.3 | 0.56 | 99 | 0.60 | 0.35 | 0.17 |
| Chlorobenzene | 5.9 | .97 | 103 | .56 | .29 | .135 |
| o-Dichlorobenzene | 7.5 | 1.26 | 100 | .51 | .26 | .097 |

[a] Conditions: 2,6-Dimethylphenol 0.2 M; copper(I) chloride 0.005 M; pyridine 0.015 M; anhydrous magnesium sulfate, 0.2 mole/l.; 30°.

In order to assess the effects of steric hindrance in the ligand, oxidations of 2,6-dimethylphenol were carried out with quinoline or 2,6-lutidine in place of pyridine, with the results summarized in Table VII. Owing to the relatively low reaction rates observed with these ligands compared to pyridine, it was necessary in these experiments to increase the copper(I) chloride concentration to 0.05 M. Insufficient data were obtained to determine the precise form of the dependence of the fractional yields on ligand ratio, but comparison data are available at both low and high ratios (1.0 and 55.8). Using the fractional yield of C–C coupled product as the most reliable measure of relative coupling rates, it is seen that at the low ligand ratio both quinoline and 2,6-lutidine favor C–C coupling appreciably in comparison to pyridine. Increasing the ligand ratio favors C–O coupling and results in polymers of higher intrinsic viscosity in each case, although the over-all rate is not enhanced in the hindered examples.

### TABLE VII
#### OXIDATION OF 2,6-DIMETHYLPHENOL WITH PYRIDINE AND DERIVATIVES[a]

| Ligand | Ligand ratio, N/Cu | $R_{max} \times 10^3$, mole l.$^{-1}$ min.$^{-1}$ | Oxygen absorbed, % | Fractional yields $f_{C-O}$ | $f_{C-C}$ | Intrinsic viscosity, decil. g.$^{-1}$ |
|---|---|---|---|---|---|---|
| Pyridine | 1.0 | 3.27 | 101 | 0.465 | 0.18 | 0.16 |
| | 55.8 | 21.3 | 100 | .85 | 0 | 1.35 |
| Quinoline | 1.0 | 0.935 | 105 | .48 | 0.30 | .13 |
| | 55.8 | .53 | 104 | .82 | 0 | 1.15 |
| 2,6-Lutidine | 1.0 | 1.80 | 118 | .29 | 0.375 | 0.08 |
| | 10.0 | 1.54 | 107.5 | .73 | 0 | .205 |
| | 55.8 | 1.98 | 103 | .93 | 0 | .55 |

[a] Conditions: 2,6-Dimethylphenol, 0.2 M; copper(I) chloride 0.05 M; anhydrous magnesium sulfate, 0.2 mole/l.; o-dichlorobenzene solvent; 30°.

The effects of the variables examined on the relative coupling rates can be summarized as follows. Carbon–carbon coupling is favored by increasing temperature or steric hindrance in the ligand, while carbon–oxygen coupling is favored by increasing ligand ratio or catalyst concentration at constant ligand ratio. The concentration of 2,6-dimethylphenol and the dielectric constant of the solvent have relatively little effect, at least over the ranges examined. Thus, the most critical variables are those which would be expected to affect the structure of the catalytic complex.

It will be shown in a following publication that both C–O and C–C coupling in the present system are brought about by oxidized forms of the copper–amine catalytic system. It is well established that in a solution of a copper salt and a coördinating ligand, various complexes are capable of existence in equilibrium. These will differ in the number of ligand molecules coördinated with the metallic ion, and their relative concentrations will be governed by the stoichiometric concentrations of ligand and metal, and by the various associative equilibrium constants.[13] The results of the present investigation strongly indicate that such equilibria are important here, and constitute the key to catalytic specificity. It is proposed that two copper–amine complexes are catalytically active, differing in coördination number with respect to the amine ligand, and that the complex with the lower coördination number leads predominantly to C–C coupling, and the complex with the higher coördination number leads to C–O coupling. This situation can be represented schematically as in equation 2 where L represents the amine ligand, with these qualifications: the two complexes may actually differ in nuclearity, and the difference in coördination number is not necessarily unity.

$$Cu^{II}L_n + L \;\rightleftarrows\; Cu^{II}L_{n+1}$$

$$\downarrow + ArOH \qquad \downarrow + ArOH \qquad (2)$$

$$C\!-\!C \qquad\qquad C\!-\!O$$
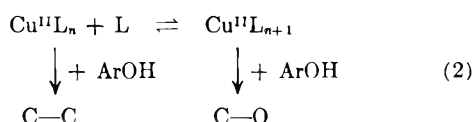
The other ligands involved in the complexes (chloride, oxide, or hydroxide ions) are omitted for the sake of clarity. Indeed, since both reactions are believed to involve intermediate complexes in which the anion derived from 2,6-dimethylphenol is coördinated with copper, this anion could be shown as a ligand on both sides of equation 2. In any event, this scheme accounts qualitatively for the observed effects of ligand ratio, catalyst concentration and steric hindrance in the ligand.[14] It is believed reasonable to expect that the predominant structures present in oxidized solutions of copper(I) chloride and amines in a noncoördinating solvent should change drastically as the stoichiometric ligand ratio is increased from a low value like 0.67 or 1.0. Succeeding papers will present evidence concerning the structure and role of the catalytic complexes, and the nature of the bond-forming processes in carbon–oxygen and carbon–carbon coupling.

(13) For the formation constants of pyridine–copper ion complexes in aqueous media, see (a) J. Bjerrum, *et al.*, "Stability Constants of Metal–Ion Complexes," Part I, "Organic Ligands," The Chemical Society, London, 1957, p. 28; (b) B. R. James and R. J. P. Williams, *J. Chem. Soc.*, 2007 (1961).

(14) The decrease in oxidation rate observed with pyridine at high ligand ratio may be due to formation of catalytically inactive complexes of higher coördination number. Both valence states of the copper ion can achieve four-coördination with pyridine (ref. 13.)

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# The Synthesis of 2-Purin-6-ylaminoethanethiol and Some Related Compounds[1]

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Syntheses of 2-purin-6-ylaminoethanethiol (II), 2-purin-8-ylaminoethanethiol (VI), and 2-(2-pyrimidinyl-amino)ethanethiol (VII) were achieved by the surprisingly facile catalytic hydrogenolysis of the corresponding disulfides in basic media. An N → S migration of the purin-6-yl group under acidic conditions and a novel formation of 7,8-dihydrothiazolo[2,3-i]purine (V) were encountered during development of the hydrogenolysis procedure for II. Compound II was also prepared from purine-6(1H)-thione in low yield *via* a rearrangement of the intermediate 6-(2-aminoethylthio)purine (I) under basic conditions.

As an extension of the previously reported series of S-substituted derivatives of purine-6-thiol,[2] the preparation of 6-(2-aminoethylthio)purine (I) was attempted by the reaction of purine-6(1H)-thione and 2-bromoethylamine hydrobromide in N,N-dimethylformamide containing potassium carbonate. This effort led to the isolation of pure 2-purin-6-ylaminoethanethiol (II) in low yield (5%), an equal yield of the impure disulfide III, unchanged purine-6(1H)-thione, but none of the intended product I. The thiol II reacted positively in the sodium nitroprusside test and showed ultraviolet absorption compatible with that of $N^6$-alkyladenines[3] and incompatible with that of 6-(alkylthio)-purines[2]; it obviously resulted from an intramolecular

rearrangement of I. The limited preparative value of this procedure prompted an investigation of other synthetic routes to II and related N-(heteroaromatic-substituted) aminoethanethiols.

SCH₂CH₂NH₂ structure and NHCH₂CH₂SR structure
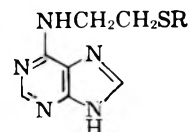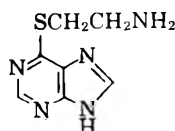
II.  R = H
IV.  R = CH₂C₆H₅

$N^6$-[2-(Benzylthio)ethyl]adenine (IV), prepared from 6-chloropurine and 2-(benzylthio)ethylamine, was debenzylated with sodium in liquid ammonia, but the product isolated was apparently a mixture of the desired thiol II and the disulfide III; a pure monohydrate of III was obtained in low yield by dilution of a 2-methoxyethanol solution of the crude product with an equal volume of water. Chu and Mautner[4] performed a

(2) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, **80**, 6265 (1958).

(3) For example, *cf.* the spectra of $N^6$-methyladenine [S. F. Mason, *J. Chem. Soc.*, 2071 (1954)].
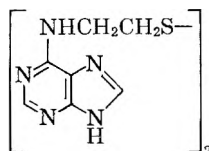
III

similar debenzylation of 6-amino-8-[2-(benzylthio)-ethylamino]purine and isolated the product as the corresponding disulfide after intentional peroxide oxidation. The disulfide III was more conveniently prepared from 6-chloropurine and 2,2'-dithiobisethylamine dihydrochloride in refluxing propanol in the presence of potassium carbonate. In the preparation of III a 2:1 molar ratio of diamine to 6-chloropurine gave an 87% yield; the ratios 1:1 and 0.5:1 gave 82 and 59% yields, respectively, with no attempted isolation of monosubstituted diamine as a probable by-product.[5]

Low pressure hydrogenolysis of III over palladium on charcoal was then investigated as a means of obtaining the thiol II in quantity. In 0.1 $N$ sodium hydroxide solution the hydrogen uptake was surprisingly rapid, and the pure thiol II, identical with that prepared from purine-6(1$H$)-thione was isolated when normal precautions were taken to avoid air oxidation. (A reliable assay of II by iodometric titration could not be worked out.) Catalyst poisoning, which is usually associated with sulfur compounds, was apparently minimized by carrying out the hydrogenolysis in aqueous sodium hydroxide, a good solvent for both the starting material and the product.

The hydrogenolysis of III in 0.3 $N$ hydrochloric acid was slow, even with intermittent additions of fresh catalyst. The ultraviolet absorption spectrum of an aliquot of the reduction mixture indicated the product to be a hydrochloride of I ($\lambda_{max}$ at pH 7, 285 m$\mu$), which could have resulted from a rearrangement of II ($\lambda_{max}$ at pH 7, 269 m$\mu$) in acid solution. An analogous N → S migration of an acyl group has been previously described.[6] Refluxing an aliquot of the solution containing I in 0.1 $N$ hydrochloric acid for three hours resulted in the formation as a major product not the expected hypoxanthine[2] but 7,8-dihydrothiazolo[2,3-i]-purine (V), which was identified by comparison of paper chromatograms and ultraviolet absorption spectra with those of an authentic sample.[7] These results
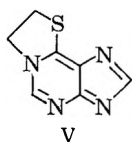


V

clearly show that I, which rearranged to II under basic conditions, underwent ring closure with loss of ammonia (as ammonium chloride) under acidic conditions to form the hydrochloride of V.

Catalytic hydrogenolysis under basic conditions was then applied to the preparation of 2-purin-8-ylamino-ethanethiol (VI) and 2-(2-pyrimidinylamino)ethane-thiol (VII) from the corresponding disulfides, the latter reduction being carried out in 90% ethanol. The

disulfides, 8,8'-[dithiobis(ethyleneimino)]dipurine and 2,2'-[dithiobis(ethyleneimino)]dipyrimidine, were obtained by displacement reactions of 2,2'-dithiobisethyl-amine with 8-(methylsulfonyl)purine and 2-chloro-pyrimidine, respectively.
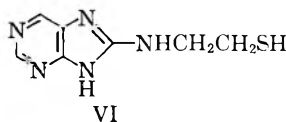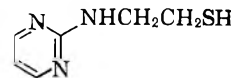


VI                                    VII

Several attempts to find the proper conditions for a similar catalytic reduction of 2,2'-[dithiobis(ethylene-imino)]bisbenzothiazole over palladium on charcoal were unsuccessful; this reduction was achieved, however, with sodium borohydride,[8] and near pure 2-(2-benzothiazolylamino)ethanethiol (VIII, 95% by iodo-metric titration) was isolated and subsequently characterized as the $S$-2,4-dinitrophenyl derivative. The intermediate disulfide was prepared in two ways: displacement by 2,2'-dithiobisethylamine of (1) the chlorine atom of 2-chlorobenzothiazole and (2) the phenylsulfonyl group of 2-(phenylsulfonyl)benzothi-azole.
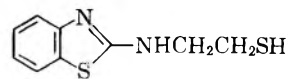


VIII

## Experimental[9]

**2-(Benzylthio)ethylamine.**—To a stirred mixture of 96% 2-aminoethanethiol hydrochloride[10] (5.00 g., 42.4 mmoles), anhydrous potassium carbonate (12.3 g., 89.0 mmoles), and $N,N$-dimethylformamide (50 ml.) was added $\alpha$-chlorotoluene (5.0 ml., 45 mmoles). After the exothermic reaction had ceased, the mixture was heated at 60° for 1 hr., then poured into water (375 ml.). The aqueous mixture was acidified (pH 3) with hydrochloric acid and washed with ether; it was then made basic (pH 11) with sodium hydroxide and extracted with ether. The ether layer, washed with water and dried over sodium sulfate, was evaporated to a colorless oil, which was further dried under reduced pressure at 60° for 2 hr.; yield 6.08 g. (86%), $n^{23}$D 1.5770. Vacuum distillation of a portion of the crude product afforded analytically pure 2-(benzylthio)ethylamine, b.p. 92–96° (0.5–0.6 mm.), $n^{22}$D 1.5763.[11] The product was stored under nitrogen (a small portion formed a solid carbonate when exposed to air).

*Anal.* Calcd. for $C_9H_{13}NS$: C, 64.56; H, 7.83; S, 19.17. Found: C, 64.89; H, 8.06; S, 18.96.

**$N^6$-[2-(Benzylthio)ethyl]adenine (IV).**—A solution of crude 2-(benzylthio)ethylamine (4.00 g., 24.0 mmoles) and 6-chloro-purine (1.48 g., 9.60 mmoles) in 1-propanol (15 ml.) was heated under reflux for 3 hr. The solution was evaporated under reduced pressure to near dryness and poured into water (100 ml.). The white solid that precipitated was washed with water and then ether and dried *in vacuo* over phosphorus pentoxide at 80°; yield of IV, 2.43 g. (89%); m.p. 175°; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 275–276 (15.1) at pH 1, 269 (16.8) at pH 7, 275 (17.0) at pH 13.

A pilot run carried out in $N,N$-dimethylformamide at 105° produced the analytical sample (recrystallized from water and then benzene); m.p. 176° with softening from 163°; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 276 (14.6) at pH 1, 269 (16.3) at pH 7, 275 (16.8) at pH 13, 269 (18.7) in ethanol.

*Anal.* Calcd. for $C_{14}H_{15}N_5S$: C, 59.12; H, 5.32; S, 11.26. Found: C, 58.94; H, 5.32; S, 11.04.

**$N^6,N^{6'}$-(Dithiodiethylene)diadenine (III).**—To a stirred mix-

(4) S.-H. Chu and H. G. Mautner, *J. Org. Chem.*, **26**, 4498 (1961).

(5) *Cf.* H. Lettré and H. Ballweg, *Ann. Chem., Liebig's*, **649**, 124 (1961).

(6) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).

(7) R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).

(8) *Cf.* T. P. Johnston and A. Gallagher, *ibid.*, **27**, 2452 (1962).

(9) Melting points under 260° were determined on a Kofler Heizbank (unless otherwise noted); those above 260° were determined in a capillary and are uncorrected.

(10) Evans Chemetics, Inc., New York, N. Y.

(11) Chu and Mautner[4] reported b.p. 78–80° (0.15 mm.) and $n^{25.4}$D 1.5740 for the product from aziridine and $\alpha$-toluenethiol.

ture of 2,2'-dithiobisethylamine dihydrochloride[12] (10.3 g., 46.0 mmoles), anhydrous potassium carbonate (14.0 g., 101 mmoles), and 1-propanol (60 ml.) was added 6-chloropurine (7.10 g., 46.0 mmoles), and the resulting suspension was heated under reflux for 6 hr. The reaction mixture was evaporated *in vacuo* to 45 ml. and then poured into water (900 ml.). After the mixture was neutralized with hydrochloric acid, the off-white precipitate was washed with water and dissolved in boiling 1 N hydrochloric acid (1 l.), an insoluble tan solid being removed by filtration. The cooled filtrate was brought to pH 8 with concentrated ammonium hydroxide, and the resulting cream-colored precipitate was washed with water and dried *in vacuo* over phosphorus pentoxide at 100°; yield of III, 7.27 g. (81%); $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 275 (31.0) at pH 1, 265 (29.2) at pH 7,274 (32.5) at pH 13. For analysis, a sample was precipitated from *N,N*-dimethylformamide by the addition of water; m.p. 290° dec. (from 200°) with darkening from 285°; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 276 (31.8) at pH 1, 266 (29.1) at pH 7, 275 (32.8) at pH 13.

*Anal.* Calcd. for $C_{14}H_{16}N_{10}S_2$: C, 43.28; H, 4.15; S, 16.51. Found: C, 43.11; H, 4.15; S, 16.54.

**2-Purin-6-ylaminoethanethiol (II). (1) From Purin-6(1H)-thione.**—2-Bromoethylamine hydrobromide (663 mg., 3.24 mmoles) was added to a well stirred mixture of purine-6(1H)-thione monohydrate (500 mg., 2.94 mmoles), anhydrous potassium carbonate (815 mg., 5.90 mmoles), and *N,N*-dimethylformamide (4 ml.). After the exothermic reaction had ceased, the mixture was heated at 50° for 2 hr. and then poured into water (20–25 ml.). Neutralization of the resulting solution with hydrochloric acid caused the precipitation of a light yellow solid, which was extracted with hot chlorobenzene; the residue (316 mg., 63%) was unchanged purine-6(1H)-thione ($\lambda_{max}$ in m$\mu$: 324 at pH 1, 321 at pH 7, 308 at pH 13). The aqueous *N,N*-dimethylformamide filtrate, adjusted to pH 6 and left overnight in a refrigerator, was filtered to remove a small additional precipitate of purine-6(1H)-thione and the filtrate evaporated to dryness under reduced pressure. The residue, triturated in water and dried *in vacuo*, was a pinkish white solid (45 mg., m.p. 234°), recrystallization of which from chlorobenzene afforded pure II as colorless crystals, which were dried *in vacuo* at 110°; yield 31 mg. (5%); m.p. 236°; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 274 (16.2) at pH 1, 268 (17.2) at pH 7, 276 (17.4) at pH 13; strongly positive nitroprusside test.[13]

*Anal.* Calcd. for $C_7H_9N_5S$: C, 43.08; H, 4.65; N, 35.88. Found: C, 43.05; H, 4.42; N, 35.83.

The refrigerated aqueous filtrate from the trituration deposited an additional 30 mg. (5%) of white solid, which apparently was a mixture of II and III; m.p. 266° dec.; $\lambda_{max}$ in m$\mu$: 276 at pH 1, 267 at pH 7, 275 at pH 13; transitorily positive nitroprusside test.

**(2) From N⁶,N'⁶'-(Dithiodiethylene)diadenine.**—A solution of III (1.55 g., 4.00 mmoles) in 0.1 N sodium hydroxide (160 ml.) was hydrogenated at room temperature in a Parr shaker apparatus at an initial pressure of 45 p.s.i. over 5% palladium on charcoal (310 mg., 20% weight of disulfide). When the hydrogen uptake was complete (*ca.* 1 hr.), the catalyst was removed by filtration under nitrogen. The filtrate, carefully neutralized with 6 N hydrochloric acid with cooling, deposited II as a white crystalline solid, which was collected under nitrogen and dried *in vacuo* over phosphorus pentoxide; yield 990 mg. (64%); m.p. 236°; positive nitroprusside test; positive Rheinboldt test[14] (red in hydrochloric acid); $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 274 (16.3) at pH 1, 268 (17.4) at pH 7, 276 (18.3) at pH 13.

A similar 2-hr. hydrogenolysis of III on a 20-mmole scale gave an 80% yield of II, m.p. 238°.

**8,8'-[Dithiobis(ethyleneimino)]dipurine.**—8-(Methylsulfonyl)purine[16] (3.96 g., 20.0 mmoles) was added to a solution of 2,2'-dithiobisethylamine[12] (3.35 g., 22.0 mmoles) in 1-propanol (30 ml.). The resulting mixture was refluxed for 5 hr. and evaporated to dryness under reduced pressure. A suspension of the residue in water (50 ml.) was brought to pH 7 with 1 N hydrochloric acid. The precipitated gum slowly solidified to a tan solid, which was collected and dried *in vacuo;* yield of crude disulfide, 2.78 g. (72%); $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 298 (31.4) at pH 1, 288–289 (25.4) at pH 7, 298 (25.4) at pH 13. For analysis, a small sample of the crude product was twice recrystallized from water; re-

covery of the product as a white microcrystalline powder, 18%; m.p. 282° dec.; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 296 (38.6) at pH 1, 286 (33.2) at pH 7, 296 (30.8) at pH 13.

*Anal.* Calcd. for $C_{14}H_{16}N_{10}S_2$: C, 43.28; H, 4.15; S, 16.50. Found: C, 43.51; H, 4.55; S, 16.22.

**2-(Purin-8-ylamino)ethanethiol (VI).**—A clarified 0.1 N sodium hydroxide solution (200 ml.) containing approximately 1.6 g. (4.1 mmoles) of 8,8'-[dithiobis(ethyleneimino)]dipurine was hydrogenated over 390 mg. of 5% palladium on charcoal at an initial pressure of 50 p.s.i. at room temperature in a Parr shaker apparatus; the calculated amount of hydrogen was absorbed within an hour. The catalyst was removed by filtration under nitrogen, and the filtrate was neutralized with 6 N hydrochloric acid and evaporated to dryness *in vacuo*. The residue was triturated in water (3 × 5 ml.) and dried *in vacuo* over phosphorus pentoxide; yield of crude VI, 1.0 g. (*ca.* 63%). A solution of the crude thiol in boiling ethanol (*ca.* 40 ml.) was treated with Norit, filtered under nitrogen, and evaporated to dryness under reduced pressure; recovery 96%; m.p. 209°; positive nitroprusside and Rheinboldt tests; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 297 (19.2) at pH 1, 289 (17.) at pH 7, 299 (15.6) at pH 13.

*Anal.* Calcd. for $C_7H_9N_5S$: C, 43.05; H, 4.64; S, 16.42. Found: C, 43.20; H, 4.88; S, 16.31.

**2,2'-[Dithiobis(ethyleneimino)]dipyrimidine.**—A solution of 2-chloropyrimidine[16] (12.1 g., 0.106 mole) and 2,2'-dithiobisethylamine[12] (17.0 g., 0.111 mole) in 1-propanol (75 ml.) was refluxed for 5 hr. Dilution of the cooled reaction mixture with water (750 ml.) gave 13.4 g. of vacuum-dried product as a white powder, m.p. 166°. The aqueous filtrate yielded a second crop of 1.03 g., m.p. 165°. The total yield was 88%. [2,2'-Dithiobisethylamine dihydrochloride (10.3 g., 87%), m.p. 218° (lit.,[12] m.p. 216°), was isolated from the last filtrate.] For analysis, a small sample of the first crop was recrystallized from ethanol with Norit treatment. The white needles obtained melted at 166° after being dried *in vacuo* over phosphorous pentoxide at 80°; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 230 (37.1), 315 (7.54) at pH 1; 235 (36.4), 305 (5.38) at pH 7; 235 (36.4), 305 (5.38) at pH 13.

*Anal.* Calcd. for $C_{12}H_{16}N_6S_2$: C, 46.42; H, 5.19; S, 20.66. Found: C, 46.76; H, 5.56; S, 20.91.

**2-(2-Pyrimidinylamino)ethanethiol (VII).**—A solution of 2,2'-[dithiobis(ethyleneimino)]dipyrimidine (1.55 g., 5.50 mmoles) in ethanol was treated with 0.903 N sodium hydroxide solution (11.1 ml.), and the resulting solution was diluted so that the final volume was 300 ml. and the medium was 90% ethanol (by volume). Hydrogenation was carried out in a Parr shaker apparatus over 310 mg. of 5% palladium on charcoal at an initial pressure of 50 p.s.i. for 2 hr. The catalyst was removed by filtration under nitrogen; the filtrate, after neutralization with the calculated volume of 1 N hydrochloric acid, was evaporated *in vacuo* to near dryness. The orange-colored oil that separated was extracted with ether (3 × 15 ml.); the ether extract, washed once with water (10 ml.) and dried over sodium sulfate, was evaporated to dryness under reduced pressure. The residual pale yellow semisolid was triturated in ethanol (5 ml.): the insoluble solid (78 mg., m.p. 165°) was identified as the starting disulfide, whereas evaporation of the ethanol solution *in vacuo* gave 1.15 g. (74%) of a pale yellow oil, which gave a positive nitroprusside test. The oil was distilled under reduced pressure. The distillate, b.p. 86° (0.3 mm.), solidified to a white crystalline solid having a pepper-like odor; m.p. 40–41° (capillary); $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 229 (17.9), 315 (3.62) at pH 1; 235 (18.5), 305 (2.74) at pH 7; 237 (22.8), 309 (2.50) at pH 13.

*Anal.* Calcd. for $C_6H_9N_3S$: C, 46.42; H, 5.84; S, 20.66; SH, 21.3. Found: C, 46.38; H, 5.84; S, 20.52; SH, 21.6, 21.3 (iodometric).

**2-(Phenylsulfonyl)benzothiazole.**—A stirred mixture of 2-chlorobenzothiazole (12.0 g., 71.5 mmoles), sodium benzenesulfinate (12.3 g., 75.0 mmoles), and *N,N*-dimethylformamide (50 ml.) was heated at 70–80° for 3 hr. Pouring the resulting mixture into water (500 ml.) caused the precipitation of a white solid, which was washed with water and dried *in vacuo* over phosphorus pentoxide; yield 18.6 g. (94%), m.p. 161–162° (lit.,[17] m.p. 161°).

**2,2'-[Dithiobis(ethyleneimino)]bisbenzothiazole.**—A mixture of 2-(phenylsulfonyl)benzothiazole (1.65 g., 6.00 mmoles), 2,2'-

(12) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **26**, 3780 (1961).

(13) R. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *Radiation Research*, **7**, 22 (1957).

(14) H. Rheinboldt, *Ber.*, **60**, 184 (1927).

(15) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957).

(16) I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Syn.*, **35**, 34 (1955).

(17) O. Bayer and H. Schindhelm, German Patent 609,025 (February 6, 1935); *Chem. Abstr.*, **29**, 3174 (1935).

dithiobisethylamine (930 mg., 6.10 mmoles), and 1-propanol (20 ml.) was refluxed for 3.5 hr. The resulting solution was cooled and poured into water (100 ml.), and the solid that precipitated was collected and dried *in vacuo;* yield 1.04 g., (83%), m.p. 180°. Recrystallization of a 150-mg. sample of the crude product from acetonitrile (45 ml.) gave 120 mg. of the disulfide as a white solid, which melted at 188° after being dried *in vacuo* over phosphorus pentoxide at 80°; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): 250 (20.7), 281 (17.9), 288 (18.7) at pH 1; $\lambda_{max}$ at pH 7 and pH 13 unrecorded because solutions became cloudy.

*Anal.* Calcd. for $C_{18}H_{18}N_4S_4$: C, 51.64; H, 4.33; S, 30.64. Found: C, 51.73; H, 4.66; S, 30.72.

**2-(2-Benzothiazolylamino)ethanethiol (VIII).**—A 5% solution of 2,2'-[dithiobis(ethyleneimino)]bisbenzothiazole (2.09 g., 5.00 mmoles) in 2-methoxyethanol was added to a 5% solution of sodium borohydride (1.28 g., 30.0 mmoles) in methanol over a period of 5 min. The resulting solution was heated at 60° for 15 min. and then evaporated to dryness under reduced pressure. The semisolid residue was suspended in water (50 ml.) and the pH of the mixture adjusted to 8 with hydrochloric acid. The white solid was collected, washed with water, and extracted with ether (3 × 50 ml.). The ether solution, after being dried over magnesium sulfate and filtered, was evaporated to dryness under reduced pressure. The residual white solid was dried *in vacuo* over phosphorus pentoxide; yield 1.13 g. (54%); m.p. 85–86° with opaque melt (capillary); % VIII by iodometric titration 95. The ether-insoluble substance, m.p. 185°, was identified as the starting disulfide (recovery 23%).

The thiol VIII was further characterized as the S-2,4-dinitrophenyl derivative, which was prepared from VIII, 1-chloro-2,4-dinitrobenzene, and potassium carbonate in N,N-dimethylformamide. The crude 2-[2-(2,4-dinitrophenylthio)ethylamino] benzothiazole was recrystallized from an acetonitrile–water solvent pair as an orange solid, which decomposed without melting at 187–189° (capillary).

*Anal.* Calcd. for $C_{15}H_{12}N_4O_4S_2$: C, 47.86; H, 3.21; S, 17.04. Found: C, 47.54; H, 3.10; S, 16.68.

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# Transoxazolination. Preparation of Disulfides of 2-(2-Mercaptoethylamino)-2-oxazolines

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The products obtained from the aminoethylation of several 2-thiooxazolidones underwent rearrangement in alkaline solution to 2-(2-mercaptoethylamino)-2-oxazolines, which were readily oxidized to the corresponding disulfides. The disulfides required for identification were prepared by the reaction of 2-methylthio-2-oxazolines with 2-mercaptoethylamine hydrochloride. An intermediate with anomalous properties was encountered in the latter reaction.

The rearrangement of *S*-(2-aminoethyl)isothiourea (AET), a radioprotective agent, to 2-mercaptoethylguanidine by transguanylation through a proposed cyclic intermediate in neutral or weakly alkaline solution has been described by Doherty, *et al.*[1,2] The study of this transformation was extended by these workers to a number of aminoalkylisothioureas and to 2-(2-aminoethylthio)-2-imidazoline.[3] We have recently reported the rearrangement of 2-(2-aminoethylthio)-2-thiazoline to 2-(2-mercaptoethylamino)-2-thiazoline by transthiazolination through a proposed bicyclic intermediate.[4]

In the case of the transthiazolination described, the similarity of the rings comprising the hypothetical bicyclic intermediate permitted the formation of only a single product. We have attempted to extend the rearrangement to 2-oxazoline derivatives, in which unsymmetrical bicyclic intermediates of type III would be involved.

From the reaction of 4,4-dimethyl-2-thiooxazolidone (Ia) and 2-bromoethylamine hydrobromide in refluxing isopropyl alcohol a crystalline hydrobromide of type II could not be isolated. However, when an aqueous solution of the reaction product was adjusted to pH 7.3, there was obtained, after standing, 2-(2-mercaptoethylamino)-4,4-dimethyl-2-oxazoline (IVa), isolated as the picrate, in 23% yield from the thiooxazolidone.[5] Adjust-

ment of the solution of the reaction product to higher pH values, accompanied by aeration, resulted in the formation in 5–7% yield of the disulfide (Va) of the mercaptan.

Since sodium ethylate has been used effectively in the alkylation of 2-thiooxazolidones with alkyl halides,[6] the reaction of Ia and 2-bromoethylamine hydrobromide was carried out with this reagent. After aeration in alkaline solution, a 12% over-all yield of the disulfide dipicrate was obtained.

Similarly, the reaction of both 2-thiooxazolidone (Ib) and 4-methyl-5-phenyl-2-thiooxazolidone (Ic) with 2-bromoethylamine in the presence of sodium ethylate, followed by aeration in alkaline solution, afforded the rearranged disulfides. Bis[2-(2-oxazolin-2-ylamino)ethyl] disulfide (Vb) and bis[2-(4-methyl-5-phenyl-2-oxazolin-2-ylamino)ethyl] disulfide (Vc), isolated as the dipicrates, were obtained in 10–15% yield.

The compounds required for identification of the rearrangement products were prepared by the reaction of the appropriate 2-methylthio-2-oxazoline with 2-mercaptoethylamine hydrochloride. The reaction of 2-methylthio-2-thiazoline with various amines[4,7] and an instance of the reaction of a 2-methylthio-2-oxazoline

(1) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Am. Chem. Soc.*, **79**, 5667 (1957).

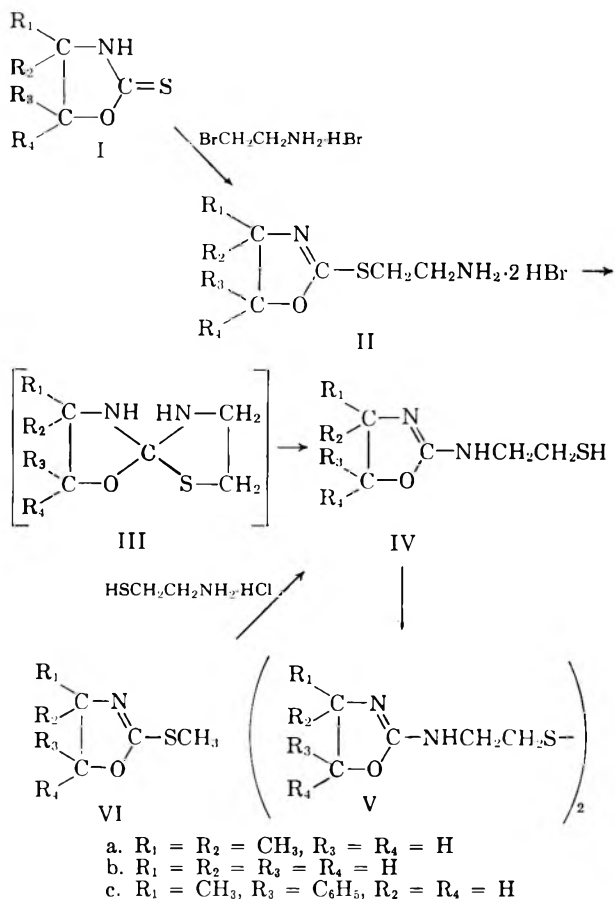(2) J. X. Khym, R. Shapira, and D. G. Doherty, *ibid.*, **79**, 5663 (1957).

(3) J. X. Khym, D. G. Doherty, and R. Shapira, *ibid.*, **80**, 3342 (1958).

(4) R. C. Clapp, L. Long, Jr., and T. Hasselstrom, *J. Org. Chem.*, **26**, 1666 (1961).

(5) In the preparation of 2-(2-aminoethylthio)-2-thiazoline dihydrobromide from 2-thiothiazolidone and 2-bromoethylamine hydrobromide, a yield of 27% was obtained.[4] Thus the 23% over-all yield obtained here might indicate a rather high yield in the rearrangement step.

(6) L. Long, Jr., R. C. Clapp, F. H. Bissett, and T. Hasselstrom, *J. Org. Chem.*, **26**, 85 (1961).

(7) A. F. McKay, D. J. Whittingham, and M.-E. Kreling, *J. Am. Chem. Soc.*, **80**, 3339 (1958).

a. $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$
b. $R_1 = R_2 = R_3 = R_4 = H$
c. $R_1 = CH_3$, $R_3 = C_6H_5$, $R_2 = R_4 = H$

with an amine[8] have been reported. The reaction of 2-methylthio-4,4-dimethyl-2-oxazoline (VIa) and 2-mercaptoethylamine hydrochloride proceeded normally to 2-(2-mercaptoethylamino)-4,4-dimethyl-2-oxazoline (IVa), which could be isolated as the picrate. Treatment of the reaction product with base in the air yielded the disulfide Va.

The preparation of the desired disulfides starting from 2-methylthio-4-methyl-5-phenyl-2-oxazoline (VIc) and 2-methylthio-2-oxazoline (VIb), however, proceeded through an intermediate with anomalous properties. When the product from VIc and 2-mercaptoethylamine hydrochloride was treated with sodium hydroxide, elementary and molecular weight analyses of the crystalline base initially obtained in 50–60% yield indicated the formula $C_{12}H_{16}N_2OS$. This formula corresponds to the mercaptan IVc rather than to the disulfide Vc. However, chemical and spectroscopic tests failed to show the presence of a mercapto group. On standing in neutral or basic solution in the air this compound was slowly converted to the disulfide Vc.

The reaction of 2-methylthio-2-oxazoline and 2-mercaptoethylamine hydrochloride yielded a crystalline hydrochloride, the properties of which indicated that it was analogous to the anomalous intermediate. In alkaline solution with aeration this compound similarly afforded the desired disulfide (Vb).

The infrared spectrum of the $C_{12}H_{16}N_2OS$ intermediate failed to show the presence of hydroxyl and primary amino groups as well as of mercapto, and its n.m.r. spectrum presented evidence that the molecule contained two NH groups. These observations have suggested the possibility that a stable compound corre-

sponding to the proposed bicyclic intermediate in the transoxazolination (i.e., IIIc) has been obtained in this case, by ring closure of the 2-mercaptoethylamino side chain. On the other hand, a strong band at 6.16 μ in the infrared spectrum would appear to indicate the presence of unsaturation in the heterocyclic ring,[6,9] which would require the formation of a side chain containing a terminal hydroxyl, amino, or mercapto group.[10] The investigation of the structure of this compound is being continued.

### Experimental[11]

**2-Methylthio-4,4-dimethyl-2-oxazoline (VIa).**—To a solution of 2.15 g. (0.094 g.-atom) of sodium in 100 ml. of absolute ethanol was added 12.3 g. (0.094 mole) of 4,4-dimethyl-2-thiooxazolidone (Ia).[8] A solution of 13.5 g. (0.095 mole) of methyl iodide in 50 ml. of ethanol was added, and after standing 1 hr. at room temperature the mixture was refluxed for 50 min. The alcohol was removed, and the concentrate was extracted with ether. Concentration of the ether extract and distillation afforded 9.14 g. (67% yield) of a colorless liquid, b.p. 63–64° (16 mm.).

*Anal.* Calcd. for $C_6H_{11}NOS$: C, 49.62; H, 7.64. Found: C, 49.47; H, 7.66.

The picrate, prepared in ethanol and crystallized from chloroform–heptane, melted at 157–159°.

*Anal.* Calcd. for $C_{12}H_{14}N_4O_8S$: C, 38.50; H, 3.77; S, 8.56. Found: C, 38.38; H, 3.75; S, 8.72.

**2-(2-Mercaptoethylamino)-4,4-dimethyl-2-oxazoline (IVa) Picrate.**—A solution of 7.88 g. (0.054 mole) of VIa and 6.4 g. (0.056 mole) of 2-mercaptoethylamine hydrochloride in 150 ml. of methanol was refluxed for 4 hr. Concentration of the solution under reduced pressure gave 12.52 g. of a viscous oil that was stored under nitrogen. Treatment of a 237-mg. portion of this oil with ethanolic picric acid solution yielded 225 mg. (55%) of picrate, m.p. 157–159°. Crystallization from ethyl acetate afforded glistening yellow plates, m.p. 159–160°.

*Anal.* Calcd. for $C_{13}H_{17}N_5O_8S$: C, 38.71; H, 4.25; S, 7.95. Found: C, 38.81; H, 4.16; S, 8.02.

The picrate gave a positive nitroprusside test for mercapto. Its infrared spectrum (potassium bromide) showed a mercaptan band at 3.90 μ and strong bands at 5.85 (N=C—N) and 6.10 μ.

**Bis[2-(4,4-dimethyl-2-oxazolin-2-ylamino)ethyl] Disulfide (Va).**—An 11.36-g. portion of the 12.52 g. of oil obtained in the previous experiment was dissolved in 170 ml. of water, and the solution was made strongly alkaline with sodium hydroxide. After aeration for several hours and cooling, filtration yielded 3.33 g. (39%) of white solid, m.p. 130–133°. Prismatic crystals, m.p. 134–136°, were obtained by crystallization from aqueous ethanol.

*Anal.* Calcd. for $C_{14}H_{26}N_4O_2S_2$: C, 48.53; H, 7.56; S, 18.51; mol. wt., 346. Found: C, 48.55; H, 7.36; S, 18.42; mol. wt., 345 (Rast).

Additional product could be precipitated by aeration of the filtrate. In another run, a 48% yield was obtained.

A positive nitroprusside test was obtained only after treatment with potassium cyanide, as anticipated for a disulfide.[12] The strong (N=C—N) absorption in the infrared (chloroform) was at 6.00 μ. The spectrum (potassium bromide) of the dipicrate of the disulfide had strong bands at 5.85 and 6.10 μ, similar to the picrate of the mercaptan. The dipicrate melted at 203–204.5° after crystallization from acetone.

*Anal.* Calcd. for $C_{26}H_{32}N_{10}O_{16}S_2$: C, 38.80; H, 4.01; S, 7.97. Found: C, 38.76; H, 4.00; S, 7.97.

**IVa and Va from Rearrangement. A. Without Sodium Ethylate.**—A solution of 1.32 g. (0.01 mole) of 4,4-dimethyl-2-thiooxazolidone (Ia) and 2.04 g. (0.01 mole) of 2-bromoethylamine hydrobromide in 16 ml. of isopropyl alcohol was refluxed for 4 hr. Concentration under reduced pressure afforded 4.21 g. of viscous oil. A solution of a 1-g. portion of the oil in 10 ml. of

(8) M. Skulski, D. L. Garmaise, and A. F. McKay, *Can. J. Chem.*, **34**, 815 (1956).

(9) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4699 (1950).

(10) The failure of the infrared spectrum to show hydroxyl, for example, might be attributable to internal hydrogen bonding to a basic nitrogen atom.

(11) Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected

(12) I. W. Grote, *J. Biol. Chem.*, **93**, 25 (1931).

water was adjusted to pH 7.3 by the addition of 1 $N$ sodium hydroxide. After 22–23 hr. at room temperature the solution was filtered and acidified with hydrochloric acid. Saturated ethanolic picric acid solution (5 ml.) was added, and after cooling 228 mg. of crude picrate that melted from 140 to 150° was obtained. Crystallization from ethanol–acetone gave 168 mg. of yellow crystals, m.p. 155–157°. Together with 52 mg. of crystalline picrate, m.p. 153–156°, from a second crop this represented a 23% yield. Recrystallization from ethanol-acetone gave a product that was identical by mixture melting point and infrared spectrum to the picrate of IVa previously obtained.

A solution of a 1.03-g. portion of the viscous oil from the reaction in 10 ml. of water was adjusted to pH 9.5 with 1 $N$ sodium hydroxide. After aeration for 4 hr. and 18–19 hr. at room temperature, filtration, acidification, and treatment with picric acid yielded a gummy precipitate. On trituration with ethanol and acetone 55 mg. (5.6%) of picrate, m.p. 193–196°, was obtained. Crystallization from ethanol–acetone afforded yellow crystals identical (mixture melting point and infrared spectrum) to the dipicrate of Va.

**B. With Sodium Ethylate.**—To a solution of 0.68 g. (0.030 g.-atom) of sodium in 40 ml. of absolute ethanol were added 1.96 g. (0.015 mole) of Ia and 3.06 g. (0.015 mole) of 2-bromoethylamine hydrobromide. The solution was refluxed for 2.5 hr., cooled, and filtered. The concentrate from one-half of the filtrate was dissolved in 25 ml. of water, and the pH of the solution was brought to 10.9. After about 16 hr. at room temperature with 4 hr. of aeration, the mixture was acidified and treated with picric acid. Trituration of the crude precipitate with warm ethanol and acetone yielded 373 mg. (12.4%) of picrate, m.p. 195–198°. Crystallization from acetone gave 231 mg. of disulfide dipicrate, m.p. 202.5–204°.

**4-Methyl-5-phenyl-2thioöxazolidone (Ic).**—The method of Ettlinger[13] for the preparation of 2-thioöxazolidones was used. A solution of 30.8 g. (0.164 mole) of $\alpha$-(1-aminoethyl)benzyl alcohol (norephedrine) hydrochloride and 22 g. of 85% potassium hydroxide in 400 ml. of water and 140 ml. of dioxane was cooled in ice, and 13.1 g. (0.171 mole) of carbon disulfide in 80 ml. of dioxane was added. After 25 min. of shaking, there were added 11 g. of 85% potassium hydroxide in 200 ml. of water and 55 g. of lead nitrate in 300 ml. of water. The mixture was heated for 30 min. at 60–65°, and the black precipitate was filtered off. The precipitate that separated from the filtrate was crystallized from aqueous ethanol; 11.54 g. (36%) of glistening white plates, m.p. 92–94°, were obtained. An analytical sample melted at 93–94.5°.[14]

*Anal.* Calcd. for $C_{10}H_{11}NOS$: C, 62.14; H, 5.74; S, 16.59. Found: C, 62.10; H, 5.80; S, 16.84.

**2-Methylthio-4-methyl-5-phenyl-2-oxazoline (VIc).**—4-Methyl-5-phenyl-2-thioöxazolidone was alkylated with methyl iodide and sodium ethylate, similarly to Ia. The product was obtained (85–90% yield) as a colorless liquid, b.p. 103–105° (3 mm.). The C=N band (chloroform) was at 6.21 $\mu$.

*Anal.* Calcd. for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; S, 15.47. Found: C, 63.93; H, 6.52; S, 15.43.

**$C_{12}H_{16}N_2OS$ Intermediate.**—A solution of 12 g. (0.058 mole) of VIc and 6.6 g. (0.058 mole) of 2-mercaptoethylamine hydrochloride in 185 ml. of methanol was refluxed for 4 hr. After cooling, it was concentrated under reduced pressure to a viscous liquid. Water (250 ml.) was added to the concentrate, and the mixture was extracted with ether to remove a little insoluble material. The aqueous solution, cooled in ice, was made basic by the addition of sodium hydroxide in portions. Crystallization of the precipitated solid (11.35 g.) from heptane–ethyl acetate gave 8.23 g. (60% yield) of white crystals, m.p. 131–134°. Recrystallization from heptane–ethyl acetate afforded 6.61 g. (48%), m.p. 134.5–136°.

*Anal.* Calcd. for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.83; N, 11.86; S, 13.57; mol. wt., 236. Found: C, 60.84; H, 6.91; N, 11.85; S, 13.62; mol. wt., 238 (Rast), 234 (vapor pressure osmometer).

The infrared spectrum (chloroform) showed a band at 2.91 $\mu$ (NH) and strong maxima at 6.16 and 6.69 $\mu$. The n.m.r. spectrum[15] in deuteriochloroform contained a peak at 4.65 p.p.m.,

analogous to the peak at 4.73 p.p.m. attributable to NH in Va, that represented two protons and indicated two NH groups.

The pure compound did not give a positive nitroprusside test for mercapto. However, after treatment with potassium cyanide or on standing a positive test was obtained. When a solution of the compound in chloroform or ethanol was allowed to stand open to the air, a slow transformation took place, as evidenced by the formation of a strong band in the infrared spectrum at 6.01 $\mu$, characteristic of disulfides of type V, and the simultaneous disappearance of the strong band at 6.16 $\mu$. In ethanol this transformation was incomplete after 2 days but complete after 6 days. In aqueous ethanolic sodium hydroxide solution it was complete after three days.

The compound formed a monopicrate that separated from ethanol as fine yellow crystals, m.p. 174–176°. Its infrared spectrum (potassium bromide), similarly to that of the base, did not show a mercaptan band at 3.9 $\mu$ and showed a single strong peak at 6.10 $\mu$.

*Anal.* Calcd. for $C_{18}H_{19}N_5O_8S$: C, 46.45; H, 4.11; S, 6.89. Found: C, 46.36; H, 4.19; S, 7.08.

**Bis[2-(4-methyl-5-phenyl-2-oxazolin-2-ylamino)ethyl] Disulfide (Vc).**—A solution of 0.5 g. of the $C_{12}H_{16}N_2OS$ intermediate in 16 ml. of ethanol and 5 ml. of 10% sodium hydroxide was allowed to stand in an unstoppered flask for 64 hr. After aeration for 2 hr., a small quantity of solid that had separated was filtered off, and the filtrate was concentrated. The concentrate was dissolved in chloroform and water, and the chloroform layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to an oil. To this concentrate (0.51 g.) was added ethanolic picric acid, and treatment of the resulting crude precipitate with warm ethyl acetate yielded 0.51 g. (52%) of picrate, m.p. 197–200°. Crystallization from ethanol–acetone afforded 0.39 g. (40%) of small yellow crystals, m.p. 202–204°.

*Anal.* Calcd. for $C_{36}H_{36}N_{10}O_{16}S_2$: C, 46.55; H, 3.91; S, 6.90; mol. wt., 929. Found: C, 46.71; H, 3.92; S, 6.96; mol. wt., 976 (vapor pressure osmometer).

The free base of the disulfide could not be obtained as a crystalline solid. The base recovered from the crystallized picrate formed a glass that became an amorphous solid. The cyanide-nitroprusside color test given by this product and its infrared spectrum (strong N=C—N band at 6.00 $\mu$) were consistent with its formulation as the disulfide, by comparison with the other disulfides. It was also characterized as the distyphnate, m.p. 194–197° (from ethanol–acetone).

*Anal.* Calcd. for $C_{36}H_{36}N_{10}O_{18}S_2$: C, 45.00; H, 3.78; S, 6.67. Found: C, 44.87; H, 3.92; S, 6.62.

The infrared spectra (potassium bromide) of both the dipicrate and distyphnate showed strong maxima at 5.85 and 6.10 $\mu$.

**Vc from Rearrangement.**—The reaction was carried out with sodium ethylate, similarly to the method used for the preparation of Va by rearrangement. A solution of 0.96 g. (0.042 g.-atom) of sodium, 4.02 g. (0.021 mole) of 4-methyl-5-phenyl-2-thioöxazolidone (Ic), and 4.26 g. (0.021 mole) of 2-bromoethylamine hydrobromide in 100 ml. of absolute ethanol was refluxed for 3 hr. and filtered. After the concentrate from the filtrate had been allowed to stand in aqueous ethanolic sodium hydroxide at pH 10.7 for 4 days with intermittent aeration, there was obtained a 13.5% yield of picrate that melted from 190 to 195° and that gave an infrared spectrum nearly identical to that of the dipicrate of Vc. Crystallization from ethanol–acetone afforded a picrate, m.p. 195.5–198.5°, that represented an 11.4% yield in the reaction. Identity to Vc was established, after further purification, by mixed melting point and infrared spectra.

In another run, in which the standing in alkaline solution was omitted, the $C_{12}H_{16}N_2OS$ intermediate, isolated as the crystalline base, was obtained in 3.6% yield.

**2-Methylthio-2-oxazoline (VIb).**—The alkylation of 2-thioöxazolidone (Ib)[13] was carried out similarly to the alkylation of Ia. Distillation gave a 67% yield of colorless liquid, b.p. 69–71° (14 mm.).

*Anal.* Calcd. for $C_4H_7NOS$: S, 27.36. Found: S, 27.34.

The picrate was identical to the one previously reported.[6]

**Hydrochloride of $C_5H_{10}N_2OS$ Intermediate.**—A solution of 6.6 g. (0.056 mole) of VIb and 6.4 g. (0.056 mole) of 2-mercaptoethylamine hydrochloride in 150 ml. of methanol was refluxed for 4 hr. The solution was concentrated under reduced pressure, and crystallization of the concentrate from 110 ml. of isopropyl alcohol yielded 6.58 g. of crystalline solid. Recrystallization from isopropanol gave 5.52 g. (54% yield) of colorless crystals, m.p. 115–117°. An analytical sample melted at 116–118°.

(13) M. G. Ettlinger, *J. Am. Chem. Soc.*, **72**, 4792 (1950).

(14) *threo*-4-Methyl-5-phenyl-2-thioöxazolidone, m.p. 128–130°, and the *erythro* isomer, m.p. 108–109°, prepared from the amino alcohols by a different method, have been reported by M. Kojima, *J. Pharm. Soc. Japan*, **79**, 11 (1959).

(15) Determined on a Varian A-60 spectrometer.

*Anal.* Calcd. for $C_5H_{11}ClN_2OS$: C, 32.87; H, 6.07; S, 17.55. Found: C, 33.04; H, 6.12; S, 17.82.

The picrate was obtained as small yellow crystals, m.p. 142–144°, from ethyl acetate.

*Anal.* Calcd. for $C_{11}H_{13}N_5O_8S$: C, 35.20; H, 3.40; S, 8.54. Found: C, 35.42; H, 3.60; S, 8.80.

The hydrochloride did not give a nitroprusside test for mercapto. Its infrared spectrum (potassium bromide) did not contain a mercaptan band at 3.9 $\mu$ and showed a strong band at 6.10 $\mu$. The picrate (potassium bromide) similarly did not give a mercaptan band and exhibited a single strong band at 6.10 $\mu$, analogously to the picrate of the $C_{12}H_{16}N_2OS$ intermediate rather than to the picrate of the mercaptan IVa.

**Bis[2-(2-oxazolin-2-ylamino)ethyl] Disulfide (Vb).**—To 0.6 g. of the $C_5H_{10}N_2OS$ hydrochloride in 6 ml. of water was added 3 ml. of 10% sodium hydroxide, and the solution was allowed to stand for 4 days with intermittent aeration. The white crystalline precipitate that separated amounted to 0.37 g. (78% yield), m.p. 131–133°. Crystallization from ethyl acetate afforded 0.32 g. (67%) of glistening plates, m.p. 133.5–135.5°.

*Anal.* Calcd. for $C_{10}H_{18}N_4O_2S_2$: C, 41.36; H, 6.25; S, 22.08; mol. wt., 290. Found: C, 41.54; H, 6.30; S, 22.02; mol. wt. (vapor pressure osmometer), 288.

The picrate separated from ethanol–acetone as fine yellow crystals, m.p. 202–204°.

*Anal.* Calcd. for $C_{22}H_{24}N_{10}O_{16}S_2$: C, 35.30; H, 3.23; S, 8.56. Found: C, 35.62; H, 3.38; S, 8.42.

In the infrared the base showed the strong bands at 6.0 and 6.6 $\mu$ and the picrate the strong bands at 5.85–5.9 and 6.1 $\mu$, characteristic of the disulfides.

**Vb from Rearrangement.**—In the usual manner, equimolar quantities of 2-thiooxazolidone, 2-bromoethylamine, and sodium ethylate were refluxed in ethanol for 3 hr. After the product had been allowed to stand in solution at pH 9–10 for 5 days, there was obtained a 28% yield of crude picrate that melted from 170 to 182° but that gave an infrared spectrum similar to that of the dipicrate of Vb. The yield of twice-crystallized picrate, m.p. 199–201°, was 11.5%. Identity to Vb dipicrate was demonstrated after further purification, and a crystalline base identical to Vb was recovered from the picrate.

Without sodium ethylate, Vb dipicrate was obtained in very low yield.

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# The Base-catalyzed Oxidation of Mercaptans. III. Role of the Solvent and Effect of Mercaptan Structure on the Rate Determining Step[1,2]

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*n*-Butyl mercaptan has been oxidized in dimethylformamide (DMF)–methanol and diethyleneglycol dimethyl ether (diglyme)–methanol mixtures at 23.5 ± 0.2° using sodium methoxide as the base. The relative rates of oxidation of the mercaptan decreased at the same rate in the two solvent systems as the quantity of methanol was increased in each solvent mixture suggesting that similar transition states are involved in both systems. A series of ion pair complexes which ultimately involve an intimate ion pair complex between methanol and the sodium mercaptide are suggested as possible explanations for the observed results. In addition, benzyl mercaptan, thiophenol, *p*-aminothiophenol, *p*-nitrothiophenol, and cyclohexyl mercaptan were oxidized under a variety of conditions. The observed results indicate that the rate determining step is reaction of the anion ($RS^\ominus$) with oxygen.

Until recently, most studies on the base-catalyzed oxidation of mercaptans (thiols) to disulfides with molecular oxygen have been limited to an aqueous sodium hydroxide media.[3] Some structural effects of mercaptans on the rate of oxidation in this medium have been observed[4] but the results have been somewhat difficult to interpret since solubilities and salting-out effects vary for the mercaptans studied. Barringer[5] has reported that N,N'-disubstituted-*p*-phenylene-diamines are capable of accelerating this coupling reaction. The use of various transition metal phthalocyanines and other organic chelates in basic media has also been recommended.[6] In the latter case, the rate-limiting step appears to be diffusion of oxygen and the mercaptide ion to the surface of the catalyst.[7] We have recently observed in these laboratories[1] that various dipolar and ethereal solvents greatly enhanced

the homogeneous, base-catalyzed oxidation rate of *n*-butyl mercaptan with molecular oxygen.

The present study was undertaken to determine how the addition of a hydroxylic material (methanol) to an aprotic base–solvent system would effect the rate of oxidation of *n*-butyl mercaptan. Further, it also seemed of interest to ascertain how the rate of oxidation varied with the structure of the mercaptan since this would provide information on the rate determining step in this reaction.

## Results

One-tenth of a mole of *n*-butyl mercaptan was oxidized in DMF–methanol and diglyme–methanol mixtures at 23.5 ± 0.2° under a constant oxygen pressure of one atmosphere. 0.2 mole of sodium methoxide was used in each oxidation reaction. Each reaction was carried out to about 30% completion. The amount of mercaptan converted to the disulfide was determined from the amount of oxygen consumed as a function of time according to the derived first-order rate expression. The apparent first-order rate constants obtained for the oxidation of *n*-butyl mercaptan to the disulfide in each hydroxylic–aprotic solvent mixture are summarized in Table I and calculated relative to the rate obtained in

(1) T. J. Wallace and A. Schriesheim, *J. Org. Chem.*, **27**, 1514 (1962).

(2) T. J. Wallace, J. M. Miller, H. Pobiner, and A. Schriesheim, *Proc. Chem. Soc.*, 384 (1962).

(3) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., Inc., New York, N. Y., 1958.

(4) J. Xan, E. A. Wilson, L. D. Roberts, and N. H. Horton, *J. Am. Chem. Soc.*, **63**, 1139 (1941).

(5) C. M. Barringer, *Ind. Eng. Chem.*, **47**, 1022 (1955).

(6) W. K. T. Gleim and P. Urban, U. S. Patent 714,937 (Feb. 13, 1958).

(7) T. J. Wallace, A. Schriesheim, and D. L. Baeder, unpublished results.

TABLE I

OXIDATION OF n-BUTYL MERCAPTAN IN DMF–METHANOL AND
DIGLYME–METHANOL SOLUTIONS AT 23.5 ± 0.2°

| | Volume % solvent | $k \times 10^2$, min.$^{-1}$ | $k$ Relative to methanol |
|---|---|---|---|
| DMF | 100 | 1077 | 334 |
| | 75 | 368 | 114 |
| | 50 | 68.6 | 21.3 |
| | 25 | 9.16 | 2.8 |
| | 10 | 3.93 | 1.2 |
| Diglyme | 100 | 323 | 100 |
| | 75 | 138 | 43 |
| | 50 | 36.5 | 11 |
| | 35 | 6.21 | 1.9 |
| Methanol | 100 | 3.22 | 1.00 |

100% methanol. A plot of $k$ relative DMF/$k$ relative diglyme vs. the volume per cent of methanol in each reaction mixture (Fig. 1) gives a linear relation-
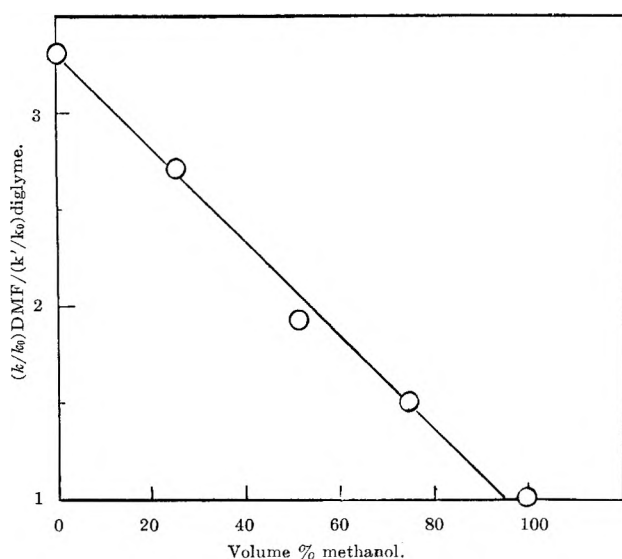


Fig. 1.—A plot of $(k/k_0)$ DMF/$(k'/k_0)$ diglyme vs. volume % methanol; $k_0$ = rate in methanol; $k$ = rate in DMF solutions; $k'$ = rate in diglyme solutions.

ship which decreases with increasing amounts of methanol.

Due to the paucity of information on structural effects in the oxidation of sulfur anions a second aspect of this research was concerned with how the rate of oxidation is influenced by the structure of the mercaptan. Benzyl mercaptan, thiophenol, p-aminothiophenol, p-nitrothiophenol, and cyclohexyl mercaptan were oxidized in several solvents at 23.5 ± 0.2° to their corresponding disulfides. In each reaction, an excess of either sodium methoxide or potassium tert-butoxide was used. The specific conditions employed and the results obtained are summarized in Table II. Results previously obtained with n-butyl mercaptan are also included for convenience of comparison. Thiophenol oxidized at a considerably slower rate than n-butyl and benzyl mercaptans under the reaction conditions listed. Cyclohexyl mercaptan and p-aminothiophenol are oxidized some four- to tenfold faster than thiophenol. p-Nitrothiophenol was not oxidized over a 20-hr. period.[8]

(8) A similar result in dimethyl sulfoxide-tert-butyl alcohol was recently communicated: G. A. Russell, A. J. Moye, and K. Nagpal, *J. Am. Chem. Soc.*, **84**, 4154 (1962).

TABLE II

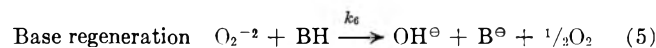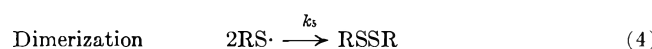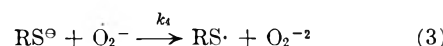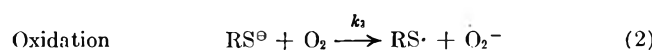VARIATION OF THE RATE OF OXIDATION WITH
MERCAPTAN STRUCTURE

| Mercaptan | Solvent | Base | $k \times 10^3$, min.$^{-1}$ | $pK_a{}^a$ |
|---|---|---|---|---|
| n-C$_4$H$_9$SH | CH$_3$OH | NaOMe | 3.22 | 11.5 |
| n-C$_4$H$_9$SH | tert-C$_4$H$_9$OH | KOtBu | 34.7 | |
| n-C$_4$H$_9$SH | DMF | NaOMe | 1077 | |
| C$_6$H$_5$SH | CH$_3$OH | NaOMe | 0.23 | 6.5 |
| C$_6$H$_5$SH | tert-C$_4$H$_9$OH | KOtBu | 8.19 | |
| C$_6$H$_5$SH | DMF | NaOMe | 76.6 | |
| C$_6$H$_{11}$SH | CH$_3$OH | NaOMe | 0.88 | .. |
| p-NH$_2$—C$_6$H$_4$SH | CH$_3$OH | NaOMe | 2.53 | .. |
| p-NO$_2$—C$_6$H$_4$SH | CH$_3$OH | NaOMe | N.R. | .. |
| C$_6$H$_5$CH$_2$SH | CH$_3$OH | NaOMe | 5.57 | 9.4 |

$^a$ All $pK_a$ values listed were taken from the following sources: M. M. Kreevoy, et al., *J. Am. Chem. Soc.*, **82**, 4899 (1960); D. L. Yabroff, *Ind. Eng. Chem.*, **32**, 257 (1940).

## Discussion

To date, no detailed study on the mechanism of mercaptan oxidation in basic media has been attempted. In the present study, a mechanism, which takes into account both the rate determining step and the role of the solvent in this reaction, is proposed and discussed in detail.

In the present investigation, the oxidation of mercaptans was studied under such conditions that the reaction rate became independent of the rate of agitation. Thus, it may be assumed that the rate of diffusion of oxygen gas into the solution did not control the chemical reaction rate. In the base-solvent systems employed the oxidation of a mercaptan to its corresponding disulfide may be described by the following mechanistic paths.

Ionization
$$RSH + B^\ominus \underset{k_2}{\overset{k_1}{\rightleftharpoons}} RS^\ominus + BH \qquad (1)$$

Oxidation
$$RS^\ominus + O_2 \xrightarrow{k_3} RS\cdot + O_2{}^- \qquad (2)$$

$$RS^\ominus + O_2{}^- \xrightarrow{k_4} RS\cdot + O_2{}^{-2} \qquad (3)$$

Dimerization
$$2RS\cdot \xrightarrow{k_5} RSSR \qquad (4)$$

Base regeneration
$$O_2{}^{-2} + BH \xrightarrow{k_6} OH^\ominus + B^\ominus + \tfrac{1}{2}O_2 \qquad (5)$$
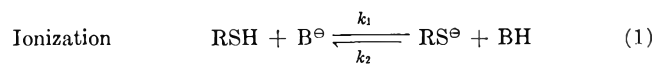
The above reaction scheme yields an over-all stoichiometry in agreement with the experimental results of this study.

$$2RSH + \tfrac{1}{2}O_2 + B^\ominus \longrightarrow RSSR + HO^\ominus + BH \qquad (6)$$

Since, in these experiments, the base, $B^\ominus$, was employed in excess with respect to mercaptan concentration, the interconversion of alkoxide ions into hydroxide ions is not expected to influence appreciably the reaction kinetics. Further, it has been demonstrated that even in 1 $N$ sodium hydroxide solution the ratio of $(RS^\ominus)/(RSH)$ (see equation 1) is at least $2 \times 10^3$ for all mercaptans investigated.[3] Based on this mechanism, the rate of oxygen consumption is given by

$$\frac{d(O_2)}{dt} = -k_3(RS^\ominus)(O_2) + \tfrac{1}{2}k_6(O_2{}^\ominus) \qquad (7)$$

where the bracketed quantities denote the concentrations of the various species in the solution. Assuming that the $O_2{}^{-2}$ and $O_2{}^\ominus$ ions are present in steady state concentrations, the rate equation reduces to

$$\frac{d(O_2)}{dt} = \frac{-k_3}{2}(RS^\ominus)(O_2) \tag{8}$$

The concentration of mercaptide ions is determined by the ionization equilibrium constant $K = k_1/k_2$.

$$(RS^\ominus) = K\frac{(RSH)(B^\ominus)}{(BH)} \tag{9}$$

The stoichiometric concentration of mercaptan, $C_{RSH}$, is given by

$$C_{RSH} = (RS^\ominus) + (RSH) \tag{10}$$

thus

$$(RSH) = C_{RSH} - (RS^\ominus) \tag{11}$$

Substituting into the equilibrium expression for (RSH) and simplifying the relationship between $C_{RSH}$ and $(RS^\ominus)$ is given by equation 12.

$$(RS^\ominus) = \frac{C_{RSH}}{[1 + \frac{1}{K}(BH)/(B^\ominus)]} \tag{12}$$

hence

$$\frac{d(O_2)}{dt} = \frac{-k_3}{2}\frac{C_{RSH}(O_2)}{[1 + 1/K(BH)/(B^-)]} \tag{13}$$

With an alkoxide as the base, it is evident from equation 13 that the rate of oxidation is inversely proportional to the concentration of added alcohol, BH (when no alcohol is added the oxidation would be inhibited to a small extent in its latter stages because of alcohol formed during the reaction). For low levels of conversion the concentration of BH may be considered to be constant, i.e., (BH) = (BH) initial. Thus, for highly acidic species and a given initial base concentration [1 + (BH)/$K$(B$^-$)] = 1 and

$$\frac{d(O_2)}{dt} = \frac{-k_3}{2}C_{RSH}(O_2) \tag{14}$$

From the over-all stoichiometry, each mole of RSH requires $1/4$ mole of $O_2$. Therefore,

$$\frac{d(RSH)}{dt} = 4\frac{d(O_2)}{dt} = -2k_3 C_{RSH}(O_2) \tag{15}$$

The equilibrium concentration of oxygen in the solution can be expressed as

$$O_2 = K_s P_{O_2} \tag{16}$$

where $K_s$ = constant and $P_{O_2}$ = partial pressure of oxygen gas. Thus, the rate of mercaptan disappearance is given by

$$\frac{d(RSH)}{dt} = -2k_3 K_s C_{RSH} P_{O_2} \tag{17}$$

which under constant oxygen pressure yields upon integration

$$\ln\frac{(RSH)}{(RSH) \text{ initial}} = -kt \tag{18}$$

where $t$ = duration of oxidation and $k = [2k_3 K_s P_{O_2}]$. Thus, at a given initial base concentration, a constant alcohol concentration, and a constant partial pressure of oxygen the rate equation simplifies to a first-order rate expression which is in agreement with the observed results and proposed mechanistic speculations.

The mercaptans investigated in the present study are relatively acidic species and in the base-solvent systems listed the ratio of the concentration of the anion, $RS^\ominus$, to the concentration of the unionized mercaptan should be greater than $2 \times 10^{3.3}$. Thus, for low levels of conversion it is reasonable to assume that the rate determining step is reaction of the anion with oxygen (equations 2 and 3). An examination of the results in Table II indicates that the structure of the anion plays a key role in the rate determining step of this reaction. For example, p-nitrothiophenol forms the most stable anion and it is not oxidized. The thiophenolate ion, which is resonance stabilized by interaction of the electron pair on the sulfur atom with the $\pi$ system of the benzene ring, is less reactive toward oxygen than either the cyclohexyl mercaptide of p-aminothiophenolate ions. In the latter case, resonance interactions would lead to decreased stability of the resulting ion. This reactivity sequence may be rationalized by assuming that reaction of the anion with oxygen is rate limiting. The reverse order of reactivity would be observed if ionization of the mercaptan was rate limiting. This is substantiated by the results obtained with n-butyl and benzyl mercaptans. Both mercaptans are less acidic than thiophenol and p-nitrothiophenol and their resulting anions are not resonance stabilized. However, they are oxidized at a relatively rapid rate. A similar reactivity sequence has recently been observed by Russell and co-workers[3] for the oxidation of carbanions, i.e., the most stable carbanion is the most difficult to oxidize.

Previous studies on solvent effects in the oxidation of mercaptans indicated that the rate of oxidation of n-butyl mercaptan was 35 to 300 times faster in various ethereal and dipolar, aprotic solvents than in methanol.[1] These results were rationalized on the basis of a specific cation solvation of the sodium cation initially associated with the mercaptide ion in an ion-pair intermediate. Further, an $sp^3$ complex involving $s$–$p$ overlap between the oxygen atom of the solvent and the empty 3-$s$ orbital of the sodium cation was suggested. Thus, it seemed reasonable to presume that any species capable of interacting with both the aprotic solvent and the sodium mercaptide would lead to a decreased rate of oxidation.

The results show that the relative rates of oxidation in DMF and diglyme $((k/k_0)\text{DMF}/(k/k_0)\text{diglyme})$ decrease linearly as a function of the volume per cent of added methanol in each solvent mixture. This suggests that similar transition states are involved in both solvents. It seems reasonable to assume that initially the transition state consists of an "external" ion-pair involving the aprotic solvent (DMF) and the sodium mercaptide (Figure 2). Depending upon the quantity of methanol added, the transition state can be transformed into an "intermediate" ion-pair complex composed of sodium mercaptide–solvent–methanol (Figure 3) which in the presence of excess methanol can exist as an "intimate" ion-pair involving sodium mercaptide–methanol (Figure 4). Based on the rate determining step, the energy difference between reactants and transition state must be less for the nonhydrogen-bonded system than it is for the hydrogen-bonded case where methanol is present.

Similar explanations have been advanced concerning the greater catalytic activity of potassium tert-butoxide ($K^{\oplus\ominus}Ot$-Bu) in dimethyl sulfoxide as opposed to tert-butyl alcohol or dimethyl sulfoxide–tert-butyl alcohol mixtures.[9,10] However, this is the
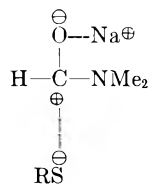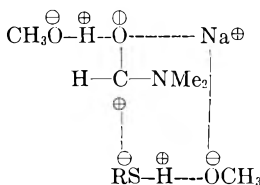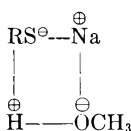
Figure 2         Figure 3         Figure 4

first reported case in which the fate of the reacting entity, $RS^{\ominus}Na^{\oplus}$, can be speculated on with any reasonable certainty.

## Experimental

**Reagents.**—The following materials were distilled under a nitrogen atmosphere through a 14-in. silvered column equipped with a tantalum-wire spiral: $n$-butyl mercaptan (Matheson Coleman, and Bell, b.p. 96–98°, $n^{20}$D 1.4411), cyclohexyl mercaptan [Columbia Organic Chemicals, b.p. 62–65° (12 mm.), $n^{20}$D 1.4925] benzyl mercaptan [Evans Chemetics Inc., b.p. 70° (3 mm.), $n^{20}$D 1.5776], and thiophenol [Matheson Coleman and Bell, b.p. 75° (5 mm.) $n^{20}$D 1.5805]. $p$-Aminothiophenol, $p$-nitrothiophenol and $p$-aminophenyl disulfide (Kek Labs) were used without further purification. All mercaptans were stored under a nitrogen atmosphere in a cold box.

**Purification of Solvents.**—Dimethylformamide, diglyme, *tert*-butyl alcohol, and methanol were dried over indicating Drierite and then distilled over 13X Linde Molecular Sieves to remove any water that was present. The sieves had previously been calcined under nitrogen at 750° for 4 hr. All solvents were stored in a nitrogen dry box.

**Synthesis and Identification of Disulfides.**—Each authentic disulfide was prepared according to the method described in Vogel.[11] One-tenth mole of each mercaptan was added to 50 ml. of a 15% sodium hydroxide solution in a flask equipped with a stirrer and nitrogen bubbler. Iodine (11.0 g.) was added over a 2-hr.

period and each reaction mixture was then stirred overnight. $n$-Butyl and cyclohexyl disulfide were purified by distillation under reduced pressure through a 14-in. silvered column equipped with a tantalum wire spiral. Boiling points and indices of refraction agreed with those tabulated in Reid.[12] Phenyl and benzyl disulfides, when recrystallized from methanol, had respective melting points of 62 and 74° (reported[12] 62 and 74°, respectively). The yields of all disulfides varied between 65 and 80%.

In the isolation of disulfides from the oxidation reactions, the reaction mixture was neutralized with hydrochloric acid, diluted with an equal volume of water, and the disulfide removed by extraction with petroleum ether. The disulfides were purified as above and the physical properties agreed with the literature values. In addition, the infrared spectrum of each disulfide was identical to the synthesized materials. In the case of the phenyl, $p$-aminophenyl, and benzyl disulfides mixture melting points with the authentic disulfides showed no depression.

**Preparation of Reaction Mixtures and Actual Oxidation Experiments.**—All base-solvent systems were made up to the appropriate molarity in a specially adapted heavy-walled 500-ml. erlenmeyer flask in a nitrogen drybox. Each solvent contained 0.20 mole of the desired alkoxide base. One-tenth mole of each mercaptan was then added, the reaction flask sealed, and transferred to the oxidation apparatus which consisted of a polyethylene gas balloon, wet-test meter, drying tower, and a water-cooled condenser. Kinetic measurements were determined from the rate of oxygen consumption as a function of time using the previously derived first-order rate expression. This method of analysis as well as a detailed description of the apparatus employed have been discussed in detail previously.[1,13,14]

(9) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 3688 (1961).

(10) A. Schriesheim and C. A. Rowe, Jr., *ibid.*, **84**, 3160 (1962).

(11) A. I. Vogel, "A Textbook of Practical Organic Chemistry, Longman's Green and Co., London, England, 1959.

(12) E. E. Reid. "Organic Chemistry of Bivalent Sulfur Compounds," III, Chemical Publishing Co., Inc., New York, N. Y., 1960, pp. 395–9.

(13) W. Bartok, D. D. Rosenfeld, and A. Schriesheim, *J. Org. Chem.*, **28**, 410 (1963).

(14) T. J. Wallace, W. Bartok, and A. Schriesheim, *J. Chem. Educ.*, **40**, 39 (1963).

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# Telomerization by Free Radical Mercaptan Chain Transfer. I. Styrene and Ethanethiol[1]

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One- and two-unit telomers (only) have been obtained from styrene using ethanethiol as a free radical chain transfer agent in the liquid phase. Reversibility of telomer formation under the conditions studied was found to be slight. Chain transfer constants for one- and two-unit telomers and also long chain polymers have been determined. The significance of the increase of transfer constant with chain length is discussed.

The formation of short chain polymer fragments (telomers and cotelomers) by free radical chain transfer has been known for some time. However, its potential versatility as a synthetic tool has thus far received little application owing in part to separation problems and in part to lack of fundemental data on chain transfer in very short chains. A number of workers[3] have studied haloalkane agents and determined chain transfer constants for a few monomers measuring

the relative rate of displacement (equation 1) to propagation (equation 2) for short chains containing $n$ units. (Here M refers to monomer units and A and

$$B-M_n\cdot + A-B \xrightarrow{k_{dn}} B-M_n-A + B\cdot \qquad (1)$$

$$B-M_n\cdot + M \xrightarrow{k_{pn}} B-M_{n+1}\cdot \qquad (2)$$
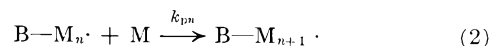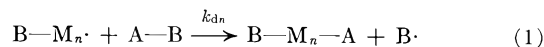
B to fragments of the transfer agent, A–B. The sym-

(3) (a) For a review and earlier references, see C. Walling. "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 243–259 and 313–326; (b) J. C. Robb and E. Senogles, *Trans. Faraday Soc.*, **58**, 708 (1962); (c) W. J. Kirkham and J. C. Robb, *ibid.*, **57**, 1757 (1961); (d) J. C. Robb and D. Vofsi, *ibid.*, **55**, 558 (1959); (e) W. I. Bengough and R. A. M. Thomson, *ibid.*, **57**, 1928 (1961); (f) **56**, 407 (1960).

bol B—$M_n$· represents the $n$-unit radical. The transfer constant $C_n = k_{dn}/k_{pn}$.)

Earlier work[3a] indicated that $C_n$ was small when $n = 1$ but increased rapidly to a constant value for chains of four units or longer. Recent work[3b–f] using bromotrichloromethane as the transfer agent has included studies of individual rate constants and has shown a more complex variation of $C_n$ with chain length. Kirkham and Robb[3c] ascribe this to a reactivity minimum of the growing radical chain at three or four monomer units length and suggest that the formation of a "semi bond" between the radical bearing carbon and the $CCl_3$ group may be involved.

Although telomer formation has been observed with mercaptan chain transfer agents[4], no corresponding studies of transfer constants or other kinetic data for short chains have been reported. This paper describes such a study involving telomer formation in the styrene–ethanethiol system.

The object of the study was to determine first whether telomers could be obtained from this system in appreciable quantities and whether their formation was significantly reversible in the liquid phase. It was then hoped to determine several telomerization chain transfer constants to be compared with the polymerization transfer constant, $C_\infty$. Polymerization transfer constants for numerous primary alkanethiols with styrene have been reported[5]; however, the value for ethanethiol seems to have been omitted. It was, therefore, determined in this work.

## Experimental[6]

**Preparation and Characterization of the Telomers.**—Ethanethiol (9.42 g.; 0.152 mole), redistilled styrene (22.73 g.; 0.218 mole) and azobisisobutyronitrile (AIBN; 2.0 mole % of the styrene) were sealed in a nitrogen filled pyrex reaction tube and heated for 6 hr. in a constant temperature bath at 50°. Excess mercaptan was removed by distillation at 0° using a water aspirator. The residue was distilled through a 7-in. Vigreux column under vacuum. After removal of the styrene, two fractions boiling over a narrow range were collected. Redistillation of these gave the two telomers. The one-unit telomer boiled at 68–69° (0.4 mm.), $n^{20}D$ 1.5395.

*Anal.* Calcd. for $C_{10}H_{14}S$: C, 72.34; H, 8.42; S, 19.25. Found: C, 72.47; H, 8.22; S, 19.13.

The two-unit telomer boiled at 145° (0.06 mm.), $n^{20}D$ 1.5685.

*Anal.* Calcd. for $C_{18}H_{22}S$: C, 80.00; H, 8.17; S, 11.81. Found: C, 79.73; H, 7.84; S, 11.88.

Sulfones of the telomers were prepared by adding an excess of a solution of equal volumes of 30% hydrogen peroxide and glacial acetic acid and allowing the mixture to stand in a water bath at 50° for 2 hr. The acetic acid and hydrogen peroxide were removed by evaporation on a steam bath. The products were recrystallized from an ethanol–water mixture.

The sulfone from the one-unit telomer melted at 78.5–79.5°. Fehnel and Resnick[7] report a melting point of 79–80° for this compound.

The sulfone from the two-unit telomer melted at 67.5–68.5°.

*Anal.* Calcd. for $C_{18}H_{22}SO_2$: C, 71.48; H, 7.33; S, 10.59. Found: C, 71.33; H, 7.20; S, 10.32.

**Reversibility of Telomer Formation.**—A sample of one-unit telomer (2.30 g.) together with one mole % of AIBN was sealed in one leg of an evacuated H-shaped pyrex tube. The leg containing the telomer was placed in constant temperature bath

at 50° for 24 hr. while the other leg was dipped in a Dry Ice-acetone bath. Only a small trace of material resulted in the cold leg of the tube. Gas chromatograms of material in both legs compared to gas chromatograms of prepared mixtures of one-unit telomer and ethanethiol indicated that not more than a few % of the telomer had decomposed.

A similar experiment with two-unit telomer likewise indicated very little decomposition at 50° for many hours. An additional experiment with one-unit telomer carried out in a similar manner but with excess mercaptan added, confirmed the stability of the telomer under these conditions (presumably in the presence of thiyl radicals).

**Determination of the Polymerization Chain Transfer Constants.**—Solutions containing freshly distilled styrene and small quantities of ethanethiol and AIBN were prepared in quantity. Several pyrex reaction tubes (30-ml. capacity) were filled nearly to the top with solution, sealed, and allowed to stand from 1–12 hr. in a constant temperature bath at 50°. Two aliquots (5.00 ml.) from each tube and from the original solutions were titrated amperometrically with 0.0050 N silver nitrate by the method of Kolthoff and Harris.[8] Titration was carried out in a closed flask, using a glycerine seal for the rotating electrode and a magnetic stirrer, to avoid loss of ethanethiol. The polymer was isolated from two aliquots (5.00 ml.) by precipitating in 50-ml. quantities of methanol. The supernatant methanol and styrene were decanted and evaporated rapidly at room temperature, and the small residue (about 0.1 to 0.2 part of the total) was added to the precipitated polymer. Solvent was removed by freeze drying and the precise weight of each yield determined.

**Determination of Telomer Chain Transfer Constants.**—Quantities of ethanethiol varying from 1–15 g. were placed in 30–60-ml. nitrogen filled Pyrex reaction flasks, the weight of the mercaptan being determined by the increase in weight of the flask. The flasks were cooled quickly in Dry Ice and acetone. After adding weighed quantities of styrene varying from 8–50 g, and (in most experiments) small weighed quantities of initiator, the flasks were quickly sealed and placed in a constant temperature bath set at 50 ± 0.1° with initial shaking to make the mixture homogeneous. After 0.5–3 hr., the tubes were cooled, unsealed, and connected directly to a water aspirator. Mercaptan was then removed by placing an ice bath around the tube and evaporating the mixture at 0°. In the majority of experiments, the weight of the residue was then determined, and the mixture was analyzed by gas chromatography on an ethylene glycol terephthalate column to determine the per cent of styrene approximately so that the degree of conversion could be estimated. The residue was then further distilled at a temperature of 50° under reduced pressure to remove most of the unchanged styrene. It should be pointed out that some polymerization may have occurred during this phase of the process; however, this should not affect the resulting quantities of telomers since the chromatogram showed that the mercaptan had been effectively removed at 0°.

The analysis of the final mixture was accomplished by running several gas chromatograms interspersed with chromatograms of mixtures of the pure telomers approximating the composition found. Ratios of the peak heights of each telomer to those of the corresponding standards were used to determine quantities of telomers, and from these the ratio of one-unit telomer to two-unit telomer was calculated in each case.

## Results

**Observed Telomer Formation.**—It was found to be relatively easy to isolate the one-unit telomer (the simple adduct) and the two-unit telomer from reaction mixtures obtained by reaction of ethanethiol with a moderate excess of styrene. These products and their sulfones gave analyses corresponding to the expected thioethers, $C_6H_5CH_2CH_2SCH_2CH_3$ and $C_6H_5CH_2CH_2CH(C_6H_5)CH_2SCH_2CH_3$. In spite of several attempts, however, no identifiable sample of any higher telomer was isolated either in pure form or as a mixture of diastereomers.

(4) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, **13**, 97 (1948).

(5) (a) R. A. Gregg, D. M. Alderman, and F. R. Mayo, *J. Am. Chem. Soc.*, **70**, 3740 (1948); (b) V. A. Dinaburg and A. A. Vanscheidt, *Zh. Obshch. Khim.*, **24**, 840 (1954); *Chem. Abstr.*, **49**, 8157d (1955).

(6) Boiling points and melting points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(7) E. A. Fehnel and P. R. Resnick, *J. Org. Chem.*, **20**, 996 (1955).

(8) I. M. Kolthoff and W. E. Harris, *Ind. Eng. Chem., Anal. Ed.*, **18**, 161 (1946).

In most experiments small amounts of AIBN were used as the initiator; however, as the reaction of styrene with carbon tetrachloride,[3a] the process proceeded slowly in the absence of any initiator.

It has been suggested[3a] that both steps of mercaptan addition may be reversible. The experiments described above, appear to indicate a very slight tendency for the reaction to reverse. This was shown to be too small to complicate the determination of the chain transfer constants under the conditions used, although no quantitative estimate of the degree of reversibility can be made.
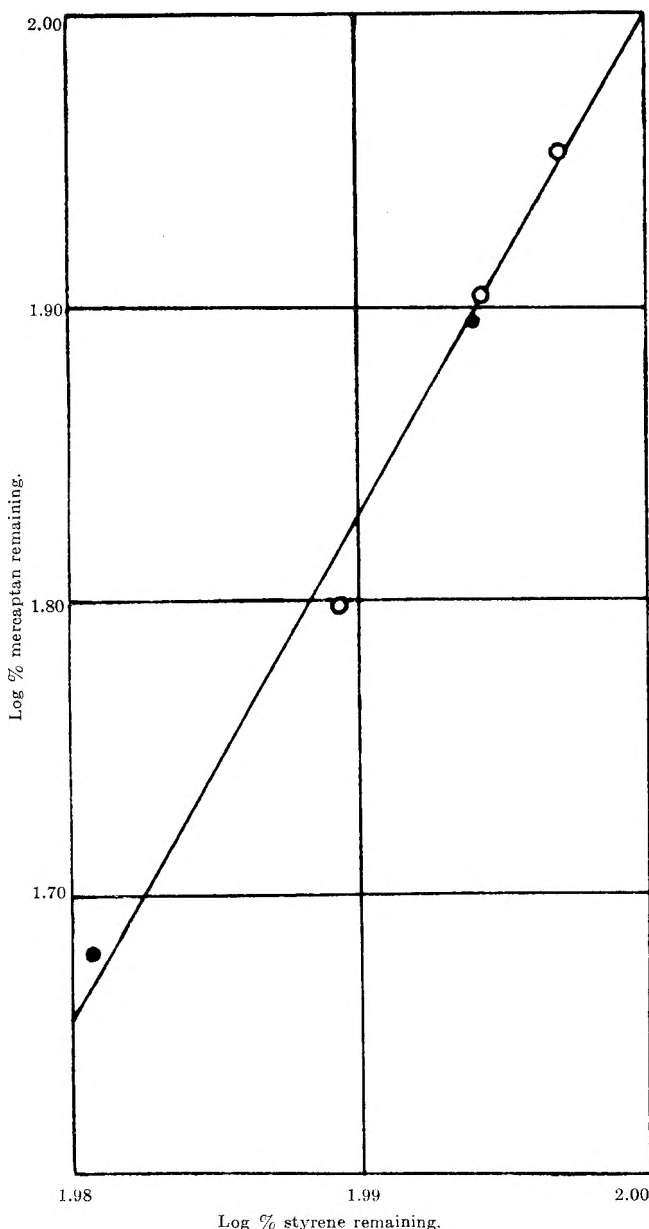
**Determination of Chain Transfer Constants.—**Fig.



Fig. 1.—Determination of polymerization chain transfer constant: moles mercaptan per mole styrene; $O = 9.4 \times 10^{-4}$; $\bullet = 31.1 \times 10^{-4}$.

1 shows the experimental linear variation of the logarithms of the per cents of styrene and ethanethiol remaining in five polymerizaition reactions. The slope of this line corresponds to the polymerization chain transfer constant.[5a] The value of the slope as determined by the method of least squares is 17.1 with a

standard deviation of 0.51, the error at the 5% probability level being about ±1.4.

It has been pointed out[3a] that the following simple expression involving telomerization transfer constants can be obtained directly from the rate expressions for the addition and displacement reactions (1 and 2),

$$d[B{-}M_n{-}A] / \sum_{n+1}^{\infty} d[B{-}M_i{-}A] = C_n[AB]/[M] \qquad (3)$$

where [AB], [M], and [B—$M_n$—A] = concentrations of transfer agent, monomer, and $n$-unit telomer, respectively. If the extent of reaction is kept low (10% or less), the left-hand side can be approximated by measured ratios of product concentrations, and values for $C_n$ can be determined.

The denominator of the left-hand side of equation 3 refers to the total concentrations of all telomers having more than $n$ monomer units. However, in the course of this work, it was soon found that the quantity of telomers having more than two units formed at low conversions was too small to obtain even a rough approximation of the denominator in the expression for the second chain transfer constant; in fact at a one to one mole ratio of transfer agent to monomer, almost no mixture of high telomers was obtained. It was therefore concluded that the chain transfer constant $C_2$ was relatively large.

This situation is better adapted to the use of equation 4, which is readily derived from 3, for determination of the chain transfer constants,

$$\frac{d[B{-}M_n{-}A]}{d[B{-}M_{n+1}{-}A]} = C_n[AB]/[M] + C_n/C_{n+1} \qquad (4)$$

(where the left side is the ratio of $n$-unit telomer to $n + 1$-unit telomer). Thus the ratio of concentrations of one-unit to two-unit telomer at low conversion should show a simple linear relationship to the ratio of reactants. The first chain transfer constant should correspond to the slope and the second chain transfer constant should equal this slope divided by the intercept. Sets of these ratios determined in ten experiments are listed in Table I and the plot (Fig. 2) shows a good approximation of the linear relationship.

TABLE I

DATA FOR CALCULATION OF TELOMER CHAIN
TRANSFER CONSTANTS

| Run no. | Mole ratio EtSH/styrene | Mole % AIBN (compared to EtSH) | Time, hr. | % Styrene consumed | Mole ratio, one-unit/ two-unit |
|---|---|---|---|---|---|
| 1 | 1.00 | 0.20 | 1.0 | 6.6 | 7.53 |
| 2 | 1.01 | .20 | 2.5 | 11.0 | 7.38 |
| 3[a] | 1.00 | .20 | 6.0 | 25.0 | 7.28 |
| 4 | 0.753 | .27 | 0.5 | | 5.48 |
| 5 | .502 | .40 | .5 | | 3.76 |
| 6 | .501 | .39 | 1.0 | | 3.77 |
| 7 | .310 | .00 | 1.0 | 3.0 | 2.48 |
| 8 | .200 | .98 | 1.5 | 2.6 | 1.75 |
| 9 | .196 | 1.11 | 3.0 | 5.4 | 1.58 |
| 10 | .068 | 0.00 | 1.0 | | 0.88 |

[a] Not plotted in Fig. 2 or used in direct calculation of the slope.

The slope, as determined by the least squares method, is 7.15 and the intercept 0.24, corresponding to values of 7.15 for $C_1$ and 30 for $C_2$. The standard deviations are 0.12 for slope and 0.074 for the intercept, corre-

sponding to limits of error of about ±0.3 for $C_1$ and ±10 for $C_2$ at the 5% probability level. However, examination of the results for runs number 1–3, 8, and 9 in Table I shows that a small but significant constant error is introduced by the change in mercaptan to monomer ratio as the reaction proceeds. Correction for this would raise the line slightly especially at the lower end. The resulting change in slope is small, but the relative change in intercept is substantial.[9]

## Discussion

It is of interest to note that Sivertz[10] in reporting a study of the kinetics of addition of butanethiol to styrene estimated a value for the average $k_p$ of 230 at thiol concentrations at which the propagation was assumed to be chiefly due to the one-unit radical. Combination of this with his value of $1.24 \times 10^3$ for $K_d$ indicates a value of about 5.4 for $C_1$, which is comparable to the value reported above for the styrene–ethanethiol system.

The increase by a factor of 2.4 in the styrene ethanethiol transfer constant going from $C_1$ to $C_\infty$ is substantially less than has been reported for the haloalkanes.[3] Since the electronegativity of sulfur on the Pauling scale is essentially the same as carbon, it seems unlikely that any polar effect would account for even this difference. Models indicate, however, that there

(9) Extrapolation of results from runs 1–3, 8 and 9 to zero per cent styrene consumed and substitution of the resulting ratios in equation 4 would lead to values of 7.03 for $C_1$ and 14 for $C_2$.
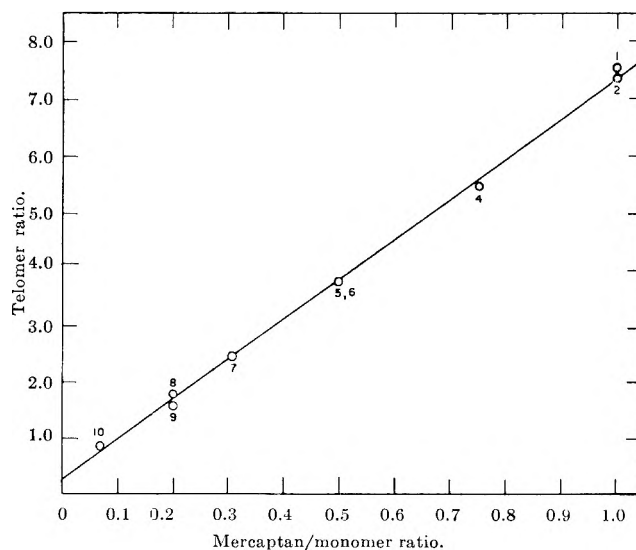(10) C. Sivertz, J. Phys. Chem., **63**, 34 (1959).



Fig. 2.—Relationship between one-unit to two-unit telomer mole ratio and ethanethiol to styrene mole ratio.

should be appreciably less interference with the formation of the transition state for addition of monomer units to the one-unit radical as compared to radicals possessing two or more styrene units. Results indicate that the value for $C_2$ is certainly substantially higher than $C_1$ and may possibly be even higher than $C_\infty$.

Information about the chain transfer constants $C_3$ to $C_5$ would be especially interesting for comparison with the bromotrichloromethane–styrene system[3c]; however, a different approach will probably be required because of the difficulty in isolating higher telomers.

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# Photodimers of 4'-Substituted 2-Styrylpyridines[1]

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Photodimers of 2-styrylpyridine and 5-ethyl-2-styrylpyridine substituted with $CH_3O$, $CH_3$, $NO_2$, and $(CH_3)_2N$ in the 4'-positions have been prepared. Irradiation of the free bases or the methiodide salts in solution gave difficultly separable mixtures of dimers, *cis* isomers, and *trans* isomers. Irradiation of the methiodide salts in the solid state yielded the dimeric salts in the cases of 2-styrylpyridine, 5-ethyl-2-styrylpyridine, and to a lesser degree with 4'-methyl-2-styrylpyridine. All other methiodide salts failed to dimerize when irradiated as solids. Solid-state dimerization of the methosulfate derivatives except the two 4'-dimethylamino-substituted derivatives was achieved. The dimeric methosulfates were then converted by anion exchange to the corresponding methiodide salts. Photodimerizations of the substituted styrylpyridine hydrochlorides in aqueous solution were successful in all cases except those of the 4'-nitro-substituted derivatives. Irradiation of suspensions of the hydrochloride salts in heptane gave similar results.

In preceding papers[2,3] the preparation of two photodimers of *trans*-2-styrylpyridine (Ia) was described and their relationship to the *trans–cis* photoisomerization of *trans*-2-styrylpyridine (Ia) was demonstrated. Solid-state irradiation of the methiodide (Ic) and the hydrochloride (Ie) salts to *trans*-2-styrylpyridine (Ia) produced dimers with the same configurations, as indicated by physical data. Solution irradiation of Ia produced only a mixture of *cis* and *trans* isomers. On the other hand, solution irradiation of the methiodide (Ic) or the hydrochloride (Ie) gave mixtures of

*cis* and *trans* isomers as well as dimers. Dimer Id, obtained by irradiation of 2-styrylpyridine hydrochloride (Ie), in solution or in the solid state, followed by isolation and quaternization of the dimeric free base (Ib), was identical with dimer Id, obtained by solid-state irradiation of *trans*-2-styrylpyridine methiodide (Ic). In order to extend the dimerization study to substituted derivatives of *trans*-2-styrylpyridine and *trans*-5-ethyl-2-styrylpyridine, a group of derivatives with $CH_3O$, $CH_3$, $NO_2$, and $(CH_3)_2N$ in the 4'-positions were prepared.[4]

In the present work, it was found that 5-ethyl-2-styrylpyridine methiodide (VIc) photodimerized quan-

(1) Contribution no. 2331 from the Kodak Research Laboratories.
(2) J. L. R. Williams, J. Org. Chem., **25**, 1839 (1960).
(3) J. L. R. Williams, S. K. Webster, and J. A. VanAllan, *ibid.*, **26**, 4893 (1961).

(4) J. L. R. Williams, et al., J. Org. Chem., in press.

TABLE I

DIMERS OF SUBSTITUTED 2-STYRYLPYRIDINES

| Code | Empirical formula | Analysis Found (calcd.) | | | M.p., °C. | Mol. wt., found (Calcd.) | $\lambda_{max}$, m$\mu$ | $\epsilon \times 10^{-3}$ |
| | | C | H | N | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ib | $C_{26}H_{22}N_2$ | | | | 190–191 | | 264 | 13.5 |
| IIb | $C_{28}H_{26}O_2N_2$ | 79.1 (79.6) | 5.9 (6.2) | 6.7 (6.2) | 164–165 | 409 (422.5) | 264 | 10.5 |
| IIIb | $C_{28}H_{26}N_2$ | 85.7 (86.1) | 6.8 (6.7) | 7.4 (7.2) | 184–185 | 401 (390.5) | 264 | 9.8 |
| IVb | $C_{26}H_{20}N_4O_4$ | 68.7 (69.0) | 4.5 (4.4) | 12.1 (12.4) | 161–162 | a | 271 | 34.0 |
| Vb | $C_{30}H_{32}N_4$ | 80.0 (80.3) | 7.6 (7.2) | 12.0 (12.5) | 248–250 | 505 (448.6) | 260 | 47.0 |
| VIb | $C_{30}H_{30}N_2$ | 85.9 (86.2) | 7.3 (7.2) | 6.5 (6.6) | 143 | 430 (418) | 270 | 10.0 |
| VIIb | $C_{32}H_{34}N_2O_2$ | 80.2 (80.3) | 6.9 (7.2) | 6.4 (6.7) | 120 | 536 (479) | 270 | 10.8 |
| VIIIb | $C_{32}H_{34}N_2$ | 86.1 (85.7) | 7.6 (7.6) | 6.3 (6.1) | 115 | 431 (446) | 269 | 15.4 |
| IXb | $C_{30}H_{28}N_4O_4$ | 70.5 (70.9) | 5.7 (5.5) | 10.9 (11.0) | 180 | b | 273 | 28.6 |
| Xb | $C_{34}H_{40}N_4$ | 81.3 (81.0) | 7.9 (7.9) | 10.8 (11.1) | 158–159 | 504 (504.8) | 261 | 36.4 |

$^a$ Prepared by direct nitration of Ib.    $^b$ Prepared by direct nitration of VIb.

TABLE II

DIMERS OF SUBSTITUTED 2-STYRYLPYRIDINE METHIODIDES

| Substituents | | Code | Empirical formula | Analysis Found (calcd.) | | | | M.p., °C. | $\lambda_{max}$, m$\mu$ | $\epsilon \times 10^{-3}$ |
| 5-Position | 4'-Position | | | C | H | N | I | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| H | H | Id | $C_{28}H_{28}N_2I_2$ | | | | | 310 | 271 | 19.3 |
| H | CH$_3$O | IId | $C_{30}H_{32}N_2I_2O_2$ | 51.1 (51.0) | 4.8 (4.6) | 4.6 (4.6) | 36.0 (35.9) | 251–252 | 270 | 17.0 |
| H | CH$_3$ | IIId | $C_{30}H_{32}N_2$ | 53.0 (53.5) | 4.8 (4.8) | 4.3 (4.2) | 37.5 (37.6) | 245 | 270 | 13.1 |
| H | NO$_2$ | IVd | $C_{28}H_{26}N_4I_2O_4$ | 46.0 (45.7) | 3.5 (3.5) | 8.0 (7.6) | a | 265 | 271 | 40.1 |
| H | (CH$_3$)$_2$N | Vd | c | | | | | | | |
| C$_2$H$_5$ | H | VId | $C_{32}H_{36}N_2I_2$ | 54.7 | 5.2 | 4.0 | 36.3 | | | |
| C$_2$H$_5$ | CH$_3$O | VIId | $C_{34}H_{40}N_2I_2O_2$ | 53.7 (53.4) | 5.1 (5.3) | 3.6 (3.7) | 33.1 (33.2) | 243–244 | 277 | 17.6 |
| C$_2$H$_5$ | CH$_3$ | VIIId | $C_{34}H_{40}N_2I_2$ | 55.6 (56.0) | 5.7 (5.6) | 3.8 (3.8) | 34.2 (34.6) | 256–257 | 275 | 19.8 |
| C$_2$H$_5$ | NO$_2$ | IXd | $C_{32}H_{34}N_4I_2O_4$ | 48.5 (48.3) | 4.3 (4.0) | 7.1 (7.3) | b | 245–246 | 277 | 36.1 |
| C$_2$H$_5$ | (CH$_3$)$_2$N | Xd | c | | | | | | | |

$^a$ Prepared by nitration and quaternization of Ib.    $^b$ Prepared by nitration and quaternization of VIb.    $^c$ Quaternization of Vb and Xb led to doubly quaternized salts, not Vd and Xd.

titatively when irradiated in the solid state. Attempts to photodimerize 4'-methyl-2-styrylpyridine methiodide (IIIc) in the solid state by the benzene suspension method were only partly successful since the dimerizations were shown by ultraviolet studies to be only 90% complete. Similar treatment of 4'-methoxy-2-styrylpyridine methiodide (IIc), 4'-nitro-2-styrylpyridine methiodide (IVc), and 4'-dimethylamino-2-styrylpyridine methiodide (Vc) failed to produce dimers. The analogous 4'-substituted compounds in the 5-ethyl series, VIIc, VIIIc, and Xc, behaved similarly.

When aqueous solutions of the *trans* isomers of Ic to Xc were irradiated, mixtures of dimers, residual *trans* isomers and *cis* isomers resulted. The ratios of the products varied with substitution, and in all cases tedious fractional crystallization of the irradiation mixtures was required to yield the dimers. A more general and facile method for dimer preparation was realized when $5 \times 10^{-2}$ M aqueous solutions of the various 2-styrylpyridine hydrochlorides (Ie–Xe) were

irradiated as previously reported[3] for Ie. In preliminary experiments, 500-watt, water-cooled, medium-pressure, immersion-type Hanovia lamps were employed. However, it was found more convenient to expose the stirred aqueous dimerization solutions in open dishes to the light from General Electric GRS lamps. The dimerizations in aqueous solution of 4'-nitro-2-styrylpyridine hydrochloride (IVe) and 4'-nitro-5-ethyl-2-styrylpyridine hydrochloride (IXe) were unsuccessful. Under similar conditions, 4'-dimethylamino-2-styrylpyridine dihydrochloride (Ve) and 4'-dimethylamino-5-ethyl-2-styrylpyridine dihydrochloride (Xe) were converted in low yield to the corresponding dimers Vf and Xf. In all other cases (Ie, IIe, IIIe, VIe, VIIe, VIIIe), the desired dimers were obtained and converted to the free bases, the physical constants of which are listed in Table I. The corresponding methiodides listed in Table II were prepared by quaternization of the dimeric bases.

Since the dimerizations of the nitro derivatives (IVc

and IVe, and IXc and IXe) were unsuccessful, direct nitration of Ia and IXa was carried out in order to obtain the 4'-substituted nitro dimers, IVb and IXb, which were then converted through the methosulfates to the dimer methiodides, IVd and IXd.

The differences in the degree of photodimerization of the various substituted methiodides, Ib–Xb, in the solid state are considered to be related to the crystal parameters which dictate the distance between the double bonds of different adjacent molecules in the crystal lattices. Topochemical control by lattice parameters during photodimerization of a group of substituted cinnamic acids has been described by Schmidt.[5] It thus seemed reasonable that substitution and the nature of the anion might control the crystal parameters and therefore the ease of dimerization. Accordingly, a group of 1-alkyl-2-styrylpyridinium salts was prepared in each of which the iodide anion was replaced by the methosulfate in the hope that modification of the lattice parameters might facilitate dimerization. By this method, the solid-state benzene suspension irradiation of 4'-methyl-2-styrylpyridine methosulfate (IIIe), 4'-methoxy-2-styrylpyridine methosulfate (IIe), 4'-nitro-2-styrylpyridine methosulfate (IVe), 4'-ethyl-4'-methoxy-2-styrylpyridine methosulfate (VIIe), and 5-ethyl-4'-nitro-2-styrylpyridine methosulfate (IXe) provided the corresponding methosulfate dimers (IIIf, IIf, IVf, VIIf, and IXf) in quantitative yields. The analogous, doubly quaternized dimethosulfate salts of 4'-dimethylamino-2-styrylpyridine (Ve) and 5'-ethyl-4-dimethylamino-2-styrylpyridine (Xe) failed to yield the corresponding photodimers (Vf and Xf). The methosulfate photodimers, IIIf, IIf, IVf, VIIf, and IXf, were converted by anion exchange in water solution to the corresponding methiodides, all of which were identical in physical properties with those prepared by the other methods mentioned. Compounds IVd and IXd prepared by this route were identical with samples prepared by nitration of the dimers of Ia and VIa.

The 4'-dimethylamino-substituted dimer (Vb) was prepared by solid-state irradiation of the suspension

(5) G. M. J. Schmidt, at the XVIIIth International Congress of Pure and Applied Chemistry, Montreal, August, 1961.

| Dimer | In aqueous solution[a] | | In solid state[a] | |
|---|---|---|---|---|
| | Yield, % | Time, min.[c] | Yield, % | Time, hr.[c] |
| Ib | | | 67 | 7 |
| IIb | 81 | 44 | 23 | 6 |
| IIIb | 38 | 48 | 65 | 11 |
| IVb | 0 | 44 | 0 | 16 |
| Vb | 10 | 55 | 67 | 7 |
| VIb | 48 | 44 | 47 | 8 |
| VIIb | 38 | 46 | 47 | 11 |
| VIIIb | 24 | 72 | 40 | 7 |
| IXb | 0 | 44 | 0 | 16 |
| Xb | 26 | 237 | [b] | 7 |

[a] The yield reported is based on isolated dimer. Yields of *cis* isomers produced simultaneously were not determined. [b] Product failed to crystallize. [c] The times listed indicate the period to reach approximate photostationary condition for the equilibrium, *trans* isomer : *cis* isomer : dimer.

which resulted when a benzene solution of Va was saturated with dry hydrogen chloride. The dimeric free base was then produced by neutralization of the dimer hydrochloride (Vg) with aqueous sodium carbonate. This method failed to give the corresponding dimer from 5-ethyl-4'-dimethylamino-2-styrylpyridine dihydrochloride since a noncrystallizable oil resulted when the irradiated hydrochloride was treated with aqueous sodium carbonate. The method was successful when Ic, IIc, IIIc, VIc, VIIc, and VIIIc were irradiated in the solid state as suspensions in heptane. Compounds IVc and IXc did not dimerize under these conditions. The yields and irradiation times for the preparation of the dimeric bases by irradiation of suspensions of the various hydrochlorides are listed in Table III.

## Experimental

The methosulfate salts were prepared by quaternization of the corresponding styrylpyridines with dimethyl sulfate. The salts were recrystallized from acetone or acetone–methanol mixtures and submitted for analyses as indicated in Table IV.

The preparations of the *trans*-2-styrylpyridines used in this work were described previously.[4]

All ultraviolet spectra were determined in methanol solution ($5 \times 10^{-5} M$), using a 1-cm. quartz cell in a Cary Model 14 instrument.

TABLE IV

2-STYRYLPYRIDINE METHOSULFATES

| 5-Position | 4'-Position | Code | Empirical formula | Analysis Found (calcd.) | | | | M.p., °C. |
|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S | |
| H | CH₃O | IIg | $C_{16}H_{19}NO_5S$ | 56.5 (57.0) | 5.7 (5.7) | 3.9 (4.2) | 9.2 (9.5) | 158 |
| H | CH₃ | IIIg | $C_{16}H_{19}NO_4S$ | 59.5 (59.8) | 5.8 (5.9) | 4.2 (4.4) | 10.1 (10.0) | 209–211 |
| H | NO₂ | IVg | $C_{15}H_{16}N_2O_6S$ | 51.2 (51.2) | 4.5 (4.6) | 7.7 (8.0) | 9.1 (9.1) | 172 |
| C₂H₆ | CH₃O | VIIg | $C_{18}H_{23}NO_5S$ | 59.3 (59.2) | 6.5 (6.3) | 3.9 (3.8) | 8.7 (8.8) | 134 |
| C₂H₅ | NO₂ | IXg | $C_{17}H_{20}N_2O_6S$ | 53.7 (53.7) | 5.3 (5.3) | 7.0 (7.4) | 8.8 (8.4) | 175 |
| H | H | Ig | $C_{21}H_{21}NO_3S$ | 68.5 (68.8) | 5.9 (5.8) | 3.6 (3.8) | 8.4 (8.5) | 189–190 |
| C₂H₅ | H | VIg | $C_{17}H_{21}NO_4S$ | 61.0 (60.9) | 6.4 (6.3) | 4.0 (4.2) | 9.3 (9.6) | 109–111 |
| C₂H₅ | CH₃ | VIIIg | $C_{18}H_{23}NO_4S \cdot H_2O$ | 59.1 (58.9) | 6.7 (6.9) | 3.8 (3.8) | 9.4 (8.7) | [a] |

[a] An oily solid was obtained and was irradiated as such in suspension.

**Irradiations. A. Solid State.**—Solid-state photodimerizations of the styrylpyridine methiodides and methosulfates were conducted as benzene suspensions according to the previous description.[3]

Solid-state photodimerizations of the styrylpyridine hydrochlorides were conducted in a manner similar to that described earlier,[3] except that the suspension medium used was heptane since certain of the 5-ethyl-2-styrylpyridinium salts show slight solubility in benzene and irradiations of the salts in solution generally promoted photoisomerization.

**B. Solution.** In previous work a Hanovia medium-pressure lamp was used. A more convenient method is as follows: In a typical irradiation, a solution of 10 g. (0.55 mole) of *trans*-2-styrylpyridine in a mixture of 10 ml. of concentrated hydrochloric acid and 1 l. of water was placed in a 2-l. evaporating dish. The solution was stirred by means of a Teflon-covered stirrer bar magnetically driven through the bottom of the dish. A GRS sunlamp was placed 12 in. above the surface of the solution. Periodically, aliquots were withdrawn and diluted with water to give $2.5 \times 10^{-5}$ $M$ solutions for ultraviolet examination. Prior to irradiation, the solution had the following characteristics: $\lambda_{max}$ 328 m$\mu$, $\epsilon$ 25,300. After 21 hr. of irradiation, the characteristics of the solution were: $\lambda_{max}$ 264 m$\mu$, $\epsilon$ 8,800, and $\lambda_{max}$ 321 m$\mu$, $\epsilon$ 4,640. The irradiation product was isolated in the manner described.[3]

**Nitration of the Dimer of 2-Styrylpyridine (Ib): IVb.**—A solution of 7.2 g. of the dimer of Ia (Ib) in 50 ml. of concentrated sulfuric acid was cooled to 10° in an ice bath and to this stirred solution was slowly added 2.6 ml. of concentrated nitric acid.

The mixture was allowed to warm up to room temperature, poured into 250 ml. of ice-water, and made basic with ammonium hydroxide. The precipitated solid was collected, washed with water, and recrystallized from ethanol to yield 6.5 g. of product (IVb), m.p. 161–162°.

*Anal.* Calcd. for $C_{26}H_{20}N_4O_4$: C, 69.0; H, 4.4; N, 12.4. Found: C, 68.7; H, 4.5; N, 12.1.

**Nitration of the Dimer of 5-Ethyl-2-styrylpyridine (Vb): IXb.**—By the procedure described for IVb there was obtained from 8.4 g. of the dimer (Vb), 6 g. of the dinitro derivative (IXb), melting at 180°.

*Anal.* Calcd. for $C_{30}H_{28}N_4O_4$: C, 70.9; H, 5.5; N, 11.0. Found: C, 70.5; H, 5.7; N, 10.9.

**Quaternization of IVb: Di(1-methyl-2-pyridinium)di(4-nitrophenyl)cyclobutane Iodide (IVd).**—A mixture of 1 g. of IVb, obtained by nitration of the dimer of Ia (Ib), and 5 ml. of dimethyl sulfate was heated on a steam bath for 30 min. The solid that separated from the solution was collected, washed with ether, dissolved in 15 ml. of warm water, and 1 g. of potassium iodide was added to the solution. The solid that separated was collected and dried to yield 1.1 g. of the quaternary salt (IVd), m.p. 265°.

*Anal.* Calcd. for $C_{28}H_{26}N_4O_4I_2$: C, 45.7; H, 3.5; N, 7.6. Found: C, 46.0; H, 3.5; N, 8.0.

**Quaternization of IXb: Di(1-methyl-5-ethyl-2-pyridinium)-di(4-nitrophenyl)cyclobutane (IXd).**—The preparation of IXd was carried out by the procedure used for the quaternization of IVb. The dimer IXd melted at 245–246°.

*Anal.* Calcd. for $C_{32}H_{34}N_4O_4I_2$: C, 48.5; H, 4.3; N, 7.1. Found: C, 48.3; H, 4.0; N, 7.3.

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# The Chemistry of Pyridine. I. Nucleophilic Substitution of 1-Alkoxypyridinium Salts by Mercaptide Ions

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The reaction of 1-alkoxypyridinium salts with propyl- and octylmercaptide ions is described. In each instance, the product consisted of pyridine and a mixture of 3- and 4-alkylmercaptopyridines, predominantly the 3-isomer. These reactions are discussed in the light of existing knowledge of nucleophilic attack on pyridine N-oxides. Unequivocal syntheses of the corresponding 2-, 3-, and 4-alkylmercaptopyridines as reference compounds is reported.

Current interest is centered on the use of pyridine N-oxide and 1-alkoxypyridinium salts as intermediates for the synthesis of substituted pyridines.[2] Nucleophilic substitution in the 1-alkoxypyridinium cation, I, has received considerable attention recently. It was shown that cyanide ion (X = CN) reacted with these salts to form 2- and 4-pyridinecarbonitriles[3] (equation 1) and no substitution was observed at the 3-position of the pyridine ring. The reaction of Grignard reagents with 1-alkoxypyridinium salts was reported recently to yield only 2-substituted pyridines and apparently substitution did not occur at the 3- or 4-position of the ring.[4] These authors offer a mechanism which satisfactorily accounts for the formation of the 2- and 4-substituted pyridines (equation 1).

In our studies, we treated 1-alkoxypyridinium salts with mercaptide and thiophenoxide ions with the aim of introducing the alkyl- and arylmercapto group into the pyridine ring. Initially, this reaction was explored with



$$(1)$$

$$(2)$$
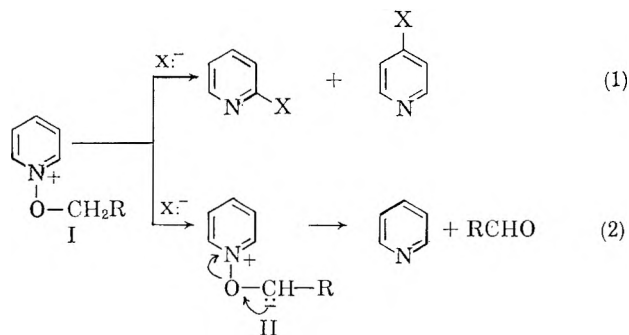
the anions of propyl- and octylmercaptide ions and these were found to effect substitution in the pyridine ring to yield the corresponding alkylmercaptopyridines. The reaction of 1-ethoxypyridinium ethyl sulfate with sodium *n*-propylmercaptide was studied in some detail and is presented first. When this reaction was conducted in a mixture of 1-propanethiol and ethanol (10:1) two major fractions were obtained. The first one was identified as pyridine (70%). This product can arise from nucleophilic attack at the $\alpha$-carbon of the 1-alkoxy side chain *via* the intermediate, II, which decomposes to pyridine and an aldehyde (equation 2).[5]

(1) Taken from the Ph.D. thesis of Libero A. Gardella, University of Illinois at the Medical Center, Chicago 12, Ill., June, 1962.

(2) For recent reviews on this topic, see (a) D. V. Ioffe and L. S. Eiros, *Russ. Chem. Rev. (Eng. Transl.)*, **30**, 569 (1961); (b) K. Thomas and D. Jerchel, in W. Foerst's "Neuere Methoden der Präparativen Organischen Chemie," Band III, Verlag Chemie, GmbH, Weinheim/Bergstr., 1961, p. 61; (c) A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1960, pp. 61, 102; (d) E. N. Shaw, "Pyridine and Its Derivatives," Part Two," E. Klingsberg, ed., Interscience Publishers, Inc., New York, N. Y., 1961, Chap. IV, pp. 97–153.

(3) (a) W. E. Feeley and E. M. Beavers, *J. Am. Chem. Soc.*, **31**, 4004 (1959); (b) H. Tani, *Chem. Pharm. Bull., Japan*, **7**, 930 (1959); *J. Pharm. Soc., Japan*, **81**, 141 (1961), and papers quoted therein.

(4) O. Cervinka, *Collection Czech. Chem. Commun.*, **27**, 567 (1962).

The higher boiling fraction was a colorless oil with correct analysis for a propylmercaptopyridine (30% yield) but proved to be a mixture of isomers which could not be separated by distillation. However, by means of chromatography on alumina, this mixture was resolved into 3- and 4-propylmercaptopyridines, with the 3-isomer being the dominant constituent (6:1). The 2-isomer could not be detected in the mixture although it was one of the expected products (equation 1). Whereas the formation of the 4-pyridyl sulfide can be explained by the mechanism proposed for the nucleophilic attack of cyanide on I, it is difficult at present to rationalize the formation of the 3-isomer. Although β-substitution has been observed when pyridine N-oxides were treated with a variety of reagents, the reactions are not comparable.[6] Further experiments are planned to gain insight into the mechanism of the reaction of I with mercaptide ion.

A number of attempts were made to improve the total yield or change the nature of the products in the reaction of I with mercaptide ion. Since the reactants are ionic species, the nature of the solvent was thought to play an important role. This aspect was investigated with varying results. When 1-ethoxypyridinium ethyl sulfate was added to sodium n-propylmercaptide in 1-propanethiol, a heterogeneous mixture resulted. The mixture of propylmercaptopyridines did not change materially whether the reaction was heated at the reflux for 0.5 or 24 hours (22 and 27% yield, respectively). Although the yield did not change materially, the product proved to be a cleaner one when to this reaction mixture some ethanol (1/10 of the volume of thiol) was added. However, as the amount of ethanol to thiol was increased (1:1) the yield of sulfides dropped to 9% while the reaction in ethanol furnished barely 1% yield.

We also turned our attention to explore other solvent media for this reaction. The reaction between 1-ethoxypyridinium ethyl sulfate and two moles of sodium n-propylmercaptide in either tetrahydrofuran (1 hour of reflux) or toluene (23 hours of reflux), yielded in each case only 8% of the mixture of sulfides and pyridine was isolated in 70 and 60%, respectively. The yield of the sulfide mixture was only 5% when the reaction was conducted in a non-acidic yet polar medium such as N,N-dimethylformamide (100°, 0.5 hours) while in a

basic medium such as triethylamine (100°, 5 hours) the sulfides were formed in 18% yield. Since two possible competing reactions can occur between the 1-ethoxypyridinium cation and the mercaptide ion (equations 1 and 2, attack on the ring or alkoxy side chain, respectively) it was sought to minimize or eliminate the latter by increasing the size of the N-alkoxy side chain.[3b] Thus, the reaction of 1-butoxypyridinium benzenesulfonate with sodium n-propylmercaptide in propanethiol containing some ethanol (4:1) at 100° for two hours yielded 23% of the sulfides and only 1.5% of pyridine. Although the formation of pyridine by nucleophilic attack on the side chain was inhibited in the last reaction, the substitution by mercaptide ion was not greatly enhanced.

The reaction of 1-ethoxypyridinium ethyl sulfate with sodium n-octylmercaptide in a mixture of 1-octanethiol and ethanol (10:1 by volume) was also studied. This reaction yielded a mixture of 3- and 4-octylmercaptopyridines (6.7%) and pyridine (12.7%) as identified by means of infrared spectroscopy. Interestingly enough, the reaction of 1-ethoxypyridinium ethyl sulfate with sodium thiophenoxide in thiophenol did not furnish a detectable amount of phenylmercaptopyridines. The only product of the reaction which could be identified was pyridine (25%). No explanation is offered at present why the thiophenoxide ion failed to effect nuclear substitution.

## Experimental[7]

**Synthesis of Reference Compounds.**—2- and 4-Alkylmercaptopyridines were prepared by the direct displacement of the corresponding halo group by alkylmercaptide ion. The solvent of choice was N,N-dimethylformamide and the procedure of Profft[8] was modified by substituting sodium hydride for potassium hydroxide as the base.

**2-Propylmercaptopyridine.**—1-Propanethiol[9] (7.6 g.; 0.1 mole) was added dropwise with stirring, to a suspension of sodium hydride (2.4 g.; 0.1 mole) in N,N-dimethylformamide (40 ml.). After the evolution of hydrogen had ceased, 2-chloropyridine[10] (11.35 g., 0.1 mole) was added and the mixture refluxed in an oil bath for 4.0 hr. The reaction mixture was cooled, acidified with 10% hydrochloric acid, and the solvents were removed by distillation *in vacuo*. Water (200 ml.) was added to the residue and the solution extracted with a 1:1 ether–benzene solution (four 50-ml. portions). The aqueous layer was made basic with a 20% sodium hydroxide solution and extracted with methylene chloride (eight 50-ml. portions). Distillation of the methylene chloride extract furnished 2-propylmercaptopyridine (3.1 g.; 20%), b.p. 108–110° (18 mm.). This sulfide had previously been made from the reaction of 2-mercaptopyridine and 1-bromopropane in 62% yield and its b.p. was recorded at 53–55° at 1 mm.[11]

The picrate was crystallized from ethanol, m.p. 122–123° (lit.,[11] m.p. 124–125°).

**4-Propylmercaptopyridine.**—This sulfide was prepared in the same manner as above from 4-chloropyridine (11.35 g.; 0.1 mole) and 1-propanethiol (7.6 g.; 0.1 mole) with the modification that the mixture was heated on a steam bath for 4.0 hr. The sulfide boiled between 130–133° at (16 mm.) and weighed 12.2 g. (80%), $n^{25}D$ 1.5632.

*Anal.* Calcd. for $C_9H_{11}NS$: C, 62.70; H, 7.24; N, 9.14. Found: C, 62.65; H, 7.05; N, 9.23.

(5) This reaction is quite a general one and for examples of it see, (a) W. E. Feeley, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957), and references quoted therein; (b) A. R. Katritzsky, *J. Chem. Soc.*, 2408 (1956); (c) J. M. Tien, I. M. Hunsberger, and A. M. Javallans, Abstracts of the 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959, p. 76-O; (d) C. H. DePuy and E. F. Zaweski, *J. Am. Chem. Soc.*, **81**, 4920 (1959). This reaction proceeds readily at 0° and has been utilized in the synthesis of aromatic aldehydes,[5a] glyoxylic esters,[5c] and cyclopentene-3,5-dione.[5d] In these instances, the nucleophile, X, was the hydroxide ion.

(6) To explain β-substitution, a mechanism has been proposed by (a) E. Ochiai and M. Ikehara, *Pharm. Bull., Japan*, **3**, 454 (1955); (b) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1957). For example, the reaction of isoquinoline 2-oxide with acetic anhydride gives (after hydrolysis) mainly 1-isoquinolinol (53%) and a smaller quantity of 4-isoquinolinol (8.9%),[6b] while 3-chloroisoquinoline 2-oxide with the same reagent produces mainly 3-chloro-4-isoquinolinol (61%) with less than 1% of the expected 3-chloro-1-isoquinolinol [M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, **80**, 3443 (1958)]. Furthermore, the reaction of p-toluenesulfonyl chloride with pyridine N-oxide yields (among other products) mainly 3-p-toluenesulfonyloxypyridines [M. Marakami and E. Matsumura, *Chem. Abstr.*, **45**, 4698 (1951); **47**, 1745 (1953); E. Matsumura, *ibid.*, **48**, 6442 (1954); H. J. den Hertog, D. J. Buurman, and P. A. deVilliers, *Rec. trav. chim.*, **80**, 325 (1961)]. Exclusive β-substitution was observed when isoquinoline 2-oxide was treated with p-toluenesulfonyl chloride to give 4-p-toluenesulfonyloxyisoquinoline only.[6a]

(7) All melting points and boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and Dr. Kurt Eder, Geneva, Switzerland. Some of the nitrogen analyses were performed using a Coleman Nitrogen Analyzer, Model 29.

(8) E. Profft and W. Rolle, *J. prakt. Chem.*, (4) **11**, 22 (1960).

(9) We gratefully acknowledge the generous gift of this chemical from (a) Pennsalt Chemicals Corp., Philadelphia, Pa.; (b) Phillips Petroleum Co., Bartlesville, Okla.

(10) Purchased from Aldrich Chemical Company, Milwaukee, Wis.

(11) D. S. Tarbell and M. A. McCall, *J. Am. Chem. Soc.*, **74**, 48 (1952).

*p*-Toluenesulfonate crystallized from acetone, m.p. 110–112°.

*Anal.* Calcd. for $C_{15}H_{19}NO_3S_2$: C, 55.36; H, 5.88; N, 4.30; Found: C, 55.33; H, 5.82; N, 4.27.

The picrate was recrystallized from ethanol, m.p. 134–136°. This salt was found to be sensitive to light and turned dark in it.

*Anal.* Calcd. for $C_{14}H_{14}N_4O_7S$: N, 14.65. Found: N, 14.62.

**2-Octylmercaptopyridine.**—This sulfide was prepared in the same manner as described for 2-propylmercaptopyridine from 2-chloropyridine (5.78 g.; 0.05 mole) and 1-octanethiol[9a] (7.30 g.; 0.05 mole). The product distilled at 113–115° (2.0 mm.) and weighed 3.0 g. (27%).

*Anal.* Calcd. for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 70.05; H, 9.25; N, 6.14.

The picrate was crystallized from ethanol, m.p. 77–78°.

*Anal.* Calcd. for $C_{19}H_{24}N_4O_7S$: N, 12.38. Found: N, 12.25.

**4-Octylmercaptopyridine.**—This sulfide was synthesized as described for the 4-propyl analog from 4-chloropyridine (2.84 g.; 0.025 mole) and 1-octanethiol (3.65 g.; 0.025 mole). The fraction which was collected weighed 3.2 g. (57.5%) and boiled at 127–129° (2.0 mm.).

*Anal.* Calcd. for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 69.91; H, 9.33; N, 6.43.

The picrate (from ethanol) melted between 110–113°.

*Anal.* Calcd. for $C_{19}H_{24}N_4O_7S$: N, 12.38. Found: N, 12.50.

**3-Propylmercaptopyridine from 3-Aminopyridine.**—The synthesis of this sulfide was adapted from that outlined by Albert[12] for his synthesis of 3-benzoylthioquinoline from 3-aminoquinoline.

Sodium nitrite (8.5 g.; 0.1 mole) in water (20 ml.) was added dropwise, with stirring, to a solution of 3-aminopyridine (9.4 g.; 0.1 mole) in concentrated hydrochloric acid (21 ml.) and ice (21 g.), the temperature being kept between −5 and 0°. The solution of the diazonium salt was added slowly to a solution of potassium ethyl xanthate[13] (22 g.; 0.14 mole) in water (25 ml.) at 40–50°. When the addition was completed, the mixture was heated to 80°, cooled and extracted with ether (five 100-ml. portions). Ether was removed *in vacuo* and no attempt was made to isolate ethyl 3-pyridyl xanthate, but rather the residue was hydrolyzed immediately by boiling it with potassium hydroxide (15 g.; 0.25 mole) in 95% ethanol (125 ml.) for 23 hr. The intermediate thiol was not isolated but alkylated in the basic medium by the addition of 1-iodopropane (51 g.; 0.3 mole). Heating at reflux was continued for an additional 4.0 hr. and the reaction mixture then acidified with concentrated hydrochloric acid. Solvents were removed *in vacuo*, the residue was dissolved in water (500 ml.) and extracted with a 1:1 ether-benzene solution (four 100-ml. portions). The aqueous layer was made basic with a 20% sodium hydroxide solution, extracted with methylene chloride (five 200-ml. portions) and this extract was distilled. The sulfide (4.25 g.; 28% based on 3-aminopyridine), boiled at 124–128° (16 mm.), $n^{26}$D 1.5548.

*Anal.* Calcd. for $C_8H_{11}NS$: C, 62.70; H, 7.24; N, 9.14. Found: C, 62.80; H, 7.13; N, 8.99.

The picrate melted between 113–115° (from ethanol).

*Anal.* Calcd. for $C_{14}H_{14}N_4O_7S$: N, 14.65. Found: N, 14.40.

An attempt to prepare this sulfide from 3-chloropyridine proved abortive. By heating this halo compound with sodium *n*-propylmercaptide neat at 175° for 36 hr. led to the recovery of 60% of 3-chloropyridine as the only recognizable product.

**3-Octylmercaptopyridine from 3-Pyridinesulfonic Acid.**—The sulfonic acid was converted to the sulfonyl chloride[14] which was reduced to the 3-pyridinethiol hexachlorostannate.[15] This double salt (4.44 g.; 0.01 mole) was dissolved in 10% sodium hydroxide solution (40 ml.). 1-Iodoöctane (4.8 g., 0.02 mole) was added to this solution and the mixture first stirred at room temperature for 1.5 hr., then at 100° for 2.5 hr. The reaction mixture was extracted with methylene chloride (150 ml.) and this extract shaken with 1:3 hydrochloric acid (200 ml.), but treatment with base of the acidic aqueous phase did not yield a product. Since the methylene chloride layer might have dissolved the product (possibly as its hydrochloride) the methylene chloride solution was shaken with 10% sodium carbonate, and then distilled. The sulfide was obtained, b.p. 122–124° at 0.4 mm. It weighed 2.3 g. (50%). It was redistilled for analysis, b.p. 120° at 0.1 mm.

(12) A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959).

(13) C. C. Price and G. W. Stacy, *Org. Syn.*, **28**, 82 (1948); the displacement of the diazonium group by the ethyl xanthate ion has recently been reinvestigated in detail by J. R. Cox, *et al.*, *J. Org. Chem.*, **25**, 1083 (1960).

(14) H. G. Machek, *Monatsh.*, **72**, 84 (1939).

(15) N. Steiger, British Patent 637,130 (May 10, 1959); *Chem. Abstr.*, **44**, 8380 (1950).

*Anal.* Calcd. for $C_{13}H_{21}NS$: C, 69.90; H, 9.48; N, 6.27. Found: C, 70.08; H, 9.30; N, 6.31.

Its picrate crystallized from ethanol, m.p. 91°.

*Anal.* Calcd. for $C_{19}H_{24}N_4O_7S$: N, 12.38. Found: N, 12.06.

**1-Ethoxypyridinium Ethyl Sulfate.**—The method for the preparation of 1-methoxypyridinium methyl sulfate as described by Feeley and Beavers[3a] was adapted. Unlike the 1-methoxy analog, this salt was exceedingly difficult to crystallize. Usually, a gum was obtained and was used as such immediately in the next step. Although it was induced to crystallize once on prolonged scratching, it was even to hygroscopic to insert into a melting point tube. The salt was characterized by its picrate which crystallized from ethanol by the addition of a 1:1 solution of ether and hexane, m.p. 76–78° (lit.,[4] m.p. 76–76.5°).

**Reaction of 1-Ethoxypyridinium Ethyl Sulfate with Sodium *n*-Propylmercaptide.**—Sodium hydride [4.8 g.; 0.2 mole (9.2 g. of a 53.2% suspension in mineral oil as obtained from Metal Hydrides, Inc., Beverly, Mass.)], was added slowly, with stirring, to 1-propanethiol (76 g.; 1.0 mole) contained in a 1-l. flask. (Since it was observed that the mixture foamed considerably during the reaction, it is advisable to use a large vessel.) To this stirred suspension of sodium *n*-propylmercaptide in 1-propanethiol was added 1-ethoxypyridinium ethyl sulfate as a sirup (pre-

### TABLE I

**INFRARED ABSORPTION BANDS (CM.⁻¹) OF 2-, 3-, AND 4-ALKYLMERCAPTOPYRIDINES**

In chloroform

| Propylmercaptopyridines | | | Octylmercaptopyridines | | |
|---|---|---|---|---|---|
| 2-ᵃ | 3- | 4- | 2- | 3- | 4- |
|  | 3305 w-bᵇ | 3275 w-bᵇ |  | 3300 vw-bᵃ | 3275 vw-bᵇ |
| 3038 m | 3081 sh | 3076 sh |  |  |  |
| 2970 vs | 2974 | 2964 |  |  | 2959 sh |
| 2930 s |  |  | 2935 vs | 2920 vs | 2935 vs |
| 2861 s | 2876 s | 2866 s | 2861 s | 2851 s | 2861 s |
|  | 2492 vw-b | 2467 w |  | 2492 vw-b | 2467 w-b |
|  |  |  |  |  | 2261 vw |
|  |  | 1931 w |  |  | 1931 vw-b |
|  |  |  |  |  | 1676 vw-b |
| 1582 vs | 1580 s | 1580 vs | 1580 vs | 1578 m | 1583 vs |
| 1560 s | 1565 s |  | 1560 s | 1565 m |  |
|  |  | 1542 s |  |  | 1543 s |
|  | 1470 vs | 1486 vs |  |  | 1485 s |
| 1452 vs |  | 1465 s | 1456 s | 1471 vs | 1468 s |
|  | 1440 vw | 1440 m |  |  | 1441 w |
|  |  | 1427 m |  |  | 1431 w |
| 1414 vs | 1408 vs | 1412 vs | 1417 vs | 1408 s | 1413 s |
| 1378 m | 1382 m | 1381 m | 1381 w | 1379 w | 1381 w |
|  | 1340 vw | 1341 vw |  |  |  |
|  | 1322 vw | 1321 vw |  |  | 1321 vw |
| 1291 s | 1293 m | 1288 m |  |  | 1294 vw-b |
| 1279 s |  |  | 1282 m |  | 1265 vw-b |
| 1238 s | 1238 s-b | 1242 s | 1241 w | 1242 m-b | 1240 m |
|  | 1187 w |  |  | 1184 w |  |
|  |  |  | 1145 s |  |  |
| 1126 vs-b | 1121 s |  | 1124 vs | 1122 m |  |
|  | 1111 s | 1111 s-b |  | 1109 s | 1111 s-b |
| 1096 m | 1096 s | 1096 sh |  | 1091 m |  |
|  | 1052 vw | 1065 s |  |  | 1066 m |
| 1041 s | 1035 m | 1049 vw | 1043 m | 1034 w |  |
|  | 1019 s |  |  | 1019 s |  |
|  |  | 994 sh |  |  | 998 sh |
| 982 s |  | 984 s | 984 m |  | 985 s |
| 897 w | 897 w | 897 w |  |  |  |
|  | 803 s | 807 s |  |  | 809 s |

Absorption bands between 700 and 800 cm.⁻¹ in carbon disulfide

| | | | | | |
|---|---|---|---|---|---|
|  | 798 s | 799 vs |  | 790 s | 797 vs |
| 756 vs |  |  |  | 759 vs |  |
|  |  | 743 sh |  |  | 740 sh |
| 732 m | 731 sh |  |  |  |  |
| 726 s |  | 728 m | 729 s | 727 sh | 726 m |
|  | 710 s | 714 s |  | 710 vs | 710 s |

ᵃ The sulfide has been recorded previously as a liquid film.[11]
ᵇ This broad band was absent in the spectrum determined in chloroform from which ethanol had been removed nor was it present in the spectrum in carbon tetrachloride or carbon disulfide. This band was observed in the spectra of 3- and 4-substituted, but absent in 2-substituted pyridines even when recorded in spectral grade chloroform. Since chloroform is stabilized by ethanol, this broad band is attributed to the OH stretching frequency, the hydroxyl group bonded to the ring nitrogen atom of the less hindered 3- and 4-substituted pyridines.

pared as above). The heterogeneous mixture did not show signs of reaction. After stirring this mixture for 5.0 min., ethanol (10 ml.) was added and the reaction mixture began to reflux vigorously and foamed considerably. When the foaming lessened, the reaction mixture was refluxed an additional 0.5 hr. on a steam bath, cooled and acidified with 10% hydrochloric acid and most of the solvent removed by distillation *in vacuo*. The residue was treated with water (300 ml.) and extracted with a 1:1 benzene–ether solution (four 100-ml. portions). The aqueous layer was then made basic with a 20% solution of sodium hydroxide, extracted with methylene chloride (five 200-ml. portions). After methylene chloride had been distilled, the residue was fractionated (the receiver placed in a 1:1 chloroform–carbon tetrachloride and Dry-ice bath) to yield pyridine (5.5 g.; 69.6% based on pyridine 1-oxide), b.p. 30–40° (16 mm.) and a mixture of 3- and 4-propylmercaptopyridines, (4.91 g.; 32.1% based on pyridine 1-oxide), b.p. 64–68° (1 mm.). Infrared spectra confirmed the presence of 3- and 4-isomers.

*Anal.* Calcd. for C$_8$H$_{11}$NS: C, 62.70; H, 7.24; N, 9.14. Found: C, 62.56; H, 7.34; N, 8.86.

The fraction containing the mixture of 3- and 4-propylmercaptopyridines (4.91 g.) was placed on a column of alumina (100 g.; Alcoa activated alumina, grade F-20) in petroleum ether (10 ml.), b.p. 30–60°. The column was eluted with petroleum ether (b.p. 30–60°) with 500-ml. portions. The residue of each fraction was examined by its infrared spectrum, and carefully scrutinized for its components using the infrared spectra of pure 2-, 3- and 4-propylmercaptopyridines (recorded in Table I) as references. In particular, each fraction was examined for the presence of small quantities of isomeric impurities. For this purpose certain strong bands in the spectrum of each isomer were chosen. The first eluates from the column contained only the 3-isomer, characterized by strong sharp band at 1019 cm.$^{-1}$ which is apparently featured in many 3-substituted pyridines.[16] If the 2- and/or 4-isomers were present in these fractions, the presence of them would have been detected by absorption near 980 cm.$^{-1}$ since both isomers possess strong bands there. Furthermore, the 2- and 4-isomers show very strong bands near 1580 compared to a much weaker band at 1577 cm.$^{-1}$ for the 3-isomer. To distinguish if the 2- or the 4-isomer was the only contaminant, use of the overall patterns of the 2- and 4-isomers was made. The most distinguishing feature between these two isomers was the very strong band at 1452 for the 2-isomer, the strong band at 1465 cm.$^{-1}$ for the 4-isomer. Further elution then afforded the pure 4-isomer, free from 2- and 3-isomers shown by the absence of the 1452- and 1019-cm.$^{-1}$ bands, respectively.

In this particular experiment, 4500 ml. of petroleum ether eluted only 3-propylmercaptopyridine (4.50 g.; prior to distillation) which boiled between 123–124° at 16 mm., and weighed 4.1 g. (26.8% based on pyridine 1-oxide). Its refractive index ($n^{26}$D

(16) It had been shown that 3-substituted pyridines absorb in the vicinity of 1020 cm.$^{-1}$ [A. R. Katritzky, A. R. Hands, and R. A. Jones, *J. Chem. Soc.*, 3165 (1958)]. For example, 3-chloropyridine absorbs at 1025, 3-amino-pyridine at 1010, 3-nitropyridine at 1021, and 3-acetylpyridine at 1023 cm.$^{-1}$.

1.5550) and infrared spectrum were identical to the authentic sample made from 3-aminopyridine. Furthermore, its picrate (m.p. 113–115°) did not depress that made from the authentic sample.

Further elution of the column with anhydrous benzene (in 100-ml. portions, checking each fraction for its contents by means of infrared spectroscopy; a total of 200 ml.) yielded 4-propylmercaptopyridine (0.7 g.) which when distilled, b.p. 128–130° at 16 mm., weighed 0.55 g. (3.6% based on pyridine 1-oxide). Its infrared spectrum was identical to that of the sample made from 4-chloropyridine.

Reaction of 1-Ethoxypyridinium Ethyl Sulfate and Sodium *n*-Octylmercaptide.—Sodium hydride [4.8 g.; 0.2 mole (9.2 g. of a 53.2% suspension in mineral oil)] was added slowly in very small portions, with stirring, to 1-octanethiol (146 g.; 1.0 mole) contained in a 1-l. flask. Extreme care must be taken during the addition of sodium hydride to the 1-octanethiol, since the reaction is extremely exothermic and there is a tendency to char the sodium *n*-octylmercaptide. To the stirred suspension of sodium *n*-octylmercaptide in 1-octanethiol was added the gummy 1-ethoxy-pyridinium ethyl sulfate prepared from pyridine 1-oxide (9.5 g., 0.1 mole) as previously described. The rest of the procedure was the same as described. On work-up of the reaction mixture the fractions collected were pyridine, b.p. 30–40° (20 mm.), 1.0 g. (12.7%), and the 3- and 4-octylmercaptopyridines, b.p. 114–118° (2 mm.), 1.5 g. (6.7%). The presence of the mixture of the two isomeric sulfides was proven by the analysis of the infrared spectrum as evident from the strong bands at 1019 and 809 cm.$^{-1}$.

*Anal.* Calcd. for C$_{13}$H$_{21}$NS: C, 69.90; H, 9.48; N, 6.27. Found: C, 69.71; H, 9.32; N, 6.29.

This mixture afforded a picrate which crystallized from ethanol to a constant m.p. 83–85° which is below the melting points of the picrates of either the 3- and 4-isomers.

*Anal.* Calcd. for C$_{19}$H$_{24}$N$_4$O$_7$S: N, 12.38. Found: N, 12.09.

When 1.0 g. of this mixture was placed on 20 g. of alumina (Alcoa, grade F-20), no sulfide was eluted with petroleum ether (b.p. 30–60°). However, each fraction (25-ml. portions; 675 ml. in all) eluted with 10% benzene in petroleum ether or benzene alone consisted only of mixture of the 3- and 4-isomers. The absence of the 2-isomers was established since all fractions did not show bands at 1456, 1043 and 984 cm.$^{-1}$ (see Table I).

# The Chemistry of Pyridine. II. The Reaction of 1-Alkoxypicolinium Salts with Mercaptide and Thiophenoxide Ions

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The reaction of 1-alkoxy-2- and 4-picolinium salts with thiophenoxide ion furnished 2- and 4-[(arylmercapto)-methyl]pyridines, respectively, but no nuclear substitution was observed. However, the similar reaction with mercaptide ion was considerably more complex. It was found that 1-alkoxy-4-picolinium salts with mercaptide ions yielded besides 4-[(alkylmercapto)methyl]pyridine also 2- and 3-alkylmercapto-4-picolines and 1,2-di(4-pyridyl)ethane. Explanations are rendered for the formation of these various products. Syntheses of a number of these thioethers as reference compounds are described.

Nucleophilic attack by mercaptide ion on 1-alkoxy-pyridinium salts gave rise to a mixture of pyridine and

3- and 4-alkylmercaptopyridines.[2] However, thiophenoxide ion, under identical conditions, yielded only pyridine and no arylmercaptopyridines could be detected.[2] Pyridine produced in these reactions arises

(2) L. Bauer and L. A. Gardella, part I, *J. Org. Chem.*, **28**, 1320 (1963).

from nucleophilic attack by mercaptide or thiophenoxide ion on the N-alkoxy side chain, while the formation of the thioethers is the outcome of nuclear substitution. When the reaction of mercaptide and thiophenoxide ions was extended to 1-alkoxy-2- and -4-picolinium salts a variety of products were isolated. The reaction of thiophenoxide ions with 1-alkoxypicolinium salts is discussed first.

When 1-methoxy-4-picolinium methyl sulfate was added to an ethanol solution of sodium thiophenoxide, a vigorous reaction ensued. There was isolated a mixture of 4-picoline, its N-oxide and a crystalline unknown sulfur compound, m.p. 48–51°, $C_{12}H_{11}NS$. Three isomeric structures can be written for this unknown solid, viz., 2- and 3-(phenylmercapto)-4-picoline and 4-[(phenylmercapto)methyl]pyridine, III (R' = $C_6H_5$). Its nuclear magnetic resonance (n.m.r.) spectrum[3] clearly distinguished between the three isomeric thioethers. Its spectrum showed resonance characteristics of a pyridine possessing two pairs of equivalent protons ($A_2B_2$ type) as witnessed by the doublets centered at $\delta = 7.00$ and 8.33 and also featured two other sharp bands, one due to the phenyl ($\delta = 7.12$) and the other due to alkyl protons ($\delta = 3.85$). Integration of the peaks due to the pyridine, phenyl and alkyl protons revealed them to be in ratio of 4:5:2. It then became apparent, that only structure III (R' = $C_6H_5$) can be accommodated by this spectrum. Further confirmation of this structure was obtained when this thioether was synthesised from 4-(chloromethyl)pyridine hydrochloride, IV, and (two moles of) sodium thiophenoxide.
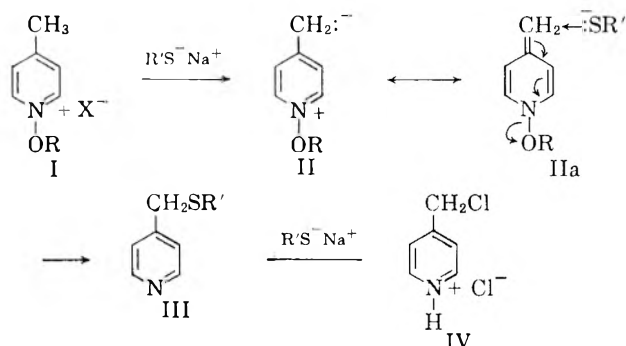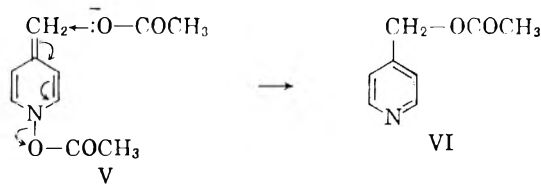


To explain the formation of III from I, the following mechanism is advanced. Abstraction of a proton by thiophenoxide ion from the active methylene group of I leads to the dipolar ion II, better represented by the neutral resonance hybrid, IIa. Further nucleophilic attack by thiophenoxide ion on the excyclic methylene group of IIa, with concerted departure of the alkoxide ion restores aromaticity to form III. This mechanism is in keeping with that proposed for the transformation of 4-picoline 1-oxide with acetic anhydride to 4-(acetoxymethyl)pyridine, VI. For that reaction, it has been postulated that the intermediate anhydro base, V, undergoes nucleophilic attack by acetate ion to form VI.[4]

The formation of 4-picoline and its N-oxide during the reaction of I with thiophenoxide ion stem from

nucleophilic attack of thiophenoxide ion at the α-carbon of the N-alkoxy side chain.[2,5] In order to hinder reac-



tion at that site, the bulk of the alkoxy substituent was increased. When R in I was changed from methyl to ethyl, the yield of III increased from 10 to 24%. It was found further that when I (R = ethyl) reacted with two moles of sodium thiophenoxide, the yield of III (R = $C_6H_5$) jumped from 24 to 65%. For these reactions, ethanol was found to be the best solvent.

The reaction of I (R = $C_2H_5$) was extended to p-t-butylthiophenoxide and p-chlorothiophenoxide to form the thioethers, III [R' is p-($t$-$C_4H_9C_6H_4$) and p-$ClC_6H_4$, respectively]. The reaction of 1-ethoxy-2-picolinium ethyl sulfate, VII, with sodium thiophenoxide was also explored. There was isolated 2-picoline (31%), its N-oxide (16%) and 2-[(phenylmercapto)methyl]pyridine, VIII (38%).
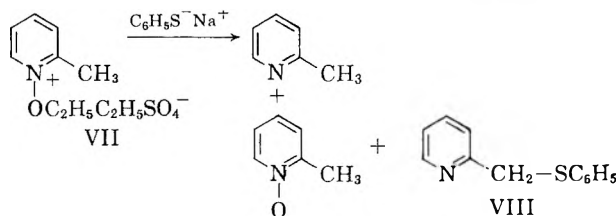


The reaction of I with mercaptide ions was considerably more complex and was studied extensively with two thiols, 1-propane- and 1-octanethiol. Treatment of I (R = $C_2H_5$) with sodium propylmercaptide in excess 1-propanethiol (containing a little ethanol) yielded the cleanest product. It consisted of 4-picoline, a mixture of (propylmercapto)pyridines (IX, X, and XI), and a high-boiling fraction which contained mostly 1,2-di(4-pyridyl)ethane, XII. The separation and identification of the thioethers is discussed first.
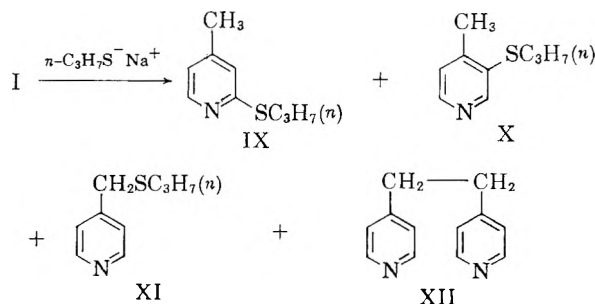


Column chromatography on alumina was attempted to separate the thioethers. Elution of successive fractions was followed by infrared spectroscopy and the spectra compared to reference compounds. For the purpose of identifying components of this mixture, 2-propylmercapto-4-picoline, IX, and 4-[(propylmer-

(3) Determined in carbon tetrachloride using tetramethylsilane as internal standard using the Varian A-60 spectrometer. We are indebted to Dr. L. F. Johnson of Varian Associates, Palo Alto, Calif., for this spectrum.

(4) For a study of mechanism of this reaction see (a) V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **82**, 2744 (1960); (b) S. Oae, T. Kitao and Y. Kitaoka, *ibid.*, **84**, 3359 (1962).

(5) It had previously been reported by N. A. Coats and A. R. Katritzky [*J. Org. Chem.*, **24**, 1836 (1959)] that the reaction of 1-methoxypyridinium p-toluenesulfonate with sodium benzylmercaptide formed pyridine N-oxide, isolated as the picrate in 35% yield. This reaction can be regarded as a nucleophilic displacement reaction by mercaptide ion on the α-alkoxy group to form the N-oxide:

$$R_2S^- \rightarrow R-O-NC_5H_4CH_3(4) \rightarrow R'SR + O-NC_5H_4CH_3.$$
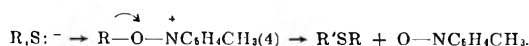
capto)methyl]pyridine, XI, were synthesized (see below). The first pure component was proved to be pure IX, identified by comparison with an authentic sample. The second compound corresponded to "a" (propylmercapto)methylpyridine. Raney nickel desulfurization of this sulfide yielded 4-picoline. But since the infrared spectrum and its picrate were different to those of authentic IX and XI, this thioether was assigned the remaining isomeric structure, X. The remaining fractions proved to be an inseparable mixture of X and XI, in varying proportions, as witnessed by the appearance in the infrared spectrum of the 1606- and 999-cm.$^{-1}$ bands, characteristic of XI. All attempts to effect complete separation of X and XI on acid or basic alumina of different activities as well as on silica gel, proved futile. The presence of XI in this mixture was proved when a $p$-toluenesulfonate could be crystallized from the original mixture.

The formation of these three sulfides by the reaction of I (R = ethyl) with propylmercaptide ion can be explained in the following manner: Nucleophilic attack of the mercaptide ion on the active methylene group of I follows the path suggested for that for thiophenoxide ion (see above). Since the 4-position of the pyridine ring is blocked, nuclear substitution may occur at the 2- and 3-position. Attack at the 3-position may follow the mechanism, which has been suggested to explain the formation of 3-acetoxy-4-picoline during the reaction of 4-picoline 1-oxide with acetic anhydride.[4] This involves nuclear attack by the acetate ion on V with the departure of the N-acetoxy moiety to form 3-acetoxy-4-picoline. To apply this mechanism to our reaction it would involve nucleophilic attack of mercaptide ion on IIa (the counterpart on the anhydrobase, V) with the concomitant loss at alkoxide ion to form XIII or its stable tautomer XIV.



IIa       XIII       XIV
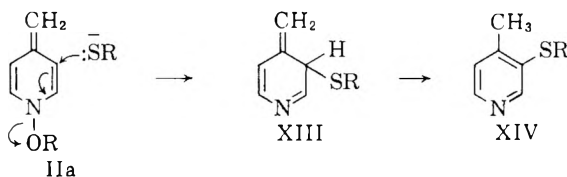
The unexpected formation of 1,2-di(4-pyridyl)ethane, XII, during this reaction remains to be explained. It may be produced in the following manner: Attack of the mercaptide ion on the $\alpha$-carbon of the N-alkoxy side chain can give rise to 4-picoline (equation 2 in ref. 2). In the medium of the reaction, mercaptide ion can act as a strong base and abstract a proton from 4-picoline to form its anion, XV. Acting as a competing nucleophile, XV may also attack IIa in a manner similar to the mercaptide ion to form XII.



XV
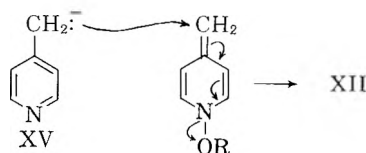
The reaction of I (R = C$_2$H$_5$) with octylmercaptide ion in excess thiol containing some ethanol (10:1; v./v.) afforded 4-picoline, a "middle" fraction which consisted of a mixture of three sulfides, the $n$-octyl analogs IX, X, and XI, and some 1,2-di(4-pyridyl)ethane, XII. The mixture of sulfides was partially resolved by column

chromatography. For an effective separation, it became necessary to use a large ratio of alumina to thioether (100:1) and collect the eluate in small volumes. It was found that petroleum ether (b.p. 30–60°) first eluted pure 2-octylmercapto-4-picoline and then pure 3-octylmercapto-4-picoline. However, subsequent eluates of the latter were contaminated by 4-[(octylmercapto)methyl]pyridine. Again, the presence of these three isomers were spotted by using the characteristic infrared bands.

**Synthesis of Reference Compounds.**—For the purpose of identifying the products of the reaction described above, a number of alkyl- and arylmercapto substituted 2- and 4-picolines were synthesized by alternate routes. These sulfides are listed in Table II. The reaction of 2- and 4-(chloromethyl)pyridine hydrochloride with two moles of thiol and sodium ethoxide (to form the anion) in ethanol furnished the corresponding sulfides. The reaction for the 4-isomers is represented by the conversion of IV to III. A series of 2-alkylmercapto-4-picolines was prepared from 2-chloro-4-picoline by reaction with mercaptide ion as described before.[2] 2-Chloro-4-picoline was made unequivocally from 2-amino-4-picoline by the low temperature diazotization in the presence of fuming hydrochloric acid.[6] Reaction of 2-chloro-4-picoline with thiophenol afforded 2-phenylmercapto-4-picoline, made for comparison with 4-[(phenylmercapto)methyl] pyridine obtained from the reaction of I with thiophenoxide ion.

Another method for the preparation of 2-chloro-4-picoline seemed feasible to us based on some related reactions reported in the literature. It has been shown that the reaction of 2-picoline 1-oxide and 2,6-lutidine 1-oxide with phosphorus oxychloride affords predominantly 4-chloro-2-picoline and 2,6-dimethyl-4-chloropyridine, respectively.[7] However, these reaction products were accompanied by a small amount of the halogenated sidechain products, viz., 2-(chloromethyl)pyridine and 2-(chloromethyl)-6-methylpyridine. By an analogous reaction, it seemed possible to us to treat 4-picoline 1-oxide with phosphorus oxychloride and obtain 2-chloro-4-picoline. When this reaction was carried out as described for the 2-picoline 1-oxide, a (chloromethyl)pyridine was obtained. Reaction of it with thiophenol (hydrogen chloride to be absorbed by the pyridine moiety) furnished a 55% yield of 4-[(phenylmercapto)methyl]pyridine identical in all respects to that made from 4-(chloromethyl)pyridine. From this observation, we conclude that the reaction of 4-picoline 1-oxide with phosphorus oxychloride yields predominantly 4-chloromethylpyridine. The first intermediate of this reaction may be XVI which loses the elements of hydrogen chloride to give XVII. Nucleo-



XVI       XVII
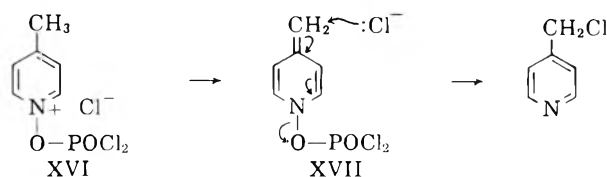
philic attack by chloride ion on XVII with the simultaneous loss of the phosphorus moiety leads to 4-chloromethylpyridine. This reaction may proceed

(6) O. Seide, Ber., **57**, 791 (1924).

(7) T. Kato, J. Pharm. Soc. Japan, **75**, 1239 (1955); Chem. Abstr., **50**, 8665 (1956).

along lines similar to the reaction of 2,6-lutidine 1-oxide with *p*-toluenesulfonylchloride to give 2-(chloromethyl)-6-methylpyridine in 43% yield.[8]

The infrared spectra of the two isomers, 2-(phenylmercapto)-4-picoline and 4-[(phenylmercapto)methyl] pyridine as well as the three isomeric propylmercaptomethylpyridines, IX, X, XI, are listed in Table I.

## Experimental[9]

**Starting Materials.**—2- and 4-picoline 1-oxide were obtained from Reilly Coal Tar and Chemical Corp., Indianapolis, Ind.; 2- and 4-(chloromethyl)pyridine hydrochlorides from Aldrich Chemical Co., Milwaukee, Wis. We gratefully acknowledge the

generous and kind gifts of: 1-propane and 1-octanethiols from Pennsalt Chemical Corp., Philadelphia, Pa. and Phillips Petroleum Co., Bartlesville, Okla.; *p*-chlorothiophenol from Evans Chemetics, Inc., New York, N. Y.

**Synthesis of Reference Compounds: (A) 2-and 4-[Aryl (or Alkyl)mercaptomethyl]pyridines from 2- and 4-(Chloromethyl)-pyridine Hydrochlorides.**—A general procedure has been developed for the synthesis of these thioethers. To a solution of sodium ethoxide (0.2 g.-atom of sodium dissolved in 100 ml. in ethanol) was added the thiol (0.2 mole) followed by the requisite (chloromethyl)pyridine hydrochloride (0.1 mole). The mixture was heated on a steam bath for 2 hr., cooled, and solvents removed at 30 mm. (If one expects a highly volatile thioether, the solution may be acidified prior to the last step.) The residue was acidified with 10% hydrochloric acid (100 ml.) and extracted with a mixture of ether–benzene (1:1; five 30-ml. portions to remove neutral and acidic products). Methylene chloride may be used for this extract, but we have found that several of the hydrochlorides were appreciably soluble in that solvent. The aqueous phase was made alkaline with 20% sodium hydroxide and extracted with methylene chloride (eight 30-ml. portions). Distillation of this extract afforded the thioethers. Their physical constants, analyses, and derivatives are listed in Table II under method A.

**Preparation of 4-[(Phenylmercapto)methyl]pyridine *via* the Product of Reaction of 4-Picoline 1-Oxide with Phosphorus Oxychloride.**—A chloroform solution of 4-picoline 1-oxide (10.9 g.; 0.1 mole in 50 ml.) was added dropwise, with stirring, to a chloroform solution of phosphorus oxychloride (19.2 g.; 0.125 mole (in 50 ml.), and the mixture was refluxed for 5.5 hr. The mixture was poured onto ice and made alkaline with sodium hydroxide at 5°. The inorganic salts were removed by filtration. The filtrate was extracted with chloroform (eight 50-ml. portions). and the organic extract distilled. The yield of the "chloropico,line" was 4.5 g. (35%), b.p. 39–40° (1.5 mm.). This "chloropicoline" (2.60 g.; 0.02 mole) and thiophenol (2.20 g.; 0.02 mole) were heated at 150–160° for 4 hr. On cooling crystals formed. The product was made basic with 10% aqueous sodium hydroxide and extracted, worked up as in A to yield 4-[(phenylmercapto)-methyl]pyridine 2.25 g. (55% yield based on the chloro compound) identical to the thioether described in method A.

**(B) 2-Alkylmercapto-4-picolines.**—These were prepared essentially by the method of Profft.[10] A typical experiment is described for the synthesis of 2-octylmercapto-4-picoline: Potassium hydroxide (1.4 g.; 0.025 mole) was dissolved in a solution of N,N-dimethylformamide (40 ml.) and 1-octanethiol (3.65 g., 0.025 mole). To this was added 2-chloro-4-picoline[6] (3.18 g.) and the reaction mixture heated on a steam bath for 3.0 hr., cooled, acidified with concentrated hydrochloric acid, and worked up as in method A. The products are listed in Table II.

**2-Phenylmercapto-4-picoline.**—The method follows that of Brooker, *et. al.*[11] Triethylamine (2.02 g.; 0.02 mole) was added in small portions, with shaking, to a mixture of 2-chloro-4-methylpyridine (1.27 g.; 0.01 mole) and thiophenol (2.20 g.; 0.02 mole). When the addition was completed, the reaction mixture was refluxed on a steam bath for 5.0 hr. The reaction mixture was cooled, made alkaline, and worked up as in A and the product recorded in Table II.

**(C) Reaction of 1-Ethoxy-2- and 4-Picolinium Salts with Thiophenoxide Ions.**—A typical experiment is described. 1-Ethoxy-4-picolinium ethyl sulfate[12] was prepared by heating 4-picoline 1-oxide (10.9 g., 0.1 mole) with ethyl sulfate (15.4 g.; 0.1 mole) at 100° for 2 hr. The sirup which was washed with dry ether (two 25-ml. potions) was dissolved in ethanol (25 ml.) and used immediately in the next step.

To a stirred ice-cold solution of sodium thiophenoxide in ethanol [made by dissolving sodium (4.6 g.; 0.2 g.-atom) in 100 ml. ethanol and adding thiophenol (22.0 g.; 0.2 mole)] was added the ethanol solution of 1-ethoxy-4-picolinium ethyl sulfate prepared above. The addition was controlled to maintain the temperature between 10 and 30°. After the completion of the addition, the reaction was stirred at room temperature for 0.5

TABLE I

INFRARED ABSORPTION BANDS (CM.$^{-1}$) OF SOME OF THE THIOETHERS

| 4-[(Phenyl-mercapto)-methyl]-pyridine | 2-Phenyl-mercapto-4-picoline | 4-[(Propyl-mercapto)-methyl]-pyridine | 2-Propyl-mercapto-4-picoline | 3-Propyl-mercapto-4-picoline |
|---|---|---|---|---|
| 3275 w-b | 3350 w-b | 3305 m-b | 3353 w-b | 3253 w-b |
| 3070 s | 3050 sh | | 3058 sh | |
| 2975 s-b | 3000 vs | 2959 vs | 2959 vs | 2959 vs |
| | | | 2935 sh | 2935 sh |
| | 2875 sh | 2885 sh | 2870 s | 2861 s |
| 2486 w-b | 2492 w-b | 2492 w-b | 2467 vw-b | 2467 w-b |
| 1941 w-b | | 2000 vw | 1926 vw | |
| | | | 1614 sh | |
| 1603 vs | 1596 vs-b | 1606 vs | 1595 vs | |
| 1586 s | | | | 1580 s |
| 1565 s | | 1567 m | 1549 s | |
| | 1536 s | | 1539 sh | |
| | | 1509 sh | | |
| 1496 sh | | 1495 w | | |
| 1483 s | 1478 sh | | | 1478 s |
| | 1465 vs | 1465 s | 1465 s-b | 1463 s |
| 1442 s | 1444 vs | 1442 sh | 1442 sh | 1442 sh |
| 1420 s | | 1422 s | | |
| | 1396 sh | | | 1401 s |
| | 1381 vs | 1381 m | 1374 s | 1381 s |
| | | | | 1365 sh |
| | | 1335 w | 1335 vw | |
| | 1304 w | 1297 m | 1289 sh | 1289 m |
| | 1284 s | | 1284 s | |
| 1248 s-b | 1243 s-b | 1243 s-b | 1253 sh | |
| | | | 1238 s | 1238 s |
| | | 1223 sh | | |
| | | 1207 sh | | |
| | | 1194 sh | | 1172 w |
| | | 1141 vw-b | | |
| | 1121 vs | | 1120 vs | |
| 1088 s | 1087 vs | 1091 w | 1096 s | 1106 s |
| 1069 s | 1067 m | 1067 m | | 1060 w |
| | | 1050 vw | 1050 vw | |
| 1024 s | 1024 s | | 1045 vw | 1043 s |
| | | | 1041 vw | |
| 999 sh | 999 m | 999 s | | |
| 995 s | 989 s | | 985 s | |
| 887 s | | 892 m-b | 897 w | 897 vw |
| | 872 s | | 872 s | |
| 831 m | | 837 sh | | 827 s |
| 819 m | 823 s | | 820 s | |
| | | 804 s | | |

(8) E. Matsumura, T. Hirooka and K. Imagawa, *Nippon Kagaku Zasshi*, **82**, 616 (1961).

(9) All melting points and boiling points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Dr. Kurt Eder, Geneva, Switzerland. Some of the nitrogen analyses were performed using a Coleman Nitrogen Analyzer, Model 29.

(10) E. Profft and W. Rolle, *J. prakt. Chem.*, (4) **11**, 32 (1960). The method of Brooker[11] as described below for the preparation of 2-arylmercaptopyridines failed to yield thioethers when mercaptans were used.

(11) L. G. S. Brooker, *et. al.*, *J. Am. Chem. Soc.*, **73**, 5326 (1951).

(12) The salt was not crystallized but was characterized as the picrate, m.p. 96–97° (from ethanol). O. Červinka, *Collection Czech. Chem. Commun.*, **27**, 567 (1962), reports its m.p. 99°.

TABLE II

In each analysis cell values are given as Calcd. / Found.

| Substituents of pyridine ring | B.p., °C. (pressure), refractive index (m.p., solvent of cryst.) | Method | Yield, % | Mol. formula | Analyses, % C | Analyses, % H | Analyses, % N | Derivative | Solvent of cryst. | M.p., °C. | Mol. formula | Analyses, % C | Analyses, % H | Analyses, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2-(Phenylmercapto)methyl | 123–127° (0.4 mm.) $n^{27.5}$D 1.6210 | A | 81 | $C_{12}H_{11}NS$ | 71.60 / 71.76 | 5.51 / 5.54 | 6.96 / 7.12 | Hydrochloride | Ethanol–ether | 137–138 | $C_{12}H_{12}NSCl$ | … / … | … / … | 5.89 / 6.21 |
|  |  | C | 38 |  |  |  |  | … | … | … | … |  |  |  |
| 2-(Propylmercapto)methyl | 90–93° (4 mm.) $n^{30.5}$D 1.5373 | A | 97 | $C_9H_{13}NS$ | 64.61 / 65.06 | 7.83 / 7.76 | 8.38 / 8.12 | … | … | … | … |  |  |  |
| 4-(Phenylmercapto)methyl | 126–128° (1 mm.) $n^{24}$D 1.6194 (48–51°) from pet. ether, b.p. 30–50° | A | 89 | $C_{12}H_{11}NS$ | 71.60 / 71.67 | 5.51 / 5.59 | 6.96 / 7.19 | Hydrochloride | Ethanol–ether | 142–144 | $C_{12}H_{12}NSCl$ | 60.62 / 60.74 | 5.09 / 5.26 | 5.89 / 6.01 |
|  |  | C | 65 |  |  |  |  | Picrate | Ethanol | 131–132 | $C_{18}H_{14}N_4O_7S$ | … / … | … / … | 13.02 / 12.94 |
| 4-(p-Chlorophenylmercapto)methyl | 136–141° (0.3 mm.) | C | 50 | $C_{12}H_{10}NSCl$ | … / … | … / … | 5.94 / 6.27 | Hydrochloride | Ethanol | 212–213 | $C_{12}H_{11}NSCl_2$ | 52.95 / 52.85 | 4.07 / 4.15 | 5.15 / 5.03 |
| 4-(p-4-Butylphenylmercapto)methyl | 152–157° (0.06 mm.) (52–54°) from pet. ether, b.p. 30–60° | C | 53 | $C_{16}H_{19}NS$ | 74.66 / 74.72 | 7.47 / 7.42 | 5.44 / 5.21 | Hydrochloride | Acetone–ethanol (trace) | 215–217 | $C_{16}H_{20}NSCl$ | 65.40 / 65.84 | 6.86 / 6.96 | 4.77 / 4.51 |
| 4-(Propylmercapto)methyl | 100–105° (3 mm.) | A | 96 | $C_9H_{13}NS$ | 64.61 / 64.38 | 7.83 / 7.81 | 8.38 / 8.09 | p-Toluenesulfonate | Acetone | 115–117 | $C_{16}H_{21}NO_3S_2$ | … / … | … / … | 4.13 / 4.37 |
|  |  |  |  |  |  |  |  | Picrate | Ethanol | 129–131 | $C_{15}H_{16}N_4O_7S$ | … / … | … / … | 14.14 / 13.89 |
| 4-(Octylmercapto)methyl | 142° (1.1 mm.) | A | 93 | $C_{14}H_{23}NS$ | 70.82 / 70.64 | 9.77 / 9.75 | 5.90 / 6.06 | p-Toluenesulfonate | Acetone | 116–117 | $C_{21}H_{31}NO_3S_2$ | … / … | … / … | 3.42 / 3.56 |
| 2-Phenylmercapto-4-methyl | 125° (0.3 mm.) | B | 100 | $C_{12}H_{11}NS$ | 71.60 / 71.35 | 5.51 / 5.67 | 6.96 / 7.46 | … | … | … | … |  |  |  |
| 2-Propylmercapto-4-methyl | 67° (2 mm.) | B | 42 | $C_9H_{13}NS$ | 64.61 / 64.40 | 7.83 / 7.98 | 8.38 / 8.34 | Picrate | Ethanol | 137–139 | $C_{15}H_{16}N_4O_7S$ | … / … | … / … | 14.14 / 13.91 |
| 2-Octylmercapto-4-methyl | 135–138 (0.5 mm.) $n^{29}$D 1.5120 | B | 79 | $C_{14}H_{23}NS$ | 70.82 / 70.09 | 9.77 / 9.87 | 5.90 / 5.64 | … | … | … | … |  |  |  |
| 3-Propylmercapto-4-methyl | 139–140° (21 mm.) $n^{25}$D 1.5510 | D | … | $C_9H_{13}NS$ | 64.61 / 64.65 | 7.83 / 7.89 | 8.38 / 8.29 | Picrate | Ethanol | 140–143 | $C_{15}H_{16}N_4O_7S$ | … / … | … / … | 14.14 / 14.60 |
| 3-Octylmercapto-4-methyl | 125–127° (0.25 mm.) $n^{34}$D 1.5188 | D | … | $C_{14}H_{23}NS$ | 70.82 / 70.87 | 9.77 / 9.97 | 5.98 / 5.90 | Picrate | Ethanol | 120–122 | $C_{20}H_{26}N_4O_7S$ | … / … | … / … | 12.01 / 11.70 |

hr. and then evaporated at 35° *in vacuo*. The residue was acidified and worked up as described in method A.

The only modification in the work-up was to wash the methylene chloride extract containing the **thioether** several times with water prior to distillation. This procedure was found to be of advantage as it removes most of 4-picoline 1-oxide due to its inherent solubility in water. This avoided contamination of the higher boiling thioethers with the N-oxide.

The reaction with thiophenoxide afforded 4-picoline, b.p. 40–50° at 13 mm. (3.2 g.; 34%) and 13 g. of 4-[(phenylmercapto)-methyl]pyridine (listed in Table II). Other thioethers made in this fashion are listed in Table II under method C.

When 2-picoline 1-oxide was substituted in this reaction, the same procedure was followed. In its reaction with sodium thiophenoxide, there was obtained 2-picoline (3.0 g.; 31%) b.p. 40–50° at 13 mm., 2-picoline 1-oxide (1.7 g.; 16%) b.p. 85–100° at 0.5 mm., and the thioether listed in Table II.

**(D) Reaction of 1-Ethoxy 4-Picolinium Salts with Mercaptide Ions. (a) With Propylmercaptide Ion.**—Sodium propylmercaptide was prepared by the addition of sodium hydride (4.8 g.; 0.2 mole) to 1-propanethiol (76 g.; 1 mole). To the resulting suspension was added the ethanol solution of the 1-ethoxy salt prepared above under C (but dissolved in 10 ml. ethanol only) and the mixture heated under reflux for 0.5 hr. The solvents were then evaporated *in vacuo* and the residue worked up as described in method A. Distillation of the basic fraction gave 4-picoline, b.p. 40–50° at 20 mm. (4.0 g.; 43%), a mixture of thioethers (see below), b.p. 80–95° at 2.0 mm. (8.0 g.; 47.9%), and 1,2-di(4-pyridyl)ethane XII, b.p. 130–150° at 2 mm. (0.8 g.; 8.7%), whose identification is described below.

**Separation of the Thioethers IX, X, and XI.**—The mixture (5.0 g.) was placed on alumina (100 g.; Alcoa, activated, Grade F-20) with petroleum ether (b.p. 30–60°). Elution with the first two fractions (two 200-ml. lots) yielded 0.71 g. whose infrared spectrum was identical to 2-propylmercapto-4-picoline. Distillation yielded 0.38 g. of the thioether, b.p. 133–136° (20 mm.), $n^{25}D$ 1.5500, whose picrate m.p. 137–139° was underpressed by the picrate of the sample prepared in B.

Continued elution with an additional 200 ml. of petroleum ether (b.p. 30–60°) affords a fraction which consisted of a mixture. Further elution with the same solvent furnished seven fractions (1400 ml. in all) which contained pure 3-propylmercapto-4-picoline (1.87 g. in all). Distillation gave an analytical sample (0.88 g.) whose physical constants are recorded in Table II. Its picrate (m.p. 140–143°) depressed the m.p. of that of 2-propylmercapto-4-picoline (m.p. 137–139°) to 113–127°. Desulfurization of this thioether (0.5 g.) was achieved with W-5 Raney nickel (three teaspoons, *ca.* 20 g.) in boiling acetone (150 ml.) for 20 hr. Work-up of the reaction mixture yielded 4-picoline (0.3 g.), b.p. 30–50° (20 mm.). The picrate, m.p. 161–163° (from ethanol), did not depress that of an authentic sample, m.p. 165–166°, and the infrared spectra of the two picrates were superimposable.

Further elution of the chromatograph with an additional fifteen fractions (3000 ml. of petroleum ether, b.p. 30–60°) yielded in each a mixture of 3-propylmercapto-4-picoline and 4-[(propyl-mercapto)methyl]pyridine in varying proportions. Rechromatography of this fraction (after it was redistilled) on fresh alumina again only effected partial separation as described above.

The highest boiling fraction obtained in this experiment was dissolved in acetone and treated with an excess of *p*-toluenesulfonic acid. The salt so formed crystallized from acetone or ethanol, m.p. 245–246°.

*Anal.* Calcd. for $C_{26}H_{28}N_2S_2O_6$: C, 59.06; H, 5.34; N, 5.30. Found: C, 59.12; H, 5.49; N, 5.56.

The *p*-toluenesulfonate made from sample of 1,2-di(4-pyridyl)-ethane (purchased from Aldrich Chemical Co., Milwaukee, Wis.) was identical to the sample isolated above (melting point, mixture melting point, and infrared spectrum).

When the reaction described above is carried out in ethanol alone, there was isolated 4-picoline (67.7%), the mixture of sulfides (18%), and XII (15%). A similar reaction performed in N,N-dimethylformamide produced the mixture of sulfides in 30% and XII in 11% yield.

**(b) With Octylmercaptide Ion.**—The experiment was performed essentially as in a. 1-Ethoxy-4-picolinium ethyl sulfate (from 0.1 mole of 4-picoline 1-oxide) was dissolved in 25 ml. ethanol. Sodium octylmercaptide was prepared by dissolving sodium (4.6 g.) in ethanol (50 ml.) and 1-octanethiol (100 ml.). The 1-ethoxy salt was now added and the reaction heated at 100° for 0.5 hr. and then worked up as in A. Two fractions were isolated: 4-picoline (6.8 g.; 73%), b.p. 40–50° (14 mm.), and the **thioethers** and 1,2-(4-pyridyl)ethane, XII (4.2 g.), b.p. 130–150° (0.7 mm.). Separation of XII from the thioethers was accomplished as follows: When the mixture was treated with excess dry *p*-toluenesulfonic acid in acetone and a small amount of dry ether, the *p*-toluenesulfonate of XII (see above), m.p. 240–244°, crystallized. The solid was filtered off and the mother liquor[13] evaporated to dryness. The residue was treated with 20% sodium hydroxide, extracted with methylene chloride, and redistilled. The **thioethers** boiled at 138–141° (1.1 mm.).

Chromatography of the thioethers (5.0 g.) on Alcoa activated alumina (100 g., grade F-20) effected the following separations when 200-ml. portions were collected. The first fraction eluted by petroleum ether, b.p. 30–60°, contained pure 2-octylmercapto-4-picoline (0.5 g.). The next seven fractions (1400 ml. of the same eluent) yielded 1.2 g. of 3-octylmercapto-4-picoline whose constants are recorded in Table II. Further elution by petroleum ether simply gave mixtures of 3-octylmercapto-4-picoline and 4-[(octylmercapto)methyl]pyridine, as ascertained by the examinations of the infrared spectra of these fractions.

When this reaction was performed by the addition of the 1-ethoxy-4-picolinium salt (in N,N-dimethylformamide) to a suspension of sodium octylmercaptide in N,N-dimethylformamide and excess 1-octanethiol, the fraction containing the thioethers and XII (b.p. 133–160° at 0.8 mm.) was improved (7.5 g. from 0.1 mole of 4-picoline 1-oxide). Separation of the components as shown above indicated it to be a similar mixture.

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(13) In one experiment, another crop of crystals, m.p. 113–115°, was obtained on slow evaporation of this mother liquor. The m.p. was undepressed on admixture with a sample of 4-[(octylmercapto)methyl]pyridine *p*-toluenesulfonate made in A, (m.p. 116–117°). However, the yield of this salt was poor and no other fractions could be separated by fractional crystallization. Hence, chromatography was resorted to again as described previously.

# Pyrimido[5,4-d][1,2,3]triazines

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The products obtained from the reactions of 5-amino-6-methyluracils (I, Ia, and Ib) with nitrous acid are shown to be pyrimido[5,4-d][1,2,3]triazine 3-oxides (II, IIa, and IIb). Hydrolyses of the 4-chloropyrimidotriazines, VIa and b, yield 5-diazobarbituric acids, VIIa and b. A mechanism is postulated for this unusual hydrolysis.

Our interest in the possible physiological activity of derivatives of 1H-pyrazolo[4,3-d]pyrimidine-5,7(4H,-6H)-dione[2] (III), an isomer of xanthine, prompted us to reinvestigate the nature of the reactions and intermediates used for its synthesis. Compound III has been synthesized by the action of nitrous acid on 5-amino-6-methyluracil (I)[3] followed by the reduction, with stannous chloride, of the intermediate compound II so formed. The intermediate II has been formulated by Behrend as IIx and by Rose as diazouracil-6-aldoxime IIy. The evidence presented in this paper will establish the correct structure for the intermediate II to be pyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide.

Since, for pharmacological reasons, we were largely interested in alkylated derivatives of the pyrimidines, we chose as our starting materials 1,3,6-trimethyluracil and 1,3-diethyl-6-methyluracil. The reactions in the two series closely paralleled each other. Only the reactions of the methyl derivatives will be discussed. Descriptions of the comparable ethyl derivatives are given in Experimental.

1,3,6-Trimethyl-5-aminouracil (Ia), prepared *via* nitration of 1,3,6-trimethyluracil and catalytic reduction of the 5-nitro compound so obtained, was treated with nitrous acid under conditions similar to those used by Behrend.[3a] The compound so formed, IIa, agreed with $C_7H_7N_5O_3$. The analysis was not consistent with a formula corresponding to Behrend's IIx (see also ref. 3b) and the compound could not be formulated by a structure analogous to Rose's IIy. The infrared spectrum of IIa showed no absorption in the 4-$\mu$ region as would be expected for a diazo ketone.[4] On the other



I. R = H
Ia. R = CH₃—
Ib. R = C₂H₅—

III

IIx  IIy  II

IV. R = CH₃— or C₆H₅—

V. R = CH₃— or C₆H₅—
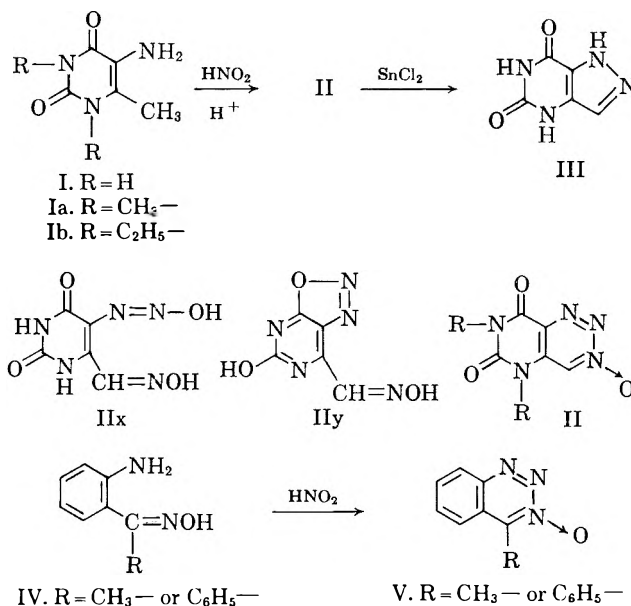
hand, Meisenheimer[5] had shown that treatment of the *syn*-oximes of o-aminoacetophenone and o-aminobenzophenone (IV) with nitrous acid led to the formation of products best formulated as 4-substituted 1,2,3-benzotriazine 3-oxides (V). In a similar manner, compounds of structures IIx or IIy, if formed as intermediates, would be expected to give the pyrimido[5,4-d][1,2,3]-triazine 3-oxide (II).

Further evidence that IIa was actually a triazine 3-oxide was obtained by the following series of reactions. Treatment of IIa with thionyl chloride at room temperature, followed by chromatography of the products so formed, yielded the pyrimidotriazinetrione VIIIa and 1,3-dimethyl-5-diazobarbituric acid (VIIa). Since it appeared very probable that both VIIa and VIIIa were products of hydrolysis of an initially formed 4-chloropyrimidotriazine VIa, an attempt was made to isolate this expectedly rather unstable compound.[6] By repeated and rapid crystallizations of the product from the reaction of IIa with thionyl chloride,[7] pure 4-chloro-5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione (VIa) was obtained in moderate yield. Hydrolysis of VIa with dilute hydrochloric acid produced both VIIa and VIIIa.

It was realized that VIIIa could be formulated as 5,7-dimethylpyrimido-[5,4-d][1,2,3]triazine-4,6,8-

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(2) The compounds in this paper are named as derivatives of 1H-pyrazolo[4,3-d]pyrimidine and pyrimido[5,4-d][1,2,3]triazine. Throughout this
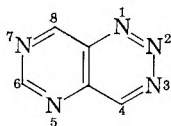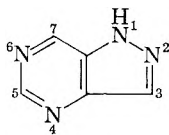


paper, with the exception of formulas IV and V, where the nature of R is clearly designated, Roman numerals without letters refer to compounds in which R = H; Roman numerals combined with "a" (*e.g.*, VIIIa) refer to compounds in which R = CH₃— and combined with "b" (*e.g.*, VIIIb) to compounds in which R = C₂H₅—. Combinations with x and y refer to alternate ways of formulating a given compound.

(3) (a) R. Behrend, *Ann.*, **245**, 213 (1888); (b) F. L. Rose, *J. Chem. Soc.*, 3448 (1952). The pyrazolopyrimidinedione (III) has also been prepared by R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones [*J. Am. Chem. Soc.*, **78**, 2418 (1956)], by the fusion of 4-aminopyrazole-3-carboxamide with urea. The preparation and proof of structure of alkylated derivatives of III will be reported in the future.

(4) For a brief discussion of the structure and spectra of diazo phenols (diazo ketones, "1,2,3-oxadiazoles") see "Heterocyclic Compounds," R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y.; J. H. Boyer, Vol. 7, 1961, p. 522. See also J. D. C. Anderson, R. J. W. LeFèvre, and I. R. Wilson, *J. Chem. Soc.*, 2082 (1949); R. J. W. LeFèvre, J. B. Sousa, and R. L. Werner, *ibid.*, 4686 (1954).

(5) J. Meisenheimer, O. Senn, and P. Zimmermann, *Ber.*, **60**, 1736 (1927). For a discussion of the chemistry of 1,2,3-triazines see. "The Chemistry of Heterocyclic Compounds," A. Weissberger, consulting ed., Interscience Publishers, Inc., New York, N. Y., "The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines," J. G. Erickson, P. F. Wiley, and V. P. Wystrach, 1956, p. 1.

(6) For the synthesis and properties of 4,5,6-triphenyl-1,2,3-triazine, see E. A. Chandross and G. Smolinsky, *Tetrahedron Letters*, **13**, 19 (1960).

(7) For related reactions on pyridine 1-oxide using sulfuryl chloride, see B. Bobranski, L. Kochanska, and A. Kowalewska, *Ber.*, **71**, 2385 (1938).

VIa. R = CH₃—
b. R = C₂H₅—



VII  VIII  IX



VIIIx  VIIIy
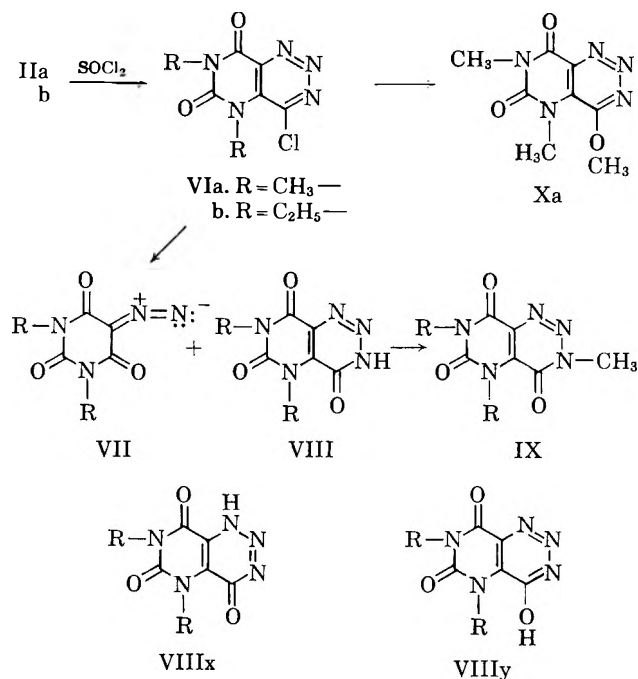
(3H,5H,7H)-trione, as the corresponding 1H-trione VIIIax or as the 4-hydroxypyrimidotriazinedione VIIIay. To obtain further evidence for its structure, VIIIa was methylated with dimethyl sulfate to IXa. The 4-chlorotriazine VIa, in turn, was converted to the 4-methoxytriazine Xa with sodium methoxide in methanol. The ultraviolet spectra of VIa, VIIIa, IXa, and Xa fell into two groups: the spectra of VIa and Xa were very similar in form, and position and intensity of maxima; the spectra of VIIIa and IXa were also very similar in form, and position and intensity of maxima (see Experimental). On the other hand, there was little resemblance in form between the ultraviolet spectra of the two groups. From the structures of VIa and Xa and the comparison of spectra, VIIIay probably can be eliminated as an important tautomer for VIIIa. The structure IXa was assigned to the methylation product of VIIIa on the basis of analogous methylations in the benz[d][1,2,3]triazin-4-one series.[8] Because of the similarity of the ultraviolet spectra of VIIIa and IXa, formula VIIIa is considered to be the most important tautomer of that compound. However, it is realized that the position of methylation of VIIIa is not rigorously established.

To relate more clearly the structure of pyrimido-[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (II) to that of its dimethylated and diethylated derivatives, IIa and IIb, a sample of II was prepared by the method described by Rose.[3b] The observation by Rose of the existence of a very stable hydrate of II was confirmed. Comparison of the ultraviolet spectra of II, IIa, and IIb showed a great similarity in form and intensity of maxima. The $\lambda_{max}$ 256.5 m$\mu$ of II was at slightly lower wave length than that of IIa ($\lambda_{max}$ 263 m$\mu$) and IIb ($\lambda_{max}$ 264 m$\mu$).

**5-Diazobarbituric Acid.**—The formation of 1,3-dimethyl-5-diazobarbituric acid (VIIa) by the hydrolysis of 4-chloro-5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione (VIa) came as a surprise to us. The compound VIIa was identified by its analysis, by the presence of strong absorption at 4.62 $\mu$ in its in-

(8) K. Kratz, *J. prakt. Chem.*, **53**, 210 (1896).

frared spectrum,[4] and by direction comparison of its infrared spectrum with that of authentic sample.[9] Its formation can be rationalized on the basis of the following equations. The liberation of HCN from the hydrolysis was detected by the use of picric acid test
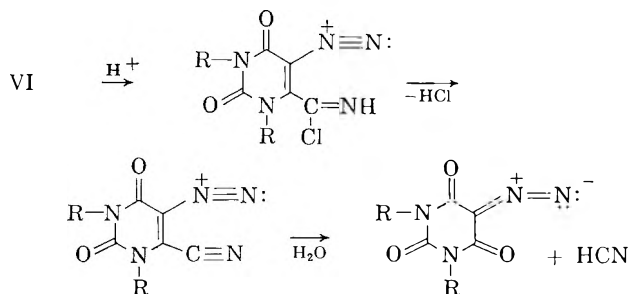


paper.[10] The reactions postulated above resemble those that were recently described by M. S. Gibson[11] to explain the isomerization of substituted pyrazolo-[2,3-c][1,2,3]benzotriazines to pyrazolo[4,3-c]cinnolines. They are also related to the conversion of 3,4-dihydro-4-oxobenzo-1,2,3-triazine to o-chlorobenzonitrile by reaction with a mixture of phosphorus pentachloride and phosphorus oxychloride.[12]

**1,3,6-Trimethyl-5-nitrouracil.**—To a solution of 1.5 ml. of fuming nitric acid (d 1.50) in 39 ml. of concentrated sulfuric acid cooled to 10° was added 12.7 g. of 1,3,6-trimethyluracil at such a rate that the temperature never exceeded 20°. When all of the 1,3,6-trimethyluracil had dissolved, an additional 5.23 ml. of fuming nitric acid was added at temperatures below 20°. The resulting solution was poured over ice, and the resulting precipitate (13.5 g., m.p. 146–148°) was separated by filtration and was washed thoroughly with ice-water. Crystallization of a portion of this material from dilute alcohol gave analytically pure 1,3,6-trimethyl-5-nitrouracil, m.p. 153–154°.

*Anal.* Calcd. for C₇H₉N₃O₄: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.12; H, 4.78; N, 20.85.

**1,3-Diethyl-5-nitro-6-methyluracil**, m.p. 85–86°, was prepared from 1,3-diethyl-6-methyluracil by a similar procedure.

*Anal.* Calcd. for C₉H₁₃N₃O₄: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.59; H, 5.63; N, 18.83.

**1,3,6-Trimethyl-5-aminouracil (Ia).**—1,3,6-Trimethyl-5-nitrouracil (36 g.) in 1 l. of absolute alcohol was hydrogenated at 70–99° and 740–750 p.s.i. using 3.6 g. of a 5% palladium-on-carbon catalyst. After completion of the hydrogenation, the solution was filtered, then evaporated *in vacuo* to 125 ml. On being cooled this solution deposited 14 g. of 1,3,6-trimethyl-5-aminouracil (Ia), m.p. 169–171°. An additional 7.7 g. of the same product, m.p. 167–169°, was obtained by further evaporation of the mother liquors.

*Anal.* Calcd. for C₇H₁₁N₃O₂: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.56; H, 6.74; N, 25.25.

**1,3-Diethyl-5-amino-6-methyluracil (Ib)**, m.p. 96–99°, was prepared from the corresponding 5-nitro derivative by a similar method.

*Anal.* Calcd. for C₉H₁₅N₃O₂: C, 54.80; H, 7.67; N, 21.31. Found: C, 54.89; H, 7.57; N, 21.15.

(9) E. Fahr, *Ann.*, **627**, 213 (1959); F. G. Fischer, W. P. Neumann, and J. Roch, *Chem. Ber.*, **85**, 752 (1952); F. J. DiCarlo, A. S. Schultz, and A. M. Kent, *J. Biol. Chem.*, **194**, 769 (1952). We are indebted to Dr. E. Fahr, University of Würzburg, Germany, for a copy of this infrared spectrum.

(10) Houben-Weyl, "Methoden der Organischen Chemie, Analytische Methoden," Georg Thieme Verlag, Stuttgart, 1953, p. 21.

(11) M. S. Gibson, *Chem. Ind.* (London), 698 (1962).

(12) D. Buckley and M. S. Gibson, *J. Chem. Soc.*, 3242 (1956).

(13) We are indebted to Drs. R. T. Dillon and W. H. Sause of the Analytical Division of G. D. Searle and Co. for the analytical and optical data reported, to Mr. W. M. Selby for help with catalytic reductions, to Dr. E. G. Daskalakis for help with chromatographic separations, and to Dr. W. M. Hoehn and the Special Synthesis Group for the preparation of larger quantities of some of these materials. All ultraviolet spectra were determined in methanol.

**5,7-Dimethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione 3-Oxide (IIa).**—A solution of 29.8 g. of 1,3,6-trimethyl-5-aminouracil (Ia) in 245 ml. of concentrated hydrochloric acid and 190 g. of ice was treated at 0–5° with 25 g. of sodium nitrite in 41.5 ml. of water. The sodium nitrite solution was added slowly with stirring under the surface of the amine hydrochloride solution. Toward the end of the reaction a precipitate formed. The mixture was stirred for an additional 1.5 hr. while the temperature was allowed to rise to room temperature. The resulting precipitate was separated by filtration, washed with water to remove the acid, then washed with alcohol, and dried. From the reaction 30 g. of the N-oxide IIa, m.p. 247–249° dec., was obtained. Crystallization of this material from acetic acid raised the m.p. to 249–250° dec.; $\lambda_{max}$ 263 m$\mu$ ($\epsilon$ 35,000), $\lambda_{shoulder}$ 290 m$\mu$ ($\epsilon$ 10,480), $\lambda_{shoulder}$ 340 m$\mu$ ($\epsilon$ 2,050); $\lambda_{max}^{KBr}$ 5.75, 5.91, 6.33, 6.89, 7.28, 7.51, and 7.71 $\mu$.

*Anal.* Calcd. for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 40.04; H, 3.35; N, 33.54.

**5,7-Diethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (IIb),** m.p. 244–245° dec., $\lambda_{max}$ 264 m$\mu$ ($\epsilon$ 36,800), $\lambda_{shoulder}$ 290 m$\mu$ ($\epsilon$ 9,600); $\lambda_{max}$ 340 m$\mu$ ($\epsilon$ 1,620); $\lambda_{max}^{KBr}$ 5.78, 5.91, 6.31, 6.63, 6.95, 7.06, 7.22, 7.40, and 7.48 $\mu$.

*Anal.* Calcd. for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.52. Found: C, 45.58; H, 4.59; N, 29.12.

**1,3-Dimethyl-5-diazobarbituric Acid (VIIa) and 5,7-Dimethylpyrimido[5,4-d][1,2,3]triazine-4,6,8(3H,5H,7H)-trione (VIIIa).**—5,7-Dimethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (IIa) (15.0 g.) and 150 ml. of thionyl chloride were stirred at room temperature in a closed vessel for 18 hr. The excess thionyl chloride was removed *in vacuo* at a temperature of less than 35°. The residue was dissolved in 1800 ml. of benzene by prolonged stirring at room temperature and was then chromatographed on 800 g. of silica gel. The column was washed with benzene and then with a gradually increasing proportion of ethyl acetate in benzene.

Elution of the column with 15% ethyl acetate in benzene yielded 9.16 g. of 1,3-dimethyl-5-diazobarbituric acid. Repeated crystallizations of this material from methanol, after decolorization with carbon, gave 5.9 g. of 1,3-dimethyl-5-diazobarbituric acid (VIIa), m.p. 165–166° dec., $\lambda_{max}$ 261 m$\mu$ ($\epsilon$ 13,800), $\lambda_{max}^{KBr}$ 4.62, 5.81, 5.98, 6.75, 6.99, 7.21, 13.18, and 13.32 $\mu$; (reported m.p. 165°).[9] The infrared spectrum of this material was identical with that of an authentic sample.[9]

*Anal.* Calcd. for $C_6H_6N_4O_3$: C, 39.57; H, 3.32; N, 30.77. Found: C, 39.90; H, 3.76; N, 30.68.

Elution of the column with a gradually increasing proportion of ethyl acetate in benzene was continued. Finally, elution with 75% ethyl acetate, 25% benzene gave 2.47 g. of the crude trione VIIIa, which after repeated crystallizations from ethyl acetate yielded pure 5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-4,6,8-(3H,5H,7H)-trione, m.p. 202–203° dec.; $\lambda_{max}$ 281 m$\mu$ ($\epsilon$ 8,350), 323 m$\mu$ ($\epsilon$ 7,350), $\lambda_{shoulder}$ 233 m$\mu$ ($\epsilon$ 4,820), 314 m$\mu$ ($\epsilon$ 7,080), $\lambda_{min}$ 301 m$\mu$ ($\epsilon$ 6,150).

*Anal.* Calcd. for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 40.21; H, 3.23; N, 33.81.

**1,3-Diethyl-5-diazobarbituric Acid (VIIb) and 5,7-Diethylpyrimido[5,4-d][1,2,3]triazine-4,6,8(3H,5H,7H)-trione (VIIIb).**—5,7-Diethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (IIb) (10.0 g.) and 100 ml. of thionyl chloride were stirred overnight at room temperature. The resulting solution was evaporated *in vacuo* and the residue chromatographed as described above. Elution of the column with 5% ethyl acetate in benzene yielded 6.25 g. of 1,3-diethyl-5-diazobarbituric acid (VIIb), which, after crystallization from petroleum ether (b.p. 28–38°), gave 5.3 g. of pure material, m.p. 54–55°; $\lambda_{max}$ 261.5 m$\mu$ ($\epsilon$ 13,600); $\lambda_{max}^{CHCl_3}$ 4.59 and 4.64 $\mu$.

*Anal.* Calcd. for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 46.02; H, 4.99; N, 27.02.

Elution of the column with 25% ethyl acetate in benzene gave 1.032 g. of the triazinetrione VIIIb, m.p. 179–180° dec. Crystallization of this material from water raised its m.p. to 193–194° dec.; $\lambda_{max}$ 282 m$\mu$ ($\epsilon$ 8,540), 323 m$\mu$ ($\epsilon$ 7,650), $\lambda_{shoulder}$ 315 m$\mu$ ($\epsilon$ 7,350).

*Anal.* Calcd. for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.71; H, 4.87; N, 29.13.

**4-Chloro-5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-6,8-(5H,7H)-dione (VIa).**—A suspension of 70 g. of the triazine N-oxide IIa in 1400 ml. of thionyl chloride was stirred overnight. The resulting solution was evaporated *in vacuo* at a temperature not exceeding 35°. The residue (72 g.) consisted largely of the 4-chlorotriazine VIa contaminated with a small quantity of the diazobarbituric acid VIIa (infrared spectrum). Repeated crystallization of this material from benzene–ethyl acetate failed to raise the melting point above 154° (39 g.). Crystallization of a 10-g. portion of this product from 300 ml. of methanol made weakly basic with a few drops of 10% sodium hydroxide yielded 7.0 g. of 4-chloro-5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione (VIa), m.p. 161–162° dec. The analytical sample, m.p. 165–166° dec., $\lambda_{max}$ 275 m$\mu$ ($\epsilon$ 9,780), $\lambda_{shoulder}$ 310 m$\mu$ ($\epsilon$ 4,380), was obtained by chromatography of 3.0 g. of this material on silica gel. A small quantity of the triazinetrione VIIIa was also eluted from the column.

*Anal.* Calcd. for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.66; Cl, 15.58; N, 30.78. Found: C, 36.91; H, 2.84; Cl, 15.31, N, 30.61.

Hydrolysis of an analytically pure sample of 4-chloro-5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione (VIa) with boiling 5% hydrochloric acid for 1 min. produced a mixture of 1,3-dimethyl-5-diazobarbituric acid (VIIa) and 5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-4,6,8(3H,5H,7H)-trione (VIIIa) (ca. 1 part VIIa:3 parts VIIIa). The products were identified by isolation of the pure materials and comparison (m.p., m.m.p., infrared spectra) with those produced above. Hydrocyanic acid was evolved from the hydrolysis (picric acid test).

**4-Chloro-5,7-diethylpyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H) dione (VIb),** m.p. 137–138° dec., $\lambda_{max}$ 275 ($\epsilon$ 9,720), $\lambda_{shoulder}$ 310 ($\epsilon$ 4,390), was prepared by a similar process. The product was purified by crystallizations from ethyl acetate–ether.

*Anal.* Calcd. for $C_9H_{10}ClN_5O_2$: C, 42.28; H, 3.94; Cl, 13.87; N, 27.40. Found: C, 42.40; H, 4.09; Cl, 14.04; N, 27.25.

**4-Methoxy-5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-6,8-(5H,7H)-dione (Xa).**—To a suspension of 1.1 g. of the 4-chloropyrimidotriazinedione VIa, m.p. 161–162° dec., in 50 ml. of methanol, cooled in an ice bath, was added a solution of 0.25 g. of sodium methoxide in 3 ml. of methanol. The reaction mixture was stirred for 15 min., the precipitate was separated by filtration, then crystallized from water. In this manner, 0.65 g. of the 4-methoxypyrimidotriazinedione Xa was obtained; m.p. 192–194° dec.; $\lambda_{max}$ 274 m$\mu$ ($\epsilon$ 10,250), $\lambda_{shoulder}$ ca. 305 m$\mu$ ($\epsilon$ 5,580).

*Anal.* Calcd. for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 42.68; H, 3.76; N, 31.49.

**3,5,7-Trimethylpyrimido[5,4,d][1,2,3]triazine-4,6,8(3H,5H,-7H)-trione (IXa).**—To a suspension of 1.6 g. of 5,7-dimethylpyrimido[5,4-d][1,2,3]triazine-4,6,8-(3H,5H,7H)-trione (VIIIa) and 0.8 ml. of dimethyl sulfate in 20 ml. of methanol and 8 ml. of water was added, slowly and with stirring, 3.0 ml. of a 10% solution of sodium hydroxide in water. The clear solution that resulted was evaporated to a small volume, cooled, and the precipitate that resulted was separated by filtration. After two crystallizations from water, there was obtained 430 mg. of 3,5,7-trimethylpyrimido[5,4-d][1,2,3]triazine-4,6,8(3H,5H,7H)-trione (IXa), m.p. 174° dec.; $\lambda_{max}$ 241 m$\mu$ ($\epsilon$ 6,430), 283.5 m$\mu$ ($\epsilon$ 7,510), 323 m$\mu$ ($\epsilon$ 7,940), $\lambda_{shoulder}$ 314 m$\mu$ ($\epsilon$ 7,140), $\lambda_{min}$ 301 m$\mu$ ($\epsilon$ 5,900).

*Anal.* Calcd. for $C_8H_9N_5O_3$: C, 43.05; H, 4.06; N, 31.38. Found: C, 43.08; H, 4.02; N, 31.21.

**Pyrimido[5,4-d][1,2,3]triazine-6,8(5H,7H)-dione 3-oxide (II),** m.p. 232° dec. (reported m.p. 239° dec., 245° dec.),[3b] $\lambda_{max}$ 256.5 m$\mu$ ($\epsilon$ 31,900), $\lambda_{inflection}$ ca. 280 m$\mu$ ($\epsilon$ 14,700), $\lambda_{shoulder}$ 330 m$\mu$ ($\epsilon$ 2,540), was prepared by the method described by Rose.[3b]

*Anal.* Calcd. for $C_5H_3N_5O_3 \cdot H_2O$: C, 30.16; H, 2.53; N, 35.17. Found: C, 30.15; H, 2.57; N, 35.33.

The anhydrous material was also prepared by the method described by Rose.[3b]

*Anal.* Calcd. for $C_5H_3N_5O_3$: C, 33.16; H, 1.67; N, 38.67. Found: C, 33.00; H, 1.46; N, 38.61.

# Compounds in the Pyrrolo[3,4-*d*]pyrimidine Series. Syntheses Based on 2,3-Dioxopyrrolidines[1]

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Three procedures have been developed for the synthesis of the pyrrolo[3,4-*d*]pyrimidine ring system: (1) condensation of a 4-carbethoxy-3-amino-2-oxo-3-pyrroline (III) with guanidine, (2) condensation of a 4-carbethoxy-2,3-dioxopyrrolidine (enol form, I) with urea or guanidine, or (3) condensation of a 4-benzylidene-2,3-dioxopyrrolidine (VIII) with guanidine.

The efficacy of analogs of the naturally occurring purines and pyrimidines as antimetabolites, and in particular the useful antitumor activity of such compounds as 6-mercaptopurine and 5-fluorouracil, has prompted the synthesis of a large number of these analogs. The present investigation is concerned with the pyrrolo[3,4-*d*]pyrimidine series, which appears to have received no attention previously.[2] Such compounds can be regarded as purine analogues as well as pyrimidine derivatives of a new type. Moreover, in the members of the series which will be described here (see formulas IV, VII, and X) the pyrrolidone carbonyl group is attached to the 4-position of the pyrimidine ring, the position occupied by the carboxyl group in orotic acid (A), which is a precursor in the biosynthesis of pyrimidines and pyrimidine nucleotides both in animals and in microörganisms.[3] Examination of the new synthetic compounds for possible antimetabolite activity therefore should be of considerable interest.
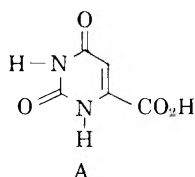


A

Chart I illustrates the reactions investigated. In the discussion of individual compounds, the letter h following the numeral which designates the formulas in Chart I will indicate that R is hydrogen, b that R is benzyl, and c that R is cyclohexyl. In order to keep the nomenclature as simple as possible, the common practice of naming pyrimidines as derivatives of the fully aromatic form of the pyrimidine system has been followed. The formulas in Chart I correspond to these names, with oxygens shown as incorporated in hydroxyl groups, although the infrared data indicate the presence of carbonyl groups in the pyrimidine portions of structures IV and VII.

2,3-Dioxopyrrolidines with functional substituents in the 4-position appeared to be suitable starting materials for the preparation of compounds in the pyrrolo[3,4-*d*]pyrimidine series. However, the 4-carbethoxy-2,3-dioxopyrrolidines, which, as β-keto esters, might perhaps have been expected to yield the pyrimidine ring readily by reaction with guanidine or urea,[4] afforded the desired products only after the usual procedures for related pyrimidine syntheses were considerably modified. It seems evident that the difficulty resided in the fact that the 4-carbethoxy-2,3-dioxopyrrolidines actually exist almost entirely in the form of enols (I), which are exceptionally acidic ($pK_a = ca.$ 4.25),[5] and evidently yield enolate anions which are stabilized by resonance against nucleophilic attack at either the ester or ketonic function. Thus treatment of Ib with guanidine yielded the guanidinium salt IIb, which did not readily undergo the elimination of water and ethanol which would have produced the pyrrolopyrimidine IVb; initial attempts to obtain IVb from IIb by refluxing with excess guanidine in ethanol led to partial decomposition to blue-colored by-products, and recovery of most of the salt (IIb) unchanged.

To obtain compounds with the increased reactivity toward guanidine, it proved expedient to convert the compounds of type I into 2-amino derivatives (III), which do not form enolate anions. The 3-amino derivatives were easily obtained in satisfactory yield (*ca.* 85%) by treatment of compounds of type I with ammonium formate. Unfortunately, no guanidino derivatives analogous to III were obtained when guanidine salts (carbonate, acetate or hydrochloride) were used in place of ammonium formate; the esters I were recovered unchanged from such experiments.

The 3-amino derivatives (IIIh and IIIb) reacted satisfactorily with excess guanidine in refluxing absolute ethanol in the presence of one mole of sodium ethoxide to yield 2-amino-4-hydroxyl-5*H*-pyrrolo[3,4-*d*]pyrimidin-7(6*H*)-ones (IVh and IVb). In the absence of sodium ethoxide, yields of the benzyl derivative IVb were somewhat reduced and there were indications of the presence of lower-melting products. The best of the procedures thus far investigated afforded *ca.* 85% yields of IVb and *ca.* 58% yields of IVh. Yields were unreliable unless the ethanol used was thoroughly dried and purified by distillation from magnesium ethoxide. A recent experiment has shown, moreover, that by using highly purified ethanol and a large excess of

(1) This investigation was supported by a research grant (RG-4371) from the National Institutes of Health, U. S. Public Health Service.

(2) On the other hand, a considerable amount of work on compounds in the pyrrolo[2,3-*d*]pyrimidine series has appeared recently. See (a) R. A. West, K. Ledig, and G. H. Hitchings, British Patent 812,366 (April 22, 1959); *Chem. Abstr.*, **54**, 592 (1960); (b) R. A. West and L. Beauchamp, *J. Org. Chem.*, **26**, 3809 (1961); (c) R. A. West, *ibid.*, **26**, 4959 (1961); (d) J. Davoll, *J. Chem. Soc.*, 131 (1960).

(3) See, for example, (a) F. W. Chattaway, *Nature*, **153**, 250 (1944); (b) H. J. Rogers, *ibid.*, **153**, 251 (1944); (c) H. S. Loring and J. G. Pierce, *J. Biol. Chem.*, **153**, 61 (1944); (d) H. K. Mitchell, M. B. Houlahan, and J. F. Nyc, *ibid.*, **172**, 525 (1948); (e) S. Bergstrom, *et al.*, *ibid.*, **177**, 495 (1949); (f) H. Arvidson, *et al.*, *ibid.*, **179**, 167 (1949); (g) L. L. Weed, M. Edmunds, and D. W. Wilson, *Proc. Soc. Exptl. Biol. Med.*, **75**, 192 (1950); (h) L. D. Wright, *et al.*, *J. Am. Chem. Soc.*, **73**, 1898 (1951); (i) R. B. Hurlbert and V. R. Potter, *J. Biol. Chem.*, **195**, 257 (1952); (j) I. Lieberman and A. Kornberg, *ibid.*, **207**, 911 (1954).

(4) *Cf.*, for example, the review of synthetic methods for pyrimidines by G. W. Kenner and A. Todd in R. C. Elderfield's "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 234.

(5) (a) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956); (b) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953).

CHART I
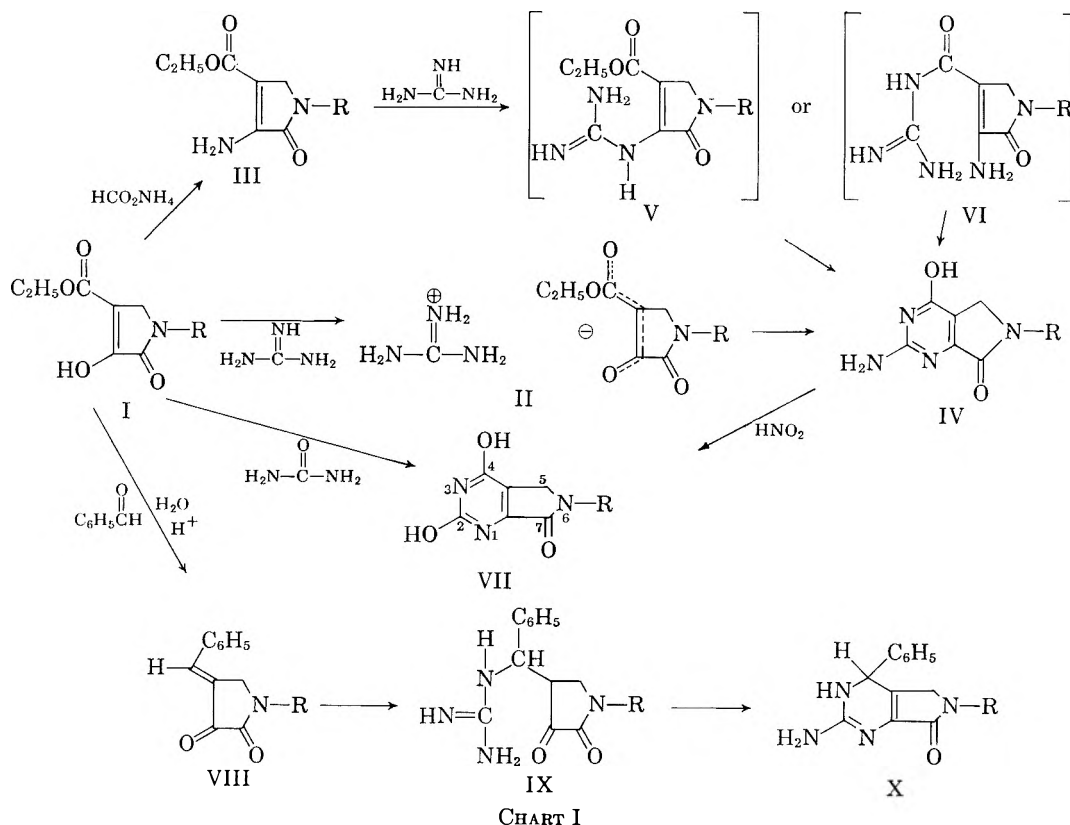
guanidine, a partial conversion of the ester Ib to the pyrrolopyrimidine IVb can be achieved; decomposition of the guanidine salt IIb evidently is retarded under these conditions, and the pyrimidine ring closure takes place slowly. There are several mechanisms by which compounds of type IV could be formed by base-promoted reactions of compounds of type III with guanidine. Presumably, intermediates of the types V and/or VI are involved, but it has not been determined whether the ammonia which is eliminated arises from the amino group of III or from the guanidine.[6]

After a number of unsuccessful attempts had been made to condense urea with Ib with the aid of bases or acids in ethanol or dioxane, the desired reaction was obtained by heating Ib in fused urea under reduced pressure at 180°.[7] The conversion of Ib to the dihydroxypyrrolopyrimidine VIIb was rather low (14%), but much of the starting material (ca. 69%) was recovered in the form of the 3-amino derivative IIIb, which could be used in the preparation of the amino hydroxy pyrrolopyrimidine IVb.

The dihydroxy derivative VIIb could also be obtained through the nitrous acid deamination of compound IVb. This conversion, achieved in 42% yield without any extended study of reaction conditions, provided confirmation of the assumed close structural relationship between compounds VIIb and IVb. Compound VIIh, the dihydroxy derivative having an unsubstituted pyrrolidine nitrogen, was not obtained by means of the reaction of urea with the unsubstituted 4-carbeth-

oxy-2,3-dioxopyrrolidine Ih; even fusion of these reactants failed to yield any of the desired pyrrolopyrimidine. However, compound VIIh was obtained in 47% yield by nitrous acid deamination of compound IVh.

The pyrrolo[3,4-d]pyrimidines of the types IV and VII displayed the expected properties. They melted with decomposition or decomposed without melting only at high temperatures, and, while insoluble in water, dissolved in aqueous sodium hydroxide solutions. The 2-amino compound IVb, although insoluble in aqueous ethanol alone, dissolved in aqueous ethanol to which some hydrochloric acid had been added; the expected basicity of the 2-aminopyrimidine structure was evident. Compound IVh dissolved easily in hot water when acid was added. The ultraviolet spectra (Table I), most of which were measured in 0.1 N sodium hydroxide solution because of the low solubility of the compounds in other solvents, were rather similar to those of related pyrimidines such as orotic acid,[8] but in alkaline solution the absorption bands for the pyrrolopyrimidines occurred at somewhat longer wave lengths, apparently as a result of the presence of the pyrrolidone carbonyl group, which in these structures would be held in the plane of the pyrimidine ring. The infrared spectra (see Experimental), as expected, showed absorption in the 3-μ region (OH, NH, NH₂, and/or =NH groups) and the 6-μ region (lactam carbonyl, imino, and/or olefinic groups). The large number of absorption bands in the 6.0-μ region of the Nujol mull spectra of several of these compounds probably reflects splitting of carbonyl absorptions by hydrogen bonding.

As expected, the nuclear magnetic resonance (n.m.r.) spectra of IVb and VIIb, which were measured at 60

(6) If it is the amino nitrogen of the compounds III which is retained in the final products, this pyrimidine ring closure could be regarded as somewhat analogous to the synthetic method recently introduced by Taylor, in which formamidine acetate reacts with o-aminonitriles to form fused-ring structures incorporating the pyrimidine system. See E. C. Taylor and W. A. Ehrhart, J. Am. Chem. Soc., 82, 3138 (1960).

(7) Heating of suitable intermediates in fused urea occasionally has been employed in the past to form 2,4-dihydroxypyrimidine derivatives. See, for example, E. Fischer and G. Roeder, Ber., 34, 3751 (1901).

(8) Cf., The table of ultraviolet data provided by A. Bendich and E. Chargaff and J. N. Davidson's "The Nucleic Acids," Vol. I, Academic Press, Inc., New York, N. Y., 1955, p. 108.

TABLE I

ULTRAVIOLET DATA. PYRROLO[3,4-$d$]PYRIMIDINES

| Compound | Solvent | Maxima | | Minima | | "End" absorption[a] at 220 mμ, |
|---|---|---|---|---|---|---|
| | | $\lambda_{m\mu}$ | log ε | $\lambda_{m\mu}$ | log ε | log ε |
| IVb | NaOH, 0.1 $N$ | 223 | 4.26 | 277 | 3.30 | .. |
| | | 306 | 3.67 | | | |
| IVh | NaOH, 0.1 $N$ | 220 | 4.17 | 265 | 3.08 | .. |
| | | 304 | 3.70 | | | |
| VIIb | NaOH, 0.1 $N$ | 314 | 3.79 | 278 | 3.33 | 4.23 |
| | Ethanol, 95% | 264 | 4.04 | 228 | 3.75 | 3.92 |
| VIIh | NaOH, 0.1 $N$ | 312 | 3.82 | 266 | 3.05 | 4.16 |
| Orotic acid | NaOH, 0.1 $N$ | 286 | 3.74 | 248 | 3.34 | 3.92 |
| Xb | HCl, 0.1 $N$ | ca. 275[b] | 3.34 | .. | .. | 4.26 |
| | | ca. 255[b] | 3.52 | | | |
| | | ca. 245[b] | 3.68 | | | |
| Xc | HCl, 0.1 $N$ | ca. 275[b] | 3.36 | .. | .. | 4.26 |
| | | ca. 255[b] | 3.62 | | | |
| | | ca. 245[b] | 3.74 | | | |

[a] Log ε values at 220 mμ are listed for those compounds showing strong and evidently rising absorption at that point. Some pyrimidines (see ref. 8) show an additional maximum not far below this lower limit of the wave-length range measured in the present work. [b] Inflection.

Mc. in trifluoroacetic acid solution, showed two unsplit lines of equal intensity which could be assigned to the two equivalent hydrogens of the methylene portion of the benzyl group and the two equivalent hydrogens of the methylene group at position 5 of the ring system. Compounds IVh and VIIh showed an unsplit line due to the methylene protons of position 5. A detailed discussion of the n.m.r. results will be provided elsewhere.[9]

Suitable starting materials were also at hand for the preparation of pyrrolo[3,4-$d$]pyrimidine derivatives containing a dihydropyrimidine ring. The 4-benzylidene-2,3-dioxopyrrolidines VIII,[10] which have a bright yellow color, were decolorized rapidly when treated with guanidine in ethanol solution, evidently due to formation of colorless, ethanol-soluble guanidine adducts for which the structure IX is suggested. In experiments with VIIIb a precipitate was deposited over a period of three days when the solutions were stirred at room temperature following this loss of color. As discussed below, this product showed the composition and properties expected for 2-amino-6-benzyl-4-phenyl - 3,4 - dihydro - 5$H$ - pyrrolo[3,4 - $d$]pyrimidin-7(6$H$)-one (Xb). A similar result was obtained starting with compound VIIIc, but the product Xc did not precipitate, and was isolated by removal of the solvent. The apparent second (ring-closure) phase of these reactions could be brought about in a one-hour period by heating the solutions at temperatures in the range 60 to 80°.[11]

Compounds Xb and Xc were high-melting and insoluble in water, but quite soluble in aqueous alcoholic hydrochloric acid. The acid solutions of these compounds showed a strong blue-green fluorescence when exposed to ultraviolet light. In 0.1 $N$ hydrochloric acid the compounds gave ultraviolet absorption curves

(see Table I) which increased rapidly in intensity as the lower end (220 mμ) of the measured wave-length range was approached, and showed several inflections, but no maxima.[12] The n.m.r. spectra of Xb and Xc, obtained in trifluoroacetic acid solution, showed the expected one-proton singlet due to the hydrogen at position 4, and an AB pattern[13] assigned to the methylene group at position 5 which indicates two spin-coupled protons separated in the spectrum by a very small chemical shift. In the spectrum of Xb, the N-benzyl methylene protons give rise to an additional similar AB pattern of equal intensity. The methylene groups in these compounds contain nonequivalent protons because of the unsymmetrical (phenyl) substitution at position 4.[14] The n.m.r. data are consistent only with a structure in which the two carbons of the ring junction are joined by a double bond; compounds Xb and Xc may be regarded as derivatives of 1,4 or 3,4-dihydropyrimidine (depending upon the tautomeric form of the guanidino portion of the ring) but not as 4,5 or 5,6-dihydropyrimidines.

Work is in progress on preparation of additional members of the pyrrolo[3,4-$d$]pyrimidine series.

## Experimental[15,16]

**3-Amino-1-benzyl-4-carbethoxy-2-oxo-3-pyrroline (IIIb).**— 1-Benzyl-4-carbethoxy-2,3-dioxopyrrolidine (Ib)[6] (41.6 g.; 0.16 mole) and 20.0 g. (0.32 mole) of ammonium formate in 200 ml. of absolute ethanol were refluxed for 24 hr. The solution was then concentrated to dryness under reduced pressure over a steam cone, and the solid residue was washed with 100 ml. of water, filtered and dried. The crude product was dissolved in 300 ml. of boiling 95% ethanol, and the hot solution was treated with Norit, concentrated to 200 ml., and cooled. The product (31.0 g.) separated as white needles, m.p. 114–115°. An additional 7.8 g. of product, m.p. 112–114° was obtained from the mother liquor; the total yield was 38.8 g. (93%). The m.p. remained at 114–115° following two further recrystallizations from ethanol.

*Anal.* Calcd. for $C_{14}H_{16}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.62; H, 5.97; N, 10.68.

Infrared spectrum (Nujol mull): 2.84m, 2.97i, 3.06sm, 3.14m, 3.39i, 3.46i, 5.91i, 6.07i, 6.12i, 6.35i, 6.68m, 6.82i, 6.89i, 6.97i, 7.07m, 7.22w, 7.28w, 7.35m, 7.43m, 7.54w, 7.73bi, 7.85bi, 8.05i, 8.27m, 8.57w, 8.65w, 8.95i, 9.09i, 9.26m, 9.79m, 10.04w, 10.32-w, 11.22w, 11.66w, 12.18w, 12.72w, 12.98m, 13.08i, 13.64m, 14.24i.

Acid hydrolysis of the product IIIb reconverted it to the starting material (Ib).

**3-Amino-4-carbethoxy-2-oxo-3-pyrroline (IIIh).**—4-Carbethoxy-2,3-dioxopyrrolidine (Ih)[5b] (10.0 g.; 0.058 mole) and 7.3 g. (0.106 mole) of ammonium formate in 500 ml. of absolute ethanol were refluxed for 48 hr. The crude product, isolated in the same way as the 1-benzyl derivative (IIIb) described above, consisted of 8.7 g. of pink crystals, m.p. 212–215°. Recrystallization from 250

(9) The authors are indebted to Mr. George E. Milliman and Dr. R. J. Kurland for the n.m.r. measurements.

(10) P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, **27**, 98 (1962).

(11) The formation of 2-amino-5,6-dihydropyrimidines by condensation of guanidine with α,β-unsaturated ketones has been described by W. Traube and R. Schwarz, *Ber.*, **32**, 3163 (1899).

(12) 5,6-Dihydropyrimidines also lack ultraviolet maxima above 220 mμ when measured in acid solutions. See K.-Y. Zee-Cheng, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 1877 (1961).

(13) See (a) H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957); (b) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 119–123; (c) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp. 89–90.

(14) See ref. 13c, p. 101–103.

(15) Melting points are uncorrected. Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England; A. Bernhardt, Max Planck Institute for Coal Research, Mülheim (Ruhr), Germany; and Galbraith Laboratories, Inc., Knoxville, Tenn.

(16) Infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer. Figures quoted are wave lengths in microns. Letters following the figures describe bands as follows: i = intense—>60% absorption; m = medium—30–60% absorption; w = weak—<30% absorption; b = broad band; s = shoulder. Ultraviolet spectra were measured with a Cary recording spectrophotometer.

ml. of 95% ethanol with decolorization by Norit yielded 8.3 g. (84%) of white plates, m.p. 214–215°, which were not changed in m.p. by further recrystallizations.

*Anal.* Calcd. for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.68; H, 5.90; N, 16.14.

Infrared spectrum (Nujol mull): 2.89i, 2.98i, 3.10i, 3.21m, 3.42i, 3.49i, 5.80i, 5.84i, 5.89i, 5.95i, 6.08i, 6.13i, 6.25i, 6.30bi, 6.44sm, 6.67w, 6.79sm, 6.83i, 6.92i, 7.22i, 7.35i, 7.88bi, 8.08i, 8.62m, 8.95i, 9.10bi, 9.55m, 9.80m, 10.10w, 10.89bw, 11.55w, 12.62m, 12.81m, 13.02bi, 13.53bm.

**2-Amino-6-benzyl-4-hydroxy-5H-pyrrolo[3,4-d]pyrimidin-7-(6H)-one (IVb).**—A solution of guanidine and sodium ethoxide in absolute ethanol was prepared from 2.7 g. (0.12 g.-atom) of sodium dissolved in 100 ml. of absolute ethanol (freshly dried over magnesium ethoxide[17]), and 9.6 g. (0.10 mole) of guanidine hydrochloride, also dissolved in 100 ml. of specially dried absolute ethanol. Compound IIIb (5.2 g.; 0.02 mole) was added and the mixture was refluxed with stirring for 73 hr. in an apparatus protected from moisture. Removal of nearly all of the ethanol under reduced pressure over a steam cone left a residue containing the sodium derivative of IVb, which was dissolved in 100 ml. of water. Addition of glacial acetic acid until a pH of 6 was reached caused precipitation of 4.4 g. (86%) of a white product, m.p. > 340°.[18] After it was washed with 50 ml. of ethanol and dried, the product was recrystallized from 500 ml. of dimethylformamide to yield 2.5 g. of white plates, m.p. *ca.*, 360° dec. The analytical sample was recrystallized again from the same solvent.

*Anal.* Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.81; H, 4.83; N, 21.82.

Infrared spectrum (Nujol mull): 3.03m, 3.14m, 3.39i, 3.46m, 5.95i, 5.99i, 6.19m, 6.24sm, 6.62w, 6.73w, 6.84m, 6.91m, 7.04w, 7.25bm, 7.59w, 7.74m, 7.91w, 8.28w, 8.33sw, 8.72w, 9.03w, 9.30w, 9.40w, 9.69w, 11.91w, 12.13w, 12.29bm, 12.68w, 13.13m, 13.88w, 14.27m, 14.93m.

**2-Amino-4-hydroxy-5H-pyrrolo[3,4-d]pyrimidine-7(6H)-one (IVh).**—The procedure for conducting the reaction was the same as that described above for preparation of IVb; 7.6 g. (0.33 g.-atom) of sodium, 28.7 g. (0.3 mole) of guanidine hydrochloride, 5.0 g. (0.029 mole) of compound IIIh, and a total of 600 ml. of specially dried absolute ethanol were used. The sodium derivative of the crude product, isolated as described above for IVb, was dissolved in 100 ml. of water and decolorized by treatment of the solution with Norit at the boiling point. The filtered solution was cooled to room temperature and adjusted to pH 6 by addition of glacial acetic acid. The product, which was precipitated as a pale yellow solid, weighed 2.8 g. (58%) after being washed on the filter with water and dried. It did not melt below 360°. It was suspended in boiling water and dissolved by portionwise addition of 20% hydrochloric acid until a clear solution was obtained. After decolorization with Norit and cooling of the filtered solution, the product separated as yellow needles. The analytical sample, which was further treated by a period of heating in suspension in boiling distilled water, was a white, microcrystalline material.

*Anal.* Calcd. for $C_6H_6O_2N_4$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.50; H, 3.74; N, 33.41.

Infrared spectrum (Nujol mull): 3.01i, 3.14i, 3.40i, 3.47m, 5.83i, 5.90i, 6.01i, 6.17sm, 6.23m, 6.60w, 6.85m, 6.95sw, 7.24-bm, 7.42sw, 7.60w, 7.79m, 8.20bw, 8.65bw, 9.00w, 9.44w, 10.29-w, 12.03m, 12.32bm, 13.20m, 13.57bw, 14.53bm.

**6-Benzyl-2,4-dihydroxy-5H-pyrrolo[3,4-d]pyrimidin-7(6H)-one (VIIb). (A) From Compound Ib.**—A 15.6-g. quantity (0.06 mole) of compound Ib was mixed thoroughly with 72 g. (1.2 moles) of urea and heated at 180° for 15 min. in an oil bath. During this period the flask containing the melt was evacuated with an aspirator. The mixture was allowed to cool and then was treated with 300 ml. of boiling water. The water-insoluble fraction was collected by filtration, then extracted with 200 ml. of 95% ethanol at the boiling point. The remaining insoluble residue (2.2 g.; 14% yield) was a white solid, m.p. *ca.* 315–320° dec. It was recrystallized from 50 ml. of dimethylformamide to yield 2 g. of compound VIIb, m.p. *ca.* 315–318° dec.

*Anal.* Calcd. for $C_{13}H_{11}O_3N_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.96; H, 4.29; N, 16.54.

Infrared spectrum (Nujol mull): 3.24m, 3.38i, 3.45i, 5.74i, 5.94si, 6.02i, 6.33m, 6.42m, 6.75w, 6.86m, 6.89sm, 6.97m, 7.09m, 7.30w, 7.36w, 7.59bw, 7.76w, 7.93m, 8.33m, 8.49w, 8.64w, 8.68w, 9.20bw, 9.35w, 9.76w, 9.93w, 11.82bw, 12.15bm, 13.03m, 13.53m, 13.75w, 14.15m, 14.64w.

The ethanol extract of the water-insoluble fraction yielded 8.2 g. (69%) of compond IIIb as white needles, m.p. 110–113°, when concentrated to 50 ml. and cooled to induce crystallization.

**(B) From Compound IVb.**—Compound IVb (2.56 g.; 0.01 mole) was dissolved in 150 ml. of boiling water to which sufficient concentrated hydrochloric acid had been added (*ca.* 50 ml.) to give a clear solution. An additional 10 ml. of concentrated hydrochloric acid was added and the mixture was stirred and maintained at 90° while a solution of 2.07 g. (0.03 mole) of sodium nitrite in 20 ml. of water was added dropwise. The temperature was kept at 90° for an additional 15 min. after the nitrite addition was complete, then the mixture was filtered while still hot to collect the precipitated product, which was washed on the filter and dried.[19] The yield was 1.08 g. (42%) of a white solid, m.p. *ca.* 315–317° dec., which was identical to the product obtained by the urea condensation described under A above.

**2,4-Dihydroxy-5H-pyrrolo[3,4-d]pyrimidin-7(6H)-one (VIIh).** —Compound IVh (1.0 g.; 0.006 mole) was suspended in a solution prepared from 10 ml. of concentrated sulfuric acid and 20 ml. of water. To the stirred suspension, cooled to 0–5°, 0.41 g. (0.006 mole) of sodium nitrite dissolved in 10 ml. of water was added dropwise. After the addition was complete the reaction was allowed to proceed at room temperature for 27 hr.[20] The product was removed by filtration, washed on the filter with water, and dried to yield 0.47 g. (47%) of a pale yellow solid, m.p. >360°. It was purified for analysis first by washing in 10 ml. of boiling 20% hydrochloric acid followed by 10 ml. of boiling water. The washed product was then dissolved in 50 ml. of boiling concentrated ammonium hydroxide, and decolorized with Norit. When the filtered, cooled solution was acidified to pH 6 with glacial acetic acid, a white microcrystalline solid precipitated and was collected by filtration, washed on the filter with water, and dried. The recovery was 0.2 g. of material which did not melt below 360°.

*Anal.* Calcd. for $C_6H_5O_3N_3$: C, 43.13; H, 3.02; N, 25.15. Found: C, 42.93; H, 2.88; N, 25.07.

Infrared spectrum (Nujol mull): 2.99m, 3.13m, 3.25m, 3.38i, 3.45i, 5.78si, 5.83i, 5.89si, 5.94si, 6.01i, 6.45m, 6.86m, 6.93m, 7.00m, 7.10m, 7.20bm, 7.60m, 8.04m, 8.24m, 8.65w, 9.01bw, 9.62m, 10.37bw, 11.45bm, 12.02bm, 12.70bm, 13.05m, 13.56bm, 13.82bm.

**2-Amino-6-benzyl-4-phenyl-3,4-dihydro-5H-pyrrolo[3,4-d]pyrimidin-7(6H)-one (Xb).**—An ethanolic sodium ethoxide solution prepared from 1.15 g. (0.05-g. atom) of sodium and 50 ml. of absolute ethanol was added with stirring to a solution of 5.0 g. (0.05 mole) of guanidine hydrochloride in 50 ml. of absolute ethanol. The precipitated sodium chloride was removed by filtration, and the filtered guanidine solution was added over a period of *ca.* 15 min. to a stirred suspension of 2.75 g. (0.01 mole) of compound VIIIb in 250 ml. of absolute ethanol. After compound VIIIb had dissolved, the solution was heated to 60° and held at this temperature for 1 hr. while stirring was continued. Precipitation of the product started after *ca.* 15 min. After the reaction mixture had cooled to room temperature, 2.80 g. (88%) of a pale yellow precipitate was removed by filtration. The product melted at 272–273° dec. No satisfactory method of crystallization was found for this compound.

Infrared spectrum (Nujol mull): 2.88i, 2.93sm, 3.05i, 3.38i, 3.45i, 5.97i, 6.05i, 6.11i, 6.31sm, 6.38m, 6.53i, 6.62i, 6.82i, 7.13i, 7.56m, 7.76i, 8.09w, 8.52sm, 8.60m, 8.66bm, 8.99w, 9.14m, 9.31m, 9.74w, 9.99bw, 10.26w, 10.52w, 10.85w, 11.91w, 12.10w, 12.20w, 12.45w, 12.82w, 13.33m, 13.58i, 14.26i.

The hydrochloride was prepared in order to permit recrystallization of a sample for analysis. One gram of Xb was suspended in 100 ml. of absolute ethanol and dry hydrogen chloride was passed into the suspension with stirring. The free base dissolved and the hydrochloride precipitated after a few minutes. After 15 min., introduction of the gas was stopped and the reaction mixture was concentrated to dryness under reduced pressure over a steam cone. The residue was recrystallized twice from

(17) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931); H. Lund, *ibid.*, **37**, 936 (1934); *J. Am. Chem. Soc.*, **74**, 3188 (1952).

(18) A reaction between the enol Ib and guanidine carried out in the same fashion, but without sodium ethoxide (omitted to avoid sodium enolate formation), led to a 24% yield of crude IVb and recovery of *ca.* 60% of Ib.

(19) Procedure based on the deamination method of H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 3046 (1959).

(20) Procedure based on the deamination method of L. O. Ross, L. Goodman, and B. R. Baker, *ibid.*, **81**, 3108 (1959).

95% ethanol to yield 0.6 g. of the hydrochloride of Xb, m.p. 273–274° dec.

*Anal.* Calcd. for $C_{19}H_{19}ON_4Cl$: C, 64.31; H, 5.40; N, 15.79. Found: C, 64.61; H, 5.44; N, 15.93.

Infrared spectrum of the hydrochloride of Xb (Nujol mull): 2.91m, 3.02m, 3.40i, 3.47i, 5.87i, 5.97i, 6.29m, 6.39i, 6.71m, 6.90i, 6.99sm, 7.18m, 7.30w, 7.36m, 7.59m, 7.90w, 8.06w, 8.44m, 8.61w, 8.91bw, 9.34w, 9.76w, 10.05w, 10.31w, 10.49w, 12.03w, 12.65bw, 12.99m, 13.90m, 14.09m, 14.40bm.

**2-Amino-6-cyclohexyl-4-phenyl-3,4-dihydro-5*H*-pyrrolo[3,4-*d*]-pyrimidin-7(6*H*)-one (Xc).**—A solution of guanidine in absolute ethanol was prepared from 2.0 g. (0.02 mole) of guanidine hydrochloride, 0.46 g. (0.02 g.-atom) of sodium and a total of 50 ml. of absolute ethanol, by the same procedure used in the preparation of Xb, described previously. Reaction of the guanidine solution with 2.7 g. (0.01 mole) of compound VIIIc in 200 ml. of ethanol was carried out at the reflux temperature, but otherwise the procedure was as described above. When the reaction mixture was then concentrated nearly to dryness under reduced pressure over a steam cone, a yellow gum separated and was washed with 200 ml. of water. The resulting cream-colored solid was collected by filtration and dried in a desiccator. The yield was 3.0 g. (95%); m.p. 244–247° dec. The compound was obtained as a white microcrystalline solid, m.p. 247–249° dec., after it had been washed with dimethylformamide, then with acetone. After

recrystallization from a small volume of methanol the m.p. was 254–256° dec.

*Anal.* Calcd. for $C_{18}H_{22}ON_4$: C, 69.65; H, 7.14; N. 18.05. Found: C, 69.14; H, 6.85; N, 18.16.

Infrared spectrum (Nujol mull): 2.86m, 2.95i, 3.06m, 3.38i, 3.45i, 6.02i, 6.07i, 6.24i, 6.34i, 6.61i, 6.71sm, 6.82sm, 6.92i, 7.04m, 7.19i, 7.28sm, 7.46bm, 7.80i, 7.90m, 8.13m, 8.26w, 8.45m, 8.54m, 8.73bm, 9.18m, 9.73w, 10.16w. 11.19w, 11.36w, 11.98w, 12.28w, 12.52w, 12.72m, 12.89w, 13.32m, 14.20i.

The substance yielded a hydrochloride in the form of white crystals, m.p. 298–299° dec. when recrystallized from 10% hydrochloric acid containing some ethanol.

*Anal.* Calcd. for $C_{18}H_{23}ON_4Cl$: C. 62.33; H, 6.68; N, 16.15. Found: C, 62.65; H, 6.75; N, 15.84, 15.70.

Infrared spectrum (Nujol mull): 3.03bm, 3.19m, 3.38i, 3.45i, 5.83m, 6.00i, 6.19m, 6.34i, 6.71w, 6.89i, 7.09m, 7.13sm, 7.30w, 7.46w, 7.88m, 8.00w, 8.01m, 8.33m, 8.39sw, 8.50w, 8.75bw, 9.03bw, 10.14w, 11.20w, 12.13bw. 12.54w, 12.89bm, 14.23bm, 14.35m.

It was advantageous to obtain the purified free base Xc from the purified hydrochloride rather than by the direct methanol recrystallization. The hydrochloride was dissolved in boiling water and the free base was precipitated by addition of a few drops of concentrated ammonium hydroxide, then collected and washed on the filter with water and acetone to give material melting at 254–256° dec.

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# Investigations in Heterocycles. XII. The Synthesis of Pyrazolo[1,5-*c*]quinazolines[1]

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The facile rearrangement of 4-hydroxyquinoline and its derivatives in the presence of excess hydrazine hydrate gives rise to 5(*o*-aminophenyl)pyrazoles. These compounds in turn serve as intermediates in the synthesis of some new heterocycles, pyrazolo[1,5-*c*]quinazolines. The chemical and spectral properties of these substances are discussed.

In a recent review[2] we discussed the application of the intramolecular Mannich reaction and the organic acid ring closure condensations in the synthesis of several new heterocyclic systems; *e.g.*, dihydrobenzothiadiazine 1,1-dioxide, tetrahydro-1,3-benzodiazepines, and indolo[2,3-*a*]quinolizines. The principle therein expounded, *i.e.*, insertion of a one carbon fragment between two hetero atoms to form a ring, has now been extended to include the preparation of other heterocycles. Thus, the synthesis and the chemical and physical properties of pyrazolo[1,5-*c*]quinazolines will be the subject of this report.

The preparation of this new heterocycle has been facilitated by the ready availability of 5(*o*-aminophenyl)-pyrazole (I). This substance was reported recently by Alberti[3] to be obtainable *via* a one-step synthesis. Compound I is similar from a reactivity standpoint to *o*-aminobenzamide. This was indeed manifested by its condensation with aldehydes or acid chlorides, and acid anhydrides. Some of these reactions leading to the synthesis of various pyrazolo[1,5-*c*]quinazolines are outlined in Scheme I and the compounds prepared in this series are listed in Table I.

Condensation of I with excess formic acid under reflux gave a 78% yield of the parent heterocycle (compound 1, Table I). However, when I was allowed to react with excess acetic anhydride under reflux, the sole
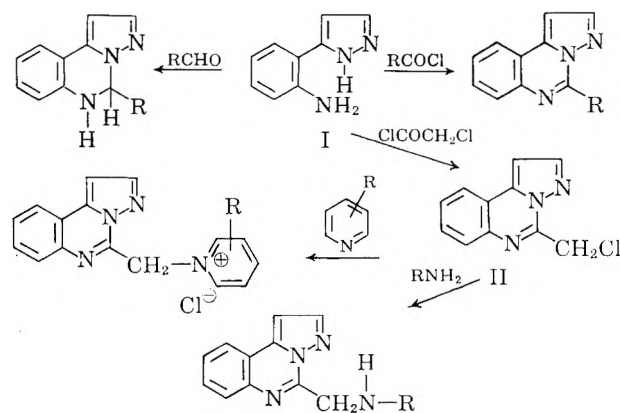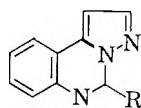


**Scheme I**

(3) G. Alberti, *Gazz. chim. ital.*, **87**, 772 (1957). Although this author did not express a mechanistic rationale for this transformation, it seems more than likely that a pseudo base is generated leading to an α,β-unsaturated
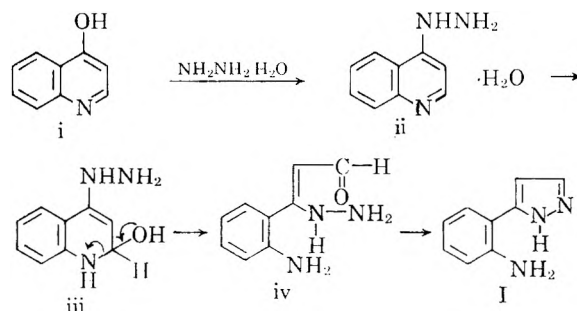


aldehyde which undergoes intramolecular dehydrative condensation with the hydrazino portion of the molecule to form I.
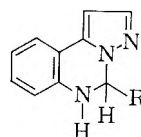
(1) This subject was discussed in part by G. deStevens in a Symposium lecture on The Chemistry of Nitrogen Heterocycles sponsored by the Medicinal Chemistry Division, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(2) G. deStevens, *Record Chem. Progr.*, **23**, No. 2, 195 (1962).

TABLE I

PYRAZOLO[1,5-c]QUINAZOLINES[a]



| | R | M.p., °C. | Yield, % | Empirical formula | Calcd., % | | | Found, % | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | C | H | N |
| 1 | —H | 83–84 | 78 | $C_{10}H_7N_3$[a] | 70.95 | 4.17 | 24.82 | 71.00 | 4.20 | 24.96 |
| 2 | —CH₃ | 91 | 70 | $C_{11}H_9N_3$[b] | 72.10 | 4.95 | 22.93 | 71.74 | 5.24 | 22.23 |
| 3 | —C₂H₅ | 65 | 51 | $C_{12}H_{11}N_3$[a] | 73.07 | 5.62 | 21.30 | 72.75 | 5.73 | 20.87 |
| 4 | —CH₂Cl | 142 | 65 | $C_{11}H_8ClN_3$[c] | 60.70 | 3.71 | 19.31 | 60.47 | 3.88 | 19.09 |
| 5 | —CHCl CH₃ | 154 | 40 | $C_{12}H_{10}ClN_3$[c] | 62.20 | 4.35 | 18.13 | 62.17 | 4.38 | 17.86 |
| 6 | —C₆H₁₁[d] | 64.5–65 | 32 | $C_{16}H_{17}N_3$[e] | 76.43 | 6.82 | 16.71 | 75.92 | 6.89 | 16.45 |
| 7 | —CH₂—C₅H₉[f] | B.p. 148 0.3 mm. | 41 | $C_{16}H_{17}N_3$ | 76.43 | 6.82 | 16.71 | 76.48 | 6.79 | 16.37 |
| 8 | —CH₂—N(H)—CH₃ | 235 | 45 | $C_{12}H_{12}N_4 \cdot HCl$[c] | 57.95 | 5.27 | 22.53 | 57.93 | 5.39 | 22.35 |
| 9 | —CH₂—N(H)—CH₂—C₆H₄—F | 230 | 22 | $C_{18}H_{15}FN_4 \cdot HCl$[c] | 63.07 | 4.71 | 16.35 | 62.68 | 4.94 | 15.95 |
| 10 | —C₆H₅ | 125–127 | 72 | $C_{16}H_{11}N_3$[c] | 78.32 | 4.52 | 17.14 | 78.01 | 4.71 | 16.97 |
| 11 | 3,4,5(OCH₃)₃—C₆H₂— | 124–125 | 30 | $C_{19}H_{17}N_3O_3$[c] | 68.05 | 5.11 | | 68.37 | 5.24 | |
| 12 | —CH₂—N⊕( )Cl⊖ | 270–272 | 44 | $C_{16}H_{13}ClN_4$[g] | 64.74 | 4.42 | 18.88 | 64.65 | 4.53 | 18.66 |
| 13 | —CH₂—N⊕( )Cl⊖ (H₃C) | 231 | 54 | $C_{17}H_{15}ClN_4$[g] | 65.69 | 4.86 | 18.03 | 65.47 | 5.02 | 17.71 |

Solvents used in recrystallization:   [a] Ethyl alcohol–water.   [b] Ether–petroleum ether (low boiling).   [e] Ethyl alcohol.   [d] Cyclohexyl group.   [e] Acetone–hexane.   [f] Cyclopentyl group.   [g] Ethyl alcohol–ether.

TABLE II

1,2-DIHYDROPYRAZOLO[1,5-c]QUINAZOLINES



| | R | M.p., °C. | Yield, % | Empirical formula | Calcd., % | | | Found, % | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | C | H | N |
| 14 | —H | 150 | 15 | $C_{10}H_9N_3$[c] | 70.45 | 5.25 | | 70.12 | 5.16 | |
| 15 | —C₆H₅ | 105–106 | 64 | $C_{16}H_{13}N_3$[b] | 77.78 | 5.30 | 16.98 | 77.68 | 5.44 | 16.68 |
| 16 | 4-Cl—C₆H₄ | 137–138 | 61 | $C_{16}H_{12}ClN_3$[d] | 68.20 | 4.29 | 14.91 | 67.95 | 4.58 | 14.61 |
| 17 | 4-F—C₆H₄ | 196–197 | 59 | $C_{16}H_{12}FN_3$[a] | 72.44 | 4.56 | 15.84 | 72.56 | 3.94 | 15.55 |
| 18 | 3,4-(Cl₂)₂—C₆H₃— | 99–100 | 60 | $C_{16}H_{11}Cl_2N_3$[a] | 60.78 | 3.51 | 13.23 | 60.41 | 3.69 | 12.85 |
| 19 | 3,4,5-(OCH₃)₃—C₆H₂ | 122–124 | 35 | $C_{19}H_{19}N_3O_3$[a] | 67.64 | 5.67 | 12.46 | 67.49 | 5.85 | 12.67 |

Solvents used in recrystallizations:   [a] Ethyl alcohol–water.   [b] Ether–petroleum ether (low boiling).   [c] Ethyl alcohol.   [d] Cyclohexyl group.

product obtained was 1-acetyl-5-(o-acetomidophenyl)-pyrazole (III). Elemental analytical data in addition to infrared absorption studies provided strong support for this structural assignment. A strong band at 1685 cm.⁻¹ corresponds to the acetamido grouping whereas an intense sharp absorption band at 1750 cm.⁻¹ is typical of the acetyl pyrazole grouping.[4] It was observed subsequently that an equivalent amount of acid chloride usually served as an effective condensing agent giving rise to good yields of 2-substituted pyrazolo-[1,5-c]quinazolines.

On the other hand, interaction of I with formaldehyde in the presence of acid or base catalyst, or even under neutral conditions, gave a poor yield of 1,2-dihydro-pyrazolo[1,5-c]quinazoline whereas condensation with other aliphatic aldehydes did not afford the desired

tricyclic compounds. When I was allowed to react with aromatic aldehydes, fairly good yields of products were obtained. However, the dihydropyrazolo[1,5-c]quinazoline structure for these compounds could not be readily assumed from the mode of preparation. The Schiff base derivative could also be formed under these conditions. Several factors favor the closed ring system (compounds 15 through 19, Table II). First of all no reaction with sodium borohydride was observed with any of these compounds, starting material being recovered almost quantitatively. The Schiff base surely would have been reduced to the benzylamine derivative under these conditions.[5] In addition, the spectral data lend support to the cyclic structures. The 2-aryl sub-

(4) W. Ried and F. J. Königstein, Ann. Chem., 625, 54 (1959).

(5) This type of reaction proved very useful in establishing unequivocally the structure of 1,2,4,5-tetrahydro-1,3-benzodiazepines. See ref. 2 and others therein.

### Table III

Ultraviolet Absorption Data on Pyrazolo[1,5-c]quinazo-
lines and 1,2-Dihydropyrazolo[1,5-c]quinazolines[a]

| Compound | $\lambda_{max}$ in ethyl alcohol, m$\mu$ | $\epsilon$ |
|---|---|---|
| 1 | 255 | 36,090 |
|  | 316 | 3,680 |
|  | 328 | . . . |
| 2 | 237 | 27,480 |
|  | 253 | 31,580 |
|  | 315 | 4,670 |
|  | 328 | 4,230 |
| 3 | 237 | 30,390 |
|  | 253 | 34,260 |
|  | 314 | 4,910 |
|  | 327 | 4,380 |
| 4 | 254 | 33,030 |
|  | 278 | 5,200 |
|  | 326 | 3,280 |
| 5 | 255 | 34,960 |
|  | 280 | 4,740 |
|  | 323 | 3,390 |
| 6 | 237 | 33,110 |
|  | 253 | 35,900 |
|  | 314 | 5,710 |
|  | 327 | 5,290 |
| 7 | 237 | 29,250 |
|  | 254 | 31,950 |
|  | 315 | 4,730 |
|  | 329 | 4,270 |
| 8 | 236 | 28,100 |
|  | 254 | 34,830 |
|  | 316 | 19,140 |
|  | 326 | 3,070 |
| 9 | 237 | 28,330 |
|  | 254 | 33,830 |
|  | 316 | 4,040 |
|  | 329 | 3,300 |
| 10 | 255 | 39,760 |
|  | 298 | 8,180 |
| 11 | 256 | 33,290 |
|  | 308 | 14,270 |
| 12 | 238 | 28,120 |
|  | 252 | 35,400 |
|  | 317 | 3,370 |
| 13 | 238 | 26,830 |
|  | 254 | 35,320 |
|  | 317 | 3,390 |
| 14 | 230 | 28,100 |
|  | 318 | 2,787 |
| 15 | 227 | 25,920 |
|  | 328 | 4,480 |
| 16 | 227 | 31,880 |
|  | 328 | 4,550 |
| 17 | 227 | 25,520 |
|  | 329 | 4,640 |
| 18 | 227 | 31,070 |
|  | 329 | 4,670 |
| 19 | 230 | 34,200 |
|  | 329 | 4,500 |

[a] A Beckman recording spectrophotometer, Model DK, was used.

stituted compounds give two maxima in the ultraviolet (see Table III), one from 228 to 230 m$\mu$ and the other at 328 m$\mu$. These maxima are at wave lengths comparable to those of the parent dihydropyrazolo[1,5-c]-quinazoline (compound 15). As a rule, Schiff bases absorb at 255 to 260 m$\mu$ and at 310 to 320 m$\mu$.[6] Also, the n.m.r. of these compounds offer confirmatory evi-

dence for the cyclic structure. The azomethine proton of benzalaniline absorbs at 8.35 $\delta$[7] whereas the methine proton of the 2-aryl substituted dihydropyrazolo[1,5-c] quinazoline is found at 6.37 $\delta$.[8]

Compound I was allowed to react with a wide variety of aliphatic and aromatic acid chlorides. However, chloroacetyl chloride proved to be the most versatile agent. (See Scheme I and Table I.) Condensation of chloroacetyl chloride with I dissolved in dioxane containing sodium hydroxide gave a 65% yield of 2-chloromethylpyrazolo[1,5-c]quinazoline (II). The halogen group in this compound is very reactive and thus II served as a useful intermediate in other transformations. For instance, when II was allowed to react with primary and secondary amines, compounds with basic moieties at the methylene group of position 2 were formed. The condensation of II with pyridine and picoline gave rise to the corresponding quaternary salts.

### Experimental[9]

**Pyrazolo[1,5-c]quinazoline.**—5(o-Aminophenyl)pyrazole[3,10] (1.6 g.; 0.01 mole) was dissolved in 10 ml. of formic acid and the resulting solution was refluxed for 2 hr. The excess formic acid was then removed in vacuo and the resulting white powder was collected on a Büchner funnel and was washed well with water. One recrystallization of this powder from ethyl alcohol–water (1:2) yielded analytically pure needles.

**Pyrazolo[1,5-c]quinazoline Hydrochloride.**—Two hundred milligrams of pyrazolo[1,5-c]quinazoline dissolved in 5 ml. of ethyl alcohol was treated with 3 ml. of ethyl alcohol saturated with hydrogen chloride. After stirring for a few minutes a white precipitate was obtained which was recrystallized from ethyl alcohol to afford white crystals, m.p. 184–185°.

*Anal.* Calcd. for $C_{10}H_8N_3Cl$: C, 58.41; H. 3.92; N, 20.44. Found: C, 58.02; H, 4.05; N, 19.82.

The dissolution of the above salt in water resulted in the precipitation of the free base from solution on standing at room temperature.

**5-Methylpyrazolo[1,5-c]quinazoline.**—5(o-Aminophenyl)-3-methylpyrazole[3] (3.4 g.; 0.02 mole) was allowed to react under reflux with 20 ml. of formic acid for 2 hr. The reaction mixture was worked up in the same manner as described above. Recrystallization of the crude product from ethyl alcohol–water (1:2) gave a 75% yield of pure substance, m.p. 93–94°.

*Anal.* Calcd. for $C_{11}H_9N_3$: C, 72.07; H, 4.95; N, 22.93. Found: C, 71.85; H, 4.98; N, 22.56.

**1-Acetyl-5-(o-acetamidophenyl)pyrazole (III).**—2-(o-Aminophenyl)pyrazole (I) (1.6 g.; 0.01 mole) was dissolved in 15 ml. of acetic anhydride and the resulting solution was heated at reflux temperature for 2 hr. The acetic anhydride was removed at the water pump and the remaining crystalline residue was recrystallized twice from ethyl alcohol to give 0.5 g. of white needles, m.p. 153–155°.

*Anal.* Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.22. Found: C, 64.22; H, 5.41; N, 17.12.

Infrared spectra: 1750 cm.$^{-1}$ (CH$_3$CO of pyrazole); 1685 cm.$^{-1}$ (N-acetamidophenyl), as a mull in Nujol.

**General Procedure for the Preparation of 2-Substituted Pyrazolo[1,5-c]quinazolines (Compounds 2, 3, 4, 5, 6, 7, 10 and 11 in Table I). 2-Chloromethylpyrazolo[1,5-c]quinazoline (II).**—5(o-Aminophenyl)pyrazole (I) (9.6 g.; 0.06 mole) was dissolved in 100 ml. of dioxane containing 2.4 g. of sodium hydroxide and 2 ml. of water. To this solution there was added 6.8 ml. of chloroacetyl chloride and the whole was heated on the steam bath for 3 hr. After standing overnight at room temperature the mixture was added with stirring to 1 l. of water whereupon a precipitate was formed. This light tan solid material was collected on a filter, washed well with water, and then dried in vacuo. The yield

(6) F. W. Holly and A. C. Cope, J. Am. Chem. Soc., 82, 3977 (1960).

(7) J. F. King and T. Durst, Can. J. Chem., 40, 883 (1962).

(8) The spectra of these compounds were run in deuteriochloroform using an A60 Varian n.m.r. spectrometer. The internal standard was tetramethylsilane.

(9) The melting points reported herein and in Tables I and II are uncorrected.

(10) E. Koenig and J. Freund, Chem. Ber., 80, 143 (1947).

of crude compound, m.p. 135–140°, was 8.8 g. One recrystallization from ethyl alcohol gave analytically pure substance.

**Condensation of II with Primary Amines. 2-(N-Methylaminomethyl)pyrazolo[1,5-c]quinazoline.**—One hundred milliliters of ethyl alcohol containing methylamine (0.17 g. per ml.) was added dropwise over a period of 15 min. to 2.0 g. of II dissolved in 100 ml. of ethyl alcohol. After stirring the reaction mixture at room temperature for 20 hr. the solution was concentrated to a viscous residue at the water pump. The residue was taken up in a minimum amount of ethyl alcohol and the solution was treated with 5 ml. of ethyl alcohol saturated with hydrogen chloride gas. Addition of this solution to 1 l. of dry ether resulted in the formation of a white precipitate which was collected and recrystallized from ethyl alcohol–ether. The desired compound was isolated as the monohydrochloride salt.

**Preparation of 1-(Pyrazolo[1,5-c]quinazolin-2-ylomethyl)pyridinium Chloride. Method A.**—A mixture of 1.6 g. (0.01 mole) I, 1.13 g. (0.01) mole of chloroacetyl chloride and 10 ml. of pyridine was heated on the steam bath for 3 hr. On chilling the solution, a white crystalline mass was obtained which was collected on a filter and then recrystallized from ethyl alcohol–ether.

**Method B.**—A mixture of 2.17 g. (0.01 mole) of 2-chloromethylpyrazolo[1,5-c]quinazoline and 10 ml. of pyridine was heated in a sealed tube at 100° for 4 hr. The crystalline mass that was formed was collected on a Büchner funnel and recrystallized from ethyl alcohol–ether. Compound 13 in Table I was prepared in similar manner.

**1,2-Dihydropyrazolo[1,5-c]quinazoline.**—5(o-Aminophenyl)-pyrazole (1.6 g.; 0.01 mole) and a molar equivalent of 37% formalin were added to 25 ml. of ethyl alcohol containing one pellet of sodium hydroxide. The solution was heated at reflux on the steam bath for 15 min. After filtering off some amorphous material, the filtrate was neutralized and evaporated to viscous residue *in vacuo*. This residue was extracted with a small amount of hot alcohol. On standing at room temperature, a crystalline substance was obtained which was recrystallized from ethyl alcohol to give an analytically pure product.

**General Method for the Preparation of 2-Aryl Substituted 1,2-Dihydropyrazolo[1,5-c]quinazolines.**—One-tenth molar equivalents of I and of an aromatic aldehyde were dissolved in 50 ml. of ethyl alcohol and the resulting solution was refluxed on the steam bath for 3 hr. After removal of the solvent *in vacuo* the remaining semisolid residue was triturated well with water. The precipitate was collected and recrystallized from a suitable solvent for analysis.

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# Synthesis of D- and L-2-Aminobutylisothiourea Dihydrobromide Isomers and Their Conversion to Guanidothiols, Disulfides, and Thiazolines

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Optically active D- and L-2-aminobutyl bromide was prepared from the enzymatically resolved 2-aminobutyric acids, establishing their configuration. Condensation with thiourea yielded the D- and L-2-aminobutylisothioureas, which readily underwent a pH-dependent intramolecular rearrangement to give the D- and L-2-guanidobutane thiols or D- and L-4-ethyl-2-aminothiazolines. Oxidation of the thiols yielded the optically active 2-guanidobutyl disulfides.

Among the many aminoalkylisothioureas that are capable of protecting mice against a single lethal dose of X radiation, one compound, DL-S, 2-aminobutylisothiourea·HBr (2-ABT), seemed of particular interest. Treatment with this compound at a dose level of 4–5 μmoles per mouse (as compared with 16 μmoles per mouse for a parent compound, S,2-aminoethylisothiourea·di·HBr, AET[3]) prior to 900 r. whole-body X-irradiation enables 95–100% of the mice to survive more than 30 days. Ion exchange analysis[4] confirms that 2-ABT(I) participates in the same intramolecular rearrangements as the parent compound, AET, forming 2-amino-4-ethylthiazoline, II, at a pH of 2.5–5.0, and 2-guanidobutane thiol, III, at a pH of 6.0–9.0. Oxidation of the thiol with air or oxygen at an alkaline pH yields the corresponding 2-guanidobutyldisulfide, IV.

In view of these findings, especially the increased activity on a molar dose level, it seemed desirable to prepare the optically active isomers of 2-ABT and the corresponding thiazolines and examine them for protective activity in mice. If a difference in protective activity exists between the optical isomers, then these compounds, isotopically labeled, might provide some insight to the sensitive cellular and biochemical processes affected by radiation. Indeed, when prepared by the methods described herein, the D-2-ABT is twice as active as the L isomer in protecting mice against 900 r. X-radiation. Intracellular distribution studies using S[35]- and C[14]-labeled compounds[5] reveal significant differences in binding in the cellular fractions between the two compounds. In addition, the 2-ABT isomers were found to have interesting pharmacological proper-



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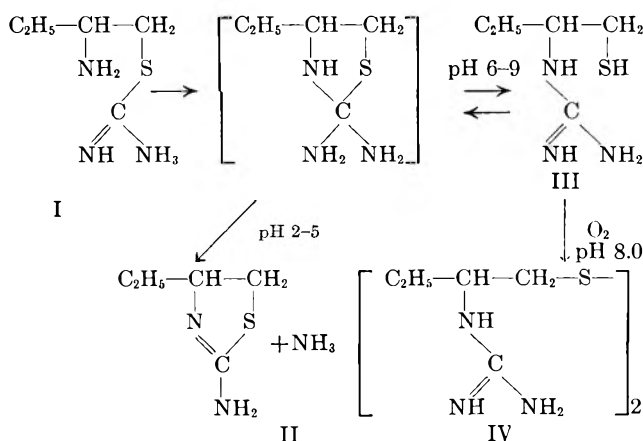
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(2) Operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

(3) R. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *Radiation Res.*, **7**, 22 (1957).

(4) J. X. Khym, D. G. Doherty, and R. Shapira. *J. Am. Chem. Soc.*, **80**, 3342 (1958).

(5) R. H. Bradford, R. Shapira, and D. G. Doherty, *Intern. J. Radiation Biol.*, **3**, 595 (1961).

ties when compared to the other radioprotective isothioureas.[6]

A direct method for the preparation of the necessary starting materials, D- and L-2-aminobutanols, in quantity, is the enzymic resolution of DL-2-aminobutyric acid followed by the reduction of the stereoisomers with lithium aluminum hydride to the corresponding amino alcohols. This procedure offers the additional advantage of correlating the configuration of the alcohol with that of the α-amino acid. Previous experience with the papain-catalyzed asymmetric anilide synthesis[7] had indicated that its specificity is probably broad enough to include 2-aminobutyric acid and prompted us to use this method rather than the acylase resolution of Birnbaum, et al.[8] After the initial preparation of D- and L-2-aminobutanol by this procedure, the resolution of DL-2-aminobutanol via salt formation by Radke, et al.,[9] came to our attention, and was used for subsequent batches. The [−]-2-aminobutanol was isolated in satisfactory yield from the D-tartrate salt and proved to be equivalent to the D-2-aminobutanol prepared from D-2-aminobutyric acid. However, contrary to the statement by Radke, et al.,[9] that seeding with [−]-2-amino-butanol-L-glutamate precipitates the [+]-2-aminobutanol-L-glutamate, we found it essential to seed with the L-2-aminobutanol-L-glutamate to achieve the desired resolution. The corresponding 2-aminoalkyl bromides, not previously reported, were readily prepared by treatment of the amino alcohols with concentrated hydrobromic acid.[10] It was essential, in order to avoid the formation of thiazoline, to prepare the isothiourea in a relatively anhydrous medium. Both optically active isothioureas exhibit polymorphism in their crystallization, the lower melting form being the first one obtained. The polymorphs were identical in their analyses and properties in solution. They also yielded the same derivatives and possessed the same biological activity. In addition, the melting point of an analytical sample of D-2-ABT, stored two years at room temperature in a desiccator, had risen from its initial value of 157–158° to 177–178° and, on re-analysis, yielded results identical with those obtained initially.

The optical properties of the guanidothiols and disulfides are similar to those of cysteine–cystine. Conversion of the L-thiol to the disulfide changes $[\alpha]^{21}D$ from −7.3 to +200°. The disulfides exhibit a large temperature coefficient—1.2°/degree—as well as a marked solvent effect, the specific rotation of the L-disulfide at 0° being +225° in water and at 21° being +200° in water, +175° in N HCl, +92° in N NaOH, and +175° in 8 M urea (c, 1%). The disulfides also have a weak absorption band in the ultraviolet, $\epsilon_{max}^{247} = 335$ (water), which is absent in the thiol. The alkaline solution of the L-disulfide disproportionates on standing to the equilibrium mixture of thiol–disulfide as indicated by the decrease in rotation, loss of the ultraviolet peak, and confirmed by the nitroprusside reaction, the equilibrium value being approximately 60% —S—S—/40%

—SH. Inclusion of the asymmetric carbon atom in the ring, L-2-amino-4-ethylthiazoline, increases the negative rotation from +7.3° of the thiol to −25.8° for the cyclic compound. The conversion of the isothiourea to the thiazoline at an acid pH can readily be followed by the change in rotation, and was in good agreement with the results obtained with the DL isomer utilizing ion exchange analysis.[4]

The high anomalous rotation observed when an optically active thiol is oxidized to the disulfide has been the subject of speculation since it was noted by Van't Hoff for the conversion of cysteine $[\alpha]^{20}D = +20.5°$ to cystine $[\alpha]^{20}D = -223°$ (c, 1%, 1 N HCl). Kauzmann and Eyreing[11a] suggested that it was due to forces restricting the freedom and orientation of the groups in the molecule. Fieser[11b] extended this, proposing that cystine formed a symmetrical, intramolecular hydrogen bonded three-ring system at pH's where the rotatory power was maximum. In homocystine, $[\alpha]^{25}D = +75.5°$ (c, 1%, N HCl) the lack of high rotation was attributed to the presumably less stable nonsymmetrical hydrogen bonded ring system. Fregda[11c] compared the rotations of a series of carboxylic acid disulfides and concluded that ring formation played a negligible role, the high optical activity arising from a disulfide bond in the molecule in proximity to an asymmetric center. Additional support for this was provided by Balenović, et al.,[11d] who prepared β-homocystine and found that, contrary to Fiesers' proposition, it had a rotation, $[\alpha]^{14}D = -262°$ (c, 1%, N HCl), higher than cystine. They also observed that disulfides, in contrast to the thiols, have weak absorption bands in the ultraviolet, a region associated with specific rotation in the visible spectrum. The important consequences of the nonplanarity of the —S—S— bond to the steric properties of the disulfides was pointed out by Calvin,[11e] and Foss[11f] noted the intrinsic asymmetry of the disulfide bond. Taking these facts into consideration, Strem, et al.,[11g] in a discussion of the rotatory dispersion of cystine, postulated that the 90° dihedral angle gave rise to a screw sense in all disulfides. With no asymmetric center, right and left senses could occur with equal frequency, but when asymmetric R groups are present, such as in cystine or the basic disulfides we report, a preferred configuration would give rise to an intrinsic rotation associated with the disulfide bond. This last explanation, with the additional corollary that the asymmetric atom be separated by not more than one methylene group from the disulfide bond, seems to fit best the present experimental observations.

Configurationally, the optically active compounds in this series are given the designation D and L since they arise from the corresponding amino acids by reactions not involving the asymmetric carbon atom. Alternatively, the absolute notation of Cahn, Ingold, and Prelog[12] may be used, the D series corresponding to the (R) and the L series to the (S). It is interesting to note than in L-cysteine, the exception in this system, the

(6) V. DiStefano and D. E. Leary, *Pharmacol. Exptl. Therap.*, **126**, 304 (1959).

(7) D. G. Doherty and E. A. Popenoe, Jr., *J. Biol. Chem.*, **189**, 447 (1951).

(8) S. M. Birnbaum, L. Levintow, R. B. Kingsley, and J. P. Greenstein, *ibid.*, **194**, 455 (1952).

(9) F. H. Radke, R. B. Fearing, and S. W. Fox, *J. Am. Chem. Soc.*, **76**, 2801 (1954).

(10) F. Cortese, *Org. Syn.*, **2**, 91 (1943).

(11) (a) W. Kauzmann and H. Eyring, *J. Chem. Phys.*, **9**, 49 (1941); (b) L. Fieser, *Rec. trav. chim.*, **69**, 410 (1950); (c) A. Fregda, *Acta Chem. Scand.*, **4**, 1307 (1950); (d) K. Balenović, I. Jambrešić, B. Gašpert, and D. Cerar, *Rec. trav. chim.*, **75**, 1252 (1956); (e) M. Calvin, in "Glutathione, A Symposium," Academic Press, New York, N. Y., 1954, p. 7; (f) O. Foss, in "Organic Sulfur Compounds," N. Kharasch, ed., Pergamon Press, New York, N. Y., 1961, p. 78; (g) J. Strem, Y. S. R. Krishna-Prasad, and J. A. Schellman, *Tetrahedron*, **13**, 180 (1961).

(12) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

naturally occurring amino acid has the (R) configuration, as does the more radioprotective (D-2-ABT) of the two isothioureas.

## Experimental[13]

**N-Isocaproyl-DL-2-aminobutyric Acid.**—A solution of 103 g. (1 mole) of DL-2-aminobutyric acid in 250 ml. of 4 N sodium hydroxide was cooled in ice and 148 g. (1.1 moles) of isocaproyl chloride and 275 ml. of 4 N sodium hydroxide added in portions with vigorous shaking over 0.5 hr. Acidification with concd. hydrochloric acid yielded a gum, which crystallized on scratching. The precipitate was filtered, washed with water, and dried. Yield: 182 g. (90%) m.p. 106–110°. Recrystallization from ethyl acetate–petroleum ether raised the m.p. to 111–113°.

*Anal.* Calcd. for $C_{10}H_{19}O_3N$ (201.3): C, 59.68; H, 9.51; N, 6.97. Found: C, 59.69; H, 9.60; N, 7.11.

**N-Isocaproyl-L-2-aminobutyryl Anilide.**—The acyl amino acid was resolved essentially by the procedure of Doherty and Popenoe.[7] Finely ground papain was mixed with 100 ml. of 0.1 M citrate buffer (pH 5), 150 ml. of water, 2.5 g. potassium cyanide, and adjusted to pH 5 with acetic acid. The mixture was stirred 1 hr. and filtered with suction through a pad of Hyflo filter aid. Isocaproyl-DL-aminobutyric acid, 100.5 g. (0.5 mole) was dissolved in a mixture of 150 ml. of N sodium hydroxide, 150 ml. of 0.1 M citrate buffer, 270 ml. of 2 N sodium acetate, and 45.5 ml. of redistilled aniline, and warmed to 45°. The enzyme solution was added, the mixture made up to 1 l. with water, and incubated at 37°. The anilide, which began crystallizing after 10 min. was filtered off after 24 hr., washed with water, and dried. The filtrate was reincubated and reserved for the isolation of isocaproyl-D-aminobutyric acid. Yield: 68 g. (99%), m.p. 166–168°, $[\alpha]^{23}D$ −67.5°, (c, 2%, $CH_3CO_2H$). The anilide was dissolved in 300 ml. of hot absolute ethanol, treated with Norite, and filtered to remove a small amount of protein, diluted to 1 l. with water, and allowed to crystallize overnight at 0°. Yield: 57 g., m.p. 171–172.5°, $[\alpha]^{23}D$ −70.0° (c, 2%, AcOH).

*Anal.* Calcd. for $C_{16}H_{24}N_2O_2$ (275.37): C, 69.53; H, 8.75; N, 10.10. Found: C, 69.43; H, 8.86; N, 9.91.

**L-2-Aminobutyric Acid.**—The L-anilide, 56 g., was refluxed 4 hr. in 300 ml. of 20% hydrochloric acid, concentrated *in vacuo* to dryness three times with additional amounts of water to remove excess hydrochloric acid, taken up in 500 ml. of water, and treated with Norite. The colorless filtrate was neutralized by passing through an IR-4B column in the OH⁻ form,[7] and the eluate wash water concentrated *in vacuo* to 100 ml. The pH was adjusted to 6.6 with acetic acid, 500 ml. of ethanol was added, and the mixture allowed to crystallize overnight at −5°. Yield: 17 g. (81%), $[\alpha]^{23}D$ + 21.0° (c, 5%, N HCl).[8] Alternatively, the filtrate, after hydrolysis, could be neutralized by Dowex-3 OH⁻ in a batch process and a similar yield obtained.

*Anal.* Calcd. for $C_4H_9O_2N$ (103.12): C, 46.59; H, 8.79; N, 13.58. Found: C, 46.70; H, 8.92; N, 13.33.

**D-2-Aminobutyric Acid.**—The small precipitate that formed in the reincubated anilide filtrate was filtered off after 3 days and the filtrate concentrated *in vacuo* to ca. 100 ml. Acidification with cold 2 N hydrochloric acid to pH 1.5 yielded 57 g. of crystalline N-isocaproyl-D-2-aminobutyric acid mixed with some denatured protein. Recrystallization from ethyl acetate–petroleum ether gave 35 g. of pure compound. Yield: 70%, m.p. 102–103°, $[\alpha]^{23}D$ + 16.4° (c, 5% EtOH). The acyl D-amino acid was hydrolyzed and the amino acid isolated as previously described for the L isomer. Yield: 16 g. (90%), $[\alpha]^{23}D$ −21.0° (c, 5%, N HCl).

*Anal.* Calcd. for N-Isocaproyl-D-2-aminobutyric acid, $C_{10}H_{19}O_3N$ (201.25): C, 59.68; H, 9.51; N, 6.97. Found: C, 59.74; H, 9.49; N, 6.98. Calcd. for D-2-aminobutyric acid, $C_4H_9O_2N$ (103.12): C, 46.59; H, 8.79; N, 13.58. Found: C, 46.50; H, 8.95; N, 13.45.

**D- and L- 2-Aminobutanols.**—The isomeric aminobutyric acids were reduced to the corresponding alcohols by lithium aluminum hydride in tetrahydrofuran according to the method of Vogel and Pöhm[14] and isolated by a modified procedure. Lithium aluminum hydride, 4.2 g. (0.11 mole), was added to 100 ml. of dry tetrahydrofuran (dried over sodium hydride and distilled from lithium aluminum hydride) in a 200-ml., three-necked flask fitted

with a stirrer and condenser. The mixture was cooled to 0°, 10.3 g. (0.1 mole) of 2-aminobutyric acid was added in 1-g. portions over 1 hr. and, following the last addition, the mixture was refluxed for 6 hr. The mixture was cooled in ice, diluted with an equal volume of ether, and the excess hydride decomposed by the cautious addition of a few drops of water. The precipitate was filtered, dried, and added to 20 ml. ice-cold 40% sodium hydroxide. The resulting solution was extracted with three 50-ml. portions of ether, and the combined extracts dried over sodium hydroxide pellets and distilled through a 50-cm. vacuum-jacketed, Vigreux column. Yield: 6.2 g. (69%), b.p. 178° (740 mm.),[9] D $[\alpha]^{21}D$ − 10.0°, L $[\alpha]^{21}D$ +10.2° (neat).

**Resolution of DL-2-Aminobutanol.**—The procedure of Radke *et al.*,[9] gave a good yield of the D-2-aminobutanol L-tartrate, which was readily converted to the free D-2-aminobutanol. Resolution with L-glutamic acid, however, did not follow the exact course reported by these authors. Copious seeding of three separate batches of the resolution mixture with pure D-2-aminobutanol L-glutamate, as recommended, over a 3-week period failed to yield any precipitate. However, seeding with pure L-2-aminobutanol L-glutamate obtained *via* the 2-aminobutyric acid route gave an immediate and nearly quantitative precipitation of the L-2-aminobutanol L-glutamate.

**DL-, D-, and L-2-Aminobutylbromide·HBr.**—Two methods were used for the preparation of the aminoalkyl bromides.

**Method A.**—A mixture of 34 g. (0.2 mole) of 2-aminobutanol and 250 ml. of dry chloroform was cooled in an ice bath in a 500-ml. round bottom flask and 46 g. (0.22 mole) of thionyl bromide added dropwise with stirring. After it was allowed to stand overnight at room temperature, the mixture was evaporated *in vacuo* to dryness, taken up in absolute ethanol, and precipitated with ethyl acetate. Yield: 39.6 g. (85%).

**Method B.**—2-Aminobutanol, 34 g. (0.2 mole), was added dropwise to 160 ml. of 48% hydrobromic acid in a 300-ml. three-necked round-bottom flask fitted with a stirrer and short Vigreux column and cooled in an ice bath. Upon completion, the solution was refluxed and slowly distilled, 80 ml. being collected in 3 hr. This was replaced with 80 ml. of 48% hydrobromic acid and the distillation continued for an additional 3 hr. The resultant solution was evaporated *in vacuo* to dryness and the product recrystallized from an absolute ethanol–ethyl acetate mixture. Yield: 37 g. (79%), DL- m.p. 188–189°.

*Anal.* Calcd. for $C_{10}H_{11}NBr_2$ (232.97): C, 20.63; H, 4.76; N, 6.01. Found: C, 20.69; H, 4.58; N, 6.18. D-, M.p. 185–187°, $[\alpha]^{22}D$ −5.08° (c, 2% abs. EtOH). Found: C, 20.61; H, 4.59; N, 6.05. L-, M.p. 181–183°, $[\alpha]^{22}D$ +5.06° (c, 2% abs. EtOH). Found: C, 20.60; H, 4.82; N, 6.15.

**DL-, D-, and L-2-Aminobutylisothiourea·Di·HBr.**—Two procedures were used to prepare these compounds. For the DL isomer only one crystalline form was obtained by either method while the D and L isomers both gave polymorphic crystal forms by either method. Initially only the lower melting form was obtained, subsequent preparations yielded the higher melting form.

**Method A.**—Thiourea, 7.6 g. (0.1 mole), was mixed with 12 ml. of absolute ethanol, and 50 ml. of ethyl acetate and heated on a steam bath to boiling. DL-2-Aminobutylbromide·HBr, 23.3 g. (0.1 mole), was added and the mixture refluxed 1 hr. Complete solution occurred, followed by precipitation of an oil in 10–20 min. Crystallization was induced by scratching with a glass rod and, after short cooling in an ice bath, the precipitate was filtered off, washed with ethyl acetate, and dried *in vacuo*. Yield: 25 g. (81%), 170–172°. It was recrystallized by solution in a minimum amount of hot absolute ethanol, dilution with four volumes of isopropyl alcohol, and cooling to 0°. Yield: 21.6 g., m.p. 177–179°. The same procedure with the optically active halides using half quantities of all components yielded 9–11 g. of crude product.

**Method B.**—Thiourea, 7.6 g. (0.1 mole), was dissolved in 60 ml. of hot isopropyl alcohol, 23.3 g. (0.1 mole) of DL-2-aminobutylbromide·HBr added, and the solution refluxed 1 hr. on the steam bath. Ethyl acetate, 30 ml., was added to the hot solution, the mixture seeded, cooled to 0°, and the precipitate treated as in A. Yield: 22 g., m.p. 170–173°. Recrystallization gave 19.5 g., m.p. 177–179°. On a one-half scale using the optically active halides, this procedure yielded 9–11 g. of crude product.

*Anal.* Calcd. for $C_5H_{15}N_3SBr_2$ (309.11): C, 19.43; H, 4.89; N, 13.59; S, 10.37. DL-, Found: C, 19.59; H, 4.84; N, 13.52; S, 10.50. Low melting form D-crude, m.p. 152–154°; recrystal-

(13) All melting points in capillary tube were uncorrected. Analyses by Galbraith Laboratories, Knoxville, Tenn.

(14) O. Vogel and M. Pöhm, *Monatsh. Chem.*, **83**, 541 (1952).

lized, 157–158°. Found: C, 19.49; H, 4.94; N, 13.33; S, 10.39. L-crude, m.p. 148–150°; recrystallized, m.p. 155–157°. Found: C, 19.30; H, 4.70; N, 13.43; S, 10.32. High melting form D-crude, m.p. 177–179°; recrystallized, m.p. 183–185°. Found: C, 19.34; H, 5.00; N, 13.40; S, 10.58. L-crude, m.p. 176–179°; recrystallized, m.p. 184–186°. Found: C, 19.35; H, 4.80; N, 13.50; S, 10.45.

The optical rotations of the polymorphic forms of the L and D isomers are identical: D- $[\alpha]^{22}$D $-12.5°$ (c, 5% 0.2 $M$ HCl). Converted to the mercaptoguanidine by the addition of sodium hydroxide to pH 8.0, the rotation is $[\alpha]^{22}$D $+7.50°$ (c, 2%, 0.4 $M$ phosphate buffer pH 8.0). Correspondingly, the L isomer in acid gives a rotation of $[\alpha]^{22}$D $+12.0°$ (c, 5% 0.2 $M$ HCl), and as the mercaptoguanidine $[\alpha]^{22}$D $-7.3°$ (c, 2% 0.4 $M$ phosphate buffer pH 8.0).

**D- and L-2-Guanidobutanethiol Flavianate.**—D-2-Aminobutyl-isothiourea (1.1 g.) was dissolved in 5 ml. of water, and the pH brought to 8.0 by the addition of 3.4 ml. of sodium hydroxide. The addition of 3.5 ml. of 1 $M$ flavianic acid precipitated a yellow gum, which crystallized upon scratching with a glass rod. The product was filtered, dried (1.3 g.), and recrystallized from 10 ml. of hot 50% ethanol; 1.1 g., m.p. sinter 115°; melts 128–30°. The L-flavianate was prepared in a similar fashion, and had the same melting point.

*Anal.* Calcd. for $C_{15}H_{19}N_5O_8S_2$ (461.48): C, 39.04; H, 4.15; N, 15.18; S, 13.89. Found: D-, C, 39.16; H, 3.97; N, 15.09; S, 13.61. L-, C, 38.90; H, 4.08; N, 15.06; S, 13.70. D-, $[\alpha]^{22}$D $+6.6°$; L-, $-6.2°$ (c, 0.5% water).

**Bis-DL-, D-, and L-(2-Guanidobutyl) Disulfide Dihydrobromide.**—A solution of DL-2-aminobutylisothiourea dihydrobromide, 15.5 g. in 50 ml. of water, was immediately converted to 2-guanido-butanethiol by the addition of 50 ml. of 1 $N$ sodium hydroxide, the pH adjusted to 9.0, a few milligrams of cupric chloride added and oxygen bubbled through until the nitroprusside test was negative (ca. 3–4 hr.). The solution was acidified to pH 4 with hydrobromic acid, evaporated to dryness *in vacuo*, and the solid extracted with absolute ethanol. Ether was added to the ethanol extract to turbidity, and the mixture allowed to crystallize at $-5°$. Yield: 8.2 g. (72%), m.p. 173–175°. Recrystallization from absolute ethanol-acetone raised the melting point to 180–182°. The D and L disulfides were obtained in a similar manner.

*Anal.* Calcd. for $C_{10}H_{26}N_8S_2Br_2$ (454.34): C, 26.43; H, 5.77; N, 18.50; S, 14.11. Found: DL-, C, 26.22; H, 5.74; N, 18.23; S, 13.95. D-, M.p. 183–184°, $[\alpha]^{22}$D $-198°$. Found: C, 26.66; H, 5.75; N, 18.21; S, 14.24. L-, M.p. 183–185°, $[\alpha]^{22}$D $+200°$. Found: C, 26.71; H, 5.90; N, 18.30; S, 13.90.

**DL-, D-, and L-2-Amino-4-ethylthiazoline Hydrobromide.**—The thiazolines were prepared by the method of Gabriel.[15] For the corresponding aminoalkyl bromide hydrobromide, 11 g. (0.05 mole) was mixed with 5.0 g. (0.05 mole) potassium thiocyanate and 25 ml. water in an evaporating dish and heated on the steam bath overnight. The residue was extracted with 100 ml. hot iso-propanol, potassium bromide filtered off and the filtrate evaporated *in vacuo* to dryness. The crystalline product was removed with ethyl acetate, filtered, and dried. Yield: 8 g. (75%), DL-, m.p. 102–104°.

*Anal.* Calcd. for $C_6H_{11}N_2S$ Br (211.14): C, 28.44; H, 5.25; N, 13.27; S, 15.19. Found: C, 28.46; H, 5.06; N, 13.12; S, 15.39. D-, M.p. 121–22°, $[\alpha]^{21}$D $+26°$ (c, 2% H$_2$O). L-, M.p. 121–122.5°, $[\alpha]^{21}$D $-25.8°$ (c, 2%, H$_2$O). Found: C, 28.54; H, 5.19; N, 13.10; S, 15.35.

The DL thiazoline yielded a flavianic acid salt identical with that obtained by Khym, *et al.*,[4] from the rearrangement of the isothiourea in acid solution.

(15) S. Gabriel, *Ber.*, **22**, 1141 (1889); G. W. Raiziss and W. C. Le Roy. *J. Am. Chem. Soc.*, **63**, 3124 (1941); A. Schoberl, R. Hamm, and M. Kawobl. *Chem. Ber.*, **84**, 571 (1951).

# Aroyldiazoacetic Esters. II. Synthesis with Anhydrous Methyl Diazoacetate. Hydrolysis of Aroyl Halides in 96% Methyl Diazoacetate[1-4]

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Preparation of aroyldiazoacetic esters by direct interaction of aroyl halides and methyl diazoacetate (I) is a general procedure if I is anhydrous. There is described a procedure for drying I azeotropically with *n*-pentane, which permits quantitative estimation of water present. Interaction of aroyl chlorides with 96% methyl diazo-acetate resulted in hydrolysis products, either alone or together with the aroyldiazoacetic ester. A bimolecular hydrolysis of aroyl chlorides in 96% methyl diazoacetate is proposed. A new mechanism for aroyldiazoacetic ester formation is postulated.

The reaction of acyl halides with diazoacetic esters to give acyldiazoacetic esters is well known. However, benzoyl bromide appears to be the sole example of an *aroyl* halide undergoing this reaction.[6] The hetero-cycles, furoyl bromide and chloride, react with methyl diazoacetate (I) to give methyl ($\alpha$-furoyl)diazoacetate in 80% and unstated yields, respectively.[7] Our attempts to extend this reaction led to carboxylic an-hydrides and an O-aroylglycollate as products.[8] The

present paper describes a procedure for drying I azeo-tropically, reaction of anhydrous I with several aroyl halides to give crystalline aroyldiazoacetic esters, and reaction of I containing known amounts of water with aroyl halides.

The products obtained from interaction of methyl diazoacetate with aroyl chlorides in our previous study indicated water to be present in I. In the preparation of I by the procedure of Womack and Nelson,[9] the effect of certain operations on the water content of the prod-uct diazoacetic ester had not been previously deter-mined. We report that I can be dried azeotropically with *n*-pentane, and the azeotrope collected in a modifi-cation of the distilling head used in the Dean–Stark procedure[10] to afford a direct measure of water present. The modification substitutes a capillary tube of known cross section for the usual graduated test tube of the

(1) Paper I: J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957).

(2) From the Ph.D. thesis of Charles H. Hayes, University of Nebraska, 1959.

(3) Presented before the 138th National Meeting of the American Chemi-cal Society, New York, N. Y., September, 1960.

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(5) Dow Chemical Company Fellow, 1955–1956.

(6) H. Staudinger, J. Becker, and H. Hirzel, *Ber.*, **49**, 1978 (1916).

(7) T. Reichstein and H. J. Morsman, *Helv. Chim. Acta*. **17**, 1119 (1934).

(8) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **23**, 403 (1958). This paper contains references to extensive review articles on aliphatic diazo chemistry.

(9) E. B. Womack and A. B. Nelson, *Org. Syn.*, **24**, 56 (1944).

(10) The unmodified Dean–Stark distilling receiver is available from E. H. Sargent & Co., and is listed as a water trap for determination of water in petroleum products in accordance with A.S.T.M. method D-95.

TABLE I

REACTION CONDITIONS[a] AND YIELD DATA

$$RCOX + 2CHN_2CO_2CH_3 \longrightarrow RCOCN_2CO_2CH_3 + CH_2XCO_2CH_3 + N_2$$
$$I$$

| RCOX | Ordinal | Reaction period, days | Product isolation method[b] | Solvent for crystallization[c] | Ratio: moles I/- moles RCOX | Yield, % |
|---|---|---|---|---|---|---|
| Benzoyl chloride | II | 12 | A | M–P | 2.2 | 62.5 |
| m-Bromobenzoyl bromide | III | 8[d] | B | M–P | 2.2 | 68.5 |
| m-Bromobenzoyl bromide | III | 2.5 hr. | .. | ... | 2.0 | 0 (Explosion) |
| m-Bromobenzoyl chloride | IV | 37 | C | M–P | 2.2 | 69.7 |
| 3,5-Dinitrobenzoyl chloride | V | 3 | A | M–P | 2.2 | 90.1 |
| o-Iodobenzoyl chloride | VI | 16 | C | M–P | 2.2 | 53.2 |
| p-Mesyloxybenzoyl chloride | VII | 3 | A | M–P | 2.2 | 73.2 |
| o-Nitrobenzoyl chloride | VIII | 50[d] | B | M–P | 3.0 | 61.7 |
| m-Nitrobenzoyl chloride | IX | 22 | A | M–P | 2.2 | 72.5 |
| p-Nitrobenzoyl chloride | X | 2 | A | M | 2.2 | 91.4 |
| o-Chlorobenzoyl chloride | XI | 47 | D | ... | 2.2 | (Oil) |
| m-Chlorobenzoyl chloride | XII | 33 | C | M–P | 2.2 | 64.0 |
| p-Chlorobenzoyl chloride | XIII | 29 | A | M–P | 2.2 | 57.3 |
| o-Methoxybenzoyl chloride | XIV | 18 | D | ... | 2.2 | (Oil) |
| m-Methoxybenzoyl chloride | XV | 38 | D | ... | 2.2 | (Oil) |
| Furoyl chloride | XVIII | 18[d] | A | ET | 2.2 | 51.2 |
| Furoyl chloride | XVIII | 14[e] | A | M | 2.1 | 52.4 |
| 5-Nitrofuroyl chloride | XIX | 4 | A | M–P | 2.2 | 80.6 |
| Hydrocinnamoyl chloride | XX | 35 | E | ... | 2.7 | (Oil) |
| Phenoxyacetyl chloride | XXI | 20 hr.[f] | A | B–SK and M–P | 2.1 | 72.4 |

[a] Anhydrous I employed except where otherwise noted. [b] A: Product crystallized from reaction mixture; reaction vessel scraped with stirring rod if necessary. B: Product isolated by nucleation, or by scratching of reaction vessel, and strong cooling. C: Small portion of reaction mixture permitted to evaporate in air; crystalline residue used to seed reaction mixture. D: Reaction mixture was steam distilled at reduced pressure; solvent removal from dry ethereal solution of residue gave oily product. E: As in D, except that 2 g. of Ba(OH)$_2$ present during steam distillation, and solvent removal from dry benzene solution. [c] M = methanol; P = petroleum ether, b.p. 60–69°; ET = ether; B = benzene; SK = Skellysolve C (petroleum ether, b.p. 88–98°). [d] I contained trace of water. [e] I contained 2.1% of water. [f] I contained 4.0% of water.

TABLE II

AROYLDIAZOACETIC ESTERS[a]: PROPERTIES AND ANALYTICAL DATA

| Aroyldiazo- acetic ester | Acid halide for synthesis | M.p., °C. | Infrared absorption bands,[b] cm.$^{-1}$ CN$_2$ | Ester CO | Keto CO | Analysis, % N Calcd. | Found |
|---|---|---|---|---|---|---|---|
| XXII | II | 84.5–85.5 | 2162 | 1716 | 1616 | ... | ... |
| XXIII | III or IV | 65–67 | 2140 | 1724 | 1622 | 9.90 | 9.76 |
| XXIV | V | 126.5 dec. | 2156 | 1710 | 1640 | 19.05 | 18.73 |
| XXV | VI | 73.5–75 | 2148 | 1709 | 1638 | 8.94 | 8.58 |
| XXVI | VII | 105–106 dec. | 2160 | 1721 | 1623 | 9.39 | 9.02 |
| XXVII | VIII | 90–92 | 2156 | 1712 | 1634 | 16.86 | 16.89 |
| XXVIII | IX | 87.5–89 | 2156 | 1726[c] | 1625 | 16.86 | 17.02 |
| XXIX | X | 91.5–92.5 | 2160 | 1726 | 1632 | 16.86 | 17.30 |
| XXX | XII | 64.5–66.5 | 2156 | 1726[d] | 1624 | 11.74 | 11.27 |
| XXXI | XIII | 105.5–107.5 | 2144 | 1717 | 1623 | 11.74 | 11.17 |
| XXXII | XVIII | 111–112 | 2140 | 1732 | 1623 | 14.28 | 14.47 |
| XXXIII | XIX | 97–99 | 2134 | 1739 | 1629 | 17.14 | 17.39 |
| XXIV[e] | XXI | 105.5–106.5 | 2148 | 1706 | 1668 | 11.96 | 11.92 |
| XXXV[f] | III | 56–58 | 2156 | 1727[g] | 1622 | 9.42 | 8.86 |

[a] Methyl ester, unless otherwise indicated. [b] Of Nujol mull. [c] Shoulder on strong band at 1695 cm.$^{-1}$. [d] Shoulder on strong band at 1688 cm.$^{-1}$. [e] Acyldiazoacetic ester. [f] Ethyl ester. [g] Shoulder on strong band at 1687 cm.$^{-1}$.

distilling head. Distillation of I itself is not necessary. Freshly prepared methyl diazoacetate and the reagent which has been stored in a refrigerator for ca. six months contain 2.1% and 4.0% water, respectively. In contrast, ethyl diazoacetate which had been stored for one to two years under the same conditions possessed only a trace of water. When I was prepared by the method of Hammond,[11] I contained only a trace of water.

Data pertaining to the reactions of I with acid halides are reported in Table I. Acid halide for synthesis,

properties, and analytical data for product aroyldiazoacetic esters are outlined in Table II. In Table II, the structure of the aroyldiazoacetic ester is apparent from that of the acid halide for synthesis. Product distributions from, and reaction conditions for, interaction of aroyl halides with I containing up to 4.0% water are given in Table III.

The combined data of Tables I and II establish the general nature of the reaction of I with aroyl chlorides to give aroyldiazoacetic esters, with the important provision that I must be anhydrous. The reaction conditions employed are not considered optimum, however, with the exception of those for preparation of aroyl-

(11) J. A. Hammond, U. S. Patents 2,691,649 and 2,691,650; Chem. Abstr., 49, 11690 (1955).

TABLE III

PRODUCTS FROM INTERACTION OF AROYL HALIDES WITH METHYL DIAZOACETATE (I) CONTAINING 4.0%[a] WATER

| ArCOX | Ratio: moles I/- moles RCOX | Reaction period, days | Product distribution Yield, % ArCOCN₂-CO₂CH₃ | ArCO₂H | (ArCO)₂O |
|---|---|---|---|---|---|
| III | 2.0 | 14[b] | 49.4 | ... | ... |
| IV | 3.0 | 50[c] | ... | 1.1 | ... |
| VII | 2.1 | 16 (hr.) | 6.2 | ... | 34.5 |
| IX | 2.1 | 3 | 10.5 | ... | 42.5 |
| X | 2.1 | 3 | 40.0 | ... | 33.6 |
| XI | 2.1 | 2 | ... | ... | 33.3 |
| XII | 3.0 | 161[c] | 8.5 | 2.1 | ... |
| XIII | 2.8 | 3 | 10.4 | ... | 39.0 |
| XIII | 2.1 | 2 | ... | 0.8 | 27.8 |
| XIV | 2.1 | 0.5 | ... | ... | 43.8 |
| XV | 3.0 | 77[c] | ... | 5.75 | ... |
| XVI | 2.1 | 8 | ... | 6.0 | 32.0 |
| XVII | 3.0 | 160[c] | ... | 19.4 | 12.3 |
| XVIII | 2.9 | 7 | 26.7 | ... | ... |

[a] Unless otherwise indicated. [b] In this experiment, I contained approximately 2% water. [c] In this experiment, I contained a trace of water initially.

diazoacetic esters XXIV and XXIX which gave yields of over 90%. In the majority of cases, the reaction product crystallized from the reaction mixture directly, but also very slowly in certain instances. The synthesis of XXII has been previously reported, but not from benzoyl chloride. Acid chlorides XI, XIV, and XV gave oily reaction products, which resisted all attempts at purification. However, these products gave positive tests with bromine in acetic acid (sequel), and very probably were the aroyldiazoacetic esters. Anisoyl chloride (XVI) and p-toluyl chloride (XVII) were the least reactive of the acid chlorides studied. At least 61% of XVI was present after 18 days, and the only products isolated from XVII and I were toluic acid and its anhydride. These latter two products apparently resulted from a reaction with water, slowly introduced into I during the long reaction period (82 days at −24°, after 78 days at room temperature). The heterocyclic acid derivatives, furoyl chloride (XVIII) and its 5-nitro derivative (XIX), reacted satisfactorily with I. The aliphatic acid chloride XXI gave a satisfactory yield of methyl (phenoxyacetyl)diazoacetate, even when I contained 4.0% water. This property is in marked contrast to that of most aroyl chlorides. With anhydrous I, hydrocinnamoyl chloride (XX) gave as reaction product an orange oil, which gave a positive test with bromine in acetic acid.

Certain properties of the crystalline aroyldiazoacetic esters obtained in this study are given in Table II. In addition, all such substances gave a moderate evolution of nitrogen with 1% bromine in acetic acid. This test is based on the known reaction of the aliphatic diazo group with halogen,[12] and presumably proceeds as in equation 1. Although I also undergoes the test, its

Ar—COCN₂COOCH₃ + Br₂ ⟶

$$Ar—COCBr_2COOCH_3 + N_2 \quad (1)$$
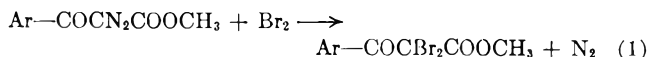
reaction is more violent than that with the aroyldiazoacetic esters. The test with bromine is of added significance because of the acid-stability of the diazo function in acyl- and aroyldiazoacetic esters. This acid-stability was so striking that, at one time, an
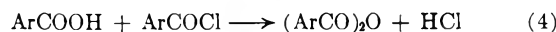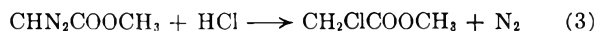
(12) L. Wolff, Ann., 394, 23 (1912); ref. 6.

oxadiazole structure was advocated for such molecules.[13] Subsequent infrared[1] and chemical[14] studies do not permit such a view today, however.

Comparison of infrared spectra of aroyldiazoacetic esters (Table II) with those of diazo ketones[15] indicates that the diazo group in aroyldiazoacetic esters absorbs somewhat higher frequency radiation. Possibly this property is due to enhanced triple bond character in the diazo function of diazoacetic ester derivatives (XXXVI B, C, and D).



XXXVIA    XXXVIB

XXXVIC    XXXVID
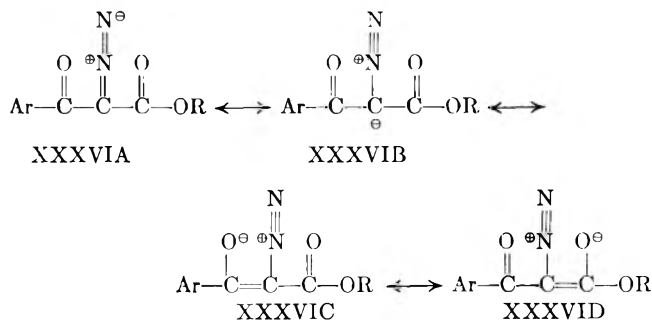
The data of Table III give the product distribution resulting from interaction of aroyl halides with I containing from a trace to as much as 4.0% water, and afford convincing evidence for the importance of anhydrous methyl diazoacetate in synthesis of aroyldiazoacetic methyl esters. Of particular interest are reactions of acid chlorides IV, VII, IX, X, XII, XIII, and XVIII (Table III), which gave moderate to excellent yields of aroyldiazoacetic esters with anhydrous I (Table I).

The general course of the reaction of aroyl chlorides with water and I is clear. Part of the aroyl chloride is first hydrolyzed to the carboxylic acid, which then reacts with unreacted acid chloride to give the anhydride. In both steps, I acts as a base. The proposed sequence is outlined in equations 2–5.

$$ArCOCl + H_2O \longrightarrow ArCOOH + HCl \quad (2)$$
$$CHN_2COOCH_3 + HCl \longrightarrow CH_2ClCOOCH_3 + N_2 \quad (3)$$
$$ArCOOH + ArCOCl \longrightarrow (ArCO)_2O + HCl \quad (4)$$
$$CHN_2COOCH_3 + HCl \longrightarrow CH_2ClCOOCH_3 + N_2 \quad (5)$$

Presumably the over-all reaction for anhydride formation is that given in equation 6.

$$2ArCOCl + 2CHN_2COOCH_3 + H_2O \longrightarrow$$
$$(ArCO)_2O + 2CH_2ClCOOCH_3 + 2N_2 \quad (6)$$
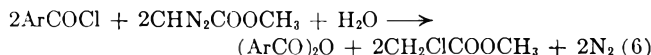
One example of ester formation in I was observed, namely, reaction of benzoyl chloride with excess methanol to give methyl benzoate (equation 7).

$$C_6H_5COCl + CH_3OH + CHN_2COOCH_3 \longrightarrow$$
$$C_6H_5COOCH_3 + CH_2ClCOOCH_3 + N_2 \quad (7)$$
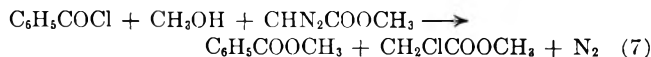
Data of theoretical interest pertain to whether or not hydrolysis of aroyl bromides and chlorides in methyl diazoacetate containing water occurs. Benzoyl bromide and m-bromobenzoyl bromide react with I containing 4.0% and 2% of water respectively to give the aroyldiazoacetic ester in 78 and 49% yields. Furoyl bromide gives an 80% yield of the furoyldiazoacetic
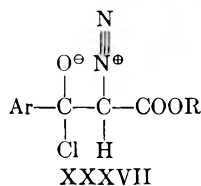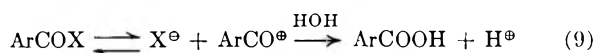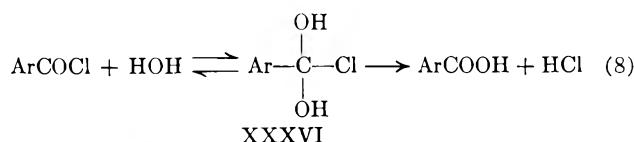
(13) L. Wolff, ibid., 325, 129 (1902); L. Wolff and A. A. Hall, Ber., 36, 3612 (1903).
(14) H. Staudinger, ibid., 49, 1884 (1916).
(15) P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, J. Am. Chem. Soc., 79, 5756 (1957). This work contains the spectrum of one acyldiazo ester.

ester with I of unstated water content.[16] In this study, the carboxylic anhydride was not detected as a reaction product from aroyl bromides and I, even when I contained water. Hydrolysis of benzoyl bromide can be effected with water and I, but the 25% water present probably would permit an $S_N1$ type hydrolysis (sequel), and the product was benzoic acid. We conclude that aroyl bromides are not readily hydrolyzed in methyl diazoacetate containing small amounts of water (under 5%). In contrast, the common reaction path of aroyl chlorides with 96% methyl diazoacetate leads to a mixture of the aroyldiazoacetic ester and hydrolysis product, or hydrolysis product exclusively. Under consistent conditions, of 2.1 moles of I per mole of acid chloride and 4.0% water in the methyl diazoacetate, VII, IX, and X formed both aroyldiazoacetic ester and anhydride, while XI, XIII, and XIV (Table III) gave no aroyldiazoacetic ester, with the anhydride being the main product. We conclude that aroyl chlorides are hydrolyzed rather readily in 96% methyl diazoacetate. Apparently the acyl chloride (XXI) (Table I) resembles aroyl bromides in its reaction with 96% methyl diazoacetate.

Two extreme mechanisms for acid halide hydrolysis have been recognized.[17] First (equation 8), hydrolysis is effected *via* a bimolecular reaction, probably involving addition of water to the carbonyl group to give the intermediate XXXVI. Second (equation 9), an $S_N1$ type ionization occurs without formation of a geminal diol intermediate. Kinetic hydrolysis studies by other workers[17] indicate that many acid chlorides can undergo hydrolysis by either mechanism, *depending on the concentration of water in the hydrolysis medium.* Low concentrations of water favor the path in equa-

$$ArCOCl + HOH \rightleftharpoons Ar\!-\!\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}\!-\!Cl \longrightarrow ArCOOH + HCl \quad (8)$$

XXXVI

$$ArCOX \rightleftharpoons X^{\ominus} + ArCO^{\oplus} \overset{HOH}{\longrightarrow} ArCOOH + H^{\oplus} \quad (9)$$

$$Ar\!-\!\underset{\underset{Cl}{|}}{\overset{\overset{O^{\ominus}}{|}}{C}}\!-\!\underset{\underset{H}{|}}{\overset{\overset{N}{\overset{|||}{N^{\oplus}}}}{C}}\!-\!COOR$$

XXXVII

tion 8, high concentrations that in 9. The hydrolysis media in this study contained from a trace to as much as 4% water, low concentrations, and we postulate that most of the aroyl chloride hydrolyses (Table III) occur *via* the path of equation 8. The $S_N1$ mechanism (equation 9) very probably is important in the hydrolysis of benzoyl bromide with 25% water present.

The dichotomy of hydrolysis mechanisms for acid halides, and the importance of medium in determining mechanism, indicate the possibility of two extreme mechanisms for formation of aroyldiazoacetic esters from acid halides. The first, the Eistert mechanism,[18]
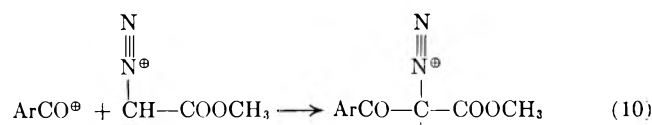
(16) Presumably the methyl diazoacetate used would have contained at least traces of water, since no drying step was described (ref. 7).

(17) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 225-227; E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 501 (1956), and preceding papers; H. K. Hall, Jr., *J. Am. Chem. Soc.*, **77**, 5993 (1955).
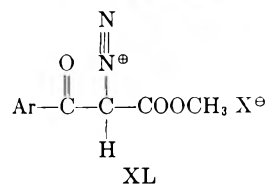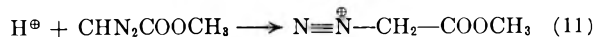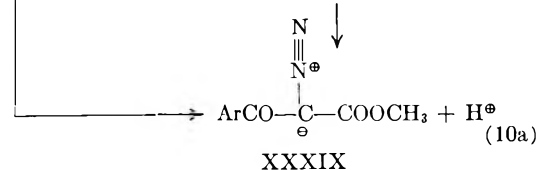
(18) B. Eistert, *Ber.*, **68**, 208 (1935)

is a bimolecular one in which the intermediate XXXVII is formed by addition of the diazoacetic ester molecule to the carbonyl group of the acid chloride. In the second, not known to be previously postulated, ionization of the aroyl halide would occur as in equation 9; and the carbonium ion formed would react with methyl diazoacetate (I) to give the C-aroyldiazonium ion XXXVIII (equation 10). Interaction of XXXVIII, possibly associated with bromide ion as in XL, with the base (I) would give the product diazonium ion (equation 11). Although less likely, a displacement (equation 10a) is conceivable. The exact species involved in proton transfer to I is not known, although a formal ionization of XXXVIII to XXXIX and the "bare proton" is indicated for convenience. We term this second mechanism the aroyldiazonium ion mechanism for aroyldiazoacetic ester formation.

The Eistert mechanism[18] is quite adequate if acid halide hydrolysis is impossible and ionization cannot occur in the reaction medium, as in reaction of aroyl halides with either diazomethane or diazoacetic ester in anhydrous ether solution. In general, the aroyldiazonium ion mechanism would be important if the medium is sufficiently polar to facilitate ionization of readily ionizable acid halides. In the present work, the reaction medium, initially either anhydrous liquid I or a homogeneous mixture of I with small quantities of water, very probably would support ionization. A rough correlation between hydrolysis mechanism and aryoldiazoacetic ester formation mechanism is possible. Acid halides undergoing hydrolysis by the path of equation 9 would be expected to form aroyldiazoacetic esters by the aroyldiazonium ion mechanism, *providing the polarity of the medium would permit ionization of the acid halide.* Acid halides undergoing hydrolysis by the path of equation 8 would form aroyldiazoacetic esters by the Eistert mechanism, assuming a suitable medium. Benzoyl bromide, *m*-bromobenzoyl bromide, and phenoxyacetyl chloride are probable specific examples of acid halides which react with 96% or 98% I to form the aroyldiazoacetic (or acyldiazoacetic) ester by the aroyldiazonium (acyldiazonium) ion mechanism.

$$ArCO^{\oplus} + \underset{\ominus}{CH}\!-\!COOCH_3 \longrightarrow ArCO\!-\!\underset{\underset{H}{|}}{\overset{\overset{N}{\overset{|||}{N^{\oplus}}}}{C}}\!-\!COOCH_3 \quad (10)$$

XXXVIII

$$\overset{\overset{N}{\overset{|||}{N^{\oplus}}}}{\downarrow}$$

$$\longrightarrow ArCO\!-\!\underset{\ominus}{C}\!-\!COOCH_3 + H^{\oplus} \quad (10a)$$

XXXIX

$$H^{\oplus} + CHN_2COOCH_3 \longrightarrow N\!\equiv\!\overset{\oplus}{N}\!-\!CH_2\!-\!COOCH_3 \quad (11)$$

$$Ar\!-\!\underset{\underset{H}{|}}{\overset{\overset{O}{||}}{C}}\!-\!\underset{}{\overset{\overset{N}{\overset{|||}{N^{\oplus}}}}{C}}\!-\!COOCH_3 \; X^{\ominus}$$

XL

## Experimental

Melting points are uncorrected unless stated otherwise. Temperatures of $-4°$ and $-24°$ represent average temperatures of the middle of main box and freezing compartment respectively of the refrigerator used. Unless stated otherwise, yields were determined from crude product after it had stood over phosphorus pentoxide in a vacuum desiccator at room temperature and 15–20 mm. for a minimum of 12 hr. All reactions were carried out at room temperature unless otherwise noted. EK designates an Eastman Kodak chemical of White Label purity.[19] Infrared spectra were determined as Nujol mulls unless otherwise noted, on a Perkin–Elmer Model 21 spectrophotometer (sodium chloride optics). Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

**Methyl Diazoacetate.**—This substance was prepared from glycine methyl ester hydrochloride by the method of Womack and Nelson,[9] and by the procedure of Hammond.[11]

**Azeotropic Purification of Methyl Diazoacetate.**—The apparatus used consisted of a round-bottom flask of suitable size, an efficient water-cooled condenser, and a modification of the Dean–Stark water determination apparatus.[10] A capillary tube of known cross section, uniform bore, and approximately 15 cm. in length, with a stopcock at the lower end, was substituted for the graduated test tube of the latter apparatus. Heat was supplied carefully by means of a heating mantle. The azeotrope involved was n-pentane–water.

A sample of methyl diazoacetate (32.7 g.), prepared by Womack and Nelson's procedure, that had been stored in a brown, glass-stoppered bottle at $-4°$ for approximately 6 months was heated with 50 ml. of n-pentane under reflux until no further condensation of water could be observed in the condenser; water content, 1.30 g. (4.0%). A freshly prepared sample of methyl diazoacetate (51.7 g.) was heated with n-pentane under reflux as before to give dry methyl diazoacetate and water (1.10 g., 2.1%).

**Preparation of Aroyldiazoacetic Esters. Procedure A.[20]**—Recrystallized 3,5-dinitrobenzoyl chloride, m.p. 69–71° (15.0 g., 0.065 mole) was added in portions to dry methyl diazoacetate (14.3 g., 0.143 mole) over a 45-min. period with stirring in a three-neck round-bottom flask equipped with thermometer, efficient stirrer, and a device consisting of a 19/38 ground glass joint and a 50-ml. erlenmeyer flask joined by a short section of large rubber tubing. The acid chloride was added through the latter device. The system was isolated from atmospheric moisture by a calcium chloride drying tube. Nitrogen was evolved rapidly from the initial addition of acid chloride; stirring was continued for 1 hr. after completion of the addition, with periodic strong cooling. The reaction mixture was allowed to stand in ice–water for 1 hr. without stirring, then at room temperature for 72 hr.; the entire reaction mixture had set to a semisolid mass. The crude, crystalline, yellow methyl (3,5-dinitrobenzoyl)diazoacetate (XXIV; Table II) was collected by filtration and dried. Two additional crops of crude product were combined with the first; total yield, 17.20 g. (90.1%), m.p. 90–120° dec. Recrystallization from methanol–petroleum ether (b.p. 60–69°) gave analytically pure material, m.p. 126.5°.

**Procedure B.[20]**—Freshly distilled m-bromobenzoyl bromide (14.6 g., 0.055 mole) was added dropwise to methyl diazoacetate (12.2 g., 0.122 mole) (cooled in an ice–water bath) in a three-neck flask equipped with dropping funnel, thermometer, and efficient stirrer. The system was protected from atmospheric moisture. The addition required 50 min. Initially, nitrogen was evolved rapidly. The reaction mixture stood undisturbed in an ice–water bath for 2 hr. It then was cooled intermittently until the reaction no longer became vigorous at room temperature, and was allowed to stand for 8 days. The yellow solution was seeded with authentic methyl (m-bromobenzoyl)diazoacetate; after standing overnight at $-24°$, the entire mixture had set to a semisolid mass. After standing 8 more days at $-24°$, the crude methyl (m-bromobenzoyl)diazoacetate (XXIII; Table II) (3 crops) was collected and dried.

**Procedure C.[20]**—Freshly prepared m-chlorobenzoyl chloride (b.p. 104° at 12 mm.) was added dropwise to dry methyl diazoacetate (15.6 g., 0.0156 mole) in apparatus as in procedure B. The addition to the stirred mixture required 10 min. Nitrogen

was evolved at a moderate rate initially. Stirring was continued 15 min. after completion of the addition, and the resulting mixture stood for 33 days. A small portion of the yellow solution was allowed to evaporate in air. The crystalline residue was used to seed the solution, which stood overnight at $-4°$. There occurred crystallization of methyl (m-chlorobenzoyl)diazoacetate (XXX; Table II), which was collected and dried.

**Procedure D.[20]**—Freshly prepared m-methoxybenzoyl chloride, b.p. 96.5–98° at 2.5 mm., was added dropwise to dry methyl diazoacetate over a 10-min. period with stirring. Equipment was as in procedure B. Nitrogen was evolved at a moderate rate after an induction period of several minutes; stirring was continued 15 min. after completion of the addition. The reaction mixture stood for 38 days. The entire solution was subjected to steam distillation at reduced pressure.[21] Evaporation of the dry yellow ethereal extract of the residue gave 16.48 g. (96.6%) of a yellow oil, which gave a positive bromine in acetic acid test (sequel). Attempted crystallization of the oily product from methanol (charcoal) was unsuccessful, as was attempted distillation at reduced pressure. Repeated attempts to purify this material chromatographically on alumina did not lead to a demonstrably pure product.

**Bromine in Acetic Acid Test.**—A 1% by volume solution of bromine in glacial acetic acid was used as a reagent for determining presence of the diazo group. The procedure involved adding a portion of a possible diazo compound, about the size of a small pea, to approximately 1 cc. of the reagent. A positive test consisted of an immediate evolution of nitrogen and partial decoloration of the acetic acid solution.

**Attempted Preparation of Methyl Anisoyldiazoacetate. Isolation of Anisic Acid.**—EK anisoyl chloride (12.4 g., 0.073 mole) was added dropwise to dry methyl diazoacetate (16.0 g., 0.160 mole) over a period of 10 min. with stirring. Apparatus was as in procedure B. Initially nitrogen was evolved slowly. Stirring was continued for 15 min. after completion of the addition. The reaction mixture was allowed to stand for 16 days; however, no crystallization of product had occurred. All attempts to induce crystallization failed. The entire solution was subjected to vacuum steam distillation,[21] during which a vigorous reaction occurred. On completing the distillation, the crystalline solid present was collected, dried, and recrystallized from methanol–petroleum ether (b.p. 60–69°) to a m.p. of 182–185°; yield, 6.76 g. (61.0%), lit.,[22] m.p. 184.2°. Mixture melting point with authentic anisic acid showed no depression. Bromine in acetic acid test was negative.

**Interaction of Acid Halides with 96% Methyl Diazoacetate. o-Chlorobenzoyl Chloride.**—EK o-chlorobenzoyl chloride (3.98 g., 0.023 mole) was added dropwise to 96% methyl diazoacetate (5.00 g., 0.048 mole of methyl diazoacetate) over a period of 1 hr. Nitrogen was evolved at a moderate rate initially. After 48 hr., crystallization of product had not occurred. All attempts to induce crystallization failed. The yellow solution was dissolved in benzene–petroleum ether (b.p. 88–98°), cooled in an ice–water bath, and the sides of the reaction vessel scratched to cause formation of a crystalline material which was collected and dried; m.p. 77–125° dec. This product gave a positive bromine in acetic acid test. The crude product was recrystallized from methanol–petroleum ether (b.p. 60–69°); yield, 1.13 g. (33.3%), m.p. and mixture m.p. with authentic o-chlorobenzoic anhydride, 78–79.5° (lit.,[23] m.p. 78–79°). Bromine in acetic acid test was negative. Filtrate evaporation from isolation of o-chlorobenzoic anhydride gave a dark brown, intractable oil.

**Reaction of Acid Chlorides with Methyl Diazoacetate Containing a Trace of Water Initially. p-Toluoyl Chloride.**—Methyl diazoacetate was prepared by method of Hammond.[11] p-Toluoyl chloride (b.p. 104° at 17 mm.) (11.02 g., 0.071 mole) was added to methyl diazoacetate (21.42 g., 0.214 mole) over a 1-hr. period. Nitrogen was evolved slowly after an induction period. The reaction mixture stood 78 days without crystallization. After 82 additional days, at $-24°$, there separated a solid, m.p. 95–168° dec. (fraction A). Four additional fractions were obtained by cooling appropriate filtrates to $-24°$:

(19) Highest purity available from Distillation Products Industries, Division of Eastman Kodak Co.

(20) For additional substances prepared by this method, see Tables I and II.

(21) The apparatus used was essentially that described by L. Gattermann and H. Wieland, "Laboratory Methods of Organic Chemistry," MacMillan and Co., New York, N. Y., 1937, pp. 277–279.

(22) A. Oppenheim and S. Pfaff, Ber., 8, 893 (1875).

(23) R. Adams, W. V. Wirth, and H. E. French, J. Am. Chem. Soc., 40, 424 (1918).

B, m.p. 69–140° dec., C, m.p. 163–180°, D, m.p. 142–168°, and E, m.p. 70–80°. The fractions were combined: A, C, and D gave first combined product, fractions B and E the second combined product. The first combined product (p-toluic acid) was recrystallized repeatedly from methanol; yield 0.78 g. (19%), m.p. and mixture m.p. 179–181.5° (lit.,[24] m.p. 181°). The second combined product (p-toluic anhydride) was recrystallized repeatedly from methanol–petroleum ether (b.p. 60–69°); yield 1.12 g. (12.3%), m.p. and mixture m.p. 95–96.5° (lit.,[25] m.p. 95°).

**Hydrolysis of Benzoyl Bromide in 75% Methyl Diazoacetate.**—EK benzoyl bromide (15.8 g., 0.087 mole) was added dropwise over 25 min. to a stirred mixture consisting of 75% methyl diazoacetate (17.58 g., 0.176 mole), previously dried azeotropically, and 25% water (5.9 g., 0.33 mole) at −4°. The temperature of the heterogeneous reaction mixture, initially cooled in ice, rose to 18° by the end of the acid bromide addition. Nitrogen was evolved rapidly from the initial addition of acid bromide. After nitrogen evolution ceased, crystals of product began to form in the mixture. Cooling in ice for several hours caused further separation of crystalline material (fraction A), m.p. 111–120°. The filtrate consisted of an upper organic layer, fraction B, and a lower aqueous layer that was separated and distilled. After collecting 2–3 ml. of distillate, b.p. 124°, the residual liquid was cooled to room temperature. A substance, m.p. 70–121°, separated (fraction C). Fractions A and C were combined and recrystallized repeatedly from water to give benzoic acid, m.p. and mixture m.p. 121–122°; yield 6.21 g. (60.1%). Bromine in acetic acid test was negative. Fraction B was a colorless liquid with an ester-like odor; yield 7.68 g., b.p. 215°. Bromine in acetic acid test was negative. This fraction was not identified.

**Formation of Methyl Benzoate from Benzoyl Chloride and Methanol in Methyl Diazoacetate.**—Benzoyl chloride (4.64 g., 0.033 mole) was added dropwise over 30 min. to a solution of

methanol (3.96 g., 0.124 mole) in methyl diazoacetate (10.0 g., 0.100 mole), previously dried azeotropically. Nitrogen was evolved rapidly from the initial addition of acid chloride. After standing for 134 days, the reaction mixture was pale yellow and completely homogeneous. Distillation of the entire reaction mixture gave three fractions: (1) yield 4.44 g., b.p. 127.5–135°; (2) yield 1.51 g., b.p. 93–187°; (3) yield 2.13 g., b.p. 189.5–191°. Redistillation of fraction 1 gave a colorless distillate with an ester-like odor, product A; yield 2.25 g., b.p. 130–132°. Fraction 2 was added to residue from redistillation of fraction 1 and distilled to give more of product A; yield 0.84 g., b.p. 131–135°. Fraction 3 was added to residue from redistillation of fraction 2 and distilled to give a colorless distillate with an ester-like odor, product B; yield 2.84 g., b.p. 190–195°.

Product A was identified as methyl chloroacetate; total yield 3.09 g. (86.4%), $n^{25}$D 1.4126 and $n^{20}_4$ 1.184; lit. b.p. 130°,[26] $n^{20}$D 1.42207[27] and $d^{15}$ 1.22.[28] Product B was identified as methyl benzoate; yield 2.84 g. (63.3%), $n^{25}$D 1.5118 and $d^{20}_4$ 1.090; lit.,[29] b.p. 199.6°, $n^{16}$D 1.51810 and $d^{20}_4$ 1.088. A 0.81-g. quantity of product B was hydrolyzed in 5% sodium hydroxide to give 0.45 g. of benzoic acid, identified by melting point and mixture melting point.

**Hydrolytic Cleavage of Methyl Benzoyldiazoacetate.**—Methyl benzoyldiazoacetate (0.50 g., 0.0025 mole) was added in one portion to 10 ml. of 5% sodium hydroxide and allowed to stand undisturbed at room temperature for 24 hr. The reaction mixture was a clear yellow solution which evolved nitrogen slowly. Concentrated hydrochloric acid was added dropwise to the mixture, cooled in an ice–water bath, until slightly acid to litmus. There separated a colorless, crystalline solid (benzoic acid), m.p. 122.5–125°, which was recrystallized from water; yield 0.28 g. (93.6%), m.p. and mixture m.p. 122–123°. Bromine in acetic acid test was negative.

(24) G. Ciamician and P. Silber, *Ber.*, **45**, 40 (1912).
(25) P. Frankland and F. M. Wharton, *J. Chem. Soc.*, **75**, 344 (1899).

(26) L. Schreiner, *Ann.*, **197**, 8 (1879).
(27) A. Karvonen, *Ann. Acad. Sci. Fennicae, Ser. A.*, **10**, 19 (1916).
(28) L. Henry, *Ber.*, **6**, 742 (1873).
(29) "Handbook of Chemistry and Physics," C. D. Hodgman, ed. Chemical Rubber Publishing Co., 1960–1961, p. 848.

# The Reaction of cis-2,6-Dibromo-4,4-dimethylcyclohexanone with Sodium Acetate in Acetic Acid, a New Elimination–Rearrangement Reaction

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Reaction of cis-2,6-dibromo-4,4-dimethylcyclohexanone (I) with sodium acetate in acetic acid gives 2-acetoxy-5,5-dimethylcyclohex-2-enone (VIII) as the major product. Evidence is presented which suggests that VIII is formed by: (1) replacement of one bromine atom by an acetoxy group; (2) abstraction of the proton alpha to the acetoxy group; (3) intramolecular rearrangement of the acetoxy group; and (4) elimination of bromide ion.

It has been reported that 2,6-dibromo-4,4-dimethylcyclohexanone (I) reacts with excess potassium acetate in hot acetic acid to give a compound formulated as 2-acetoxy-4,4-dimethylcyclohex-2-enone (II) plus 4,4-dimethylcyclohexane-1,2-dione (III).[2] Later,[3] the cis and
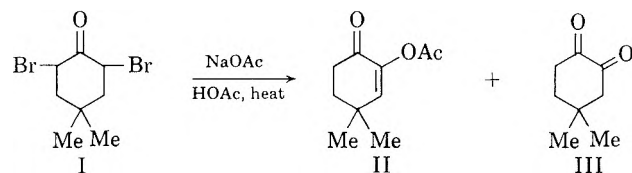
trans forms of the 2,4-dibromo-9-methyl-3-decalones were described as undergoing comparable reactions. These formulations correspond to that made by Inhof-

fen[4] for a comparable reaction between 2,4-dibromo-coprostan-3-one and potassium benzoate in a mixture of 1-butanol and toluene.

One possible explanation for the conversion of I to II is to assume an initial SN2′ displacement of bromine from the enol of I to form 2-acetoxy-2-bromo-4,4-dimethylcyclohexanone, which then undergoes elimination of hydrogen bromide to form II. Although there are certain seemingly related reactions, such as the formation of 4-α-acetoxycholestan-3-one from the reaction of potassium acetate in acetic acid with 2-α-bromocholestan-3-one, where SN2′ reactions of this type appear to be involved,[5] the postulate of an unusual reaction path applied to an intermediate that is present in only small concentration (the enol) seemed sufficiently novel to warrant further investigation. These re-

(1) Allied Chemical Corporation Fellow, 1960–1961; Eastman Kodak Company Fellow, 1961–1962.
(2) M. Yanagita and A. Tahara, *J. Pharm. Soc. Japan*, **71**, 1060 (1951).
(3) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); M. Yanagita and K. Yamakawa, *ibid.*, **22**, 291 (1957).

(4) H. H. Inhoffen, *Ann.*, **563**, 135 (1949).
(5) See E. L. Eliel, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 97, 98, and K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).
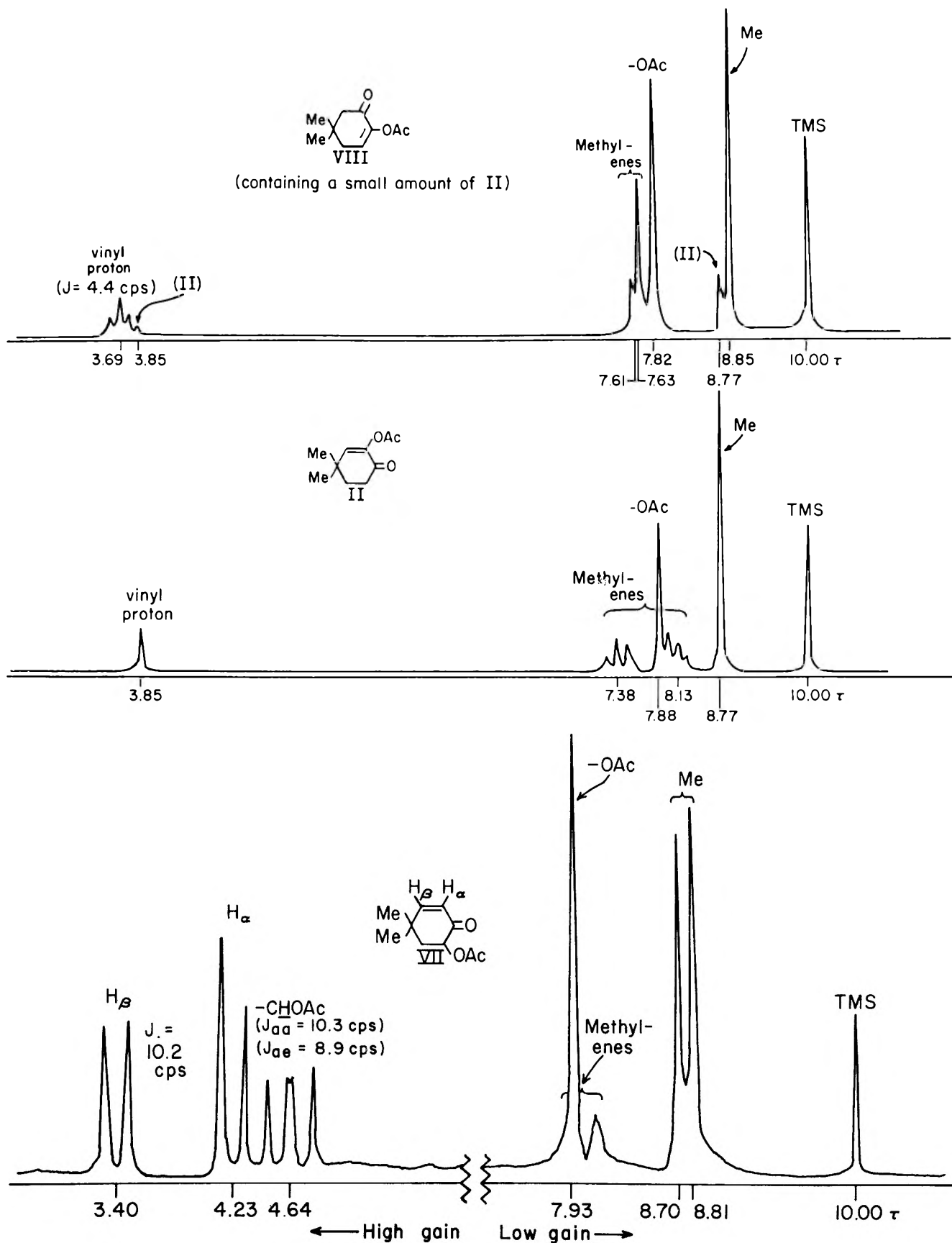
Fig. 1.—The 60-Mc. n.m.r. spectra of II, VII, and VIII in carbon tetrachloride solution with tetramethylsilane (TMS) internal standard.

sults are at possible variance with the report of Inhoffen[6] that 2,4-dibromocholestan-3-one reacts with potassium benzoate in hot toluene–butanol to give two

products which he formulated (tentatively) as having structures of a different type, namely, IV and V.

Reinvestigation of the reaction using crude I under the conditions previously described[2] gave about 18% of keto–enol acetates and appreciable amounts of diketone

(6) H. H. Inhoffen, Ber., **70**, 1695 (1937).
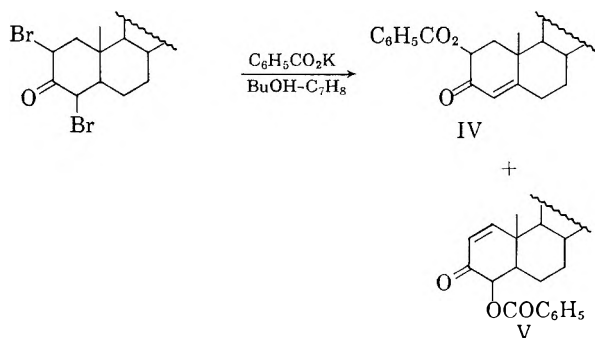
III. The ratio of these materials was found to depend on the extent to which the keto–enol acetates were hydrolyzed during processing. By using pure cis I, strictly anhydrous conditions, and a processing procedure that minimized hydrolysis, the yield of keto–enol acetates was increased to 68% and only a small amount (3%) of diketone was obtained. Gas–liquid chromatographic (g.l.c.) and n.m.r. analysis of the keto–enol acetate fraction revealed the presence of two components, A and B, in a ratio of about 1 to 7, respectively.

An authentic sample of II was prepared by hydroxylation of 4,4-dimethylcyclohex-2-enone with hydrogen peroxide in the presence of osmium tetroxide catalyst, and heating the resulting diol with excess acetic anhydride. The structure of this keto–enol acetate was confirmed as II by hydrogenation to a keto acetate (VI); VI was found to be identical with a sample of 2-acetoxy-4,4-dimethylcyclohexanone prepared by acetoxylation of 4,4-dimethylcyclohexanone with lead tetracetate as described by Cavill and Soloman.[7]
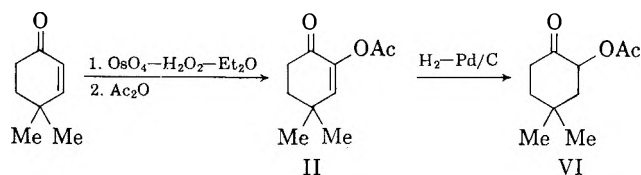


The synthetic sample of II was found to enhance the peak of the minor component (A) of the gas–liquid chromatogram of the keto–enol acetate reaction mixture obtained from I. It is, therefore, a minor product, rather than the principal product, as was previously supposed.[2] The principal product is not formed from II during the reaction, since II was found to be stable under the reaction conditions.

A structure analogous to IV (or V) for B, the major component of the reaction mixture, was also ruled out by synthesis. The analog of IV (or V), 6-acetoxy-4,4-dimethylcyclohex-2-enone (VII), was prepared by acetoxylation of 4,4-dimethylcyclohex-2-enone with lead tetraacetate.[8] It differed in properties from either II or the major reaction product.

The only reasonable structure remaining for B, the major reaction component, is then 2-acetoxy-5,5-dimethylcyclohex-2-enone (VIII). This structure was supported by demonstrating that catalytic hydrogenation of the reaction mixture gave a ketol acetate which formed a phenylhydrazone differing from that of VI. The same 2,4-dinitrophenylosazone was obtained on heating this ketol acetate with excess 2,4-dinitrophenyl-

(7) G. N. K. Cavill and D. H. Soloman, J. Chem. Soc., 4426 (1955).

(8) For leading references, see P. Narasimha Rao and L. R. Axelrod, J. Am. Chem. Soc., 82, 2830 (1960).

hydrazine as was obtained from VI, II, or the keto–enol product. This is consistent with the structures assigned.

The structures of II, VII, and VIII were confirmed by n.m.r. spectroscopy (see Fig. 1). The singlet at 3.85 τ in the spectrum of II indicates an uncoupled vinyl hydrogen, whereas coupling of the vinyl hydrogen of VIII with the two equivalent hydrogen atoms of the adjacent methylene group produces a triplet at 3.69 τ. The two vinyl hydrogen atoms of VII give separate doublets at 4.23 τ and 3.40 τ. In II the two adjacent (coupled) methylene groups give rise to two triplets (at about 7.38 and 8.13 τ). The uncoupled methylene group in VIII that is adjacent to the carbonyl group gives a signal at 7.63 τ; the methylene group coupled with the vinyl hydrogen atoms gives rise to a partially hidden doublet at 7.61 τ. In VII the signal for the single hydrogen atom attached to the same carbon atom as the acetoxy group is shifted far downfield (4.64 τ), as expected.

The results described above show that the reaction of cis- 2,6-dibromo-4,4-dimethylcyclohexanone (I) with sodium acetate gives VIII as the major product, accompanied by small amounts of II and the dione III (the n.m.r. spectra show that little or no VII is present).

Under mild conditions it is possible to isolate cis-2-acetoxy-6-bromo-4,4-dimethylcyclohexanone (IX)[9] from this reaction mixture. Furthermore, I and IX react with sodium acetate in acetic acid under comparable conditions to give the same ratio of II, VIII, and III, as shown by g.l.c. analysis, indicating that IX is an intermediate in the reaction involving I. This all but excludes the possibility that II, VIII, or III is formed from I by a direct reaction not involving IX (such as the SN2′ attack of acetate ion on the enol form of I, which conceivably could lead to II, previously described).

A variety of mechanisms can be imagined by which II, VIII, and III can be formed from IX. Several of these are summarized on p. 1350.

In all of these mechanisms acetate ion is the attacking agent. In mechanisms a and b, acetate ion attacks the carbonyl group with consequent epoxide formation. In mechanism a, a second acetate ion opens the epoxide by attack on one of the acetoxy groups. A proton shift and loss of acetate ion gives the diketone III, which can be reacetylated (by the acetic anhydride released in the previous step) to form II and VIII. In mechanism b, acetate ion removes a proton from the epoxide; 1,4-elimination of acetate ion then leads to VIII directly.

In mechanism c, acetate ion initiates an SN2′ reaction on the enol form of IX. This is followed by intramolecular rearrangement of an acetyl group and loss of acetic acid to give VIII.

In mechanism d, acetate ion removes a proton in the initial step. Intramolecular rearrangement of the acetyl group then gives an intermediate that can form VIII by a 1,4-elimination of bromide ion. Mechanism e differs from d only in the order of the steps following proton abstraction. Here the bromide ion is lost

(9) The position of the groups in IX and their steric relationship was elucidated by means of its n.m.r. spectrum (Fig. 2). The presence of two clearly resolved quartets with a relative area representing one proton each at 4.67 τ (CHOAc) and 5.17 τ (CHBr) confirm the α and α′ positions of the substituents (based on unpublished work of K. M. Wellman). The large coupling constants (of the order of 12 to 13 c.p.s.) indicate axial orientation for the protons (see K. L. Williamson and W. S. Johnson in ref. 5).
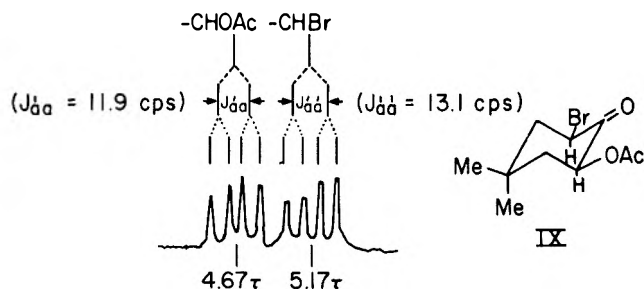
Fig. 2.—The –CHX n.m.r. spectrum for IX.

first to form a dipolar ion. Intramolecular rearrangement of the acetyl group then gives VIII.

A feature common to mechanisms a–c, but not to d and e, is incorporation of external acetate (from acetate ion or the acetic acid solvent) into the product. It was therefore of interest to investigate the reaction of IX with sodium propionate in propionic acid solvent. The g.l.c. pattern of the keto–enol product obtained from this reaction differed in some respects from that of the keto–enol product obtained from the reaction of IX with sodium acetate in acetic acid solution. Peak B (corresponding to VIII) remained the same, but peak A (corresponding to II) disappeared and was replaced by a trailing peak C, which appeared to be an unresolved doublet (presumably the propionates corresponding to II and VIII). This experiment shows that the major product (VIII) is not formed in any appreciable amount by mechanisms a–c, and indicates that mechanism d, e, or the like, pertains. The minor products, II and III, may be formed by mechanism a (propionic anhydride was detected in the product of the sodium propionate run). Further discussion of mechanisms d and e will be given in a later paper.
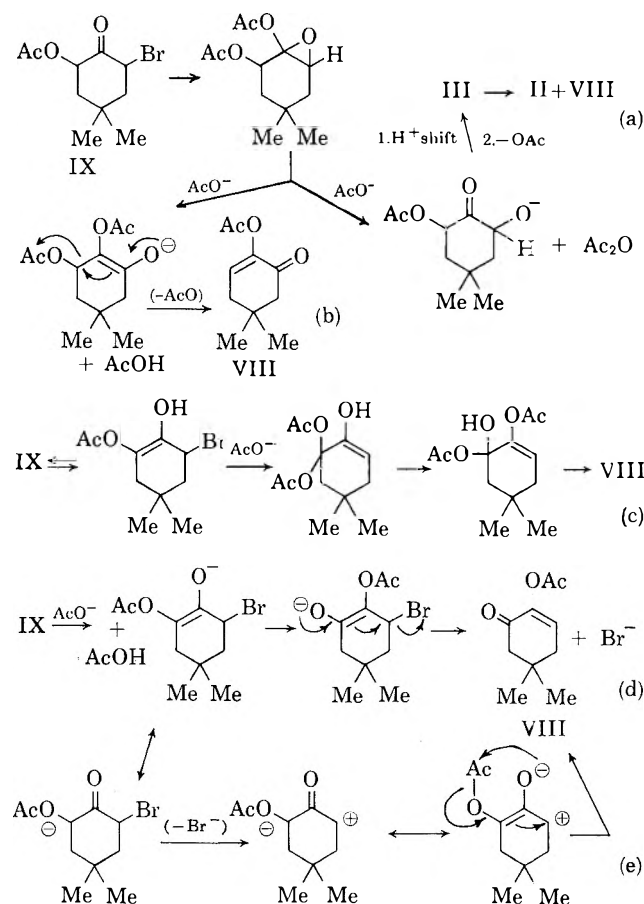


Reaction of IX with 2,4,6-trimethylpyridine gave VIII as the major product, together with some II, but only a trace of III. The formation of VIII under these circumstances is expected according to mechanism d, or e, since 2,4,6-trimethylpyridine should be able to play the role of acetate ion. (No reaction occurs in the absence of base.) A mechanism other than mechanism a must, however, be used to account for the formation of the small amount of II under these conditions.

The demonstration that VIII, rather than II, is the major product of the reaction of I with sodium acetate in acetic acid casts doubt as to the correctness of the structure assignments made to the products formed under similar conditions from the 2,4-dibromo-9-methyl-3-decalones,[3] 2,4-dibromo-3-coprostanone,[4] and 2,4-dibromo-3-cholestanone.[6] The latter reaction is under current investigation.

## Experimental[10]

**4,4-Dimethylcyclohex-2-enone** was prepared by a modification of an earlier procedure.[11] A solution of 104.3 g. (1.45 moles) of isobutyraldehyde and 118.5 g. (1.70 moles) of methyl vinyl ketone (Chas. Pfizer and Company, Inc., technical grade) was added dropwise with stirring over a period of 45 min. to a solution of 15 ml. of a 40% aqueous (or methanolic) solution of Triton "B" in 300 ml. of t-butyl alcohol. The temperature was maintained at 18–22° by cooling during addition. When about 40 ml. of the aldehyde–ketone solution remained, 15 ml. more of the Triton B solution was added, and the addition completed. The solution was warmed to 30°, and allowed to stand for 30 min. The dark red-brown solution was then poured into a mixture of 500 ml. of cold, dilute hydrochloric acid and 1000 ml. of ether. The ethereal layer was washed three times with 500 ml. portions of water, dried, and concentrated by atmospheric distillation to remove t-butyl alcohol. The residue was vacuum distilled, and the first fraction [b.p. 50–70° (4 mm.)] was redistilled to give 42 g. (0.339 mole; 23%) of 4,4-dimethylcyclohex-2-enone, b.p. 54–56° (4 mm.); $\lambda_{max}^{CS_2}$ 5.95, 12.40 $\mu$; $\lambda_{max}^{EtOH}$ 224 m$\mu$ ($\epsilon$ 16,000); $n^{25}$D 1.4696.

**4,4-Dimethylcyclohexanone.**—Twenty grams of 4,4-dimethylcyclohex-2-enone were dissolved in 125 ml. of glacial acetic acid and 0.40 g. of 10% palladium on carbon was added. The mixture was shaken under 2–3 atm. of hydrogen for 10 min. after the uptake of hydrogen had ceased. The mixture was filtered twice through diatomaceous earth, and then poured into a mixture of 700 ml. of water and 600 ml. of ether. The acetic acid was neutralized by slow addition of solid sodium bicarbonate. The aqueous layer was separated and washed twice with ether. The ether layers were combined and dried. Concentration gave 18.1 g. of prism-like needles, m.p. 37–39°. Sublimation removed a small amount of residual oil and raised the melting point to 39–40° (reported[12] m.p. 38–41°); $\lambda_{max}^{KBr}$ 5.82, 8.67 $\mu$. The semicarbazone melted at 201–202° (reported[12] m.p. 203–204°).

*cis*-2,6-**Dibromo-4,4-dimethylcyclohexanone** (I).—Sublimed 4,4-dimethylcyclohexanone (10.05 g.; 0.0798 mole) in 30 ml. of glacial acetic acid was treated dropwise with 25.6 g. (0.16 mole) of bromine over a period of 20 min. with stirring and cooling so as to keep the temperature between 15 and 20°. The slightly yellow-tinged solution was poured into 300 ml. of water and 400 ml. of ether was added to dissolve the precipitated solid. The ethereal layer was washed with water and 125 ml. of pentane was added. After washing with water and dilute sodium bicarbonate, the solution was dried and concentrated to give 23.7 g. of slightly oily solid dibromide ("crude dibromide").

One recrystallization from hexane gave, after washing with 20 ml. of pentane, 14.6 g. of dibromo ketone, m.p. 94–96°, as colorless plates. The filtrate and pentane washings were combined and concentrated to about 10 ml. After a seed crystal of dibromo ketone was added, a small amount of anhydrous hydrogen bromide gas was bubbled through the solution and the flask was

(10) Microanalyses were determined by Miss Hilda Beck. N.m.r. spectra were obtained by Larry Shadle.

(11) E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, **79**, 5986 (1957).

(12) E. B. Reid and T. E. Gomp, *J. Org. Chem.*, **18**, 661 (1953).

stoppered and allowed to stand at room temperature overnight. An additional 3.3 g. of product, m.p. 93–95°, was thus obtained; the total yield was 17.9 g. (80%). Further recrystallization gave material melting at 95–96° (reported[2] m.p. 97°).

**Reaction of *cis*-2,6-Dibromo-4,4-dimethylcyclohexanone with Sodium Acetate in Acetic Acid.**—Repetition of the previous work[2] with 9.00 g. (0.0318 mole) of crude I gave 1.01 g. (0.0056 mole; 18% yield; $n^{20}$D 1.4750) of liquid keto–enol acetates[13] and 1.89 g. (0.0135 mole; 43%) of solid diketone, m.p. 65–68°. Several recrystallizations from methanol–water gave pure 4,4-dimethyl-cyclohexane-1,2-dione (III), m.p. 75–76° (reported[2] m.p. 76–77°), as long, glistening, colorless needles.

Freshly distilled glacial acetic acid (56 ml.) and 27.2 g. (0.33 mole) of anhydrous, freshly fused sodium acetate, were heated at 87° for 30 min. I, m.p. 94–96°, (16.5 g.; 0.058 mole) was added and the mixture stirred and heated for 3 hr. at 87–89°. The solidified mixture, obtained on cooling, was broken up and added to 400 ml. of water. The precipitated oil was taken up in 400 ml. of ether, and the aqueous layer was washed with 250 ml. of 1:1 ether–pentane. The combined organic fractions were washed with water and with aqueous sodium bicarbonate. The ethereal layer was dried and concentrated to give 9.18 g. of an oil. A g.l.c. analysis showed three components, the diketone (3%; identified by enhancement of the peak by adding an authentic sample of III to the reaction mixture), and two partially resolved keto–enol acetates. The minor component keto–enol acetate was shown to be II by enhancement of the minor peak (peak A) on addition of authentic II (see below) to the reaction mixture. Vacuum distillation of the reaction mixture gave III as a low boiling fraction (0.228 g; 2.8% yield) which solidified (m.p. 65–68°) in the condenser; its infrared spectrum was identical to that of authentic III. Further distillation gave 7.18 g. (68%) yield of keto–enol acetates, b.p. 74.5–75.0° (0.2 mm.), $n^{20}$D 1.4740, $\lambda_{max}^{CS_2}$ 5.65, 5.89, 6.05, 8.25, 8.45, 8.70, 9.14 $\mu$, $\lambda_{max}^{EtOH}$ 232 m$\mu$ ($\epsilon$ 10,000). An n.m.r. analysis indicated the ratio of VIII to II to be 5.2 to 1.

***cis*-2,3-Dihydroxy-4,4-dimethylcyclohexanone.**—A mixture of 5.00 g. (0.0323 mole) of 4,4-dimethylcyclohex-2-enone, 100 ml. ether, and 15 ml. of hydrogen peroxide (30% aqueous) was cooled to 0–2° and a solution of 0.25 g. of osmium tetroxide in 10 ml. of ether added. The cold solution turned dark brown; it decolorized slowly when shaken for 20 min. at 0.5°. The cooling bath was removed, and the reaction mixture allowed to stand in the cold room (17°) for 10 hr. After drying, the ether layer became discolored. Two milliliters of aqueous hydrogen peroxide were added, and the mixture shaken until the dark color disappeared. The ethereal fraction was washed with 5 ml. of water, and concentrated to 10 ml. under vacuum at room temperature using a Rinco concentrater. The residue was placed under high vacuum and warmed to 35–45° for 3 hr. giving 5.00 g. of solid dihydroxy ketone. One recrystallization from ether–hexane gave 2.68 g. (0.017 mole; 53% yield) of *cis*-2,3-dihydroxy-4,4-dimethylcyclo-hexanone, m.p. 97–99°, $\lambda_{max}^{KBr}$ 2.80, 2.88, 5.83, 8.85, 9.06, 9.42 $\mu$. An analytical sample melted at 100–101° (colorless plates).

*Anal.* Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.89; H, 9.07.

**2-Acetoxy-4,4-dimethylcyclohex-2-enone (II).**—A solution of 2.507 g. (0.0159 mole) of *cis*-2,3-dihydroxy-4,4-dimethylcyclo-hexanone in 60 ml. of acetic anhydride was refluxed for 3.5 hr. The reflux condenser was replaced with a Vigreux column, the acetic acid and excess acetic anhydride were removed under vacuum, and the residue (2.43 g.) was distilled; b.p. 100–103° (2 mm.) (1.87 g.; 0.01 mole; 65% yield). A middle cut was taken as an analytical sample of II; b.p. 100.5° (2 mm.); $n^{20}$D 1.4703; $\lambda_{max}^{CS_2}$ 5.65, 5.89, 6.05, 8.25, 9.16 $\mu$. G.l.c. and n.m.r. analyses indicated the absence of any appreciable amount of VIII.

*Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.34; H, 7.45.

**Attempted Rearrangement of II.**—Glacial acetic acid (2.5 ml.), sodium acetate (0.62 g.), and II (0.25 g.) were combined and heated at 85–90° (bath temperature) for 2 hr. The infrared spectrum of the resulting oil (0.20 g.) was superimposible on that

of the starting material; g.l.c. analysis indicated less than 1% diketone and no appreciable amount of VIII.

**6-Acetoxy-4,4-dimethylcyclohexanone (VI). A. By Hydrogenation of II.**—Ten milliliters of absolute alcohol, 0.243 g. of II, and 0.024 g. of 10% palladium on carbon were combined and stirred magnetically under 2–3 atm. of hydrogen until the up-take of hydrogen ceased. The reaction mixture was filtered through diatomaceous earth, and the filter cake was washed with 10 ml. of ether. The ether and alcohol were removed by distillation to yield 0.158 g. of crude acetoxy ketone VI. The infrared spectrum was essentially that of pure ketol acetate VI (see below).

**B. By Acetoxylation of 4,4-Dimethylcyclohexanone.**—According to the general method of Cavill and Soloman,[7] 19.6 g. (0.0432 mole) of lead tetraacetate, which had been dried under vacuum over sodium hydroxide pellets for 24 hr., 5.17 g. (0.041 mole) of 4,4-dimethylcyclohexanone, and 33 ml. of benzene (freshly distilled from over sodium) were heated for 10.5 hr. at 70° in a flask fitted with a condenser and calcium chloride tube. The mixture was filtered and the residue washed with ether. The ether–benzene solution was freed of acetic acid by washing with saturated sodium bicarbonate solution, dried, and concentrated under vacuum to yield 5.79 g. of an oil. Fractionation of the product through a Vigreux column under vacuum gave 3.87 g. (0.0210 mole; 51%) of 6-acetoxy-4,4-dimethylcyclohexanone (VI); b.p. 65–68° (0.2 mm.); $n^{20}$D 1. 4560; $\lambda_{max}^{CS_2}$ 5.70, 5.75, 8.08, 9.20, 9.47 $\mu$.

To 243 mg. of VI was added, with stirring, 147 mg. of phenyl-hydrazine. A yellow-orange solid formed immediately. Recrystallization from ether–hexane gave colorless prisms, m.p. 102° (turning yellow at 97°). This derivative decomposed in 2 hr. at room temperature on the desk. Decomposition occurred in 3 days in a dark cold room (17°).

*Anal.* Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08. Found: C, 69.44; H, 8.11.

**6-Acetoxy-3,3-dimethylcyclohexanone Phenylhydrazone.**—Crude 6-acetoxy-3,3-dimethylcyclohexanone ($\lambda_{max}^{CS_2}$ 5.70, 5.75, 8.08, 9.30 $\mu$) was obtained by hydrogenation of the keto–enol acetate product from I (see above) in the same manner as II was hydrogenated to VI. The infrared absorption spectrum of the crude ketol acetate showed weak absorptions at positions where VI had medium-strong bands (9.20 $\mu$ and 9.47 $\mu$). The crude ketol acetate (129 mg.) was stirred with 89.9 mg. of phenyl-hydrazine until the mixture had completely solidified to the orange-yellow phenylhydrazone. Recrystallization was effected from ether–hexane to give colorless prisms, m.p. 113–114°—dependent on rate of heating—turning yellow at 107°. The phenylhydrazone decomposed overnight at room temperature but was relatively stable in the cold room (17°) or in the dark under vacuum.

*Anal.* Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08. Found: C, 69.84; H, 8.03.

**4,4-Dimethyl-1,2-cyclohexadione 2,4-Dinitrophenylosazone.**—Brady's reagent was prepared by dissolving 1.925 g. of 2,4-di-nitrophenylhydrazine in a solution of 4 ml. of concd. sulfuric acid, 30 ml. of methanol, and 10 ml. of water and decanting the solution from a small amount of dark red residue.

Using this reagent the same osazone (identified by mixture melting points) was obtained from III, II, VIII, VI, and from the crude ketol acetate formed by the catalytic hydrogenation of VIII.

In each instance the procedure was the same. For example, when 0.5053 g. of 2-acetoxy-4,4-dimethylcyclohexanone was added to the freshly prepared reagent at room temperature, a pale yellow precipitate formed immediately. After heating at reflux for 1 hr., the initial colloidal precipitate was transformed to a finely divided dark red precipitate. After drying, the crude osazone (1.36 g.) melted at 190–195°. Two recrystallizations from methanol–chloroform gave small, dark red prisms, m.p. 224–225°.

*Anal.* Calcd. for $C_{20}H_{20}N_8O_8$: N, 22.39. Found: N, 22.58.

**6-Acetoxy-4,4-dimethylcyclohex-2-enone (VII).**—A mixture of 5.00 g. (0.0403 mole) of 4,4-dimethylcyclohex-2-enone, 17.84 g. (0.0402 mole) of lead tetracetate and 30 ml. of benzene (freshly distilled from sodium) was heated at reflux for 20 hr. The mixture was filtered and the residue washed with two 50-ml. portions of ether. The ether–benzene solution was washed with water and with dilute sodium bicarbonate, dried, and concentrated to yield 5.5 g. of an oil. Vacuum distillation gave a forerun (0.598 g., 0.0048 mole) of starting material (by infrared analysis) boiling mainly at 60° (5 mm.), a small intermediate fraction [b.p.

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(13) A gas–liquid chromatogram[14] of the keto–enol acetates showed only two partially resolved components. An n.m.r. analysis using the areas under appropriate absorptions indicated the two components to be in the ratio of 1 to 7.3.

(14) Throughout this work an F and M Model 300 vapor phase chromatograph containing a 6-ft. column packed with 20% diisodecyl phthalate on 100–120-mesh firebrick was used at a temperature of about 150°.

65–115° (5 mm.)], and a main fraction consisting of 2.319 g. (0.0128 mole; 36% yield) of **6-acetoxy-4,4-dimethylcyclohex-2-enone**, b.p. 115–116° (5 mm.). An analytical sample had the following characteristics: b.p. 116° (5 mm.), $n^{22}$D 1.4736, $\lambda_{max}^{CS_2}$ 5, 70, 5.87, 8.03, 8.16, 9.24, 9.49, 12.20 $\mu$.

*Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.76; H. 7.70.

*cis*-2-**Bromo-6-acetoxy-4,4-dimethylcyclohexanone** (IX).—In unsuccessful attempts to isolate IX, the reaction of I with sodium acetate was carried out with excess sodium acetate for varied times at temperatures from 25 to 65°. Success was finally achieved as follows: 5.00 g. (0.0176 mole) of I and 1.44 g. (0.0176 mole) of fused sodium acetate were dissolved in 20 ml. of glacial acetic acid, the reaction vessel stoppered, and placed in an oil bath at 85°. After 125 min. the reaction mixture was cooled, poured into water, and the precipitated oil taken up in ether. The ethereal layer was washed free of acetic acid with concentrated aqueous sodium bicarbonate. After drying, the ethereal solution was concentrated under vacuum to yield 3.10 g. of an oil. The oil was dissolved in hot petroleum ether and the solution cooled slowly, and then placed in the cold room overnight; the resulting large prisms melted at 65–67°. Recrystallization from petroleum ether gave 0.769 g. of pure *cis*-2-bromo-6-acetoxy-4,4-dimethylcyclohexanore as large diamond-shaped crystals, m.p. 76.5°, $\lambda_{max}^{KBr}$ 5.69, 5.73, 8.08 $\mu$. Chromatography of the mother liquors from the recrystallizations over silica gel (eluting with 10% ether-in-hexane) gave 1.006 g. (m.p. 73–74°) more of the bromo-acetoxyketone (total yield: 39%).

*Anal.* Calcd. for $C_{10}H_{15}BrO_3$: C, 45.64; H, 5.75. Found: C, 45.71; H, 5.61.

**Reaction of** *cis*-2-**Bromo-6-acetoxy-4,4-dimethylcyclohexanone (IX) with Various Bases. A. With Sodium Acetate.**—Three milliliters of acetic acid was distilled from acetic anhydride and anhydrous sodium acetate into a reaction vessel containing 0.41 g. (5.0 mmole) of hot, freshly fused sodium acetate. The flask was tightly stoppered and heated at 87° (bath temperature) for about 20 min.; a small amount of the fused sodium acetate remained undissolved. Then 0.2647 g. (1.00 mmole) of IX was added and heating continued for 2.5 hr. at 84–87°. After standing for 20 min. at room temperature, the reaction mixture was poured into a mixture of 50 ml. water and 75 ml. of ether. After vigorous shaking, the aqueous layer was discarded and 25 ml. of pentane was added. The organic solution was washed with water, followed by sufficient sodium bicarbonate to remove the remaining acetic acid. The organic layer was then dried and concentrated under vacuum to yield 0.165 g. (0.91 mmole, assuming pure keto–enol acetates) of slightly yellow colored oil. G.l.c. analysis showed three components (III, II, and VIII) with areas in the ratio of about 0.45:1.0:4.1, respectively. (Since the keto–enol acetates are only partially resolved on the column, the ratio between them is only approximate in this and other runs; the ratio between the acetates and the diketone should, however, be accurate.)

A reaction carried out concurrently and under the same conditions using *cis*-2,6-dibromo-4,4-dimethylcyclohexanone (I) in place of IX gave 0.98 mmole of crude product from 1.06 mmoles of dibromo ketone. The infrared spectra from this and the foregoing run were superimposable, even to small detail. A g.l.c. analysis gave the ratios of III, II and VIII as 0.50:1.0:4.5 in good agreement with the same ratios of products obtained from IX.

**B. With Sodium Propionate.**—Freshly fused sodium propionate (0.4740 g., 5.0 mmole) and 3 ml. of freshly distilled propionic acid were heated for 20 min. at 84°. Then 0.26 g. (1.0 mmole) of IX was added, and the heating was continued for 2.5 hr. at 84–87°. The reaction mixture was processed as above to give 0.158 g. (0.87 mmole) of oil. The infrared spectrum of this crude product was essentially the same as that of the product from run A above, except for a weak band at 5.53 $\mu$ believed to be due to propionic anhydride. The enhancement of one of the peaks in the gas–liquid chromatogram on addition of propionic anhydride gave additional evidence for its presence (to the extent of about 3%).

In contrast to the runs made in acetic acid, no peak A was present in the gas–liquid chromatogram (keto–enol acetate II was absent). Instead, peak B (due to VIII) was followed by two partially resolved components (peak C). These new components are probably the propionates corresponding to II and VIII. The ratio of III to VIII to the propionates was 0.52:4.1:1.0.

**C. With 2,4,6-Trimethylpyridine.**—A solution of 0.1594 g. (0.6 mmole) of IX and 1.6 ml. of freshly distilled 2,4,6-trimethylpyridine was heated at 98–106° (bath temperature) for 22 hr. The reaction mixture was cooled and poured into a mixture of 50 ml. of 10% hydrochloric acid and 75 ml. of ether. The ethereal layer was separated and washed again with 50 ml. of 10% hydrochloric acid and finally with water. The organic layer was dried and concentrated to yield 0.087 g. of an oil. The infrared spectrum of this product indicated a small amount of starting material remaining. Analysis (g.l.c.) showed only a trace of diketone III; the ratio of VIII to II was at least 11 to 1.0.

**Attempted Solvolysis of IX.**—A solution of 0.106 g. of IX in 3 ml. of propionic acid and 1 ml. of propionic anhydride was heated at 84–88° (bath temperature) for 2.5 hr. The solution was allowed to stand at room temperature for about an hour and then poured into 50 ml. of concentrated sodium bicarbonate solution. Processing by ether extraction gave back IX, m.p. 71–72°.

# Debromination of $N,N$-Diethylcinnamamide Dibromide

A. J. SPEZIALE AND C. C. TUNG

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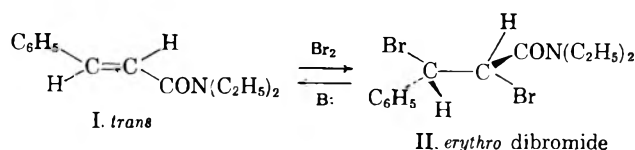
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Attempts to prepare *trans*-$N,N$-diethyl-3-phenylglycidamide from the corresponding *erythro*-$N,N$-diethyl-cinnamamide dibromide (II) and bases gave unexpectedly the debromination product, *trans*-$N,N$-diethylcin-namamide (I). The debromination of *erythro*-ethyl *p*-nitrocinnamate dibromide (VIIa) and *erythro*-ethyl cinnamate dibromide (VIIb) to the corresponding *trans* olefins occurred with highly nucleophilic reagents such as triphenylphosphine and pyridinium thiolacetate. However, when VIIa,b were treated with alcoholic sodium acetate, *trans* elimination of hydrogen bromide became the only reaction. These results are explicable on the basis of the preferred conformation in the transition state of the respective dibromides for the debromination and the dehydrohalogenation reactions and the nucleophilicity of the base in its attack on "positive" $\alpha$-halogen or $\alpha$-hydrogen.

The reaction of branched vicinal dibromides with sodium thiophenolate was reported[1,2] to yield olefins. However, with ethylene and propylene dibromides, only substitution products were isolated.[1,3] The formation of olefins from vicinal dibromides with iodide ion is well known.[4] The reaction is second order and proceeds by a *trans* elimination mechanism.[4e,5–7] Thus, *meso*-stilbene dibromide and *meso*-2,3-dibromobutane yield *trans* olefins whereas the corresponding *threo* dibromides give *cis* olefins.[8] The debromination of acyclic dibromides with metals, *e.g.*, zinc, magnesium, and sodium is also well known.[4d,9]

Bickel[10] reported the debromination of chalcone dibromide with bases in the presence of alcohol-free acetone or aqueous acetone. However, Abell,[11] Bickel,[12] and Lutz, *et al.*,[13] noted that the chalcone dibromide on treatment with potassium acetate in 95% ethanol or triethylamine in acetone gave only $\alpha$-bromochalcone. The debromination of vicinal dibromides adjacent to a carbonyl group by trialkyl-phosphite has also been reported.[14,15]

Our attempt to prepare *trans*-$N,N$-diethyl-3-phenyl-glycidamide from the corresponding *erythro* dibromide (II)[16] with sodium carbonate in aqueous acetone gave unexpectedly *trans*-$N,N$-diethylcinnamamide (I) as the only product. This finding prompted us to in-



vestigate further the results of the treatment of this dibromide with other bases.

The debromination of the *erythro*-dibromide (II) under the conditions studied (Table I) led only to *trans*-cinnamamide.

### TABLE I
#### DEBROMINATION OF II BY BASES

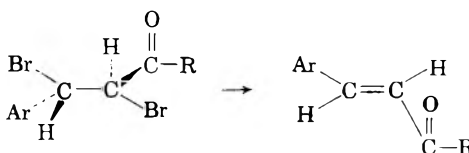| Base | % Yield of I |
|---|---|
| $Na_2CO_3$, $H_2O$ | 97.0 |
| KOH, $H_2O$ | 96.0 |
| $CH_3COONa$, $C_2H_5OH$ | 51.3[a] |
| $(C_6H_5)_3P$, $CHCl_3$ | 95.5 |
| $C_5H_5N$, $CH_3COSH$, $C_6H_6$ | 90.0 |

[a] Quantitative yield based on 48.7% recovered II.

Two alternate competitive reactions of II with base, *trans* elimination of hydrogen bromide and S$_N$2 displacement of either or both bromine atoms, were not observed.

The stereospecific elimination of bromine undoubtedly proceeds *via* a concerted E2 mechanism which is facilitated by the favored *trans* coplanar transition state (III). The partial accumulation of negative
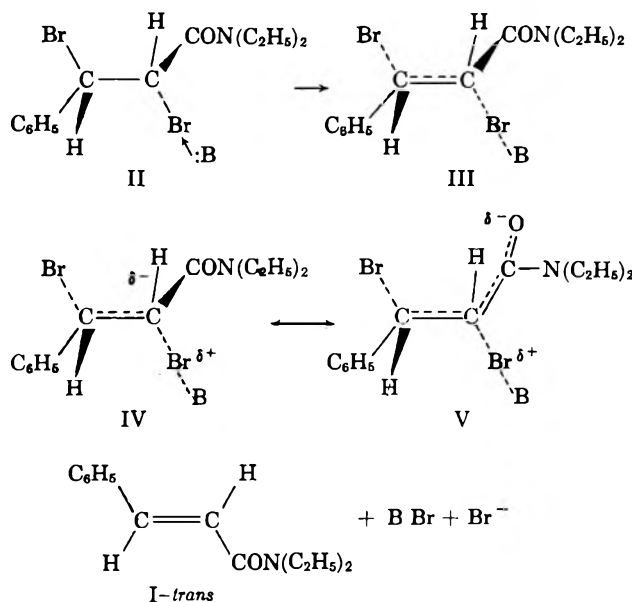


(1) R. Otto, *J. prakt. Chem.*, [2] **51**, 299 (1895).

(2) E. Eliel and R. G. Haber, *J. Org. Chem.*, **24**, 143 (1959).

(3) J. Hine and W. H. Brader, Jr., *J. Am. Chem. Soc.*, **75**, 3964 (1953).

(4) (a) R. T. Dillon, W. G. Young, and H. J. Lucas, *ibid.*, **52**, 1953 (1930); (b) R. T. Dillon, *ibid.*, **54**, 952 (1932); (c) W. G. Young and S. Winstein, *ibid.*, **58**, 102 (1936); (d) W. G. Young, Z. Jasaitis, and L. Levanas, *ibid.*, **59**, 403 (1937); (e) S. Winstein, D. Pressman, and W. G. Young, *ibid.*, **61**, 1645 (1939); (f) W. G. Young, S. J. Cristol, and T. S. Skei, *ibid.*, **65**, 2099 (1943); (g) J. Weinstock, S. N. Lewis, and F. G. Bordwell, *ibid.*, **78**, 6072 (1956).

(5) W. G. Young, D. Pressman, and C. D. Coryell, *ibid.*, **61**, 1640 (1939); **65**, 2099 (1943).

(6) (a) D. H. R. Barton and E. Miller, *ibid.*, **72**, 1066 (1950); (b) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951); (c) G. H. Alt and D. H. R. Barton, *ibid.*, 4284 (1954).

(7) W. M. Schubert, H. Steahly, and B. S. Rabinovitch, *J. Am. Chem. Soc.*, **77**, 5755 (1955).

(8) When ethanolic potassium hydroxide was used instead of iodide, *meso*-stilbene dibromide yielded *cis*-bromostilbene, and *threo*-stilbene dibromide yielded *trans*-bromostilbene [P. Pfeiffer, *Z. physik. Chem.*, **48**, 40 (1904)].

(9) W. M. Schubert, B. S. Rabinovitch, N. R. Larson, and V. A. Sims, *J. Am. Chem. Soc.*, **74**, 4590 (1950).

(10) C. L. Bickel, *ibid.*, **72**, 349 (1950).

(11) R. D. Abell, *J. Chem. Soc.*, **101**, 1000 (1912).

(12) C. L. Bickel, *J. Am. Chem. Soc.*, **68**, 865 (1946).

(13) R. E. Lutz, D. F. Hinkley, and R. H. Jordan, *ibid.*, **73**, 4647 (1951).

(14) V. S. Abramov and N. A. Ilyina, *J. Gen. Chem., USSR*, **26**, 2245–2249 (1956).

(15) S. Dershowitz and S. Proskauer, *J. Org. Chem.*, **26**, 3595 (1961).

(16) The transformation of a dibromide to an epoxide with base proceeds through the bromohydrin [D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc.*, **78**, 4064 (1956)].

TABLE II

DEBROMINATION OF *erythro*-DIBROMIDES WITH TRIPHENYLPHOSPHINE AND THIOLACETATE ION



| | Ar | R | $\alpha,\beta$-Unsat., % | $(C_6H_5)_3PBr_2$, % | $(CH_3C—S)_2$, % | $C_5H_5NHBr^-$, % |
|---|---|---|---|---|---|---|
| II | $C_6H_5$ | $N(C_2H_5)_2$ | 96 | 86 | .. | |
| II | $C_6H_5$ | $N(C_2H_5)_2$ | 90 | | 87 | Theory |
| VIIa | $4\text{-}NO_2C_6H_4$ | $OC_2H_5$ | 87 | 99 | .. | |
| VIIa | $4\text{-}NO_2C_6H_4$ | $OC_2H_5$ | 95 | | 89 | Theory |
| VIIb | $C_6H_5$ | $OC_2H_5$ | 92 | 93 | .. | |
| VIIb | $C_6H_5$ | $OC_2H_5$ | 84 | | 85 | 96.5 |
| XIa | $3,4\text{-}Cl_2C_6H_3$ | $N(C_2H_5)_2$ | 80 | | 78 | 98.5 |
| XIb | $C_6H_5$ | $OH$ | 82 | | 74 | 91.5 |

charge on the α-carbon atom would also be stabilized by resonance forms IV ⟷ V.

The *trans* elimination of hydrogen bromide from II to from *cis* α-bromoölefin (VI) would be sterically unfavored because of the repulsion associated with eclipsing a phenyl and a diethylamido group (as in II''). However, *trans* debromination of II would involve the more favored conformer II' (eclipsed phenyl and hydrogen). The S_N2 displacement of bromine atoms is also sterically hindered in either II' or II''.
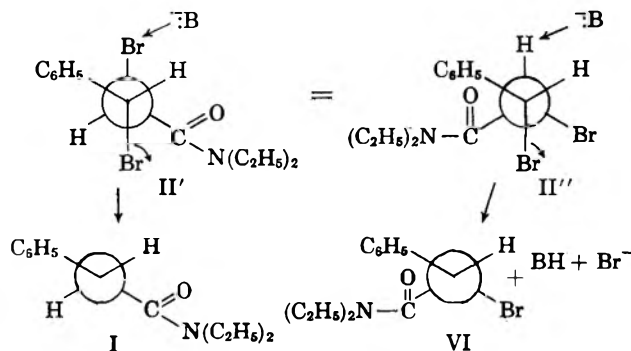


The debromination of *erythro*-ethyl *p*-nitrocinnamate dibromide (VIIa) and *erythro*-ethyl cinnamate dibromide (VIIb) with highly nucleophilic reagents (triphenylphosphine or pyridinium thioacetate) gave the corresponding *trans* olefins (VIIIa,b).
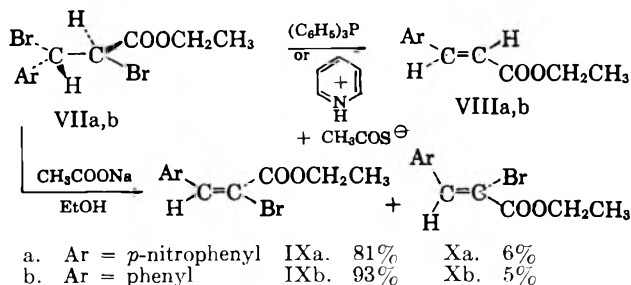


a.  Ar = *p*-nitrophenyl   IXa. 81%   Xa.  6%
b.  Ar = phenyl   IXb. 93%   Xb.  5%

However, when VIIa,b were treated with alcoholic sodium acetate, *trans* elimination of hydrogen bromide became the only reaction. Thus, VIIa,b were converted to the *cis*-α-bromoölefins (IXa,b) with 5–7% of *trans*-α-bromoölefins (Xa,b).[17] Even though the preferred conformation of VIIa,b is that depicted by II' [$N(C_2H_5)_2$⇌$OC_2H_5$], debromination did not occur. A plausible explanation for these results is

that since acetate ion is a poor nucleophile, abstraction of a proton from the less favored conformation II'' [$N(C_2H_5)_2$⇌$OC_2H_5$] is preferred. The difference in behavior of the bromo amides and bromo esters may be due to the fact that the α-hydrogen atom of the amide is considerably less acidic than that of the ester.[18] Because the debromination of II by acetate ion proceeded to only 51.3% in twelve hours (Table I) and dehydrobromination of VIIa and VIIb proceeded to 89.9% and 97.5% in six hours, it is suggested that the acidities (or positive character) are in the following orders: αH in VIIa,b > αBr in II > αH in II.

Treatment of *erythro*-dibromides (XIa,b) with pyridinium thiolacetate also gave the debromination products, XIIa,b.



a.  Ar = 3,4-dichlorophenyl;  R = $N(C_2H_5)_2$
b.  Ar = phenyl;  R = OH
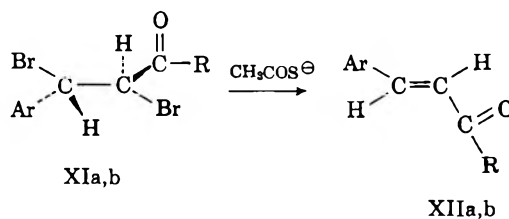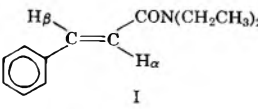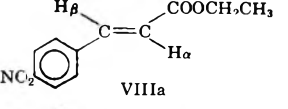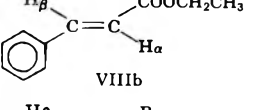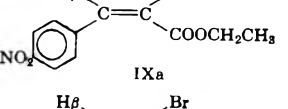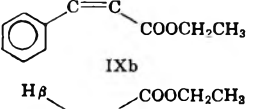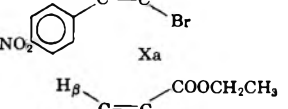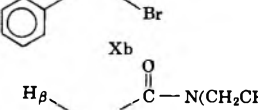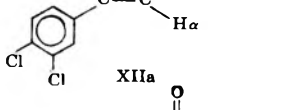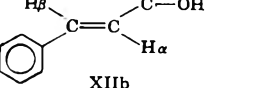
The mechanism proposed for the debromination of the *erythro*-dibromides involves the attack by base on a positive bromine atom. (The one occupying the α-position is the most reasonable.) Although no attempt was made to isolate hypobromite or acetyl hypobromite from the reaction of I with carbonate, hydroxide, or acetate ions, the reactions of triphenylphosphine and thioacetate ion with II, VIIa,b, and XIa,b were investigated in some detail. The results are tabulated in Table II.

The *erythro*-dibromides (II, VIIa,b, and XIa,b) with triphenylphosphine gave high yields of triphenylphosphine dibromide. Its infrared spectrum was identical with an authentic sample prepared from triphenyl-

(17) Since the formation of *trans* α-bromoölefins does not arise from the isomerization of the corresponding *cis* olefins,[13] *trans* α-bromoölefins Xa,b, could result either (a) from the *trans* elimination of hydrogen bromide from traces of the *threo* dibromides which could be formed during the preparation of *erythro* dibromides, or (b) from the *cis* elimination of hydrogen bromide from the *erythro* dibromides. Although *cis* eliminations of this type are unsatisfactory, they, however, are derived in this case from the favored conformer (II').

(18) A. J. Speziale and H. W. Frazier, *J. Org. Chem.*, **26**, 3176 (1961).

## TABLE III
### CHEMICAL SHIFTS[a] AND SPIN–SPIN COUPLING CONSTANTS OF CINNAMAMIDE AND CINNAMATES

| Compound | Chemical shifts, $\tau$ | | | | Coupling constants, c.p.s. | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | $CH_3$ triplet | $CH_2$ quartet | $H\alpha$ doublet | $H\beta$ doublet | $J_{CH_3}$ | $J_{CH_2}$ | $J_{H\alpha H\beta}$[b] |
| I | 8.78 | 6.50 | 3.18 | 2.25 | 7.5 | 7.5 | 16.0 |
| VIIIa | 8.67 | 5.75 | 3.40 | 2.20 | 8.0 | 8.0 | 16.5 |
| VIIIb | 8.67 | 5.72 | 3.56 | 2.30 | 8.0 | 8.0 | 16.0 |
| IXa | 8.80 | 5.75 | .. | 1.83[c] | 8.0 | 8.0 | .. |
| IXb | 8.82 | 5.77 | .. | 1.83[c] | 7.5 | 7.5 | .. |
| Xa | 8.63 | 5.60 | .. | 1.84[c] | 7.5 | 7.5 | .. |
| Xb | 8.70 | 5.71 | .. | 1.83[c] | 7.5 | 7.5 | .. |
| XIIa | 8.85 | 6.68 | 3.45 | 2.52 | 7.0 | 7.0 | 15.0 |
| XIIb | .. | .. | 3.52 | 2.15 | .. | .. | 16.0 |

[a] N.m.r. spectra were measured at 60 Mc./sec. on a modified Varian Model A-60 spectrometer. The samples contained tetramethylsilane (TMS) as internal reference. [b] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., 1959, p. 238. [c] Singlet.

phosphine and bromine. The triphenylphosphine dibromide was further identified by its quantitative conversion to triphenylphosphine oxide by stirring in water. With thiolacetic acid in pyridine, II, VIIa,b, and XIa,b gave high yields of diacetyl disulfide. The disulfide would arise from the reaction of acetylsulfur bromide with thioacetate ion as shown.
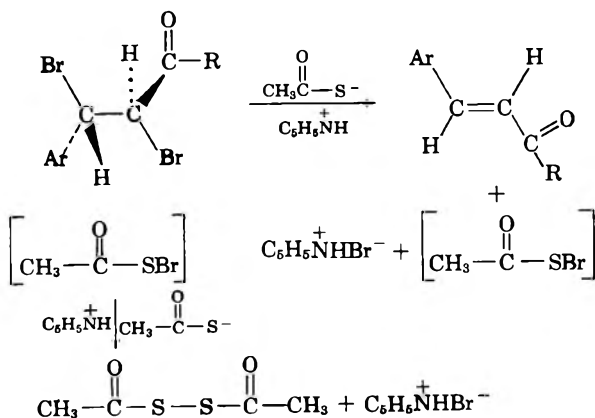
The *trans-α*-bromoölefins (Xa,b) were identical with authentic samples prepared from the ylid (XIV)[19] and the corresponding aldehydes (XVa,b).[20]

$$(C_6H_5)_3P{=}\overset{H}{C}{-}COOEt \xrightarrow[\text{2. KOH}]{\text{1. Br}_2} (C_6H_5)_3P{=}\overset{\overset{Br}{|}}{C}{-}COOEt \xrightarrow{\text{ArCHO}} Xa,b$$

XIII      XIV      XVa,b
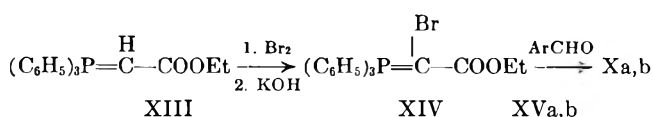
a.   Ar = *p*-nitrophenyl
b.   Ar = phenyl

The assignment of *trans* configuration for I, VIIIa,b, IXa,b, Xa,b, and XIIa,b was confirmed by n.m.r. spectra (Table III). Their coupling constants ($JH_\alpha$, $H_\beta$) are in full agreement with known data.

(19) The conversion of ylids of the type XI to XII and reaction of XII with aldehydes is based on the unpublished work of K. W. Ratts.

(20) For the stereoselective synthesis of an α,β-unsaturated ester from an ylid see [H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961)].

## Experimental

*trans-N,N*-Diethylcinnamamide (I) (m.p. 71–72°) was prepared in 95.0% yield from cinnamoyl chloride and diethylamine *via* the procedure employed by Cromwell and Coughlan.[21]

*trans-N,N*-Diethyl-3',4'-dichlorocinnamamide (XIIa) (m.p. 65.5–66.2°) was prepared in 83% yield (recrystallized from hexane) from 3,4-dichlorocinnamoyl chloride (m.p. 57.8–58.2) and diethylamine.

*Anal.* Calcd. for $C_{13}H_{15}Cl_2NO$: C, 57.40; H, 5.55; N, 5.14; Cl, 26.02. Found: C, 57.52; H, 5.74; N, 5.03; Cl, 26.22.

*erythro-N,N*-Diethylcinnamamide dibromide[22] (II) (m.p. 129.8–130.5°) was prepared in 96.8% yield (recrystallized from hexane-benzene) from bromination of I in carbon tetrachloride solution.

*erythro-*Ethyl *p*-nitrocinnamate dibromide[23] (VIIa) (m.p. 116–117°) (recrystallized from hexane), was obtained in quantitative yield from bromination of *trans*-ethyl *p*-nitrocinnamate (Eastman Distillation Products).

*Anal.* Calcd. for $C_{11}H_{11}Br_2NO_4$: Br, 41.95. Found: Br, 42.40.

*erythro-*Ethyl Cinnamate Dibromide[24] (VIIb).—The bromination of *trans*-ethyl cinnamate (Eastman Distillation Products) in chloroform gave 97.0% yield of VIIb, m.p. 77–78° (recrystallized from hexane-benzene).

*erythro-N,N*-Diethyl-3',4'-dichlorocinnamamide dibromide (XIa) (m.p. 142.9–143.6) (recrystallized from hexane–benzene) was obtained in 77% yield from bromination of *trans*-XIIa in carbon tetrachloride solution.

*Anal.* Calcd. for $C_{13}H_{15}Br_2Cl_2NO$: C, 36.20; H, 3.51; Br, 37.10; Cl, 16.48; N, 3.24. Found: C, 36.22; H, 3.60; Br, 37.18; Cl, 16.38; N, 3.14.

*erythro-*Cinnamic acid dibromide (XIb) (m.p. 205–206°) was prepared from *trans*-cinnamic acid (Eastman Distillation Products) and bromine in carbon tetrachloride solution.

Debromination of *erythro-N,N*-Diethylcinnamamide Dibromide (II). (a) With Sodium Carbonate in Aqueous Acetone.—A solution of 5.0 g. (0.0137 mole) of *erythro*-dibromide II in 150 ml. of acetone and 150 ml. of 7% aqueous sodium carbonate was heated at reflux temperature for 7 hr. After removal of the acetone by evaporation, the oil was extracted with ether. The ether solution was then washed with water and dried over magnesium sulfate. Removal of the ether gave 2.9 g. of colorless solid, m.p. 69–70°. One recrystallization from hexane gave 2.7 g. (97.0% yield) of *trans-N,N*-diethylcinnamamide (I), m.p. 71–72°, identified by infrared data and mixture melting point.

(b) With Potassium Hydroxide in Aqueous Acetone.—A solution of 3.0 g. (0.00826 mole) of *erythro*-dibromide II in 80 ml. of acetone and 6.6 g. of potassium hydroxide in 200 ml. of water was heated at reflux temperature for 0.5 hr. The product was worked up as described in method a to obtain 1.7 g. of solid, m.p. 68–70°. One recrystallization from hexane gave 1.6 g. (96.0% yield) of *trans-N,N*-diethylcinnamamide (I).

(c) With Anhydrous Sodium Acetate in Ethanol.—A mixture of 11.7 g. (0.032 mole) of *erythro*-dibromide II, 13.2 g. (0.16 mole) of anhydrous sodium acetate and 400 ml. of 99.5% ethanol was heated at reflux temperature (80°) for 12 hr. The ethanol solution was evaporated to dryness under reduced pressure and the residue was washed repeatedly with water. The solid, air-dried, weighed 9.3 g. The infrared data indicated the solid to be a mixture of unchanged *erythro*-dibromide II and *trans-N,N*-diethylcinnamamide (I). It was chromatographed on alumina to give 5.7 g. (48.7%) recovery of *erythro*-dibromide II (m.p. 128–129°) and 3.4 g. (theoretical yield based on used II) of *trans-N,N*-diethylcinnamamide (I) (m.p. 70–71°).

(d) With Triphenylphosphine.—To a stirred solution (24°) of 18.2 g. (0.050 mole) of *erythro*-dibromide II in 120 ml. of chloroform was added, in one portion, 13.1 g. (0.050 mole) of triphenylphosphine. The reaction was exothermic and the temperature rose to 58°. After the reaction mixture was allowed to cool to room temperature, it was heated at reflux temperature for 1 hr. The triphenylphosphine dibromide, 13.9 g. (0.033

mole) was removed by filtration. The triphenylphosphine dibromide was hygroscopic and fumed when exposed to the air. Its infrared spectrum was identical with an authentic sample prepared from triphenylphosphine and bromine in chloroform solution. The triphenylphosphine dibromide was further identified by its quantitative conversion to triphenylphosphine oxide by stirring in water. The chloroform filtrate was evaporated to dryness under reduced pressure to give 22.4 g. of viscous oil which was found to consist of a mixture of *trans-N,N*-diethylcinnamamide I and triphenylphosphine dibromide by infrared analysis. The viscous oil was then stirred with 300 ml. of water and a solid precipitated. The solid material was triturated with 200 ml. of boiling hexane and filtered. The hexane insoluble solid weighed 2.8 g. (0.0101 mole) and was identified as triphenylphosphine oxide. The hexane filtrate, upon evaporation, gave 9.7 g. (0.0477 mole, 95.5% yield) of *trans-N,N*-diethylcinnamamide (I). The yield of triphenylphosphine dibromide based upon the recovered triphenylphosphine oxide was 86.2%.

(e) With Pyridine and Thiolacetic Acid.—To a stirred solution of 18.2 g. (0.05 mole) of *erythro*-dibromide II and 11.4 g. (0.15 mole) of distilled thiolacetic acid in 50 ml. of benzene was added dropwise 11.9 g. (0.15 mole) of pyridine over 15 min. Temperature of the reaction mixture rose from 24 to 40° and pyridine hydrobromide was precipitated immediately. The mixture was stirred at room temperature for 3 hr. The hydrobromide salt, 16.0 g. (theory), was removed by filtration. The mother liquor was evaporated to dryness and dissolved in ether. The ethereal solution was washed thoroughly to remove excess of pyridine and thiolacetic acid and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residual oil was chromatographed over silica gel to give 6.9 g. (86.5%) of diacetyl disulfide[25] and 9.1 g. (90.0%) of *trans-N,N*-diethylcinnamamide (I).

The diacetyl disulfide, b.p. 41–42° (0.3 mm.), $n^{25}$D 1.5363, solidified at 18° and exhibited infrared absorption at 1750 cm.$^{-1}$ (acetyl C=O str.), 1125 cm.$^{-1}$ (C—S str.), and 945 cm.$^{-1}$ (S—S str.).

*Anal.* Calcd. for $C_4H_6O_2S_2$: C, 31.98; H, 4.02; S, 42.70. Found: C, 31.63; H, 4.43; S, 42.90.

Debromination of *erythro-*Ethyl *p*-Nitrocinnamate Dibromide (VIIa). (a) With Triphenylphosphine.—To a stirred solution of 19.1 g. (0.05 mole) of dibromide VIIa in 50 ml. of benzene was added a solution of 13.1 g. (0.05 mole) of triphenylphosphine in 70 ml. of benzene over 5 min. Temperature of the reaction mixture rose to 52° and triphenylphosphine dibromide was immediately precipitated. An additional 50 ml. of benzene was added to facilitate stirring and the reaction mixture was heated at reflux temperature for 1 hr. After cooling to room temperature, the triphenylphosphine dibromide was collected by filtration, washed with 50 ml. of benzene, and dried under vacuum at room temperature. The weight of triphenylphosphine dibromide was 20.8 g. (98.6%) and was converted to 13.2 g. (94.6%) of triphenylphosphine oxide by hydrolysis in water. The benzene filtrate was evaporated to dryness to give 10.4 g. of colorless solid which after one recrystallization from benzene gave 9.6 g. (86.8%) of *trans*-ethyl *p*-nitrocinnamate (VIIIa).

(b) With Pyridine and Thiolacetic Acid.—To a stirred solution of 50.0 g. (0.131 mole) of *erythro*-dibromide VIIa and 30.0 g. (0.393 mole) of thiolacetic acid in 150 ml. of benzene, was added 32.0 g. (0.40 mole) of pyridine. The solution was stirred at room temperature for a period of 4 hr. and then at 40° for 7 hr. The mixture was cooled to room temperature and pyridine hydrobromide, 42.0 g. (theory), was separated by filtration. The filtrate was evaporated to dryness to give a straw colored semisolid. The semisolid was triturated with hot hexane and cooled to room temperature. The hexane insoluble solid was collected by filtration. The solid weighed 27.5 g. (94.6% yield), m.p. 135–136°, and was identified as *trans*-ethyl *p*-nitrocinnamate (VIIIa) by infrared and mixture melting point determination. The hexane mother liquor was evaporated to dryness and the residue dissolved in ether. The ethereal extract was washed with water, dried over magnesium sulfate and evaporated to dryness to give 17.4 g. (88.6%) of diacetyl disulfide, $n^{25}$D 1.5362.

Debromination of *erythro-*Ethyl Cinnamate Dibromide (VIIb). (a) With Triphenylphosphine.—To a stirred solution (22°) of 16.8 g. (0.050 mole) of *erythro*-dibromide VIIb in 80 ml. of chloroform and 80 ml. of hexane was added in one portion, 13.1 g. (0.050

(21) N. H. Cromwell and L. A. Coughlan, *J. Am. Chem. Soc.*, **67**, 903 (1945).

(22) P. Herrmann and D. Vorlander, *Chem. Zent.*, I, 730 (1899), reported m.p. 127°.

(23) (a) C. L. Muller, *Ann.*, **212**, 129 (1882); (b) V. B. Drewsen, *ibid.*, **212**, 153 (1882), reported m.p. 110–111°.

(24) "Organic Synthesis", Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y. 1943, p. 270.

(25) Kekule, E. Linnemann, *Ann.*, **123**, 278 (1862).

mole) of triphenylphosphine. The temperature of the reaction mixture rose to 48°. After being cooled to room temperature, the reaction mixture was heated to reflux temperature for 1 hr. To the reaction mixture 200 ml. of hexane was added and the triphenylphosphine dibromide, 19.6 g. (92.8% yield), was removed by filtration. The mother liquor was concentrated and the residue (9.1 g.) was distilled to give 8.1 g. (92% yield) of *trans*-ethyl cinnamate (VIIIb).

(b) **With Pyridine and Thiolacetic Acid.**—To a stirred solution of 11.9 g. (0.0354 mole) of *erythro*-dibromide VIIb and 11.4 g. (0.15 mole) of distilled thiolacetic acid in 50 ml. of benzene was added dropwise over 15 min., 11.9 g. (0.15 mole) of pyridine. The reaction mixture was stirred at room temperature for 3 hr. and pyridine hydrobromide 10.8 g. (96.5% yield) was removed by filtration. The mother liquor, treated as above, afforded 4.5 g. (84.8% yield) of diacetyl disulfide, and 5.2 g. (84.0%) of *trans*-ethyl cinnamate (VIIIb).

**Dehydrobromination of *erythro*-Ethyl *p*-Nitrocinnamate Dibromide (VIIa).** (a) **With Sodium Acetate in Ethanol.**—A solution of 18.7 g. (0.049 mole) of dibromide VIIa and 18.4 g. (0.224 mole) of anhydrous sodium acetate in 390 ml. of 99.5% ethanol was heated at reflux temperature for 6 hr. After removal of the solvent, the residual crystalline mass was stirred with 150 ml. of water to give 13.2 g. (89.9%) of cream colored solid, m.p. 42–46°. The solid, 3.0 g., was chromatographed on alumina from which was obtained 2.7 g. (90%) of solid, m.p. 60.4–61.2° and 0.2 g. (6.8%) of solid, m.p. 93.0–94.1°. The low melting solid was reported as *cis*-ethyl $\alpha$-bromo-*p*-nitrocinnamate (IXa)[26] and the high melting solid as *trans* isomer Xa.[27] The infrared data of the high melting solid was identical with an authentic sample of *trans*-ethyl $\alpha$-bromo-*p*-nitrocinnamate (Xa) from ylid XII. The mixture melting point showed no depression.

The yield of *cis* isomer was 80.8% and *trans* isomer 6.1%.

The *trans* isomer had infrared absorption (in carbon tetrachloride solution) at 1725 cm.$^{-1}$, 1730 cm.$^{-1}$ (doublet for *trans* conj. ester C=O), 1260 cm.$^{-1}$ (ester $-OC_2H_5$), and 1600 cm.$^{-1}$ (conj. C=C).

*Anal.* Calcd. for $C_{11}H_{10}BrNO_4$: C, 44.10; H, 3.34; N, 4.77; Br, 26.67. Found: *cis* isomer: C, 44.29; H, 3.40; N, 4.65; Br, 26.60. *trans* isomer: C, 44.50; H, 3.14; N, 4.54; Br, 27.06.

The *cis* isomer had infrared absorptions (in carbon tetrachloride solution) at 1725 cm.$^{-1}$ (conj. ester C=O), 1220 cm.$^{-1}$ (ester $-OC_2H_5$), and 1600 cm.$^{-1}$ (conj. C=C).

**Dehydrobromination of *erythro*-Ethyl Cinnamate Dibromide (VIIb).** (a) **With Sodium Acetate in Ethanol.**—A solution of 15.1 g. (0.045 mole) of dibromide VIIb and 18.5 g. (0.225 mole) of anhydrous sodium acetate in 400 ml. of 99.5% ethanol was heated at reflux temperature for 6 hr. The solvent was removed under reduced pressure and the residue was dissolved in 150 ml. of water. The oil was extracted with four 150-ml portions of ether and the combined ethereal extract was dried over magnesium sulfate. Removal of the solvent gave 11.2 g. (97.5% yield) of ethyl $\alpha$-bromocinnamate as a light yellow oil, $n^{25}$D 1.5654

(reported[28] for *cis*-ethyl $\alpha$-bromocinnamate $n^{25}$D 1.5657). The gas chromatogram[29] showed two peaks: a major peak corresponding to 95.3% and small peak with longer retention time corresponding to 4.7%. The small peak was assigned to the *trans* isomer since its retention time was the same as that of the authentic sample of *trans*-ethyl $\alpha$-bromocinnamate from the ylid XII and benzaldehyde. The major peak was assigned as *cis*-ethyl $\alpha$-bromocinnamate IXb which had a boiling point of 115° (2 mm.), and $n^{25}$D 1.5697.

**Debromination of *erythro*-$N,N$-Diethyl-3',4'-Dichlorocinnamamide Dibromide (XIa) with Pyridine and Thiolacetic Acid.**—Same procedure as described for the debromination of II was employed. The yields were as follows: pyridine hydrobromide (98.5% yield), diacetyl disulfide (78.0% yield), and *trans*-$N,N$-diethyl-3',4'-dichlorocinnamamide (80.1% yield).

**Debromination of *erythro*-Cinnamic Acid Dibromide (XIb).**—Same procedure as described for the debromination of II was used. The yields were as follows: pyridine hydrobromide (91.5% yield), diacetyl disulfide (73.8% yield), and *trans*-cinnamic acid (81.7% yield).

***trans*-Ethyl $\alpha$-Bromo-*p*-nitrocinnamate Xa from Ylid XIII[30].**—Bromination of 22.2 g. (0.0638 mole) of ylid XIII in chloroform at 0° yielded 33.6 g. (quantitative yield) of the crude phosphonium salt which upon neutralization with aqueous potassium hydroxide gave 19.7 g. of crude ylid XIV. Two recrystallizations from chloroform–pentane gave 15.3 g. (54.3% yield) of XIV, m.p. 155.2–156.0°.

*Anal.* Calcd. for $C_{22}H_{20}BrO_2P$: C, 61.80; H, 4.68; Br, 18.75; P, 7.27. Found: C, 61.98; H, 4.65; Br, 19.02; P, 7.41.

To a stirred solution at 22° of 8.55 g. (0.020 mole) of ylid XIV in 50 ml. of methylene chloride was added 3.02 g. (0.020 mole) of *p*-nitrobenzaldehyde in one portion. The reaction was exothermic and the temperature rose to 39°. The mixture then was heated at reflux for 3.5 hr., followed by evaporation of the solvent to dryness under reduced pressure. The yellow residue was extracted with three 150-ml. portions of pentane and the combined extract was evaporated to dryness to give 1.92 g. of colorless solid, m.p. 91–92.5°. One recrystallization from hexane gave 1.78 g. (29.7%) of pure *trans*-ethyl $\alpha$-bromo-*p*-nitrocinnamate (Xa), m.p. 93.1–94.2°.[27]

***trans*-Ethyl $\alpha$-Bromocinnamate Xb from Ylid XIV.**—A solution of 3.50 g. (0.0082 mole) of ylid XIV and 0.85 g. (0.0082 mole) of benzaldehyde in 40 ml. of methylene chloride was heated at reflux temperature for 3.5 hr. The solvent was evaporated to dryness and the resulting solid was extracted with three 50-ml. portions of heptane. Removal of the solvent yielded 2.00 g. of light yellow oil. The gas chromatogram[29] showed one major peak corresponding to 92.0% of *trans*-ethyl $\alpha$-bromocinnamate (Xb) and two small peaks corresponding to 2.1% of benzaldehyde and 5.9% of *cis*-ethyl $\alpha$-bromocinnamate (same retention time as the major peak from dehydrobromination of *erythro*-ethyl cinnamate dibromide with sodium acetate in ethanol). The yields based on benzaldehyde consumed were 96.9% for *trans*-ethyl $\alpha$-bromocinnamate (Xb) and 3.1% for the *cis* isomer IXb.

(26) (a) C. L. Mullen, *Ann.*, **212**, 137 (1882); (b) S. Reich and N. Y. Chang, *Helv. Chim. Acta*, **3**, 235 (1920), reported m.p. 63°.

(27) (a) C. L. Müller, *Ann.*, **212**, 133, 136 (1882); (b) S. Reich and N. Y. Chang, *Helv. Chim. Acta*, **3**, 235 (1920), reported m.p. 93°.

(28) K. V. Auwers and E. Schmellenkamp, *Ber.*, **54**, 626 (1921).

(29) A column packed with silicon rubber on ground firebrick was used.

(30) O. Isler, *Helv. Chim. Acta*, **40**, 1242 (1957).

# Base-induced Hydrolytic Rearrangement of *trans*-γ-Bromodypnone to 1,2-Dibenzoylethane[1,2]

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Sodium hydroxide in ethanol induces hydrolytic rearrangement of *trans*-γ-bromodypnone to 1,2-dibenzoylethane. Phenyl group migration from the 3- to the 4-position of the dypnone skeleton during this rearrangement and during the similar reductive rearrangements of *cis*- and *trans*-γ-bromodypnone oxides[5] was excluded by repeating the three reactions upon materials $C^{14}$-labeled at the 1- and 3-carbons, followed by permangnate oxidation of the respective products to benzoic acid, in each case with retention of the full $C^{14}$-activity. A rearrangement mechanism is suggested in terms of cyclopropane intermediates.

*trans*-γ-Bromodypnone (I), the vinylog of an α-bromo ketone, is at the right oxidation level for furanization, and at times[2,3] under weakly acidic or basic conditions it undergoes this reaction rather than displacement of the γ-bromine atom. We were then led to investigate the action of strong base, sodium hydroxide or methoxide, conditions under which furanization was not expected. At reaction temperatures below 5° in absolute ethanol containing a small excess of sodium hydroxide, the only crystalline product isolated proved unexpectedly to be 1,2-dibenzoylethane (II) in which the originally beta phenyl group appeared in the terminal position gamma to the original carbonyl group; it was obtained in varying yields, in one case 49%. After the bulk of the γ-bromodypnone had been used up, dibenzoylethane did not crystallize immediately from the cold ethanol solution as it would have done if it had directly been formed and if it had then been present in an amount approaching that ultimately obtained upon work-up. Preliminary attempts so far to isolate a crystalline intermediate have not been successful.



1. R = H or CH₃;
* = $C^{14}$-label

NaOH-abs. $C_2H_5OH$
(below 5°)

1,2-dibenzoylethane, a rigorous test was carried out to exclude the possibility that in these reactions the phenyl group had migrated from the 3- to the 4-carbon atom of the dypnone skeleton, even through such a migration seemed unlikely on mechanistic grounds. For this purpose *trans*-dypnone, phenacyl bromide and the *cis*- and *trans*-γ-bromodypnone oxides $C^{14}$-labeled at the β and at the carbonyl carbon atoms were made from acetophenone $C^{14}$-labeled at its carbonyl carbon. Permanganate oxidations of these intermediates and of the samples of dibenzoylethane obtained in the three rearrangements, each gave benzoic acid of the same $C^{14}$-activity; and proportional $C^{14}$-activity was directly demonstrated in the $C^{14}$-labeled γ-bromodypnone. Had phenyl group migration occurred from the β- to the γ-position at any point during the rearrangements to dibenzoylethane, the benzoic acid molecule produced from the original benzoyl group would have contained the original $C^{14}$-activity of that group, whereas the other molecule of benzoic acid with its phenyl group attached to the carbon atom originally terminal in γ-bromodypnone or its oxides, would have been inactive; and the benzoic acid sample obtained from each oxidation would have had close to half of the total $C^{14}$-activity of the starting material and of the benzoic acid obtained from it by oxidation. Phenyl group migration during the three rearrangements to dibenzoylethane, and any mechanism involving it, are thereby excluded.



VI. *cis* and *trans*
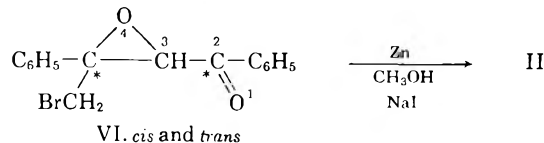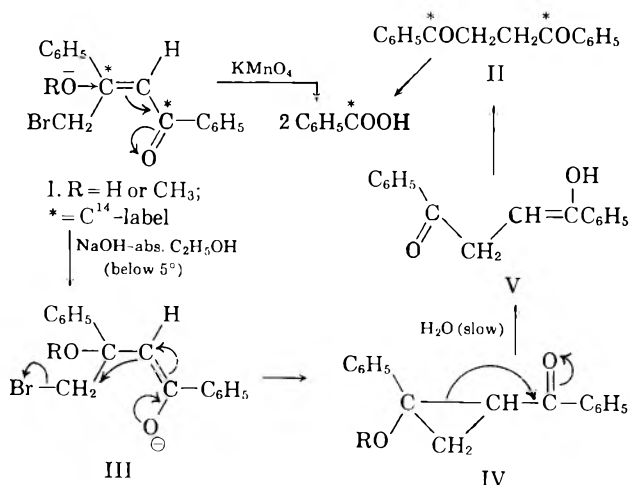
The base-induced rearrangement of γ-bromodypnone to dibenzoylethane can be explained in conventional terms as reversible hydroxide or methoxide ion attack or addition-enolization of the α,β-unsaturated ketone system with approach toward or actual formation of the enolate ion III, intramolecular carbon-alkylation to a cyclopropanol or its ether IV, fission of the cyclopropane ring by retrograde aldolization to the enol V or its equivalent and ketonization to II.[6]

Because of interest in this as a rearrangement under alkaline conditions, and because of its relation to Favorskii rearrangements[4] and to the reductive rearrangements of *cis*- and *trans*-γ-bromodypnone oxides[5] (VI) to

(1) Supported by National Science Foundation grant G 9494.

(2) R. E. Lutz and L. T. Slade, a paper presented at the 138th National Meeting of the American Chemical Society, New York, N. Y. September, 1960; Abstracts, p. 99P.

(3) (a) L. T. Slade, Ph.D. dissertation, University of Virginia, 1960; (b) R. E. Lutz and L. T. Slade, *J. Org. Chem.*, **26**, 4888 (1961).

(4) (a) A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (b) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 5352 (1962); (c) R. B. Loftfield, *ibid.*, **72**, 632 (1950); (d) E. E. Smissman and G. Hite, *ibid.*, **83**, 3980 (1961).

(5) H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *ibid.*, **75**, 96 (1953).

(6) In the reductive rearrangement of *cis*- and *trans*-γ-bromodypnone oxides (VI) to 1,2-dibenzoylethane (II) Wasserman[2] has postulated an intermediate cyclopropoxy anion corresponding to IV. This reaction might be expressed in terms of conjugate reduction, *e.g.*, of the epoxy ketone system with expulsion of bromide ion as in III–IV, which possibly would meet steric and conformational exigencies and explain the difference in yields of II from the stereoisomers of VI (28% *vs.* 8%). For analogies see Boord type reductions of β-halo ethers [(a) C. G. Schmitt and C. E. Boord, *J. Am. Chem. Soc.*, **54**, 751 (1932); (b) L. F. Small and R. E. Lutz, *ibid.*, **56**, 1738 (1934)] and 1,4-reductive-enolization of α-bromo ketone and epoxy ketone systems [(e) R. E. Lutz and W. G. Reveley, *ibid.*, **63**, 3180 (1941); (d) R. E. Lutz and F. N. Wilder, *ibid.*, **56**, 2065 (1934)].

A vinylogous Favorskii hydrolytic rearrangement[4b] of γ-bromodypnone might be envisioned in terms of the intermediate of base attack VII and reaction along the lines indicated, involving migration of the phenyl group from the β to the γ-carbon with expulsion of bromide ion; this would lead to the β-diketone enol VIII or cleavage products from it, but not to dibenzoylethane. Although no such products related to or derivable from VII were observed, losses of material were considerable and this mode of reaction is not excluded as a competing process.

$$C_6H_5-\underset{\underset{CH_2-Br}{|}}{\overset{\overset{OR}{|}}{C}}-CH=C-\overset{O^-}{C}-C_6H_5 \qquad \underset{\underset{C_6H_5CH_2}{|}}{\overset{\overset{OR}{|}}{C}}=CHCOC_6H_5$$

VII. R = H or CH₃    VIII

Further studies on hydrolytic rearrangement of γ-bromodypnones and of furanizations and pyrrole formation are in progress.

## Experimental

In one base-induced rearrangement of γ-bromodypnone at 0 to −10° in which not all of the starting material had been used up, the total isolated product mixture including the unchanged γ-bromodypnone was subjected in work-up to the prolonged action of ethanol under reflux, and the solution had become sharply acidic through alcoholysis of the unreacted γ-bromodypnone. Upon partial separation and isolation of the crystalline products there was obtained a very small amount of dibenzoylethane and a considerable amount of a mixture of two diphenylfurans consisting of roughly comparable quantities of the 2,4 and 2,5 isomers, XII and XIII. Mixtures of authentic samples of these isomers showed melting point depressions of only a few degrees. The presence and identity of the two isomers in the mixture was demstrated semiquantitatively by the approximately equal intensities of the two infrared absorption peaks of 12.3 and 12.5 μ, which are characteristic respectively of the 2,4 and 2,5 isomers, and by comparison with the spectrum of a known mixture. These two wave lengths of strong absorption constitute the most significant difference in the very similar absorption spectra of these two isomers.

$$\underset{XII}{\overset{\displaystyle C_6H_5C\!-\!\!-\!\!-\!CH}{\underset{O}{\underset{\diagdown\diagup}{HC\quad CC_6H_5}}}} \qquad \underset{XIII}{\overset{\displaystyle HC\!-\!\!-\!\!-\!CH}{\underset{O}{\underset{\diagdown\diagup}{C_6H_5C\quad CC_6H_5}}}}$$

The unlikely possibility that 2,4-diphenylfuran would be formed as an intermediate in the formation of dibenzoylethane in the above rearrangements was excluded by direct test which showed that both it and 2,5-diphenylfuran are stable under the alkaline conditions used for the rearrangements. The source of the 2,5-diphenylfuran in the above experiments evidently is the dibenzoylethane produced by the rearrangement, which in separate experiment actually was shown to furanize under the work-up conditions. The source of the 2,4-diphenylfuran must be hydrolytic furanization of the starting material, γ-bromodypnone, which had survived the initial alkali reaction; in a separate experiment under the work-up conditions the actuality of this reaction was demonstrated.

**Hydrolytic Rearrangement of** *trans*-γ-**Bromodypnone (I).**—A solution of 3 g. (0.01 mole) of I in 100 ml. of absolute ethanol at ca. 5–8° was treated dropwise under stirring with a 25-ml. absolute ethanol solution of 0.4 g. (0.01 mole) of sodium hydroxide (30 min. or longer), and the mixture was then allowed to stand at ca. 0°. No dibenzoylethane (II) precipitated at this point, but at times small amounts of unchanged material (I) was present and was filtered off and identified. Since II is less soluble than I and crystallizes very easily, it could not have yet been formed as such in significant amounts. Treatment of the reaction mixture with ether and sodium chloride solution, drying the ether extract over sodium sulfate, and concentrating then gave a crystalline residue melting in the range 143–145° (yields widely varying, in one case 49%) which was identified as nearly pure dibenzoylethane (II) by recrystallizations, analysis, ultraviolet and infrared absorption spectra, and mixture melting point with an authentic sample. (Absorption maxima: 243, 278 mμ, ε 26,900, 244; μ, 2.80w, 3.44w, 5.94s, 6.26m, 6.90m, 7.15m, 7.25w, 7.39m, 8.16s, 8.46m, 10,06m, 10.52w).

In a similar experiment in a mixture of 50 ml. each of absolute methanol and ether at −10° with dropwise addition of a solution of 0.01 mole of sodium in 50 ml. of methanol, work-up as above gave a yield of 36% of II.

A sample of 2,4-diphenylfuran (and similarly 2,5-diphenylfuran) after treatment with alcoholic sodium hydroxide under the above conditions, was recovered unchanged (88%).

**Preparations of** C¹⁴-**labeled materials,** based on the above and on references cited in the discussion, were made in a series of practice experiments to gain experience and test yields. C¹⁴-Activities were determined as counts per minute in the usual way and are summarized in the following table.

### TABLE I
#### C¹⁴-ACTIVITIES

| C₆H₅COOH, obtained by KMnO₄ oxidations[a] of the following compounds[b] | % C¹⁴-activity relative to C₆H₅COOH obtained by KMnO₄ oxidation of the C¹⁴-labeled reference compound, C₆H₅COCH₂Br [b,c] |
|---|---|
| *trans*-Dypnone[1b] | 102 |
| Dibenzoylethane (II) from base-induced rearrangement of γ-bromodypnone (I) | 98 |
| Dibenzoylethane from reductive rearrangement[d,e] of γ-bromodypnone *cis* epoxide[5] (VIII), m.p. 129–130° | 98 |
| Noncrystalline residue from this reaction | 100 |
| Dibenzoylethane from reductive rearrangement[e] of γ-bromodypnone *trans* epoxide[5] (VIII), m.p. 166–167° | 105 |
| Noncrystalline residue from this reaction | 101 |
| γ-Bromodypnone, compared directly with unoxidized γ-bromodypnone with correction for the difference in molecular weight (m.p. 68–70°) | 97 |

[a] In refluxing water–sodium hydroxide mixture. [b] All C¹⁴-labeled compounds were synthesized from C¹⁴-labeled acetophenone. [c] The C¹⁴-labeled phenacyl bromide was oxidized to benzoic acid by dioxane–water–iodine–potassium iodide–sodium hydroxide mixture. [d] In one experiment following the reported procedure for preparing the α-phenacyl bromide (*cis*-VIII[6]), with fractional crystallization of the product from ether, we obtained ca. 50% of the high-melting and 15% of the low-melting isomer. [e] The yields of dibenzoylethane in the reductive rearrangements were low, and distressingly so in the case of the low-melting isomer, and they corresponded to those reported[5] (28% from the high-melting isomer and 8% from the low-melting isomer). A reaction path involving simple deoxygenation of VIII seems excluded by separate test which indicates that the necessarily intermediate γ-bromodypnone does not produce dibenzoylethane under similar conditions.

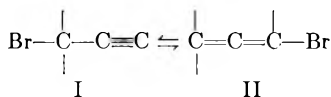# 3-Bromo-3-methyl-1-butyne, 1-Bromo-3-methyl-1,2-butadiene, and 1-Bromo-3-methyl-1,3-butadiene[1]

THOMAS L. JACOBS AND WALTER L. PETTY

*Department of Chemistry, University of California, Los Angeles 24, California*
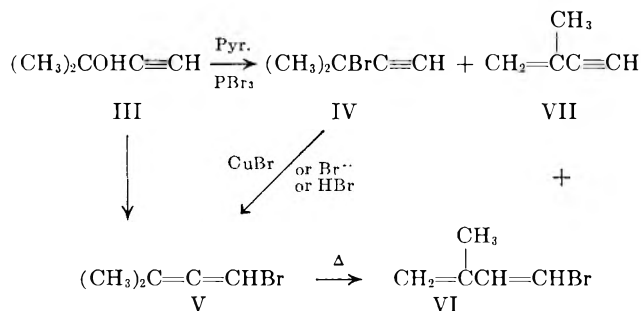
3-Bromo-3-methyl-1-butyne (IV) was obtained from 2-methyl-3-butyn-2-ol by reaction with phosphorus tribromide or thionyl bromide. It was rearranged by cuprous bromide or bromide ion to 1-bromo-3-methyl-1,2-butadiene (V). At 60–80° the latter gave 52% of *cis*- and *trans*-1-bromo-3-methyl-1,3-butadiene, 28% of the dimer *trans*-1,2-dibromo-3,4-di-isopropylidenecyclobutane, and 20% of other dimers and polymers. Displacement reactions of IV and V with iodide ion, thiophenoxide ion, and diethylamine were examined. Dehalogenation of IV, V, and the dimer by lithium aluminum hydride was also studied.

Allenic halides have been synthesized most frequently by rearrangement of the corresponding propargyl halides or from propargyl alcohols by displacement reactions which often yield rearranged halides. A number of chloroallenes are known but only two bromoallenes had been reported[2] when the present work was completed: bromoallene itself[3] and 3-bromo-5-phenyl-2,2,6,6 - tetramethyl - 3,4 - heptadiene.[4] These compounds are of interest because the anionotropic rearrangement in the acetylene–allene system I ⇌ II would be expected to occur more readily when the halogen atom is bromine instead of chlorine.

$$Br—\overset{|}{\underset{|}{C}}—C{\equiv}C \leftrightharpoons \overset{|}{C}{=}C{=}\overset{|}{\underset{|}{C}}—Br$$

$$\text{I} \qquad\qquad \text{II}$$

It was reported[5] that the reaction of 2-methyl-3-butyn-2-ol, with hydrobromic acid fails to yield either 3-bromo-3-methyl-1-butyne (IV) or 1-bromo-3-methyl-1,2-butadiene (V); only 1-bromo-3-methyl-1,3-butadiene (VI), which might result from the acetylene–allene rearrangement I → II followed by a prototropic rearrangement of the allene to the conjugated diene, was isolated.

$$(CH_3)_2COHC{\equiv}CH \xrightarrow[PBr_3]{Pyr.} (CH_3)_2CBrC{\equiv}CH + CH_2{=}\overset{\overset{CH_3}{|}}{C}C{\equiv}CH$$

$$\text{III} \qquad\qquad \text{IV} \qquad\qquad \text{VII}$$

$$(CH_3)_2C{=}C{=}CHBr \xrightarrow{\Delta} CH_2{=}\overset{\overset{CH_3}{|}}{C}CH{=}CHBr$$

$$\text{V} \qquad\qquad\qquad \text{VI}$$

Reaction of phosphorus tribromide with III was reported to yield IV which decomposed rapidly.[6] Re-

cently a modification of Moulin's method permitted isolation of relatively pure IV, b.p. 97°, which could then be purified more completely in a vacuum train.[2] Very few other aliphatic tertiary propargyl bromides RR'CBrC≡CH have been reported and in no instance has a structure of one of these been proved. It was therefore of interest to study the synthesis and rearrangement of IV more carefully.

In our hands IV could not be obtained in higher than 30% yield by the reaction of III with phosphorus tribromide with or without pyridine. Usually enyne VII and *trans* 1-bromo-3-methyl-1,3-butadiene (VI) were also obtained and under certain conditions more completely brominated products were found. The bromoallene V appeared to be absent and no III could be recovered. The amount of polymeric material was not great and did not account for low yields of IV.

A possible explanation for these yields can be derived from the known behavior of saturated alcohols with phosphorus trihalides. It was shown[7] that trialkyl phosphites are cleaved to alkyl halides and dialkyl phosphites by hydrogen halides more rapidly than succeeding cleavages of the other alkyl groups occur. With the propargyl phosphites it may be that addition reactions take place with the primary and secondary esters more rapidly than cleavage to give the propargyl bromides. No attempt was made to isolate such addition products in the present research; they might be water soluble and would then not appear as higher boiling material. As would be predicted from this explanation, addition of III to an equimolar amount of phosphorus tribromide, which should lead to decreased yield of trialkyl phosphite as an intermediate, greatly reduced the yield of IV. It may also be mentioned that the reaction of 1-phenyl-5,9-dimethyl-9-decen-1-yn-3-ol with phosphorus tribromide was reported[8] to yield a compound containing phosphorus and more bromine than the theoretical amount for the simple bromide.

Thionyl bromide was also tried for conversion of III to IV, and a yield of 39% realized; as expected[9] a tribromide was also isolated. It appears possible that the yield of IV could be markedly improved with this reagent.

(1) This paper is taken from the Ph.D. dissertation of Walter L. Petty, UCLA, 1958, and was presented in part at the Dallas meeting of the American Chemical Society, April, 1956 (Abstracts of that meeting, p. 38-N). The research was supported by a contract with the Office of Ordnance Research, U. S. Army.

(2) Very recently V. J. Shiner, Jr., and J. W. Wilson, *J. Am. Chem. Soc.*, **84**, 2402 (1962), reported the preparation of 1-bromo-3-methyl-1,2-butadiene.

(3) T. L. Jacobs and W. F. Brill, *ibid.*, **75**, 1314 (1953).

(4) J. H. Ford, C. D. Thompson, and C. S. Marvel, *ibid.*, **57**, 2619 (1935); J. Wotiz and D. Mancuso, *J. Org. Chem.*, **22**, 207 (1957). We have found by infrared examination that the compound reported [C. Moureu, D. Dufraisse, and C. Mackall, *Bull. soc. chim. France*, (4) **33**, 934 (1923)] as 3-bromo-1,3,3-triphenylpropyne is instead 1-bromo-1,3,3-triphenyl-1,2-propadiene and believe it likely that other compounds of similar structure are likewise bromoallenes. [T. L. Jacobs and D. M. Fenton, *J. Org. Chem.*, in press; Ph.D. dissertation of D. M. Fenton, UCLA, 1958; Abstracts, 135th National meeting of the American Chemical Society, April, 1959, p. 56-O.]
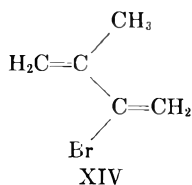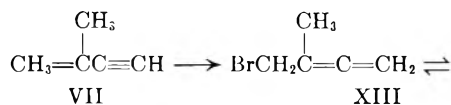
(5) T. A. Favorskaya, *Zh. Obshch. Khim.*, **10**, 461 (1940).

(6) F. Moulin, *Helv. Chim. Acta*, **34**, 2416 (1951). It has been reported that this bromide can be stabilized with *t*-butylcatechol [R. F. Kleinschmidt and S. H. Pitts, Jr., U. S. Patent 3,002,029 (September 26, 1961); *Chem. Abstr.*, **56**, 2328 (1962)].

(7) W. Gerrard and H. Herbst, *J. Chem. Soc.*, 277 (1955); W. Gerrard, M. J. D. Isaacs, G. Machell, K. B. Smith, and P. L. Wyvill, *ibid.*, 1920 (1953).

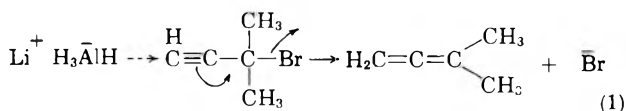(8) H. Rupe and R. Rinderknecht, *Ann.*, **442**, 61 (1925).

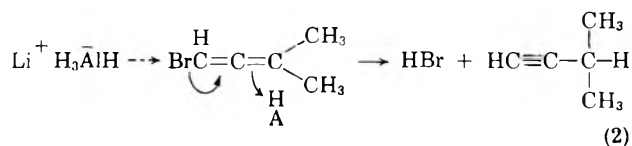(9) M. J. Frazer and W. Gerrard, *J. Chem. Soc.*, 3624 (1955).

The structure of IV is indicated clearly by its infrared spectrum which shows a strong band at 3280 cm.$^{-1}$ (acetylenic hydrogen) and a weak band at 2122 cm.$^{-1}$ (C≡C stretching).

The origin of conjugated, *trans*, diene VI among the products of the phosphorus tribromide reaction is not clear. Pyridine or its hydrobromide apparently plays a role in its formation because only when pyridine was used in the reaction could any appreciable amount of VI be isolated. It seems unlikely that it arises from rearrangement of the allene (V) because the latter was never detected among the reaction products even when the reaction was carried out entirely at 0° and rearrangement of V yields both *cis* and *trans* VI (see below). No attempt was made to prove that *cis* VI would not rearrange to *trans* under the reaction conditions, so this explanation has not been ruled out. It seems more probable, however, that VI is formed by an addition–elimination mechanism. Moulin[6] showed that the action of excess hydrogen bromide on III gives a dibromide which he believed to be 1,3-dibromo-3-methyl-1-butene (VIII), $(CH_3)_2CBrCH=CHBr$, arising from addition to IV by a radical process. We isolated a dibromide with the same properties from III and phosphorus tribromide in the absence of pyridine. Thus VIII could be an intermediate in the formation of VI. The radical addition process would probably yield the more stable *trans* isomer. It is also possible that hydrogen bromide adds similarly to the intermediate phosphites such as $[HC≡CC(CH_3)_2]_2PHO$ to form $[BrCH=CHC(CH_3)_2]_2PHO$ or $[BrCH=CHC(CH_3)_2]$ $[HC≡CC(CH_3)_2]PHO$ which undergoes elimination and cleavage to form VI.

IV is rearranged to V by cuprous bromide and less readily by other bromides (see Experimental for details and for isolation of pure V). V has a strong infrared peak at 1956 cm.$^{-1}$ (allene) and no absorption at 3280 cm.$^{-1}$ (acetylenic hydrogen) or 1580 and 1620 cm.$^{-1}$ (conjugated double bonds).

At 60 or 80° V undergoes isomerization to VI (approximately equal amounts of *cis* and *trans*), dimerization and polymerization (to a small extent). The isomerization appears to be catalyzed mildly by di-*t*-butyl peroxide and inhibited mildly by *t*-butylpyrocatechol. In the presence of the peroxide a typical run gave 52% VI, 28% of crystalline dimer IX, and 20% of other dimers and polymers. It is interesting that *t*-butylpyrocatechol has been patented as a stabilizer for IV.[6]

Structures were assigned to *cis* and *trans* VI on the basis of infrared spectra and confirmed by alkaline dehydrobromination (preferential attack of *cis*). The position of the bromine was established by conversion of VI to 4-methylpentanoic acid (formation of the lithium derivative, carbonation and hydrogenation).

The structure of the crystalline dimer was shown to be IX by analysis, molecular weight determination, and ozonization to acetone and *dl*-dibromosuccinic acid. Infrared, ultraviolet, and n.m.r. spectra are in agreement with this structure. The bromine atoms in IX are moderately reactive toward sodium iodide in acetone and toward alcoholic silver nitrate as would be expected for allylic bromines. By contrast *trans*-1,2-dibromocyclobutane is unreactive.[10] IX does not



IX

form a maleic anhydride adduct; it reacts slowly with bromine in carbon tetrachloride and yields much hydrogen bromide.

Further confirmation of the carbon skeleton was obtained by debromination with lithium aluminum hydride and hydrogenation of the resulting olefin to 1,2-diisopropylcyclobutane. The physical constants of the latter were the same as for a sample prepared by dimerization[11] of dimethylallene and hydrogenation of the dimer. One attempt to isolate the intermediate olefin, possibly 3,4-diisopropylidenecyclobutene, failed when a sticky mass was obtained as soon as the solvent had been removed.

Dimerization of V might be expected to yield X and XI as well as IX by analogy with products from dimerization of 3-methyl-1,2-butadiene.[11] It was not



possible to isolate a pure liquid dimer from the dimeric and polymeric material which remained after IX had been separated. Distillation under reduced pressure gave a dimer fraction which was debrominated and then hydrogenated to a saturated hydrocarbon which had the physical properties of 1,1,2-trimethyl-3-isopropyl-cyclobutane. The infrared spectrum is in better agreement with structure XII which can be obtained from X by a hydrogen shift analogous to that observed in V → VI.

Further work is being carried out on allene dimerization, and the nature of the products other than IX that are obtained from V will receive further attention. V is especially suitable for such a study because the dimerization occurs under such mild conditions. It is interesting that the dimerization in this instance appears to give such a large preponderance of product with *trans* bromine atoms. Allene dimerization has been discussed briefly by Roberts and Shorts.[12]

Early in this work it was thought possible that one of the volatile bromides obtained thermally from V was 2-bromo-3-methyl-1,3-butadiene (XIV). This bromide was, therefore, synthesized by the action of hydrobromic acid on 2-methyl-1-buten-3-yne (VII) in the presence of cuprous bromide. This synthesis had not been examined by others when our work was done, but it has been reported since[13]; with 62% hydrobromic acid small amounts of IV were isolated in addition to

(10) J. Weinstock, S. N. Lewis, and F. G. Bordwell, *J. Am. Chem. Soc.*, **78**, 6072 (1956).

(11) S. V. Lebedev, *J. Russ. Phys. Chem. Soc.*, **43**, 820, 1735 (1911).

(12) J. D. Roberts and C. M. Sharts, "Cyclobutane Derivatives from Thermal Cycloaddition Reactions," *Org. Reactions*, **12**, 23–25 (1962).

(13) J. C. Traynard, *Bull. soc. chim. France*, **19** (1962); *Compt. rend.* **250**, 1504 (1960). The conditions we used are similar to those reported for addition of hydrogen chloride to vinylacetylene [W. H. Carothers, G. J. Berchet, and A. M. Collins, *J. Am. Chem. Soc.*, **54**, 4066 (1932)].

$$CH_3-CC\equiv CH \longrightarrow BrCH_2C=C=CH_2 \rightleftharpoons$$
$$\overset{\overset{\displaystyle CH_3}{|}}{} \qquad \qquad \overset{\overset{\displaystyle CH_3}{|}}{}$$
$$VII \qquad \qquad XIII$$

$$H_2C=C\overset{CH_3}{\diagup} \\ \diagdown C=CH_2 \\ | \\ Br$$
$$XIV$$

XIII and XIV. Our addition was carried out in the presence of cuprous bromide which would rearrange IV to V. IV was absent from our product on the basis of infrared spectra, but small amounts of V would have escaped detection. Extended shaking of our mixture with cuprous bromide did not alter its composition which suggests that XIII and XIV might have been in equilibrium. Models indicate that the double bonds in XIV cannot be in the same plane because the bromine interferes with methyl or methylene; thus XIV may not be much more stable than XIII. The spectrum indicated that XIV was not present among the rearrangement products of V.

Dehalogenation of haloallenes and propargyl halides has been studied earlier in this laboratory.[14] Dehalogenation of 3-bromo-3-methyl-1-butyne (IV) with lithium aluminum hydride in diethylcarbitol gave a 98% yield of a mixture of hydrocarbons which was shown to be 99% 3-methyl-1,2-butadiene and 1% 3-methyl-1-butene (obtained after hydrolysis of the reaction mixture). A trace of a 1-alkyne, presumably 3-methyl-1-butyne, was also detected. A similar dehalogenation of 1-bromo-3-methyl-1,2-butadiene (V) gave a hydrocarbon mixture in 70% yield of which 61%, obtained before hydrolysis of the reaction mixture, was 3-methyl-1-butyne. After hydrolysis a mixture of isopentane (36%) and 3-methyl-1-butene (3%) was isolated. Conjugated diene VI gave a 70% yield of hydrocarbon products under similar conditions. An infrared spectrum and vapor phase chromatogram of the product showed it to be over 95% isoprene. The remaining constituents appeared to be 2-methyl-2-butene (~4%) and 2-methyl-1-butene (1%).

It was suggested earlier[14] that the dehalogenation of 3-chloro-3-methyl-1-butyne occurred by an $S_N2'$ process involving hydride ion or $AlH_4^-$ attack on the terminal acetylenic carbon with shift of the bonds to an allenic system and displacement of the halogen. This mechanism seems probable for IV (equation 1).

$$Li^+ \ H_3\bar{A}lH \dashrightarrow \overset{H}{\underset{}{}}C\equiv C-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-Br \longrightarrow H_2C=C=C\overset{CH_3}{\diagdown CH_3} + \ \bar{Br}$$
$$(1)$$

A similar process could account for formation of 3-methyl-1-butyne from 1-bromo-3-methyl-1,2-butadiene but this requires a displacement reaction on a tertiary carbon which is doubly bonded, a somewhat less likely process. A more reasonable mechanism involves nucleophilic attack on halogen with a shift of bonds and possibly concerted donation of a proton at the γ-carbon (equation 2).

(14) T. L. Jacobs, E. G. Teach, and D. Weiss, *J. Am. Chem. Soc.*, **77**, 6254 (1955). A detailed study of the dehalogenation of 3-chloro-3-methyl-1-butyne and 1-chloro-3-methyl-1,2-butadiene with lithium aluminum hydride has been completed and will be reported soon (R. D. Wilcox, Ph.D. thesis, UCLA, 1962).

$$Li^+ \ H_3\bar{A}lH \dashrightarrow Br\overset{H}{\underset{}{}}C=C=C\overset{CH_3}{\underset{\underset{H}{\diagdown}}{\diagup}}\overset{}{\diagdown}CH_3 \longrightarrow HBr + HC\equiv C-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-H$$
$$A$$
$$(2)$$

The mechanism of the process leading to hydrogenation of the carbon–carbon bonds will be discussed later.[14]

Preliminary experiments were carried out on other displacement reactions of IV and V. At low conversions IV with sodium iodide in acetone gives mainly XVIa with smaller amounts of XVa; at fairly high conversion the conjugated diene XVIIa is the main product. Thus rearrangement of XVI to XVII is much more rapid with iodide than with bromide and no attempt was made to isolate XVIa. Nearly pure

$$IV \text{ or } V \xrightarrow{Y^-} (CH_3)_2CYC\equiv CH +$$
$$XV$$

$$\overset{CH_3}{|}$$
$$(CH_3)_2C=C=CHY + CH_2=CCH=CHY$$
$$XVI \qquad\qquad XVII$$
$$XVa, XVIa, XVIIa \ (Y = I)$$
$$XVb, XVIb, XVIIb \ (Y = SC_6H_5)$$
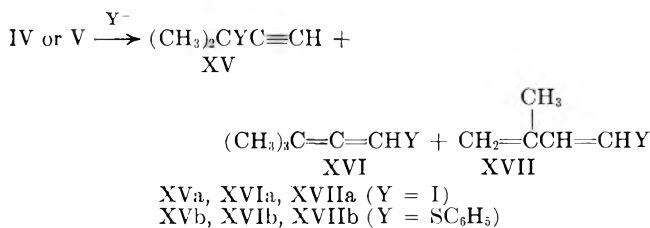
XVIIa was isolated but the study was not carried to completion because an explosion occurred toward the end of the distillation. XVIIa polymerized rapidly even in the refrigerator. The explosiveness and general instability of the iodides in this series were reported by Favorskaya,[5] who found that the reaction of carbinol III with hydroiodic acid gave a mixture of XVIa and XVIIa.

An infrared spectrum of XVIIa indicated that it contained a little XVIa. This spectrum was very similar to that of *trans* V which suggests that XVIIa is mainly *trans*. Although the large size of iodine would be expected to prevent the planar "chair" conformation XVIII for *cis* XVIIa, it is difficult to account for the different steric course of XVI → XVII when Y is

$$\overset{H}{\diagdown}\overset{}{\underset{\diagup}{}}C=C\overset{CH_3}{\diagup}\overset{}{} \qquad I$$
$$\overset{H}{\diagup}\overset{}{} \qquad \overset{}{\underset{\diagdown}{}}C=C\overset{}{\diagdown}$$
$$\qquad\qquad H \qquad H$$
$$XVIII$$
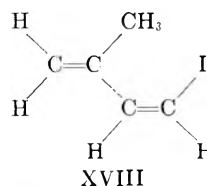
iodine. Possibly *cis–trans* isomerization occurs more readily in this system or is catalyzed by impurities that are present.

Reaction of IV with sodium thiophenoxide gave a high yield of organic sulfide consisting mainly of XVIb with perhaps 10% of XVb. Almost pure XVIb was isolated but slow distillation through an efficient column gave a less pure product probably partly rearranged to XVIIb on the basis of infrared spectra.

A similar reaction of V gave XVb and high boiling, viscous material. An infrared spectrum failed to show any XVIb although a little XVIIb may have been present.

IV reacted completely with excess diethylamine in benzene (room temperature, 24 hours) but the infrared spectrum of the product showed no absorption characteristic of either acetylenes or secondary amines; allene absorption at 1953 cm.$^{-1}$ was very weak. Strong peaks at 1753 and 1620 cm.$^{-1}$ suggested that the prod-

uct contained a carbonyl and olefinic linkage. Possibly an allenic amine was formed and hydrolyzed during the washing procedure.

Mechanisms of displacement reactions in the propargyl–allenyl system represented by IV and V appear to be complex on the basis of the work reported by Shiner, *et al.*,[2] as well as the experiments described above. Although the latter offer very little evidence on the problem, they do suggest that different nucleophiles differ greatly in their behavior with this system. Thiphenoxide ion appears especially attractive for further study and is being investigated along with other nucleophilic reagents.

## Experimental

Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics. A 0.03-mm. cell was used with neat liquids unless otherwise indicated. Ultraviolet spectra were obtained on a Cary Model 14 spectrophotometer.

**3-Bromo-3-methyl-1-butyne (IV).**—A mixture of 420 g. (5.0 moles) of 2-methyl-3-butyn-2-ol (III)[15] and 50 g. (0.63 mole) of pyridine was stirred in a 1-l., three-necked, round-bottom flask cooled in ice while 512 g. (1.89 moles) of phosphorus tribromide was added during 5 hr. The mixture was stirred for an additional 4 hr. at 0° and 20 hr. at room temperature. The volatile products were distilled from the flask under reduced pressure with mild warming, the final conditions approximating 75° and 25 mm. The distillate (343 g.) was washed twice with 500-ml. portions of sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The product was distilled under reduced pressure through an 18-in. column packed with glass helices to yield 25 g. (8%) of 2-methyl-1-buten-3-yne, b.p. 33°, $n^{25}$D 1.4118, and 184 g. (25%) of 3-bromo-3-methyl-1-butyne, b.p. 42.2° (106 mm.), $n^{25}$D 1.4583, $d^{25}_4$ 1.268.

*Anal.* Calcd. for $C_5H_7Br$: C, 40.85; H, 4.80. Found: C, 40.63; H, 4.79.

Infrared spectrum: 640 (s), 708 (w), doublet (769, 785) (s), 945 (m), 1013 (w), 1108 (s), 1167 (s), 1228 (s), 1290 (m, broad), 1370 (s), 1388 (s), triplet (1437, 1448, 1462) (s), 2122 (w), triplet (2822, 2910, 2965) (s), 3280 (s) cm.$^{-1}$. This spectrum is very similar to that of 3-chloro-3-methyl-1-butyne from 1500 to 3500 cm.$^{-1}$.

The reaction mixture from which volatile products had been removed by distillation was poured into 1400 ml. of crushed ice and water. The heavy organic layer was separated, washed with saturated bicarbonate solution, and dried over magnesium sulfate. It was combined with the pot residue from the distillation of 3-bromo-3-methyl-1-butyne and distilled under vacuum through the same column to yield 90 g. (12%) of *trans*-1-bromo-3-methyl-1,3-butadiene (VI), b.p. 42° (40 mm.), $n^{25}$D 1.5133, $d^{25}_4$ 1.319.

*Anal.* Calcd. for $C_5H_7Br$: C, 40.85; H, 4.80. Found: C, 40.94; H, 5.08.

Ultraviolet spectrum in 95% ethanol: $\lambda_{max}$ 230 m$\mu$ ($\epsilon$ 17,600); 236 (18,600); shoulder, 243 (14,400).

Infrared spectrum: 685 (w), 753 (s), 790 (s), 892 (s), 940 (s), 1021 (w), 1092 (w), 1203 (s), 1283 (m), 1310 (m), 1383 (s), doublet (1442, 1452) (s), 1478 (w), 1579 (s), 1620 (s), 1670 (w), 1724 (w), 1785 (w), group (2900–2950) (m), 3065 (m).

Addition of 93 g. (1.1 moles) of III to 100 g. (0.37 mole) of phosphorus tribromide at 0° with stirring during 2 hr., slow heating to 65°, maintenance of this temperature for 1 hr. and distillation of the volatile product gave 31% of crude IV. The pot residue was poured onto ice, separated, washed with bicarbonate solution, and dried over anhydrous magnesium sulfate to give 30 g. of crude product. Distillation through a small, glass spiral column gave material, b.p. 90° (25 mm.), $n^{26}$D 1.5442. The infrared spectrum of this distillate had a strong band at 1636 cm.$^{-1}$ suggesting an olefin. Moulin[6] reported b.p. 70–71° (8 mm.), $d^{17}_4$ 1.779, $n^{18}$D 1.5481, for the dibromide from reaction of hydrobromic acid with III.

IV was also prepared with thionyl bromide. A magnetically stirred solution of thionyl bromide (212 g., 1.02 moles) in 500 ml. of dry pentane in a 1-l., three-necked, round-bottom flask was refluxed at $-25°$ by suitable reduction of the pressure (condenser cooled with circulating methanol at $-80°$) while 84.1 g. (1.0 mole) of 2-methyl-3-butyn-2-ol was added dropwise during 45 min. The reaction mixture was maintained at $-10°$ for 1.5 hr., allowed to warm slowly to normal reflux temperature ($\sim37°$) by increase of pressure and maintained there for 2 hr. Solvent was distilled through a Vigreux column (hood) and when most of the pentane was gone vigorous evolution of sulfur dioxide began. Heating was continued until bubbling ceased. The pot residue was cooled, washed twice with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and distilled at room temperature under reduced pressure to give 57 g. (39%) of quite pure IV (no allene absorption in the infrared) boiling below room temperature at 25 mm. A fraction, b.p. 60° (1 mm.), was also obtained; redistillation gave a pale yellow liquid, $n^{25}$D 1.5840.

*Anal.* Calcd. for $C_5H_7Br_3$: C, 19.57; H, 2.30; Br, 78.13. Found: C, 19.73; H, 2.30; Br, 78.11.

The infrared spectrum of this tribromide showed a medium peak at 1615 cm.$^{-1}$ and a strong peak at 1576 cm.$^{-1}$ in the olefin region. When this compound was allowed to stand overnight with zinc bromide and then vacuum distilled the peak at 1615 cm.$^{-1}$ had increased in intensity and that at 1576 cm.$^{-1}$ had decreased. The tribromide was probably a mixture of $(CH_3)_2$CBr=CHBr and $(CH_3)_2$C=CBrCHBr$_2$.

A slightly lower yield of IV was obtained from thionyl bromide and III in the presence of pyridine.

**Rearrangement of IV.**—Cuprous bromide was the most effective catalyst found for rearrangement of IV to V. At room temperature 69% rearrangement occurred in 19 hr. of shaking with 1% of the salt, and 95% after 60 hr. The extent of rearrangement was the same with 10% catalyst. Lithium bromide was less effective; shaking for 24 hr. caused 6% rearrangement. Rearrangement was relatively complete when IV was stirred with 48% hydrobromic acid for 28 hr. or with saturated aqueous sodium bromide for 46 hr. but 1 $M$ perchloric acid produced no rearrangement. The rearrangement is reversible; pure V gave 2% IV when shaken for 15 days with cuprous bromide.

**1-Bromo-3-methyl-1,2-butadiene (V). Method I.**—IV was stirred for 60 hr. at room temperature with 10% by weight of finely powdered cuprous bromide. The infrared of the resulting mixture indicated a composition of 5% IV. Catalyst was removed by filtration and product distilled at low temperature and pressure into a Dry Ice trap. The colorless distillate was distilled through a Sargent column (1 m. long, 7-mm. i.d.) at 0.25 mm. to give excellent recovery of V, b.p. $-19°$ (0.25 mm.), 34° (18 mm.), $n^{25}$D 1.5164, $d^{25}_4$ 1.317.

*Anal.* Calcd. for $C_5H_7Br$: C, 40.85; H, 4.80. Found: C, 40.77; H, 5.20.

Ultraviolet absorption in 95% ethanol: single broad peak, $\lambda_{max}$ 221 m$\mu$ ($\epsilon$ 7000).

Infrared: 631 (s), doublet (722, 747) (s), 963 (w), 1010 (s), 1063 (w), 1161 (s), 1195 (m), 1383 (w), 1349 (s), 1364 (s), 1450 (broad, s), 1956 (s), 2682 (w), and a group of C—H stretching peaks at 2835, 2880, 2960, and 3030.

Distillation of V at pressures above 20 mm. where the boiling point is above 35° cause appreciable rearrangement to VI as indicated by infrared peaks at 1579 and 1615 cm.$^{-1}$. Our best samples of V did not show these peaks although traces of VI may have been present. VI probably boils no more than 7° below V at 18 mm. or below so separation by distillation is very difficult.

**Method 2.**—V can be synthesized from III in better yield with hydrobromic acid but it then contains a little VI. When small amounts of VI were not detrimental, V prepared as follows was used.

A mixture of 470 g. (5.6 moles) of III, 1000 ml. of 48% tech. hydrobromic acid, 200 g. of ammonium bromide and 70 g. of cuprous chloride was shaken for 4.5 hr. in a large bottle. The organic layer was separated, washed twice with sodium bicarbonate solution, once with saturated sodium bisulfite solution, and dried over anhydrous calcium chloride. Distillation at low pressure gave 500 g. (61%) of crude product which was redistilled through an 18-in. column packed with glass helices to yield almost pure V, b.p. 34° (18 mm.), $n^{25}$D 1.5163; infrared showed a trace of VI.

**Rearrangement and Dimerization of V.**—Samples of V containing, respectively, 4% by weight of di-*t*-butyl peroxide, 6%

(15) We wish to thank the Air Reduction Chemical Co. for a generous supply of this carbinol.

of *t*-butyl catechol, and no added material were kept at 60° for 43 hr. The second and third samples then had essentially identical absorption in the infrared; they were mainly unchanged V containing small amounts of dimer (absorption at 1652 cm.$^{-1}$) but almost no conjugated diene VI (absorption at 1615 and 1579 cm.$^{-1}$). The first sample contained essentially no V, about the same amount of dimer as the other samples, and large amounts of VI. Similar samples containing, respectively, 2% of benzoyl peroxide and no added catalyst were heated at 75° for 3.5 days. The sample containing the peroxide was completely converted to dimer and VI (medium absorption at 1652 cm.$^{-1}$, strong bands at 1615 and 1579 cm.$^{-1}$). The uncatalyzed sample contained some unchanged V; absorption at 1652 cm.$^{-1}$ indicated about 1.7 times the amount of dimer present in the catalyzed sample, while lower absorption at 1615 and 1579 cm.$^{-1}$ showed that less VI had been formed. Two neat samples sealed under vacuum in Pyrex and quartz, respectively, were irradiated with ultraviolet light (2537 Å) at 0° for 91 hr. The sample in the quartz tube then showed 2% more absorption at 1615 and 1579 cm.$^{-1}$ and 6% more at 893 cm.$^{-1}$ (=CH$_2$ out-of-plane deformation) than the other; transmission in the olefin region was still above 90% in both.

Unfiltered radiation from a quartz mercury vapor lamp also proved to be very poor in effecting the rearrangement.

For product isolation 300 g. of V prepared by method 2 and 0.5 g. of benzoyl peroxide were heated at 80° for 46 hr.; infrared then indicated that V was absent. The material was kept at −20° for 22 hr. to allow the dimer to crystallize (55 g. obtained). The supernatant liquid was decanted and vacuum transferred to yield 156 g. (52%) of a mixture of the *cis* and *trans* forms of VI, $n^{25}$D 1.5097. These were cleanly separated by v.p.c. at 100° with a 2-m. didecyl phthalate column (40–60-mesh firebrick as support) followed in series by a 2-m. di-2-ethylhexyl sebacate column. Peak areas indicated equal amounts of the geometric isomers. The *cis* isomer left the column first, $n^{25}$D 1.5042, $d^{25}_4$ 1.29.

*Anal.* Calcd. for C$_5$H$_7$Br: C, 40.85; H, 4.80. Found: C, 40.66; H, 5.02.

Ultraviolet spectrum in 95% ethanol very similar to that of the *trans* isomer but less intense: $\lambda_{max}$ 232 m$\mu$ ($\epsilon$ 11,200); $\lambda_{max}$ 238 m$\mu$ ($\epsilon$ 11,500); shoulder, 246 ($\epsilon$ 8900).

Infrared spectrum: 670 (s), 752 (s), 812 (m), 882 (w), 893 (s), doublet 961 and 970 (w), 1018 (m), 1132 (w), 1240 (m), 1299 (s), 1330 (s), 1378 (s), 1442 (shoulder, s), 1454 (s), 1581 (m), 1615 (s), 1670 (w), 1790 (w), 2900 (m), 2940 (s), 3060 (m) cm.$^{-1}$.

The residue from the distillation of VI gave more crystalline dimer when allowed to stand at −20° (total crystalline dimer, 84 g., 28%). Recrystallization from 95% ethanol gave only yellow crystals, but acetone and water gave white material, m.p. 90.5–92°.

*Anal.* Calcd. for C$_{16}$H$_{14}$Br$_2$: C, 40.85; H, 4.80; mol. wt., 294. Found: C, 40.78; H, 4.72; mol. wt. (cryoscopic in benzene), 285.

Ultraviolet spectrum in 95% ethanol: $\lambda_{max}$ 221 m$\mu$ ($\epsilon$ 13,400); $\lambda_{max}$ 285 m$\mu$ ($\epsilon$ 8300).

Infrared spectrum (10% solution in carbon tetrachloride): 663 (s), 879 (w), 922 (w), 1000 (w), 1085 (w), 1137 (s), 1177 (m), 1202 (m), 1255 (m), 1368 (s), 1443 (s), 1652 (s), 2693 (w), 2812 (m), 2870 (s), 2940 (m) cm.$^{-1}$.

The dark residue (60 g., 20%) which remained after all of diene VI and dimer IX had been removed was distilled at the full vacuum of an oil pump to give 46 g. of a yellow liquid, b.p. 60–90°. Only a trace of crystalline material was obtained after this liquid had stood at −20° for a week. Redistillation through a short Vigreux column gave no sharp-boiling fractions; the material came over from 64 to 90° at 0.3 mm.

*Anal.* Calcd. for C$_{10}$H$_{14}$Br$_2$: C, 40.85; H, 4.80; Br, 54.35. Found: C, 40.72; H, 4.73; Br, 54.00.

Ultraviolet spectrum in 95% methanol: rising absorption from 315 m$\mu$ to the limit of the instrument at 213 m$\mu$; some semblance of a peak around 264 m$\mu$ ($\epsilon$ ~10,000).

Infrared spectrum: strong peaks at 897, 1138, 1170, 1190, 1205, 1277, 1364, 1441, 1450, 2900, and 2930 cm.$^{-1}$; medium peaks at 760, 775, 1104, 1220, 1290, 1600, 1659, and 2840 cm.$^{-1}$. This spectrum indicates that the liquid is different from IX, although some IX may be present in the mixture.

**Dehydrohalogenation of VI.**—To a solution of 30 g. of potassium hydroxide in 100 ml. of 95% ethanol was added 45 g. (0.31 mole) of VI (mixture of *cis* and *trans*) during 10 min. The mixture was refluxed for 2 hr. and the low boiling product distilled

through a Vigreux column (b.p. 31–32°). The distillate was washed with water and dried over anhydrous magnesium sulfate to give 8.3 g. (41%) of 2-methyl-1-buten-3-yne, $n^{25}$D 1.4129, identified by infrared. The distillation residue was diluted with 300 ml. of water and extracted twice with 50-ml. portions of methylene chloride. The combined extract was washed thrice with 200-ml. portions of water, dried over anhydrous magnesium sulfate, and stripped of solvent under vacuum; the residue (15 g.) was *trans* VI free from the *cis* isomer within the limits of detection by infrared; this represents 66% recovery based on *trans* VI present in the starting material.

**Carboxylation of VI and Reduction of the Product.**—Ethyllithium was prepared from 15 g. (2.2 moles) of lithium ribbon and 118 g. (1.1 moles) of ethyl bromide in 600 ml. of anhydrous ether. This solution was transferred to a 2-l. beaker in a hood and 73 g. (0.5 mole) of VI (mixture of *cis* and *trans*) in 100 ml. of ether was added slowly with stirring. The exchange reaction was very exothermic and much ether was lost. Three minutes after all of the VI was added the mixture was poured through glass wool into excess Dry Ice in a dewar flask and allowed to stand overnight. Precipitated lithium salt was dissolved by addition of 500 ml. of water and the ether layer was separated. The aqueous solution was washed twice with 150-ml. portions of ether, acidified with 100 ml. of concentrated hydrochloric acid, and extracted twice with 125-ml. portions of ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered, and placed in a 500-ml. Parr bomb with 0.5 g. of 10% palladium on carbon. The solution was shaken for 23 hr. under a pressure of hydrogen which decreased from 44 to 26 p.s.i. The catalyst was removed by filtration, the ether removed at reduced pressure, and the residual acid distilled through a small glass helix column to yield 18.7 g. (23%) of 4-methylpentanoic acid, b.p. 200°, $n^{25}$D 1.419. An infrared spectrum of this acid was identical to that of known 4-methylpentanoic acid (Eastman Kodak, White Label, $n^{25}$D 1.4124). A phenylhydrazide, m.p. 146.8–147.2°, and anilide, m.p. 113.4–114.5°, were prepared; mixtures with known samples showed no melting point depression.

The n.m.r. spectrum[16] of IX consists of a small single peak attributable to the ring hydrogens and at higher field a large doublet arising from the twelve hydrogens of the methyl groups. One might expect the six hydrogens on the methyls that are oriented toward each other to show different shielding from the six hydrogens of the methyls that point away. Dreiding models indicate that the hydrogen nuclei are only 0.3 Å. apart at closest approach and that the farthest these nuclei can be separated if normal angles are maintained is about 1.2 Å. Since the van der Waals radius of hydrogen is 1.2 Å.[17] some interference must occur. The small peak is separated from the closer of the two large peaks by 121 c.p.s. and the two large peaks are separated by 7 c.p.s. The simplicity of the spectrum rules out most alternative structures.

**Reactivity of Bromines in IX.**—A mixture of 2.0 g. of IX and 25 ml. of acetone saturated with sodium iodide was refluxed for 4 hr. Iodine was formed and 1.2 g. (85%) of sodium bromide was isolated.

IX in 2% alcoholic silver nitrate gave an immediate precipitate of silver bromide. The solution was refluxed for 15 min. and 1.96 moles of silver bromide recovered for each mole of IX.

**Ozonization of IX.**—A solution of 10 g. (0.034 mole) of dimer IX in 100 ml. of chloroform was treated at −25° with ozonized oxygen during 5 hr. (~0.11 mole of ozone). Solvent was removed from the clear ozonide solution under vacuum (safety precautions necessary) and the viscous ozonide stirred with 30 ml. of ice–water for 2 hr. When the mixture was heated on the steam cone for 1 hr., it turned dark and carbon dioxide was evolved. The mixture was steam distilled until 50 ml. of distillate was collected. This distillate was extracted with four 10-ml. portions of methylene chloride; the extracts were combined and washed with 10 ml. of saturated potassium carbonate solution, dried over anhydrous magnesium sulfate, and distilled through a small glass helix column to yield a 4-ml. fraction, b.p. 41.5–49.0°, containing acetone. A 2,4-dinitrophenylhydra-

zone, m.p. 125.4–126.4° cor., was prepared; no melting point depression when mixed with authentic acetone 2,4-dinitrophenylhydrazone.

During the steam distillation crystals of acetone peroxide collected in the condenser: these were recovered and recrystallized from pentane to give white crystals, m.p. 130.6–131.2° cor. A peroxide of nearly the same m.p. (132–133°) has been obtained from ozonization in chloroform of other unsaturated compound expected to yield acetone (e.g., ref. 18) and also directly from acetone.[19] Attempts to isolate other identifiable products from the ozonide failed.

A second ozonization was carried out similarly. The chloroform solution of the ozonide was stirred overnight under aspirator pressure with 25 ml. of water; all solvent evaporated and a viscous, cloudy residue remained. To this was added 50 ml. of acetone and 25 ml. of water; the mixture was stirred for 2 hr. Then 10 ml. of 30% hydrogen peroxide and enough acetone to make a homogeneous solution were added and this stirred for 2.5 hr. The solution was treated with solid sodium bicarbonate until no more carbon dioxide was evolved and the resulting solution washed with methylene chloride, acidified with concentrated hydrochloric acid, and extracted with ether. The combined ether extract was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield 4.9 g. of a residue which did not crystallize. This residue was placed on a chromatographic column of 200 g. of 2:1 silica gel and Celite. Elution with 2:3 ether–pentane gave crystalline dl-dibromosuccinic acid. Recrystallization from ether–benzene gave a pure sample, m.p. 167–169° dec. (cor.). A mixture with authentic dl-dibromosuccinic acid prepared from maleic acid by addition of bromine[20] showed no melting point depression.

Anal. Calcd. for $C_4H_4O_4Br$: C, 17.40; H, 1.46; Br, 53.00. Found: C, 17.64; H, 1.60; Br, 58.18.

**Reduction of IX.**—Fifteen g. (0.051 mole) of IX in 100 ml. of ether was added during 20 min. to a refluxing solution of 4.0 g. (0.105 mole) of lithium aluminum hydride and 0.5 g. of t-butyl catechol in 100 ml. of ether. The mixture was refluxed for 16 hr., hydrolyzed with dilute hydrochloric acid (cooling), and the layers separated. The ethereal layer was washed with a solution of sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the ether under reduced pressure gave a colorless mobile liquid which rapidly increased in viscosity and soon had the consistency of semihardened glue.

A second run was carried out and the ethereal solution hydrogenated at once over 1 g. of 10% palladium on carbon at 20 p.s.i. for 27 hr. The solution was filtered and the ether removed at reduced pressure. The residue was vacuum transferred to give 1.2 g. (17%) of 1,2-diisopropyl cyclobutane, b.p. (micro) 158°, $n^{20}D$ 1.4265, $d_4^{20}$ 0.7722.

Anal. Calcd. for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.62; H, 14.31.

Lebedev[11] reported the following physical constants for this compound: b.p. 157–158.5° (760 mm.), $n^{20}D$ 1.42787, $d_4^{20}$ 0.7755.

**Reduction of Other Dimeric Products.**—To 10 g. (0.26 mole) of lithium aluminum hydride in 200 ml. of dry dioxane kept near room temperature by a water bath was added during 0.5 hr. 30.8 g. (0.105 mole) of the redistilled liquid dimer mixture in 50 ml. of dioxane. The bath was raised to 95° during 3 hr. and maintained at that temperature for 21 hr. The mixture was cooled to 0°, diluted with 250 ml. of pentane and hydrolyzed by dropwise addition of dilute hydrochloric acid. The pentane layer was separated, washed thrice with large volumes of sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure and the residue which weighed 13.5 g. (94% yield) was distilled, b.p. 45–75° (24 mm.), to give 6.8 g. of clear liquid. This was hydrogenated at 20 p.s.i. in 150 ml. of pentane over 0.55 g. of 10% palladium on carbon for 18 hr. The solution was filtered and solvent removed at reduced pressure leaving 6.1 g. of liquid which was fractionally distilled through a small helix column to give a fraction, b.p. 143–146° (752 mm.), $n^{20}D$ 1.4210, $d_4^{20}$ 0.7582.

Anal. Calcd. for $C_{10}H_{20}$: C, 85.72; H, 14.28. Found: C, 85.71; H, 14.34.

Lebedev[11] gave the following for 1,1,2-trimethyl-3-isopropyl-

cyclobutane: b.p. 145–146.5° (760 mm.), $n^{20}D$ 1.42001, $d_4^{20}$ 0.7598.

**2-Bromo-3-methyl-1,3-butadiene, (XIV).**—A mixture of 10 g. (0.15 mole) of 2-methyl-1-buten-3-yne (VII), 43 ml. of 48% hydrobromic acid, 4 g. of cuprous bromide, and 5 g. of ammonium bromide was shaken in a pressure bottle at room temperature for 14 hr. The organic product was extracted with methylene chloride, washed with sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and the methylene chloride removed at 50 mm. The dark product (10 g.) was distilled through a 12-in. Vigreux column, b.p. 36° (38 mm.), $n^{25}D$ 1.5027.

Anal. Calcd. for $C_5H_7Br$: C, 40.85; H, 4.80. Found: C, 41.07; H, 4.98.

Infrared spectrum: 630 (w), 723 (m), 747 (m), 808 (m), 880 (s), 900 (s), 940 (m), 1005 (m), 1094 (s), 1166 (m), 1196 (m), 1277 (m), 1371 (s), 1440 (s), 1450 (s), 1578 (s), 1613 (m), 1674 (m), 1772 (w), 1805 (w), 1954 (m), 2840 (m), 2915 (m), 2940 (m), 3065 (w) cm.$^{-1}$.

Reported[13] for XIV: b.p. 35.4° (40 mm.), $n^{20}D$ 1.5030, $d_4^{20}$ 1.330. Infrared: strong bands at 3100, 1610, and 1590 cm.$^{-1}$.

Reported[13] for XIII: b.p. 35–36° (21 mm.), $n^{24}D$ 1.5213. Infrared: 1960 and 850 cm.$^{-1}$.

When the product was shaken an additional 12 hr. with cuprous bromide and a saturated solution of sodium bromide in 10% hydrobromic acid, an infrared spectrum of the product showed that the allene absorption at 1954 cm.$^{-1}$ was not diminished in intensity. A sample of the diene polymerized to a yellow gel after 4 days at −20°.

**Lithium Aluminum Hydride Reductions of IV, V, and VI.**—To a stirred mixture of 25 ml. of dry diethylcarbitol and 22 g. (0.56 mole) of lithium aluminum hydride cooled in ice was added 0.5 mole of the halide dropwise during 1 hr. The mixture was stirred an additional 2 hr. at 0° and overnight at room temperature. The pressure was then reduced to ∼25 mm. and the flask warmed (finally to 85°) for 3 hr. with stirring, to permit distillation of the hydrocarbon product through the reflux condenser. The hydrocarbon distillate was collected in a Dry Ice trap, dried, and distilled through an efficient center-rod column to give the results reported. The lithium aluminum hydride reaction mixture was cooled to 0° and hydrolyzed with 100 ml. of water with stirring. After warming and brief refluxing the hydrocarbons produced were removed by distillation under reduced pressure, collected, and fractionated as before. The products were identified by means of boiling points, refractive indices, infrared spectra, and vapor phase chromatography.[14]

**Reaction of IV with Sodium Iodide in Acetone.**—A solution of 20.0 g. (0.136 mole) of IV and 40 g. (0.266 mole) of sodium iodide in 150 ml. of acetone was allowed to stand at room temperature for 68 hr. The sodium bromide recovered by filtration weighed 9.6 g. (64% reaction). Pentane (150 ml.) was added to the filtrate and the solution washed 4 times with large volumes of water. The pentane layer was dried over anhydrous magnesium sulfate and the solvent removed at reduced pressure to yield 18.5 g. (70% crude yield) of a yellow liquid. Infrared indicated some acetylenic (3277 cm.$^{-1}$) and allenic (1937 cm.$^{-1}$) material, but conjugated diene (1564 and 1614 cm.$^{-1}$) appeared to be the main component. The crude product was heated with 0.05 g. of cuprous bromide at 50° for 4 hr., the dark material vacuum transferred, and distilled through a small helix column, b.p. 49° (14 mm.), $n^{25}D$ 1.5722. An explosion occurred near the end of the distillation.

Anal. Calcd. for $C_5H_7I$: C, 30.95; H, 3.61. Found: C, 31.34; H, 3.45.

Infrared spectrum: 675 (w), 702 (s), 779 (s), 888 (s), 943 (s), 1178 (s), 1240 (w), 1286 (m), 1303 (s), 1376 (s), 1436 (s), 1447 (s), 1564 (s), 1614 (s), 1674 (w), 1722 (s), 1785 (w), 2890 (m), 2920 (m), 2955 (s), and 3060 (m) cm.$^{-1}$.

A run half the above size left at room temperature for 24 hr. gave 3.5 g. of sodium bromide (34% yield) and 5 g. (38%) of crude iodide. The infrared of this iodide showed strong peaks at 1937 and 3227 cm.$^{-1}$ but essentially no absorption at 1564 cm.$^{-1}$.

**Reaction of IV with Sodium Thiophenoxide.**—To a cold solution of 0.195 mole of sodium methoxide from 4.5 g. of sodium in 150 ml. of methanol was added 20.0 g. (0.182 mole) of thiophenol. To this was added 10.0 g. (0.068 mole) of IV and the solution was allowed to stand for 24 hr. at room temperature. Benzene (100 ml.) was then added to the pale yellow solution and the mixture washed thrice with 10% sodium hydroxide solution and twice with water; it was then dried over anhydrous magnesium

(18) I. M. Heilbron, W. M. Owens, and I. A. Simpson, J. Chem. Soc., 873 (1929).

(19) A. Baeyer and V. Villiger, Ber., **32**, 3625 (1899); **33**, 858 (1900); M. Pastureau, Compt. rend., **140**, 1591 (1905).

(20) A. McKenzie, J. Chem. Soc., 1196 (1912).

sulfate and the solvent removed at reduced pressure. The clear yellow residue (10.6 g., 88% crude yield) appeared to contain ~90% of 1-thiophenoxy-3-methyl-1,2-butadiene and ~10% of 3-thiophenoxy-3-methyl-1-butyne on the basis of infrared. Distillation through a small helix column gave fair recovery of material, b.p. 70° (0.4 mm.), $n^{25}$D 1.5954, which was mainly allenic (perhaps 3% of the acetylenic isomer as contaminant). An attempt at further purification by careful fractional distillation through a more efficient column gave mainly nonvolatile, polymeric products. The distillate was partly rearranged as shown by new infrared peaks at 810, 845, 942, 1307, and 1613 cm.$^{-1}$.

**Reaction of V with Sodium Thiophenoxide.**—A solution of 0.27 mole of sodium thiophenoxide prepared from 6.8 g. of sodium, 150 ml. of methanol and 30 g. of thiophenol was treated with 15 g. (0.10 mole) of V and allowed to stand at room temperature for 16 days. The solution was worked up as above to yield 14.0 g. (87% yield, crude) of a pale yellow product.

Infrared showed no allenic material, but a small peak at 2107 cm.$^{-1}$ and a strong one at 3242 cm.$^{-1}$ indicated an acetylenic compound. There was also a strong peak at 1578 cm.$^{-1}$ and a weak one at 1657 cm.$^{-1}$ which may indicate conjugated diene. Fractionation through a small helix column gave a moderate yield of product believed to be 3-methyl-3-thiophenoxy-1-butyne, b.p. 52° (0.4 mm.), $n^{25}$D 1.5505, $d^{20}_4$ 0.998.

*Anal.* Calcd. for $C_{11}H_{12}S$: C, 74.94; H, 6.86; S, 18.19. Found: C, 74.72; H, 6.65; S, 18.31.

Infrared spectrum: 684 (s), 735 (s), 780 (m), 833 (w), 912 (w), 935 (w), 998 (w), 1010 (m), 1021 (m), 1064 (m), 1072 (m), 1086 (m), 1122 (s), 1171 (m), 1211 (s), 1260 (m), 1301 (m), 1325 (w), 1357 (m), 1378 (m), 1437 (s), 1471 (s), 1578 (m), 1657 (w), 1745 (w), 1794 (w), 1871 (w), 1946 (w), 2107 (w), 2812 (m), 2820 (s), 3017 (m), and 3242 (s) cm.$^{-1}$. The peaks at 2107 and 3242 cm.$^{-1}$ were much stronger in the redistilled product and the peaks at 1578 and 1657 cm.$^{-1}$ much weaker.

# Reaction Rates by Distillation. X. The Condensation of Anilines with Benzoins

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The acid-catalyzed condensation of aniline with benzoin in benzene containing dimethylaniline as a "leveller" has been found to be first order with respect to each reactant and the catalyst. Electron releasing groups *para* to the carbonyl group of the benzoin tend to decrease the rate. In a group of eleven anilines the rate increased consistently as the electron releasing ability of the *meta* or *para* substituent increased. The points for the less basic anilines fell on one straight line of a $\rho$–$\sigma$ plot while those for the more basic anilines fell on a second straight line of decreased slope. Excellent yields of desylanilines were isolated in all cases. The results strongly favor reaction of the aniline with the carbonyl group rather than with the hydroxymethylene group of the benzoin. A mechanism analogous to that previously advanced for the condensation of aniline with benzaldehyde is evaluated.

The factors which determine the rate of reaction of anilines with benzoins have been studied by the distillation method previously employed for a variety of reactions which yield water as a by-product.[2]

$$\begin{matrix} ArC{=}O \\ | \\ Ar'CHOH \end{matrix} + PhNH_2 \longrightarrow \begin{matrix} ArCHNHPh \\ | \\ Ar'C{=}O \end{matrix} + H_2O$$
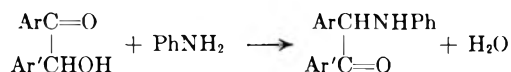
The standard conditions used are given at the top of Table I. When no dimethylaniline was employed (second experiment) the rate constants calculated at successive stages of reaction showed a distinct and consistent upward drift; this drift decreased to insignificance as the amount of dimethylaniline was increased (third and first experiments). The dimethylaniline "leveller" doubtlessly functions primarily to minimize

## TABLE I

### REACTION OF ANILINE WITH BENZOIN

Standard conditions: 0.125 mole of aniline, 0.125 mole of benzoin, 0.0005 mole of PTS,[a] and 0.250 mole of dimethylaniline with benzene to give 500 ml.

| Variable | $t_{50\%}$,[b] min. | $k \times 10^2$, l. mole$^{-1}$ min.$^{-1}$ |
|---|---|---|
| Standard conditions[c] | 210 | 2.25 ± 0.02 |
| No $C_6H_5N(CH_3)_2$ | 125 | 3.86 ± 0.21 |
| Half std. amt. $C_6H_5N(CH_3)_2$[c] | 148 | 3.12 ± 0.15 |
| Half std. amt. PTS[a] | 404 | 1.16 ± 0.01 |
| Quarter std. amt. PTS[a] | 780 | 0.61 ± 0.01 |
| Double std. amt. $C_6H_5NH_2$ | 77 | 2.33 ± 0.03 |
| Double std. amt. $C_6H_5COCHOHC_6H_5$ | 91 | 2.01 ± 0.02 |

[a] *p*-Toluenesulfonic acid monohydrate. [b] This is the time required for a 50% yield of water to collect. [c] For increased accuracy these experiments were double scale.

changes in basicity of the reaction medium as the amount of unreacted aniline decreases.

Comparison of the results for the last four experiments tabulated with those for the first experiment show that the reaction is first order with respect to the aniline, the benzoin, and the catalyst. First-order dependence on the aniline and benzoin is, of course, implicit in the fact that rate constants, calculated on the assumption of such dependence at successive stages of reaction showed no serious drift.

In Tables II and III are summarized the results for the condensation of eleven anilines with benzoin and five benzoins with aniline. The clear-cut nature of the reaction, a requirement for precise rate data, is emphasized by the high yields of products obtained and by the 98 to 102% yields of water collected in all cases; in most cases the yield of water was 99 to 101%. It would be difficult to improve on the facile distillation method as a preparative procedure. Since the reaction can be stopped as soon as complete, cyclization of the products to diarylindoles[3] is minimized.

A $\rho$–$\sigma$ plot for the experiments of Table II is given in Fig. 1. It is suggested that since the dimethylaniline leveller is less basic than the most basic anilines employed, incomplete levelling resulted for those anilines for which the line of decreased slope is drawn. In support of this view the percent average deviation for the three most basic anilines (first three experiments of Table II) was greater than for the other anilines and in these three cases the rate constants calculated at successive stages of reaction showed an upward drift analogous to that encountered in the absence of a

(1) From a portion of the Ph.D. thesis of M. J. Kamlet, March, 1954.
(2) For the preceding paper in this series, see E. F. Pratt and M. J. Kamlet, *J. Org. Chem.*, **26**, 4029 (1961).
(3) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, ed., J. Wiley and Sons, Inc., New York, N. Y., 1952, pp. 22–35.

TABLE II

REACTION OF SUBSTITUTED ANILINES WITH BENZOIN[a]

| Substituent | $t_{50\%}$, min. | $k \times 10^2$, l. mole$^{-1}$ min.$^{-1}$ | Yield,[b] % |
|---|---|---|---|
| $p$-CH$_3$O | 113 | $4.23 \pm 0.07$ | 89 |
| 3,4-di-CH$_3$ | 120 | $3.97 \pm 0.07$ | 84 |
| $p$-CH$_3$ | 137 | $3.34 \pm 0.06$ | 89 |
| $m$-CH$_3$ | 180 | $2.63 \pm 0.02$ | 84 |
| H | 210 | $2.25 \pm 0.02$ | 90 |
| $m$-CH$_3$O | 275 | $1.69 \pm 0.02$ | 84 |
| 3,4-C$_4$H$_4$[c] | 314 | $1.50 \pm 0.02$ | 90 |
| $p$-Cl | 451 | $1.02 \pm 0.01$ | 87 |
| $m$-Cl | 1150 | $0.408 \pm 0.003$ | 87 |
| $p$-COOEt | 3700 | $0.127 \pm 0.001$ | 87 |
| $m$-NO$_2$ | 7500 | $0.0633 \pm 0.0008$ | 84 |

[a] The standard conditions of Table I were used, but the scale was doubled for increased accuracy. [b] Yield of pure, recrystallized product. [c] $\beta$-Naphthylamine.

TABLE III

REACTION OF ANILINE WITH $p$-RC$_6$H$_4$COCHOHC$_6$H$_4$R'-$p'$[a]

| R | R' | $t_{50\%}$, min. | $k \times 10^2$, l. mole$^{-1}$ min.$^{-1}$ | Yield,[b] % |
|---|---|---|---|---|
| H | H | 210 | $2.25 \pm 0.02$ | 90 |
| CH$_3$O | H | 536 | $0.87 \pm 0.01$ | 70[d] |
| CH$_3$O | CH$_3$O | 510 | $0.95 \pm 0.01$ | 87 |
| CH$_2$O$_2$[c] | CH$_2$O$_2$[c] | 840 | $0.56 \pm 0.01$ | 87 |
| Cl | Cl | 222 | $2.19 \pm 0.03$ | 71 |

[a] The standard conditions of Table I were used, but the scale was doubled for increased accuracy. [b] Yield of pure, recrystallized product. [c] 3,4,3',4'-Bismethylenedioxybenzoin. [d] This was the yield of the unstable $p'$-methoxy isomer; a 2% yield of the stable $p$-methoxy isomer was also isolated.



Fig. 1.—Plot of log ($k \times 10^4$) for the reaction of benzoin with substituted anilines vs. Hammett's $\sigma$-constants. *$\beta$-Naphthylamine.

leveller. Straight line plots relating the "levelling effect" or basicity of *para*-substituted acetophenones, ethyl benzoates and benzamides to the $\sigma$ values of the substituents have been previously reported.[4,5] The line for the most basic anilines (Fig. 1) may well be the sum of a line showing the "levelling effect," or basicity, of these anilines and a line obtained by extrapolation of the line for the least basic anilines in Fig. 1. Inadequate levelling of the type considered here is a probable common cause of deviations in $\rho$–$\sigma$ plots for reactions carried out in hydrocarbon or other solvents of negligible acidity or basicity as well as of deviations from integral order kinetics frequently encountered in such solvents.[6]

The $\sigma$-value for the *para*-carbethoxyl group employed in Fig. 1 is 0.678 as recommended for reactions of anilines and phenols.[7] Since this value is based on only two reactions it is less precisely known than most of the others which may explain why it does not fall on the line. The value of $\rho$ calculated by the Jaffe method[7] for the five least basic anilines, excepting $p$-carbethoxyaniline, is $-2.204$; $s$, the standard deviation, is 0.052, and $r$, the correlation coefficient,[7] is 0.997. From this $\rho$ value, a $\sigma$ value of 0.628 for the *para*-carbethoxyl group, of anilines and phenols, may be calculated.

The data in Table II show that a strongly electron releasing methoxyl group *para* to the carbonyl group of

benzoin greatly decreases the rate. Two methoxyl groups, at the *para* and *para* prime positions, or two methylenedioxy groups, at the 3,4- and 3',4'-positions, also sharply reduce the rate. It is not clear why the methylenedioxy group has a greater effect than the methoxyl which has the larger $\sigma$-value[8] nor is it clear why two chlorine atoms at the 4- and 4'-positions slightly decreased the rate although they are electron attracting. It may be that a second substituent at the *para* prime position influences predictions based on a single substituent at the *para* position by altering the extent of intramolecular hydrogen bonding of the hydroxylic hydrogen with the carbonyl oxygen of the benzoin.

The results of this study strongly support those who believe the aniline attacks the carbonyl group[9] rather than the hydroxymethylene group[10,11] of the benzoin. Recently the factors determining the rate of reaction of anilines with benzaldehydes have been reported[2] and the parallelism with the results of the present study is extensive. In the condensation of anilines with both benzoins and benzaldehydes the rate depends on the first power of the concentration of the aniline, the carbonyl compound, and the catalyst and electron releasing *para* substituents in the aniline increase the rate while such groups *para* to the carbonyl group of the benzoin or benzaldehyde decrease the rate; the $\rho$-values obtained for reaction with the substituted

(4) E. F. Pratt and K. Matsuda, *J. Am. Chem. Soc.*, **75**, 3739 (1953).

(5) E. F. Pratt and J. Lasky, *ibid.*, **78**, 4310 (1956).

(6) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 288.

(7) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(8) Ref. 6. p. 188.

(9) R. M. Cowper and T. S. Stevens, *J. Chem. Soc.*, 347 (1940).

(10) A. Bischler and P. Fireman, *Ber.*, **26**, 1336 (1893).

(11) P. L. Julian, E. W. Meyer, A. Magnani, and W. Cole, *J. Am. Chem. Soc.*, **67**, 1203 (1945).

anilines was −2.004 in the case of benzaldehyde and −2.204 in the case of benzoin. If the aniline attacked the hydroxymethylene group the most probable rate controlling step would be formation of the ArCOCHAr ion[12]; the rate would then be independent of both the concentration of, and the substituent on, the aniline and electron-releasing groups at the *para* and *para* prime positions of the benzoin would greatly increase rather than decrease the rate. A mechanism entirely analogous to that recently advanced[2] for the reaction of aniline with benzaldehyde is outlined below.
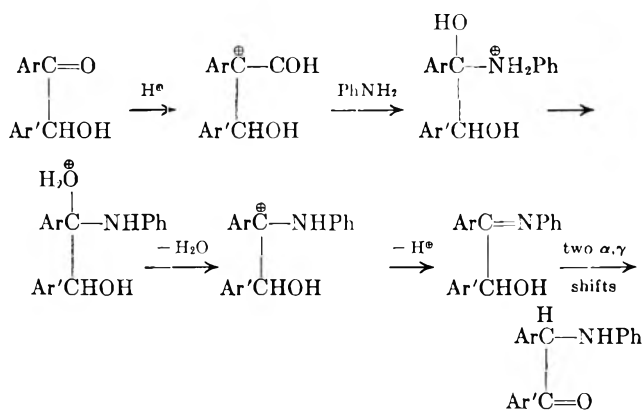


A 70% yield of $p'$-methoxydesylaniline ($C_6H_5$COCH-(NHPh)$C_6H_4$OCH$_3$-$p'$) and a 2% yield of the $p$-methoxydesylaniline were isolated from the reaction mixture for the second experiment of Table III. The minor product is the more stable[13] since in it the carbonyl carbon which bears a partial positive charge can more readily receive electrons from the methoxyl group. It appears, therefore, that because of the mild conditions of the distillation method it is well adapted to the preparation of the unstable isomers which may be rearranged to the stable forms under more rigorous conditions.[11,14−18]

## Experimental[19,20]

**General Considerations.**—The $p$-toluenesulfonic acid monohydrate was Eastman's White Label grade. It was used as obtained since it was found to have close to the calculated neutralization equivalent. All other constituents of the reaction mixtures were purified by standard methods until their melting points or refractive indices agreed closely with the literature values.

The apparatus and procedure employed were entirely analogous to that previously described[2] for the reaction of aniline with benzaldehyde except that a nitrogen atmosphere was not used. Allowance was made in the calculations for the fact that 500- and 1000-ml. volumes of the benzene solutions at room temperature expand to 531 and 1062 ml. at the reflux temperature. The tabulated constants were calculated on the assumption the reactions were first order with respect to aniline and benzoin. In a given experiment successive rate constants were calculated from the time and water volume data at 10 and 20% reaction,

then from the data at 10 and 30% reaction, and so on, to and including the data at 10 and 70% reaction. The tabulated values are the arithmetic mean of the six successive values plus or minus the average deviation of a single value from this mean.

Unless otherwise noted, the products were isolated as follows. When 1000 ml. of reaction mixture was used it was concentrated to 500 ml. before washing, by distilling benzene, while the 500-ml. reaction mixtures were washed without concentration. The benzene solutions were washed once with 100 ml. of water, twice with 30 ml. of concentrated hydrochloric acid in 70 ml. of water, and then three times more with 100 ml. of water. The benzene was removed by distillation using reduced pressure for the final stages and the products recrystallized from suitable solvents. New products were recrystallized to constant melting point while known compounds were recrystallized until their melting points agreed with the literature values.

**Experiments of Table I.**—The temperature range within an experiment was never more than ±0.2° for the 10 to 70% portion of the reaction. Proceeding downward in Table I the median temperatures were 83.5, 81.9, 82.8, 84.6, 83.9, 83.6, 84.5, and 84.5°. As might be expected, increasing the amount of dimethylaniline, aniline, or benzoin slightly increases the boiling point of the reaction mixtures.

The average yield of pure product was 89% for the four experiments of Table I for which the product was isolated. Except for the second experiment which was stopped at 77% water, the total yield of water was always 99.0 to 101.6%.

Three repetitions of the first experiment of Table I gave values for $k \times 10^2$ of 2.30 ± 0.03, 2.33 ± 0.04, and 2.20 ± 0.02 l. mole$^{-1}$ min.$^{-1}$. Repetition of the second and last experiments gave values for $k \times 10^2$ of 3.80 ± 0.20 and 2.03 ± 0.03 l. mole$^{-1}$ min.$^{-1}$.

**Experiments of Table II.**—For all of these experiments the temperature range was 83.1–83.7° for the 10 to 70% portion of the reaction; within a given experiment the maximum temperature variation was ±0.2°.

The product from the first experiment, desyl-$p$-anisidine, was recrystallized from cyclohexane and melted at 92–92.5°.

*Anal.* Calcd. for $C_{21}H_{19}O_2N$; C, 79.47; H, 6.03; N, 4.41. Found: C, 79.50; H, 5.90; N, 4.71; a repetition of this experiment gave a value for $k \times 10^2$ of 4.10 ± 0.06 l. mole$^{-1}$ min.$^{-1}$.

Recrystallization of the product from the second experiment from aqueous ethanol and then from a mixture of ethanol, benzene, and water gave pure desyl-3,4-dimethylaniline which melted at 120.5–121.5°.

*Anal.* Calcd. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.57; H, 6.61; N, 4.52.

The desyl-$m$-anisidine formed in the sixth experiment was recrystallized from cyclohexane, then from absolute ethanol, and then from methanol. It melted at 96–96.5°.

*Anal.* Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.18; H, 5.84; N, 4.64.

A fluffy solid precipitated from the ethanolic mother liquors. Two recrystallizations of the 1.55 g., which melted at 190–200°, raised the melting point to 212–213°. The analytical results indicate it is 2,3-diphenyl-6-methoxyindole.

*Anal.* Calcd. for $C_{21}H_{17}NO$: C, 84.30; H, 5.73; N, 4.71. Found: C, 84.53; H, 5.88; N, 4.77.

The products of the experiments of Tables II and III not individually described are known compounds whose melting points agreed closely with the literature values.

The tenth point was repeated since the point for the *para* carbethoxy substituent does not fall on the line in Fig. 1. A value for $k \times 10^2$ of 0.130 ± 0.001 l. mole$^{-1}$ min.$^{-1}$ was obtained.

**Experiments of Table III.**—With one minor exception the temperature range for the 10 to 70% portion of all these experiments was 83.2–83.8°; the temperature range within an experiment was ±0.15°.

A repetition of the second experiment of Table III gave a $k \times 10^2$ value of 0.89 ± 0.01 l. mole$^{-1}$ min.$^{-1}$.

The 3,4,3',4'-bismethylenedioxydesylaniline obtained in the fourth experiment was recrystallized from hot ethanol. It melted at 135–135.5°.

*Anal.* Calcd. for $C_{22}H_{17}NO_3$: C, 70.38; H, 4.56; N, 3.73. Found: C, 70.56; H, 4.58; N, 4.03. A repetition of this experiment gave a $k \times 10^2$ value of 0.54 ± 0.1 l. mole$^{-1}$ min.$^{-1}$.

A 3% yield of $p,p'$-dichlorobenzil was isolated along with the expected product from the last experiment of Table III. A repetition of this experiment gave a $k \times 10^2$ value of 2.15 ± 0.02 l. mole$^{-1}$ min.$^{-1}$.

(12) E. F. Pratt and P. W. Erickson, *J. Am. Chem. Soc.*, **78**, 76 (1956); E. F. Pratt and H. J. F. Segrave, *ibid.*, **81**, 5369 (1959).

(13) Ref. 3, p. 33.

(14) S. N. McGeoch and T. S. Stevens, *J. Chem. Soc.*, 1032 (1935).

(15) F. Brown and F. G. Mann, *ibid.*, 858 (1948).

(16) R. M. Cowper and T. S. Stevens, *ibid.*, 1041 (1947).

(17) Ref. 3, pp. 29, 30.

(18) K. LeRoi Nelson and R. L. Seefeld, *J. Am. Chem. Soc.*, **80**, 5957 (1958).

(19) All melting points are corrected.

(20) We wish to thank Dr. Mary Aldridge and Mrs. Raymond Baylouny for all microanalyses reported herein.

# High Pressure–High Temperature Reactions.   II.   The Reactions of Aliphatic Nitriles and Amides[1]

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Under the extreme conditions of high pressure (35,000–50,000 atm.) and temperatures ranging from ambient to 475°, certain aliphatic nitriles are not trimerized to *sym*-triazines as previously observed for aromatic nitriles. Instead, phenylacetonitrile, ethyl cyanoacetate, and adiponitrile undergo polymerizations which probably involve the addition of α-methylene groups to the triply bonded nitrile function (Thorpe reaction). Acrylonitrile is converted to a carbonaceous residue by the mere application of high pressure alone. Amides, due to resonance stabilization, are relatively unreactive under these conditions; acrylamide, like the nitrile, is also degraded to a carbonaceous product, but the simultaneous application of pressure and heat is required.

## Discussion

**Nitriles.**—Pure aromatic nitriles have been observed to trimerize readily, in the course of a few minutes, to the corresponding 2,4,6-tris(aryl)-1,3,5-triazines under the extreme conditions of high pressure (35,000–50,000 atm.) and high temperature (350–500°).[3]
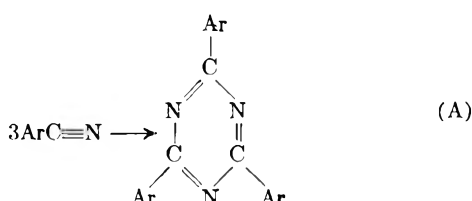


The reaction involves a decrease in multiple bond character ($C=N$ of the product as compared to $C≡N$ of the reagent); such aggregation reactions are facilitated by the application of pressure since the reaction's transition state is of smaller volume than that of the uncombined reagents.[4]

In their pioneering work on the subjection of solutions of nitriles to pressures of 7000–8500 atm., Cairns, Larchar, and McKusick[5] observed that aliphatic nitriles as well as aromatic nitriles, are trimerized to the corresponding triazines; the trimerization, however, did not occur either in the absence of a solvent (especially methanol), or at pressures below 1000 atm. It was of interest, therefore, in the present survey of the behavior of organic compounds under the simultaneous application of high pressures and high temperatures (HPHT) to determine whether aliphatic nitriles, without solvents, would trimerize under the extreme reaction conditions.

It has been observed that although the products from the HPHT treatment of an organic reagent differ in *degree* of reaction, they are usually of the same *kind* as those obtained by the acid- or base-catalyzed treatment of that reagent at atmospheric pressure. Thus, the condensation of cyclohexanone to dodecahydrotriphenylene is an example of acid-catalysis mimetic HPHT behavior, while the base-catalysis mimetic character has been observed in the polymeric condensation reaction of acetone.[6]

Because of this acid- or base-catalysis behavior, the HPHT reactions of aliphatic nitriles are more complex than the simple trimerizations observed for their aromatic analogues. The complicating factor is due to the reactivity of the α-methylene group of the nitrile which can add *inter-* or *intra*-molecularly to the triplybonded $-C≡N$ group to give rise to cyanoketimines; the latter, which still contain both α-methylene and nitrile groups, are then capable of further similar reaction to yield polymeric materials. The behavior of aliphatic nitriles under HPHT conditions, therefore, represents an extension of their behavior upon treatment with base (Thorpe reaction),[7] along with their trimerization reaction.

$$-CH_2C≡N + B: \longrightarrow B:H^+ + -\overset{\cdot\cdot}{C}HC≡N \qquad (B)$$

$$-CHC≡N + -CH_2C≡N \xrightarrow{B:H^+} -CH-\overset{\overset{\displaystyle C≡N}{|}}{C}=NH + B: \quad (C)$$
$$\underset{\displaystyle CH_2-}{|}$$
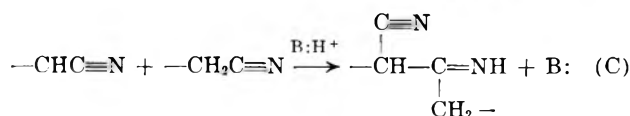
Thus, adiponitrile, an unactivated aliphatic dinitrile, gives HPHT products which are clear, brown, infusible, insoluble, amberlike resins. The elementary analyses and infrared spectral data suggest that the HPHT product is derived from a series of Thorpe-like addition reactions and trimerizations. The HPHT experiments with adiponitrile are particularly satisfying for they provide a clear-cut example of the primary and dominating effects of temperature and time at a given pressure. Thus, at 40 kbars (1 bar = 0.98692 atm.) and 155° for 30 min., the dinitrile is recovered unchanged. For a similar pressure and reaction time but an increased temperature (255°), however, the reaction product is the amber-like resin. If the pressure is still maintained at 40 kbars and the temperature is further increased to 370–400°, one can now decrease the reaction time in half (15 min.) and still obtain the same polymeric resinous product. A further increase of reaction temperature to 475° and the pressure to 50 kbars results in the production of a similar polymeric material after only six minutes' reaction time. Even at these high temperatures, the polymerization of the dinitrile proceeded with a minimum of decomposition; no odor of ammonia was present.

The HPHT situation with acetonitrile, a simple unactivated mononitrile, however, is different. Most of this liquid reagent at 50 kbars and 300–325° for 6–8

(1) Presented at the 134th National Meeting of the American Chemical Society, Chicago, Ill., September, 1958.

(2) U. S. Borax Research Corporation, Anaheim, Calif.

(3) I. S. Bengelsdorf, *J. Am. Chem. Soc.*, **80**, 1442 (1958).

(4) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **31**, 875 (1935).

(5) T. L. Cairns, A. W. Larchar, and B. C. McKusick, *J. Am. Chem. Soc.*, **74**, 5633 (1952).

(6) I. S. Bengelsdorf, 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956, Abstracts, p. 74-O; *cf.* S. D. Hamann, "Physico-Chemical Effects of Pressure," Butterworths Scientific Publications, London, 1957, p. 187.

(7) The first paper in a series of works on this reaction is by H. Baron, F. G. P. Remfry, and J. F. Thorpe, *J. Chem. Soc.*, **85**, 1726 (1904).

min. is decomposed to a dark, sooty solid; the odor of ammonia is evident. Sublimation of the product at reduced pressure gives a small yield of the unsymmetrical trimer, 4-amino-2,4-dimethylpyrimidine (I). This



I
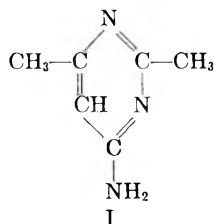
observation corroborates the previous report by Cairns, Larcher, and McCusick.[5] They found that the trimerization of acetonitrile, at pressures in the 7.5 kbar region, gives predominantly I as the reaction temperature increased. This is particularly true in the presence of a base, such as, ammonia. The pyrimidine I is also the chief product of the treatment of acetonitrile with base at atmospheric pressure.[8] All of these studies indicate that the presence of ammonia in the decomposition reaction of acetonitrile under HPHT conditions would tend, therefore, to produce some pyrimidine (I); this is observed.

If the methylene group of a mononitrile substrate, however, is more activated than is the case for acetonitrile, then the more intimate molecular environment of the severe HPHT conditions causes the nitrile to react far beyond the relatively simple reaction sequence described (B and C). Thus, instead of a decomposition and trimerization reaction as observed for the nonactivated acetonitrile, the HPHT reactions of phenylacetonitrile and ethyl cyanoacetate lead to extensive polymerization and decomposition, respectively.

The complete absence of the —C≡N group vibration in the infrared spectrum of the polymers, and the appearance of C=N and NH bands not originally present, strongly suggest the following *inter*molecular addition polymerization sequence for phenylacetonitrile.



(D)
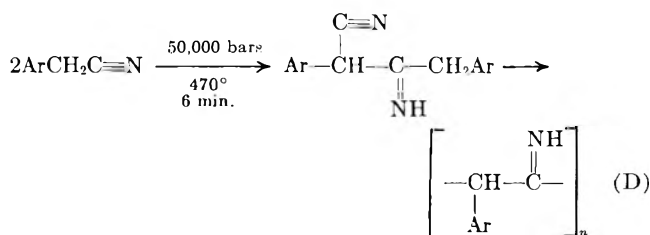
The HPHT polymerization of ethyl cyanoacetate, an even more reactive nitrile, shows marked temperature dependence. Thus, at 40 kbars, up to 170° and 30-min. reaction time, the ester is recovered unchanged. At 200° and 15 min., however, the ester is converted to dark-colored, insoluble, infusible solids. If the reaction temperature is raised to 275–340°, and the time is decreased to 12 min., one observes the production of even darker (black) solids with similar physical properties as above; the odor of liberated ammonia, a reduced molecule, is indicative of the occurrence of deep-seated decomposition reactions.

An attempt to treat acrylonitrile at 40,000 bars and 300° for 14 min., through the simultaneous trimerization of the cyano group and the polymerization of the

vinyl group led to a carbonaceous residue and ammonia. Since other unsaturated substrates, *e.g.*, isoprene, have been observed to carbonize by the application of pressure alone,[9] acrylonitrile was again subjected to 40,000 bars but with no thermal input. Again, the nitrile was decomposed to a carbonaceous solid and ammonia. This observation may be explained by the fact that the application of pressure alone must result in a rapid polymerization of the monomer. The subsequent rapid rise in temperature from the heat of polymerization cannot be dissipated from the thermally insulated reaction vessel and this internally generated energy results in the degradation of the reagent. Similar explosive polymerizations due to temperature increases under pressure have been observed and described previously.[10] A recent observation states that polyacrylonitrile reacts with bases to form polycyclic imidines[11]; that the dark color of the HPHT product may be due to such extensive polymeric cyclization reactions, of the initially produced polyacrylonitrile, in the presence of the liberated ammonia, could not be substantiated since the infrared spectrum of the HPHT product exhibited no absorption bands whatsoever.

The HPHT data concerning the experiments with furmaronitrile, $\beta,\beta'$-thio-dipropionitrile, and terephthalonitrile are presented in the table.

**Amides.**—Whereas nitriles are readily trimerized or polymerized under HPHT conditions, amides are extremely resistant towards change under similar extreme experimental conditions. This is undoubtedly due to the stabilization of amides by resonance; if any HPHT reaction occurs at all it is one of decomposition or carbonization.

One exception to the above observations is that of benzamide, an aromatic amide. It is partially dehydrated to benzonitrile *in situ;* the latter is then readily trimerized to 2,4,6-triphenyl-1,3,5-triazine (*cf.* equation A).[3]

In contrast, the HPHT treatment of *sym*-diphenylurea, a carbamide, at 50,000 bars and 360° partially converts it to a carbonaceous residue. Colorless starting urea, however, is recovered as a sublimate from the dark HPHT product. This indicates that those molecules of diphenylurea which survived the decomposition carbonization reaction are completely unaffected, *i.e.*, the HPHT reaction is one of degradation or no reaction at all.

The rather indiscriminate nature of the HPHT conditions as concluded from the above amide reactions and the ethyl cyanoacetate reactions, is pointedly illustrated by the behavior of acrylamide. The experimental data show that between 200° and 250° at 40,000 bars this monomer undergoes a violent decomposition reaction leading to carbonization and ammonia formation. Obviously, the heat of reaction added to the thermal input energy provides a thermal shock within the insulated reaction vessel which is too great to be dissipated and a violent decomposition ensues. Thus, both pressure and heat lead to the same degradative type of reaction in acrylamide as is observed for acrylonitrile by the application of pressure alone.

(8) A. R. Ronzio and W. B. Cook, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N.Y., 1951, p. 71.

(9) I. S. Bengelsdorf, unpublished work.
(10) K. H. Klaasens and J. H. Gisolf, *J. Polymer Sci.*, **10**, 149 (1953).
(11) E. M. LaCombe, *ibid.*, **24**, 152 (1957).

TABLE I.  THE HIGH PRESSURE–HIGH TEMPERATURE REACTIONS OF ALIPHATIC NITRILES AND AMIDES[a]

| Reagent | Pressure[b] bar × 10³ | Temp., °C. | Time, min. | Results and products |
|---|---|---|---|---|
| Adiponitrile NC(CH₂)₄CN | 40 | 155 | 30 | Nitrile recovered unchanged |
| | 40 | 255 | 14 | Partial polymerization |
| | 40 | 255 | 30 | Complete polymerization to clear yellow-brown resin which looked like amber. Began to darken, but did not melt at 360°. *Anal.* Calcd. for C₆H₈N₂: C, 66.6; H, 7.4.  Found: C, 65.7; H, 7.1.[c]  Strong CN band at 2240 is missing, while bands at 3300, 3130, 1634, 1582, 1515 suggest NH, C=N, NH₂ functional groups are present in the product[d] |
| | 40 | 370 | 15 | Same as above.  The absence of NH₃ indicated a minimum of degradative reactions[j] |
| | 40 | 400 | 15 | Same product and infrared spectrum as above |
| | 50 | 475 | 6 | Same product and infrared spectrum as above |
| Acetonitrile CH₃CN | 50 | 325 | 6 | Decomposition to a dark, sooty solid.  Vacuum sublimation isolated a small yield of colorless, grainy crystals of 4-amino-2,6-dimethyl pyrimidine, m.p. 183°; lit.[e] m.p. 182–183° |
| | 50 | 300 | 8 | Same as above |
| Phenylacetonitrile C₆H₅CH₂CN | 50[f] | 410 | 7 | Nitrile recovered unchanged |
| | 50 | 470 | 6 | Yellow polymeric solid.  Strong CN stretching band at 2240 is missing, while bands at 3500, 3410, 3310, 1568, 1555 suggest NH, C=N, NH₂ functional groups are present in the product.  *Anal.* Calcd. for C₈H₇N: C, 82.0; H, 6.0.  Found: C, 78.4; H, 5.9[e] |
| Ethyl cyanoacetate C₂H₅OOCCH₂CN | 40 | 55 | 30 | Ester recovered unchanged |
| | 40 | 170 | 15 | Same as above |
| | 35 | 200 | 15 | Dark orange-colored infusible solid.  Sharp 2270-CN band is missing.  Extreme broadness of bands in the 1300–1800 and 3000 region is indicative of mixtures of functional groups |
| | 40 | 200 | 15 | Dark red-purple solid insoluble in alcohol, benzene, acetone, methanol, or ether.  Begins to darken at 240°, but is not molten at 320°.  *Anal.* Calcd. for C₅H₇O₂N: C, 53.1; H, 6.2.  Found: C, 51.0; H, 4.5[e] |
| | 35 | 275 | 12 | Decomposition to ammonia and a black solid which neither sublimed or melted in a free flame |
| | 35 | 340 | 12 | Same as above |
| Acrylonitrile CH₂=CHCN | 40 | 300 | 14 | Carbonized solid product and ammonia |
| | 40 | ... | 30 | Same as above |
| | 40 | ... | 15 | Same as above.  Infrared spectrum of product revealed absence of absorption bands |
| Fumaronitrile NC>C=C<H  H>C=C<CN | 40 | 340 | 15 | The major part of the starting dinitrile was recovered |
| | 40 | 335 | 15 | Same as above.  No dimerization or polymerization was observed |
| β,β'-Thiodipropionitrile (CH₂)₂CN \| S \| (CH₂)₂CN | 40 | 305 | 10 | Extensive degradation to a carbonized solid and hydrogen sulfide |
| Terephthalonitrile[g] p-NC—C₆H₄—CN | 39 | 400 | 11 | Carbonized solid product (not molten at 330°); partial recovery of starting material |
| s-Diphenylurea C₆H₅NHCONHC₆H₅[g] | 50[h] | 360 | 6 | Partial carbonization.  Infrared spectrum of colorless solid recovered by sublimation is identical with that of starting material |
| Acrylamide CH₂=CHCONH₂ | 40 | 150 | 25 | The amide melted in the capsule, but was recovered unchanged |
| | 40 | 195 | 15 | Same as above |
| | 40 | 260 | 15 | Extensive decomposition to carbonaceous residue and ammonia |
| | 40 | 300 | 15 | Same as above |
| Oxamide H₂NCO—CONH₂ | 40 | 260 | 18 | Amide recovered unchanged |
| | 40 | 330 | 18 | Partial degradation to dark residue and ammonia |
| | 40 | 345 | 16 | Same as above |
| Urea–pyromellitic anhydride | 40 | 355 | 17 | Partial degradation to ammonia and recovery of unchanged urea |

[a] All HPHT reactions were conducted in lead reaction vessels unless otherwise indicated.  [b] 1 atm. = 1.0133 bar or 1 bar = 0.98692 atm.  [c] The analytical value for carbon in the noncarbonized polymeric products is somewhat lower, in all cases, than that for the starting nitrile; this may be due to partial loss of HCN.  [d] Infrared absorption bands are reported in wave numbers (cm.⁻¹).  [e] *Cf.* ref. 5.  [f] This reaction was conducted in a nickel capsule.  [g] An aromatic compound included in this study.  [h] This reaction was conducted in a stainless steel capsule.

The case of oxamide is further illustrative of the resistance of amides to HPHT change. Paracyanogen, a carbon–nitrogen polymer, has been reported to have been prepared in 30–40 % yield by heating oxamide at 270° for one week.[12] Attempts to accelerate this dehydration of oxamide, by HPHT conditions, failed. At 40 kbars and 260° for 18 min. oxamide is recovered unchanged. Elevation of the temperature to 333°, under identical pressure–time conditions, leads to extensive decomposition to a carbonaceous materials and ammonia.

A single experiment involving the HPHT reaction of urea with pyromellitic anhydride to produce a polymeric phthalocyanine also failed; ammonia was liberated as evidence of a deep-seated decomposition reaction.

(12) L. L. Bircumshaw, F. M. Taylor, and D. H. Whiffen, J. Chem. Soc., 931 (1954).

## Experimental

Apparatus.—The experimental apparatus used in this investigation is the "belt" high pressure–high temperature apparatus developed in this laboratory[13]; suitable modifications were made to facilitate the study of liquid and solid organic substrates. Thus, the reaction vessels are small metallic cylinders fabricated so that they are closed at one end, and capable at the other. Their dimensions (0.200-in. diameter and 0.450 in. long) permitted a sample capacity of ca. 0.2 ml. of liquid and 0.13 g. of solid. Cylinders fabricated of nickel, stainless steel, and lead were used; the latter soft metal is preferred for the reaction capsule since it can be opened easily with a razor blade after the reaction is completed. Liquid products and reagents were manipulated by suitable glass capillary milligram techniques.

Reactions.—The details of the HPHT reactions are summarized in Table I.

(13) H. T. Hall, Rev. Sci. Instr., 31, 125 (1960); H. T. Hall, J. Phys. Chem., 69, 1144 (1955).

# The Reaction of Diketene with Glycine

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The reaction between diketene and glycine in basic solution yields 3-acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).

In the course of a biosynthetic investigation, the preparation of acetoacetylglycine by the reaction of glycine with diketene was attempted. Instead, a crystalline compound was obtained in about a 15% yield which was not the desired material. We have recently re-investigated the reaction and have shown the compound to be 3-acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).

Elemental analysis gave the empirical formula $C_{10}H_{11}NO_5$ which is satisfied by the condensation of two molecules of diketene with one molecule of glycine and the elimination of one molecule of water. The compound is acidic (neutralization equivalent 112, $pK_{a_1}$, 3.25, $pK_{a_2}$, 8.0) and the infrared spectrum showed three carbonyl peaks which were assigned as follows: 5.78 $\mu$, $-CH_2CO_2H$; 6.00 $\mu$, $>NCO-$, and 6.18 $\mu$, $\alpha,\beta$-unsaturated-$\beta$-hydroxy ketone.[1] There was no hydroxyl absorption. The carbonyl of the acetyl function formed a 2,4-dinitrophenylhydrazone and also gave a positive iodoform test. Kuhn Roth oxidation gave two C-methyl groups. The ultraviolet spectrum implied a pyridone rather than a pyrrolidone structure and therefore I and II were considered most probable.

The acid could be esterified easily to give the ethyl or methyl ester and the increased solubility of these compounds in deuterated chloroform enabled their n.m.r. spectra to be studied.[2] The methyl ester showed 6 singlets at $\tau$ values, $-5.3$ (1H); 4.2 (1H); 5.35 (2H, $-CH_2CO_2CH_3$); 6.3 (3H, $-CO_2CH_3$); 7.4 (3H, $-COCH_3$); 7.75 (3H, $C-CH_3$). The singlet at $-5.3$ $\tau$ was attributed to the hydroxyl hydrogen in the $\alpha,\beta$-unsaturated-$\beta$-hydroxy ketone function.[3]

On heating with concentrated sulfuric acid, the compound was deacetylated,[4] and the acetic acid which distilled was characterized as the S-benzylthiouronium salt. The infrared spectrum of the deacetylated product lacked the band at 6.18 $\mu$ and the ultraviolet spectrum was identical with that of 1,6 dimethyl-4-hydroxy-2-pyridone and unlike that of 2,6 dihydroxypyridine. Thus structure I was assigned to the original compound and this was verified by a partial synthesis.



III                IV
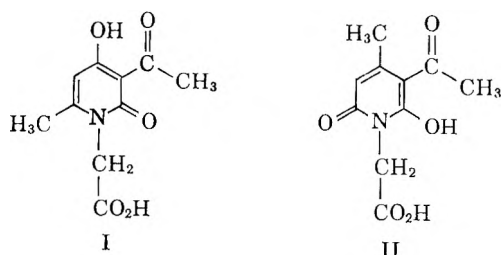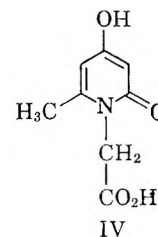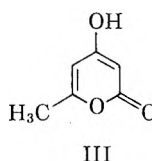
By analogy with the well known reaction of triacetic acid lactone (III) to give 1,4 dihydroxypyridines with ammonia and amines,[5] glycine reacted with triacetic acid lactone in sodium hydroxide solution and the prod-



I                II

(1) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 124.

(2) N.m.r. spectra were taken on a Varian A60 instrument at 60 Mc. using deuterated chloroform solutions and tetramethylsilane as internal reference.

(3) L. M. Jackman, "Applications of Nuclear Magnetic Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 71.

(4) O. Mumm and G. Hingst, Ber., 56, 2301 (1923).

(5) N. Collie and W. W. Myers, J. Chem. Soc., 722 (1892); H. M. Woodburn and M. Hellmann, Rec. trav. chim., 70, 813 (1951).

uct obtained was identical in all respects with the deacetylated compound obtained above. Triacetic acid lactone remains unchanged when quantitatively treated with sodium hydroxide in the same manner. The deacetylated compound therefore has structure IV and this confirms the assignment of structure I to the original condensation product.

The isomer of I, which has the acetyl group at position 5 rather than at position 3, would require the rearrangement of diketene prior to or during the condensation, and is excluded by the infrared and nuclear magnetic resonance evidence.

In considering the reaction mechanism, it is unlikely that two molecules of diketene first condense to form dehydroacetic acid which then reacts with a molecule of glycine forming the pyridone (I). It has been shown[6] that under similar reaction conditions dehydroacetic acid and glycine reacted to form a compound which, although isomeric, was reported as having physical properties unlike those of the pyridone (I). We repeated this reaction and confirmed that the compound obtained was different in all respects (melting point, mixture melting point, ultraviolet, infrared, stability to acid, etc.) from the pyridone (I).

The products of the reaction of diketene on other amino acids, under the condition described here, have not been investigated. However, Lacey[7] has reported that ethyl glycinate reacts with diketene, under neutral conditions, to give the expected N-acetoacetyl derivative.

## Experimental

**3-Acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).**—Glycine (5.0 g.) was dissolved in 40% sodium hydroxide (5 ml.) and diluted with water (17 ml.). The solution was stirred at $-5°$ and freshly distilled diketene (9.0 g.) was added in four portions during 1 hr. Stirring was continued until the reaction mixture became homogeneous. The solution was acidified to pH 2 with dilute hydrochloric acid and a white crystalline solid precipitated. The crystals were collected and washed with cold water (2.2 g.), m.p. 227–231°. Recrystallization from water gave needles (1.8 g.), m.p. 236–238°.

*Anal.* Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.94; N, 6.22. Found: C, 53.52; H, 4.77; N, 6.31. Ultraviolet spectrum ($H_2O$): $\lambda_{max}$ 230 m$\mu$ (log $\epsilon$ 4.0), 270 m$\mu$ (log $\epsilon$ 3.6), and 323 m$\mu$ (log $\epsilon$ 4.1); (0.1 NaOH), $\lambda_{max}$ 235 (log $\epsilon$ 4.3) and 300 m$\mu$ (log $\epsilon$ 3.9); infrared spectrum (Nujol): 5.78 $\mu$ (sh), 6.0 $\mu$ (sh), 6.18 $\mu$ (sh).

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(6) S. Iguchi, K. Hisatsune, M. Himeno, and S. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **7**, 323 (1959).

(7) R. N. Lacey, *J. Chem. Soc.*, 851 (1954).

**3-Acetyl-4-hydroxy-1-methoxycarbonylmethylene-6-methyl-2-pyridone.**—The acid (I) (0.502 g.) was dissolved in 25 ml. of anhydrous methanol, a few drops of concentrated sulfuric acid were added and the solution was heated under reflux for 5 hr. The solution was evaporated to a small volume diluted with water, and extracted with ether. After drying over anhydrous magnesium sulfate, the ether was removed under reduced pressure, yielding a crystalline residue (0.514 g.), m.p. 123–124°. Recrystallization from absolute ethanol gave prisms, m.p. 125°.

*Anal.* Calcd. for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48; N, 5.86. Found: C, 55.17; H, 5.60; N, 6.07. Infrared (Nujol): 5.70 $\mu$ (sh), 6.06 $\mu$ (sh): 6.18 $\mu$ (sh). N.m.r. $\tau$: $-5.3$ (1H), 4.2 (1H), 5.35 (2H), 6.3 (3H), 7.4 (3H), 7.75 (3H).

**3-Acetyl-1-ethoxycarbonylmethylene-4-hydroxy-6-methyl-2-pyridone.**—This ester was prepared from the acid (I) (0.079 g.) and absolute ethanol by the method described above. The crude ester (0.984 g.), m.p. 102–105°, was recrystallized from absolute ethanol m.p. 106–107°.

*Anal.* Calcd. for $C_{12}H_{15}NO_5$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.08; H, 5.84; N, 5.82. Infrared (Nujol): 5.78 $\mu$ (sh), 6.08 $\mu$ (sh), 6.18 $\mu$ (sh). N.m.r. $\tau$: 4.2 (1H), 5.3 (2H), 5.75 (quartet 2H), 7.3 (3H), 7.75 (3H), 8.7 (triplet 3H).

**Deacetylation of 3-Acetyl-1-carboxymethylene-4-hydroxy-6-methyl-2-pyridone (I).**—The acid (I) (4.55 g.) was dissolved in concentrated sulfuric acid (5 ml.) and heated at 200° for 30 min. The acetic acid which distilled was converted into the S-benzylthiouronium derivative, m.p. 135°, unchanged on mixing with an authentic sample. The reaction mixture was cooled and treated with saturated barium hydroxide solution until pH 5. The precipitated barium sulfate was filtered and washed with water. The filtrate was evaporated under reduced pressure and the residue dissolved in dilute potassium carbonate solution and filtered from some insoluble material. The filtrate was acidified with dilute hydrochloric acid and evaporated to dryness leaving a residue which was extracted with absolute ethanol. Evaporation of the ethanolic extracts yielded an oil which crystallized from water (2.7 g.), m.p. 239–240°. Recrystallized from water, m.p. 248°.

*Anal.* Calcd. for $C_8H_9NO_4$: C, 52.48; H, 4.95; N, 7.64. Found: C, 52.68; H, 4.92; N, 7.61. Ultraviolet spectrum (95% EtOH): $\lambda_{max}$ 230 (sh) (log $\epsilon$ 3.47) and 287 (log $\epsilon$ 3.70). Infrared (Nujol): 5.86 $\mu$ (sh), 6.05 $\mu$ (s).

**1-Carboxymethylene-4-hydroxy-6-methyl-2-pyridone (IV).**—Triacetic acid lactone (0.94 g.) was added to a solution of glycine (0.56 g.) in 0.88 N sodium hydroxide (8.5 ml.) and the solution warmed on a steam bath for 1 hr. After cooling, the reaction mixture was acidified with dilute hydrochloric acid and on evaporation of some of the water white needles precipitated, 0.508 g., m.p. 244–247°. It was recrystallized from water, m.p. 248°, and was identical in all respects (mixture melting point, ultraviolet spectrum, infrared spectrum) with the deacetylated product obtained above.

# Bridged Polycyclic Compounds. XXI. The Ionic Chlorination of 9,10-Dihydro-9,10-ethenoanthracene[1]

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The ionic chlorination of 9,10-dihydro-9,10-ethenoanthracene was shown to yield *exo-* and *endo-4-syn-8-* dichlorodibenzobicyclo[3.2.1]octadiene as the sole reaction products. The less stable of these isomers was the preponderant product. The structure proofs of these addition–rearrangement reaction products and some of their chemistry are discussed.

Ionic chlorination of 9,10-dihydro-9,10-ethenoanthracene (I) in carbon tetrachloride gave two isomeric dichlorides, A and B, neither of which were *cis-* or *trans-*11,12-dichlorodibenzobicyclo[2.2.2]octadiene (IV) and (V), which had been previously prepared in this laboratory.[2] Both isomers gave an immediate precipitate of silver chloride when treated with silver nitrate in acetone. Compounds IV and V were unreactive to this reagent under these conditions.

Addition rearrangements during the halogenation of bicyclic olefins have been previously reported,[3-5] and this type of reaction seemed to be the best explanation for the formation of compounds A and B during the chlorination reaction. The formation of four isomeric dichlorinated hydrocarbons, II, III, VI, and VII, from the addition–rearrangement to I is possible.



I II III
IV V
VI VII
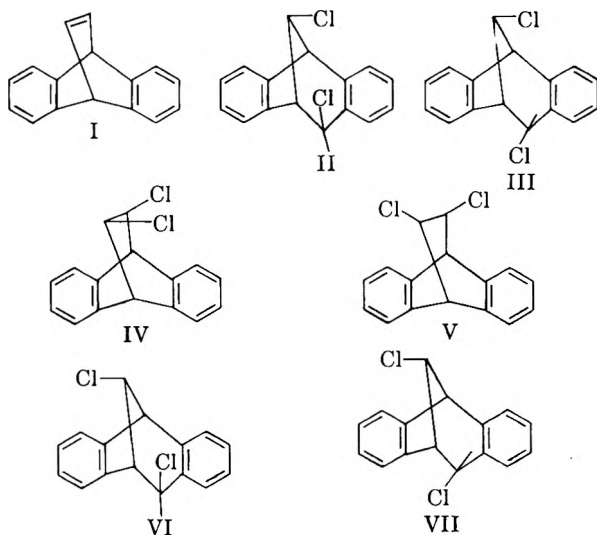
Catalytic hydrogenation of each of the dichlorinated isomers with palladium on barium sulfate yielded the same monochlorinated product (C), which might have any of the structures VIII to XI.

Since the steric arrangement of one of the chlorine atoms in each isomer was thus shown to be identical with that in the other, it then follows that the isomeric pair (A and B) could have only the following combination of structures: II, III; III, VII; VI, VII; or II, VI.

At first, it appeared obvious that hydrogenolysis of the benzyl chloride of the rearranged dichlorides A and B had taken place to produce a monochlorinated hydro-



VIII IX
X XI
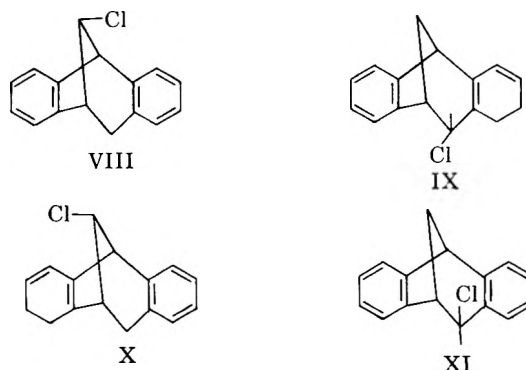
carbon with a chlorine atom substituted at the 8-position. However, it was reported that the specific rate constant for the solvolysis of *anti-*7-chloronorbornene[6] in 80% ethanol at 50° is $8.7 \times 10^{-5}$ sec.$^{-1}$, and the corresponding constant for $\alpha$-phenylethyl chloride[7] is $16.4 \times 10^{-5}$ sec.$^{-1}$. It, therefore, seemed possible that the *syn-*c8-hloride under the influence of the unsaturation from the benzene ring might undergo hydrogenolysis at a faster rate than the benzyl chloride. This involves the perhaps unjustifiable assumption that hydrogenolysis and solvolysis are comparable, and that assistance from the $\pi$-electron system is comparable to that from a carbon–carbon double bond.[8]

It, therefore, seemed necessary to establish the position of the chlorine atom which was removed upon hydrogenolysis of the chlorinated products. Addition of *t*-butyl hypochlorite to I in acetic acid gave the same chloroacetate as was obtained from the acetolysis of either A or B.[9] *t*-Butyl hypochlorite, when used as an ionic chlorinating agent, donates a chloronium ion to an olefinic double bond.[10] A positive charge when placed on the 11-position of I induces a Wagner–Meerwein rearrangement and transforms the [2.2.2] ring system into the [3.2.1] ring system[9,11] which then reacts with acetic acid at the benzyl position to give a chloroacetate (XII).

Reduction of XII with lithium aluminum hydride gave the chlorohydrin XIII. Permanganate oxidation of XIII gave a chloro ketone, XIV, which when subjected to Clemmensen reduction gave the same monochlorinated hydrocarbon which was obtained upon hy-

(1) Previous paper in series: S. J. Cristol, L. K. Gaston, and D. W. Johnson, *Tetrahedron Letters*, in press.

(2) S. J. Cristol and N. L. Hause, *J. Am. Chem. Soc.*, **74**, 2193 (1952).

(3) H. Kwart, *ibid.*, **75**, 5942 (1953).

(4) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *ibid.*, **76**, 5692 (1954).

(5) H. Kwart and L. Kaplan, *ibid.*, **76**, 4072 (1954).

(6) W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **78**, 5653 (1956).

(7) E. Grunwald and S. Winstein, *ibid.*, **70**, 846 (1948).

(8) It has subsequently been shown by P. D. Bartlett and W. P. Giddings that this type of rate enhancement in solvolysis is not so great with a benzene ring as with a double bond. P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960).

(9) D. D. Tanner, Ph.D. thesis, University of Colorado, 1961.

(10) M. Anbar and D. Ginsberg, *Chem. Rev.*, **54**, 925 (1954).

(11) S. J. Cristol and R. K. Bly, *J. Am. Chem. Soc.*, **82**, 6155 (1960).

XII      XIII      XIV



II      III
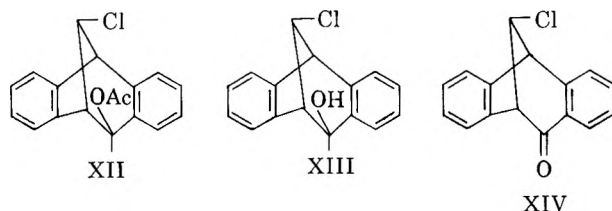
drogenolysis of either A or B. (Numbers XII through XIV refer to the correct structure assignments.)

The method of preparation of XII establishes the position of the chlorine atom which is replaced during hydrogenolysis. The position of the reactive chlorine atom was further investigated by taking an ultraviolet spectrum of XIV. The usual absorption band at 2400–2450 Å. often associated with an aromatic conjugated ketone was not seen in the ultraviolet spectrum of XIV, taken in absolute ethanol. This absence of a strong absorption maximum is not unique since the ketonic band at this wave length fails to appear in the spectra of 1-indanone,[12] 1-tetralone,[13] 2,3-benz-1-suberone,[13] 2-keto-*anti*-8-methyl-3,4,6,7-dibenzo[3.2.1]bicyclooctadiene-1-*syn*-8-dicarboxylic acid,[14] and *syn*-8-hydroxydibenzobicyclo[3.2.1]octadien-2-one.[15]

When the spectrum of XIV was taken in concentrated sulfuric acid, a strong absorption band appeared at 3030 Å. ($\epsilon$ 13,000). This observation was in good agreement with the fact that conjugated aromatic ketones show a bathochromic shift of 300–600 Å. in concentrated sulfuric acid, and the extinction coefficient of this shifted maximum is very much exalted over the weak, indistinguishable band at 2400 Å.[16,17] Similar halochromic behavior has been observed in the case of all of the above mentioned aryl ketones.

With the establishment of the hydrogenolysis product of A and B as a hydrocarbon substituted in the 8-position by a chlorine atom, the structure of compound C must be either VIII or X.

Dipole moments were utilized for the final structure assignments.[18] From the chemical evidence, the isomeric pair of dichlorinated products must either be II and III or VI and VII. Calculated dipole moments for the first pair were 4.0 and 1.9 D., respectively, and for the second pair, 2.2 and 2.7 D., respectively. The observed values for A and B were 3.40 and 1.94 D. The dipole moments of the two isomers thus unequivocally demonstrated that the chlorination products were *exo*-4- and *endo*-4-*syn*-8-dichlordibenzobicyclo[3.2.1]octadiene, II and III, respectively.

Differential infrared analysis[19] established that II and III were found in the reaction mixture at 88% and 12%, respectively

Examination of models of the rearranged dichlorides suggested that the major isomer, II, should be the less stable of the two isomers. The models clearly indicate
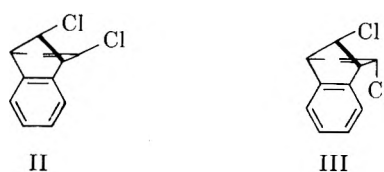
a large steric interaction between the diaxial chlorine atoms in II, which is relieved in III.

When II was dissolved in liquid sulfur dioxide and cresol at room temperature, all of the dichlorinated product that was recovered after column chromatography (55%) was shown to be isomer III.

These results made us suspect that the *endo* product III found in the chlorination was the result of an epimerization of the *exo* isomer. We found, however, that the *exo* isomer did not appear to rearrange under simulated reaction conditions or work-up conditions, even for extended time periods so it would appear that III is an initial reaction product. In addition, neither IV nor V is isomerized to II or III under reaction conditions.

The addition–rearrangement reaction is an heterolytic process, as indicated by the fact that the reaction proceeds in the dark and has no apparent induction period. Free-radical reactions in bridged bicyclic systems of this type have not led to rearrangement, although evidence for such rearrangements has been sought.[20–22]

The simplest mechanism which might be proposed involves addition of a chlorine cation to I to yield the classical carbonium ion XV which then rearranges to the more stable benzylic cation XVI. Coördination of XVI with chloride ion would give products II and III. The structure of the principal product (*syn–exo*) II is consistent with that observed in the addition of other ionic species to I[9,23] and also with the concept that XV and XVI represent resonance structures of the mesomeric cation XVII, but the formation of substantial amounts of III appears inconsistent with the latter assumption.[24] As indicated in the models described above for II and III, the *exo* isomer II has interference between the two diaxial chlorine atoms and its formation from XVI would obviously not be favored over that of III on steric grounds.



XV      XVI

XVII      XVIII

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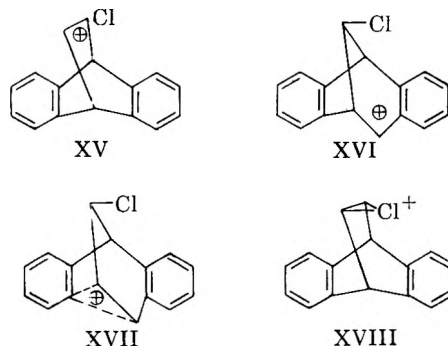
(12) R. P. Lucas and J. Jock, *Bull. soc. chim.*, [5] **2**, 327 (1935); **5**, 848 (1938).

(13) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(14) W. R. Vaughan, M. V. Andersen, Jr., and R. Q. Little, Jr., *J. Am. Chem. Soc.*, **76**, 1748, 4130 (1954).

(15) C. Bouboulis, Ph.D. thesis, University of Colorado, 1961.

(16) L. C. Anderson, *J. Am. Chem. Soc.*, **55**, 2096 (1933).

(17) L. C. Anderson and C. M. Gooding, *ibid.*, **57**, 999 (1935).

(18) D. D. Tanner and T. S. Gilman, unpublished work.

(19) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 3rd ed., The Macmillan Co., New York, N. Y., 1952, p. 632.

(20) S. J. Cristol and G. D. Brindell, *J. Am. Chem. Soc.*, **76**, 5699 (1954).

(21) J. A. Berson and W. M. Jones, *ibid.*, **78**, 6045 (1956).

(22) N. A. LeBel, *ibid.*, **82**, 623 (1960).

(23) F. Pwu, Ph.D. dissertation, University of Colorado, 1961.

(24) The *syn–exo-* configuration of the addenda in this bicyclooctane ring system is similar to the corresponding additions in bicycloheptane systems,[3–5] and to oxide-ring openings in bicycloheptane[25–27] and bicyclooctane systems.[11,28]

(25) H. M. Walborsky and D. F. Loncrini, *J. Am. Chem. Soc.*, **76**, 5396 (1954).

(26) H. Kwart and W. E. Vosburgh, *ibid.*, **76**, 5400 (1954).

(27) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960).

(28) H. Kwart and G. C. Gatos, *J. Am. Chem. Soc.*, **80**, 881 (1958).

On the other hand, stereoelectronic considerations may be invoked to rationalize the preferred formation of II from XVI. $p$–$\pi$–Overlap of the benzylic carbon atom with the benzene ring will be lost less rapidly if chloride ion coördinates from the axial (*exo*) position than from the equatorial (*endo*) position, so that the transition state for the former situation may be expected to be more stable than that for the latter. This argument is also consistent with the greater reactivity observed[9] for solvolysis reactions of *exo* (axial) substituents in these systems. Rearrangement of II to III may also proceed through XVI and is consistent with the solvolysis reactivities.

This mechanism does not rationalize the fact that only *syn*-8-chloro isomers are found—that is that only the bond *anti* to the entering chlorine cation migrates. This result could be accommodated by the assumption that XV is in fact not involved, but that donation of a chlorine cation by chlorine or by *t*-butyl hypochlorite gives the chloronium ion XVIII which opens with rearrangement directly to XVI. This latter explanation does not appear consistent with observations that the [3.2.1] ring system analogous to XVI may undergo rearrangements to the [2.2.2] systems analogous to XV under appropriate conditions, and again with stereochemical purity.[9,23] For the present, this problem remains unsettled.

## Experimental

**The Chlorination of 9,10-Dihydro-9,10-ethenoanthracene (I).—**The chlorination reactions of I are summarized as follows.

**Experiment 1.—**In a glass-stoppered flask, wrapped with aluminum foil to exclude light, was placed 2.002 g. (9.80 mmoles) of compound I,[2] m.p. 119.5–122°, dissolved in 30 ml. of dry carbon tetrachloride. The flask was cooled in an ice bath to 0°. To this mixture was added a chilled solution of 1.04 g. (0.014 mole) of chlorine in 20 ml. of dry carbon tetrachloride. The reaction mixture was stoppered and allowed to stand at room temperature for 41 hr. The solvent was removed by rotary evaporation, and 2.739 g. (101%) of a gummy, white crystalline product was obtained, m.p. 91–124°. The product was dissolved in benzene, and the benzene was removed by rotary evaporation. The product was dried under vacuum over phosphorus pentoxide and paraffin. An analysis for chlorine was obtained on this mixture.

*Anal.* Calcd. for $C_{16}H_{12}Cl_2$: Cl, 25.77. Found: Cl, 25.85.

The reaction mixture was subjected to infrared analysis and found to contain 12% of the *endo* dichloride III and 88% of the *exo* dichloride II.

**Experiment 2.—**To a continuously stirred solution of 1.361 g. (6.66 mmoles) of I in 25 ml. of dry carbon tetrachloride was added dropwise 18 ml. of dry carbon tetrachloride containing 630 mg. (8.88 mmoles) of chlorine. The solution was added in the dark over a period of 1 hr. at room temperature, and the solvent was removed by rotary evaporation. The dried reaction mixture was subjected to infrared analysis and found to contain 12% *endo* dichloride III and 88% of the *exo* dichloride II.

**Experiment 3.—**To a solution of 20 ml. of dry carbon tetrachloride containing 700 mg. (9.87 mmoles) of chlorine was added dropwise a solution of 1.352 g. (6.61 mmoles) of I dissolved in 45 ml. of dry carbon tetrachloride. The solution was added in the dark over a period of 1 hr. at room temperature, and the solvent was removed by rotary evaporation. The dried reaction mixture was subjected to infrared analysis and found to contain 12% *endo* dichloride III and 88% of the *exo* dichloride II.

**Experiment 4.—**To a solution of 344 mg. (1.68 mmoles) of I in 30 ml. of dry carbon tetrachloride was added 20 ml. of carbon tetrachloride containing 240 mg. (3.38 mmoles) of chlorine. The mixture was stoppered and allowed to stand in the dark for 13 days. The dried reaction products were subjected to infrared analysis, which showed the product composition to be 18% III and 82% II.

**Experiment 5.—**Experiment 4 was repeated, only the solvent was removed by rotary evaporation immediately after addition of the chlorine solution. The yellow color of chlorine had disappeared 13 min. after the addition of the chlorine solution, and all the solvent had been removed by the time 28 min. more had elapsed. Infrared analysis showed a product composition of 18% of III and 82% of II.

The discrepancy in the analytically determined product composition between experiments 1, 2, and 3 and experiments 4 and 5 may possibly be within experimental error. However, it must be noted that the reactions which yielded 12% *endo* dichloride (experiments 1, 2, and 3) were done under conditions where the temperature of the solution remained relatively constant, while the reactions yielding 18% *endo* product (experiments 4 and 5) were subjected to local heating due to the exothermic nature of the reaction.

**Isolation of II and III.—**A solution of 1.63 g. (8.0 mmoles) of I in 30 ml. of carbon tetrachloride was placed in a foil-wrapped flask. Then, 604 mg. (8.5 mmoles) of chlorine dissolved in 10 ml. of carbon tetrachloride was added. Evaporation of the solvent left 2.21 g. of material. Crystallization from 27 ml. of ethanol gave 1.77 g. (81%) of II, m.p. 122–128°. Purification by sublimation gave II, m.p. 128–129°.

*Anal.* Calcd. for $C_{16}H_{12}Cl_2$: C, 69.83; H, 4.40. Found: C, 69.77; H, 4.57.

The mother liquors were evaporated to dryness and absorbed on 20 ml. of activated alumina (Fisher). Elution with chloroform gave 120 mg. (5.5%) of III, m.p. 98–98.5°.

*Anal.* Calcd. for $C_{16}H_{12}Cl_2$: C, 69.83; H, 4.40. Found: C, 69.66; H, 4.65.

Both II and III gave precipitates of silver chloride within 5 min., when treated with silver nitrate in acetone.

**Infrared Analysis of the Products of Chlorination of I.—**The ratio of II and III in the chlorination of I was determined by differential quantitative infrared analysis, using a double-beam Perkin-Elmer Model 137 Infracord spectrophotometer. Potassium bromide optics were used to obtain the desired frequency range, 13–25 $\mu$. The *exo* isomer II had absorption peaks at 14.4, 15.7, 16.3, 16.6, 17.7, 18.3, 18.9, 20.7, and 22.8 $\mu$, and the *endo* isomer III had peaks at 14.6, 15.3, 16.3, 17.3, 17.7, 18.1, 19.2, 21.2, 22.3, and 23.3 $\mu$. Analytical results seem to be correct to ±3%.

**Hydrogenolysis of II and III.—**A mixture of 50 mg. of 10% palladium on barium sulfate catalyst in 18 ml. of ethanol and 2 ml. of 1.2 $N$ sodium hydroxide was pre-reduced with hydrogen at room temperature and atmospheric pressure. Then 100 mg. (0.363 mmole) of II was added and the flask shaken under an atmosphere of hydrogen for 24 hr. The catalyst was removed by filtration and water was added to precipitate the product. Recrystallization from aqueous ethanol gave 70 mg. (80%) of *syn*-8-chlorodibenzobicyclo[3.2.1]octadiene (VIII), m.p. 143.5–144.5°.

*Anal.* Calcd. for $C_{16}H_{13}Cl$: C, 79.53; H, 5.44. Found: C, 79.83; H, 5.61.

Similarly, 64 mg. of III was hydrogenated. The product was identical with the sample of VIII produced from II.

Attempts to remove the second chlorine atom by further hydrogenolysis over platinum led to saturation of one of the benzene rings without removal of the chlorine atom. Which ring was hydrogenated was not determined. Fifty milligrams of III was shaken under hydrogen with 30 mg. of Adam's platinum oxide catalyst in 14 ml. of ethanol containing 5 ml. of 5 $N$ hydrochloric acid for 24 hr. The product was precipitated with water and recrystallized from ethanol, m.p. 60–61°. A Beilstein test indicated the presence of chlorine in the product.

*Anal.* Calcd. for $C_{16}H_{19}Cl$: C, 77.87; H, 7.76. Found: C, 78.00; H, 7.49.

*syn*-8-Chlorodibenzobicyclo[3.2.1]octadien-*exo*-2-yl Acetate (XII).—To a stirred and cooled solution of 1.100 g. (5.39 mmoles) of ethenoanthracene, I, in 70 ml. of glacial acetic acid was added 1.00 g. of *t*-butyl hypochlorite (9.80 mmoles)[29] over the course of 30 min. After the addition of the hypochlorite, the reaction mixture was poured into an excess of water, and the precipitate which formed was filtered and dried over phosphorus pentoxide. The crude yield was 1.441 g. (89.5%) of an oily white gum. The product was dissolved in hot petroleum ether (b.p. 60–70°) and chromatographed on an alumina column. Three oily fractions were obtained by elution with 5% chloroform in carbon tetrachloride, 10% chloroform in carbon

(29) C. F. Irwin and G. F. Hennion, *J. Am. Chem. Soc.*, **63**, 858 (1941).

tetrachloride, and 100% chloroform, and weighed 500 mg., 675 mg. and 129 mg., respectively.

When fraction 1 was crystallized from absolute ethanol, it gave 193 mg. of a white crystalline compound, m.p. 135–148.5°; recrystallization gave 105 mg., m.p. 146.5–154.5°.

When fraction 2 was crystallized from absolute ethanol, there sesulted 390 mg. of white crystals, m.p. 150–153°. An analytical rample was taken from this product, and the recrystallized product melted at 157–158°.

*Anal.* Calcd. for $C_{18}H_{15}ClO_2$: C, 72.36; H, 5.06. Found: C, 72.31; H, 4.89.

When fraction 3 was recrystallized from absolute ethanol, it yielded 22 mg. of white crystals, m.p. 145–155°. Mixture melting points with fractions 1 and 2 were not depressed. Mixture melting points and solution infrared spectra of this compound showed it to be identical with the chloroacetate obtained from the acetolysis of II or III.[8]

*syn*-8-**Chlorodibenzobicyclo[3.2.1]octadien-*exo*-2-ol. (XIII).** —A slurry of 40 mg. of crushed lithium aluminum hydride in approximately 20 ml. of ether, which had been dried over sodium ribbon, was stirred while an ethereal solution of 134 mg. (0.448 mmole) of the combined fractions 1 and 2 above (compound XII) was slowly added. The reaction mixture was stirred at room temperature for 2.5 hr., and the excess lithium aluminum hydried was destroyed by the addition of water. The solution was decanted, the residual aluminum hydroxide was washed several times with ether, and the decantates were combined. The solvent was evaporated in an air stream and the residue was dride under vacuum over phosphorus pentoxide, leaving 112 mg. (97%) of white crystals, m.p. 111–122°. An infrared spectrum taken in carbon disulfide solution showed a strong hydroxyl peak at 2.80 μ and no acetate carbonyl absorption.

The product was recrystallized from absolute ethanol, yielding 35 mg. of white crystals, m.p. 130–134.5°. A second crop of crystals was taken, yield 13 mg., m.p. 127.5–136.5°. The crude yield was 42%. Crop 1 was recrystallized twice from absolute ethanol to give pure XIII, m.p. 137.5–138.5°.

*Anal* Calcd. for $C_{16}H_{13}ClO$: C, 74.78; H, 5.10. Found: C, 74.91; H, 5.03.

*syn*-8-**Chlorodibenzobicyclo[3.2.1]octadien-2-one (XIV).** —A mixture of 312 mg. (1.21 mmoles) of crude XIII (m.p. 120–135°). 40 ml. of benzene, 2 g. of potassium permanganate (12.7 mmoles), 20 ml. of *t*-butyl alcohol and 6 ml. of water was heated at 60° for 75 hr. with constant stirring. The excess potassium permanganate was destroyed by the addition of aqueous sodium bisulfite. The solution was dried under vacuum, 40 ml. of water was added, and the manganese dioxide precipitate was filtered and washed with water. The filter cake was extracted with hot chloroform, and the extract dried over sodium sulfate. The organic solvent was removed under vacuum, leaving 190 mg. of a white crystalline material, m.p. 106–112°. The product was dried over phos-

phorus pentoxide under vacuum, and the infrared spectrum showed no hydroxyl absorption and a strong carbonyl absorption at 5.88 μ.

Of the 190 mg. obtained, 72 mg. of the product was chromatographed on an alumina column. By dissolving in hot petroleum ether (b.p. 60–70°) and eluting with chloroform, a fraction weighing 66 mg. (60%), m.p. 114.7–116°, was obtained. Recrystallization from absolute ethanol gave *syn*-8-chlorodibenzobicyclo[3.2.1]octadien-2-one (XIV), m.p. 115.5–116.5°.

*Anal.* Calcd. for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35. Found: C, 75.47; H, 4.38.

**The Reduction of** *syn*-8-**Chlorodibenzobicyclo[3.2.1]octadien-2-one (XIV).** —A mixture of 110 mg. (0.432 mmole) of XIV, 5 g. of amalgamated zinc, 6 ml. of concentrated hydrochloric acid, 5 ml. of acetic acid, and 5 ml. of toluene was heated at reflux for 22 hr. During this time, three 5-ml. portions of concentrated hydrochloric acid were added. The reaction mixture was extracted three times with 30-ml. portions of benzene. The benzene extracts were washed with sodium carbonate solution, followed by several washings with water, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, leaving a thick, yellow oil. The product was chromatographed on an alumina column (25 g. of Merck Co., acid-washed alumina packed in petroleum ether, b.p. 60–70°) and was eluted with carbon tetrachloride. The crude yield was 73 mg., m.p. 110–143°. Recrystallization from absolute ethanol yielded a product weighing 32 mg., m.p. 142–144.5° (36%).

Mixture melting point showed no depression with the hydrogenolysis product of compound II, and the infrared spectrum was identical with that of product VIII.

**Isomerization of Dichloride II to III in Liquid Sulfur Dioxide.** —In a sealed Pyrex tube was placed 1 ml. of *o*-cresol, 398 mg. of II, and approximately 50 ml. of liquid sulfur dioxide. The mixture was allowed to stand for 4 hr. at 0° and then at room temperature for 10 hr. The sulfur dioxide was allowed to evaporate, and the solution was chromatographed on alumina by dissolving in petroleum ether (b.p. 60–70°) and eluting with carbon tetrachloride. Two fractions were obtained. The first was 220 mg. (55%) of a white crystalline product, m.p. 95–99°. After recrystallization from absolute ethanol, a melting point of 100–100.5° was obtained. The product had an infrared spectrum identical with that of III, and a mixture melting point with that compound showed no depression. A mixture melting point with II was depressed. The second fraction was an oil, 23 mg. (6%), which was not investigated.

# The Synthesis of 2-Acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-glucose[1]

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The synthesis of 2-acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-glucose, a product of degradation of a tetrasaccharide isolated from human milk and of various glycoproteins, is described, starting from D-galactose and D-glucosamine.

The structure of 2-acetamido-2-deoxy 3-O-(β-D-galactopyranosyl)-D-glucose (VI) has been assigned to a disaccharide of D-galactose and D-glucosamine, which has been isolated from the products resulting from the

degradation of oligosaccharides obtained from human milk.[3,4] This compound has also been found, together with 2-acetamido-2-deoxy-4-O-(β-D-galactopyranosyl)-D-glucose, in the controlled acid-hydrolyzate of blood group A substance,[5-7] in which it forms an essential

(1) Amino Sugars. XXXI. This is publication no. 327 of The Robert W. Lovett Memorial Unit for the Study of Crippling Disease, Harvard Medical School at the Massachusetts General Hospital, Boston 14, Mass. This investigation has been supported by research grants from the National Institutes of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service (A-3564-C-2), and the National Science Foundation (9-2312).

(2) On leave of absence from the Weizmann Institute, Rehovoth, Israel

(3) R. Kuhn, A. Gauhe, and H. H. Baer, *Chem. Ber.*, **87**, 289 (1954).

(4) R. Kuhn, H. H. Baer. and A. Gauhe, *ibid.*, **87**, 1553 (1954).

(5) R. H. Côté and W. T. J. Morgan, *Nature*, **178**, 1171 (1956).

(6) I. A. F. L. Cheese and W. T. J. Morgan, *ibid.*, **191**, 149 (1961).

(7) G. Schiffman, E. A. Kabat, and S. Leskowitz, *J. Am. Chem. Soc.*, **84**, 73 (1962).

I

+

II

→

III

→

IV. R = Ac
V. R = H

VI

Ac = COCH₃
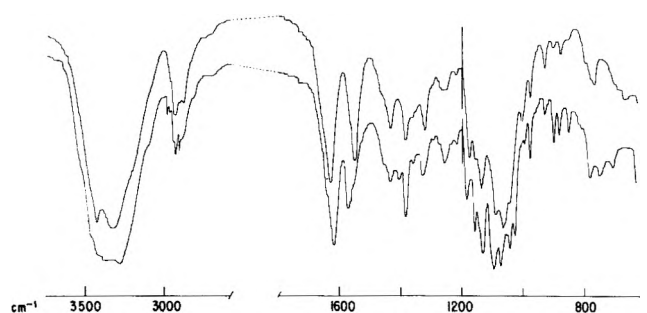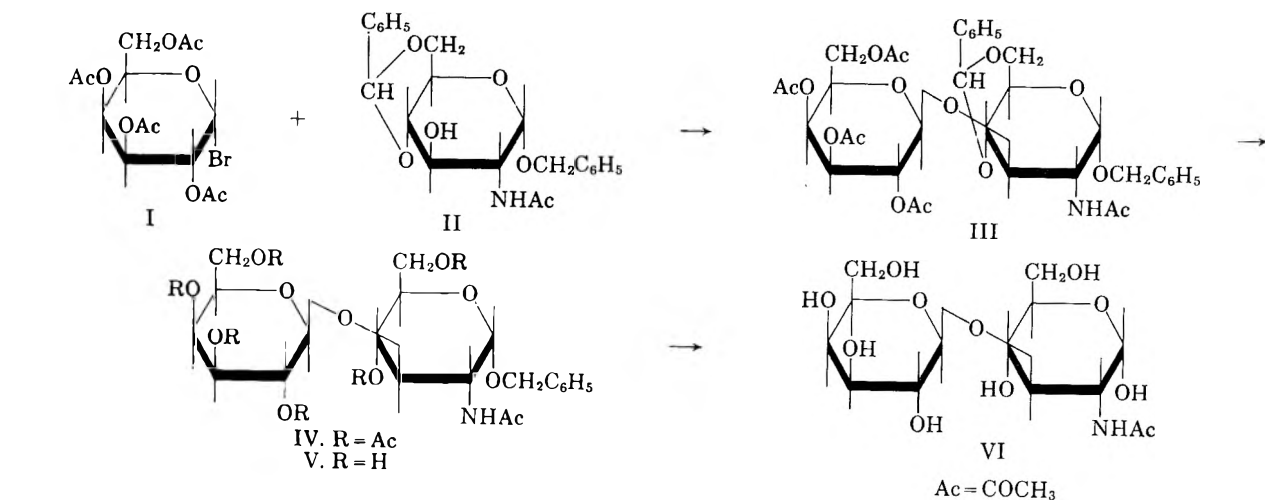


Fig. 1.—Infrared spectra of 2-acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-glucose measured immediately after preparation of compound (lower curve) and after compound had been stored six months in desiccator (upper curve). Both samples dried at 80°, over phosphorus pentoxide, under high vacuum, overnight; concentration 0.8 mg. in 200 mg. of potassium bromide.

part of the antigen. The disaccharide VI has been synthesized by an extract of bull testes[8] and by an enzymic extract of *L. bifidus var. pennsylvanicus*,[9] which also synthesizes the 4-isomer and 2-acetamido-2-deoxy-6-O-(β-D-galactopyranosyl)-D-glucose.

Both 2-acetamido-2-deoxy-4-O-(β-D-galactopyranosyl)-D-glucose[10,11] and the 6-isomer[12] have been chemically synthesized. In view of the major importance of the 3-isomer VI in the study of the chemical structure of glycoproteins, its chemical synthesis was investigated, and is reported in the present paper.

Condensation of tetra-O-acetyl-α-D-galactopyranosyl bromide (I)[13] with benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (II)[14] in a mixture of nitromethane and benzene in the presence of mercuric cyanide gave the crystalline disaccharide III in 53% yield after purification. The optical rotation, $[\alpha]_D$ +40°, was the expected one for the methyl α-D-glucoside of a β-linked disaccharide, and no α-linked disaccharide was observed.

Condensation of glycosyl halides with alcohols in the presence of mercuric cyanide was introduced by Zemplén and Gerecs,[15] who showed that, in benzene solution,

only the β-anomer was formed. Helferich and associates carried out a series of investigations, using nitromethane as solvent, establishing that the α-anomer was produced only when the acetyl halide was condensed with phenols under heating,[16,17] whereas alcohols or acetylated hexoses, at room temperature, gave only the β-anomer.[17,18] This course of the reaction has been recently confirmed in the condensation of tetra-O-acetyl-α-D-glucopyranosyl bromide and of (methyl tri-O-acetyl-α-D-glucopyranosyluronate) bromide with methyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside, in which only the β-linked disaccharides could be isolated.[19] Matsuda, however, using the same conditions, has reported the formation of α-linked disaccharides in preponderant yield when tetra-O-acetyl-α-D-glucopyranosyl bromide was condensed with 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose,[20] or with 2,3,-4,6-tetra-O-acetyl-α-D-glucopyranose.[21]

Hydrolysis of the benzylidene group of III, followed by acetylation, gave IV, which was saponified to V. Both reactions proceeded with excellent yields, and gave crystalline compounds. Catalytic hydrogenolysis of the benzyl group gave 2-acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-glucose (VI) in 77% yield. This product was identical to the "lacto-biose I" derived from human milk,[3,4] on the basis of melting point, optical rotation, infrared spectra, and paper chromatography. The infrared spectra observed presented some differences from those already reported.[9] Similar differences were found to be present in the infrared spectra of a sample kept for six months in a desiccator, despite the fact that melting point, mutarotation, and speed of migration in paper chromatography were unchanged (see spectra).

### Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro- or micro- (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A. R. grade and contained approxi-

(8) A. Alessandrini, E. Schmidt, F. Zilliken, and P. György, *J. Biol. Chem.*, **220**, 71 (1956).

(9) M. C. Glick, I. W. Chen, and F. Zilliken, *ibid.*, **237**, 981 (1962).

(10) Z. Yosizawa, *Tohoku J. Exp. Med.*, **52**, 145 (1950).

(11) R. Kuhn and W. Kirschenlohr, *Ann.*, **600**, 135 (1956).

(12) R. Kuhn, H. H. Baer, and A. Gauhe, *Chem. Ber.*, **88**, 1713 (1955).

(13) H. Ohle, W. Marecek, and W. Bourjau, *Ber.*, **62**, 833 (1929).

(14) R. Kuhn, H. H. Baer, and A. Seeliger, *Ann.*, **611**, 236 (1958).

(15) G. Zemplén and A. Gerecs, *Ber.*, **63**, 2720 (1930).

(16) B. Helferich and K. H. Jung, *Ann.*, **589**, 77 (1954).

(17) B. Helferich and A. Berger, *Chem. Ber.*, **90**, 2492 (1957).

(18) B. Helferich and K. Weis, *ibid.*, **89**, 314 (1956).

(19) R. W. Jeanloz and H. M. Flowers, *J. Am. Chem. Soc.*, **84**, 3030 (1962).

(20) K. Matsuda, *Nature*, **180**, 984 (1957); *J. Agr. Chem. Soc. Japan*, **33**, 714 (1959).

(21) K. Matsuda, *Chem. Ind.* (London), 1627 (1958).

mately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer, Model 237. Chromatograms were made with the flowing method using silica gel; "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950; 60–200 mesh) was used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluents was hexane, benzene, or dry chloroform, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be absorbed to weight of adsorbent was 1 to 50–100. The proportion of weight of substance in g. to volume of fraction of eluant in ml. was 1 to 100. The ratio of diameter to length of the column was 1 to 20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen. The microanalyses were done by Dr. M. Manser, Zürich, Switzerland, and Dr. S. M. Nagy, Cambridge, Mass.

**Benzyl 2-Acetamido-4,6-benzylidene-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside (III).—** A solution of 0.80 g. of benzyl 2-acetamido-4,6,O-benzylidene-2-deoxy-α-D-glucopyranoside[14] (II), 0.82 g. of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide (I),[13] and 0.56 g. of mercuric cyanide in a mixture of 50 ml. of nitromethane and 30 ml. of benzene was stirred at 40° for 24 hr. with exclusion of moisture. An additional quantity of II (0.40 g.) and mercuric cyanide (0.28 g.) was added and stirring continued for an additional 24 hr. at 40°. The solution was allowed to cool to room temperature, diluted with excess benzene, and washed several times with cold sodium bicarbonate solution and water, dried, and concentrated *in vacuo*. The residue (2.0 g.), dissolved in a mixture of benzene and ether (1:1), was chromatographed on silicic acid. A crystalline fraction was obtained by elution with a mixture of ether and ethyl acetate (9:1). On recrystallization from a mixture of acetone and ether, it gave 0.80 g. of needles (53%), m.p. 175–177°, [α]²⁰D +40° (in chloroform, c 1.43).

*Anal.* Calcd. for $C_{36}H_{41}NO_{15}$: C, 59.42; H, 5.68; N, 1.92. Found: C, 58.95; H, 6.03; N, 1.97.

**Benzyl 2-Acetamido-4,6-di-O-acetyl-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside (IV).—** A solution of 0.80 g. of III in 5 ml. of 60% acetic acid was heated on a steam bath for 15 min. The clear solution obtained was evaporated and the residue, after being dried by repeated azeotropic distillation with toluene, was acetylated with 2 ml. of acetic

anhydride and 2 ml. of pyridine at room temperature overnight. Evaporation of this solution and recrystallization of the residue from a mixture of acetone and ether afforded 0.65 g. of needles (82%), m.p. 173–175°. A further recrystallization from the same solvent mixture raised the m.p. to 175–176°, [α]²⁵D +45° (in chloroform, c 1.22).

*Anal.* Calcd. for $C_{33}H_{43}NO_{17}$: C, 54.61; H, 5.97. Found: C, 54.57; H, 6.14.

**Benzyl 2-Acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-glucopyranoside (V).—** Saponification of 0.30 g. of IV in 1 ml. of 2 N methanolic sodium methoxide solution gave, on cooling, 0.165 g. of needles (84%), m.p. 243–245°. The melting point remained unchanged on recrystallization from methanol, [α]²²D +101°( in 95% ethanol, c 1.03).

*Anal.* Calcd. for $C_{21}H_{31}NO_{11}$: C, 53.26; H, 6.59; N, 2.95. Found: C, 53.11; H, 6.76; N, 3.11.

**2-Acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-glucose (VI).—** A solution of 160 mg. of V in 5 ml. of 90% ethanol was hydrogenated catalytically with 10% palladium on charcoal, overnight, at room temperature, and atmospheric pressure. The residue, obtained after evaporation, was recrystallized from methanol. After filtration, it was dried for 48 hr. *in vacuo* over phosphorus pentoxide at 80°, giving 100 mg. (77%) of needles, melting at 193–194° dec., after sintering at 184°[22]; the product mutarotated from [α]²³D + 32° (0 min.) to +14.5° (after 24 hr.) (in water, c, 1.58).[23] The product migrated in descending chromatography, on paper Whatman no. 1, in the mixture of solvents *n*-butyl alcohol, ethanol, and water 10:1:2[24] with an $R_{glucose}$ 0.49.[22]

*Anal.* Calcd. for $C_{14}H_{25}NO_{15}$: C, 43.85; H, 6.57; N, 3.65. Found: C, 43.75; H, 6.52; N, 3.62.

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(22) The natural product supplied by Prof. R. Kuhn was found to melt, under our conditions, at 193–194° after sintering at 186°, and to have an $R_{glucose}$ 0.49 on paper chromatography in the system described.

(23) Kuhn, Gauhe, and Baer[4] reported a mutarotation from 32.0° (0 min.) to +14.0° (at equilibrium) (in water, c 2).

(24) R. G. Spiro, *J. Biol. Chem.*, **237**, 646 (1962).

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# A Reimer–Tiemann Reaction with 6-Trichloromethylpurine[1]

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Phenol undergoes C-acylation at the *para* position with 6-trichloromethylpurine (I) under mild, basic conditions to yield purin-6-yl 4-hydroxyphenyl ketone (III). With *p*-cresol, acylation proceeds at the *ortho* position to yield purin-6-yl 2-hydroxy-5-methylphenyl ketone (VII). An uncharged, reactive intermediate is postulated to account for these and other acylation reactions of I.

In the course of an investigation of the chemical reactivity of 6-trichloromethylpurine (I),[3] it was found that reaction of I with sodium phenoxide in methanol did not lead to the expected 6-(triphenoxymethyl)-purine. Instead, an unstable product, II, was obtained, which, upon mild treatment with aqueous acid, gave rise to a *yellow* ketone, $C_{12}H_8O_2N_4$, III. The isolation

of II proved to be difficult; III could be obtained in 79% yield, directly from the reaction mixture of I and sodium phenoxide, by treatment with dilute, aqueous hydrochloric acid.

Oxidative degradation of III by the use of hydrogen peroxide in acetic or trifluoroacetic acid solution gave rise to hypoxanthine (IV); in sodium hydroxide solution, it gave rise to purinoic acid, V.[4] A boiling solution of sodium hydroxide had no effect on III, which means, therefore, that it was not a phenyl ester of purinoic acid. Finally, a solution of ferric chloride gave a blue color reaction with III suggesting the

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(3) S. Cohen, E. Thom, and A. Bendich, *J. Org. Chem.*, **27**, 3545 (1962); proceedings of the 141st National Meeting of the American Chemical Society, Washington, D. C., March 21–29, 1962, abstract, page 23-N.

(4) The term "purinoic" has been proposed by the authors in an earlier publication [S. Cohen, E. Thom, and A. Bendich, *Biochem.*, **2**, 176 (1963)] to replace the less convenient purine-6-carboxylic.
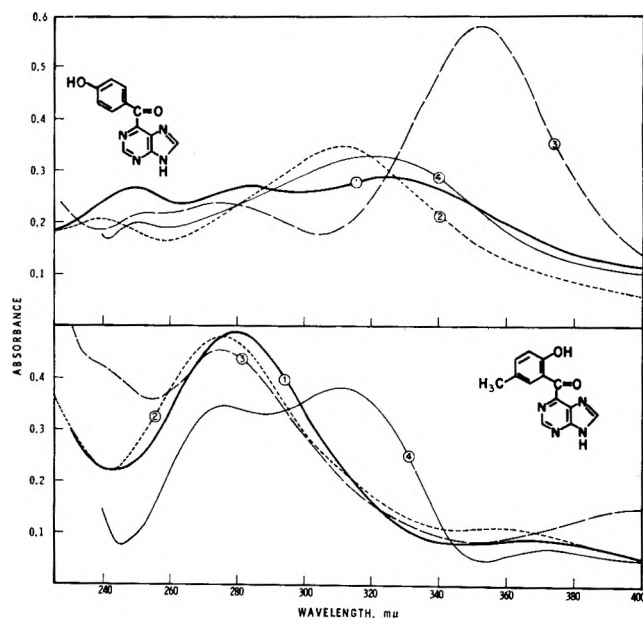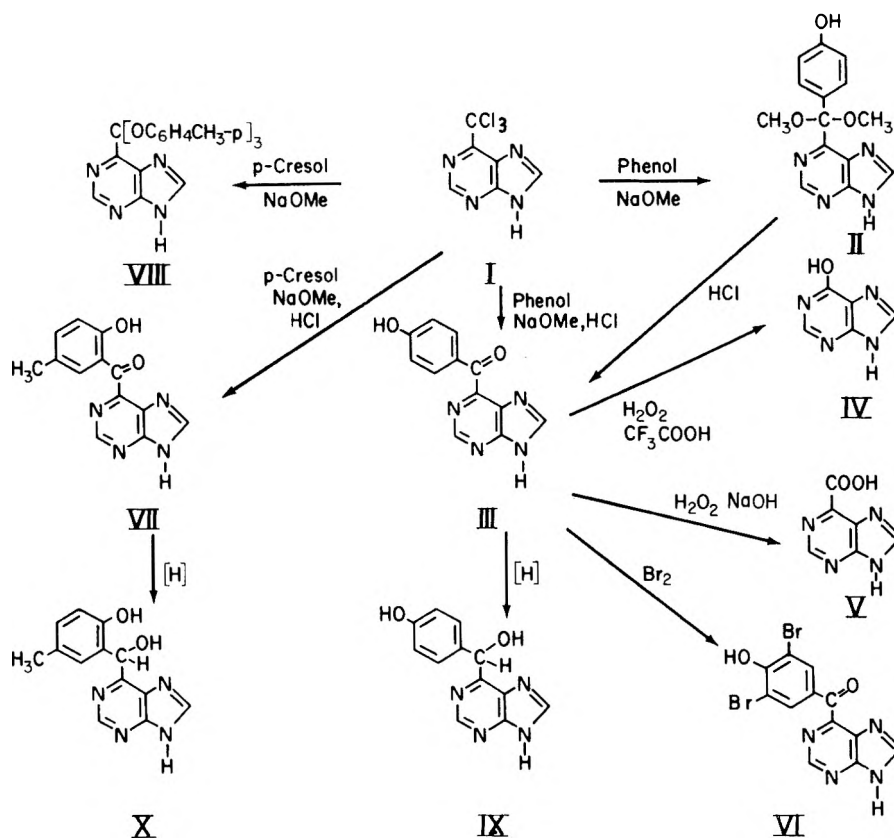
Fig. 1.—Ultraviolet absorption spectra of purin-6-yl 4-hydroxyphenyl ketone and purin-6-yl 2-hydroxy-5-methylphenyl ketone in (1) 1 $N$ HCl; (2) 0.1 $M$ phosphate buffer, pH 6.2; (3) 1 $N$ NaOH; (4) chloroform. 1, 2, and 3 are equimolar, 4 arbitrary concentration.

presence of a phenolic grouping. This was also indicated by the action of bromine which gave the dibromo derivative (VI). In view of these observations, it was concluded that III has the structure of a purin-6-yl hydroxyphenyl ketone, the hydroxyl group being either *ortho* or *para* to the purinyl residue.

Reaction of I with *p*-cresol under analogous conditions gave rise to a yellow ketone, $C_{13}H_{10}O_2N_4$, VII, which differed markedly from III in its ultraviolet spectral properties (Table I, Fig. 1) and its greater solubility in

organic solvents. Since the C-alkylation of *p*-cresol with chloroform under the conditions of the Reimer–Tiemann[5] reaction proceeds simultaneously at both the *para* and *ortho* positions to yield compounds of type (a) and (b) (R = H), VII may have either structure
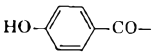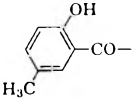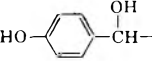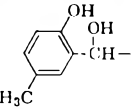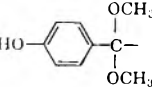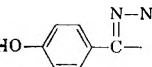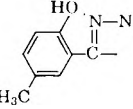


(a) or (b) (R = purin-6-yl). However, the presence of a strong O—H stretching frequency in the infrared spectrum of VII, its color reaction with ferric chloride and its behavior on hydrogenation (see below) indicate structure (a) for this compound. Indeed, steric factors should not favor the formation of (b) which, in the case of chloroform, was obtained in low yield only.[6] A minor product of the reaction of I with *p*-cresol was 6-[tri(*p*-methylphenoxy)methyl]purine, VIII.

The ultraviolet spectral differences between III and VII can, therefore, be ascribed to a difference in the position of the hydroxyl group. Accordingly, in III the hydroxyl group should be *para* to the purinoyl residue. The ultraviolet absorption spectra of these two compounds are consistent with their assigned structures. In III, near coplanarity of the two ring systems and the cumulative effect of conjugated double bonds would be expected to have a pronounced effect on both the position and molar extinction of the maximum ab-

(5) For a comprehensive review of this reaction, see H. Wynberg, *Chem. Rev.*, **60**, 169 (1960).

(6) K. Von Auwers and G. Kiel, *Ber.*, **36**, 1861 (1903).

## TABLE I
### Ultraviolet Spectral Properties of 6-Substituted Purines

| Substituent | $\lambda_{max}$, m$\mu$ ($A_M \times 10^{-3}$) | | |
|---|---|---|---|
| | 1 N HCl | pH 6.2[a] | 1 N NaOH |
| HO—C₆H₄—CO— | 325 (11.05) 285 (sh) (10.45) 248 (10.45) | 310 (13.41) 240 (7.50) | 352.5 (22.85) 275 (9.48) 250 (sh) (8.95) |
| (2-OH, 5-CH₃ phenyl)—CO— | 279 (11.94) | 276 (11.84) | 275.5 (10.75) 240–245 (sh) (9.82–9.34) |
| HO—C₆H₄—CH(OH)— | 264.5 (8.35) | 268 (10.57) | 278 (10.93) 240 (9.50) |
| (2-OH, 5-CH₃ phenyl)—CH(OH)— | 266 (8.83) | 268 (9.72) | 310 (sh) (3.69) 276 (9.28) 240 (sh) (8.15) |
| HO—C₆H₄—C(OCH₃)₂— | 264 (11.75) | 273 (12.02) | 280 (11.30) |
| HO—C₆H₄—C(=N—NH₂)— | 278 (9.18) | 316 (10.16) 277 (11.15) | 304 (12.60) 282 (sh) (11.85) |
| (2-OH, 5-CH₃ phenyl)—C(=N—NH₂)— | 360 (2.92) 266 (10.82) | 318 (12.07) 277 (11.20) | 280 (11.50) |
| [H₃C—C₆H₄—O]₃C— | 271 (9.93) | 276 (12.57) | 278 (9.50) |

[a] 0.1 M phosphate buffer.

sorbance. For the neutral species in water solution, $\lambda_{max}$ is 310.5 and 240 m$\mu$ compared to 267 for purine-6-carboxaldehyde,[7] 280 m$\mu$ for purinoic acid,[8] 246 m$\mu$ for 4-hydroxybenzoic acid, and 248 and 289 m$\mu$ for 4-hydroxybenzophenone.[9] This effect is more noticeable in base ($\lambda_{max}$, 325.5 m$\mu$; $A_M$ 22,850), where loss of a proton would result in increased $n \rightarrow \pi$ transition in the conjugated system.

In VII, presence of the hydroxyl group at the *ortho* position is expected to hinder coplanarity of the two ring systems.[10] The two chromophores absorb almost independently of each other and the resulting ultraviolet spectrum is a mixture of their respective spectra.[11] In water solution, the neutral species exhibits a single maximum at 276 m$\mu$. In nonpolar solvents, however, intramolecular hydrogen bonding between the hydroxyl group and the carbonyl oxygen may become more effective than in hydroxylic solvents. Such a bond implies coplanarity of the carbonyl group and the phenyl ring.

The spectrum of VII in chloroform solution exhibits two peaks, at 312 and 277 m$\mu$. It is interesting to compare these values to the corresponding ones for salicylaldehyde (258 and 331 m$\mu$), salicylic acid (307 m$\mu$), 2-hydroxybenzophenone (342 and 251 m$\mu$),[9] and purine (263 m$\mu$). The spectrum of III in chloroform is only slightly different from the one measured in aqueous solution.

Catalytic hydrogenation of III and VII in aqueous base and in presence of palladium on carbon proceeded slowly and stopped completely when about 1 mole of hydrogen was consumed per mole of ketone. The resulting carbinols, IX and X, retained their phenolic function as shown by the color test with ferric chloride and, in contradistinction to the parent ketones, displayed similar ultraviolet absorption spectra (Table I).

The mild conditions required for the acylation of phenols with I contrast sharply with the more drastic conditions required for chloroform in the Reimer–Tiemann reaction or for carbon dioxide in the Kolbe synthesis[12] of hydroxybenzoic acids. The same ease characterizes the reaction of I with alkoxide to yield ortho ester[3] or with amines to yield the corresponding N-purinoyl derivatives or, in case of aniline, N,N'-diphenylpurinylamidine.[13] In the closely related reactions with chloroform, there is strong evidence that di-

(7) A. Giner-Sorolla, I. Zimmerman, and A. Bendich, *J. Am. Chem. Soc.* **81**, 2515 (1959).

(8) L. B. McKay and G. H. Hitchings, *ibid.*, **78**, 3511 (1956).

(9) J. VanAllan and J. F. Tinker, *J. Org. Chem.*, **19**, 1243 (1954); data are for spectrum in ethanol.

(10) E. A. Braude, F. Sondheimer, and W. F. Forbes, *Nature*, **173**, 117 (1954).

(11) The effect of restricted rotation on coplanarity and the ultraviolet spectral properties of the hindered compounds are reviewed and discussed by (a) A. E. Gillam and E. S. Stern in "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," 2nd ed., Edward Arnold Ltd., London, 1957, p. 266; (b) E. A. Braude and E. S. Weight in W. Klyne's "Progress in Stereochemistry," Vol. 1, Academic Press, Inc., New York, N. Y., 1954.

(12) H. Kolbe, *J. prakt. Chem.*, **10**, 95 (1874).

(13) S. Cohen, E. Thom, and A. Bendich, *Biochem.*, **2**, 176 (1963).

chlorocarbene is the reactive intermediate involved.[14] Valency requirements, however, preclude formation of a carbene derivative from I. In an earlier study[13] on the acylation of amines by I, we advanced the view that the anion derived from I ($pK_a$, 7.93) may lose chloride far more rapidly than the neutral compound, giving rise to an uncharged, highly reactive intermediate, in which charge separation by resonance may con-



tribute slightly to the stability of the system. That such an intermediate may be involved in the various acylation reactions of I is supported by its close structural and electronic relation to the reactive ketene acetals.[15]
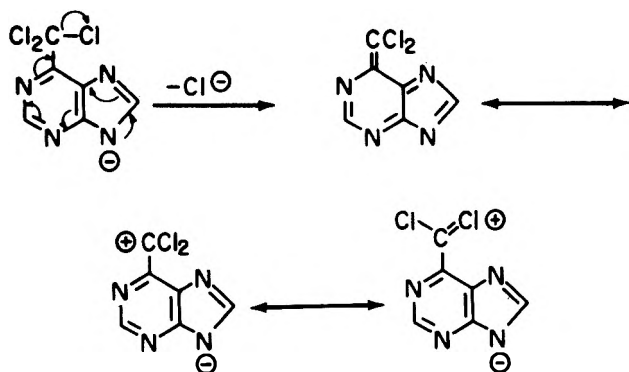
## Experimental

Melting points were determined with a Thomas–Hoover apparatus. The $R_f$ values are for ascending chromatograms on Whatman no. 1 paper, developed with the system $n$-butyl alcohol–formic acid–water (77:10:13 v./v.). The spectrophotometric measurements were made with a Cary Model 11 recording spectrophotometer at room temperature using 1-cm. quartz cells and a Perkin-Elmer Infracord spectrophotometer.

**Reaction of 6-Trichloromethylpurine (I) with Sodium Phenoxide.**—(a) A solution of phenol (0.5 g.) and I (1.2 g.) in 2 $M$ methanolic sodium methoxide (10 ml.) was refluxed for 3 hr., then brought to dryness under partial pressure. The residue was redissolved in water (10 ml.) and the pH of the solution was adjusted to 5 by the addition of glacial acetic acid. A gummy precipitate was formed (0.5 g.). It was separated by decantation, dissolved in boiling acetone, and the solution was treated with charcoal, filtered, and brought to dryness. The residue was redissolved in boiling acetone. Upon addition of anhydrous ether, the hydrochloride of purin-6-yl 4-hydroxyphenyl ketone dimethyl ketal (II) precipitated; m.p. 230–235°, $R_f$ 0.75. A solution of this compound in methanol gave a deep blue-green coloration with a trace of ferric chloride.

*Anal.* Calcd. for $C_{14}H_{15}O_3N_4Cl$: C, 52.1; H, 4.7; N, 17.3. Found: C, 52.5; H, 5.2; N, 17.3.

(b) A solution of I (2.4 g.) and phenol (3.8 g.) in methanolic 2 $M$ sodium methoxide (40 ml.) was refluxed for 2 hr., then brought to dryness under partial pressure. The residue was dissolved in water (300 ml.) and the solution was acidified with hydrochloric acid and warmed, with stirring, to 50–60°. Purin-6-yl 4-hydroxyphenyl ketone (III), 1.9 g. (79%) was obtained as a yellow precipitate; m.p. 235–240° dec., $R_f$ 0.75. A faint blue coloration was observed when a suspension of this compound in methanol was treated with a trace of ferric chloride.

*Anal.* Calcd. for $C_{12}H_8O_2N_4$: C, 60.0; H, 3.3; N. 23.3. Found: C, 60.2; H, 3.5; N, 23.1.

Infrared spectrum (KBr pellet): 3620, 3300, 3250, 3050, 2900, 2800, 2700, 1670, 1625, 1600, 1530, 1500, 1470, 1430, 1410, 1380, 1345, 1305, 1280, 1260, 1230, 1175, 1215, 1060, 1040, 970, 950, 910, 853, 822, 810, 775, 702, 683 cm.$^{-1}$.

The hydrazone of III was prepared by refluxing the compound for 2 hr. in excess anhydrous hydrazine, evaporation under reduced pressure, and recrystallization of the residue from aqueous ethanol; m.p. 285° dec.

(14) J. Hine and A. M. Dowell, *J. Am. Chem. Soc.*, **76**, 2688 (1954).
(15) S. M. McElvain, *Chem. Rev.*, **45**, 453 (1949).

*Anal.* Calcd. for $C_{12}H_{10}ON_6$: C, 56.6; H, 3.9; N, 33.1. Found: C, 56.8; H, 4.1; N, 33.5.

**Oxidation of III.**—(a) A solution of III (100 mg.) in 0.2 $N$ sodium hydroxide (10 ml.) was treated with 30% hydrogen peroxide solution (2 ml.). The resulting yellow solution lost its color completely after 4 hr. at room temperature. Acidification with hydrochloric acid caused precipitation of purinoic acid (V) (50 mg., 73%); m.p. and m.m.p. with an authentic sample,[8] 200–202° with decarboxylation; $\lambda_{max}$ 280 m$\mu$ (in water), $R_f$ 0.27.

A paper chromatogram of a sample of the original oxidation mixture did not reveal the presence of any additional ultraviolet-absorbing product.

(b) A solution of III (100 mg.) in trifluoroacetic acid (10 ml.) was treated with 30% hydrogen peroxide solution (2 ml.). After 12 hr. at room temperature, the yellow color of the solution was almost discharged. The solvents were removed under reduced pressure, the residue was treated with water, and the resulting solution was evaporated to dryness. The gummy residue was then refluxed with acetone and the insoluble material (50 mg., 89%) separated by filtration. This was shown to be hypoxanthine (IV) by its characteristic ultraviolet absorption spectrum, $R_f$ value on paper chromatograms, and its decomposition behavior on heating. A sample of the original oxidation mixture, subjected to paper chromatography, did not reveal the presence of any ultraviolet absorbing product in addition to hypoxanthine.

(c) A suspension of III (0.5 g.) in glacial acetic acid (10 ml.) was treated with 30% hydrogen peroxide (10 ml.) and the mixture was stirred at room temperature until III was almost dissolved (3 days). The solution was filtered from some unreacted material and brought to dryness under reduced pressure. The residue was taken up three times in ethanol and dried, and was finally recrystallized from excess cold aqueous ethanol to yield hypoxanthine (IV) (0.1 g., 35%) identified as stated above.

**Catalytic Hydrogenation of III.**—A solution of III (0.6 g.) in 5% aqueous ammonia (10 ml.) containing 5% palladium on carbon (0.1 g.) was shaken for 4 hr. under hydrogen at atmospheric pressure and room temperature. When about 55 ml. of hydrogen was absorbed, the solution was filtered and acidified with glacial acetic acid. (Purin-6-yl)(4-hydroxyphenyl)carbinol (IX) (0.4 g., 66%) crystallized and was purified by recrystallization from hot ethanol; m.p., 199–200°, $R_f$ 0.61.

*Anal.* Calcd. for $C_{12}H_{10}O_2N_4$: C, 59.5; H, 4.1; N, 23.1. Found: C, 59.1; H, 5.0; N, 23.0.

**Bromination of III.**—A suspension of III (0.5 g.) in glacial acetic acid (10 ml.) was stirred and treated with bromine (*ca.* 0.2 ml.) at room temperature. The mixture was further stirred for 2 hr., the precipitate (0.5 g., 61%) was separated by filtration, washed with excess water, ethanol, and ether, and dried in air; m.p. above 320°.

*Anal.* Calcd. for $C_{12}H_6O_2N_4Br_2$: C, 36.2; H, 1.5; N, 14.1; Br, 40.2. Found: C, 36.8; H, 1.9; N, 14.5; Br, 37.6.

**Reaction of I with $p$-Cresol.**—(a) A solution of I (2.4 g.) and $p$-cresol (3.5 g.) in methanolic 2 $M$ sodium methoxide (25 ml.) was refluxed for 2 hr., then brought to dryness under reduced pressure. The residue was taken up in water (50 ml.) and the solution acidified with hydrochloric acid. The resulting gummy precipitate was broken by stirring and warming the mixture. Purin-6-yl 2-hydroxy-5-methylphenyl ketone (VII) (1 g., 39%) was obtained as an orange precipitate, and was further purified by recrystallization from boiling methanol; m.p., 280–281° dec., $R_f$ 0.84. A solution of the ketone VII in methanol gave a deep purple coloration with a trace of ferric chloride.

*Anal.* Calcd. for $C_{13}H_{10}O_2N_4$: C, 61.4; H, 3.9; N, 22.1. Found: C, 61.4; H, 4.1; N, 22.1.

Infrared spectrum (KBr pellet): 3620, 3200, 3120, 3030, 2930, 2890, 1750, 1650, 1610, 1600, 1570, 1495, 1470, 1420, 1400, 1380, 1345, 1330, 1310, 1280, 1250, 1220, 1170, 1155, 1140, 955, 925, 885, 830, 800, 790, 760, 700 cm.$^{-1}$.

The hydrazone of VII was prepared as described for III. It was recrystallized from aqueous ethanol; m.p., 239–240° dec.

*Anal.* Calcd. for $C_{13}H_{12}ON_6 \cdot 2H_2O$: C, 51.3; H, 5.5; N, 27.6. Found: C, 51.2; H, 5.3; N, 28.5.

(b) The reaction of I (2.4 g.) and $p$-cresol (3.5 g.) in 2 $M$ methanolic sodium methoxide (25 ml.) was carried out as described (a). The gum was separated by decantation and taken up in hot methanol (100 ml.). Upon cooling, the methanolic solution deposited orange crystals, VII (0.5 g. 20%); the methanolic mother liquor was concentrated to a small volume, treated with charcoal, filtered, and diluted with water to yield

0.2 g. (4%) of a white substance believed to be 6-[tri(4-methylphenoxy)methyl]purine (VIII); m.p. 214–215° dec., $R_f$ 0.92.

*Anal.* Calcd. for $C_{27}H_{24}O_3N_4$: C, 71.4; H, 5.3; N, 12.7. Found: C, 71.9; H, 5.5; N, 12.2.

Compound VIII gave no color reaction with ferric chloride and could not be converted into VII by treatment with 1 N hydrochloric acid for 30 min. at 60–70°.

**Catalytic Reduction of VII.**—A solution of VII (0.55 g.) in 5% aqueous ammonia (50 ml.) containing 5% palladium on carbon (50 mg.) was shaken for 4 hr. under hydrogen at atmospheric pressure and room temperature. The total volume of hydrogen absorbed was about 62 ml. The solution was filtered and evaporated to dryness under reduced pressure. The residue (0.5 g., 91%) was recrystallized from methanol to yield pure (purin-6-yl)(2-hydroxy-5-methylphenyl)carbinol (X); m.p. 233–234° dec., $R_f$ 0.70. The carbinol gave an intense blue coloration with a trace of ferric chloride in methanol.

*Anal.* Calcd. for $C_{13}H_{12}O_2N_4$: C, 60.9; H, 4.7; N, 21.9. Found: C, 60.8; H, 5.2; N, 21.8.

# Notes

## Preparation of 4,5-Dihydroöxepine and 1,2-Divinylethylene Oxide

R. A. BRAUN

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In recent years several examples of unsaturated derivatives of seven-membered heterocyclic systems have been reported[1-6] and have been of interest because of the possibility of planarity and aromatic stability. We wish to report a three-step synthesis of the new compounds, 4,5-dihydroöxepine (III) and 1,2-divinylethylene oxide (3-epoxy-1,5-hexadiene) (IV), as well as a new example of valence isomerism of a strained ring compound.[7] 1,5-Hexadiene-3,4-diol (I) is conveniently prepared by the bimolecular reduction of acrolein through the influence of a zinc–copper couple. *sym*-divinylethylene carbonate (II) was obtained in high yield from the reaction of (I) with diethyl carbonate using potassium carbonate as catalyst.
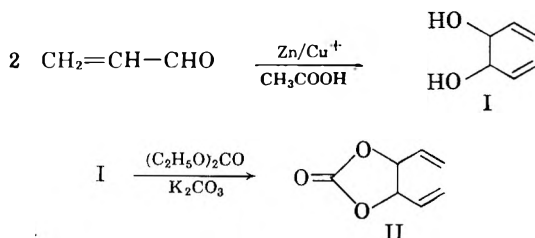


The lithium chloride-catalyzed pyrolysis of II at 200° was expected to give one or both isomers of 1,2-divinylethylene oxide. The constant boiling pyrolysate was separated into two fractions by preparative scale vapor phase chromatography.

The first fraction was shown to be one of two steric forms of 1,2-divinylethylene oxide (IV) and, on the basis of known relative stabilities of *cis*- and *trans*-divinylcyclopropanes,[8,9] we believe the *trans* form was isolated. The other fraction was identified as 4,5-dihydroöxepine (III) and presumably resulted from the Cope rearrangement of the less stable *cis* isomer 1,2-divinylethylene oxide.

The infrared, near-infrared, ultraviolet, and nuclear magnetic resonance spectra of III are consistent with the structure assigned. Hydrogenation of 4,5-dihydroöxepine resulted in the uptake of two moles of hydrogen, and reaction of (III) with aqueous acetic acid and 2,4-dinitrophenylhydrazine reagent results in the formation of the corresponding hydrazine derivative of 1-cyclopentene carboxaldehyde (V).
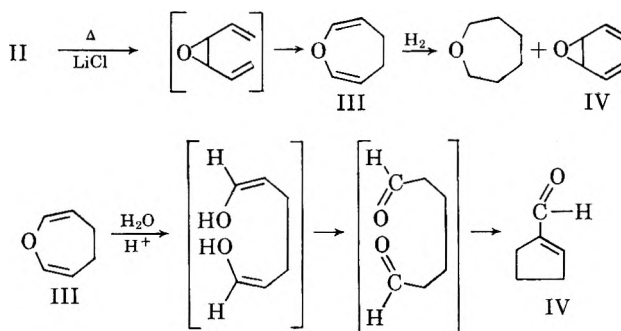


1-Cyclopentene carboxaldehyde presumably results from the acid-catalyzed hydrolysis of III to adipaldehyde which readily undergoes an internal Aldol condensation to give V.[10]

### Experimental

**1,5-Hexadiene-3,4-diol (I).**—Compound I is obtained by the bimolecular reduction of acrolein with zinc–copper couple and acetic acid using the method described previously for the reduction of crotonaldehyde.[11] Compound I is a colorless liquid, b.p. 55° (0.2 mm.), $n^{25}D$ 1.4739, $d^{25}_4$ 1.0097, which has been prepared previously only in 20–30% yields.[12] The yield can be improved to above 90% by using an ether such as tetrahydrofuran or dioxane as solvent instead of water.

(1) J. Meinwald and H. Nazaki, *J. Am. Chem. Soc.*, **80**, 3132 (1958).

(2) E. E. Schweizer and W. E. Parham, *ibid.*, **82**, 4085 (1960).

(3) J. Meinwald, D. W. Dicker, and N. Danieli, *ibid.*, **82**, 4087 (1960).

(4) S. Olsen and R. Bredoch, *Chem. Ber.*, **91**, 1589 (1958).

(5) K. Dimroth and G. Pohl, *Angew. Chem.*, **73**, 436 (1961).

(6) M. J. Jorgenson, *J. Org. Chem.*, **27**, 3224 (1962).

(7) W. Von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(8) E. Vogel, *Ann.*, **615**, 1 (1958).

(9) E. Vogel, *Angew. Chem.*, **1**, 53 (International Edition) (1962).

(10) E. Urion, *Ann. Chem.*, **1**, 5 (1934).

(11) W. G. Young, L. Levanas, and Z. Jasaitis, *J. Am. Chem. Soc.*, **58**, 2274 (1936).

(12) (a) M. Wiemann, *Compt. rend.*, **198**, 2263 (1934); (b) E. H. Farmer, *et. al.*, *J. Chem. Soc.*, 2946 (1927).

sym-Divinylethylene Carbonate (II).—A mixture of 57 g. (0.5 mole) of 1,5-hexadiene-3,4-diol, 71 g. (0.6 mole) of diethyl carbonate and 0.2 g. of anhydrous potassium carbonate was slowly heated to 110°. At this temperature reaction occurred and ethyl alcohol was distilled from the reaction mixture through a packed column. After 1 hr. the theoretical amount of ethyl alcohol was recovered. The residue was filtered and fractionated to give 51.8 g. (74%) of compound IV, b.p. 64° (0.2 mm.), $n^{25}$D 1.4598, $d^{25}_4$ 1.0650. The infrared spectrum is consistent with the proposed structure.

*Anal.* Calcd. for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.27; H, 5.94.

Compound IV does not have to be isolated before proceeding to the pyrolysis step.

**Pyrolysis of *sym*-Divinylethylene Carbonate, 1,2-Divinylethylene Oxide, and 2,3-Dihydroöxepine.**—A slurry of *sym*-divinylethylene carbonate (140 g., 1.0 mole) and 5.0 g. of lithium chloride powder[13] was heated slowly to 200–210°, and the distillate was collected in a Dry Ice trap. The distillate was washed twice with cold water and dried over magnesium sulfate to give 49.7 g. of crude product. Distillation through a 20-in., helices-packed column gave a constant boiling fraction, b.p. 108° (760 mm.), with a refractive index ranging from $n^{25}$D 1.4541 to 1.4561. A 10.7 g. sample of the distilled product was separated into two fractions by vapor phase chromatography using a 6-ft. column with 3-methyl-3-nitro-1,5-dicyanopentane on firebrick as the stationary phase. The first fraction (retention time, 12 min., column temp., 90°; flow rate, 500 ml./min.) (3.3 g.) was 4,5-dihydroöxepine (I); and the second fraction (retention time, 18 min., (6.1 g.) was 1,2-divinylethylene oxide (II).

**4,5-Dihydroöxepine.**—B.p. 108° (760 mm.), $n^{25}$D 1.4632. The infrared spectrum was consistent with the proposed structure: 3055 cm.$^{-1}$ (CH stretching of *cis*-CH=CH—), 2940 and 2860 cm.$^{-1}$ (CH stretching of $CH_2$), 1650 cm.$^{-1}$ (nonconjugated C=C), 1448 cm.$^{-1}$ ($CH_2$ deformation frequency of —CH=C—$CH_2$), 1238 cm.$^{-1}$ (*cis*-C=C adjacent to oxygen). The near-infrared spectrum showed that terminal epoxide or terminal methylene groups were absent and the ultraviolet spectrum indicated the absence of conjugated unsaturation. The proton resonance indicated three different protons in the expected ratio of 2:1:1; peaks occurring at 7.3 $\tau$, assigned to the hydrogens at the 4 and 5 position; 5.3 $\tau$, hydrogens at the 3 and 6 positions; 3.42 $\tau$, hydrogens at 2 and 7 positions (split).[14]

*Anal.* Calcd. for $C_6H_8O$: C, 74.97; H, 8.38; O, 16.65; mol. wt., 96. Found: C, 74.89; H, 8.26; O, 17.12 (Unterzaucher method); mol. wt. (f.p. benzene), 100.

Hydrogenation of 4,5-dihydroöxepine over platinum oxide resulted in a 101% uptake of 2 moles of hydrogen. The 4,5-dihydroöxepine was hydrolyzed by warming with aqueous acetic acid for 10 min. to give a solution which reduced ammoniacal silver nitrate (suggesting a rearrangement to an aldehyde). Freshly prepared 2,4-dinitrophenylhydrazine reagent was added to the hydrolyzed 4,5-dihydroöxepine. The crude derivative was purified by chromatographing it on neutral alumina and eluting with chloroform. The pure derivative was brilliant red, m.p. 215–216° (lit.,[15] m.p. for 2,4-DNP of 1-cyclopentene carboxaldehyde, 215–216°).

*Anal.* Calcd. for $C_{12}H_{12}N_4O_4$: N, 20.28. Found: N, 20.18.

*sym*-Divinylethylene Oxide.—B.p. 108° (760 mm.), m.p. 35°, $n^{25}$D 1.4474. The infrared spectrum was consistent with the proposed structure: 3125 cm.$^{-1}$ (C—H), 3030 cm.$^{-1}$ (saturated C—H with low frequency due to strained ring configuration), 1887 cm.$^{-1}$ (C=C overtone), and bands at 993, 927, and 869 cm.$^{-1}$ (epoxide). The compound gave a positive periodic acid test indicating the presence of an epoxide group. The nuclear magnetic resonance spectrum indicated two different protons in the ratio 3:1; 4.97 $\tau$, vinyl protons overlapped and 6.58 $\tau$, protons on epoxide ring.

*Anal.* Calcd. for $C_6H_8O$: C, 74.97; H, 8.39; O, 16.67; mol. wt., 96. Found: C, 74.99; H, 8.38; O, 17.32 (Unterzaucher method); mol. wt., 95.

(13) Lithium chloride is a much more effective catalyst for the pyrolysis than other salts used previously for the pyrolysis of carbonate; U. S. Patent 2,856,413.

(14) The n.m.r. spectrum rules out the possible alternative structure, 2,3-dihydroöxepine.[2]

(15) I. Heibron, *J. Chem. Soc.,* 1827 (1949).

**Acknowledgment.**—The author expresses his appreciation to Dr. Anthony J. Papa, John W. Robson, and Charles B. Matthews for helpful discussions and to Dr. Heinz F. Reinhardt who first prepared compound II.

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# A General Synthesis of 3-Indolealkanoic Acids

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3-Indolealkanoic acids are very active plant growth substances. 3-Indoleacetic and 3-indolebutyric acids are used commercially by nurseries to promote growth of plant cuttings, and many other interesting biological properties have been reported for these acids and their derivatives. 3-Indolecaproic acid and its amide also have excellent biological properties.[1,2] A simple one-step synthesis for the preparation of 3-indolealkanoic acids is described which involves the direct base-catalyzed reaction of lactones with indole or its derivatives.

3-Indolealkanoic acids have been prepared previously by the reaction of lactones with indole, but these syntheses generally involved several steps, or gave low yields. The reaction of butyrolactone with the potassium salt of indole at 200° has given 1-indolebutyric acid,[3] while with the magnesium iodide salt of indole at 120–130° has given 3-indolebutyric acid.[4] These syntheses required the prior preparation of the respective salts *via* involved procedures. The non-catalytic reaction of propiolactone with indole at 120° is reported to give 3-indolepropionic acid in 40–50% yield.[5] An attempt was made to duplicate this result, but only starting material was recovered in 90% yield. A reaction did occur when the temperature was raised to 245°, but the product was a nitrogen-containing polymeric acid which was not investigated further.

The reaction of lactones with indole, in the presence of base, takes place at 200–300° to give high yields of 3-indolealkanoic acids (Table I). The acids described in Table I were prepared at 250° using a reaction mixture comprising 1.0 mole of indole, 1.05 moles of lactone and 1.1 moles of base. The base used was potassium hydroxide, but sodium hydroxide or sodium methoxide also gave satisfactory results. Some skatole was produced when sodium methoxide was used.[6] No solvent was used in these preparations, but solvents, such as tetralin, methylnaphthalene, or diethylbenzene, can be used. When the reactions were run in the presence of a solvent the yields were generally lower. The purity of the crude acids, which were isolated by the

(1) C. H. Fawcett, R. L. Wain, and F. Wightman, *Nature*, **181**, 1387 (1958).

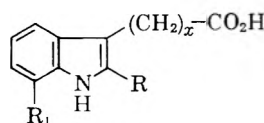(2) D. G. Crosby, J. B. Boyd, and H. E. Johnson, *J. Org. Chem.*, **25**, 1826 (1960).

(3) W. Reppe, *et al.*, *Ann.*, **596**, 1 (1955).

(4) F. N. Stepanov, U. S. S. R., Patent 66,681; *Chem. Abstr.*, **41**, 2087b (1947).

(5) J. Harley-Mason, *Chem. Ind.* (London), 886 (1951).

(6) E. F. Pratt and L. W. Botimer, *J. Am. Chem. Soc.*, **79**, 5248 (1957).

TABLE I

3-INDOLEALKANOIC ACIDS



| R | R₁ | x | Yield, % | Yield, based on unrecovered indole, % | M.p., °C. Found | M.p., °C. Lit. |
|---|---|---|---|---|---|---|
| H | H | 2 | 69 | 94 | 134–135 | 133–134ᵃ |
| H | H | 3 | 82 | 96 | 124 | 124ᵇ |
| H | H | 4 | 43 | 70 | 105–107 | 105ᶜ |
| H | H | 5 | 75 | 95 | 143–144 | . . . |
| C₆H₅ | CH₃ | 5 | 41 | 61 | 97.5–99.5 | . . . |

ᵃ R. Majima and M. Kotake, *Ber.*, **58B**, 2037 (1925).  ᵇ See ref. 7.  ᶜ R. H. F. Manske and L. C. Leitch, *Can. J. Res.*, **14B**, 1 (1936).

addition of water to the reaction mixture followed by acidification of the aqueous phase, was 85–98%, depending upon the reaction conditions and the reactants used. The acids with less than five carbons in the acid chain were not only obtained in lower purity but were much more susceptible to oxidation, and, therefore, more difficult to purify.

A series of five reactions was run using indole, butyrolactone, and potassium hydroxide to determine the optimum conditions for the preparation of 3-indole-butyric acid (Table II). The highest yields were obtained from the reactions run between 220 and 290° for twenty hours with an equimolar quantity of potassium hydroxide.

TABLE II

SYNTHESIS OF 3-INDOLEBUTYRIC ACID

Indole (117 g., 1.0 mole), butyrolactone (90 g., 1.05 moles), potassium hydroxide (72 g. of 85% purity, 1.09 moles)

| Run number | Reaction temp., °C. | Reaction time, hr. | Yield, % | 3-Indolebutyric acid, crude Yield, based on unrecovered indole, % |
|---|---|---|---|---|
| 1 | 190–200 | 22 | 16 | 81 |
| 2 | 220–250 | 20 | 67 | 88 |
| 3 | 250–290 | 20 | 82 | 96 |
| 4ᵃ | 257–280 | 30 | 11 | 20 |
| 5 | 275–280 | 1 | 44 | 88 |

ᵃ Seven grams of potassium hydrogen instead of 72 g.

Both 1- and 3-indolepropionic acids were prepared in high yield from indole, propiolactone, and potassium hydroxide by varying the reaction temperature. 3-Indolepropionic acid was obtained in 69% yield when prepared in the usual manner at 250°. However, when the reactants were slowly heated in a stainless steel flask to 60°, a sudden exothermic reaction took place and the temperature rose to 180° with the formation of potassium 1-indolepropionate.
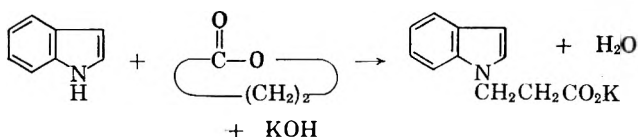


Since the 3-indolepropionic acid is obtained at higher temperatures, a rearrangement must take place. 1-Indolepropionic acid was rearranged to 3-indolepropionic acid by heating with an excess of potassium hydroxide
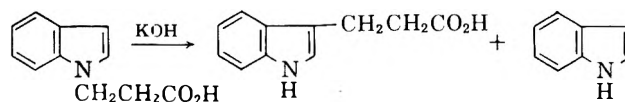


at 210° for nine hours. A 41% yield of 3-indolepropionic acid was obtained along with a 36% yield of indole.

Several unsuccessful attempts were made to isolate 1-indolebutyric acid from low temperature runs using butyrolactone, indole, and potassium hydroxide, but the only acid products were 3-indolebutyric acid and nonindole containing acids.

## Experimental

**Procedure A. Preparation of 3-Indolealkanoic Acids Demonstrated by the Following Example for 3-Indolecaproic Acid.**—There was charged to a 1-l. stainless steel rocker autoclave 117 g. (1.0 mole) of indole, 130 g. (1.14 moles) of ε-caprolactone, and 90 g. (1.36 moles) of potassium hydroxide pellets (85% purity). The mixture was heated to 250° in 1 hr. and then kept at 250° ± 5° for 19 hr. The brown solid from the autoclave was treated with 1 l. of water which dissolved most of the solid. This aqueous mixture was extracted with 250 ml. of isopropyl ether which upon evaporation of the isopropyl ether gave 3.0 g. of indole. The aqueous layer was acidified with concd. hydrochloric acid, whereupon the 3-indolecaproic acid separated as a tan solid. The washed and dried solid weighed 198 g., m.p. 136–141°. Recrystallization from acetic acid, benzene, methanol, or hexane improved the melting point to 143–144°. The structure of the 3-indolecaproic acid was confirmed by infrared and ultraviolet spectra, elemental analysis, and titration of the acidic function.

*Anal.* Calcd. for C₁₄H₁₇O₂N: C, 72.81; H, 7.41; N, 6.06; neut. equiv., 231.29. Found: C, 72.99; H, 7.49; N, 6.29; neut. equiv., 228.

**Procedure B. Use of Solvent in the Preparation of 3-Indolebutyric Acid.**—There was charged to a three-necked, 1-l. stainless steel flask equipped with a stirrer, thermowell, and a reflux condenser, which had a trapf or collecting the water of formation, 117 g. (1.0 mole) of indole, 100 g. (1.15 moles) of butyrolactone, 100 g. (1.5 moles) of potassium hydroxide pellets, and 250 g. of tetralin. The stirred mixture was heated at reflux for 10 hr. during which time a total of 36 ml. of water was collected. The mixture was treated with approximately 1 l. of water and the layers were separated. The upper organic layer weighed 269 g. and contained 11% by weight of unchanged indole. The aqueous layer was acidified with concentrated hydrochloric acid, whereupon the 3-indolebutyric acid separated as an oil which slowly crystallized. The crude product weighed 147 g., m.p. 105–118°. Recrystallizations from benzene gave crystals melting at 123–124° (lit.,⁷ m.p. 124°).

The methyl ester was prepared in 75% yield, m.p. 73–74° (reported⁷ m.p. 73–74°).

**1-Indolepropionic Acid.**—A mixture of 234 g. (2.0 moles) of indole, 160 g. (2.22 moles) of propiolactone, and 168 g. (2.43 moles) of potassium hydroxide pellets was heated with stirring in a nitrogen atmosphere. At 60°, a sudden exothermic reaction took place and the temperature rose to 180° within 1 min. and part of the reaction mixture was lost. Most of the mixture dissolved in 500 ml. of water. Extraction with isopropyl ether give 20 g. of unchanged indole. Acidification of the chilled aqueous layer with concentrated hydrochloric acid gave 269 g. (71% yield) of 1-indolepropionic acid, m.p. 80–85°, recrystallized from hexane, m.p. 89–90° (reported⁸ m.p. 91°).

*Anal.* Calcd. for C₁₁H₁₁O₂N: C, 69.82; H, 5.86; N, 7.40. Found: C, 70.15; H, 6.03; N, 7.70.

**Rearrangement of 1- to 3-Indolepropionic Acid.**—A stirred mixture of 9 g. (0.048 mole) of 1-indolepropionic acid and 5 g. (0.076 mole) of potassium hydroxide pellets in a stainless steel flask was heated at 210° for 9 hr. The cooled mixture was diluted with 100 ml. of water and extracted with isopropyl ether. Evaporation of ether gave 2 g. of indole. After acidification of the aqueous layer, 3.7 g. of 3-indolepropionic acid was recovered.

(7) R. W. Jackson and R. H. F. Manske, *J. Am. Chem. Soc.*, **52**, 5029–5035 (1930).

(8) French Patent 48,570, (April 5, 1938); *Chem. Abstr.*, **33**, 176 (1939).

Another rearrangement of 1-indolepropionic acid was made at 245° for 2 hr. in a stainless steel rocker autoclave. Again, a 41% yield of 3-indolepropionic acid was obtained.

**Acknowledgment.**—The author thanks Mr. A. H. DuVall and Mr. S. Gottlieb for analyses and Mr. M. A. Eccles and Mr. K. E. Atkins for laboratory assistance.

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## Photodehydrogenation of Resin Acids

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*Received November 21, 1962*

The photosensitized oxidation of the seven major resin acids in pine gum has been studied in these laboratories.[2-4] It was noted that in the *absence* of oxygen, irradiation of levopimaric,[2] palustric,[3] and neoabietic[4] acids, in solution with a sensitizing dye, resulted in bleaching of the dye. It was the purpose of the present work to investigate the nature and effect of the "bleaching reaction" upon the pine gum resin acids. Ergosterol under these conditions has been shown to undergo a dehydrogenation–dimerization[5] while pentaphenylcyclohexa-1,3-diene was converted to pentaphenylbenzene.[6] The photosensitized oxidation of ergosterol and lumisterol is accompanied by dehydrogenation to heteroannular trienes.[7]

Visible light irradiation of deaerated ethanol solutions of levopimaric acid (I) and erythrosin B in varying ratios indicated that about one mole of dye was required for reaction with two moles of resin acid. Under these conditions, the product of the photochemical reaction was found to be dehydroabietic acid (II; 20% isolable yield), indicating that dehydrogenation to an aromatic system had occurred.
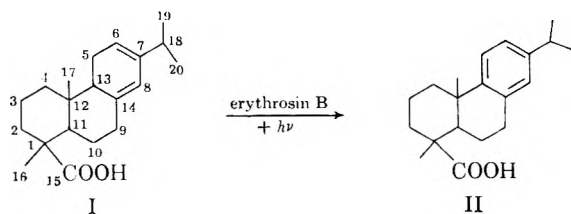


Irradiation of palustric acid ($\Delta^{7,13}$) in the presence of a molar amount of erythrosin B also gave dehydroabietic acid (21% isolable yield) as the irradiation product.

When applied to neoabietic acid ($\Delta^{7(18),8(14)}$), the reaction under investigation gave a mixture of four volatile compounds as determined by gas chromatography of the methyl ester of the crude product, plus considerable nonvolatile material, presumably polymer. None

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article is not copyrighted.

(2) R. N. Moore and R. V. Lawrence, *J. Am. Chem. Soc.*, **80**, 1438 (1958).

(3) W. H. Schuller, R. N. Moore, and R. V. Lawrence, *ibid.*, **83**, 1734 (1960).

(4) W. H. Schuller and R. V. Lawrence, *ibid.* **83**, 2563 (1961).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 104–108.

(6) G. R. Evanega, W. Bergmann, and J. English, Jr., *J. Am. Chem. Soc.*, **27**, 13 (1962).

(7) A. Windaus and J. Brunken, *Ann.*, **460**, 225 (1928); P. Bladon, *J. Chem. Soc.*, 2176 (1955).

of the volatile esters could be crystallized; however, two of the compounds exhibited ultraviolet spectra characteristic of conjugated trienes.[8]

Dehydroabietic (II), pimaric, isopimaric, and abietic ($\Delta^{7,9(14)}$) acids did not react under similar conditions. The first three have been found to be unreactive toward photosensitized oxidation as well.[4] Abietic acid has been observed to react slowly on photosensitized oxidation to give chiefly nonperoxidic products.[4,9]

An attempt was made to replace the greater part of the sensitizer with an easily reducible compound, which in itself was not a sensitizer, in order to establish a hydrogen exchange situation promoted by only a catalytic amount of light-activated sensitizer. This effort was successful with the demonstration that the irradiation of levopimaric acid in the presence of a catalytic amount of erythrosin B and a molar amount of nitromethane gave dehydroabietic acid in 17% isolable yield.

Suitable blanks were run for all the reactions herein reported which established that no reaction occurred in the dark, in the absence of sensitizing dye, in the absence of resin acid, or in the absence of nitromethane (other than a very rapid bleaching of the small amount of dye present in the latter case).

Schenck[10] has proposed that the irradiation of sensitizers results in their elevation to diradicals. He has suggested hydrogen abstraction from the substrate by the diradical to give a monoradical, as the possible course of any competing dehydrogenation reaction which might occur during photosensitized oxidation. Diradicals of the type pictured by Schuller,[3,4] *et al.*, would be especially suited geometrically for hydrogen abstraction from two adjacent carbon atoms upon a single collision, yielding a new double bond.

### Experimental[11]

**Varying Ratios of Levopimaric Acid to Erythrosin B.**—Four 95% ethanol solutions, each 0.02 $M$ in levopimaric acid, and containing $^1/_2$, $^1/_4$, $^1/_6$, and $^1/_8$ molar ratios of erythrosin B/resin acid, respectively, were charged to 100-ml. reactors,[2] purged with prepurified nitrogen, stoppered, and irradiated simultaneously, with a 15-w. fluorescent lamp. All the runs but the $^1/_2$ ratio bleached within 22 hr. while this ratio was unbleached after 111 hr. of irradiation.

A run of the $^1/_2$ ratio was made and irradiation continued until no additional change in $[\alpha]_D$ occurred. More erythrosin B was added (1.5/2 molar ratio) and irradiation continued for 21 hr. with no further change in $[\alpha]_D$ observed.

**Dehydroabietic Acid (II) from Levopimaric Acid (I).**—A solution of 11.9 g. of erythrosin B in 2700 ml. of 95% ethanol was filtered and 8.17 g. of levopimaric acid dissolved in the filtrate (0.005 $M$ in dye and 0.01 $M$ in resin acid). The solution was charged to the 40-w. reactor,[2] purged with prepurified nitrogen, the reactor sealed (stoppered), and irradiation initiated. Two external air blasts were directed on the reactor to hold the temperature around 30°. After 20 hr. of irradiation, the specific rotation became constant at $[\alpha]^{27}D$ −30°. Irradiation was continued for 10 hr. more to ensure completeness of reaction. The solvent was removed under reduced pressure and the dry residue extracted with ether. The ether was filtered, washed with water, and the ether removed. The residue (8.0 g.) exhibited no absorption maximum in the 272-mμ region. It was converted to a cyclo-

(8) K. Alder and H. von Brachel, *Ann.*, **608**, 195 (1957); H. H. Inhoffen, K. Bruckner, R. Grundel, and G. Quinkert, *Ber.*, **87**, 1407 (1954); H. H. Inhoffen and G. Quinkert, *ibid.*, **87**, 1418 (1954).

(9) W. H. Schuller and R. V. Lawrence, *FLACS*, **15**, No. 8, 23 (1962); Florida Section, Meeting-in-Miniature, American Chemical Society, May 11, 1962, Jacksonville, Fla.

(10) G. O. Schenck, *Naturwissenschaften*, **40**, 205 (1953).

(11) All melting points are uncorrected and all specific rotations and ultraviolet spectra are in 95% ethanol.

hexylamine salt in acetone solution; yield 3.59 g. (33%). The mother liquor was concentrated and gave a black viscous oil. The free acid was liberated from the salt using an aqueous phosphoric acid–ether mixture. The crude acid was placed on a silicic acid (100-mesh) column, 1.25-in. diameter, containing 68 g. of adsorbent, and eluted with 1200 ml. of benzene. The effluent was collected in 75-ml. aliquots and the solvent blown off with nitrogen. The residue from fractions 3–9 were combined and crystallized from 95% ethanol to give 0.98 g. of dehydroabietic acid; $[\alpha]^{25}$D +62.7° ($c$ 1.1); $\lambda_{max}^{alc}$ 276 m$\mu$ ($\alpha$ 2.19), 268 m$\mu$ ($\alpha$ 2.12); m.p. 169–171°; infrared spectrum essentially identical to that of an authentic sample. Two further crops of 0.48 g., $[\alpha]^{26}$D +60° ($c$ 1.0), and 0.14 g. were obtained for a total of 1.60 g. or 20% conversion from levopimaric acid. The remainder of the material from the column could not be crystallized.

**Dehydroabietic Acid (II) from Palustric Acid.**—A solution of 21.6 g. of erythrosin B and 7.42 g. of palustric acid in 2450 ml. of 95% ethanol (0.01 $M$ in dye and 0.01 $M$ in resin acid) was irradiated for 40 hr. and worked up as described in the preceding example; yield of crude residue, 6.5 g. A small portion was esterified with diazomethane; $[\alpha]^{25}$D +38° ($c$ 0.56), no absorption maximum exhibited in the 266-m$\mu$ region. The ester was gas chromatographed and a single, large peak was obtained, at the same emergence time as a sample of authentic methyl dehydroabietate. The remainder of the residue was converted to 5.28 g. (61%) of cyclohexylamine salt. The mother liquor on concentration gave a black-red oil. The acid was regenerated from the salt and the crude product cleaned up on a silicic acid column as before, employing benzene as the eluent. The purified product was crystallized from 95% ethanol to give 1.29 g. of dehydroabietic acid; m.p. 171–173°; $[\alpha]^{26}$D +62.8° ($c$ 1.1); $\lambda_{max}^{alc}$ 276 m$\mu$ ($\alpha$ 2.23) 268 m$\mu$ ($\alpha$ 2.18); infrared spectrum essentially identical to that of an authentic sample. A second crop weighing 0.26 g. was obtained of $[\alpha]^{26}$D +64.2° ($c$ 1.0) for a total yield of 21% from the starting palustric acid. The remainder of the material from the column could not be crystallized.

**Neoabietic Acid, Erythrosin B, and Light.**—A solution of 23.8 g. of erythrosin B and 8.17 g. of neoabietic acid in 2700 ml. of 95% ethanol (0.01 $M$ in dye and 0.01 $M$ in resin acid) was irradiated for 42.5 hr. and worked up as in the preceding examples. The crude residue gave only a small yield of a gummy cyclohexylamine salt. A portion of the residue, $[\alpha]^{28}$D −22 ($c$ 1.2), was esterified with diazomethane and gas chromatographed at 250° on a GE SE-52 silicone column. Four peaks were obtained: peak 1, no absorption from 220–320 m$\mu$; peak 2, $\lambda_{max}^{alc}$ 243 m$\mu$; peak 3, (major peak) $\lambda_{max}^{alc}$ 264,274 (major max.) 284 m$\mu$; peak 4, $\lambda_{max}^{alc}$ 264,274 (major max.) 285 m$\mu$. (Methyl abietate emerges between peaks 1 and 2.) A considerable proportion of the sample injected was not volatile under these conditions. None of the products from the 4 peaks could be crystallized.

**Dehydroabietic Acid (II) from Levopimaric Acid (I), Erythrosin B, Light, and Nitromethane.**—A solution of 7.55 g. of levopimaric acid, 0.125 g. of erythrosin B, and 13.4 ml. of nitromethane in 2485 ml. of 95% ethanol (0.01 $M$ in resin acid, 0.10 $M$ in nitromethane, and 0.00006 $M$ in dye) was irradiated for 54.5 hr. (final $[\alpha]$D +25°) and worked up as in the preceding examples except that the ether extraction was omitted. A quantitative yield of acidic residue was obtained; it exhibited no absorption in the 272-m$\mu$ region. The residue was converted to the cyclohexylamine salt in a yield of 7.7 g. (77%); concentration of the mother liquor gave a red oil. The salt was recrystallized from ethanol; yield 4.20 g. The acid was regenerated from the combined crops of salt as before and the crude acid purified as in the preceding examples, by elution through a silicic acid column with benzene followed by crystallization from 95% ethanol. The yield of dehydroabietic acid was 1.02 g. of m.p. 168–170°; $[\alpha]^{25}$D +64° ($c$ 0.98); $\lambda_{max}^{alc}$ 276 m$\mu$ ($\alpha$ 2.13), 268 m$\mu$ (2.06); infrared spectrum essentially identical to that of an authentic sample. A second crop of 0.28 g. of $[\alpha]^{28}$D +61.3° ($c$ 1.1) was obtained for a total yield of 1.30 g. or 17% from levopimaric acid. The remainder of the material from the column could not be crystallized.

**Sensitizers.**—The following compounds were found to function as sensitizers[3,4] for dehydrogenation after the manner of erythrosin B: 9,10-phenanthrenequinone, benzil, chloranil (in benzene solution), eosin YS, and 9,10-anthraquinone.

**Attempted Reaction of Abietic, Pimaric, Isopimaric, and Dehydroabietic Acids with Erythrosin B and Light.**—A solution of 0.05 g. of erythrosin B in 33 ml. of 95% ethanol was filtered and 0.100 g. of the resin acid dissolved in the filtrate (0.01 $M$ in resin acid and 0.0017 $M$ in dye). The solution was charged to a 100-

ml. reactor,[2] purged with prepurified nitrogen, stoppered, and irradiated with a 15-w. fluorescent lamp for 12 hr. In all four cases, essentially no change in color of the solution nor of specific rotation occurred as a result of the irradiation.

**Blank Experiments.**—A measurement of specific rotation before and after an extended test period (6 to 44 hr.) was used to determine if reaction had occurred. For all of the reactions described above, suitable blanks were run which determined that no reaction occurred in the dark, in the absence of sensitizing dye, in the absence of resin acids, or in the absence of nitromethane (other than a rapid bleaching of the small amount of dye present in the latter case).

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## Dehydrogenation of a Tetrahydrofuran. The Preparation of 3,4-Diphenylfuran

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Although the preparation of furans by dehydrogenation of 2,5-dihydrofurans has been reported in a few instances in the literature,[2,3] the tetrahydrofurans seem to have been peculiarly reluctant to undergo dehydrogenation. This note describes the first example, of which we are aware, of successful dehydrogenation of a tetrahydrofuran.

The preparation of 3,4-diphenylfuran (I) in unspecified yield according to sequence (1) was described some time ago by Backer and Stevens.[4] It seemed to us that dehydrogenation of 3,4-diphenyltetrahydrofuran (II) might provide an alternative convenient route to the furan I.
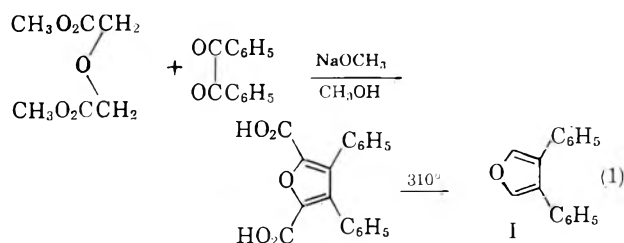


The required tetrahydrofuran was readily obtained in 97% yield by a remarkably clean acid-catalyzed cyclization of 2,3-diphenylbutane-1,4-diol (III) with continuous removal of water. The dehydrogenation of tetrahydrofuran II could not be effected with selenium at a variety of temperatures with and without solvent, nor with sulfur in boiling dimethylformamide. The latter method had been very successful in the dehydrogenation of aryldihydrofurans.[2] Pyrolysis of II with elemental sulfur at 200–210°, however, resulted in the formation of furan I, isolated in 25% yield. Hydrogen sulfide evolution was negligible below 200° in this reaction. These reactions are pictured in sequence 2.
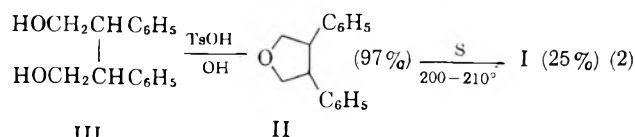


(1) Fellow of the Alfred P. Sloan Foundation.
(2) H. Wynberg, *J. Am. Chem. Soc.*, **80**, 364 (1958).
(3) J. F. Bel'skii, N. I. Shuikin, and R. A. Karakhanov, *Dokl. Akad. Nauk, SSSR*, **132**, 585 (1960); *Chem. Abstr.*, **54**, 24623 (1960).
(4) H. J. Backer and W. Stevens, *Rec. trav. chim.*, **59**, 423 (1940).

In view of Wynberg's observation that an aryl substituent seemed essential for the dehydrogenation of dihydrofurans,[2] it is probable that the aryl substituents permit dehydrogenation of II. We do not intend to pursue this investigation further.

### Experimental

**2,3-Diphenylbutane-1,4-diol (III).**—A mixture of *meso*-2,3-diphenylsuccinic acid[5] (m.p. 227–229°, 27 g., 0.10 mole) and lithium aluminum hydride (7.6 g., 0.20 mole) in dry ether (300 ml.) was boiled under reflux for 12 hr. Excess lithium aluminum hydride was destroyed by dropwise addition of wet ethanol to the stirred cooled slurry. The mixture was then shaken with cold aqueous 5% phosphoric acid and the layers separated. The aqueous layer was washed several times with methylene chloride and the combined organic extracts were dried over magnesium sulfate and evaporated to dryness. Recrystallization of the solid residue from benzene afforded colorless crystals, m.p. 142–143.5° (20 g., 83%).

*Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.21; H, 7.42.

The infrared spectrum in Nujol mull included absorption at 3.0, 6.24, and 9.6 $\mu$.

**3,4-Diphenyltetrahydrofuran (IV).**—The diol III (8.0 g., 0.033 mole) was dissolved in hot benzene (100 ml.) and *p*-toluenesulfonic acid monohydrate (3.0 g., 0.016 mole) was added. The solution was boiled under reflux and the evolved water was collected in a Dean–Stark trap. After 4 hr., 0.75 ml. (0.042 mole, 86%) of water had collected. An additional 2 hr. of boiling did not afford any more water. The mixture was cooled, washed once with water, once with dilute aqueus sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated to dryness on a rotary evaporator. The white, crystalline residue was recrystallized once from aqueous ethanol to give colorless needles m.p. 86–86.5° (7.2 g., 97%).

*Anal.* Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.39; H, 7.19.

The infrared spectrum in dichloromethane solution had no absorption at 2.5–3.2 $\mu$, but included a strong band at 9.5 $\mu$.

**3,4-Diphenylfuran (II).**—A mixture of the tetrahydrofuran IV (1.0 g., 4.5 mmoles) and sulfur (1.0 g., 31 mmoles) was melted and heated under a slow steam of nitrogen. No gas evolution was detected until the temperature reached 200°. Gas bubbles appeared and the odor of hydrogen sulfide then became evident. Heating was continued at 200–210° for 5 hr. The mixture was cooled and the crystalline mass was extracted several times with boiling ether. The ether extracts were concentrated on the steam bath, cooled, filtered, and the filtrate was evaporated to dryness. The residue was twice recrystallized from 95% ethanol to give pale yellow needles (0.25 g., 25%), m.p. 108–111° (dec. 109–110.5°[1]).

The infrared spectrum exhibited absorption at 6.24, 6.50, 9.50, and 11.40 $\mu$ in dichloromethane solution.

(5) A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 1709 (1922).

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### Formation of Tetrahydrofuran Derivatives from 1,4-Diols in Dimethyl Sulfoxide[1]

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Three methods are prominent for the preparation of tetrahydrofuran derivatives from primary, secondary, and tertiary 1,4-diols. These are strong acid,[2] sulfonyl

chloride–organic base,[3] and dehydration over alumina.[4] These methods, however, generally suffer from low yields and a mixture of products.

Recently, Traynelis, *et al.*,[5] have reported that secondary and tertiary alcohols are dehydrated to olefins when heated in dimethyl sulfoxide.

In an attempt to prepare 2,3-dimethylene[2.2.1]bicycloheptane, *endo–cis*-bicyclo[2.2.1]heptane-2,3-dimethanol was heated for thirteen hours at 156–166° in dimethyl sulfoxide. Instead of the desired diene, the cyclic ether, 2-oxatetrahydro-*endo*-dicyclopentadiene (I), was formed in 98% yield.
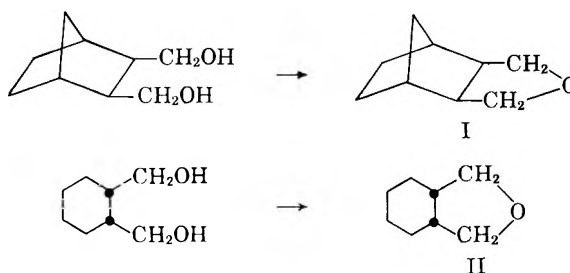


In view of this result, a study was undertaken to determine the scope of this facile dehydration using primary, secondary and tertiary 1,4-diols. A one to twelve ratio of diol to dimethyl sulfoxide was used.[6]

When *cis*-hexahydrophthalyl alcohol was heated in dimethyl sulfoxide at 159–161° for fourteen hours a 66% yield of *cis*-hexahydrophthalan (II) was obtained.

Similarly, the secondary diol, 2,5-hexanediol, when heated at 180° for eighteen hours in dimethyl sulfoxide furnished 2,5-dimethyltetrahydrofuran (III) in 68% yield.
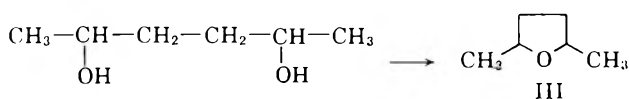


Utilization of the tertiary diols, 2,5-dimethyl-2,5-hexanediol and 3,6-dimethyl-3,6-octanediol, resulted in 52% and 70% yields of products which contained the tetrahydrofuran derivatives, 2,2,5,5-tetramethyltetrahydrofuran (IV) and 2,5-diethyl-2,5-dimethyltetrahydrofuran (V), respectively.

The former diol leading to IV was heated at 167° for seventeen hours in dimethyl sulfoxide. Investigation of liquid product by gas chromatography showed it to be a mixture with the composition of 75.5%, 9.1%, and 15.5%, respectively. The infrared spectrum of this product was devoid of —OH bands but contained a very small carbon–carbon double bond stretching band at 6.05 $\mu$. That the 15.5% component was

(2)(a) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1449 (1954); (b) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953); (c) Y. S. Zal'kind and V. Markaryan, *J. Russ. Phys. Chem. Soc.*, **48**, 538 (1916); (d) T. A. Favorskaya and N. P. Ryzkova, *Zh. Obshch. Khim.*, **26**, 423 (1956); (e) T. A. Favorskaya and O. V. Sergievskaya, *ibid.*, **25**, 150 (1955); (f) E. Pace, *Atti. Accad. Lincei*, **7**, 757 (1928); (g) I. L. Kotlyarevskii, M. S. Shvartsberg, and Z. P. Trotsenko, *Zh. Obshch. Khim.*, **30**, 440 (1960).

(3)(a) K. Alder and W. Roth, *Ber.*, **88**, 407 (1955); (b) D. D. Reynolds and W. O. Kenyon, *J. Am. Chem. Soc.*, **72**, 1593 (1950).

(4)(a) E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *ibid.*, **82**, 1218 (1960); (b) R. C. Olberg, H. Pines, and V. N. Ipatieff, *ibid.*, **66**, 1096 (1944); (c) see ref. 2b.

(5) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).

(6) Dr. Vincent Traynelis of the University of Notre Dame has found that primary 1,4-, 1,5-, and 1,6-diols are dehydrated to the cyclic ethers in dimethyl sulfoxide (private communication).
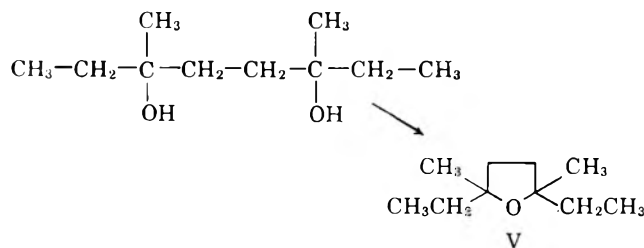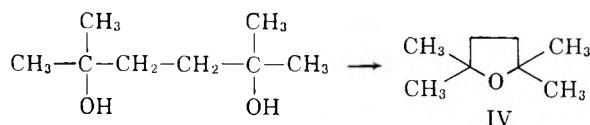
2,5-dimethyl-2,4-hexadiene was shown by the ultraviolet spectrum of the product which exhibited $\lambda_{max}^{C_2H_5OH}$ 242 m$\mu$ ($\epsilon$ 3590) or 16.7% of the conjugated diene. Retention time of 2,5-dimethyl-2,4-hexadiene and the 15.5% component were identical on the gas chromatogram. Quantitative hydrogenation of the product gave a total diene content of 27.3%. The 9.1% component is an unconjugated diene such as 2,5-dimethyl-1,4-hexadiene.

The latter diol when heated at 170° for 17.5 hours in dimethyl sulfoxide led to V. Gas chromatography of this product gave five peaks with the composition of 61.4%, 24.7%, 5.5%, 4.7%, and 3.6%, respectively. The first two peaks correspond to the *cis* and *trans* forms of 2,5-diethyl-2,5-dimethyltetrahydrofuran, while the latter three peaks are due to contaminating diene components. The infrared spectra showed no trace of —OH bands and a very small peak at 6.0 $\mu$ (C=C). The liquid exhibited an ultraviolet spectrum $\lambda_{max}^{C_2H_5OH}$ 239 m$\mu$ ($\epsilon$ 3470) and $\lambda_{max}^{C_2H_5OH}$ 245 m$\mu$ ($\epsilon$ 3620). Quantitative hydrogenation showed the total diene content to be 15.05%.

Thus, the method has been shown to offer a simple, convenient procedure for the preparation of tetrahydrofuran derivatives in good yields from primary, secondary, and tertiary 1,4-diols and is potentially superior to previous methods.[2–4]

The success encountered with 1,4-diols, quite naturally led to the postulation of a cyclic transition state (VI).
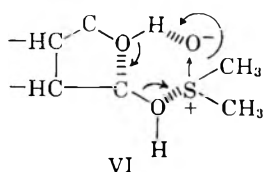


An attempted formation of 2,5-dihydrofuran from *cis*-butene-1,4-diol under these conditions gave only starting diol (40%) and polymeric material.

### Experimental[7]

**Dimethyl Sulfoxide.**—Dimethyl sulfoxide, obtained from either Crown Zellerbach Corp.,[8] Stepan Chemical Co., or East-

man Organic Chemicals, was allowed to stand over sodium hydroxide pellets and then distilled through a Vigreux column, b.p. 86° (18 mm.), $n^{26}$D 1.4753 (lit.,[5] b.p. 83° (17 mm.), $n^{20}$D 1.4795).

**Bicyclo[2.2.1]hept-5-ene-2,3-dimethanol[9]** was recrystallized three times from ether to a constant melting point of 85–86°. This material corresponded to the *endo–cis* compound (lit.,[10] m.p. 86°).

*endo–cis*-**Bicyclo[2.2.1]heptane-2,3-dimethanol** was prepared by hydrogenation of unsaturated *endo–cis* diol in ethanol over palladium-on-charcoal catalyst and melted 63–64° when crystallized from ether (lit.,[10] m.p. 62°).

**2-Oxatetrahydro-*endo*-dicyclopentadiene (I).** *endo–cis*-Bicyclo [2.2.1]heptane-2,3-dimethanol (8.0 g., 0.051 mole) and 48.0 g. (0.615 mole) of dimethyl sulfoxide were heated under a reflux condenser at 156–166° for 13 hr. On cooling, 150 ml. of water was added and the reaction mixture extracted twice with 100-ml. portions of petroleum ether (b.p. 30–60°). The combined petroleum ether extracts were dried over calcium sulfate. Upon filtration, the petroleum ether was removed by distillation and the residue solidified on standing to give 6.95 g. (98%) of the saturated cyclic ether I, m.p. 104–107°. Recrystallization from hexane gave material melting at 109–110° (reported[3a] m.p. 110°). The infrared spectrum (chloroform solvent) was devoid of OH bands and exhibited absorption at 9.2 $\mu$, which is characteristic of tetrahydrofuran and its derivatives.[11]

*cis*-**Hexahydrophthalyl alcohol** was prepared in the following manner. 1,2-Cyclohexanedicarboxylic anhydride[12] was converted to the diester by the method of Price and Schwarcz.[13] The diester was then reduced to the *cis*-diol by the method of Bailey and Golden[14] using lithium aluminum hydride, and melted at 42–43°.

*cis*-**Hexahydrophthalan (II).**—*cis*-Hexahydrophthalyl alcohol (8.55 g., 0.0594 mole) and 55.0 g. (0.71 mole) of dimethyl sulfoxide were heated at 159–161° for 14 hr. The mixture was cooled and 150 ml. of water added. The resulting mixture was extracted with two 100-ml. portions of petroleum ether. The combined petroleum ether extracts were dried over calcium sulfate and after filtration the petroleum ether was removed. The residual liquid was distilled and gave 4.96 g. (66%) of the ether II, b.p. 84° (29 mm.), $n^{26}$D 1.4667 [reported[2a] b.p. 80° (28 mm.), $n^{20}$D 1.4700]. The infrared spectrum (neat) showed no OH bands and the characteristic ether absorption was present at 9.13 $\mu$.

**2,5-Dimethyltetrahydrofuran (III).**—2,5-Hexanediol[9] (10.0 g., 0.084 mole) and 78.0 g. (1.0 mole) of dimethyl sulfoxide were heated for 18 hr. at 180°. The apparatus was arranged with a Claisen head connected to a Dry Ice–acetone trap so that the product was collected immediately as it was formed. Distillation of the liquid that collected in the trap yielded 5.72 g. (68%) of III, b.p. 91–93°, $n^{26}$D 1.4060 (lit.,[15] b.p. 92°, $n^{23}$D 1.4045). The ether band at 9.25 $\mu$ was present in the infrared spectrum (neat) and alcohol bands were absent.

**2,2,5,5-Tetramethyltetrahydrofuran(IV).**—2,5-Dimethyl-2,5-hexanediol[12] (10.0 g., 0.069 mole) and 64.0 g. (0.82 mole) of dimethyl sulfoxide were heated at 167° for 17 hr. The reaction mixture was cooled, diluted with 150 ml. of water, and extracted with two 100-ml. portions of petroleum ether. The combined petroleum ether extracts were dried over calcium sulfate, filtered, and removed. Distillation of the residual liquid yielded 4.58 g. (52%) of product, b.p. 115–117°, $n^{25.5}$D 1.4136 (lit.,[2d] b.p. 115.5–116.5°, $n^{20}$D 1.4014). The infrared spectrum (neat) showed no OH absorption but a weak band at 6.05 $\mu$ (C=C) and the characteristic ether band at 9.23 $\mu$.

Gas chromatography of the product showed three peaks, the composition being 75.5%, 9.1%, and 15.5%, respectively, as determined by the peak area method.[16]

(7) Boiling points and melting points are uncorrected. Spectra of the compounds were measured with a Beckman Model DU ultraviolet spectrophotometer and a Perkin-Elmer Model 137 double beam infrared spectrophotometer. Gas chromatographic analyses were performed on an F and M Scientific Corp. Model 21B dual heater gas chromatography apparatus using a 10 ft. long, 1/4-in. diameter Celite–silicone grease column.

(8) The authors wish to acknowledge the gift of a sample of dimethyl sulfoxide from Crown Zellerbach Corp., Camas, Wash.

(9) Purchased from Aldrich Chemical Co.

(10) K. Alder and W. Roth, *Ber.*, **87**, 161 (1954).

(11) G. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(12) Purchased from Matheson Coleman and Bell Co.

(13) C. C. Price and M. Schwarcz, *J. Am. Chem. Soc.*, **62**, 2894 (1940).

(14) W. J. Bailey and H. R. Golden, *ibid.*, **75**, 4780 (1953).

(15) J. Cologne and A. Lagier, *Compt. rend.*, **224**, 572 (1947).

(16) Retention time of the peaks were 7.27 min., 8.5 min., and 14.8 min., respectively. Flow rate of helium was 43 ml. per min. with the detector temperature 92° and the column temperature 80°. An authentic sample of 2,5-dimethyl-2,4-hexadiene[12] had a retention time of 14.8 min. under these conditions.

The ultraviolet spectrum exhibited $\lambda_{max}^{C_2H_5OH}$ 242 m$\mu$ ($\epsilon$ 3590) and indicated that 16.7% of a conjugated diene was present.[17]

Quantitative hydrogenation at atmospheric pressure of a sample of the product in 95% ethanol over 10% palladium on charcoal showed a total diene content of 16.7%.

**2,5-Diethyl-2,5-dimethyltetrahydrofuran (V).**—A mixture of 8.5 g. (0.048 mole) of 3,6-dimethyl-3,6-octanediol (from Air Reduction Chemical Co.) and 45.5 g. (0.58 mole) of dimethyl sulfoxide was heated for 17.5 hr. at 170°. Water was added to the cooled reaction mixture which was then extracted with two 100-ml. portions of petroleum ether. The combined petroleum ether extracts were concentrated after drying over calcium sulfate. Distillation of the remaining liquid furnished 4.85 g. (70%) of product, b.p. 161–163°, $n^{25}$D 1.4378 (reported[2c] b.p. 162–165°, $n^{13.6}$D 1.4300). The infrared spectrum showed no trace of OH absorption and a very small peak at 6.0 $\mu$ (C=C). The characteristic band of cyclic ethers was present at 9.23 $\mu$.

Gas chromatographic analysis of the product gave five peaks with the composition of 61.4%, 24.7%, 5.5%, 4.7%, and 3.6%, respectively, as determined by the peak area method.[18]

This liquid exhibited an ultraviolet spectrum $\lambda_{max}^{C_2H_5OH}$ 239 m$\mu$ ($\epsilon$ 3470) and $\lambda_{max}^{C_2H_5OH}$ 245 m$\mu$ ($\epsilon$ 3620).

Quantitative hydrogenation of a sample at atmospheric pressure in ethanol over 10% palladium-on-charcoal catalyst gave total diene content of 15.05%.

(17) Pure 2,5 dimethyl 2,4-hexadiene exhibits $\lambda_{max}^{C_2H_5OH}$ 242 m$\mu$ ($\epsilon$ 21,500) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1425 (1952).

(18) Retention times of the peaks were 9.9, 11.0, 11.8, 13.1, and 14.0 min., respectively. Flow rates of helium was 42.5 ml./min. with a detector temperature of 132° and column temperature 122°.

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## Steroids. CCXXXII.[1] One-step Rearrangement of 17α-Methyl-Δ$^{1,4,6}$-androstatrien-17-ol-3-one to an 18-Norequilenin Derivative

Stephen Kaufmann

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Some time ago it was reported from these laboratories that the dienone–phenol rearrangement of Δ$^{1,4,6}$-androstatrien-3-one derivatives leads to 1-methyl-Δ$^6$-estrogens.[2] We have now found that under the conditions used previously (heating with *p*-toluenesulfonic acid in acetic anhydride) 17α-methyl-Δ$^{1,6,4}$-androstatrien-17-ol-3-one (I)[3] undergoes simultaneously a Wagner–Meerwein rearrangment of the 17-hydroxy and 13-methyl groups, dehydration and migration of the Δ$^{13}$ double bond into ring B. Alkaline hydrolysis led to a crystalline substance (over-all yield, 21%), to which structure III (3′,3′,5-trimethyl-7-hydroxy-1,2-cyclopentano-1,2,3,4-tetrahydrophenanthrene) has been assigned, based on the following considerations.

Tortorella, *et al.*,[4] have shown that the Wagner–Meerwein reaction of 17α-methyl-Δ$^5$-androstene-3β-17-diol and of 17α-methylandrostane-3β-17-diol gives rise to a double bond in position 13. The migration of the latter into ring B is facilitated by the presence of the Δ$^6$ double bond in an intermediate such as II. Structure III is confirmed by the ultraviolet spectrum

(1) Paper CCXXXI. O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), in press.

(2) C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and S. Kaufmann, *J. Am. Chem. Soc.*, **72**, 4540 (1950).

(3) British Patent 854,343.

(4) V. Tortorella, G. Lucente, and A. Romeo, *Ann. chim.* (Rome), **50**, 1198 (1960).

(Fig. 1), which is similar to that of 1-methyldihydroequilenin,[2] as well as by the infrared and n.m.r. spectra.[5] In the latter the 17-*gem*-dimethyl group appears as two 3-proton singlets at 53.3 and 64.5 c.p.s., and the protons of the methyl of the aromatic ring resonate at 119.7 c.p.s. (singlet). Two broad unresolved multiplets equivalent, respectively, to two and one protons, are due to the benzylic protons at C-11 (*ca.* 209 c.p.s.) and at C-14 (*ca.* 255 c.p.s.). The aromatic protons at C-2 and C-4 both resonate close to 409 c.p.s., so that a broadened single peak is observed. Mutual long-range coupling between these two protons and between those at C-4 and C-6 may also be responsible for the broadening of this absorption. A typical AB quartet at 422.8, 431.3, 438.0, and 446.5 c.p.s. ($J$ = 8.5 c.p.s.) appears for the adjacent protons at C-6 and C-7.
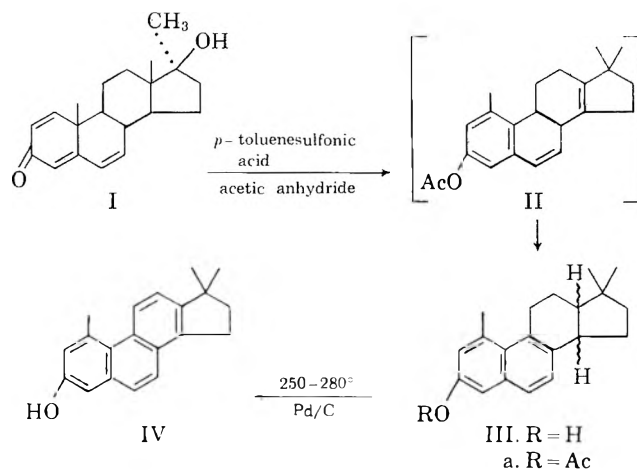


Substance III contains two asymmetric centers at C-13 and C-14, which, though present in the starting material I, had been destroyed in the intermediate Δ$^{13}$-compound (*e.g.*, II). That no racemization had occurred was shown by the fact that III was optically active ([α]D + 43.5°). The stereochemistry of II was not established but we believe the substance to possess the thermodynamically more stable *cis* C/D-ring junction.[6]

The acetate of compound III is easily dehydrogenated with palladium–carbon at 250–280°. Subsequent alkaline hydrolysis yielded the fully aromatic optically inactive 3′,3′,5-trimethyl-7-hydroxy-1,2-cyclopentenophenanthrene (IV).

### Experimental[7]

**3′,3′,5-Trimethyl-7-hydroxy-1,2-cyclopentano-1,2,3,4-tetrahydrophenanthrene (III).**—A solution of 10 g. of 17α-methyl-Δ$^{1,4,6}$-androstatrien-17-ol-3-one (I)[3] in 150 ml. of acetic anhydride containing 3 g. of *p*-toluenesulfonic acid was heated on the steam bath for 5 hr. The solution after cooling was poured into 2 l. of water and the mixture was allowed to stand overnight. The oily precipitate was extracted with ether. The extract, after being washed with water and sodium bicarbonate solution,

(5) We are indebted to Dr. Alexander Cross for the n.m.r. measurement and interpretations. The n.m.r. spectrum was taken with a *ca.* 5% solution in deuteriochloroform containing tetramethylsilane as an internal reference standard. A Varian A-60 spectrometer was used. Chemical shifts are presented as c.p.s. from the reference and are accurate to ±1 c.p.s. Coupling constants, $J$, are also expressed as c.p.s. and are accurate to ±0.5 c.p.s.

(6) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp. 461, 464.

(7) Melting points were determined in a Thomas–Hoover melting point apparatus and rotations have been recorded in chloroform. We are indebted to Dr. Claudio Zapata and his staff for the determination of all rotations and the recording of spectra.
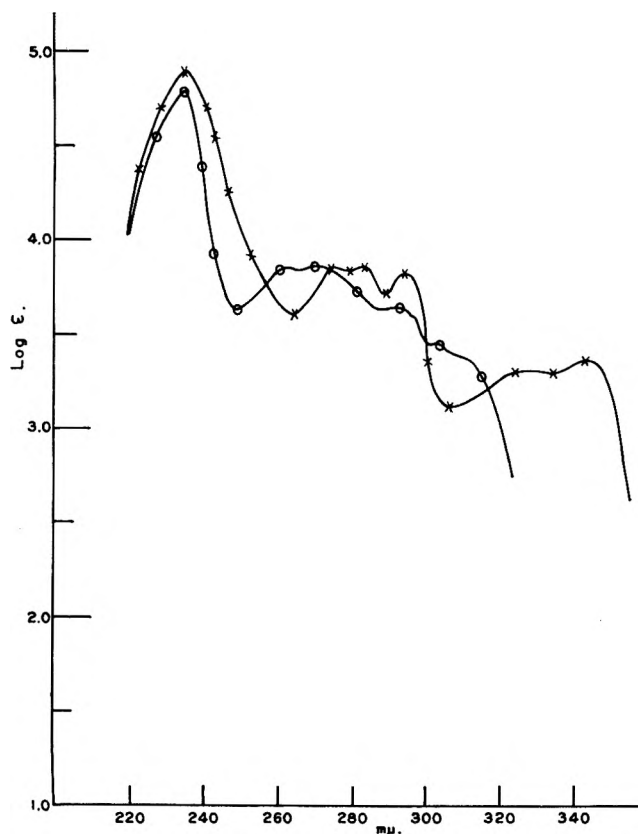
Fig. 1.—Ultraviolet absorption spectra: III O—O—O; 1-methyl-17-dihydroequilenin, x—x—x.

was dried with anhydrous sodium sulfate and evaporated to dryness. The oily residue was dissolved in 200 ml. of methanol and a solution of 10 g. of sodium hydroxide in 20 ml. of water was added. The solution was refluxed for 1 hr., when 2 l. of water was added and the mixture was acidified with 2 $N$ hydrochloric acid. After being collected, the resulting amorphous precipitate was dissolved in ether, dried, and treated with 1 g. of activated charcoal. The decolorized solution was concentrated to small volume and hexane was added when crystallization of fine needles started. Several recrystallizations from ether hexane yielded 2.1 g. (21%) of pure III, m.p. 163.5–164°, $[\alpha]D$ +43.5°, $\lambda_{max}^{MeOH}$ 235, 261, 270, 282, 293, and 314 mμ, log $\epsilon$ 4.78, 3.83, 3.84, 3.74, 3.63, and 3.28, respectively; $\lambda_{max}^{KBr}$ 3.14, 6.19, 7.39, and 7.91 μ.

*Anal.* Calcd. for $C_{20}H_{24}O$: C, 85.71; H, 8.57. Found: C, 86.06; H, 8.44.

**Acetate (IIIa).**—The acetate of compound III was prepared with acetic anhydride and pyridine at room temperature.

It crystallized from methanol as plates, m.p. 82–83.5°, $[\alpha]D$ + 45.9°, $\lambda_{max}^{MeOH}$ 235, 263, 270, 284, 315 and 325 mμ, log $\epsilon$ 4.84, 3.83, 3.68, 3.76, 3.31, and 3.31, respectively; $\lambda_{max}^{KBr}$ 2.94, 3.44, 5.69, 7.29, and 8.09μ.

*Anal.* Calcd. for $C_{22}H_{26}O_2$: C, 81.94; H, 8.13. Found: C, 82.05; H, 8.23.

**3′,3′,5-Trimethyl-7-hydroxy-1,2-cyclopentenophenanthrene (IV).**—A mixture of 2.5 g. of IIIa and 2 g. of 5% palladium–carbon was heated in an oil bath at 250–280° for 4 hr. The cooled reaction product was diluted with ether and the catalyst was removed by filtration. The filtrate was evaporated to dryness and the residual oil was saponified by being boiled for 1 hr. with a solution of 2 g. of sodium hydroxide in 5 ml. of water and 50 ml. of methanol. The reaction mixture was poured into 1 l. of water, acidified with 2 $N$ hydrochloric acid, and extracted several times with ether. The combined extracts were washed with water and sodium bicarbonate solution, and then dried with anhydrous sodium sulfate. After concentration to a small volume, compound IV was precipitated with hexane. Two crystallizations from ether–hexane yielded 1 g. of pure product m.p. 144–145°, $[\alpha]D$ 0, $\lambda_{max}^{MeOH}$ 227, 262, 284, 296, and 307 mμ, log $\epsilon$ 4.23, 4.82, 4.13, 4.03, and 4.05, respectively.

*Anal.* Calcd. for $C_{20}H_{20}O$: C, 86.91; H, 7.29. Found: C, 86.57; H, 7.22.

# Rearrangement of 2-Cyano-3-t-butyl-1-indenone

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The formation of substituted indenones and indanones from the acid treatment of $\alpha$-cyano-$\beta$-substituted cinnamonitriles I has been reported.[2] It was shown that, when the R groups in I were $CH_3$, $C_2H_5$, $i$-$C_3H_7$, or $C_6H_5$, cyclic ketoamides are produced, but that ring closure of I (R = $t$-$C_4H_9$) furnishes the cyano ketone IIa. Since the ketoamide IIb was desired, especially for ultraviolet study, several attempts to prepare it by hydration of IIa were made. Under several different acid conditions, the ketoamide was not formed; instead, a nitrile isomeric with IIa, as indicated by its elemental analysis and molecular weight determination, was isolated.
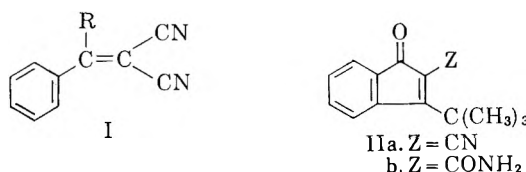


Compound IIa is a yellow solid, m.p. 198°, while the isomer is white, and melted at 165°. In contrast to the infrared spectrum of IIa, which possessed peaks at 2252 cm.$^{-1}$ (CN) and 1720 cm.$^{-1}$ (CO), the spectrum of the white compound had a peak at 2250 cm.$^{-1}$ (CN), but the carbonyl vibrational frequency had been shifted to 1662 cm.$^{-1}$. A change in the ultraviolet spectrum was also observed. The spectrum of the white compound displayed a $\lambda_{max}$ at 251 mμ ($\epsilon$ 19,300), as compared with $\lambda_{max}$ 244 mμ ($\epsilon$ 35,000) for IIa.

Josier and Fuson[3] report that substituted 1-indenones show carbonyl absorption in the region of 1710–1740 cm.$^{-1}$ and $\alpha,\beta$-unsaturated six-membered cyclic ketones near 1665 cm.$^{-1}$. Hassner and Cromwell[4] have found that 4,4-dimethyl-1-keto-1,4-dihydronaphthalene (IIIa) and 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (IIIb) have peaks in the infrared at 1665 cm.$^{-1}$ and 1662 cm.$^{-1}$, and $\lambda_{max}$ values in the ultraviolet at 242 mμ ($\epsilon$ 10,600) and 252 mμ ($\epsilon$ 11,000), respectively.

The evidence presented thus far suggests a rearrangement of IIa involving ring expansion to 2-cyano-3,4,4-
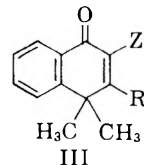


a. R = Z = H
b. R = H, Z = $CH_2C_6H_5$
c. R = $CH_3$, Z = CN
d. R = $CH_3$, Z = $CONH_2$

(1) Contribution no. 1105, taken in part from a thesis submitted to Indiana University in partial fulfillment of the requirements for the degree Doctor of Philosophy, June, 1962, by D. M., Bristol Predoctoral Fellow, 1960–1962.

(2) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, and Donald R. Maulding, *J. Org. Chem.*, **27**, 4428 (1962).

(3) M. L. Josier and N. Fuson, *Bull. soc. chim. France*, 389 (1952).

(4) A. Hassner and N. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

trimethyl-1-keto-1,4-dihydronaphthalene (IIIc), had occurred. Interpretation of the n.m.r. spectrum (60 Mc.) of the compound in question added convincing support favoring IIIc as the correct structure of the new product. It had an n.m.r. absorption peak centered at 8.39 τ, attributed to a *gem*-dimethyl group and a second peak (7.50 τ) of one-half intensity. The n.m.r. spectrum of IIa has a single resonance peak at 8.40 τ, representing the hydrogens on the tertiary butyl group.

An alternate synthesis of the cyano ketone IIIc was accomplished by the ring closure of the condensation product of malononitrile with 3-methyl-3-phenyl-2-butanone. Favorskii,[5] *et al.*, prepared 3-methyl-3-phenyl-2-butanone by heating pivalophenone with zinc chloride at 320°, but a more direct approach, using the organocadmium synthesis,[6] gave a good yield of 3-methyl-3-phenyl-2-butanone. The condensation of the ketone with malononitrile was successful, but in low yield (26%) as expected from the considerable steric hindrance caused by the groups alpha to the carbonyl group. Ring closure of purified IV gave 2-cyano-3,4,4-trimethyl-1-keto-1,4-dihydronaphthalene (IIIC), which had an infrared spectrum and melting point identical with the rearranged product from IIa.
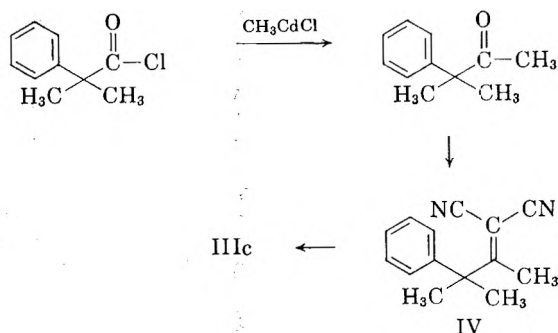


Conversion of IIa to IIIc was effected in concentrated sulfuric acid at room temperature and also by heating in polyphosphoric acid. The best yield of IIIc, however, was produced when IIa was heated in concentrated sulfuric acid on a steam bath for 10–15 minutes. When the reaction time was extended to two hours, rearrangement and hydration of the nitrile occurred, since 2-carbamoyl-3,4,4-trimethyl-1-keto-1,4-dihydronaphthalene (IIId) was isolated.

The formation of IIIc from IIa can be explained by the following reactions. Protonation of IIa leads to the formation of the resonance-stabilized carbonium ion V. This is the same type of intermediate as that proposed to explain the reaction sequence involved in the acid-catalyzed conversion of 2-carbamoyl-3-alkyl-1-indenones to 2-carbamoyl-3-alkylidene-1-indanones.[2]
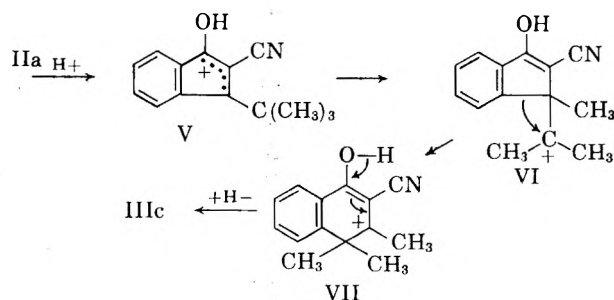


Since the tertiary butyl group prevents the formation of an indanone, IIIc is produced by an alternate path, namely methyl migration of the neopentyl carbonium ion V to yield the tertiary carbonium ion VI, ring expansion to give VII, followed by elimination of a proton.

## Experimental

All melting points reported are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Unless otherwise stated, all infrared spectra were recorded by a Perkin-Elmer Model 137 Infracord. The ultraviolet absorption spectra were determined in 95% ethanol with a Cary Model 14 recording spectrophotometer. The n.m.r. spectra were recorded in deuterated chloroform with a Varian Associates high-resolution n.m.r. spectrometer, Model V4300B.

**Rearrangement of 2-Cyano-3-*t*-butyl-1-indenone (IIa).**—One gram of IIa[2] was dissolved in 50 ml. of concentrated sulfuric acid and heated on a steam bath for 10–15 min. Upon pouring the deep red solution into 400 g. of ice, a yellow solid precipitated, which, when recrystallized from benzene–hexane, yielded 0.42 g. (42%) of white crystals, m.p. 164–165°. The infrared spectrum (Perkin-Elmer Model 137-G grating spectrophotometer) showed peaks at 3075 (aromatic CH), 3010 (aliphatic CH), 2250 (CN), and 1662 cm.$^{-1}$ (CO). The ultraviolet spectrum had a $\lambda_{max}$ at 251 mμ ($\epsilon$ 19,200). The n.m.r. spectrum (60 Mc.) had a resonance peak at 8.39 τ and another at 7.50 τ, having one-half the intensity (tetramethylsilane as standard).

*Anal.* Calcd. for $C_{14}H_{13}NO$: C, 79.57; H, 6.20; N, 6.63; mol. wt., 211. Found: C, 79.35; H, 6.09; N, 6.63; mol. wt., 210–211 (Mechrolab vapor pressure osometer, Model 301A, determined in chloroform).

Dissolving 0.5 g. of IIa in 10 ml. of concentrated sulfuric acid and allowing to stand at room temperature for (a) 12 hr. and (b) 24 hr., then pouring over ice produced (a) 90 mg. (18%) and (b) 25 mg. (5%) of IIIc. Heating 0.5 g. of IIa dissolved in 20 ml. of polyphosphoric acid on a steam bath for 4 hr. yielded 100 mg. (20%) of IIIc after hydrolysis.

**Rearrangement and Hydration of IIa.**—One gram of the cyano ketone IIa was dissolved in 10 ml. of concentrated sulfuric acid and heated on a steam bath for 2 hr., then poured into 100 g. of ice. Extraction of the acidic solution with chloroform yielded an orange solid which, after washing with 5% sodium bicarbonate solution and recrystallization from aqueous ethanol, then benzene, gave 410 mg. (40%) of white crystals, m.p. 179–180°. $\nu_{max}^{KBr}$ 3520 (NH), 3205 (NH), 2985 (aliphatic CH), 1665 (CO), and 1640 cm.$^{-1}$ (amide CO).

*Anal.* Calcd. for $C_{14}H_{15}NO_2$: C, 73.36; H, 6.55; N, 6.15. Found: C, 73.14; H, 6.80; N, 6.22.

**Preparation of α-Phenylisobutyric Acid.**—While 75 g. (0.55 mole) of aluminum chloride and 200 ml. of dry benzene were being stirred in a 500-ml. three-necked round-bottomed flask, equipped with a condenser, calcium chloride drying tube, and stirrer, 42 g. (0.25 mole) of α-bromoisobutyric acid dissolved in 50 ml. of dry benzene was added by means of a dropping funnel. The mixture was stirred at room temperature for 1 hr., then refluxed for 6 hr. After standing overnight the dark solution was cautiously poured into one liter of 20% sulfuric acid and ice. The benzene layer was separated and washed with two portions of 10% sulfuric acid, one portion of water, and five 80-ml. portions of 5% sodium hydroxide. The dilute alkaline solution was treated with Norit and filtered into 400 ml. of 20% sulfuric acid. A white precipitate (33 g., 80%) which melted at 78–80° was collected. α-Phenylisobutyric acid has been reported to melt at 80–81°.[7]

**Preparation of α-Phenylisobutyryl Chloride.**—Freshly distilled thionyl chloride (15 g., 0.192 mole) was placed in a 500-ml. three-necked round-bottomed flask, equipped with a condenser, calcium chloride drying tube and exhaust tube. Fifteen grams (0.092 mole) of α-phenylisobutyric acid dissolved in 200 ml. of dry benzene was added by means of a dropping funnel. After the addition had been completed, the solution was refluxed for 30 min. Vacuum distillation of the crude acid chloride obtained after evaporating the excess thionyl chloride and benzene gave 15 g. of a clear liquid, b.p. 90° (2.0 mm.) [lit.,[8] 109° (13 mm.)].

(5) A. Favorskii, T. E. Zalesskaya, D. I. Rozanov, and G. U. Chelintzev, *Bull. soc. chim. France*, **3**, 239 (1936).

(6) D. A. Shirley, *Org. Reactions*, **VIII**, 28 (1954).

(7) A. Haller and E. Bauer, *Compt. rend.*, **155**, 1582 (1912).

(8) O. Wallach, *Chem. Zent.*, **II**, 1047 (1899).

**Preparation of 3-Methyl-3-phenyl-2-butanone.**—Six grams of magnesium metal turnings washed with a solution of iodine and ethyl ether was placed in a 500-ml. three-necked round-bottomed flask containing a Dry Ice condenser, stirrer, and gas inlet tube. One hundred milliliters of anhydrous ethyl ether was added and methyl bromide (b.p. 4.5°) was bubbled into the ether. The reaction started after adding a crystal of iodine and warming the ether. All the magnesium was dissolved after 2 hr. The Dry Ice condenser was replaced with a water-cooled condenser and 49 g. of cadmium chloride, previously dried to constant weight, was added. The slurry was refluxed for 50 min. until the solution gave a negative Gilman test. The ether was evaporated under nitrogen and 100 ml. of anhydrous benzene was added. With good stirring a solution of 25.7 g. (0.068 mole) of $\alpha$-phenyliso-butyryl chloride in 100 ml. of anhydrous benzene was added to the benzene solution of methylcadmium chloride. The solution was refluxed for 4 hr., cooled, and acidified with 20% sulfuric acid and ice. The benzene layer was separated and washed with 10% hydrochloric acid, 10% sodium hydroxide and water. After drying with sodium sulfate, the benzene solution was evaporated, and the resulting oil (19.1 g., 84%) distilled at 97° (0.5 mm.) [lit.,[5] 97–98° (11 mm.)]; $\nu_{max}^{KBr}$ 2985 (with shoulders; aliphatic and aromatic CH) and 1701 cm.$^{-1}$ (CO). A vapor phase chromatogram (F and M 500 programmed temperature gas chromatograph with Carbowax 20 M column) showed the ketone was over 99% pure.

*Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.23; H, 8.55.

**3-Methyl-3-phenyl-2-butylidenemalononitrile (IV).**—Sixteen grams of 3-methyl-3-phenyl-2-butanone was dissolved in 150 ml. of anhydrous benzene and refluxed for 48 hr. with 8 g. of malononitrile, 3 g. of ammonium acetate, and 9 ml. of glacial acetic acid. Evaporation of the solvent gave an oil, which was distilled under reduced pressure. The first fraction collected (10.8 g.) was the starting ketone, b.p. 88–90° (0.2 mm.), and the second fraction, 5.2 g., b.p. 130–135° (0.25 mm.), had a peak in the infrared at 2220 cm.$^{-1}$. Redistillation gave an analytical sample collected at 133° (0.25 mm.).

*Anal.* Calcd. for $C_{14}H_{14}N_2$: C, 80.00; H, 6.67; N, 13.33. Found: C, 80.12; H, 7.03; N, 12.98.

**Ring Closure of 1-Methyl-2-phenylisobutylidenemalononitrile (IV).**—Two hundred milligrams of IV was allowed to react in 4 ml. of concentrated sulfuric acid at room temperature for 1 hr. A white solid precipitated after the dark green solution was poured into 40 g. of ice and allowed to stand overnight. Recrystallization from alcohol gave 152 mg. (78%) of white needles, m.p. 164–165°. The infrared spectrum was identical to IIIc and a mixture melting point showed no depression.

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# Reaction of *t*-Butoxy Radical with 4-Vinyl-cyclohexene

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In continuation of a study of the reaction of free radicals with olefins, it became evident that further work was required to elucidate one phase of the work previously reported.[2]

(1) Present address: Research Laboratories, Celanese Corp., Summit, N. J.

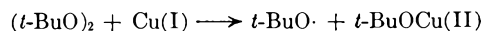(2) J. R. Shelton and J. N. Henderson, *J. Org. Chem.*, **26**, 2185 (1961).

The previous work had reported that the slow photolysis of di-*t*-butyl peroxide in 4-vinylcyclohexene yielded dehydrodimers and that the more rapid copper-induced decomposition resulted in both *t*-butyl vinylcyclohexenyl ethers and dehydrodimers. Reference was made to the work of Kharasch and Fono,[3] but it was also suggested that perhaps increased radical concentration resulting from more rapid peroxide decomposition might explain the production of the *t*-butyl vinylcyclohexenyl ether. Recent studies reported by Kochi[4] on the mechanism of the copper salt-catalyzed reactions of peroxides suggested the possibility of involvement of cupric *t*-butoxide in the reaction to form the ether provided the copper salt was sufficiently soluble in the reaction medium.

In order to test these two hypotheses, four reactions of di-*t*-butyl peroxide with 4-vinylcyclohexene were carried out at a temperature of 80°. These are written below in equation form with the major products indicated.

$$(t\text{-BuO})_2 + C_8H_{12} \xrightarrow{\text{heat}} t\text{-BuOH} + (C_8H_{11})_2 \qquad (1)$$

$$(t\text{-BuO})_2 + C_8H_{12} \xrightarrow[\text{heat}]{\text{CuCl}_2} t\text{-BuOH} + t\text{-BuO-}C_8H_{11} + (C_8H_{11})_2 \quad (2)$$

$$(t\text{-BuO})_2 + C_8H_{12} \xrightarrow[\text{heat}]{h\nu} t\text{-BuOH} + (C_8H_{11})_2 \qquad (3)$$

$$(t\text{-BuO})_2 + C_8H_{12} \xrightarrow[\text{heat}]{h\nu,\text{CuCl}_2} t\text{-BuOH} + (C_8H_{11})_2 \qquad (4)$$
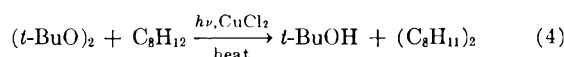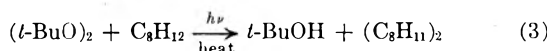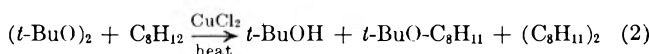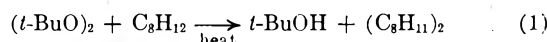
The rate of disappearance of di-*t*-butyl peroxide was observed to be the same in reactions 3 and 4 which was more rapid than 1 and 2. Comparison of 1 and 2 at 115° showed that reaction 2 is faster than 1. One also observes that reaction 2 in which the reactants are heated in the presence of copper salt is the only reaction to produce *t*-butyl vinylcyclohexenyl ether and that the photolysis reactions with or without cupric chloride produce no ether. In the case of reaction 2 the ether is formed in approximately the same amount as the dehydrodimer as determined by gas chromatography. One concludes from these data that the production of *t*-butyl vinylcyclohexenyl ether is definitely not a result of a radical concentration effect.

The formation of *t*-butyl vinylcyclohexenyl ether is visualized as occurring through a mechanism analogous to the one proposed by Kochi[4] in which a free radical R· is oxidized by a cupric salt, Cu(II)OX, to form ROX and Cu(I).

$$(t\text{-BuO})_2 + \text{Cu(I)} \longrightarrow t\text{-BuO·} + t\text{-BuOCu(II)}$$

$$t\text{-BuO·} + C_8H_{12} \longrightarrow t\text{-BuOH} + C_8H_{11}·$$

$$t\text{-BuOCu(II)} + C_8H_{11}· \longrightarrow t\text{-BuO-}C_8H_{11} + \text{Cu(I)}$$

$$2C_8H_{11}· \longrightarrow (C_8H_{11})_2$$
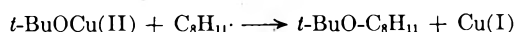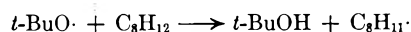
Although cupric chloride was used in this study, some cuprous salt would soon be formed as a result of slow thermal decomposition of peroxide to produce free radicals which would initiate the above sequence. The production of dehydrodimer probably results from a coupling of vinylcyclohexenyl radicals.

Gas chromatography also indicated that a small amount of lower boiling materials was formed in the reactions. Infrared analysis was consistent with a product formed by attack of $CH_3$· radicals on 4-vinyl-cyclohexene. The spectra of two of the materials

(3) M. S. Kharasch and A. Fono, *ibid.*, **24**, 606 (1959).

(4) J. K. Kochi, *Tetrahedron*, **18**, 483 (1962).

showed, in one case, no vinyl absorption but internal unsaturation and methyl absorption; the other material examined showed absorptions corresponding to a methyl group and both vinyl and internal unsaturation. The spectra were otherwise similar to that of 4-vinyl-cyclohexene. Thus both addition and substitution products are found. Acetone was also found to be produced in these reactions showing that some cleavage of t-butoxy radical to form $CH_3\cdot$ must also have occurred.

### Experimental

**Reagent.**—Di-t-butyl peroxide (Shell) was distilled at reduced pressure before use. The 4-vinylcyclohexene (Cities Service) was passed through an activated alumina column immediately before use.

All experiments were performed in a 1-l., three-necked, round-bottom flask equipped with a quartz test tube in the center neck. A length of hypodermic tubing was inserted through a serum cap attached to one of the flask necks. Samples were removed by placing evacuated sample vials onto this tubing and withdrawing approximately 1 ml. of solution. The reactions were stirred at all times by a magnetic stirring bar.

4-Vinylcyclohexene (165 g., 1.5 moles) was heated in the flask described above, and di-t-butyl peroxide (36 g., 0.25 mole) was heated simultaneously under nitrogen in a dropping funnel attached to the flask. When both were at the desired temperature (80 or 115°) the peroxide was added. Samples were withdrawn at appropriate time intervals. In those reactions involving cupric chloride, 0.3 g. of cupric chloride (dihydrate) was added to the 4-vinylcyclohexene before heating. The photolysis reactions were performed using a G.E. H85A3/UV lamp inserted into the quartz test tube mentioned above.

t-Butyl peroxide concentration was measured by gas chromatography at 75° on a 6-ft. silicone gum rubber column. Product analysis was also carried out by gas chromatography on a 6-ft. Carbowax (20M) column, programming from 100–250°. Product identification was by infrared spectroscopy. The following absorptions were observed in the 4-vinylcyclohexenyl ethers: 3090 cm.$^{-1}$ vinyl unsaturation, 3030 cm.$^{-1}$ cis-internal unsaturation, the typical aliphatic C–H absorptions around 2900 cm.$^{-1}$, 1640 cm.$^{-1}$ vinyl unsaturation, 1390 cm.$^{-1}$ and 1360 cm.$^{-1}$ assigned to t-butyl, 1155 cm.$^{-1}$ typical of ethers, 997 cm.$^{-1}$ and 915 cm.$^{-1}$ vinyl unsaturation, and 690 cm.$^{-1}$ assigned to internal unsaturation. The dehydrodimers showed the following absorptions: 3080 cm.$^{-1}$ vinyl unsaturation, 3030 cm.$^{-1}$ cis-internal unsaturations, aliphatic C–H absorptions between 3000 and 2800 cm.$^{-1}$, 1640 cm.$^{-1}$ vinyl unsaturation, 997 and 910 cm.$^{-1}$ vinyl unsaturation, 660 cm.$^{-1}$ internal unsaturation. The over-all infrared spectrum of the dehydrodimer showed the presence of all the major absorptions of 4-vinylcyclohexene, the only marked exception being the moderately strong 4-vinylcyclohexene peak at 1140 cm.$^{-1}$ (unassigned) absent in the dehydrodimer. Comparison with previous work,[2] in which both the ether and dehydrodimer were isolated and characterized by infrared, hydrogenation, and elemental analysis, further confirmed the identification.

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### Dibenzyl Carbethoxy Phosphate

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Several anhydrides of phosphoric acid with carboxylic acids of the type RCO—O—PO(OH)$_2$ have been described,[1] in which R is a simple alkyl or aryl group. Much interest has been directed to the chemical and biological properties of acetyl phosphate.[2] No anhydride of phosphoric acid with a monoalkyl carbonic acid, in which R = alkoxy, has been described.

In the present work, dibenzyl carbethoxy phosphate was prepared by reaction of dibenzyl silver phosphate with ethyl chloroformate.

$$(C_7H_7O)_2\,POOAg + ClC(O)OC_2H_5$$
$$= (C_7H_7O)_2P(O)OC(O)OC_2H_5 + AgCl$$
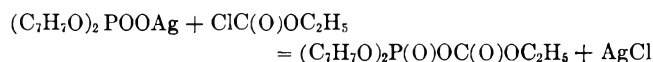
The product is colorless oil, which is stable at 0°.

In aqueous dioxan (1:1 by volume), dibenzyl carbethoxy phosphate undergoes hydrolysis and dibenzyl hydrogen phosphate is formed. The progress of hydrolysis can be followed by neutralizing the acid as it is produced, using an automatic pH-stat titrator. The reaction observed first-order kinetics. At a constant pH of 6.0 and 37°, $k = (3.53 \pm 0.02) \times 10^{-5}$ sec.$^{-1}$, using initial concentrations of 2 to 9 mmoles of the anhydride.

Attempts were made to remove the benzyl groups and to obtain carbethoxy phosphate, $C_2H_5O\ C(O)-OPO(OH)_2$. Various debenzylating agents were tried, but in each case extensive decomposition occurred and carbon dioxide was evolved.

### Experimental

**Dibenzyl Carbethoxy Phosphate.**—Ethyl chloroformate (8 ml., freshly distilled) was added to a suspension of silver dibenzyl phosphate[3] (m.p. 213°, 1.05 g., prepared from dibenzyl phosphorochloridate[4]) in dry dioxan (30 ml.). A precipitate formed instantly. The mixture was stirred for 2 hr. at room temperature and the precipitate of silver chloride was then filtered off. The solvents were evaporated by high vacuum distillation, yielding 0.94 g. (98%) of a colorless viscous oil, which was stored in the cold.

*Anal.* Calcd. for $C_{17}H_{19}O_6P$: C, 58.2; H, 5.44; P, 8.9%. Found: C, 57.8; H, 5.46; P, 9.1.

The infrared absorption of the product was measured in carbon tetrachloride solution, using a Perkin-Elmer Model 12 spectrometer. Strong absorption bands occurred at 1024 cm.$^{-1}$ (due to the POC vibration[5]), at 1235 cm.$^{-1}$ (phosphoryl stretching), at 1372 cm.$^{-1}$ (methyl group vibration), at 1459 cm.$^{-1}$ (benzyl group vibration), at 1731 cm.$^{-1}$ (carbonyl stretching), and at 2955 cm.$^{-1}$ (C–H vibration).

**Hydrolysis.**—Dibenzyl carbethoxy phosphate (about 100 mg.) was dissolved in aqueous dioxan (100 ml.; 1:1 by volume) in a beaker fitted with a magnetic stirrer and covered by a rubber stopper. This stopper had three holes, through which the glass and calomel electrodes as well as the capillary glass outlet of a magnetic valve-operated buret led into the solution. The beaker was placed into a thermostat at 37.0°, above a rotating permanent magnet enclosed in a brass can. The electrodes were connected to a Radiometer Model TTT 1a automatic pH meter, which was set to keep a constant pH of 6.00 ± 0.05. The buret contained standard 0.10 $N$ sodium hydroxide solution and titrated the dibenzyl hydrogen phosphate as it was formed. In a separate experiment, the end point in the titration of dibenzyl hydrogen phosphate had been shown to be pH = 6.0. Example of a kinetic experiment: dibenzyl carbethoxy phosphate (initially 1.9 mmoles) at 37.0°.

(1) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 348.

(2) F. Lynen, *Chem. Ber.*, **73**, 367 (1940); R. Bentley, *J. Am. Chem. Soc.*, **70**, 2183 (1948); **71**, 2765 (1949); D. E. Koshland, Jr., *ibid.*, **74**, 2286 (1952). F. Lipmann, *Advan. Enzymology*, **6**, 231 (1946); A. W. D. Avison, *J. Chem. Soc.*, 732 (1955).

(3) A. R. Atherton, H. T. Openshaw, and A. R. Todd, *ibid.*, 385 (1945).

(4) G. W. Kenner, A. R. Todd, and F. J. Weymouth, *ibid.*, 3678 (1952).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., London, 1958, p. 311.

| Time (sec.) | 0 | 780 | 3600 | 5400 |
|---|---|---|---|---|
| x = mmoles NaOH | 0.585 | 0.635 | 0.785 | 0.89 |
| Time (sec.) | 7200 | 9000 | 10800 | Infinity |
| x = mmoles NaOH | 0.98 | 1.07 | 1.15 | 2.34 |

From the slope of a plot of log (a–x) against time, the first-order rate was derived $k_1 = 3.55 \times 10^{-6}$ sec.$^{-1}$.

**Hydrogenation of dibenzyl carbethoxy phosphate** in dry ethanol in the presence of a 10% palladium catalyst (on carbon powder) yielded after several hours shaking at 30–40 lbs./sq. in. pressure of hydrogen an equivalent amount of carbon dioxide (collected in barium hydroxide). Similar results were obtained by treatment of the material with barium iodide in acetone,[6] and hydrogen bromide in acetic acid.[7]

**Acknowledgment.**—The authors are indebted to Dr. S. Pinchas for the infrared measurements. This investigation was supported in part by grant RG-5842 from the National Institutes of Health, U. S. Public Health Service.

(6) L. Zervas and I. Dilaris, J. Am. Chem. Soc., **77**, 5354 (1955).
(7) D. Ben-Ishai and A. Berger, J. Org. Chem., **17**, 1564 (1952).

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# Potential Inhibitors of Cancerous Growth.
## III. Dibenzyl Acetals as Synthetic Intermediates

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In the attempted synthesis of N,N-bis(2-chloroethyl)-3,5-cyclophosphamido-D-ribose, the corresponding dimethyl acetal[1] was hydrolyzed in dilute mineral acid. Although the cyclic phosphamide structure was apparently retained, the removal of the acetal grouping was unsatisfactory under these conditions. In a typical run, using 0.01 N hydrochloric acid in 50% aqueous dioxane, the amount of liberated aldehyde, estimated by the quantitative Benedict procedure, initially increased to 70% of the calculated value and then decreased for some unknown reason.

In view of the relative acid lability of cyclic phosphamides[2] and certain phosphate esters,[3] it seemed desirable to investigate the possibility of using an aldehyde blocking group in the above synthesis which could be removed by some reaction that does not involve the use of acid. The cleavage of O- and N-benzyl compounds by catalytic hydrogenation is a well known and widely used reaction in other fields for similar purposes.[4,5] In the carbohydrate field the cleavage of benzyl β-D-glycosides with hydrogen and metal catalysts has been described.[6] The dibenzyl acetal derivatives of D-ribose therefore appeared to be suitable intermediates for our projected synthesis, particularly in view of the reported stability of phosphate esters toward hydrogenolysis.[7] However, the

dibenzyl acetals of D-ribose and its derivatives do not appear to have been described or used as synthetic intermediates. We have, therefore, prepared the dibenzyl acetal of D-ribose as well as that of D-ribose tetraacetate and 2,4-O-benzylidene-D-ribose.
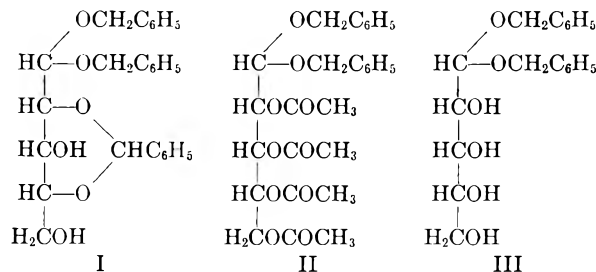


In order to determine the suitability of dibenzyl acetals as synthetic intermediates, we have studied the behavior of these compounds toward hydrogenation. By choice of a suitable catalyst,[6] O-benzyl groups can be removed selectively by hydrogenation. In the case of the above-mentioned dibenzyl acetals, 10% palladized charcoal was found to be a suitable catalyst for the preparation of the corresponding free aldehyde compounds by hydrogenolysis.

## Experimental[18]

**2,4-O-Benzylidene-D-ribose dibenzyl Acetal (I).**—Yellow mercuric oxide (3.24 g., 15 mmoles) and anhydrous calcium sulfate (5 g.) were added to a solution of 2,4-O-benzylidene-D-ribose di-n-propyl dithioacetal[9] (1.86 g., 5 mmoles) in 68 ml. of pure anhydrous benzyl alcohol in a 500-ml. three-necked flask fitted with a mercury-sealed mechanical stirrer and a calcium chloride tube. The mixture was stirred vigorously with the flask submerged in a water bath maintained at 70°. A solution of 3.4 g. of mercuric chloride in 68 ml. of anhydrous benzyl alcohol was added slowly from a dropping funnel over a period of 5 min. Stirring was continued for a further 3 hr., the mixture filtered under suction onto 0.5 g. of yellow mercuric oxide, and the residue washed thoroughly with anhydrous benzyl alcohol. The benzyl alcohol was then removed from the combined filtrates as completely as possible in a rotary vacuum evaporator (0.5 mm., 65°). The residue was taken up in 100 ml. of chloroform, filtered, and washed with five 100-ml. portions of 10% aqueous potassium iodide and then with water until the washings were free from iodide ions. The chloroform solution was then dried over anhydrous sodium sulphate and evaporated to dryness. The remaining oil crystallized immediately on addition of 50 ml. of dibutyl ether. The crystals were filtered off and recrystallized from dibutyl ether; yield 1.6 g. (73%), m.p. 96–97°, $[\alpha]^{20}$D +18.6 (c 8.75, methanol); $\lambda_{max}^{CH_3OH}$ 258 mμ ($a_m$ 570); $\lambda_{max}^{KBr}$ 2.93, 9.05 μ.

*Anal.* Calcd. for $C_{26}H_{28}O_6$: C, 71.55; H, 6.46. Found: C, 71.34; H, 6.34.

**Hydrogenolysis of 2,4-O-Benzylidene-D-ribose Dibenzyl Acetal.**—Two grams of 10% palladized charcoal[10] was saturated with hydrogen in 50 ml. of methanol. A solution of 2,4-O-benzylidene-D-ribose dibenzyl acetal (200 mg.) in 10 ml. of methanol was added and the hydrogenation continued. After approximately 3 hr., the calculated volume of hydrogen had been taken up. The catalyst was filtered off, washed with four 25-ml. portions of

(1) W. J. Serfontein and J. H. Jordaan, J. Org. Chem., **27**, 3332 (1962).
(2) H. Arnold and H. Klose, Arzneimittel-Forsch., **11**, 430 (1957).
(3) H. G. Khorana, G. M. Tener, R. S. Wright, and J. G. Moffatt, J. Am. Chem. Soc., **79**, 430 (1957).
(4) W. H. Hartung and R. Simonoff, Org. Reactions, **7**, 263 (1953).
(5) H. J. Haas, Ber., **94**, 2442 (1961).
(6) N. K. Richtmeyer, J. Am. Chem. Soc., **56**, 1633 (1934).
(7) H. O. L. Fischer and E. Baer, Ber., **65**, 337 (1932).

(8) Microanalyses were performed by the Microanalytical Section of the South African Council for Scientific and Industrial Research. Spectra of the compounds were measured with a Beckman DK 2 recording ultraviolet spectrophotometer and a Perkin-Elmer 21 infrared spectrophotometer. Paper chromatograms were run on Whatman no. 1 paper using acetone-butanol–water (7:2:1), butanol–acetic acid–water (4:1:5), butanol–pyridine–water (6:4:1), and water-saturated butanol as mobile phases.
(9) D. J. J. Potgieter and D. L. MacDonald, J. Org. Chem., **26**, 3934 (1961).
(10) A. I. Vogel "Practical Organic Chemistry," 3rd ed., Longmans, Green and Co., London, 1956, p. 950.

methanol, and then with five 10-ml. portions of distilled water. The combined filtrate was concentrated in vacuum at 40° and traces of water removed from the residue by repeated evaporation *in vacuo* with small quantities of absolute ethanol. Paper chromatography using acetone–butanol–water (2:2:1) as mobile phase revealed the presence of a high concentration of D-ribose ($R_f$ 0.41) as well as traces of two nonreducing components ($R_f$ 0.33 and 0.73) which could be revealed by periodic acid–benzidine coloration. Confirmation of the identity of the main component as D-ribose was obtained by means of comparative paper chromatography employing various other mobile phases as well as by conversion of the crude oily product into D-ribose di-*n*-propyl dithioacetal[11] (m.p. 81–82°).

**2,3,4,5-Tetra-O-acetyl-D-ribose Dibenzyl Acetal (II). (a).**— 2,3,4,5-Tetra-O-acetyl-D-ribose diethyl dithioacetal[12] (6.37 g., 15 mmoles) was demercaptalated in the presence of yellow mercuric oxide (9.72 g., 45 mmoles), anhydrous calcium sulfate (15 g.), and anhydrous benzyl alcohol (100 ml.) by the addition of a solution of mercuric chloride (10.2 g., 37.5 mmoles) in 200 ml. of benzyl alcohol as described previously. After removal of the chloroform an oily residue was obtained. Traces of benzyl alcohol were removed by repeatedly dissolving the product in 25 ml. of ethanol and precipitating the oil with 400 ml. of water at 40°. Finally the product was repeatedly evaporated to dryness with small quantities of absolute ethanol to remove traces of water. The oily product, dried at 50° and 0.5 mm. for 3 hr., was soluble in methanol, ethanol, chloroform, ether, etc., and insoluble in water and petroleum ether. $[\alpha]^{20}D$ + 11.2 (c 10, methanol); $\lambda_{max}^{CH_3OH}$ 258 m$\mu$ ($a_m$ 346); $\lambda_{max}^{film}$ 5.72, 8.20, 9.52 $\mu$.

*Anal.* Calcd. for $C_{27}H_{32}O_{10}$: C, 62.78; H, 6.25. Found: C, 63.88; H, 6.32.

After unsuccessful attempts to purify the material by crystallization, the product was further characterized by conversion into the crystalline D-ribose dibenzyl acetal by deacetylation.

**(b).**—D-Ribose di-*n*-propyl dithioacetal[11] was acetylated as described by Zinner[12] for other D-ribose dithioacetals and 2,3,4,5-tetra-O-acetyl-D-ribose di-*n*-propyl dithioacetal obtained as an oil which could not be crystallized. Upon demercaptalation of the product in benzyl alcohol as described previyusly. 2,3,4,5-tetra-O-acetal-D-ribose dibenzyl acetal was obtained as an oil and was shown to be identical to the product obtained from 2,3,-4,5-tetra-O-acetyl-D-ribose diethyl dithioacetal (a), by infrared spectroscopy.

**D-Ribose Dibenzyl Acetal (III).**—2,3,4,5-Tetra-O-acetyl-D-ribose dibenzyl acetal (7 g.) was dissolved in 90 ml. of anhydrous methanol in a 250-ml. round-bottomed flask fitted with a reflux condenser and a calcium chloride drying tube. Barium methylate solution (3 ml., 1.7 N) in anhydrous methanol was added, the mixture shaken well, and heated under reflux on a water bath for 2 hr., cooled to room temperature, and carbon dioxide bubbled through. The precipitated barium carbonate was filtered off and the yellow filtrate decolorised with activated charcoal. The solution was taken to dryness *in vacuo* at 40° and the oily residue redissolved in 50 ml. of hot benzene. Upon concentration of the benzene solution the product crystallized. A seeding crystal was retained and the product recrystallized from benzene; yield 3.0 g. (96%); m.p. 91–92°; $[\alpha]^{20}D$ + 10.0 (c 10, methanol); $\lambda_{max}^{CH_3OH}$ 258 m$\mu$ ($a_m$ 325); $\lambda_{max}^{KBr}$ 2.94, 9.60 $\mu$.

*Anal.* Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.39; H, 7.12.

**Hydrogenolysis of D-Ribose Dibenzyl Acetal.**—D-Ribose dibenzyl acetal was hydrogenated in the presence of 2 g. of palladized charcoal in 60 ml. of methanol. After 4 hr. 32 ml. of hydrogen had been consumed (calcd. 32.18 ml.; press., 651.6 mm.; temp., 20°). The catalyst was filtered off and the filtrate taken to dryness *in vacuo*. The residue (77 mg., 90% as D-ribose) consisted of a viscous oil. The material was shown to be practically pure D-ribose by comparative paper chromatography using various mobile phases and by conversion into the crystalline D-ribose di-*n*-propyl dithioacetal (m.p. 81–82°).

(11) H. Zinner, *Ber.*, **83**, 275 (1950).
(12) H. Zinner, *ibid.*, **83**, 418 (1950).

# The Halogenation of 8-Hydroxy- and 8-Methoxyacridizinium Salts[1]

C. K. BRADSHER AND R. C. CORLEY

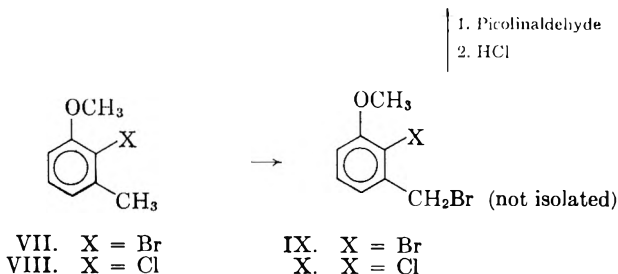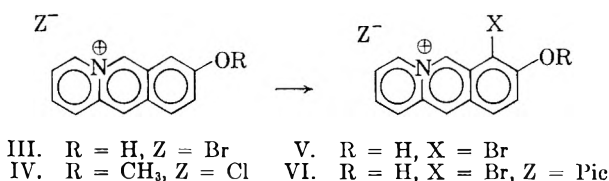*Department of Chemistry, Duke University, Durham, North Carolina*

The aromatic nature of the acridizinium ion (I) results in an extensive delocalization of the positive charge. A consequence is that the system undergoes nucleophilic reactions,[2] but does not easily undergo electrophilic substitution. It has been reported[3] that the related quinolizinium iodides (II) react with bromine in acetic acid to yield dibromoiodides ($R^+$-$IBr_2^-$) rather than substitution products.[4] The present communication describes the first examples of the electrophilic substitution of an acridizinium derivative, the halogenation of 8-hydroxy (III)- and 8-methoxyacridizinium (IV) salts.

The bromination of 8-hydroxyacridizinium bromide



I                                    II
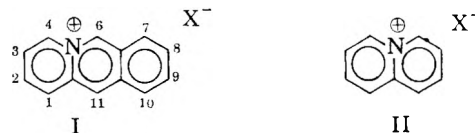
(III)[5] was carried out in refluxing acetic acid, using a onefold molar excess of bromine. The product (68% yield) had the composition of a monobromination product. Analogy suggested that bromination had occurred at the 7-position, and the synthesis of the 7-



III.  R = H, Z = Br        V.   R = H, X = Br
IV.  R = CH₃, Z = Cl       VI.  R = H, X = Br, Z = Pic

1. Picolinaldehyde
2. HCl



VII.  X = Br               IX.  X = Br
VIII. X = Cl               X.   X = Cl

bromo-8-hydroxyacridizinium ion was undertaken. The bromination of 2-bromo-3-methoxytoluene[6] (VII) with N-bromosuccinimide gave crude 2-bromo-3-

(1) This research was supported by a research grant (H-2170) from the National Heart Institute, National Institutes of Health.
(2) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **81**, 1983 (1959).
(3) A. Richards and T. S. Stevens, *J. Chem. Soc.*, 3067 (1958).
(4) G. Jones has succeeded in brominating hydroxyquinolizinium derivatives (private communication).
(5) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).
(6) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, **127**, 498 (1925).

methoxybenzyl bromide (IX). The crude quaternary salt formed by reaction of the benzyl bromide (IX) with picolinaldehyde was cyclized by refluxing it for nine hours in hydrochloric acid solution. Since ether cleavage occurred during the long heating, the product was 7-bromo-8-hydroxyacridizinium bromide (V. Z = Br) rather than the corresponding methyl ether. This material was identical in melting point and infrared spectrum with that obtained by direct bromination of 8-hydroxyacridizinium bromide.

The chlorination of 8-methoxyacridizinium chloride[5] (IV) was carried out in dimethylformamide using sulfuryl chloride as the chlorinating agent. The monochlorination product, isolated in 60% yield as the picrate, was demonstrated to be 7-chloro-8-methoxyacridizinium picrate by synthesis from 2-chloro-3-methoxytoluene (VIII). The procedure used was analogous to that used in the synthesis of the 7-bromo-8-hydroxyacridizinium ion (V) except that the cyclization time was limited to three hours so that the 7-chloro-8-methoxyacridizinium ion (VI) was obtained with a minimum amount of ether cleavage.

### Experimental

All melting points were taken on the Fisher Johns hot stage and are uncorrected. Except as noted, all analyses were by the Galbraith Laboratories, Knoxville, Tenn.

**7-Bromo-8-hydroxyacridizinium Salts (V). (a) By Direct Bromination.**—A solution containing 0.45 g. of 8-hydroxyacridizinium bromide[5] in 150 ml. of acetic acid was refluxed for 20 min. with 0.2 ml. of bromine. When the mixture cooled a yellow product was obtained, m.p. 280–295°. Recrystallization from ethanol afforded yellow needles of the bromide, m.p. 291–296°, yield, 0.39 g. (68%).

The picrate, m.p. 231–233° formed as long needles from ethanol.

(b) **From 2-bromo-3-methoxytoluene (VII).**—In a flask containing 4.5 g. of 2-bromo-3-methoxytoluene,[6] 3.91 g. of N-bromosuccinimide, and 50 ml. of dry carbon tetrachloride, 0.5 g. of dibenzoyl peroxide was added, and the resulting suspension refluxed for 1 hr. The solid was removed by filtration, and the filtrate concentrated under reduced pressure. A small quantity of benzene was added and removed under reduced pressure. The residual oil (5.33 g.), which consisted chiefly of 2-bromo-3-methoxybenzyl bromide, was dissolved in 20 ml. of methanol and refluxed for 3 hr. with 2.03 g. of picolinaldehyde. The solvent was evaporated under reduced pressure and the residual oil washed with ether. The ether was decanted and the oil taken up in 20 ml. of concentrated hydrochloric acid and the solution refluxed for 9 hr. Removal of the acid under vacuum and recrystallization of the residue from ethanol afforded 2.51 g. (39%) of the bromide, m.p. 293–296°. The preparations of the bromide obtained by methods a and b were shown to be identical by mixture melting point determinations and comparison of infrared spectra.

*Anal.* Calcd. for $C_{13}H_9Br_2NO\cdot H_2O$: C, 41.80; H, 2.95; N, 3.76. Found[7]: C, 42.12; H, 2.96; N, 3.94.

The picrate formed as needles from ethanol, m.p. 231–233°. By means of mixture melting point determinations and comparison of infrared spectra, it was shown that this picrate is identical with that obtained by procedure a.

*Anal.* Calcd. for $C_{19}H_{11}BrN_4O_8$: C, 45.34; H, 2.20; N, 11.14. Found: C, 45.45; H, 2.79; N, 11.52.

**7-Chloro-8-methoxyacridizinium Picrate (VI). (a) By Chlorination.**—To a solution containing 0.7 g. (0.0028 mole) of 8-methoxyacridizinium chloride in 15 ml. of dry dimethylformamide, in a flask protected by drying tubes, 0.4 g. (0.003 mole), of sulfuryl chloride was added and the solution was warmed for 20 min., after which an additional 0.1 g. of sulfuryl chloride was added, and heating continued for 0.5 hr. longer. After vacuum evaporation of the dimethylformamide the residue was converted to the picrate and crystallized from ethanol as very small yellow needles, m.p. 215–216°, yield 0.81 g. (60%).

(7) Analysis by Dr. Ing. A. Schoeller, Kronach, Germany.

(b) **From 2-Chloro-3-methoxytoluene (VIII).**—The bromination of 2-chloro-3-methoxytoluene[8] (1.85 g.) was carried out as in the case of the 2-bromo analog (VII). The crude 2-chloro-3-methoxybenzyl bromide (X) was allowed to react with 0.96 g. of picolinaldehyde in refluxing methanol. The crude quaternary salt was cyclized by refluxing it for 3 hr. in 20 ml. of concentrated hydrochloric acid. The crude salt was converted to the picrate for purification, m.p. 215–216°. This material was identical in melting point and infrared spectrum with the picrate obtained from the product of the chlorination reaction.

*Anal.* Calcd. for $C_{20}H_{13}ClN_4O_8$: C, 50.80; H, 2.77; N, 11.85. Found: C, 50.49; H, 2.51; N, 11.57.

(8) G. P. Gibson, J. Chem. Soc., 123, 1269 (1923).

## The Preparation of N,N-Dimethyl- and N,N-Diethylenamines from Ketones

E. P. BLANCHARD, JR.

Recent interest in enamine chemistry[1] prompts the reporting of a simple but useful modification of the Mannich–Davidsen[2] procedure for the preparation from ketones of N,N-dimethyl- and N,N-diethylenamines which previously could not be synthesized readily. The modification involves substituting granular calcium chloride for the normally employed potassium carbonate or calcium oxide to serve as catalyst and dehydrating agent. Although Mannich and Davidsen[2] report the formation of aminals which thermally decompose to the enamine in the reaction of cyclohexanone with piperidine, no evidence for such precursors has been observed in this work. Examination of the ether solution by infrared spectroscopy revealed the presence of the enamine double bond (1640 cm.$^{-1}$) prior to distillative work up. The enamines tabulated were prepared by the general procedure, given in detail for N,N-dimethylamino-1-cyclohexene, of treating the appropriate ketone with either dimethyl- or diethylamine. These enamines were found stable to storage at room temperature in the absence of moisture and oxygen. (See Table I, p. 1398.)
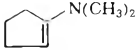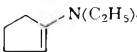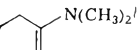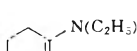
### Experimental

**Materials.**—Commercially available cyclopentanone, cyclohexanone, dimethylamine, diethylamine, anhydrous diethyl ether, and anhydrous 12-mesh calcium chloride were used without further purification.

**Dimethylamino-1-cyclohexene.**—To a solution of dimethylamine (150 g., 3.4 moles) in anhydrous diethyl ether (400 ml.) was added cyclohexanone (196 g., 2 moles) and 12-mesh calcium chloride (150 g.). The mixture was vigorously stirred at room temperature under a nitrogen atmosphere for 64 hr. The slurry was filtered, and the residue washed with diethyl ether (200 ml.). Evaporation of the ether and fractionation of the residue afforded the desired enamine (108.3 g., 0.87 mole) as a colorless liquid, b.p. 81° (35 mm.). Ninety-four and a half grams (0.97 mole) of cyclohexanone was recovered.

(1) See, for example, the Abstracts from the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961, "Symposium on Enamine Chemistry," pp. 44Q–46Q, 53Q–56Q.
(2) C. Mannich and H. Davidsen, Chem. Ber., 69, 2106 (1936).

TABLE I
N,N-DIMETHYL- AND N,N-DIETHYLENAMINES

| Enamine | Conv.,[a] % | Yield,[a] % | B.p., °C. (mm.) | $n^{25}D$ | Anal. Calcd. | Found |
|---|---|---|---|---|---|---|
| (cyclopentylidene)N(CH₃)₂ | 56 | 87 | 85–86 (104) | 1.4801 | C, 75.62 | 75.85 |
| | | | | | H, 11.76 | 12.10 |
| | | | | | N, 12.59 | 12.89 |
| (cyclopentylidene)N(C₂H₅)₂ | 65 | 63 | 99–101 (60) | 1.4777 | C, 77.63 | 77.81 |
| | | | | | H, 12.31 | 12.19 |
| | | | | | N, 10.06 | 9.66 |
| (cyclohexylidene)N(CH₃)₂[b] | 52 | 83 | 81 (35) | 1.4851 | C, 76.74 | 76.54 |
| | | | | | H, 12.08 | 12.18 |
| | | | | | N, 11.18 | 11.29 |
| (cyclohexylidene)N(C₂H₅)₂ | 35 | 51 | 64 (6) | 1.4820 | C, 78.36 | 78.28 |
| | | | | | H, 12.50 | 12.42 |
| | | | | | N, 9.14 | 8.86 |

[a] Based on ketone used. [b] R. A. Benkeser, R. F. Lambert, P. W. Ryan, and D. G. Stoffey, *J. Am. Chem. Soc.*, **80**, 6573 (1958) report this enamine but fail to give either a synthetic procedure or physical constants.

## Pteridine Chemistry. IX.
## 2-Amino-4-hydroxy-6(and 7)-phenylpteridines

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The isomeric 2-amino-4-hydroxy-6(and 7)-phenyl-pteridines (VIIa and IVa) and their 3-methyl derivatives were considered to be useful compounds for a continuation of the study of the methylation of 2-amino-4-hydroxypteridines.[1] However, the published reports by two groups of investigators on the synthesis of VIIa and/or IVa do not agree on the nature of the products obtained.

In 1952, King and Spensley[2] reported that the reaction between 2,4,5-triamino-6-hydroxypyrimidine (Ia) and phenylglyoxal or α-nitroacetophenone gave the 7-phenyl derivative IVa, while Ia and α,α-dichloro-acetophenone gave the 6-phenyl derivative VIIa. In 1956, Dick, Wood, and Logan[3] re-examined the same three reactions and claimed that in each case the product was the 6-phenyl derivative VIIa. In connection with the use of phenylglyoxal in the above reaction, it should be noted that the reaction between 4,5-diaminopyrimidines and ketoaldehydes has been reported many times in the literature. Under weakly acidic conditions similar to those used by King and Spensley,[2] the primary product has almost invariably been a 7-substituted pteridine.[4,5] The 6-substituted derivatives have been prepared only in special systems containing either strong acid[5] or aldehyde binding agents such as hydrazine or sodium bisulfite.[4] Therefore, it was our opinion that King and Spensley were correct with respect to the phenylglyoxal reaction. This was verified as outlined.

2,4,5-Triamino-6-hydroxypyrimidine (Ia) was condensed with phenylglyoxal hydrate in a weakly acidic water–ethanol solution at room temperature.[2] An ultraviolet absorption spectrum of the initial product

indicated that it was primarily the anil IIa. When this product was dissolved in 2.5 N sodium hydroxide, ring closure occurred to give a pteridine which was 2-amino-4-hydroxy-7-phenylpteridine (IVa) contaminated with a small amount of 6-phenyl isomer as shown by paper chromatography and ultraviolet absorption spectra (see p. 1399). The impurity was successfully removed by crystallization. The structure of IVa was proved by its conversion to 2,4-dihydroxy-7-phenylpteridine (III)[3] followed by methylation to produce 1,3-dimethyl-7-phenyl-2,4(1H,3H)-pteridine-dione (V). The latter compound V was then synthesized unequivocally as described by Dick, Wood, and Logan[3] from 6-amino-1,3-dimethyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (VI) and acetophenone. The two products were identical as shown by infrared and ultraviolet absorption spectra and mixture melting point.
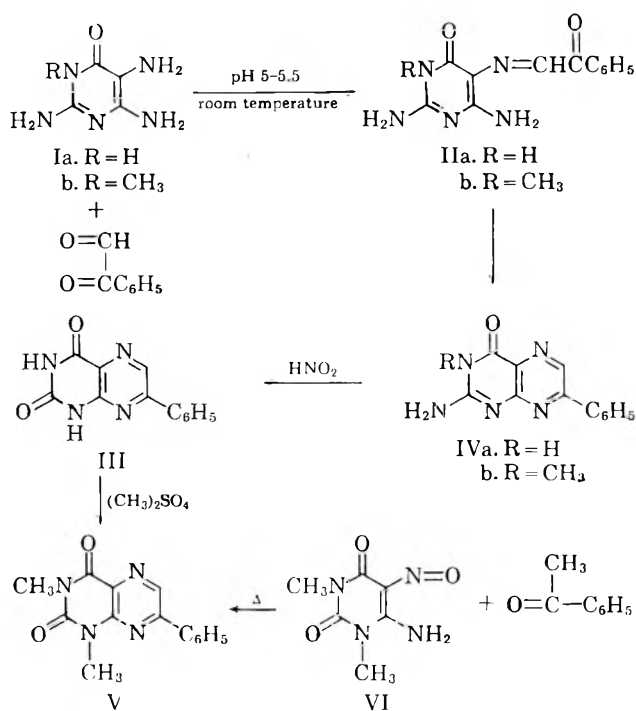


A synthesis of the isomeric 6-phenyl derivative VIIa was discovered during an attempt to utilize directly commercially available phenylglyoxal diethyl acetal. 2,4,5-Triamino-6 hydroxypyrimidine (Ia) was con-

(1) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **27**, 892 (1962).
(2) F. E. King and P. C. Spensley, *J. Chem. Soc.*, 2144 (1952).
(3) G. P. G. Dick, H. C. S. Wood, and W. R. Logan, *ibid.*, 2131 (1956).
(4) A. Albert, *Quart. Rev.*, **6**, 227, 228 (1952).
(5) W. R. Boon, *J. Chem. Soc.*, 2146 (1957).

densed with phenylglyoxal diethyl acetal in a weakly acidic water–ethanol solution under reflux for ten hours. The product was primarily 2-amino-4-hydroxy-6-phenyl-pteridine (VIIa) which was readily purified, although with considerable loss of material.

Since our results differed from those of Dick, *et al.*,[3] the structure of VIIa was also proved by conversion to 2,4-dihydroxy-6-phenylpteridine (IX) followed by methylation to give 1,3-dimethyl-6-phenyl-2,4($1H,3H$)-pteridinedione (VIII). Compound VIII was then synthesized unequivocally from the nitrosopyrimidine VI and phenylacetaldehyde.[3] The two products were identical as shown by infrared and ultraviolet absorption spectra and mixture melting point.
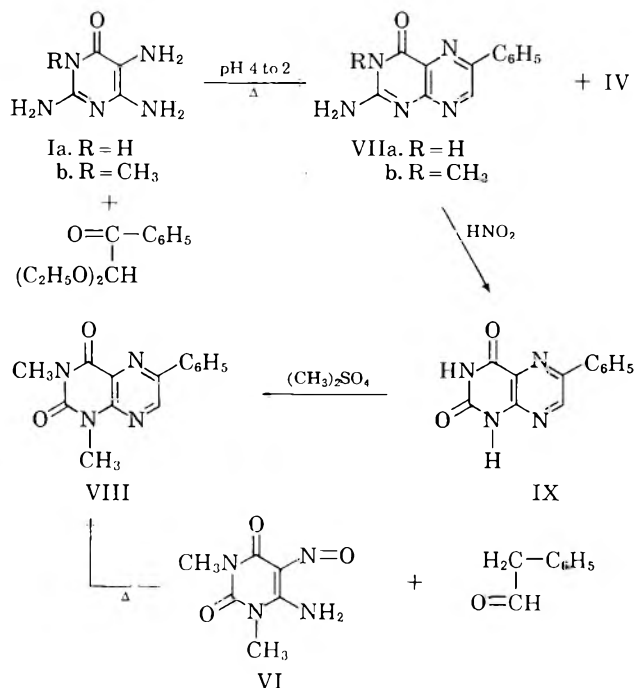


Attempts were made to utilize both sodium bisulfite[4] and 6 $N$ sulfuric acid[5] in the reaction between Ia and phenylglyoxal in order to produce the 6-phenyl isomer VIIa. In each case the added reagent did increase the per cent of 6-isomer produced. However, the product was always a mixture of isomers which could not be separated by the methods used in the reactions described previously.

Using modifications of methods outlined previously, the 3-methyl derivatives IVb and VIIb were synthesized. 2,5,6-Triamino-3-methyl-4($3H$)-pyrimidinone (Ib) and phenylglyoxal hydrate at room temperature gave the anil IIb which was recrystallized to give a pure product. Cyclization of this anil IIb to a pteridine could not be carried out in an alkaline solution since the product, a 3-methyl-4-pteridinone IVb, would be expected[6] to rearrange to a 2-methylamino derivative. However, cyclization of IIb was accomplished in refluxing 2-methoxyethanol using a take-off to remove water formed during the reaction. A good yield of 2-amino-3-methyl-7-phenyl-4($3H$)-pteridinone (IVb) was obtained uncontaminated with any of the 6-phenyl isomer.

The reaction between 2,5,6-triamino-3-methyl-4($3H$)-pyrimidinone (Ib) and phenylglyoxal diethyl acetal under weakly acidic conditions gave a product which

(6) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958).

was shown by paper chromatography to be a mixture of approximately equal parts of the 6-phenyl VIIb and 7-phenyl IVb isomers. However, a fortunate and unexpected difference in solubilities permitted a rather easy separation of pure 2-amino-3-methyl-6-phenyl-4($3H$)-pteridinone (VIIb). The structures of these 3-methyl derivatives (VIIb and IVb) were confirmed through the use of ultraviolet absorption spectra, discussed below.

In order to resolve the other differences between King and Spensley,[2] and Dick, Wood, and Logan[3] the reaction between pyrimidine Ia and α-nitroaceto-phenone was repeated[2] and found to give the 6-phenyl derivative VIIa in a poor yield. This is in agreement with Dick, Wood, and Logan. Furthermore, this is the expected product since the intermediate anil should logically involve the 5-amino group of Ia rather than the 4-amino group as suggested by King and Spensley.[2] The two groups agreed that Ia and α,α-dichloroaceto-phenone gave the 6-phenyl isomer VIIa. We concur in this, but in our limited study of this reaction the product always contained enough of the 7-phenyl isomer IVa to make purification difficult. Finally, the synthesis of 2,4-dihydroxy-7-phenylpteridine as reported by Dick, *et al.*,[3] was repeated and the product was found to be identical with our compound III.

**Ultraviolet Absorption Spectra and Structure.**—Although the infrared absorption spectra of pure 6-phenyl and 7-phenyl isomers (VIIa and IVa) are distinctively different, the best method for differentiating these compounds and for determining isomer ratios in reaction mixtures involves the use of their ultraviolet absorption spectra. Petering and Schmitt[7] have shown that isomer contents of crude mixtures of 2-amino-4-hydroxy-6(and 7)-alkylpteridines can be determined by measuring the ratio of the absorptions at two specific wave lengths. In the same manner we have found that in 0.1 $N$ hydrochloric acid the ratio $E$ 276 m$\mu$/$E$ 351 m$\mu$ is 2.1 for 2-amino-4-hydroxy-6-phenylpteridine (VIIa) *vs.* 0.30 for the isomeric 7-phenyl derivative IVa. A curve prepared from known mixtures of VIIa and IVa was then used to calculate the isomer contents described in the experimental section. We have also shown[8] that in 0.1 $N$ hydrochloric acid 3-methyl derivatives of 2-amino-4-hydroxypteridines have essentially the same ultraviolet absorption spectra as the parent 2-amino-4-hydroxypteridines. Thus the structures of the isomeric 3-methyl-6(and 7)-phenylpteridines (VIIb and IVb) were confirmed by comparison of their absorption spectra with those of the parent 2-amino-4-hydroxy-6-(and 7)-phenylpteridines (VIIa and IVa).

Descending paper chromatography on Whatman no. 1 paper was used routinely to follow reactions and purifications. Isopropyl alcohol–1 $N$ ammonium hydroxide (7:3) was the most useful solvent for separating and identifying the 6- and 7-phenyl isomers of 2-amino-4-hydroxypteridine and their 3-methyl derivatives. The spots were detected using an ultraviolet lamp provided with a filter to give primarily light of wave length 254 m$\mu$.

(7) H. G. Petering and J. A. Schmitt, *ibid.*, **71**, 3977 (1949).

(8) R. B. Angier and W. V. Curran, *J. Org. Chem.*, **26**, 2129 (1961).

(9) All melting points are corrected for the exposed stem of the thermometer.

**2-Amino-4-hydroxy-7-phenylpteridine[2] (IVa). A.**—A solution containing 14.0 g. (67.5 mmoles) of phenylglyoxal diethyl acetal, 80 ml. of dioxane, 20 ml. of water, and 2.0 ml. of concentrated hydrochloric acid was heated for 3 hr. on a steam bath. This was evaporated to a small volume, diluted with 50 ml. of 50% dioxane–water and 1.2 ml. of concentrated hydrochloric acid, and heated 3.5 hr. on a steam bath. The solution was evaporated to a sirup, redissolved in ca. 30 ml. of ethanol, and added to a solution of 9.76 g. (45.6 mmoles) of 2,4,5-triamino-6-hydroxy-pyrimidine dihydrochloride and 22.0 g. (244 mmoles) of sodium acetate in 120 ml. of water. The mixture stood at room temperature for 3 hr. and in an ice bath for 2 hr., after which the solid was collected. This was primarily the anil IIa.[10] It was cyclized to the pteridine by dissolving in 800 ml. of hot 2.0 $N$ sodium hydroxide which was treated with charcoal, filtered, acidified to pH 4, and cooled; yield 11.0 g.; the pteridine content consisted of 92% 7-phenyl and 8% 6-phenyl derivatives.[11]

This was dissolved in 400 ml. of hot 0.2 $N$ sodium hydroxide which was clarified with charcoal and treated with 160 ml. of 10.0 $N$ sodium hydroxide to give a crystalline sodium salt. The mixture stood several hours at room temperature and 2 hr. in the chill room. The product was collected and redissolved in 800 ml. of hot water. The solution was treated with charcoal, filtered and acidified to pH 2.5 with hydrochloric acid; yield 4.5 g. (41%); 95% 7-phenyl derivative IVa.

To remove the last traces of the 6-phenyl isomer the reaction product[12] was dissolved in 225 ml. of hot dimethylformamide by adding 3.6 ml. of concentrated hydrochloric acid. After clarifying the solution with charcoal it was reheated, 110 ml. of water was added slowly, and after a few minutes the crystalline product was collected while still hot; yield 3.5 g. (32%); $R_f$ 0.5 [isopropyl alcohol–1.0 $N$ ammonium hydroxide (7:3)], 0.38 (0.1 $N$ HCl) (light blue); $\lambda_{max}^{0.1\ N\ NaOH}$ 237 m$\mu$ ($\epsilon$ 19,800), 264 m$\mu$ ($\epsilon$ 19,900), 373 m$\mu$ ($\epsilon$ 12,900); $\lambda_{max}^{pH\ 7.0}$ 236 m$\mu$ ($\epsilon$ 20,800), 275 m$\mu$ ($\epsilon$ 16,700), 362 m$\mu$ ($\epsilon$ 13,800), $\lambda_{max}^{0.1\ N\ HCl}$ 225 m$\mu$ ($\epsilon$ 23,900), 260–280 m$\mu$ (sh) ($\epsilon$ 6,200), 347 m$\mu$ ($\epsilon$ 21,500); $E$ 276 m$\mu/E$ 351 m$\mu$ in 0.1 $N$ HCl = 0.30; $\lambda_{max}^{KBr}$ 8.1, 12.3 $\mu$. (These two peaks are absent in the 6-phenyl isomer.)

*Anal.* Calcd. for $C_{12}H_9N_5O$ (239): C, 60.2; H, 3.8; N, 29.3. Found: C, 60.5; H, 3.9; N, 29.8.

**B.**—This reaction was also carried out using crystalline phenylglyoxal hydrate. The results were the same as described under A.

**2,4-Dihydroxy-7-phenylpteridine[3] (III).**—2-Amino-4-hydroxy-7-phenylpteridine (500 mg., 2.1 mmoles) was suspended in 220 ml. of boiling water to which was added 15 ml. of concd. hydrochloric acid. Sodium nitrite (8.0 g.) was added in portions to the hot solution. The mixture was again brought to boiling for a few minutes, then cooled to 40°, and filtered; yield of product 400 mg. (80%); m.p. 374–378° dec.; $R_f$ 0.13 (0.1 $N$ HCl) (deep blue); $\lambda_{max}^{0.1\ N\ NaOH}$ 234 m$\mu$ ($\epsilon$ 17,800), 268 m$\mu$ ($\epsilon$ 18,000), 371 m$\mu$ ($\epsilon$ 10,600); $\lambda_{max}^{pH\ 9.2}$ 230 m$\mu$ ($\epsilon$ 19,200), 273 m$\mu$ ($\epsilon$ 15,600), 363 m$\mu$ ($\epsilon$ 12,900), $\lambda_{max}^{0.1\ N\ HCl}$ 221 m$\mu$ ($\epsilon$ 20,400), 350 m$\mu$ ($\epsilon$ 20,200).

*Anal.* Calcd. for $C_{12}H_8N_4O_2$ (240): C, 60.0; H, 3.4; N, 23.3. Found: C, 59.7; H, 3.4; N, 23.2.

This was identical with a sample prepared from phenylglyoxal hydrate and Ia in the presence of sodium bisulfite and sodium sulfite as described by Dick, et al.[3]

**1,3-Dimethyl-7-phenyl-2,4(1H,3H)-pteridinedione[3] (V).**—2,4-Dihydroxy-7-phenylpteridine (360 mg., 1.5 mmoles) (III), 9 ml. of dimethylformamide (DMF), 12 ml. of water, 1.5 ml. of 1 $N$ sodium hydroxide and 0.15 ml. of dimethyl sulfate were mixed and stirred with a magnetic stirrer. At 15-min. intervals four 0.15-ml. portions of dimethyl sulfate were added followed each time by the addition of 1.5 ml. of 1 $N$ sodium hydroxide over a 2–3 min. interval. After an additional 30 min. of stirring the pH was adjusted to 5, the mixture was cooled and the product was collected; yield 325 mg. (81%). Two recrystallizations from dimethylformamide using decolorizing charcoal gave 170 mg. of product; m.p. 308–309°. Using infrared and ultraviolet absorption spectra and mixture melting point this material was found to be identical with a sample prepared unequivocally from 6-amino-1,3-dimethyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (VI)

and acetophenone as described by Dick, Wood, and Logan[3] and recrystallized from DMF: $\lambda_{max}^{CH_3OH}$ 230 m$\mu$ ($\epsilon$ 23,600), 274–282 m$\mu$ (plateau) ($\epsilon$ 8,900), 352 m$\mu$ ($\epsilon$ 19,500); $\lambda_{max}^{KBr}$ 7.0 $\mu$. (This peak is not present in the isomeric 6-phenyl derivative VIII.)

*Anal.* Calcd. for $C_{14}H_{12}N_4O_2$ (268); C, 62.7; H, 4.5; N, 20.9. Found: C, 62.8; H, 4.6; N, 21.1.

**2-Amino-4-hydroxy-6-phenylpteridine (VIIa).**—A mixture of 10.3 g. (40 mmoles) of 2,4,5-triamino-6-hydroxypyrimidine·$H_2SO_4$·$H_2O$, 9.8 g. (40 mmoles) of barium chloride, and 110 ml. of water was heated on a steam bath for 15 min. and then filtered through a Celite pad. The filtrate was mixed with 3.6 g. (44 mmoles) of sodium acetate and a solution of 8.6 g. (41 mmoles) of phenylglyoxal diethyl acetal in 20 ml. of ethanol and heated on a steam bath for 3.5 hr. The mixture was cooled overnight and the product collected, washed with water, then ether and air-dried under suction in the funnel, thus evaporating the ether in the filtrate; yield 2.7 g.; 46% 6-phenyl isomer VIIa and 54% 7-phenyl isomer IVa.[11]

The filtrate was mixed with 20 ml. of ethanol, heated on a steam bath for 6.5 hr., cooled, and filtered; yield 6.0 g.; 91% 6-phenyl isomer VIIa.[11]

This second crop was recrystallized from 2500 ml. of 1.0 $N$ hydrochloric acid using 6.0 g. of Norit. The product was collected, the damp filter cake was slurried in hot water containing a little pyridine to remove hydrochloric acid. The mixture was cooled and the product was collected; yield 2.2 g. (23%); $R_f$ 0.3 [isopropyl alcohol–1.0 $N$ ammonium hydroxide (7:3)] (blue), $R_f$ 0.4 (0.1 $N$ HCl); $\lambda_{max}^{0.1\ N\ NaOH}$ 271 m$\mu$ ($\epsilon$ 23,200), 377 m$\mu$ ($\epsilon$ 10,000); $\lambda_{max}^{pH\ 7.0}$ 293 m$\mu$ ($\epsilon$ 18,900), 370 m$\mu$ ($\epsilon$ 8,100); $\lambda_{max}^{0.1\ N\ HCl}$ 276 m$\mu$ ($\epsilon$ 20,000), 351 m$\mu$ ($\epsilon$ 9,600); $E$ 276 m$\mu/E$ 351 m$\mu$ in 0.1 $N$ HCl = 2.1; $\lambda_{max}^{KBr}$ 6.75, 7.8 and 11.85 $\mu$. (These three peaks are absent in the 7-phenyl isomer II.)

*Anal.* Calcd. for $C_{12}H_9N_5O$ (239): C, 60.2; H, 3.8; N, 29.3. Found: C, 59.8; H, 4.1; N, 29.1.

**2,4-Dihydroxy-6-phenylpteridine (IX).**—2-Amino-4-hydroxy-6-phenylpteridine (300 mg., 1.26 mmoles) was suspended in 150 ml. of boiling water and dissolved by the addition of 2.0 ml. of 1.0 $N$ sodium hydroxide. The clear, hot solution was acidified with 15.0 ml. of concentrated hydrochloric acid, reheated almost to boiling, and treated with 5.0 g. of sodium nitrite which was added in portions with swirling. The mixture was reheated to boiling, allowed to stand at room temperature for one hour, and filtered; yield of solid 200 mg. (67%). This was recrystallized from 20 ml. of 2-methoxyethanol; yield 120 mg. (40%); m.p. 380–382°; $R_f$ 0.17 (0.1 $N$ HCl); $\lambda_{max}^{0.1\ N\ NaOH}$ 280 m$\mu$ ($\epsilon$ 22,300), 382 m$\mu$ ($\epsilon$ 9,100); $\lambda_{max}^{pH\ 9.2}$ 292 m$\mu$ ($\epsilon$ 21,600), 370 m$\mu$ ($\epsilon$ 8,000); $\lambda_{max}^{0.1\ N\ HCl}$ 272 m$\mu$ ($\epsilon$ 21,600), 353 m$\mu$ ($\epsilon$ 9,600).

*Anal.* Calcd. for $C_{12}H_8N_4O_2$ (240): C, 60.0; H, 3.4; N, 23.3. Found: C, 59.7; H, 3.6; N, 23.2.

**1,3-Dimethyl-6-phenyl-2,4-(1H,3H)-pteridinedione[3] (VIII).**—2,4-Dihydroxy-6-phenylpteridine (360 mg., 1.5 mmoles) (IX) was methylated exactly as described above for the isomeric 7-phenyl derivative; yield 350 mg. Two recrystallizations from dimethylformamide gave 185 mg. of product, m.p. 258–259°. Using infrared and ultraviolet absorption spectra and mixture melting point this was found to be identical with a sample prepared unequivocally from 6-amino-1,3-dimethyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (VI) and phenylacetaldehyde as described by Dick, Wood, and Logan[3] and recrystallized from DMF: $\lambda_{max}^{CH_3OH}$ 280 m$\mu$ ($\epsilon$ 21,200), 357 m$\mu$ ($\epsilon$ 8,500); $\lambda_{max}^{KBr}$ 6.7, 7.4, 8.9 and 13.65 $\mu$. (These 4 peaks are not present in the isomeric 7-phenyl derivative V.)

*Anal.* Calcd. for $C_{14}H_{12}N_4O_2$ (268); C, 62.7; H, 4.5; N, 20.9. Found: C, 63.0; H, 4.6; N, 20.5.

**2,6-Diamino-3-methyl-5[N-(2-phenyl-2-oxoethylidene)amino]-4-(3H)-pyrimidinone (IIb).**—3-Methyl-2,5,6-triamino-4-hydroxypyrimidine hydrochloride[6] (0.4 g., 2.1 mmoles) and 0.67 g. (8.4 mmoles) of sodium acetate were dissolved in 8.0 ml. of water and immediately mixed with a solution of 0.35 g. (2.3 mmoles) of phenylglyoxal hydrate in 6.0 ml. of 50% ethanol. An orange precipitate appeared immediately. After 3 hr. at room temperature the mixture was diluted with 10 ml. of water and the product was collected; yield 0.6 g. (98%).

A solution of 200 mg. of this material in 20 ml. of hot ethanol was clarified with charcoal and then diluted with 15 ml. of water and cooled to give reddish hair-like crystals; yield 120 mg.; dried at room temperature; $\lambda_{max}^{CH_3OH}$ 262 m$\mu$ ($\epsilon$ 15,000), 415 m$\mu$ ($\epsilon$ 18,800).

*Anal.* Calcd. for $C_{13}H_{13}N_5O_2$·$H_2O$ (289): C, 54.0; H, 5.2; N, 24.2. Found: C, 53.9; H, 5.3; N, 24.2.

(10) The ultraviolet absorption spectra of this anil IIa showed maxima in methanol at 263 m$\mu$ and 415 m$\mu$. This is similar to the anil IIb and entirely different from the 7-phenylpteridine IVa.

(11) This isomer ratio was determined as described under "Ultraviolet Absorption Spectra and Structure."

(12) As prepared by previous investigators the 7-phenyl isomer IVa undoubtedly contained a small amount of the 6-phenyl isomer VIIa.

A sample of this material recrystallized from ethanol gave orange prisms which also contained a mole of solvent.

*Anal.* Calcd. for $C_{13}H_{13}N_5O_2 \cdot C_2H_5OH$ (317): C, 56.8; H, 6.0; N, 22.1. Found: C, 56.6; H, 6.2; N, 22.6.

**2-Amino-3-methyl-7-phenyl-4(3H)-pteridinone (IVb).**—A mixture of 8.0 g. (42 mmoles) of 2,5,6-triamino-3-methyl-4(3H)-pyrimidinone hydrochloride[6] and 13.6 g. (165 mmoles) of sodium acetate was slurried in 160 ml. of water and quickly mixed with a warm (35°) solution of 7.0 g. (45 mmoles) of phenylglyoxal hydrate in 120 ml. of ethanol. After several hours at room temperature the product was collected; yield 11.6 g. (97%).

A solution of this anil in 450 ml. of 2-methoxyethanol was heated to reflux for 5.5 hr. using a take-off intermittently to remove water (about 150 ml. of fresh 2-methoxyethanol was added during this period while a total of 300 ml. of distillate was collected). The reaction solution was evaporated to a small volume and slurried with warm water to give a volume of about 450 ml. This was cooled well and the product was collected; yield 10 g. (98%). This material was chromatographically pure and contained none of the 6-phenyl isomer. It was recrystallized from 450 ml. of acetic acid. The product was collected, air-dried and then dried in an oven at 100° for 4 hr.; yield 6.7 g. (63%); m.p. 352–355°; $R_f$ 0.6 [isopropyl alcohol–1.0 N NH₄OH (7:3)] (blue); $\lambda_{max}^{pH\ 7.0}$ 236 m$\mu$ ($\epsilon$ 21,800), 277 m$\mu$ ($\epsilon$ 18,400), 369 m$\mu$ ($\epsilon$ 11,900); $\lambda_{max}^{0.1\ N\ HCl}$ 225 m$\mu$ ($\epsilon$ 24,800), 260–280 (sh) ($\epsilon$ 6,600), 347 m$\mu$ ($\epsilon$ 21,000); the spectrum in 0.1 N sodium hydroxide was essentially the same as at pH 7.0. The spectrum in 0.1 N hydrochloric acid is almost superimposable on the spectrum of 2-amino-4-hydroxy-7-phenylpteridine (IVa).

*Anal.* Calcd. for $C_{13}H_{11}N_5O$ (253): C, 61.6; H, 4.4; N, 27.7. Found: C, 61.4; H, 4.4; N, 27.9.

**2-Methylamino-4-hydroxy-7-phenylpteridine.**—2-Amino-3-methyl-7-phenyl-4(3H)-pteridinone (200 mg., 0.8 mmole) (IVb) was suspended in a solution of 10 ml. of 2-methoxyethanol and 15 ml. of 1.0 N sodium hydroxide and heated on a steam bath for 1.5 hr. The hot solution was acidified with 1.5 ml. of acetic acid and cooled; yield 125 mg. This was recrystallized from 15 ml. of dimethylformamide; yield 85 mg.; $R_f$ 0.5 [isopropyl alcohol–1.0 N ammonium hydroxide (7:3)] (blue); $\lambda_{max}^{0.1\ N\ NaOH}$ 238 m$\mu$ ($\epsilon$ 20,500), 270 m$\mu$ ($\epsilon$ 25,300), 388 m$\mu$ ($\epsilon$ 12,900); $\lambda_{max}^{pH\ 7.0}$ 239 m$\mu$ ($\epsilon$ 21,500), 281 m$\mu$ ($\epsilon$ 20,800), 369 m$\mu$ ($\epsilon$ 13,100); $\lambda_{max}^{0.1\ N\ HCl}$ 230 m$\mu$ ($\epsilon$ 28,200). 349 m$\mu$ ($\epsilon$ 22,000).

*Anal.* Calcd. for $C_{13}H_{11}N_5O$ (253): C, 61.6; H, 4.4; N, 27.7. Found: C, 61.9; H, 4.0; N, 27.5.

**2-Amino-3-methyl-6-phenyl-4(3H)-pteridinone (VIIb) and Its Isomer IVb.**—A solution of 10.2 g. (53.0 mmoles) of 2,5,6-triamino-3-methyl-4(3H)-pyrimidinone·hydrochloride[6] in 270 ml. of water was mixed with a solution of 12.0 g. (58.0 mmoles) of phenylglyoxal diethyl acetal in 75 ml. of water and heated to reflux for 8 hr. This was cooled overnight, the product was collected, and washed with water and ether and dried; yield 12.4 g. (92%). (Paper chromatography showed this to be a mixture of the isomeric 6-phenyl VIIb and 7-phenyl IVb derivatives).

This material was suspended in a solution of 250 ml. of dimethylformamide (DMF) and 6.2 ml. of concentrated hydrochloric acid, which was heated to boiling for several minutes and filtered hot; yield 5.5 g. (fraction A). (Paper chromatography showed this product to be the 6-phenyl derivative VIIb contaminated with a small amount of 2-amino-4-hydroxy-6-phenylpteridine but very little of the 7-phenyl isomer.) Fraction A was probably sufficiently pure for most purposes. However, it was purified further as follows. It was suspended in 900 ml. of dimethylformamide and 24 ml. of concentrated hydrochloric acid, heated to boiling, and filtered; yield 2.5 g. (fraction B). The filtrate was cooled, diluted with 600 ml. of water, and cooled some more; yield 2.4 g. (fraction C). Fraction B was dissolved in a solution of 600 ml. of dimethylformamide and 18 ml. of concentrated hydrochloric acid which was then cooled and diluted with 300 ml. of water; yield 2.2 g. (fraction D).

Fractions C and D were combined, added to a hot solution of sodium acetate, mixed well, and cooled; yield 4.1 g. (30%) of the 6-phenyl isomer.

For analyses a small sample was recrystallized from a dimethylformamide–hydrochloric acid solution and then freed of hydrochloric acid by slurrying in a sodium acetate solution just as described above; m.p. 355–358°; $R_f$ 0.5 [isopropyl alcohol–1.0 N NH₄OH (7:3)] (blue); $\lambda_{max}^{pH\ 7.0}$ 296 m$\mu$ ($\epsilon$ 23,800), 375 m$\mu$ ($\epsilon$ 8,500); $\lambda_{max}^{0.1\ N\ HCl}$ 278 m$\mu$ ($\epsilon$ 19,700), 352 m$\mu$ ($\epsilon$ 9,400). The spectrum of this compound in 0.1 N hydrochloric acid is almost

superimposable on the spectrum of 2-amino-4-hydroxy-6-phenylpteridine (VIIa).

*Anal.* Calcd. for $C_{13}H_{11}N_5O$ (253): C, 61.6; H, 4.4; N, 27.7. Found: C, 61.6; H, 4.4; N, 28.1.

The filtrate from fraction A was warmed, diluted with 375 ml. of water, adjusted to pH 5.5 with sodium acetate, and cooled; yield 4.7 g. This was recrystallized from 180 ml. of acetic acid and a second time from 80 ml. of acetic acid using charcoal to clarify the solution each time. The product was dried in an oven at 100°; yield 2.2 g.; m.p. 346–349°. Chromatography indicated that this was fairly pure 7-phenyl isomer IVb.

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# Synthesis of 5-Amino-5-deoxy Derivatives of L-Idose[1]

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Synthesis of suitably substituted C-5 hydroxyls of aldopentoses and aldohexoses offers a direct route for the introduction of selected hetero atoms into pyranose rings. Preparation of a thiapyranose and thiapyranosides, obtained through the placement of a mercapto group on carbon 5 of several pentoses and hexoses, has been reported recently.[2-5]

This work describes the synthesis of 5-amino-5-deoxy derivatives of L-idose from new derivatives of D-glucose.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-$\alpha$-D-glucofuranose (I) is hydrolyzed selectively to remove the 5,6-O-isopropylidene group. Subsequent tritylation of compound I gives crystalline 3-O-benzyl-1,2-O-isopropylidene-6-O-triphenylmethyl-$\alpha$-D-glucofuranose (II) in 94% yield. Tosylation of compound II then affords crystalline 3-O-benzyl-1,2-O-isopropylidene-5-O-p-tolylsulfonyl-6-O-triphenylmethyl-$\alpha$-D-glucofuranose (III) in 95% yield. A heterogeneous solution, observed in a conventional hydrazinolysis[6] of compound III, markedly diminishes the yield of 3-O-benzyl-5-deoxy-5-hydrazino-1,2-O-isopropylidene-6-O-triphenyl-$\beta$-L-idofuranose (IV). However, when compound III is dissolved in absolute 1-butanol with anhydrous hydrazine, a homogeneous solution is maintained and the reaction gives a smooth SN2 displacement of the 5-O-tosyloxy group with the formation of crystalline compound IV in 75% yield. Thus, hydrazinolysis of compound III is more seriously inhibited by solution heterogeneity, than by molecular steric effects. An L-idose configuration is assigned to compound IV, since experimental evidence presented by previous in-

(1) Journal Paper no. 2006 of the Purdue University Agricultural Experiment Station.
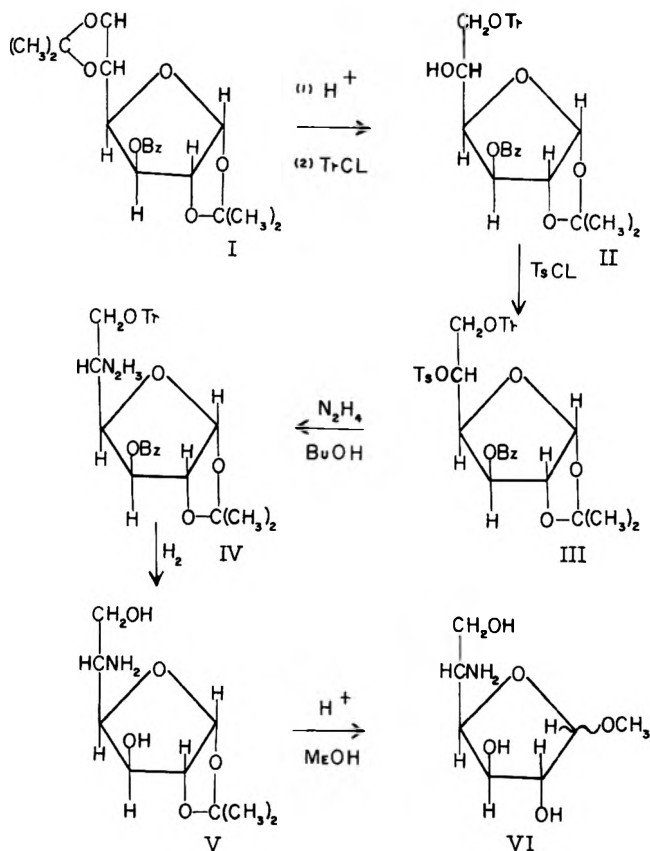
(2) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Am. Chem. Soc.*, **84**, 122 (1962).

(3) J. C. P. Schwartz and K. C. Yule, *Proc. Chem. Soc.*, 417 (1961).

(4) T. J. Adley and L. N. Owen, *ibid.*, 418 (1961).

(5) M. S. Feather and R. L. Whistler, *Tetrahedron Letters*, **15**, 667 (1962).

(6) M. L. Wolfrom, F. Shafizadeh, and R. K. Armstrong, *J. Am. Chem. Soc.*, **80**, 4885 (1958).

vestigators[7-9] shows that hydrazine displaces, with inversion, tosyloxy groups located on asymmetric carbon atoms.

Although hydrogenolysis of benzyl and trityl groups with Raney nickel has been demonstrated,[10] compound IV was not completely freed of these groups. Therefore, the resulting sirup was further reduced with palladium on carbon to produce crystalline 5-amino-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose (V).

Methanolysis of compound V furnishes methyl 5-amino-5-deoxy-α,β-L-idofuranoside (VI). The observation, that compound VI consumes two moles of periodate with the release of one mole of formaldehyde, shows the presence of a furanose ring structure, and suggests that under the conditions employed for methyl glycoside formation, the five-membered oxygen-containing ring is preferred to a six-membered nitrogen-containing ring.

### Experimental

**Analytical Methods.**—Chromatographic identification and purification of sugar derivatives were performed at 25° on Whatman no. 1 and 3 MM filter papers, which were developed in irrigants (A) ethyl acetate–pyridine–water (10:4:3 v./v.) and (B) 1-butanol–ethanol–water (40:11:19 v./v.). Spray indicators employed were (C) permanganate–periodate and (D) ninhydrin. A calibrated Fisher-Johns apparatus was used for melting point determinations.

**3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (I).**—1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (180 g.) was added in small portions to a stirred solution of 38 g. of sodium sand in 600 ml. of diethyl ether. The reaction mixture, after stirring for 24 hr. at 25°, was rapidly filtered and concen-

trated to a sirup to which was added 85 ml. of freshly distilled benzyl chloride. Benzylation was accomplished by stirring the reaction mixture for 8 hr. at 60°. The product was dissolved in 600 ml. of petroleum ether, washed five times with 200-ml. portions of water, and dried over anhydrous magnesium sulfate. After filtration and evaporation to a thick yellow sirup, distillation gave pure sirupy 3-O-benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (I); yield, 155 g. (64%); b.p. 160–165°, $[\alpha]^{25}D$ −26.2 (c 1.60 in ethanol).

**3-O-Benzyl-1,2-O-isopropylidene-6-O-triphenylmethyl-α-D-glucofuranose (II).**—Selective hydrolysis of 128 g. of compound I, in 500 ml. of 60% aqueous acetic acid at 35° for 5 hr., removed the 5,6-O-isopropylidene group. The hydrolyzate was concentrated under reduced pressure to a sirup. This sirup was dissolved in chloroform, washed sequentially with dilute sodium bicarbonate solution and water, and was dried over anhydrous magnesium sulfate. After filtration and evaporation 107 g. (95%) of the sirupy product, namely, 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose, $[\alpha]^{25}D$ −48.4° (c 2.50 in chloroform), was dissolved in 600 ml. of dry pyridine to which was added 110 g. of trityl chloride (chlorotriphenylmethane). The reaction mixture was maintained at 25° for 3 days, then cooled to 5°. Water was added until a constant turbidity of the solution was obtained. After 2 hr. the turbid solution was poured into 4 l. of ice–water and stirred until the gummy derivative had settled. The aqueous phase was poured off and replenished with fresh ice–water. After several successive washings the product was dissolved in 600 ml. of chloroform, washed with 10% aqueous acetic acid, neutralized with sodium bicarbonate solution, and finally washed with water. The chloroform phase was dried over anhydrous magnesium sulfate. Compound II crystallized from a chilled benzene and ethanol mixture; yield, 188 g. [over-all yield from I, 94%; m.p. 116°, $[\alpha]^{25}D$ −36.0 (c 2.97 in chloroform)].

*Anal.* Calcd. for $C_{35}H_{36}O_6$ (552.64): C, 76.06; H, 6.56. Found: C, 76.06; H, 6.74.

**3-O-Benzyl-1,2-O-isopropylidene-5-O-p-tolylsulfonyl-6-O-triphenylmethyl-α-D-glucofuranose (III).**—Tosylation was performed by the addition of 165 g. of compound II to 280 ml. of dry pyridine, to which was added 240 ml. of alcohol free chloroform, containing 165 g. of tosyl chloride (p-toluenesulfonyl chloride). After 3 days at 37°, the reaction mixture was cooled to 0° and 10 ml. of water were added in order to hydrolyze excess tosyl chloride. Within 0.5 hr. the solution was poured into 3 l. of water and 600 ml. of chloroform was then added. The water layer was drawn off, extracted twice with chloroform, and the combined washings and chloroform phase were washed free of pyridine with several portions of chilled 10% aqueous acetic acid. Upon neutralization with sodium bicarbonate solution, the chloroform phase was washed free of salts and dried over anhydrous magnesium sulfate. After filtration and evaporation, a light yellow sirup was obtained. Complete crystallization of this sirup from a chilled benzene and ethanol mixture gave compound III; yield, 200 g. (95%); m.p. 133–134°, $[\alpha]^{25}D$ −13.8° (c 7.48 in chloroform).

*Anal.* Calcd. for $C_{42}H_{42}O_8S$ (706.81): C, 71.36; H, 5.99; S, 4.53. Found: C, 71.30; H, 5.79; S, 4.54.

**3-O-Benzyl-5-deoxy-5-hydrazino-1,2-O-isopropylidene-β-L-idofuranose (IV).**—A 33-g. portion of compound III was added to a stirred solution of 200 ml. of absolute 1-butanol and was dissolved by raising the temperature to 95°. A homogeneous solution was still observed after 210 ml. of anhydrous hydrazine was added. The solution was gently refluxed at 117–119°. After 24 hr. the solution was cooled to 25° and extracted five successive times with fresh 75-ml. portions of diethyl ether. The combined ether extracts were washed four successive times with 50-ml. portions of 50% potassium hydroxide solution, three successive times with 75-ml. portions of ice-cold water, and were dried over anhydrous potassium carbonate. This solution was filtered and evaporated under reduced pressure at less than 40° to approximately 100 ml. The hydrazino derivative crystallized when the solution was cooled to 5°. Crystalline compound IV was filtered and triturated with chilled ether; yield, 20 g. (75%); m.p. 126–127°, $[\alpha]^{25}D$ −18.3 (c 2.00 in benzene).

*Anal.* Calcd. for $C_{35}H_{38}N_2O_5$ (566.67): C, 74.18; H, 6.76; N, 4.94. Found: C, 74.30; H, 6.40; N, 4.67.

**5-Amino-5-deoxy-1,2-O-isopropylidene-β-L-idofuranose (V).**—Compound IV (10 g.) was dissolved in 100 ml. of absolute ethanol containing 30 g. of freshly prepared Raney nickel. This mixture was subjected to 1700 p.s.i. of hydrogen in a Paar bomb

(7) M. L. Wolfrom, F. Shafizadeh, R. K. Armstrong, and T. M. Shen Han, *J. Am. Chem. Soc.*, **81**, 3716 (1959).

(8) R. V. Lemieux and P. Chu, *ibid.*, **80**, 4743 (1958).

(9) B. Coxon and L. Hough, *Chem. Ind.* (London), 1249 (1959); *J. Chem. Soc.*, 1643 (1961).

(10) J. Kenner and G. N. Richards, *ibid.*, 1810 (1955).

and was gently agitated for 12 hr. at 60°. After filtration, this solution was evaporated to dryness and 8.83 g. of a clear sirupy product was obtained. Hydrogenolysis quantitatively converted the C-5 substituent of compound IV to the 5-amino-5-deoxy group, as evidenced by negative tests[11,12] for the presence of hydrazino group activity. Since complete removal of the C-3 and C-6 substituents had not occurred, further reduction was employed. A 5-g. portion of the sirup, obtained from the Raney nickel reduction, was dissolved in 100 ml. of absolute ethanol containing 15 g. of 5% palladium on carbon. The mixture was subjected to 50 p.s.i. of hydrogen in a hydrogenation apparatus and shaken at 25° for 4 days. Filtration and evaporation of the product gave a sirup which was taken up in chloroform and extracted three successive times with water. The combined water extracts were evaporated under reduced pressure to a sirup which crystallized spontaneously from a methanol–chloroform mixture to produce compound V; yield, 517 mg; m.p. 178°, $R_f$ 0.68 in irrigant A and 0.60 in irrigant B, $[\alpha]^{25}D$ −3.0 ($c$ 0.89 in methanol).

*Anal.* Calcd. for $C_9H_{17}NO_5$ (219.23): C, 49.30; H, 7.81; N, 6.39. Found: C, 49.58; H, 7.78; N, 6.25.

**Methanolysis of V.**—A 400-mg. portion of compound V was treated with 50 ml. of 0.8 $N$ methanolic hydrogen chloride at 25°, until constant optical rotation was maintained (37 hr.). The hydrolyzate was neutralized with silver carbonate, filtered, and concentrated under reduced pressure to a thin sirup. The sirup was dissolved in 30 ml. of water, treated with hydrogen sulfide to remove excess silver ions, filtered, concentrated to 20 ml., then placed on a column of Amberlite IR-400 (OH⁻). The column was eluted successively with water and a dilute ammonium hydroxide solution. The effluent, containing amino sugar VI as the free base, was concentrated under reduced pressure to a sirup (235 mg.); $[\alpha]^{25}D$ + 20.5 ($c$ 0.73 in methanol). Compound VI, after chromatography on paper, revealed $R_f$ values of 0.34 in irrigant A and 0.43 in irrigant B when developed with spray indicators C or D. A positive 5-nitrosalicylaldehyde[13] test and nitrous acid test indicated that product VI contained a primary amino group. Periodate oxidation showed that two moles of oxidant were consumed, and one mole of formaldehyde was produced per mole of methyl glycoside. Oxidant consumption was determined by a method specific for amino sugars[14] and formaldehyde by the chromotropic acid procedure.[15,16] After destruction of excess periodate with ethylene glycol, an aliquot of periodate oxidized VI was adjusted to pH 2.0 with potassium hydrogen sulfate and steam distilled.[17,18] No formic acid was detected in the distillate. Nitrogen content of compound VI was determined by micro-Kjeldahl analysis.

*Anal.* Calcd. for $C_7H_{15}NO_5$ (193.20): OCH₃, 16.06; N, 7.25. Found: OCH₃, 15.93; N, 7.21.

(11) F. Feigl, V. Anger, and O. Frehden, *Mikrochemie*, **15**, 184 (1934).
(12) F. Feigl, V. Anger, and R. Zappert, *ibid.*, **15**, 190 (1934).
(13) F. R. Duke, *Ind. Eng. Chem., Anal. Ed.*, **17**, 196 (1945).
(14) R. Jeanloz and E. Forchielli, *J. Biol. Chem.*, **188**, 361 (1951).
(15) A. C. Corcoran and I. H. Page, *ibid.*, **170**, 165 (1947).
(16) M. Lambert and A. C. Neish, *Can. J. Res.*, **B28**, 83 (1950).
(17) D. J. Bell, Anne Palmer, and A. T. Johns, *J. Chem. Soc.*, 1536 (1949).
(18) R. Markham, *Biochem. J.*, **36**, 790 (1942).

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## The Chemistry of Perfluoro Ethers. IV.
## The Structure of the Monocyclic Diether $C_8F_{16}O_2$

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The reaction of aluminum chloride with perfluoroethers, resulting in replacement of all $\alpha$ fluorine atoms by chlorine,[1–3] is valuable for the proof of structure of these exceedingly unreactive materials. In the present instance the reaction is extended to characterize a monocyclic diether, $C_8F_{16}O_2$.[4]

The products of the reaction with aluminum chloride were identified as $n$-perfluorobutyryl chloride[2] (in small amounts), 1,1,1-trichloroperfluorobutane[2] and 4,4,4-trichlorotetrafluorobutyryl chloride.[3] No higher homologs[3] of the latter, nor any $\alpha,\alpha,\alpha'$-trichloroperfluoroethers, were found; considerable amounts of decomposition products, notably hexachloroethane, were present as is usual in these reactions.[1–3] While the first two materials might arise from perfluorodibutyl ether, the elemental analysis, phsyical properties and infrared spectrum of $C_8F_{16}O_2$ indicate that it contains little or no $(n\text{-}C_4F_9)_2O$; one may, therefore, conclude that the $n\text{-}C_3F_7CFO_2$ or the $n\text{-}C_4F_9O$ group is present in the diether, and that it yields mainly $n$-$C_3F_7CCl_3$ upon cleavage. The third product had previously been obtained by reaction of aluminum chloride with perfluorotetrahydrofuran,[3] and its formation indicates the presence of a similar grouping in the compound $C_8F_{16}O_2$.

Only two structures, I and II, are consistent with the foregoing facts. Each of these has five $\alpha$-fluorines, corresponding to the five chlorine atoms found in the
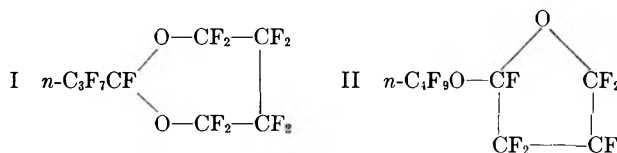


major products which also retain the two oxygen atoms. The less likely structure I contains a seven-membered ring, and theoretically might be excluded by the n.m.r. spectrum; however, owing to the accidental spectral equivalence of certain fluorines, an absolute proof cannot at present be given. The cyclic diether $C_8F_{16}O_2$ thus may be either I or II. This is believed to be the first reported example of a perfluorinated acetal structure.

### Experimental

Physical properties of the diether have been reported.[4] By the elementary analysis and the absence of infrared absorptions for the C=C or C=O groups it is shown to be a monocyclic diether.

*Anal.* Calcd. for $C_8F_{16}O_2$: C, 22.24; F, 70.36. Found: C, 22.3; F, 70.8.

The diether, 20.0 g. (0.046 mole), and aluminum chloride, 18.0 g. (0.135 mole), were heated together at 200° for 14 hr. in a rocking autoclave of 43-ml. volume. The reaction mixture was worked up as previously described,[2] products being separated by distillation. Unchanged $C_8F_{16}O_2$ amounted to *ca.* 3 g. A relatively poor yield of $n$-$C_3F_7COCl$, *ca.* 1 g., was obtained in the fractions boiling slightly above room temperature; it was identified beyond question by infrared spectroscopy.[2] The major products were $n$-$C_3F_7CCl_3$,[2] b.p. 89–94°, 6.0 g., also readily identified by infrared spectroscopy,[2] and $CCl_3CF_2CF_2COCl$,[2] b.p. 145–153°, 3.4 g., characterized not only by infrared analysis but also by conversion to the amide, m.p. 126–127°, m.m.p. with authentic 4,4,4-trichlorotetrafluorobutyramide,[3] 126–127°.

(1) G. V. D. Tiers, *J. Am. Chem. Soc.*, **77**, 4837 (1955).
(2) G. V. D. Tiers, *ibid.*, **77**, 6703 (1955).
(3) G. V. D. Tiers, *ibid.*, **77**, 6704 (1955).
(4) T. J. Brice and R. I. Coon, *ibid.*, **75**, 2921 (1953).

# The Formation of Hexachlorocyclopropane by the Addition of Dichlorocarbene to Tetrachloroethylene

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The addition of dihalocarbenes to olefins discovered by Doering and Hoffmann[1] has provided an exceptionally useful and widely used synthesis of dihalocyclopropanes. Studies by Skell[2] and Doering[3] have established that dibromocarbene and dichlorocarbene behave as electrophilic reagents since electron-donating groups on an olefin facilitate addition. Accordingly, a highly negatively substituted olefin would be expected to be quite unreactive[3] toward dihalocarbenes. In particular, it appeared to be of interest to examine the addition of dichlorocarbene to tetrachloroethylene, an olefin which is resistant to electrophilic attack, since the potential adduct, hexachlorocyclopropane, which might prove to be of intrinsic interest, was reported by Stevens[4] to be unavailable by way of chlorination of cyclopropane. To this end, dichlorocarbene was generated in the presence of tetrachloroethylene by treatment of chloroform with strong bases[1] and by the thermal decomposition of sodium trichloroacetate[5] in 1,2-dimethoxyethane. Hexachlorocyclopropane was formed in these reactions, but in low yields (*ca.* 0.2–1%).[6]

The structure of the compound, a white crystalline solid, m.p. 104–104.5°, was established by elemental analysis, which gave an empirical formula of $CCl_2$, and the determination of the molecular weight cryoscopically and by mass spectrometry. The mass spectrum of $C_3Cl_6$ does not show any peak due to the molecular ion, but no fragments are formed which have more than three carbon atoms. The most abundant fragment is $C_3Cl_5$, corresponding to loss of a single chlorine atom. Inasmuch as there can be only two compounds with a molecular formula of $C_3Cl_6$, namely hexachlorocyclopropane and hexachloropropylene, and the latter is a well known commercially available liquid, it is clear that the solid referred to above is perchlorocyclopropane.

In retrospect, it appears likely that Stevens[4] did prepare hexachlorocyclopropane. He reported that chlorination of 1,1,2,2-tetrachlorocyclopropane for seven days at 63° in the presence of ultraviolet light gave hepta- and octachloropropane as the main products, but also gave a very small amount of a white crystalline solid, m.p. 102–102.5°, which on the basis of elemental analysis he believed to be the then unknown 1,1,1,3,3,3-

hexachloropropane.[7] Subsequently, Davis and Whaley[8] have prepared 1,1,1,3,3,3-hexachloropane by chlorination of 1,1,1,3,3-pentachloropropane followed by fractionation to separate the two hexachloropropanes which are formed and have reported that 1,1,1,3,3,3-hexachloropropane is a liquid, b.p. 205°, m.p. −27°. Since all four hexachloropropanes have Raman spectra[9] which are consistent with the assigned structures, we believe that Stevens probably did succeed in preparing hexachlorocyclopropane.

The fact that perchlorocyclopropane was formed at all in the present study, albeit in very low yields, takes on greater significance when one considers that dichlorocarbene apparently fails to react with ethylene[3] (in preference to reaction with *t*-butoxide). Tetrachloroethylene is far less reactive than ethylene in typical electrophilic reactions (*e.g.*, addition of bromine). Thus it is possible that in reacting with tetrachloroethylene, dichlorocarbene may be exhibiting either radical or nucleophilic character.

## Experimental

**Reaction of Chloroform with Potassium *t*-Butoxide.**—Chloroform (36 g.) was added dropwise with stirring over a period of 1 hr. to a mixture of 50.5 g. of potassium *t*-butoxide (freed of alcohol by heating at 140° at 1 mm.) and 325 g. of freshly distilled tetrachloroethylene. The reaction mixture was cooled intermittently with an ice bath. The mixture was stirred at room temperature for an hour and then was poured into water. The organic layer was separated, dried, and the bulk of the tetrachloroethylene was removed by distillation at atmospheric pressure leaving a dark oil, a portion of which distilled at 70–120° (1–2 mm.) leaving a considerable quantity of residual tar. The distillate, shown by gas chromatography to be mainly tetrachloroethylene, was redistilled slowly under reduced pressure, leaving a solid residue. The latter was sublimed five times at 40–50° (0.5 mm.) giving 0.21 g. of hexachlorocyclopropane, m.p. 104.0–104.5°.

*Anal.* Calcd. for $C_3Cl_6$: C, 14.46; Cl, 85.54; mol. wt., 249. Found: C, 14.46; Cl, 85.69; mol. wt., 241.[10]

In solution (carbon disulfide and carbon tetrachloride), perchlorocyclopropane shows prominent bands in the infrared at 850 (s), 905 (m), and 930 (w) cm.$^{-1}$. Mass spectrum was measured on a Consolidated Electrodynamics Corporation Model 21–103C mass spectrometer with a heated inlet system (140°) at an ionizing potential of 70 v. The mass number of the largest isotopic peak of each monopositive carbon-containing fragment is given as a percentage of the largest peak in the spectrum. Normal isotopic distribution of $Cl^{35}$ and $Cl^{37}$ was observed within each fragment (thus all fragments listed contain only $Cl^{35}$ except the last three each of which contains one $Cl^{37}$).

Fragment, mass number (percentage): CCl, 47 (35.4); $C_2Cl$, 59 (6.4); $C_3Cl$, 71 (30.3); $CCl_2$, 82 (22.2); $C_2Cl_2$, 94 (12.2); $C_3Cl_2$, 106 (15.4); $CCl_3$, 117 (26.4); $C_2Cl_3$, 129 (4.4); $C_3Cl_3$, 141 (16.8); $C_2Cl_4$, 166 (12.8); $C_3Cl_4$, 178 (0.9); $C_3Cl_5$, 213 (100.0).

**Use of Sodium Hydride.**—Methyl alcohol (9.6 g., 0.30 mole) was added dropwise with stirring over a period of 9.5 hr. at room temperature to a mixture of 298 g. of tetrachloroethylene, 7.2 g. (0.30 mole) of sodium hydride, and 44.6 g. (0.37 mole) of chloroform. The mixture was processed as above to give 0.42 g. of hexachlorocyclopropane. When the methyl alcohol was omitted (reflux, 40 hr.) or replaced by *t*-butyl alcohol (60°, 11 hr.), only a trace of this product was isolated.

**Use of Sodium Trichloroacetate.**—A mixture of 18.5 g. of sodium trichloroacetate, 80 g. of tetrachloroethylene, and 150 ml. of 1,2-dimethoxyethane was refluxed 24 hr. After processing in the usual way, the mixture was concentrated by distillation and and both distillate and residue were analyzed by gas chromatog-

(1) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

(2) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956).

(3) W. von E. Doering and W. A. Henderson, Jr., *ibid.*, **80**, 5274 (1958).

(4) P. G. Stevens, *ibid.*, **68**, 620 (1946).

(5) W. M. Wagner, *Proc. Chem. Soc.* (London), **229** (1959).

(6) (a) Since this work was completed, the formation of hexachlorocyclopropane by similar means (chloroform and fused potassium hydroxide at 105°), but in higher yields (5–10%), has been reported by S. W. Tobey and R. C. West, Abstracts of Papers presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 9–14, 1962, p. 95Q; (b) after submission of this manuscript we learned that E. K. Field and S. Meyerson have also prepared this compound and measured its mass spectrum.

(7) Analysis indicated 0.53% hydrogen, a value in between the required values of 0.00 for hexachlorocyclopropane and 0.80 for hexachloropropane.

(8) H. W. Davis and A. M. Whaley, *J. Am. Chem. Soc.*, **73**, 2361 (1951).

(9) H. Gerding and H. G. Haring, *Rec. trav. chim.*, **74**, 841 (1955).

(10) Determined by Dr. C. M. Starks by freezing point lowering of benzene solutions.

raphy which indicated formation of *ca.* 1% of hexachlorocyclopropane ($t_R$ = 6.6).[11] The chromatograms showed peaks due to several other minor components, one of which was collected ($t_R$ = 2.7) and found to have a strong band at 1763 cm.$^{-1}$ but which was not characterized further.

In a similar experiment, the gas evolved during the reflux period was collected and analyzed by infrared spectroscopy which indicated that the sample consisted of carbon dioxide that did not contain more than a small amount (< 5%) of carbon monoxide. This result apparently precludes significant reaction of dichlorocarbene with trichloroacetate ion to give, over-all, carbon monoxide, trichloroacetyl chloride, and chloride ion by a reaction path formally similar to that described[12] for the reaction of dichlorocarbene with alkoxide ions. In other control experiments it was found that the thermal decomposition of sodium trichloroacetate in 1,2-dimethoxyethane did not produce significant quantities of materials with retention times greater than that of the solvent.

(11) Retention time relative to tetrachloroethylene, $t_R$ = 1.00; 1,2-dimethoxyethane, $t_R$ = 0.33 on silicone oil at 150°.

(12) P. S. Skell and I. Starer, *J. Am. Chem. Soc.*, **81**, 4117 (1959).

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# Addition Reactions of *m-* and
# *p*-Nitronitrosobenzene[1]

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The addition reactions of aromatic nitroso compounds to conjugated dienes are well known.[2] The reaction products I, dihydroöxazines, generally are isolated in high yields. Side products of the reaction have not been reported.

*o*-Nitronitrosobenzene[2] conforms to this pattern, but for the reaction of *m-* or *p*-nitrosobenzene with 2,3-dimethyl-1,3-butadiene, we have found two reaction products. One of these reaction products was found to be the expected adduct I. The second reaction product II showed an elemental analysis and molecular weight corresponding to an adduct consisting of one mole of diene and two moles of nitroso compound.

Aromatic nitroso compounds have been reported to react smoothly with suitably substituted alkenes,[3] yielding oxazetidines III. Product II, therefore, might be the result of the normal 1,4-addition of nitroso compound to diene, followed by a 1,2-addition of the nitroso compound to the dihydroöxazine, yielding compound IV or its isomer.
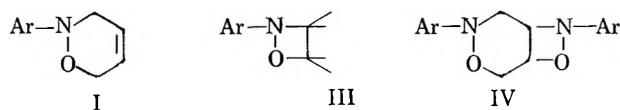
In order to test this hypothesis, we attempted to treat the normal 1,4-adduct of *p*-nitronitrosobenzene and 2,3-dimethyl-1,3-butadiene with the equivalent amount of *p*-nitronitrosobenzene. We were unable to detect a reaction with the aid of infrared spectra. Unsuccessful attempts were also made to prepare an oxazetidine from *p*-nitronitrosobenzene and the follow-

ing alkenes: cyclohexene, cyclopentene, isobutylene, *cis-* and *trans*-2-butene.

Considering the evidence, this hypothesis concerning the structure of product II was then rejected. It was also considered unlikely that the conjugated diene would add two moles of the nitroso compound in a 1,2-fashion.

It is well established that many aromatic nitroso compounds are in a state of equilibrium between monomer and dimer in solution.[4] The monomeric state is generally favored by electron-donating groups. The electron-withdrawing nitro group will cause a considerable fraction of the nitronitrosobenzenes to be in the dimeric state V. It is also well known that electron-poor azo groups are excellent dienophiles in Diels–Alder reactions.[5]

The formation of the products II may then be accounted for by a reaction between the diene and the electron-poor N=N group of the dimeric nitronitrosobenzene, to form a tetrahydro-1,2-diazine-N,N-dioxide



VI. Steric hindrance may explain the failure of *o*-nitronitrosobenzene to give an adduct of this type, while the low yield of this adduct for *m*-nitronitrosobenzene may be ascribed to the decreased resonance effect.

The infrared absorption band at about 1050 cm.$^{-1}$ associated with the oxazine ring,[2] was absent from the spectra of products II. Although the spectra of a small number of tertiary amine oxides have been reported,[6] we have not been able to assign bands in the 970–950-cm.$^{-1}$ region unequivocally to the amine oxide. The insolubility of products II in suitable solvents ruled out the determination of an nuclear magnetic resonance spectrum.

Conclusive evidence for the assertion that products II have structure VI was furnished by the deoxygenation of the N,N-dioxide IIa by Ochai's method,[7] employing phosphorus trichloride as the deoxygenation agent. The known substance 4,5-dimethyl-1,2-bis-(*p*-nitrophenyl)-1,2,3,6-tetrahydropyridazine[8] was obtained as the deoxygenation product.

## Experimental[9]

*m*-Nitronitrosobenzene, m.p. 89–90°, and *p*-nitronitrosobenzene, m.p. 118°, were prepared by oxidation with Caro's acid from the corresponding amines.[10]

**Adducts of *p*-Nitronitrosobenzene.**—*p*-Nitronitrosobenzene, 0.50 g. (3.3 mmoles), and 2,3-dimethyl-1,3-butadiene, 0.37 g. (4.5 mmoles), were dissolved in 20 ml. of nitromethane at 0°. The green color of the solution, caused by the monomeric nitroso compound, changed in about 15 min. to orange, indicating the



(1) This work was supported by the Petroleum Research Fund; it was presented at the 14th Southeastern Regional Meeting, Gatlinburg, Tenn., November 3, 1962.

(2) J. Hamer and R. E. Bernard, *Rec. trav. chim.*, **81**, 734 (1962).

(3) C. K. Ingold and J. D. Weaver, *J. Chem. Soc.*, **125**, 1146 (1924).

(4) B. G. Gowenlock and W. Luetkke, *Quart. Rev.* (London), **12**, 321 (1958).

(5) A. Rodgman and G. F. Wright, *J. Org. Chem.*, **18**, 465 (1953).

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 308.

(7) E. Ochai, *J. Org. Chem.*, **18**, 550 (1953).

(8) P. Baranger, J. Levisalles, and M. Vuidart, *Compt. rend.*, **236**, 1365 (1953).

(9) All melting points are uncorrected. Analysis by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra measured in potassium bromide with a Beckman IR-5.

(10) E. Bamberger and E. Huebner, *Ber.*, **36**, 3803 (1903).

termination of the reaction. Upon cooling in a salt–ice bath, dark orange crystals of product IIa precipitated, m.p. 199–201°, yield, 0.3 g. Calculated for a 2:1 adduct C₁₈H₁₈N₄O₆: mol. wt., 386. Found (Rast method): mol. wt., 420.

*Anal.* Calcd. for C₁₈H₁₈N₄O₆: C, 55.89; H, 4.67; N, 14.51. Found: C, 55.80; H, 4.46; N, 15.02.

The filtrate was concentrated further at 0°, and the formed precipitate isolated. This product, Ia, was also orange, m.p. 119–120°, yield, 0.3 g. It was identified as the normal 1,4-adduct by its infrared spectrum.[2]

*Anal.* Calcd. for C₁₂H₁₄N₂O₃: C, 61.54; H, 5.98; N, 11.96. Found: C, 61.34; H, 6.09; N, 12.00.

Product Ia, 0.19 g. (0.8 mmole), was mixed with *p*-nitronitrosobenzene, 0.75 g. (5 mmole). An infrared spectrum in potassium bromide was taken from some of this mixture. The rest was dissolved in nitromethane at 0°, and allowed to stand for 24 hr. The solvent was then evaporated, and an infrared spectrum in potassium bromide was made of the residue. The two spectra were identical.

Product IIa, 0.39-g. (1 mmole), was suspended in 20 ml. of ice-cold chloroform, to which was added phosphorus trichloride, 2 ml. The suspension was allowed to reach room temperature and left overnight. The liquids were then removed under reduced pressure until a solid remained, which was the recrystallized from ethanol. The yield of 4,5-dimethyl-1,2-bis(*p*-nitrophenyl)-1,2,3,6-tetrahydropyradizine was 0.26 g. (74%), yellow crystals, m.p. 271–273° (lit.,[8] m.p. 272–272.5°).

Adducts of *m*-Nitronitrosobenzene.—*m*-Nitronitrosobenzene, 0.30 g. (1.9 mmoles), reacted with 2,3-dimethyl-1,3-butadiene, 0.22 g. (2.7 mmoles), in 35 ml. of dichloromethane at 0°. The solvent was evaporated, and a yellow solid was isolated. This solid was dissolved in anhydrous ether, and filtered through a column a column (12 × 10 cm.) packed with alumina. The first fraction yielded bright yellow crystals, m.p. 94–99°, yield, 0.26 g. It was identified as the normal 1,4-adduct (product Ib) by its infrared spectrum.[2]

*Anal.* Calcd. for C₁₂H₁₄N₂O₃: C, 61.54; H, 5.98; N, 11.96. Found: C, 61.34; H, 5.93; N, 11.91.

The second fraction yielded 25 mg. of bright yellow crystals, product IIb, m.p. 161.5–163°.

*Anal.* Calcd. for C₁₈H₁₈N₄O₆: C, 55.98; H, 4.67; N, 14.51. Found: C, 55.01; H, 4.37; N, 14.02.

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# Displacement Reactions of Neopentyl-type Sulfonate Esters[1]

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During the course of an investigation involving synthesis of derivatives of pentaerythritol, we observed that *O*-benzylidenepentaerythritol dibenzenesulfonate reacted with sodium iodide in acetone to form *O*-benzylidene-*O*-benzenesulfonylpentaerythritol iodide in high (89%) yield. A previous investigation[3] demonstrated that *O*-isopropylidenepentaerythritol di-*p*-toluenesulfonate reacted with potassium thiolacetate to give the product of monosubstitution in good yield. The high degree of selectivity at one of the two functional groups prompted a study directed towards a better understanding of this type of reaction.

A series of sulfonate esters of *O*-benzylidene- and *O*-isopropylidenepentaerythritol was prepared (Table I),

(1) Abstracted from portions of the Ph.D. theses of Donald L. Schmidt and Samuel M. Dorrence and of the M.S. thesis of Vincent D. Calbi.
(2) An Air Force Officer on an Air Force Scholarship.
(3) P. Bladon and L. N. Owen, *J. Chem. Soc.*, 585 (1950).

and their reactivities with sodium iodide in acetone determined by varying reaction time and temperature (Table II). Although the monosubstitution product could be isolated in high yield from *O*-benzylidenepentaerythritol dibenzenesulfonate, this intermediate could then be converted into *O*-benzylidenepentaerythritol diiodide in high (85%) yield by a second reaction for a longer period of time and at a higher temperature. As expected, *O*-benzylidenepentaerythritol di-*p*-bromobenzenesulfonate reacted to allow isolation of essentially the same high yields of mono- and di-substitution products under somewhat milder conditions. In the experiment in which the monodisplacement compound was isolated as the principal product, a small amount (5%) of the diiodide was also separated. The di-*p*-toluenesulfonate was found to yield less of the monosubstitution product under conditions comparable to that applied with the dibenzenesulfonate. *O*-Isopropylidenepentaerythritol dibenzenesulfonate and di-*p*-toluenesulfonate were found to yield products of mono- and di-substitution under milder conditions than required for the corresponding *O*-benzylidene compounds.

A variety of displacement reactions has also been studied using cyanide ion as the nucleophilic reagent. Because of complications attending this type of reaction, several acyclic substrates were included in the study (Table III). 2,2-Dimethyl-1-propanol benzenesulfonate was found to react with sodium cyanide in a *N*,*N*-dimethylformamide (DMF) solution to give 3,3-dimethylbutyronitrile in a yield of 56%, and 1,3-propanediol dibenzenesulfonate gave glutaronitrile in a yield of 81%, accompanied by varying amounts of polymeric materials depending upon the reaction conditions employed. Nelson, Maienthal, Lane, and Benderly[4] reported that no products were isolable from the reactions of di-*p*-toluenesulfonates of 1,3-propanediol and 2-methyl-1,3-propanediol with potassium cyanide in ethylene glycol. 2,2-Dimethyl-1,3-propanediol dibenzenesulfonate reacted with sodium cyanide in a dimethylformamide solution to give 3,3-dimethylglutaronitrile, isolated in a yield of 28%, and 2,2-dimethylcyclopropanecarboxylic acid, separated from the reaction mixture following base-catalyzed hydrolysis in a yield of 28%. Its precursor, 2,2-dimethylcyclopropanecarbonitrile, was undoubtedly formed in a somewhat larger amount, but undoubtedly less than the 63% previously reported[4] from the reaction of 2,2-dimethyl-1,3-propanediol di-*p*-toluenesulfonate and potassium cyanide in ethylene glycol.
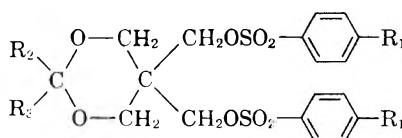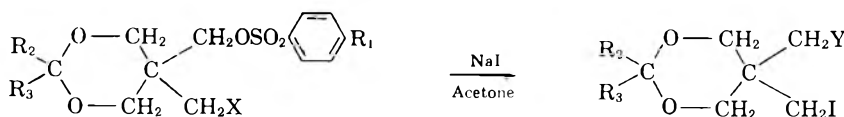
Displacement reactions of *O*-benzylidenepentaerythritol derivatives with sodium cyanide gave a single crystalline compound in all instances. The structure of this compound was assigned to be *O*-benzylidene-2,2-bis(hydroxymethyl)cyclopropanecarbonitrile (I) on the basis of a variety of observations. Alkaline hydrolysis gave a crystalline compound, with analysis agreeing with *O*-benzylidene-2,2-bis(hydroxymethyl)cyclopropanecarboxamide (II). Acid hydrolysis with hydrochloric acid gave a liquid in low yield, presumed to be 2-chloromethyl-2-hydroxymethylcyclopropanecarboxylic acid lactone (III) on the basis of elemental analysis and of the nuclear magnetic resonance spec-

(4) E. R. Nelson, M. Maienthal, L. A. Lane, and A. A. Benderly, *J. Am. Chem. Soc.*, **79**, 3467 (1957).

## TABLE I
### SULFONATE ESTERS



| | Compound | | M.p., | Yield,[a] | | Calcd., % | | Found, % | |
| R1 | R2 | R3 | °C. | % | Formula | C | H | C | H |
|---|---|---|---|---|---|---|---|---|---|
| H | C6H5 | H | 150.8–151.1 | 79 | $C_{24}H_{24}O_8S_2$ | 57.13 | 4.79 | 57.38 | 5.13 |
| CH3 | C6H5 | H | 176.8–177.1 | 66 | $C_{26}H_{28}O_8S_2$ | 58.63 | 5.30 | 58.11 | 5.43 |
| Br | C6H5 | H | 209.5–210.0[b] | 84 | $C_{24}H_{22}Br_2O_8S_2$ | 43.52 | 3.35 | 43.34 | 3.42 |
| H | CH | CH3 | 116.8–117.0 | 67 | $C_{20}H_{24}O_8S_2$ | 52.62 | 5.30 | 52.29 | 5.30 |

[a] Yields based upon materials with melting points within 2–3° or less of the analytical samples. [b] Benzene used as recrystallization solvent.

## TABLE II
### DISPLACEMENT REACTIONS OF SULFONATES WITH SODIUM IODIDE



| | Substrate | | | Reaction time, | Reaction temp., | Product | Yield,[a] | M.p. | | Calcd., % | | Found, % | |
| R1 | R2 | R3 | X | hr. | °C. | Y | % | °C. | Formula | C | H | C | H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | C6H5 | H | OSO2C6H5 | 2 | 100 | OSO2C6H5 | 89 | 136.5 | $C_{18}H_{19}IO_5S$ | 45.58 | 4.04 | 45.93 | 4.07 |
| H | C6H5 | H | I | 3 | 130 | I | 85 | 66.3 | $C_{12}H_{14}I_2O_2$ | 32.46 | 3.18 | 32.52 | 3.25 |
| Br | C6H5 | H | OSO2C6H4Br(p) | 1.5 | 100 | OSO2C6H4Br(p) | 84 | 136.5–136.7 | $C_{18}H_{18}BrIO_5S$ | 39.08 | 3.28 | 39.07 | 3.28 |
| | | | | | | I | 5 | | | | | | |
| Br | C6H5 | H | OSO2C6H4Br(p) | 2.5 | 100 | I | 80 | | | | | | |
| CH3 | C6H5 | H | OSO2C6H4CH3(p) | 2.5 | 100 | OSO2C6H4CH3(p) | 65 | 118.5–118.7 | $C_{19}H_{21}IO_5S$ | 46.73 | 4.33 | 46.55 | 4.50 |
| CH3 | CH3 | CH3 | OSO2C6H4CH3(p) | 2.25 | 85 | OSO2C6H4CH3(p) | 78 | 89.6–90.0 | $C_{15}H_{21}IO_5S$ | 40.92 | 4.81 | 41.11 | 4.93 |
| H | CH3 | CH3 | OSO2C6H5 | 1.5 | 100 | I | 84 | 48.5–48.7 | $C_8H_{14}I_2O_2$ | 24.26 | 3.56 | 24.46 | 3.74 |
| CH3 | CH3 | CH3 | OSO2C6H4CH3(p) | 2.5 | 100 | I | 80 | | | | | | |

[a] Yields based upon materials with melting points within 2° or less of the analytical samples.

trum. Cleavage of the benzylidene acetal group, hydrolysis of the nitrile function, lactonization, and solvolysis of the remaining primary alcohol function would account for this substance. The depressed yield of compound III was expected since hydrochloric acid is known[5] to effect ring opening of compounds containing cyclopropane rings with an attached hydroxymethyl group. Hydrogenation of I gave a sirupy amine, which formed a crystalline acetate, with analysis agreeing with N-acetyl-O-benzylidene-2,2-bis(hydroxymethyl)cyclopropanecarbinylamine (IV). The amine was also converted into a crystalline quaternary ammonium iodide with correct analysis for O-benzylidene-N,N-dimethyl-2,2-bis(hydroxymethylcyclopropanecarbinylamine methiodide (V).
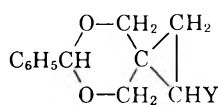


I. Y = CN
II. Y = CONH2

IV. Y = CH2NHCOCH3

V. Y = CH2$\overset{+}{N}$(CH3)3I⁻
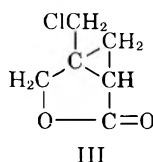


III

The ease of displacement of arenesulfonate or iodide by cyanide was determined by experiments effected on a series of O-benzylidenepentaerythritol derivatives (Table IV). Assuming that a two-step mechanism

(5) R. Stoermer and F. Schenck, Ber., 61, 2312 (1928).

prevails as demonstrated for iodide displacement, the order of reactivity in the first step appears to be: OSO2-C6H4Br(p) ∼ I > OSO2C6H5 > OSO2C6H4CH3(p). In the second step, the ease of displacement appears to be: OSO2C6H4Br(p) > OSO2C6H5 > I > OSO2C6-H4CH3(p). Other effects found in these experiments were: dimethyl sulfoxide is less effective than dimethylformamide. A sufficient amount of water is necessary to dissolve in part the sodium cyanide. Ethanol in a sealed tube is less effective than dimethylformamide as a solvent.

### Experimental

Melting points are corrected. Microanalyses were made by K. W. Zimmerman, Australian Microanalytical Service, University of Melbourne.

**Sulfonate Esters (Table I).**—O-Benzylidenepentaerythritol[6] (0.075 mole) and 0.160 mole of the sulfonyl chloride in 100 ml. of anhydrous pyridine reacted at 0° for 3 hr. to yield a crystalline mass, which was transferred to a funnel with a minimum of ethanol, and recrystallized once from benzene and repeatedly from absolute ethanol to provide an analytical sample. O-Isopropylidenepentaerythritol dibenzenesulfonate was prepared by the procedure described[7] for the synthesis of O-isopropylidenepentaerythritol di-p-toluenesulfonate.[3]

1,3-Propanediol dibenzenesulfonate was similarly prepared but required a chloroform extraction of the reaction mixture, removal of pyridine with sulfuric acid, concentration of solvent to leave a sirup, which crystallized from a solution of ethanol, acetone, and water (5:3:2, by vol.). A single recrystallization from ethanol gave 60% yield of product, m.p. 40–40.5°.

(6) E. Bograchov, J. Am. Chem. Soc., 72, 2268 (1950).
(7) R. S. Tipson, J. Org. Chem., 9, 235 (1944).

TABLE III

DISPLACEMENT REACTIONS OF ACYCLIC SULFONATE ESTERS WITH SODIUM CYANIDE

| Substrate | Product | Yield[a] % | B.p., °C. (mm.) Obsd. | Lit. | M.p., °C. Obsd. | Lit. |
|---|---|---|---|---|---|---|
| $(CH_3)_3CCH_2OSO_2C_6H_5$[b] | $(CH_3)_3CCH_2CH_2CN$ | 56 | 129–130 (656) | 135–136.4[c] (737) | 31–33 | 32.5[c] |
| $C_6H_5SO_2O(CH_2)_3OSO_2C_6H_5$ | $NC(CH_2)_3CN$[d] | 81 | 144 (14) | 144–147 (13)[e] | | |
| $(CH_3)_2C(CH_2OSO_2C_6H_5)_2$[f] | $(CH_3)_2C\begin{smallmatrix}CH_2\\ \mid \\ CHCO_2H\end{smallmatrix}$ | 28 | 98 (10) | 100 (10)[g] | | |
| | $(CH_3)_2C(CH_2CN)_2$[h] | 28 | | | 100.5–101 | |

[a] Yields based upon analytical samples. [b] P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **33**, 1207 (1955). [c] A. Homeyer, F. Whitmore, and V. Wallingford, *J. Am. Chem. Soc.*, **55**, 4209 (1933). Hydrolysis of 3,3-dimethylbutyronitrile in 75% sulfuric acid containing sodium chloride gave 3,3-dimethylbutyramide, after recrystallization from absolute ethanol, m.p. 130.5–131.5°, reported in ref. *c*, 131–131.5°. [d] Hydrolysis of glutaronitrile in hydrochloric acid gave glutaric acid, m.p. and m. m.p. with an authentic sample, 95–97°. [e] C. S. Marvel and E. M. McColm, *Org. Syn.*, **5**, 103 (1925). [f] G. S. Skinner and P. R. Wunz, *J. Am. Chem. Soc.*, **73**, 3814 (1951). [g] *Anal.* Calcd. for $C_6H_{10}O_2$: equiv. wt., 114. Found: equiv. wt. (by titration), 115. M. Blanc, *Compt. rend.*, **145**, 78 (1907). 2,2-Dimethylcyclopropanecarboxamide, m.p. 175.5–177°, reported in ref. *g*, 177°, was prepared from the acid by initial formation of the acid chloride with thionyl chloride followed by treatment with ammonia. *N-p*-Tolyl-2,2-dimethylcyclopropane carboxamide, m.p. 117.2–117.6°, was similarly prepared using *p*-toluidine. *Anal.* Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.71; H, 8.22; N, 7.14. [h] *Anal.* Calcd. for $C_7H_{10}N_2$: C, 68.81; H, 8.25; N, 22.94. Found: C, 68.88; H, 8.10; N, 23.53. Incomplete hydrolysis of 3,3-dimethylglutaronitrile in concentrated hydrochloric acid provided crystalline 3,3-dimethylglutarimide, purified by sublimation, m.p. 147–147.5°, reported 147° by F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 422 (1911). *Anal.* Calcd. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.82; H, 7.73; N, 9.81. From the same hydrolysis solution, 3,3-dimethylglutaric acid was isolated, m.p. 100–100.5°, reported 100–101° by K. Auwers, *Ber.*, **28**, 1130 (1895) and 101–102° by F. Blaise, *Compt. rend.*, **126**, 1153 (1898). 3,3-Dimethylglutaric anhydride, m.p. 124–125°, reported 124–125° by W. Perkin and W. Goodwin, *J. Chem. Soc.*, **69**, 1457 (1896), was prepared from 3,3-dimethylglutaric acid by dehydration in acetic anhydride.

*Anal.* Calcd. for $C_{15}H_{16}O_6S_2$: C, 50.57; H, 4.53. Found: C, 50.89; H, 4.61.

**Displacement Reactions of Sulfonates with Sodium Iodide (Table II).**—In a typical procedure, 0.015 to 0.022 mole of substrate, 0.13 mole of sodium iodide, and 100 ml. of acetone were sealed in a 6-oz. carbonated beverage bottle and were heated for various lengths of time. The bottle was then cooled, the precipitated salts were separated by filtration, and the resulting solution was evaporated under reduced pressure to dryness. The residue was dissolved in a minimum of hot ethanol to recrystallize colorless products. Analytical samples were prepared by repeated recrystallizations from absolute ethanol.

**Displacement Reactions of Acyclic Sulfonate Esters with Sodium Cyanide (Table III).**—Sodium cyanide (30% excess) and the sulfonate ester were mixed with *N,N*-dimethylformamide (500 ml. for 0.2 mole NaCN; 2 l. for 1.2 moles) and heated for 5 hr. at the reflux temperature with 2,2-dimethyl-1-propanol benzenesulfonate and 1,3-propanediol dibenzenesulfonate and at 170° in a sealed carbonated beverage bottle with 2,2-dimethyl-1,3-propanediol dibenzenesulfonate. 3,3-Dimethylbutyronitrile was recovered by drowning the reaction mixture in ice and water, ether extraction, solvent removal, and distillation. Glutaronitrile was isolated by removal of solvent using a flash-evaporator and distillation. Cyclopropanecarbonitrile was not found in the reaction mixture. 3,3-Dimethylglutaronitrile was obtained by the same removal of reaction solvent, extraction with ether and its subsequent evaporation, and crystallization of the residue from ethanol–water. 2,2-Dimethylcyclopropanecarboxylic acid was isolated from another batch of the same reactants by evaporation of the reaction solvent, hydrolysis of the residue in aqueous sodium hydroxide, ether extraction of the acidified mixture, evaporation of solvent, and distillation.

**Displacement Reactions of *O*-Benzylidenepentaerythritol Derivatives with Sodium Cyanide (Table IV).**—In a typical procedure, 0.18 mole of sodium cyanide was dissolved in 10 ml. of water (except in experiments 5 and 6), and the resulting solution was poured into 125 ml. of boiling *N,N*-dimethylformamide or dimethyl sulfoxide. The *O*-benzylidenepentaerythritol derivative (0.015 to 0.023 mole) was added, and the reaction mixture refluxed for 1.5 hr. and then poured onto ice and water. The solid derived was filtered and dissolved in benzene. The solution was decolorized with carbon and ligroine added to crystallize out *O*-benzylidene-2,2-bis(hydroxymethyl)cyclopropanecarbonitrile (I). An analytical sample, m.p. 116.5–117°, was prepared by a combination of sublimation and recrystallization from benzene-ligroine and from ethanol. *Anal.* Calcd. for $C_{13}H_{13}NO_3$: C, 72.54; H, 6.09; N, 6.51; mol. wt., 215. Found: C, 72.94; H, 6.06; N, 6.85; mol. wt. (ebullioscopic in benzene), 220, 211.

I decolorized bromine in carbon tetrachloride slowly when warmed. I and authentic cyclopropanecarbonitrile exhibited very similar behavior toward tetranitromethane. The infrared spectrum (potassium bromide disk) had a peak at 3.3 $\mu$ characteristic of stretching vibrations of C–H bonds in cyclopropane rings.[8] The 60-Mc. proton magnetic resonance spectrum in an acetone solution contained cyclopropane ring hydrogen peaks at $\tau = 8.54$ p.p.m. The relative peak areas for the phenyl, methine, six-membered ring methylene, and cyclopropane hydrogen atoms were 5, 1, 4, and 3.

*N*-Acetyl-*O*-benzylidene-2,2-bis(hydroxymethyl)cyclopropanecarbinylamine (IV) was prepared by treating an ethanol solution of I with Raney nickel at 100° at a hydrogen pressure of 1000 p.s.i. and converting the sirupy amine into IV with acetic anhydride in pyridine. An analytical sample, m.p. 143.5°, was prepared by repeated recrystallizations from ethanol. *Anal.* Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.42; H, 7.48; N, 5.46.

*O*-Benzylidene-*N,N*-dimethyl-2,2-bis(hydroxymethyl)cyclopropanecarbinylamine methiodide (V), m.p. 217–219°, was obtained in 49% yield by treating the sirupy amine two times with methyl iodide and sodium hydroxide, and crystallizing the product from ethanol–water. Repeated recrystallizations from ethanol–water gave an analytical sample, m.p. 218–220°. *Anal.* Calcd. for $C_{16}H_{24}INO_2$: C, 49.36; H, 6.21; N, 3.60. Found: C, 49.65; H, 6.22; N, 3.53.

*O*-Benzylidene-2,2-bis(hydroxymethyl)cyclopropanecarboxamide (II), m.p. 200–200.5°, was obtained in a yield of 74% by treating I with aqueous sodium hydroxi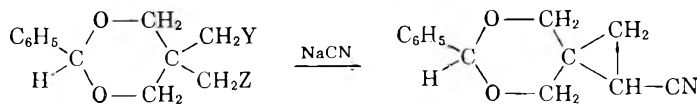de and recrystallizing the product from alcohol. *Anal.* Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48. Found: C, 67.30; H, 6.54.

2-Chloromethyl-2-hydroxymethylcyclopropanecarboxylic acid lactone (III), b.p. 95° (0.5 mm.), 84° (0.1 mm.), $n^{25}D$ 1.4935, was obtained in a 15% yield by refluxing 54 g. of I and 100 ml. of concentrated hydrochloric acid for 30 min., extracting with benzene-ligroin, separating phases, and adding 30 ml. more of concentrated hydrochloric acid to the aqueous portion, which was refluxed for 12 hr. longer, adding 30 g. of sodium hydroxide after cooling, extracting the reaction mixture with benzene-ligroin and then with ethanol-ether, drying the latter extract and evaporating the solvent, and distilling under reduced pressure. *Anal.* Calcd. for $C_6H_7ClO_2$: C, 49.16; H, 4.82. Found: C, 49.09; H, 4.90.

The 60-Mc. proton magnetic resonance spectrum of a carbon tetrachloride solution showed large peaks at $\tau = 5.76$ and

(8) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).

## Table IV

### Displacement Reactions of $O$-Benzylidenepentaerythritol Derivatives with Sodium Cyanide



| Experiment no. | Substrate Y | Substrate Z | Yield,[a] % | Solvent |
|---|---|---|---|---|
| 1 | $OSO_2C_6H_5$ | $OSO_2C_6H_5$ | 45 | DMF |
| 2 | $OSO_2C_6H_5$ | I | 77 | DMF |
| 3 | I | I | 45 | DMF |
| 4 | $OSO_2C_6H_5$ | I | 36 | DMSO[b] |
| 5 | $OSO_2C_6H_5$ | I | 31 | Anhydrous DMSO,[b] solid NaCN introduced |
| 6 | $OSO_2C_6H_5$ | I | 30 | Anhydrous DMF, solid NaCN introduced |
| 7 | $OSO_2C_6H_4Br(p)$ | $OSO_2C_6H_4Br(p)$ | 85 | DMF |
| 8 | $OSO_2C_6H_4Br(p)$ | I | 82 | DMF |
| 9 | $OSO_2C_6H_4CH_3(p)$ | $OSO_2C_6H_4CH_3(p)$ | 7.5[c] | DMF |
| 10 | $OSO_2C_6H_4CH_3(p)$ | I | 34 | DMF |
| 11 | $OSO_2C_6H_5$ | $OSO_2C_6H_5$ | Very low | $C_2H_5OH$[d] |

[a] Yields based upon materials with melting points within 2° or less of the analytical samples. [b] Reaction at 130–135°. [c] 38% substrate recovered. [d] Reaction carried out in a Carius bomb tube at 130° for 8 hr.

6.26 p.p.m., assignable to the methylene hydrogens of the lactone ring and the chloromethyl group, respectively. The upfield peaks were located at $\tau = 7.93, 8.53,$ and 8.86 p.p.m. for the three nonequivalent cyclopropane ring hydrogens. The approximate peak areas were 2, 2, 1, 1, and 1 for the different types of hydrogens in the order described.

**Acknowledgment.**—We are grateful to the Strasenburgh Laboratories for support of a portion of this investigation and thank Robert C. Hirst for the nuclear magnetic resonance spectral data and interpretation.

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## Synthesis of 1,5,9-Cyclododecatriene

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Cyclic dimers[1] and trimers[2] of butadiene have been obtained by several workers. We have now found that a trimer, *trans,trans,cis*-1,5,9-cyclododecatriene, is produced upon treatment of butadiene with a novel catalyst system which consists of a combination of an alkylaluminum halide and a titanium tetraalkoxide. The action of trialkylaluminum–titanium tetraalkoxide complex on butadiene has been reported by Wilke[3] to afford 1,2-polymer.

A benzene solution of diethylaluminum chloride containing titanium tetrabutoxide in a mole ratio of about 20 (Al/Ti) was treated with butadiene gas until the absorption rate decreased rapidly. Distillation of the reaction products gave a cyclododecatriene fraction in 81% yield, no appreciable quantities of dimer and tetramer being isolated. The cyclododecatriene consisted only of *trans,trans,cis*-1,5,9-cyclododecatriene and no *trans,trans,trans* isomer was isolated upon careful distillation in any case. However, the *all trans* isomer was isolated in about 5% yield from trimerization products of butadiene in the presence of a mixture of titanium tetrachloride and dialkylaluminum halide, as reported by Wilke. Consequently, it appears that our catalysts containing titanium tetraalkoxides have higher stereospecificity for trimerization of butadiene than catalysts reported by Wilke.

*trans,trans,cis*-1,5,9-Cyclododecatriene has been identified by measurements of molecular weight and infrared spectrum and by formation of silver nitrate complex in quantitive yield.[4] Catalytic hydrogenation and ozonization yielded cyclododecane and succinic acid, respectively, in high yeilds.

Effects of reaction variables on yields of cyclododecatriene have been examined. As summarized in Table I, the organic groups of titanium tetraalkoxides and organoaluminum compounds had minor effects on the yields of cyclododecatriene. Alkylaluminum bromides and chlorides were equally active. The halogen content of organoaluminum compounds or $n$ in $R_{3-n}AlX_n$ must be between 0.5 and 1.5. When $n$ was 0.5 or less, linear polymer was produced in quantities and cyclododecatriene was obtained with poor yields or in trace. Similar results were also observed when $n$ was 1.5 or more.

Data in Table II show that the mole ratio of alkylaluminum halides to titanium tetraalkoxides must be greater than 12. When the mole ratio was less than 12, little, if any, butadiene was absorbed and polymer was produced instead of cyclododecatriene. At a mole ratio of 18 or higher, the absorption rate of butadiene was increased appreciably and yields of cyclododecatriene were greatly improved. The yields remained approximately constant at higher mole ratios. In each case certain induction period was recognized.

As shown in Table III, the reaction temperature should be kept below 65°. Higher temperatures than

(1) (a) K. Ziegler, *Angew. Chem.*, **59**, 177 (1947); H. W. B. Reed, *J. Chem. Soc.*, 685 (1951); (b) G. Wilke, *Angew. Chem.*, **73**, 33 (1961).

(2) (a) G. Wilke, *ibid.*, **69**, 397 (1957); Studiengesellschaft Kohle m. b. H., Belg. Patent 555,180 (1957); G. Wilke, *J. Polymer Sci.*, **38**, 45 (1959); (b) Studiengesellschaft Kohle m. b. H., Belg. Patent 566,436 (1958); G. Wilke and H. Müller, German Patent 1,043,329 (1958); (c) *cf.* also ref. 1b.

(3) G. Wilke, *Angew. Chem.*, **68**, 306 (1956).

(4) Compared with a silver nitrate complex of *trans,trans,cis*-1,5,9-cyclododecatriene obtained by method of Wilke.

### TABLE I
### THE EFFECT OF CATALYSTS

| Ti(OR)₄ R | g. | R₃₋ₙAlXₙ R | X | n | g. | Al/Ti[a] | Time, hr. | Temp., °C. | C₁₂H₁₈[b] g. | % |
|---|---|---|---|---|---|---|---|---|---|---|
| $C_4H_9$ | 0.5 | $C_2H_5$ | Br | 1 | 5 | 20.6 | 3 | 30–35 | 33 | 85 |
| $C_4H_9$ | 0.5 | $CH_3$ | Cl | 1 | 2.6 | 19 | 2 | 30–35 | 2 | 33 |
| $C_4H_9$ | 0.5 | $CH_3$ | Cl | 1 | 5.2 | 38 | 2 | 30–35 | 7 | 70 |
| $C_4H_9$ | 1.3 | $CH_3$ | Cl | 1 | 7.4 | 20.8 | 2 | 62 | 10 | 42 |
| $C_4H_9$ | 0.36 | $CH_3$ | Cl | 1.5 | 2.2 | 20 | 3 | 30–35 | Trace | |
| $C_4H_9$ | 0.48 | $CH_3$ | Cl | 1.5 | 5.7 | 40 | 3 | 30–35 | 0.5 | 7 |
| $C_4H_9$ | 0.34 | $C_2H_5$ | Cl | 0.5 | 1.1 | 10 | 2 | 40 | 0[c] | |
| $C_4H_9$ | 0.34 | $C_2H_5$ | Cl | 0.5 | 2.1 | 20 | 2 | 40 | 3 | 35 |
| $C_4H_9$ | 0.34 | $C_2H_5$ | Cl | 0.5 | 3.3 | 30 | 2 | 40 | 2 | 27 |
| $C_6H_5$ | 0.8 | $C_2H_5$ | .. | 0 | 2 | | | | | |
| | | $CH_3$ | Cl | 1.5 | 2[d] | 21 | 2 | 30–35 | 11 | 73 |

[a] Mole ratio of $R_{3-n}AlX_n/Ti(OR)_4$.   [b] Cyclododecatriene, b.p. 85–95° at 5 mm.   [c] No absorption of butadiene was observed but a trace of linear polymer was obtained.   [d] To a benzene solution of titanium tetraphenoxide was added triethylaluminum and then methylaluminum sesquichloride.

### TABLE II
### THE EFFECT OF Al/Ti MOLE RATIO[a]

| Ti(OC₄H₉)₄ g. | (C₂H₅)₃₋ₙAlClₙ n | g. | Al/Ti[b] | Time, min. | Temp., °C. | C₄H₆[c] l. | C₁₂H₁₈[d] g. | % |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.24 | 4.2 | 12.0 | 120 | 40–50 | 8 | 2 | 10 |
| 0.6 | 1.24 | 2.8 | 13.4 | 180 | 40–50 | 17 | 21 | 54 |
| 1 | 1.24 | 6 | 17.2 | 120 | 40–50 | 6.9 | 14 | 85 |
| 0.17 | 1.27 | 0.96 | 15.7 | 50 | 31 | 1.2 | Trace | |
| 0.17 | 1.27 | 1.2 | 20.0 | 121 | 31 | 13.4 | 28.1 | 86.7 |
| 0.17 | 1.27 | 1.2 | 20.0 | 41 | 45 | 6.8 | 14.6 | 89 |
| 0.085 | 1.27 | 0.78 | 24.0 | 36 | 45 | 5.4 | 11.7 | 90 |
| 0.17 | 1.27 | 1.0 | 24.6 | 57 | 31 | 2.6 | 5.0 | 79 |
| 0.17 | 1.27 | 1.8 | 29.4 | 110 | 28 | 4.5 | 8.1 | 75 |
| 0.17 | 1.27 | 3.0 | 49.2 | 95 | 31 | 5.1 | 10.0 | 80 |

[a] The reactions were carried out in 40 ml. of benzene.   [b] Mole ratio of $(C_2H_5)_{3-n}AlCl_n/Ti(OC_4H_9)_4$   [c] Absorbed butadiene.   [d] Cyclododecatriene, b.p. 85–95° at 5 mm.

### TABLE III
### THE EFFECT OF TEMPERATURE[a]

| Ti(OC₄H₉)₄ g. | (C₂H₅)₃₋ₙAlClₙ n | g. | Al/Ti[b] | Temp. °C. | Time, min. | C₁₂H₁₈[c] g. | % |
|---|---|---|---|---|---|---|---|
| 1.0 | 1.24 | 6.5 | 18 | 30–35 | 60 | 14 | 81 |
| 1.0 | 1.24 | 6.5 | 18 | 64 | 60 | 9 | 30 |
| 0.034 | 1.73 | 0.47 | 39 | 30 | 65 | 1.0 | 55 |
| 0.034 | 1.73 | 0.47 | 39 | 45 | 77 | 4.5 | 82 |
| 0.034 | 1.73 | 0.47 | 39 | 59 | 85 | 9.2 | 83 |
| 0.034 | 1.73 | 0.47 | 39 | 72 | 50 | 0.8 | 72 |

[a] The reactions were carried out in 40 ml. of benzene.   [b] Mole ratio of $(C_2H_5)_{3-n}AlCl_n/Ti(OC_4H_9)_4$.   [c] Cyclododecatriene, b.p. 85–95° at 5 mm.

65° during preparation of catalyst or reaction resulted in nearly complete loss of catalyst activity and negligible yields of cyclododecatriene.

After butadiene was passed for eight hours into a benzene solution of diethylaluminum chloride and titanium tetrabutoxide in a mole ratio of 22, the absorption slowed down rapidly. Addition of diethylaluminum chloride to the reaction mixture regenerated the activity of the catalyst system allowing the reaction proceeding for an additional several hours. Cyclododecatriene was obtained in about 80% yield from this reaction mixture and the production of linear polymer was not appreciably increased.

#### Experimental[5]

Synthesis of *trans,trans,cis*-1,5,9-Cyclododecatriene.—To a solution of 1.7 g. of titanium tetrabutoxide in 50 ml. of benzene, 13 g. of diethylaluminum chloride was added in a nitrogen atmos-

phere, with stirring while the temperature was maintained below 55°. Immediately gas was evolved and the solution became brown-black. To the catalyst solution thus obtained and held at 50–55°, butadiene was introduced through calcium chloride tube at such a rate that most of the added butadiene was consumed. The absorption rate was about 4 l. per 10 min. for a period of 8 hr. but after that it decreased rapidly. The total volume of butadiene absorbed was 165 l. After standing overnight, the reaction mixture was treated with alcohol and dilute hydrochloric acid, and organic layer was combined with benzene extracts of water layer and distilled to afford a fraction (320 g. or 81%) boiling at 85–95° (5 mm.) and residue (70 g.). The fraction was redistilled with a high-efficiency rotating band column, to afford *trans,trans,-cis*-1,5,9-cyclododecatriene boiling at 96° (10 mm.) in more than 95% recovery. Though the forerun of the redistillation was cooled at −20° for several days, no crystalline *trans,trans,trans* isomer was obtained. Infrared spectrum of the forerun agreed with that of *trans,trans,cis* isomer.

The molecular weight of *trans,trans,cis*-1,5,9-cyclododecatriene was determined by mass spectrometric analysis as 162; $n^{25}D$ 1.5051, $d^{25}_4$ 0.8895. The silver nitrate complex melted at 166–167°[6]. Mixtures of the complex with authentic sample

(5) All temperatures are uncorrected.

(6) D. N. Saxarkin and B. B. Korneba, *Dokl. Akad. Nauk, SSSR*, 132, 1078 (1960).

melted at 166–167°. Infrared absorptions (liquid film) of *trans* and *cis* double bonds were observed at 970 and 705 cm.$^{-1}$, respectively, and the *trans* absorption was stronger than *cis*. Catalytic hydrogenation over palladium–charcoal yielded cyclododecane melting at 58–59°[7] in 91% yield.

**Synthesis of Cyclododecatrienes by Method of Wilke.**[8]—A mixture of 9 g. of diethylaluminum bromide and 1.7 g. of titanium tetrachloride was treated with butadiene at about 50° for 6 hr. A cyclododecatriene fraction (60 g.) was obtained in 80% yield. The fraction consisted largely of *trans,trans,cis*-1,5,9-cyclododecatriene boiling at 96° (10 mm.) and about 5% of *trans,trans,trans* isomer boiling at 92° (10 mm.), which was separated as a forerun on distillation through a high-efficiency rotating band column. The *trans,trans,trans* isomer fraction crystallized on cooling and the solid melted at 31–32°.[9]

(7) M.p. 60°, L. Ruzicka, M. Stoll, H. W. Huyser, and H. A. Boekenogen, *Helv. Chim. Acta*, **13**, 1152 (1930).

(8) See also ref. 2a.

(9) G. Wilke and M. Kröner, *Angew. Chem.*, **71**, 574 (1959), reported m.p. 33–34°.

# Methylation of Benzimidazole and Benzothiazole Carboxaldoximes[1]

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In the course of our studies on quaternary heterocyclic aldoxime salts, we had occasion to prepare 1,3-dimethyl-2-formylbenzimidazolium iodide oxime (I) and 2-formyl-3-methylbenzothiazolium iodide oxime (II) through schemes involving methylation of 1-methylbenzimidazole-2-carboxaldoxime and benzothiazole-2-carboxaldoxime, respectively. The usual synthesis of quaternary heterocyclic aldoximes involves alkylation of the appropriate heterocyclic aldoximes in acetone or alcohol.[4] With oximes that
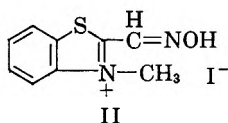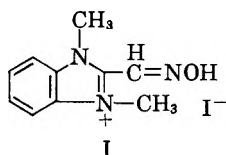


are difficult to alkylate it has been reported that nitromethane is a better choice of solvent.[5] When the ring nitrogen is hindered sterically, alkylation is very difficult and in the case of quinoline-2-aldoxime it was unsuccessful.[4a] In the case where a methyl group at the 6-position of picolinaldehyde oxime hinders the ring nitrogen sterically, it was shown that alkylation occurs on the nitrogen of the oxime rather than on the ring.[6]

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) U. S. Army Chemical Research and Development Laboratories.

(3) Battelle Memorial Institute.

(4) (a) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957); (b) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958).

(5) E. Profft and G. Kruger, *Wiss. Z. Tech. Hochsch. Chem. Leuna-Merseburg*, **2**, 281 (1959–1960); *Chem. Abstr.*, **55**, 1607e (1961).

(6) B. E. Hackley, Jr., E. J. Poziomek, G. M. Steinberg, and W. A. Mosher, *J. Org. Chem.* **27**, 4220 (1962).

The studies presented in this paper are somewhat different in that five-membered rings are being methylated and the basicity of the 1-methylbenzimidazole ring is much stronger and that of the benzothiazole ring much weaker than the basicities of the pyridines and quinolines studied previously. No difficulty was found in synthesizing I in ethanol through a room temperature methylation of 1-methylbenzimidazole-2-carboxaldoxime. In contrast, the more vigorous reaction conditions of refluxing nitrobenzene–alcohol were needed in the methylation of the much less basic benzothiazole-2-carboxaldoxime. Besides II, a dimethylation product, N-methyl 2-formyl-3-methyl-benzothiazolium iodide oxime (V) was isolated. It appears that the side product was formed through a methylation of II because with lower reflux temperature and longer reaction time only II was isolated.

The more facile synthesis of I than that of II is understandable in view of the stronger basic center in the 1-methylbenzimidazole ring. Failure to find 1-methylbenzimidazolium or benzothiazolium hydroiodides in which monomethylation had occurred on either the oxime nitrogen or oxygen, *e.g.*, III or IV, would indicate that the ring nitrogens were not hindered sterically to any serious extent.
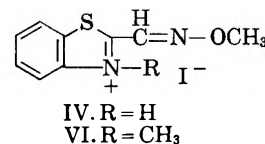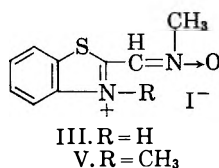


The nuclear magnetic resonance spectrum of I in deuterium oxide consists of three resonances: a singlet at 522 c.p.s. (area = 1), =C—CH=N—, a symmetrical multiplet centered at 468 c.p.s. (area = 4), aromatic protons, and a single sharp peak at 249 c.p.s. (area = 6), =N$\overset{+}{—}$CH$_3$ and —N—CH$_3$ protons. The resonance at 249 c.p.s. is undoubtedly a result of the average electronic environment experienced by the two methyl groups because of the resonance of the quaternary center between the two nitrogens. The spectrum of N-methyl-2-pyridone shows a methyl resonance at 215 c.p.s. while that of 1,3,5-trimethylpyridinium iodide of 2-pyridone exhibits 1-methyl resonance at 275 c.p.s.[7] The average of these two values is 245 c.p.s., which is in good agreement with the observed frequency of the methyl groups in I. Traces of water, and possibly some exchange, precluded detection of the =NOH proton in the spectrum obtained in deuterium oxide. By the use of redistilled, dry acetonitrile, the =NOH proton resonance was observed near 740 c.p.s. (area = 1). Oxime protons generally absorb in this region in nonbonding solvents.

A nuclear magnetic resonance spectrum of II could not be obtained, because of the limited solubility of II in solvents commonly used in this work (D$_2$O and CDCl$_3$). Instead, structure proof was achieved on the basis of elemental analysis, neutralization equivalent, a broad OH stretching band found in the infrared absorption spectrum in potassium bromide, and an observed bathochromic shift of the long wave length

(7) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

band of maximum absorption from dilute acid to dilute base. Alternative structures would be N-(or O-) methyl benzothiazole-2-carboxaldoxime hydroiodides III (or IV), but these choices were eliminated since both N-(and O-) methyl 6-methylpicolinaldehyde oxime hydroiodides exhibit hypsochromic shift of the long wave length absorption band from dilute acid to base.[6]

On the basis of elemental analysis, the side product isolated in the methylation of benzothiazole-2-carboxaldoxime could correspond to either V or VI. Authentic samples were obtained by methylation of N(and O)-methyl benzothiazole-2-carboxaldoximes. A comparison of infrared absorption spectra with those of the side product led to the assignment of the N-methyl oxime structure (V).

It may be of interest to note that I and II are the most acidic of the heterocyclic aldoxime methiodides reported to date (Table I). There is a general trend for oxime acidity to increase as the ring basicity decreases. Major exceptions are I and the 2-formylpyridinium derivative. In order to rationalize these differences it would be necessary to take into account effects on oxime acidity by intramolecular dipole interactions.[8] This would require placing the compounds in categories of *syn* and *anti* configuration and position of substitution on the ring. The configuration of most of the quaternary heterocyclic aldoximes known has not been established. However, an examination of molecular models illustrates clearly that the oxygen of *anti* aldoximes could most readily participate in electrostatic interactions with the positive ring nitrogen. A weakening of the O–H bond with a corresponding increase in acidity would be anticipated and may be reflected in the low $pK_a$ of I relative to the high basicity of its heterocyclic nucleus.

TABLE I

ACID DISSOCIATION CONSTANTS OF QUATERNARY HETEROCYCLIC ALDOXIME IODIDES

| Heterocyclic ring | Relative basicity of ring nucleus[a] | $pK_a$ | Ref. |
|---|---|---|---|
| 1,3-Dimethyl-2-formylbenzimidazolium (I) | 1.00 | 7.0 | .. |
| 2-Formyl-1-methylpyridinium | .91 | 8.0 | b |
| 4-Formyl-1-methylpyridinium | .88 | 8.5,[c] 9.0[d] | e |
| 4-Formyl-1-methylquinolinium | .80 | 8.3 | b |
| 1-Formyl-2-methylisoquinolinium | .. | 7.7 | f |
| 2-Formyl-3-methylbenzothiazolium (II) | .39 | 6.3 | .. |

[a] The relative basicities had been determined by an indirect method involving comparison of the spectrum of a cyanine dye containing the particular heterocyclic ring as a constituent.[9] It involves a measurement of the deviation in $\lambda_{max}$ which is assumed to be due to the basicity of the heteroaromatic structure. [b] See ref. 4a. [c] *syn* Isomer. [d] *anti* Isomer. [e] See ref. 10. [f] See ref. 11.

(8) E. J. Poziomek, Ph.D. dissertation, University of Delaware, June, 1961.

(9) L. G. S. Brooker, A. L. Sklar, H. W. J. Cressman, G. H. Keyes, L. A. Smith, R. H. Sprague, E. Van Lare, G. Van Zandt, F. L. White, and W. W. Williams, J. Am. Chem. Soc., 67, 1875 (1954).

(10) E. J. Poziomek, D. N. Kramer, W. A. Mosher, and H. O. Michel, ibid., 83, 3916 (1961).

(11) R. H. Poirier, unpublished results.

## Experimental[12]

1-Methylbenzimidazole-2-carboxaldehyde.—M.p. 107–108° (reported[13] 110°). The presence of a strong carbonyl absorption band at 5.9 $\mu$ distinguished it from its precursor 1,2-dimethylbenzimidazole, m.p. 109–110°.

1-Methylbenzimidazole-2-carboxaldoxime.—M.p. 224–225° (reported[13] m.p. 204°).

1,3-Dimethyl-2-formylbenzimidazolium Iodide Oxime (I).—1-Methylbenzimidazole-2-carboxaldoxime (0.3 g.) was treated with an excess of methyl iodide in an acetone–ethyl alcohol mixture. After the mixture was allowed to stand at room temperature for 2 days, the 0.1 g. of pale yellow needles, m.p. 204–205° dec., that had crystallized from the reaction mixture was isolated and characterized.

*Anal.* Calcd. for $C_{10}H_{12}IN_3O$: C, 37.9; H, 3.8. Found: C, 37.9; H, 3.9.

Benzothiazole-2-carboxaldehyde.—M.p. 75–76°, recrystallized from petroleum ether (reported,[14] m.p. 75–77°). Recrystallization from methanol gave the hemiacetal, m.p. 89–91°.

*Anal.* Calcd. for $C_9H_9NO_2S$: C, 55.4; H, 4.7; S, 16.4. Found: C, 55.5; H, 5.0; S, 16.5.

Benzothiazole-2-carboxaldoxime.—M.p. 168–169° (reported,[15] m.p. 186–187°).

*Anal.* Calcd. for $C_8H_6N_2OS$: N, 15.7; neut. equiv., 178. Found: N, 15.7; neut. equiv., 172; $pK_a$, 9.3.

Methylation of Benzothiazole-2-carboxaldoxime. Procedure A.—A solution of benzothiazole-2-carboxaldoxime (11.5 g., 0.065 mole) and methyl iodide (24.6 g., 0.195 mole) in 75 ml. of nitrobenzene–ethanol (4:1) was refluxed for 11 hr. The reaction solution (colored red with a green cast) was cooled to room temperature and allowed to stand for 1 week. Filtration gave 11.0 g. of a red-brown solid. The product was dissolved in 300 ml. of warm methanol; the solution was boiled with activated charcoal and filtered. Fractional crystallization by the addition of ethyl ether and cooling gave three fractions:

Fraction A, N-methyl 2-formyl-3-methylbenzothiazolium iodide oxime (V), 0.4 g., m.p. 226–228°.

*Anal.* Calcd. for $C_{10}H_{11}IN_2OS$: C, 35.9; H, 3.3; O, 4.8. Found: C, 35.7; H, 3.4; O, 4.6.

Fraction B, 7.6 g., m.p. 198–200°; potentiometric titration data indicated that this product was a mixture containing 75% of II.

Fraction C, 2-formyl-3-methylbenzothiazolium iodide oxime (II), 1.0 g., m.p. 203–204° dec.

*Anal.* Calcd. for $C_9H_9IN_2OS$: C, 33.8; H, 2.8; O, 5.0; neut. equiv., 320. Found: C, 34.1; H, 2.9; O, 5.2; neut. equiv., 322; $pK_a$ 6.3. The $pK_a$ was determined spectrophotometrically in water.[16] $\lambda_{max}$ 0.1 N HCl, 329 m$\mu$; 0.1 N NaOH, 363 m$\mu$.

Procedure B.—A solution of 2.4 g. (0.0135 mole) of benzothiazole-2-carboxaldoxime in 5 ml. of methyl iodide and 15 ml. of methanol was refluxed for 24 hr. The mixture was concentrated, diluted with ethyl ether, and a salt was isolated by filtration; orange solid, 1.3 g., m.p. 189–190° dec. The 1.6 g. of unchanged oxime that was recovered by evaporation of the filtrate was again treated with methyl iodide. After 6 hr. of refluxing, the methiodide was isolated as before; 0.3 g. m.p. 189–190° dec. The products were combined, dissolved in 100 ml. of methanol–ethanol mixture, treated with Norite, concentrated to 50 ml., and allowed to crystallize. Orange crystals were obtained, 1.2 g. (28%), m.p. 190–191°, dec. An infrared absorption spectrum obtained in potassium bromide was identical to that of II isolated in procedure A.

O-Methyl-2-formyl-3-methylbenzothiazolium Iodide Oxime (VI).—To 5.0 g. of benzothiazole-2-carboxaldoxime in 100 ml. of hot methanol was added 8.0 g. of O-methylhydroxylamine hydrochloride. The solution was allowed to warm for 30 min. on a steam bath. Water was added to the point of cloudiness, then

(12) Melting points are uncorrected. Unless otherwise indicated, $pK_a$ values were obtained at room temperature, from potentiometric data, assuming $pK_a$ to be the pH of half neutralization. In each case approximately 100 mg. of sample dissolved in 25 ml. of methanol–water (1:1) was titrated with 0.1 N sodium hydroxide.

(13) Marie-Therese Le Bris and H. Wasbl, Bull. soc. chim. France, 312 (1959).

(14) D. Taber, J. Am. Chem. Soc., 77, 1010 (1955).

(15) W. Borsche and W. Doeller, Ann., 537, 53 (1939).

(16) D. H. Rosenblatt, J. Phys. Chem., 58, 40 (1954).

the mixture was cooled and filtered to give 4.6 g. of O-methyl benzothiazole-2-carboxaldoxime, m.p. 65–68°.

*Anal.* Found: C, 55.7; H, 4.4.

This product (4.0 g.) and 10 ml. of methyl iodide in 75 ml. of methanol were refluxed for 85 hr. Ether was added to give 0.6 g. of an orange solid, m.p. 201–203° dec.

*Anal.* Calcd. for $C_{10}N_{11}IN_2OS$: C, 35.9; H, 3.3. Found: C, 35.6; H, 3.3.

**N-Methyl-2-formyl-3-methylbenzothiazolium Iodide Oxime (V).**—A similar procedure as described for VI (except that N-methylhydroxylamine was used) gave 26% of an orange solid, m.p. 233–235° dec.

*Anal.* Calcd. for $C_{10}H_{11}IN_2OS$: C, 35.9; H, 3.3. Found: C, 35.7; H, 3.4.

**Nuclear Magnetic Resonance Studies.**—The spectra were obtained using a Varian Model HR-60 high resolution n.m.r. spectrometer equipped with an electronic integrator. All chemical shifts are reported in cycles per second at 60 Mc./sec. downfield from the reference signals used. Tetramethylsilane was used as a reference for spectra obtained in acetonitrile and the methyl resonance of sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as a reference for the spectra obtained in $D_2O$.[17] All chemical shifts were determined using the side band technique.[18]

(17) G. V. D. Tiers and R. I. Coon, *J. Org. Chem.*, **26**, 2097 (1961).
(18) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

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# Bridged Polycyclic Compounds. XXII. The Carbenoid Decomposition of Nortricyclenone *p*-Toluenesulfonylhydrazone

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An attempt to prepare quadricyclo[2,2,1,0²,⁶,0³,⁵]-heptane (I) by treatment of the *p*-toluenesulfonylhydrazone of nortricyclenone (II) using the general procedure described by Friedman and Shechter[2] (heating with sodium methoxide in diglyme at 160°) gave hydrocarbon material (19% yield) which apparently did not contain any I,[3] but instead was a mixture of 69% of 4-ethynylcyclopentene (III), and 29% of 4-vinylidenecyclopentene (IV). The mixture of these two materials was separated by vapor phase chromatography.
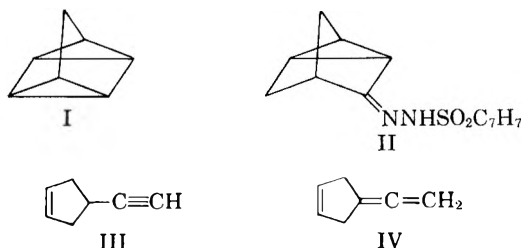


Compounds III and IV were characterized and identified as follows. III gave the correct C,H analysis and decolorized bromine in carbon tetrachloride and 2% aqueous potassium permanganate instantaneously. Catalytic hydrogenation of III with palladium-on-charcoal catalyst in ethanol at room temperature led to rapid absorption of three moles of hydrogen per mole of compound. The boiling point of III was approximately 92° (628 mm.) and indicates a monomer. The infrared spectrum of III clearly showed the presence of an acetylenic function, exhibiting a strong, sharp absorption peak at 3.02 $\mu$ and a sharp, but less intense peak at 4.73 $\mu$. Sharp peaks at 3.27 and 6.21 $\mu$ are ascribed to the ethylenic hydrogens and carbon–carbon double-bond stretching vibrations. The nuclear magnetic resonance spectrum of III exhibited a singlet at 4.42 $\tau$, a complicated multiplet between 6.8 and 7.8 $\tau$, and a clear doublet at 8.12 $\tau$ with relative areas of the peaks being 1.94, 5.09, and 1.00, respectively. The singlet at 4.42 $\tau$ is ascribed to the ethylenic hydrogens. Cyclopentene itself has a sharp singlet at 4.40 $\tau$. The doublet at 8.12 $\tau$ ($J$ = 2.0 c.p.s.) is assigned to the acetylenic hydrogen which is split by the methinyl hydrogen. Several examples of such 1,3 splittings are known.[4]

It was expected that the spin–spin splitting pattern of the olefinic hydrogens in the nuclear magnetic resonance spectrum of the acetylene would distinguish between the symmetrical compound III and its unsymmetrical isomer, 3-ethynylcyclopentene. However, when the nuclear magnetic resonance spectra of similar isomers, $\Delta^2$ and $\Delta^3$-cyclopentenylacetamide,[5] were obtained, it was found that the splitting pattern of the olefinic hydrogens of the isomers was essentially the same, although the appearance of the over-all spectrum clearly indicated two isomers.

Although IV was unstable, its structure was established unequivocally by spectral means. The infrared spectrum of IV clearly indicated the presence of the allene function by a sharp intense absorption peak at 5.10 $\mu$. The allene function is reported[6] to absorb at 5.08 to 5.12 $\mu$. Sharp peaks of medium intensity at 3.27 and 6.21 $\mu$ are again ascribed to the ethylenic hydrogen and carbon–carbon double-bond stretching vibrations. The nuclear magnetic resonance spectrum of IV consists of a sharp singlet at 4.48 $\tau$, a pentuplet centered at 5.40 $\tau$, and a triplet centered at 6.87 $\tau$ with relative peak areas of 0.95, 1.00, and 1.97, respectively. The relative intensities of the components of the triplet were 1:2:1 and of the pentuplet 1:4:6:4:1, indicating that the multiplicity is the result of groups of equivalent nuclei splitting with each other.[7] The spectrum is clearly compatible only with the structure IV for the allene. Finally, the fact that the acetylene isolated is isomerized to IV makes it most probable that it is the 4-ethynyl derivative. It is unlikely that the conditions employed are drastic enough to isomerize the carbon–carbon double bond concurrently with the acetylene–allene transformation.

(1) Previous paper in series: S. J. Cristol, Dennis D. Tanner, and Robert P. Arganbright, *J. Org. Chem.*, **28**, 1374 (1963).
(2) (a) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959); (b) **82**, 1002 (1960); (c) G. L. Closs, *ibid.*, **84**, 809 (1962).
(3) W. G. Dauben and R. L. Cargill, *Tetrahedron*, **15**, 197 (1961).
(4) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.
(5) S. J. Cristol and P. K. Freeman, *J. Am. Chem. Soc.*, **83**, 4427 (1961).
(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 61.
(7) The nuclear magnetic resonance spectrum of IV is being considered in detail elsewhere: M. W. Hanna and J. K. Harrington, *J. Phys. Chem.*, in press.

Friedman and Shechter[2b] have observed that acetylene and ethylene are formed in the carbenoid decomposition of cyclopropanecarboxyaldehyde p-toluenesulfonylhydrazone and methylacetylene and ethylene from the related reaction starting with cyclopropyl methyl ketone. It would appear that the formation of an acetylene and an olefin may be general for carbenes in which one of the substituents is a cyclopropane ring. The transformation involved in the formation of III can be represented as follows.
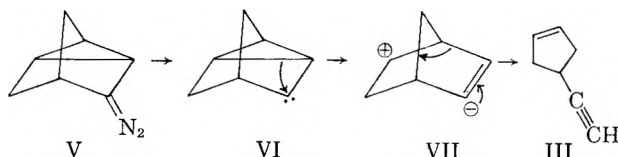


There is, of course, no certainty regarding the existence of intermediates VI and VII. The formation of allene IV seems best rationalized on the basis that it is the result of base-catalyzed isomerization[8] of the acetylene III rather than a direct product of the carbene reaction. This rationalization is supported by the fact that only III was formed (in 42% yield) upon thermal decomposition of the potassium salt of II or upon irradiation of the salt of II according to the general procedure of Dauben and Willey.[9] It is also supported by the fact that III was isomerized to IV under conditions similar to those used in the decomposition of II.

## Experimental

Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee. Infrared spectra were recorded on a Beckman IR-5 double beam spectrophotometer equipped with sodium chloride optics. Spectra were obtained in carbon tetrachloride solution. Nuclear magnetic resonance spectra were obtained in carbon tetrachloride solution with an A-60 analytical spectrometer of Varian Associates using tetramethylsilane as an internal standard. Vapor phase chromatograms were obtained with a Perkin-Elmer Model 154-D vapor fractometer. Analyses and separations were effected on a 1-m. glass column charged with 30% UCON Oil LB-550-X on Chromosorb W. All runs were made at 72° with a flow rate of 87 ml. of helium/min. Peak areas were determined by triangulation and corrected for variation in thermal conductivity except that thermal conductivities of III and IV were considered equal.

**Nortricyclenone.**—The preparation of nortricyclenone was accomplished according to the method of Schaefer.[10] The ultraviolet spectrum and melting point of its 2,4-dinitrophenylhydrazone agreed with the values given by Roberts, Trumbull, Bennett, and Armstrong.[11] The ketone was stored as the stable sodium bisulfite addition compound and regenerated as needed by hydrolysis with aqueous sodium carbonate.

**Nortricyclenone p-Toluenesulfonylhydrazone.**—To a solution of p-toluenesulfonylhydrazine (27.0 g., 0.145 mole) in 300 ml. of 1% ethanolic sulfuric acid, nortricyclenone (15.5 g., 0.144 mole) was added all at once. The mixture was heated to 55° for approximately 5 min., then poured into ice–water, and allowed to crystallize at 10°. Filtration yielded 37.4 g. (94%) of the dry p-toluenesulfonylhydrazone, m.p. 157–159° dec. An analytical sample was prepared by recrystallization from ethanol–water, m.p. 158.5–160° dec., $\lambda_{max}$ (in ethanol), 275 m$\mu$, $\epsilon$ 700; 225 m$\mu$, $\epsilon$ 15,000.

*Anal.* Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.84. Found: C, 60.93; H, 5.99.

**Decomposition of Nortricyclenone p-Toluenesulfonylhydrazone with Excess Sodium Methoxide.**—The decomposition was carried out by a modification of the procedure of Closs.[2c] A three-neck flask was equipped with dropping funnel, magnetic stirrer, fritted nitrogen inlet, and a 30-cm. Vigreux column. The Vigreux column was wrapped with electrical heating tape and connected with two receiving traps in series which were cooled in a mixture of Dry Ice and acetone. The jacketed Vigreux column was heated to 100° and the system purged with prepurified nitrogen which was used as a carrier gas to sweep out the products of the reaction. Dry reagent-grade sodium methoxide (7.71 g., 0.143 mole) was suspended in diglyme (distilled twice from lithium aluminum hydride) and the suspension was heated in a stirred oil bath at 160°. A solution of II (12.0 g., 0.044 mole) in diglyme (150 ml.) was added dropwise over a period of 3 hr. The contents of the two traps were diluted with a fivefold excess of water and extracted three times with 25-ml. portions of pentane. The combined extracts were dried and the pentane was removed by careful distillation through a 30-cm. coiled wire column. Hydrocarbon material, 748 mg. (19%), composed essentially of III and IV, was obtained. III and IV were then separated by vapor phase chromatography. III had a retention volume of 1650 ml. and IV a retention volume of 2300 ml. The ratio of III to IV was 71/29. III instantly decolorized bromine in carbon tetrachloride in a capillary test. III dissolved in acetone decolorized a drop of 2% aqueous potassium permanganate. A sample of III was purified for analysis by vapor phase chromatography, $n^{20}D$ 1.4592.

*Anal.* Calcd. for $C_7H_8$: C, 91.25; H, 8.75. Found: C, 91.42; H, 8.55.

The boiling point of III, taken by Emrich's method,[12] was approximately 92° (628 mm.). Reduction of III (43.3 mg., 0.470 mmole) in 95% ethanol (20 ml.) was effected over 50 mg. of prereduced 10% palladium on charcoal in a low pressure apparatus at 632 mm. and 22.5°. Hydrogen (40.4 ml.) was taken up in 5–6 min., corresponding to an uptake of 2.95 moles of hydrogen per mole of III.

IV was obtained in pure form (a single peak on reinjection) by vapor phase chromatography but proved to be unstable. Upon standing at room temperature, IV changed to a yellow gum in a few hours and to a solid in approximately 24 hr. The structure of IV was established by analysis of its nuclear magnetic resonance spectrum.

**Neutralization of Nortricyclenone p-Toluenesulfonylhydrazone with One Equivalent of Sodium Methoxide.**—A dry 50-ml. two-neck flask was equipped with a nitrogen inlet and distilling head. The system was purged with prepurified nitrogen. To it was added II (5.913 g., 0.0214 mole), dry sodium methoxide (1.129 g., 0.0209 mole), and absolute methanol (15.0 ml.). A clear solution was obtained. Methanol was then removed by distillation under reduced pressure. The residue was ground in an agate mortar and pestle in a dry box under an atmosphere of prepurified nitrogen and dried under reduced pressure over phosphoric anhydride.

**Thermal Decomposition.**—This dry product (most probably the salt of II, m.p. > 200°) and diglyme (25 ml., distilled from lithium aluminum hydride) were placed in a flask fitted with a nitrogen inlet and a heated Vigreux column connected with two receiving traps cooled in a mixture of Dry Ice and acetone. The apparatus was lowered into a stirred oil bath held at 160° and heated for two hours with nitrogen flowing through the system. The contents of the traps were analyzed by vapor phase chromatography and only III (42% using benzene as an internal standard) was found. No observable amounts of IV were detectable. The contents of the traps were poured into water (100 ml.) and extracted with pentane. The combined extracts were dried and the pentane removed by careful distillation to give III (687 mg., 36%) contaminated by a small amount of pentane. Analysis by vapor phase chromatography again showed IV to be absent.

**Photolytic Decomposition.**—A sample of the product (730 mg.) obtained by treating II with one equivalent of sodium methoxide was suspended in dry diglyme (10 ml.) in a quartz tube, stirred with a magnetic stirrer, and subjected to irradiation by a 450-w. Hanovia high pressure ultraviolet lamp for 1.75 hr. The contents of the quartz tube were analyzed by vapor phase chromatography and only the presence of III (in low yield) was detected.

(8) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Academic Press, Inc., New York, N. Y., 1955, pp. 134–39.

(9) W. G. Dauben and F. G. Willey, *J. Am. Chem. Soc.*, **84**, 1497 (1962).

(10) J. P. Schaefer, *J. Am. Chem. Soc.*, **82**, 4091 (1960).

(11) J. D. Roberts, E. R. Trumbull, W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).

(12) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1956, p. 86.

Isomerization of 4-Ethynylcyclopentene to 4-Vinylidenecyclo-pentene.—To a small glass tube was added sodium methoxide (34.1 mg., 0.632 mmole), dry diglyme (0.30 ml.), and III (0.0147 g., 0.160 mmole) which was purified by vapor phase chromatography and contained no detectable amount of IV. The tube was sealed and heated at 160° for 8 min. in a stirred oil bath. The tube was quickly cooled in an ice bath, opened, and the contents analyzed by vapor phase chromatography. The ratio of III to IV was found to be 83/17.

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## Reaction of Triphenylmethyl with Several Peroxides

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Wieland and Meyer[1] discovered that triphenylmethyl reacts with benzoyl peroxide in benzene to give trityl benzoate, benzoic acid, and tetraphenylmethane. Work on various aspects of the mechanism of this reac-

$$(C_6H_5)_3C\cdot + (C_6H_5CO_2)_2 \xrightarrow{C_6H_6}$$
$$(C_6H_5)_4C + C_6H_5CO_2C(C_6H_5)_3 + C_6H_5CO_2H$$
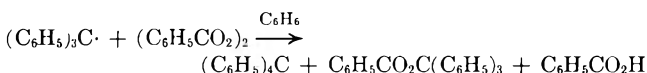
tion has been relatively extensive.[2] It seems well established that trityl benzoate is formed by attack of triphenylmethyl on benzoyl peroxide and by combination of triphenylmethyl with benzoyloxy radicals.[2d]

Several workers have shown that formation of tetraarylmethanes occurs in aromatic solvents other than benzene.[2a,c] Several mechanisms have been suggested to account for the formation of tetraarylmethanes. The most recent has been suggested by Benkeser and Schroeder,[2c] who have postulated that tetraphenylmethane is formed by reaction of a π-complex of triphenylmethyl and benzene with benzoyl peroxide or a benzoyloxy radical.

Interestingly, apparently no one has demonstrated that the tetraarylmethane-forming reaction can be effected by any peroxide other than benzoyl. It was the purpose of this work to investigate this point. Triphenylmethyl was allowed to react with benzoyl peroxide, cyclopropylformyl peroxide, hydrocinnamoyl peroxide, 3,3,3-triphenylpropanoyl peroxide, and t-butyl perbenzoate. Triphenylmethyl induced the decomposition at room temperature of all of the diacyl peroxides. It was necessary to boil the benzene-t-butyl perbenzoate-triphenylmethyl reaction mixture to effect decomposition of the perester. Even so the total time required for decomposition was considerably less than that required for the decomposition of t-butyl perbenzoate in the absence of triphenylmethyl. Only with

benzoyl peroxide and cyclopropylformyl peroxide could the formation of tetraphenylmethane be detected. With benzoyl peroxide a 14% yield was obtained,[3] while cyclopropylformyl peroxide yielded *ca.* 1% of tetraphenylmethane. It cannot be definitely stated that no tetraphenylmethane was formed with the other peroxides but if any was formed it must have been very little. For example, three separate decompositions of hydrocinnamoyl peroxide gave no evidence for tetraphenylmethane formation.

The results of these experiments show that the formation of tetraphenylmethane is dependent upon the nature of the peroxide used. Of greater significance is the correlation between the stability of the acyloxy radical derived from the peroxide and the formation of tetraphenylmethane. It seems well established, mainly on the basis of radical trapping experiments, that the benzoyloxy radical[4] is more stable towards decarboxylation than a cyclopropylcarboxy radical,[5] both of which are more stable than simple acyloxy radicals.[6]

The results obtained with the various peroxides indicate that the formation of tetraphenylmethane probably does not involve a direct reaction with the peroxide. If this were the case, it seems reasonable to suppose that all diacyl peroxides should be capable of participating in the reaction.[7] The results are in accord with a reaction path in which an acyloxy radical reacts with a π-complex of triphenylmethyl and solvent,[2c] although this is not the only possibility. For example, triphenylmethyl may react with a π-complex of the acyloxy radical with solvent.

It is interesting that other radicals, *i.e.*, various alkyl radicals which were undoubtedly present during the decompositions with the diacyl peroxides, did not promote the formation of tetraphenylmethane. Indeed the reaction seems limited to relatively stable acyloxy radicals. The true requirement may be that an electrophilic radical be present. This may well be due to a necessity for strong electron transfer contributions to the transition state which leads to tetraarylmethane.[8]

### Experimental

**Reaction of Cyclopropylformyl Peroxide and Triphenylmethyl.** —A solution of triphenylmethyl was prepared by stirring 10 g. (0.08 mole) of triphenylmethyl chloride dissolved in 75 ml. of benzene with 35 g. (0.18 g.-atom) of mercury for 8 hr. under an atmosphere of nitrogen. To this solution was added 5.1 g. (0.03 mole) of cyclopropylformyl peroxide in 75 ml. of benzene. After stirring for 1 hr., the infrared spectrum of the mixture indicated that all of the peroxide had been decomposed. The mixture was filtered and concentrated to a volume of 35 ml. and then chromatographed on 60 g. of alumina. Elution with 20% benzene in petroleum ether (30–60°) afforded a white crystalline substance in the first 150 ml. of eluate.[9] Recrystallization from

(1) H. Wieland and A. Meyer, *Ann.*, **532**, 179 (1937).

(2) (a) H. Wieland and A. Meyer, *ibid.*, **551**, 249 (1942); (b) G. S. Hammond, J. T. Rudesill, and F. J. Modic, *J. Am. Chem. Soc.*, **73**, 3929 (1951); (c) R. A. Benkeser and W. Schroeder, *ibid.*, **80**, 3314 (1958); (d) W. E. Doering, K. Okamoto, and H. Krouch, *ibid.*, **82**, 3579 (1960).

(3) Hammond and co-workers, ref. 2b, obtained yields of 20–30% of tetraphenylmethane depending upon the reaction conditions.

(4) G. S. Hammond and L. M. Soffer, *J. Am. Chem. Soc.*, **72**, 4711 (1950)

(5) H. Hart and D. P. Wyman, *ibid.*, **81**, 4891 (1959).

(6) This order of stability is based upon the amount of parent acid formed during the decomposition of the peroxide in the presence of iodine and water. Using this technique, 96% benzoic acid,[4] 47% cyclopropane carboxylic acid,[5] and 10% hydrocinnamic acid have been obtained (H. Weiss, thesis, Rutgers, The State University, 1962).

(7) Such a reaction might have involved electron or hydrogen transfer from a π-complex to the peroxide.

(8) Many radical reactions are subject to this effect. See C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 365–368, for a discussion of this matter.

(9) These conditions were determined as optimal from experiments with reaction mixtures obtained from the reaction of benzoyl peroxide and triphenylmethyl in benzene.

benzene–hexane afforded 0.25 g. of material, m.p. 279–281° (lit.,[2c] m.p. 281–282°). The melting point was not depressed on admixture with an authentic sample of tetraphenylmethane. The infrared spectrum, potassium bromide pellet, was identical to that of an authentic sample of tetraphenylmethane.

**Reaction of Triphenylmethyl with Hydrocinnamoyl Peroxide, 3,3,3-Triphenylpropanoyl Peroxide and t-Butyl Perbenzoate.**[10]—The same general procedure as described for the reaction of cyclopropylformyl peroxide was followed except in the case of t-butyl perbenzoate where it was necessary to reflux the reaction mixture for 20 hr. to decompose the perester. Chromatography of the concentrated reaction mixtures on alumina gave in no case any indication for the formation of tetraphenylmethane.

(10) Detailed descriptions of these reactions can be found in H. Weiss, Ph.D. thesis, Rutgers, The State University, 1962.

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# The Chemistry of β-Bromopropionyl Isocyanate. III. Identification of Phenols and Anilines[1]

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The use of β-bromopropionyl isocyanate (I) in making solid derivatives of alcohols has been reported.[2] The use of I in making derivatives of phenols and aromatic amines is reported herein.

The reaction of I with phenols occurred readily in chloroform solution in the absence of a catalyst. The reaction did not appear to be subject to steric hindrance, since 2,6-diallylphenol, 2,6-diisopropylphenol, and 2,6-di-tert-butylphenol gave satisfactory derivatives under these conditions. Hydroquinone and resorcinol reacted satisfactorily, but phloroglucinol gave a mixture of two products whose structures have not been determined as yet.

The most serious limitation of the use of I with phenols occurred with the polynitrophenols. Mononitrophenols reacted readily, but no reaction was observed with 2,4-dinitrophenol or picric acid under the conditions specified. In this connection it is interesting that thiophenol reacted with I whereas hydrogen sulfide did not appear to do so.

Monofunctional aromatic amines reacted with I without difficulty. The products were easily isolated and purified. Diphenylamine formed a derivative without difficulty. The N-β-bromopropionyl-N'-arylureas formed from the reaction of I with aryl amines could be dehydrohalogenated to N-acrylyl-N'-arylureas with triethylamine.[3] Reaction of I with 2,4-dinitroaniline was unsuccessful.

Aromatic diamines gave products which were very insoluble in most solvents, and thus were very difficult to purify. This difficulty is sufficient to preclude recommendation of I as a reagent for preparing derivatives of diamino compounds.

Attempts were made to use I as a reagent for aliphatic amines. Considerable difficulty was noted, and I is not

(1) Support from National Science Foundation grants G-7850 (Undergraduate Research Participation Program) and G-9914 is gratefully acknowledged.

(2) H. W. Johnson, Jr., H. A. Kreyssler, and H. L. Needles, J. Org. Chem., 25, 279 (1960).

(3) H. W. Johnson, Jr., R. E. Lovins, and M. Reintjes, ibid., 24, 1391 (1959); N. W. Gabel and S. B. Binkley, ibid., 23, 643 (1958).

### TABLE OF DERIVATIVES

| Parent compound | M.p. of derivative, °C. | Solvent[a] | %C Calcd. | %C Found | %H Calcd. | %H Found |
|---|---|---|---|---|---|---|
| Phenol | 106–107 | C | 44.1 | 44.3 | 3.70 | 3.50 |
| p-Chlorophenol | 138–139 | M | 39.2 | 39.3 | 2.96 | 2.90 |
| p-Nitrophenol | 146–147 | I | 37.9 | 38.0 | 2.86 | 2.74 |
| p-Methoxyphenol | 93–94 | C | 43.7 | 44.0 | 4.00 | 4.10 |
| p-tert-Butylphenol | 146–147 | M | 51.2 | 51.0 | 5.49 | 5.65 |
| p-Phenylphenol | 170–171 | T | 55.2 | 55.1 | 4.05 | 4.12 |
| o-Chlorophenol | 127–127.5 | E | 39.2 | 39.1 | 2.96 | 2.67 |
| o-Nitrophenol | 129–130 | M | 37.9 | 37.6 | 2.86 | 2.78 |
| o-Allylphenol | 91–92 | C | 50.0 | 50.1 | 4.52 | 4.49 |
| o-Isopropylphenol | 99–100 | E | 49.7 | 49.5 | 5.13 | 5.21 |
| 1-Naphthol | 133–133.5 | C | 52.2 | 52.1 | 3.76 | 3.60 |
| 2-Naphthol | 143–144 | M | 52.2 | 52.0 | 3.76 | 3.77 |
| 3,4-Dimethylphenol | 105–106 | M | 48.0 | 47.7 | 4.70 | 4.60 |
| 2,6-Dimethylphenol | 158–159 | M | 48.0 | 47.8 | 4.70 | 4.63 |
| 3,5-Dimethylphenol | 155–156 | M | 48.0 | 47.9 | 4.70 | 4.55 |
| 2,5-Dimethylphenol | 126–127 | M | 48.0 | 47.9 | 4.70 | 4.49 |
| 2,6-Diallylphenol | 123–124 | E | 54.6 | 54.2 | 4.58 | 4.30 |
| 2,6-Diisopropylphenol | 111–112 | E | 53.9 | 54.0 | 6.22 | 6.00 |
| 2,6-Di-tert-butylphenol | 107–109 | E | 56.2 | 56.3 | 6.82 | 6.95 |
| p-Cresol | 148–149 | I | 46.2 | 46.3 | 4.23 | 4.40 |
| Eugenol | 80–81 | C | 49.1 | 49.4 | 4.71 | 4.64 |
| Isoeugenol | 141–142 | M | 49.1 | 49.3 | 4.71 | 4.70 |
| Hydroquinone | 209–210 | T | 36.1 | 36.3 | 3.03 | 3.32 |
| Resorcinol | 165–166 | I | 36.1 | 36.3 | 3.03 | 3.12 |
| Ammonia | 181–182 | M | 24.6 | 24.9 | 3.62 | 3.51 |
| Benzylamine | 165–166 | M | 46.3 | 46.1 | 4.60 | 4.87 |
| Aniline | 183–184 | M | Previously reported | | | |
| N-Methylaniline | 92–93 | M | 46.3 | 46.1 | 4.56 | 4.40 |
| o-Toluidine | 162–163 | E | 46.3 | 46.5 | 4.56 | 4.69 |
| m-Toluidine | 151.5–152.5 | C | 46.3 | 46.3 | 4.56 | 4.64 |
| p-Toluidine | 196.5–197.5 | E | 46.3 | 46.0 | 4.56 | 4.42 |
| o-Phenetidine | 224–225 | E | 45.7 | 45.8 | 4.76 | 4.90 |
| m-Chloroaniline | 181–182 | E | 39.2 | 39.5 | 3.27 | 3.18 |
| o-Nitroaniline | 192–193 | M | 38.0 | 38.1 | 3.16 | 3.05 |
| p-Nitroaniline | 222–223 | M | 38.0 | 38.2 | 3.16 | 3.00 |
| p-Bromoaniline | 209–210 | M | 34.3 | 34.6 | 2.86 | 2.86 |
| 2-Aminopyridine | 170.5–172 | M | 39.7 | 40.0 | 3.68 | 3.76 |
| 2,5-Dimethoxyaniline | 236.5–237.5 | E | 43.5 | 43.8 | 4.53 | 4.34 |
| 2,5-Dichloroaniline | 183–184 | M | 35.3 | 35.5 | 2.65 | 2.46 |
| o-Phenylenediamine[b] | 222–225 (dec.) | | 36.2 | 37.3 | 3.45 | 3.64 |
| m-Aminophenol | 186–187 | M | 36.1 | 36.4 | 3.23 | 3.23 |
| β-Phenylethylamine | 153–152 | M | 48.2 | 48.5 | 5.02 | 4.89 |
| Diphenylamine | 129–130 | M | 55.4 | 55.2 | 4.32 | 4.45 |
| Bis(p-aminophenyl)methane[b] | 250–260 | | (None attempted) | | | |

[a] Crystallization solvents: E, ethanol; I, isopropyl alcohol; M, methanol; T, tetrahydrofuran. [b] Too insoluble for crystallization in common solvents.

recommended for use in making derivatives of them. The amines reacted readily, but the β-bromopropionylureas thus formed are easily dehydrohalogenated by any excess of amine[4] to give an oily mixture of bromopropionyl- and acrylylureas. Certain of the aliphatic amines gave derivatives when low temperatures and

(4) H. W. Johnson, Jr., and M. Schweizer, ibid., 26, 3666 (1961).

dilute solutions were used, and ammonia gave a product which was insoluble in chloroform (and thus unable to react further).

The derivatives prepared from amines and phenols appeared to be stable to ordinary laboratory storage conditions when reasonably pure.

In general, our experience with the use of I as a reagent for preparing derivatives may be summarized a follows: for aliphatic alcohols—good in most cases, particularly useful with fairly unreactive alcohols; for aliphatic amines—not recommended; for phenols—good, except for very acidic phenols; for aromatic amines—good for monoamino compounds. The principal advantage of I is that reaction with water yields β-bromopropionamide which can be removed from the product by crystallization in most cases; aryl isocyanates yield diarylureas which are more difficult to remove from the product. The increase in molecular weight of an alcohol or amine upon reaction with I is 178, which compares favorably with 119 for phenyl isocyanate and 169 for naphthyl isocyanate.

### Experimental

The phenols and amines used in this work were obtained from commercial sources. Melting points were determined with a Koffler block. Analyses were performed by Dr. Weiler and Dr. Strauss, Oxford.

The method of preparation of I has been reported previously.[2]

**Preparation of Derivatives.**—A suspension of 1.0 g. (0.0056 mole) of N-bromosuccinimide, 10 ml. of chloroform (dried over calcium chloride), 0.5 ml. of allyl chloride, and a small amount (ca. 10 mg.) of benzoyl peroxide was refluxed for 30 min. The now-clear solution was allowed to cool to room temperature, and an approximately equimolar amount of the phenol or aniline dissolved in a few milliliters of chloroform was added. If the amine or phenol was insoluble in chloroform, it was dissolved in a few milliliters of tetrahydrofuran. A vigorous reaction ensued in most instances. The solution was cooled in an ice bath, and in many instances the product crystallized from the reaction mixture. The solid was filtered and crystallized from the solvent indicated in the table. If no solid precipitated, low boiling petroleum ether was added to precipitate the product. The solid was then crystallized from the solvent indicated in the table.

The same procedure has been used to prepare derivatives on a 50-g. scale.

To prepare the derivatives of aliphatic amines, e.g., benzylamine, it was necessary to add an equimolar amount of the amine very slowly, with stirring, keeping the solution temperature below 5°. The preparation of β-bromopropionylurea (from I and ammonia) was accomplished by bubbling gaseous ammonia into the chloroform solution, from which the derivative precipitated immediately.

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## The Monoaddition of Phenylsilane to Cyclic Polyolefins[1]

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Recently several workers have reported the addition of diborane or triethylamineborane to 1,5,9-cyclododeca-

triene to give perhydro-9b-borphenalene (I).[2,3] It seemed possible that an analogous reaction might take place with silicon in place of boron. We have attempted to add phenylsilane to the same triolefin using benzoyl peroxide and chloroplatinic acid as catalysts. In neither case is any of the desired tricyclic silicon analog of I obtained. Chloroplatinic acid catalysis led only to polymeric material, but with benzoyl peroxide a
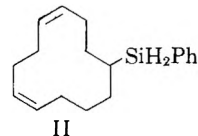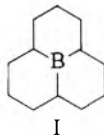


16% yield of 9-phenylsilyl-1,5-cyclododecadiene (II) was obtained. The monoaddition product is completely unreactive toward further addition, being recovered unchanged after seven days of heating with benzoyl peroxide catalyst. Similar results were obtained in the addition of phenylsilane to 1,5-cyclooctadiene, which led only to the monoadduct, 5-phenylsilylcyclooctene.

The reluctance of silicon to add to form the perhydrosilaphenalene ring may result in part from the large radius of the silicon atom, which would prevent the molecule from assuming a strainless configuration. However, unsuccessful attempts to cyclize 5-pentenyldichlorosilane by intramolecular Si–H addition suggest that the mechanism of silane addition may require a geometry which makes the formation of a six-membered ring unfavorable. With either chloroplatinic acid or benzoyl peroxide, 5-pentenyldichlorosilane gave none of the desired 1,1-dichlorosilacyclohexane, even though the latter compound can assume a strainless chair-like configuration.[4]

### Experimental

**9-Phenylsilyl-1,5-cyclododecadiene.**—Fifteen milliliters (0.12 mole) of phenylsilane and 22 ml. (0.12 mole) of 1,5,9-cyclododecatriene in 150 ml. of dry heptane were refluxed for 3 days during which time a total of 2.5 g. of benzoyl peroxide was added in 250 mg. increments at 6–10-hr. intervals. After cooling, the mixture was shaken with an aqueous solution 1 N each in ammonia and ammonium chloride in order to remove benzoic acid formed in decomposition of the peroxide. The organic layer was separated, dried, and fractionally distilled. After removal of heptane and unreacted starting materials, the only volatile product, a colorless liquid, was distilled at 114–127° (0.15 mm.); yield 5.0 g., 16%. A large residue of polymeric material was left in the flask. The product had $n^{25}D$ 1.5449, $d^{25}_4$ 1.0197.

*Anal.* Calcd. for $C_{18}H_{26}Si$: C, 79.92; H, 9.69; Si, 10.38. Found: C, 80.15; H, 9.57; Si, 10.29.

The infrared spectrum of the product showed a very strong band at 2120 cm.$^{-1}$ (Si—H) as well as a weak doublet at 1600 cm.$^{-1}$ (C=C). The proton magnetic resonance spectrum showed a cluster of lines near $\tau = 2.8$, a sharp line at $\tau = 5.83$, and a broad unresolved band from $\tau = 8.0$ to 9.4. These resonances are assigned to phenyl, silane, and a mixture of methylene and vinylic protons, respectively; the relative integrated intensities were 5.0:1.8:20. A semiquantitative base-catalyzed hydrolysis of the substance in aqueous tetrahydrofuran yielded 1.7 moles of hydrogen per mole of compound.

**Attempted Addition Using Chloroplatinic Acid Catalyst.**—A 5.8-ml. sample (0.046 mole) of phenylsilane and 8.4 ml. (0.046 mole) of 1,5,9-cyclododecatriene and a small amount of chloroplatinic acid in isopropyl alcohol were dissolved in 50 ml. of dry heptane, and the solution was refluxed for 24 hr. The heptane

(2) R. Köster, Angew. Chem., 69, 684 (1957); G. Rotermund and R. Köster, ibid., 74, 329 (1962).

(3) N. N. Greenwood and J. H. Morris, J. Chem. Soc., 2922 (1960).

(4) R. West, J. Am. Chem. Soc., 76, 6015 (1954).

and unchanged phenylsilane were removed under vacuum. Upon fractional distillation of the residue 7.0 ml. (83%) of the triene was recovered, leaving a small amount of a discolored glassy polymer which did not dissolve in hot benzene.

**5-Phenylsilylcyclooctene.**—This compound was prepared from 7.0 ml. (0.057 mole) of phenylsilane and 7.0 ml. (0.057 mole) of 1,5-cyclooctadiene in 100 ml. of heptane, following the method described above for 9-phenylsilyl-1,5-cyclododecadiene. A total of 1.5 g. of benzoyl peroxide was added in small increments during 3 days of refluxing. The desired product was again the only volatile substance to be isolated; it distilled at 67–69° (0.025 mm.). The yield was 3.5 g. (25%); $n^{25}$D 1.5380, $d_4^{26}$ 0.9818.

*Anal.* Calcd. for $C_{14}H_{20}Si$: C, 77.77; H, 9.26. Found: C, 77.55; H, 9.26.

The substance liberated hydrogen when treated with alcoholic potassium hydroxide and the infrared spectrum showed an intense Si—H stretching band at 2110 cm.$^{-1}$. The proton n.m.r. spectrum consisted of a number of lines around $\tau = 2.9$ (aromatic H), a sharp doublet at $\tau = 5.8$ (silanic H), a diffuse line at $\tau = 7.85$ (vinylic H), and a complex group centered at $\tau = 8.8$ (methylenic H). The relative integrated intensities were 5:2:2:12, in good agreement with the proposed structure.

**5-Pentenyldichlorosilane and Attempted Cyclization.**—The compound was prepared from 5-pentenylmagnesium bromide and trichlorosilane in tetrahydrofuran. After separation of the organic material from the magnesium salts, it was fractionally distilled. It proved difficult to separate the silane from a hydrocarbon by product, and the desired product was isolated in only 13% yield, boiling at 65–66° (28 mm.). The infrared spectrum showed bands characteristic of Si—H, Si—C, Si—Cl, and C=C.

*Anal.* Calcd. for $C_5H_{10}SiCl_2$: Cl, 41.7. Found: Cl, 40.5.

Intramolecular cyclization was attempted under several conditions using either chloroplatinic acid or acetyl peroxide catalysts. The majority of the product in every case was a polymeric residue, perhaps resulting from linear polymerization of the 5-pentenyldichlorosilane. Any volatile products were characterized by exhaustive methylation with methyl Grignard reagent followed by gas chromatography. None of the desired cyclopentamethylenedimethylsilane[5] was isolated in any of the reactions.

(5) A. Bygden, *Ber.*, **48**, 1236 (1915); R. West, *J. Am. Chem. Soc.*, **76**, 6012 (1954).

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# Synthesis of Substituted β-Lactams

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A novel method for the synthesis of substituted β-lactams III has been developed by Sheehan and Bose[1] in which the amide linkage is formed first and the four-membered β-lactam ring is then made by establishing carbon–carbon bond according to the following scheme.
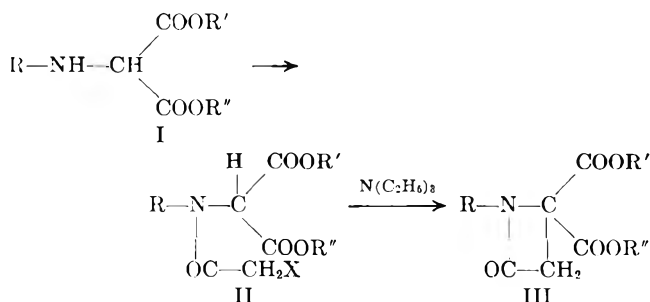


(1) J. C. Sheehan and A. K. Bose, *J. Am. Chem. Soc.*, **72**, 5158 (1950).

Further work has shown that the cyclization to β-lactam proceeds in high yield and that the reaction is a general one.[2]

When the β-lactam III is treated with one mole of alcoholic potassium hydroxide, the potassium salt IV is obtained in quantitative yield within one hour.
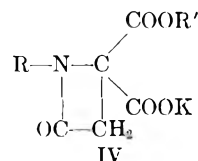


In order to compare the rate of intramolecular displacement reaction leading to cyclization of the amidomalonate II and the rate of ester hydrolysis in presence of potassium hydroxide, a set of two experiments was carried out. In the first experiment the amidomalonate II was treated with one mole of alcoholic potassium hydroxide and in the other it was treated with two moles of potassium hydroxide. There was an instantaneous precipitation of potassium chloride in both the cases and the potassium chloride from the first reaction mixture was filtered out within five minutes. The yield of potassium chloride was quantitative (based on silver chloride). The alcoholic solution was acidified with acetic acid. The product from this reaction was β-lactam III in more than 96% yield.

The second reaction mixture was allowed to stand at room temperature for one hour. The potassium salt on acidification with concentrated hydrochloric acid gave the monoacid V in about 95% yield.
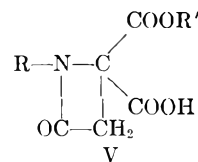


The acylation of substituted aminomalonates I to the amidomalonates II have been carried out under nonbasic condition[3] with a halo acid and phosphorus trichloride. Bose and his co-workers[4] have shown that the β-lactams III can be obtained in one step in about three days when the aminomalonate I is treated with α-haloacyl halide and excess of triethylamine at room temperature.

Additional work has now shown that the conversion of a substituted aminomalonate I to the β-lactam III as well as to the corresponding monoacid V can be carried out in one operation. The β-lactams III are

TABLE I

| R | R' | R″ | M.p., °C./$n^{30}$D | Yield, % |
|---|---|---|---|---|
| $C_6H_5$ | $C_2H_5$ | $C_2H_5$ | 38–39 | 88 |
| $C_6H_5$ | $C_2H_5$ | H | 101–103 | 79 |
| p-Cl-$C_6H_4$ | $C_2H_5$ | $C_2H_5$ | 1.5260 | 88 |
| p-Cl-$C_6H_4$ | $C_2H_5$ | H | 118–120 | 80 |
| p-Br-$C_6H_4$ | $C_2H_5$ | $C_2H_5$ | 1.5393 | 84 |
| p-Br-$C_6H_4$ | $C_2H_5$ | H | 89–91 | 77 |
| p-$CH_3C_6H_4$ | $C_2H_5$ | $C_2H_5$ | 90–91 | 85 |
| p-$CH_3C_6H_4$ | $C_2H_5$ | H | 169–170 dec. | 76 |
| $C_{10}H_7$ | $C_2H_5$ | $C_2H_5$ | 75–76 | 90 |
| $C_{10}H_7$ | $C_2H_5$ | H | 181–182 dec. | 88 |

(2) J. C. Sheehan and A. K. Bose, *ibid.*, **73**, 1761 (1951).
(3) A. K. Bose, *J. Ind. Chem. Soc.*, **31**, 108 (1954).
(4) A. K. Bose, M. S. Manhas, and B. N. Ghosh Mazumdar, *J. Org. Chem.*, **27**, 1458 (1962).

### Table II
### Effect of Temperature, Pressure, and Time

| S. no. | Substance | Solvent | Temp., °C. | Press. | Time | Yield, % | M.p., °C. |
|---|---|---|---|---|---|---|---|
| (1) | $p$-ClC$_6$H$_4$NH$_2$ | Benzene | 30 | 760 mm. | 24 hr. | . . . | |
| (2) | $p$-ClC$_6$H$_4$NH$_2$ | Benzene | 30 | 760 mm. | 21 days | 55 | |
| (3) | $p$-ClC$_6$H$_4$NH$_2$ | Acetone | 30 | 760 mm. | 24 hr. | . . . | |
| (4) | $p$-ClC$_6$H$_4$NH$_2$ | Ethanol | 30 | 760 mm. | 24 hr. | . . . | |
| (5) | $p$-ClC$_6$H$_4$NH$_2$ | Benzene | 80 | 760 mm. | 8 hr. | 5 | |
| (6) | Aniline | Benzene | 30 | 760 mm. | 24 hr. | 67 | |
| (7) | Aniline | Benzene | 80 | 760 mm. | 3 hr. | 30 | |
| (8) | Aniline | Benzene | 80 | 760 mm. | 8 hr. | 67 | |
| (9) | Aniline | . . . | 60–70 | 760 mm. | 1 hr. | 62 | |
| (10) | Aniline | . . . | 60–70 | 760 mm. | 1.5 hr. | 69 | |
| (11) | Aniline | . . . | 60–70 | 760 mm. | 8 hr. | 70 | |
| (12) | Aniline | . . . | 60–70 | 100 mm. | 8 hr. | 78 | |
| (13) | Aniline | . . . | 60–70 | 60 mm. | 8 hr. | 85 | |
| (14) | Aniline | . . . | 60–70 | 40 mm. | 8 hr. | 100 | 44–45 |
| (15) | $p$-ClC$_6$H$_4$NH$_2$ | . . . | 60–70 | 40 mm. | 8 hr. | 98 | 91–92 |
| (16) | $p$-ClC$_6$H$_4$NH$_2$ | . . . | 60–70 | 30 mm. | 8 hr. | 98 | |
| (17) | $p$-BrC$_6$H$_4$NH$_2$ | . . . | 60–70 | 40 mm. | 8 hr. | 98 | 92–93 |
| (18) | $p$-CH$_3$C$_6$H$_4$NH$_2$ | . . . | 60–70 | 40 mm. | 8 hr. | 96 | 55–56 |
| (19) | C$_{10}$H$_n$NH$_2$ | . . . | 60–70 | 40 mm. | 8 hr. | 100 | 86–87 |

obtained in more than 80% yield within a few minutes and the acids V in about 80% yield in about an hour. The substituted aminomalonates were heated with 1.2–1.5 moles of chloroacetyl chloride to about 80° for five minutes. Alcohol was then added to destroy the excess of the acid halide. When the reaction mixture was treated with 2.5 moles of alcoholic potassium hydroxide and worked up after five minutes, the product was β-lactam III, and, when it was treated with 3.5–4 moles of potassium hydroxide and worked up after forty-five minutes, the product was the monoacid V.

The preparation of several β-lactams by this one-step method is summerized in Table I.

The substituted aminomalonates I have been synthesised[5] by treating a benzene solution of the amine with diethyl bromomalonate. The usual yield of the product is about 70%. The $p$-haloanilines and β-naphthylamine, however, did not react with bromomalonate under the above condition. The $p$-haloanilines resisted condensation in alcohol solution even at the reflux temperature.

It has now been shown that all the aminomalonates mentioned above can be obtained in more than 95% yield if the amines are treated with the bromomalonate under slightly reduced pressure (40 mm.) at about 70° for eight hours. The effect of temperature, pressure, and time is summerized in Table II.

### Experimental[6]

A typical procedure for the one-step synthesis of β-lactams of type III is described.

**1-$p$-Tolyl-4,4'-dicarbethoxyazetidin-2-one.**—A 2.65-g. sample of $p$-toluidinomalonate was taken in a small dry conical flask, plugged with cotton wool. To it was added 1.0 ml. of chloroacetyl chloride and the reaction mixture was heated with occasional shaking to about 80° for 5 min. A 10–15-ml. portion of

absolute alcohol was then added and the solution was cooled to room temperature. A thick precipitate of potassium chloride was obtained on the addition of 1.5 g. of potassium hydroxide in alcohol solution. The mixture was allowed to stand for 4–5 min. and then filtered. The filtrate was acidified with glacial acetic acid and the solvent was removed under reduced pressure. The residue was taken up in ether and washed several times with water. After drying the ether layer over anhydrous magnesium sulfate, the solvent was removed under reduced pressure when a semisolid mass was obtained. This solidified on scratching. Recrystallization from cyclohexane afforded 2.6 g. (85%) of colorless needles, m.p. 90–91°. No depression in melting point was observed in mixture melting point determination with an authentic sample.

*Anal.* Calcd. for C$_{16}$H$_{19}$O$_5$N: C, 62.59; H, 6.23; N, 4.59. Found: C, 63.22; H, 6.40; N, 4.42.

A typical procedure for the synthesis of β-lactam V is illustrated.

**1-$p$-Bromophenyl-4-carboxy-4'-carbethoxyazetidin-2-one.**—A 3.30-g. sample of $p$-bromoanilinomalonate was treated with 1.0 ml. of chloroacetyl chloride and 10–15 ml. of absolute alcohol in the manner mentioned above. To the cooled solution was added 2.2 g. of potassium hydroxide in alcohol solution. The reaction mixture was allowed to stand for about 45 min. Ether was added to precipitate the potassium salt completely. The salt was taken in water and the solution was acidified with concentrated hydrochloric acid, when an oil separated which solidified on scratching. In some cases the oil had to be taken up in ether and after usual operations the solid mass was obtained. Recrystallization from ether petroleum ether mixture afforded 2.64 g. of crystalline solid, m.p. 89–91° (77%). No depression in melting point was observed in mixture melting point determination with an authentic sample.

*Anal.* Calcd. for C$_{13}$H$_{12}$O$_5$N Br: C, 45.61; H, 3.51; N, 4.09. Found: C, 45.39; H, 3.82; N, 4.26.

A typical synthesis of substituted anilinomalonates I is given below.

**Diethyl $p$-Chloroanilinomalonate.**—A mixture of 25.5 g. of $p$-chloroaniline and 23.9 g. of diethyl bromomalonate was taken in a 100-ml. round bottom flask fitted with a two-way stop cock and was evacuated to 40 mm. The reaction mixture was then kept in an oven maintained at 60–70° for 8 hr. The solid cake was powdered and extracted several times with ether. The crude $p$-chloroanilinomalonate, obtained on the removal of the solvent, was recrystallized from petroleum ether; yield, 28.0 g. (98%); m.p. 91–92°. The yield of $p$-chloroaniline hydrobromide was 20.8 g. (100%).

*Anal.* Calcd. for C$_{13}$H$_{16}$O$_4$NCl: C, 54.64; H, 5.60; N, 4.90. Found: C, 54.52; H, 5.71; N, 4.82.

(5) A. K. Bose, B. N. Ghosh Mazumdar, and B. G. Chatterjee, *J. Am. Chem. Soc.*, **82**, 2382 (1960).

(6) All melting points are uncorrected.

## Synthesis of β-Disulfones from Sulfonyl Fluorides and Organometallic Compounds

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The reaction of sulfonyl fluorides with Grignard reagents to form β-disulfones has been known for many years; however, the yields were low and the intermediate steps uncertain.[2] This method now has been improved by raising the yields, extending the reaction to an organolithium compound, and clarifying the reaction conditions and steps.

The reaction of *p*-toluenesulfonyl fluoride with ethylmagnesium bromide and with *n*-butyllithium in refluxing ether for 13–15 hours produced 1,1-bis(*p*-toluenesulfonyl)ethane and 1,1-bis(*p*-toluenesulfonyl)-butane in 83% and 66% yields, respectively. The structures of the β-disulfones were verified by mixture melting points and comparison of their infrared spectra with authentic samples. In accordance with these structures, Raney nickel hydrogenolysis[3] of each β-disulfone produced only toluene.

This over-all conversion presumably involved reaction of the organometallic compound with the sulfonyl fluoride to form a monosulfone, followed by α-metallation and reaction with more sulfonyl fluoride to produce the β-disulfone. The intermediacy of the alkyl *p*-tolyl sulfone was supported by the fact that independently prepared monosulfone reacted with the organometallic compound and sulfonyl fluoride to give the β-disulfone. *n*-Butyl *p*-tolyl sulfone was metallated and carbonated to produce an acid; cleavage with lithium in methylamine yielded pentanoic acid, thereby proving that metallation occurred alpha to the sulfone group.[4]

### Experimental

**1,1-Bis(*p*-toluenesulfonyl)ethane.**—A solution of 8.7 g. (0.050 mole) of *p*-toluenesulfonyl fluoride[5] in ether was added dropwise to ethylmagnesium bromide prepared from 10.9 g. (0.10 mole) of ethyl bromide and 3.6 g. (0.15 mole) of magnesium in ether. After refluxing for 13–15 hr., the mixture was hydrolyzed with cold hydrochloric acid and the ether layer separated, washed with water, and dried. Evaporation of ether yielded 7 g. (83%) of product, m.p. 107–109° (from ethanol).[6]

*Anal.* Calcd. for $C_{16}H_{18}O_4S_2$: C, 56.80; H, 5.32; S, 18.93. Found: C, 56.97; H, 5.43; S, 18.64.

**1,1-Bis-(*p*-toluenesulfonyl)butane.**—The previous procedure was used with 0.1 mole of *n*-butyllithium (Foote Mineral Co., 15% solution in hexane) and 8.7 g. (0.05 mole) of *p*-toluenesulfonyl fluoride. The yield was 6 g. (66%), m.p. 102–104° (from ethanol).

*Anal.* Calcd. for $C_{18}H_{22}O_4S_2$: C, 59.01; H, 6.01; S, 17.49. Found: C, 59.29; H, 6.13; S, 17.72.

**Metallation and Reactions of *n*-Butyl *p*-Tolyl Sulfone. A. Reaction with *p*-Toluenesulfonyl Fluoride.**—*n*-Butyllithium (30

g. of the solution, 0.07 mole) was added to 6.3 g. (0.03 mole) of *n*-butyl *p*-tolyl sulfone[7] in ether. *p*-Toluenesulfonyl fluoride (5.2 g., 0.03 mole) was added and the solution refluxed for 1 hr. The ether solution was washed with water, dried, and the ether evaporated to give 6.6 g. (60%) of white crystals, m.p. 102–104°. A mixture melting point with authentic 1,1-bis(*p*-toluenesulfonyl)-butane showed no depression and the infrared spectra were identical.

**B. Carbonation.**—*n*-Butyllithium (50 g. of the solution, 0.12 mole) was added to 21.2 g. (0.1 mole) of *n*-butyl *p*-tolyl sulfone in ether. The solution was carbonated with an excess of Dry Ice; the resulting viscous oil was dried in a desiccator under pressure for a month to produce 20 g. (78%) of 2-(*p*-toluenesulfonyl)pentanoic acid, m.p. 75–76°.

*Anal.* Calcd. for $C_{12}H_{16}O_4S$: C, 56.25; H, 6.25; S, 12.50. Found: C, 56.36; H, 6.45; S, 12.48.

**Cleavage of 2-(*p*-Toluenesulfonyl)pentanoic Acid.**—The acid (7 g., 0.026 mole) was dissolved in 100 ml. of methylamine; 1.11 g. (0.16 g.-atom) of lithium was placed in the thimble[8] and the reaction allowed to proceed to completion. Methanol (15 ml.) was added and the amine allowed to evaporate. Water was added; the aqueous layer was extracted with ether and then acidified with hydrochloric acid. The resulting mixture of acids was distilled to give 1.2 g. (0.01 mole) of *p*-toluenethiol and 2 g. (0.02 mole) of pentanoic acid, b.p. 183–186° (lit., b.p. 186.4°). Comparison of the vapor phase chromatogram of authentic *n*-pentanoic acid with the above verified its identity.

**1,1-Bis(*p*-Toluenesulfonyl)ethane.**—Acetaldehyde (6.6 g., 0.15 mole) was added dropwise to a solution of 24.8 g. (0.20 mole) of *p*-toluenethiol in 30 ml. of glacial acetic acid at 0–5°. After being stirred for 25 hr. at room temperature, the mixture was diluted with water, extracted with chloroform, dried, and the chloroform evaporated to yield 21 g. of crude 1,1-bis(*p*-tolyl-mercapto)ethane. To a solution of 10 g. of crude β-disulfide dissolved in 60 ml. of glacial acetic acid, 30 ml. of 30% hydrogen peroxide was added. Heating for 1 hr. was followed by pouring into water and filtering to obtain 4 g. (0.013 mole, 34% over-all based on thiol) of β-disulfone, which was crystallized from ethanol (m.p. 107°).

**1,1-Bis(*p*-Toluenesulfonyl)butane.**—A solution of 22.4 g. (0.18 mole) of *p*-toluenethiol, 37 ml. (30 g., 0.42 mole) of *n*-butyraldehyde, and 40 ml. of glacial acetic acid was stirred at 25° under nitrogen for 24 hr. Pouring into ice–water produced two layers which were separated. The organic layer was washed twice with saturated sodium bisulfite, once with 10% sodium hydroxide, once with water, and dried yielding 23.6 g. of crude β-disulfide. To a cold solution of 11.3 g. of this product and 41 ml. of glacial acetic acid, 31 ml. of 30% hydrogen peroxide was added slowly. After the solution had refluxed by itself for 1 hr., it was heated on a steam bath for another hour then poured into ice–water. The liquid was decanted and the solid washed with water to give 3.2 g. (0.0085 mole, 21% over-all) of the β-disulfone, m.p. 101–103°.

(1) Deceased, August, 1962.

(2) W. Steinkopf. *J. prakt. Chem.*, **142**, 223 (1935).

(3) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(4) J. Strating, "Organic Sulfur Compounds," Vol. I, N. Kharasch, ed., Pergamon Press, London, 1961, p. 150.

(5) W. Davies and J. H. Dick, *J. Chem. Soc.*, 2104 (1931).

(6) It was reported by E. Fromm, *Ann.*, **394**, 349 (1912), that the melting point was 156°. However, repetition of this literature preparation produced a compound (m.p. 154–155°) which by elemental analysis and n.m.r. proved to be 1,1-bis(*p*-toluenesulfonyl)propane.

(7) H. Gilman and N. J. Beaber, *J. Am. Chem. Soc.*, **47**, 1450 (1925).

(8) The apparatus is described by W. E. Truce, D. P. Tate, and D. N. Burdge, *ibid.*, **82**, 2872 (1960).

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## Fluorinated Heterocyclics

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In connection with investigations in these laboratories of biologically important heterocyclic compounds, it was

(1) Abstracted in part from the M. S. thesis of H. M. Mork.

of interest to obtain fluorinated derivatives of thiophenes and thianaphthenes. One of the simplest fluoro heterocyclics, 2-fluorothiophene, has previously been reported as obtainable, in less than 10% yields, by the reaction of thiophene with antimony pentafluoride in nitromethane as a reaction media.[2] However, simple fluorothianaphthalenes such as the 2- or 3-fluoro derivatives have, as yet, to be reported. A convenient laboratory method has now been developed in these laboratories, for the synthesis of 2-fluoro-5-methylthiophene (I), 2-fluorothiophene (II), and 2-fluorothianaphthene (III) by the exothermic reaction of gaseous perchloryl fluoride with the corresponding organolithium heterocyclic compounds in anhydrous ether as a reaction solvent. This simple procedure gives 44, 49, and 70% yields of these fluoro heterocyclics, respectively. Vapor phase chromatography, infrared spectra, nuclear magnetic resonance, and elemental analysis of these products supports the structures of these fluoro compounds.

The application of this fluorination procedure with perchloryl fluoride, in these laboratories, to the lithium derivatives of arene hydrocarbons, such as phenyllithium and 1-naphthyllithium, yielded negligible amounts of the corresponding fluoro derivatives.

The difluorination of diethyl malonate, 2,4-pentadione, and ethyl acetoacetate with perchloryl fluoride in strong base media has been reported[3] as well as the fluorination of the sodium salts of nitro compounds in metal methoxide–methanol solutions with perchloryl fluoride[4]. These findings and those reported here give some indication as to the mechanism of this fluorination reaction. With lithium derivatives of thiophene and thianaphthene the electronegativity of the sulfur atom delocalizes the carbon ion charge yielding a stable anionic system, which may react effectively with the slightly polar chlorine–fluorine bond in the perchloryl fluoride, displacing the chlorate ion. Thus, the more stable an anion is the more it should yield a fluorinated product. Evidence for this is found in the reaction of diethyl malonate in excess ethoxide with perchloryl fluoride to give an almost quantitative yield of diethyl $\alpha,\alpha$-difluoromalonate.[3] Phenyl and 1-naphthyllithium–carbon bonds are more covalent with less delocalization of the anionic charge, and apparently these less stable anionic species are unable to activate the chlorine–fluorine bond of perchloryl fluoride in the displacement step. To the limited extent that reaction occurs, less discrimination, in favor of the fluorine, is achieved in the displacement step. Experimental evidence for this was found in this study by the observation that some perchlorylbenzene results from the reaction of phenyllithium and perchloryl fluoride.

### Experimental

**2-Fluoro-5-methylthiophene**—An *n*-butyllithium–ether solution, 1.5 moles of alkyl lithium dissolved in 500 ml. of anhydrous ether, was prepared according to the method of Gilman.[5]

A 98.0-g. (1.0 mole) quantity of 2-methylthiophene dissolved in an equal volume of anhydrous ether was added dropwise during 1 hr. to the alkyl lithium ether solution kept at 0–5° by immersion in an ice bath. If a gradual color change from purple to green,

(2) R. T. Van Vleck, *J. Am. Chem. Soc.*, **71**, 3286 (1949).

(3) C. E. Inman, R. E. Osterling, and R. E. Tyczkowski, *ibid.*, **80**, 6533 (1958).

(4) H. Schecter and E. B. Roberson, Jr., *J. Org. Chem.*, **25**, 175 (1960).

(5) H. Gilman, *Org. Reactions*, **8**, 285 1954.

indicating the formation of the 5-methyl-2-thienyllithium, did not appear in the reaction mixture, the flask was evacuated to remove butane forcing the metallation equilibrium reaction to completion. The resultant organolithium–ether solution was stirred under nitrogen for an hour at 0–5°. Gaseous perchloryl fluoride was bubbled, at a moderate rate, through this solution at 0°. When the highly exothermic fluorination reaction had increased the reaction temperature to 30°, the addition of fluorination reagent was stopped, the reaction solution was cooled, and further addition of perchloryl fluoride was continued. A constant reaction temperature and the disappearance of an intense blue fluorescence indicated the completion of the reaction. During the period of reaction (2 hr.) the reaction mixture darkened considerably and a white solid precipitated. At the completion of the reaction nitrogen was passed through the mixture for an hour to remove excess perchloryl fluoride. The mixture was then poured into a saturated sodium carbonate solution and the ethereal layer was separated. It was washed with an additional amount of carbonate solution, once with water, and dried over anhydrous magnesium sulfate. The ether was removed and the residue distilled, the fraction boiling from 102–112° at atmospheric pressure being collected (74 g.). Vapor phase chromatography analysis using a 30% silicone column showed the distillate contained 69.1% of 2-fluoro-5-methylthiophene, 9.9% of 2-methylthiophene, and unidentifiable side products, accounting for over-all yield of 51.9 g. (44%) of 2-fluoro-5-methylthiphene. A sample of the major product was isolated for analysis, infrared and n.m.r. spectra by preparative gas chromatography utilizing a 30% silicone on 40-mesh Chromasorb column (108 × 0.75 in.) in a Perkin-Elmer Model 154 vapor fractometer. Infrared analysis by comparison of 2-fluoro-5-methyl and 2-fluorothiophenes gave a C–F peak at 7.6 $\mu$, and n.m.r. gave the correct ratio of methyl to ring hydrogens (3:2) and showed additional splitting from the fluorine atom.

*Anal.* Calcd. for $C_5H_5SF$: C, 51.70; H, 4.34; F, 16.36; S, 27.60. Found: C, 51.99; H, 4.58; F, 16.34; S, 27.55. Strong infrared peaks at 3.5, 4.7, 6.5, 6.6, 6.9, 7.6, 8.2, 8.3, 8.4, 9.8, and 11.9 m$\mu$.

**2-Fluorothiophene**—An 84-g. (1 mole) quantity of thiophene was added to 500 ml. of the butyllithium–ether solution as previously described. Distillation, after perchloryl fluoride addition and the usual product isolation from the reaction mixture, gave 62.5 g. of a colorless liquid boiling in the range 80–90° (760 mm.), which contained 87.4% of 2-fluorothiophene and 12.3% of thiophene, thus giving an over-all yield of 54.6 g., 48.8% of fluorinated product. A sample for analysis and infrared was isolated by preparative gas chromatography in the manner previously described.

*Anal.* Calcd. for $C_4H_3SF$: C, 47.04; H, 2.96; F, 18.60. Found: C, 47.23; H, 3.16; F, 18.23. $n^{20}D$ 1.4896.

**2-Fluorothianaphthene.**—To a solution cooled in an ice bath and containing 0.3 mole of butyllithium in 100 ml. of anhydrous ether was added 26.8 g. (0.2 mole) of thianaphthene dissolved in 50 ml. of ether followed by the addition of gaseous perchloryl fluoride. When the blue fluorescence had subsided, addition of the fluorinating agent was stopped. The reaction slurry was treated with a carbonate solution and washed with water. The ethereal layer was separated, dried, and the ether removed. Distillation of the residue gave a liquid product (21.3 g., 70%) boiling at 93–94° (25 mm.), $n^{27}D$ 1.5910, m.p. 20–20.5°. A sample for analysis, n.m.r. and infrared spectra was isolated by preparative gas chromatography. Nuclear magnetic resonance spectra showed the correct ratio of thiophene to benzene hydrogens (1:4).

*Anal.* Calcd. for $C_8H_5SF$: C, 63.16; H, 3.29; S, 21.05; F, 12.50. Found: C, 63.19; H, 3.51; S, 21.20; F, 12.67.

**2-Fluoro-3-bromothianaphthene.**—A solution of 14.9 g. (0.93 mole) of bromine in 14.0 ml. of anhydrous chloroform was added dropwise, at 25°, during a half-hour to a solution containing 14.3 g. (0.093 mole) of 2-fluorothianaphthene and 14.5 g. (0.17 mole) of anhydrous sodium acetate dissolved in 65 ml. of anhydrous chloroform. The orange-colored reaction solution was stirred an additional hour and 50 ml. of water was added to dissolve the inorganic material. The organic layer was separated, washed successively with 100 ml. of water, 50 ml. of 5% aqueous sodium hydroxide, 100 ml. of water, 100 ml. of a saturated sodium chloride solution, and finally with 100 ml. of water. The organic extract was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed on a steam bath, and the residue was distilled using a 6-in. Vigreux column to obtain 11.0 g. (0.0475 mole, 51.5%) of a pale yellow oil boiling at 76–78° (1 mm.), m.p. 21–21.5°.

*Anal.* Calcd. for $C_8H_4SFBr$: C, 41.56; H, 1.73; S, 13.85; F, 8.23; Br, 34.63. Found: C, 41.65; H, 1.86; S, 13.78; F, 8.23, 8.26; Br, 34.27, 34.35.

**2-Fluoro-3-thianaphthenecarboxylic Acid**—To 1.47 g. (0.023 mole) of *n*-butyllithium dissolved in 3 ml. of anhydrous ether was added, under a nitrogen atmosphere at −70°, a solution of 5.34 g. (0.023 mole) of 3-bromo-2-fluorothianaphthene dissolved in 5.0 ml. of anhydrous ether during 5 min. The reaction mixture was then poured rapidly over a Dry Ice–ether slurry and allowed to warm to room temperature. The ether solution was extracted with 25 ml. of water followed by two 50-ml. portions of a 5% aqueous sodium hydroxide solution. The aqueous extracts were combined, boiled to remove the ether, cooled, and acidified with concentrated hydrochloric acid. The white precipitate which formed on acidification was recovered by filtration and washed with water. It was crystallized three times from a minimum of 95% ethanol to afford 2.5 g. (0.0127 mole; 55%) of fine white needles which had a melting point of 188–188.5°.

*Anal.* Calcd. for $C_9H_5O_2SF$: C, 55.10; H, 2.55; S, 16.33; F, 9.69. Found: C, 54.94; H, 2.60; S, 16.49; F, 9.48, 9.46.

**Perchlorylbenzene**—A solution of phenyllithium, 0.1 mole, in 50 ml. of anhydrous ether was prepared according to Gilman's[6] procedure and treated with perchloryl fluoride in the manner already described. Product isolation, by procedures discussed before and vacuum distillation of the crude product gave 1.8 g. (0.011 mole, 11.0%) of perchlorylbenzene, b.p. 78–79° (2 mm.) as identified by infrared spectra.[7]

**Acknowledgment.**—This research was supported in part by a financial grant from American Cancer Society.

(6) H. Gilman, *Org. Reactions*, **8**, 286 1954.

(7) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 5286 (1958).

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## The 6-Deoxytetracyclines.[1]  VI.
## A Photochemical Transformation

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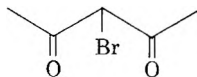
We have found that photolysis of 11a-bromo-6-demethyl-6-deoxytetracycline[2] (I) in either methanol or glacial acetic acid yields primarily 7-bromo-6-demethyl-6-deoxytetracycline[3] (II) and, as a minor component, 6-demethylanhydrotetracycline[4] (III). The remarkable selectivity of this photorearrangement indicated, at first, an intramolecular mechanism. In order to elucidate the reaction path, the bromo compound, I, was irradiated in the presence of α-naphthol. Under these conditions very little (<10%) brominated tetracycline (II) was obtained, the major product being 6-demethyl-6-deoxytetracycline[5] (V). The isolation of V establishes the intermolecular pathway of the reaction, the α-naphthol acting as a scavenger for the bromine atom produced during irradiation.
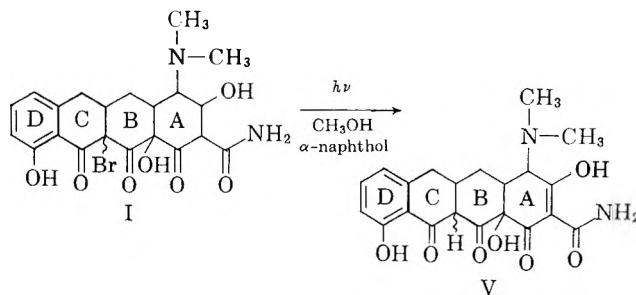




When the photolysis was run in acetonitrile, there was no aromatic bromination only dehydrohalogenation *via* 5a,11a to give 6-demethylanhydrotetracycline[4a,b] (III). Similarly the small amount of anhydro material[4a] (III) obtained from methanol or acetic acid is due to this (competing) dehydrohalogenation *via* 5a,11a.

Whatever the initial excited state(s) of the α-bromodicarbonyl system, there is probably an eventual formation of a substituted hypobromite ($CH_3OBr$ when methanol is the solvent or $CH_3COOBr$ when acetic acid is the solvent) which acts as a selective electrophilic brominating agent[6] to yield the 7-halo product, II. This intermediate hypobromite may result from either nucleophilic attack of the solvent (in the case of methanol or acetic acid) on a photoactivated carbon–halogen bond (Ia) to give the substituted hypobromite, Ib, as shown in Chart I, or from a stepwise process initiated by light-induced elimination of hydrogen bromide which in turn participates in the reaction sequence given in Chart II.

The report[7] that bromine in methanol does participate in an equilibrium with the formation of methyl

(1) For the previous paper in this series, see J. J. Hlavka, H. Krazinski, and J. H. Boothe, *J. Org. Chem.*, **27**, 3674 (1962).

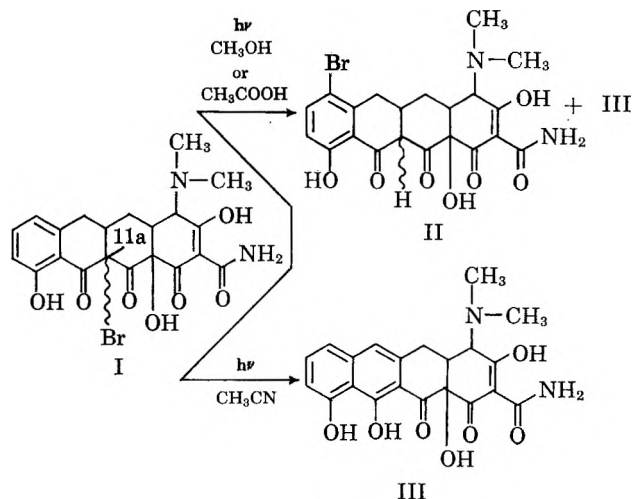(2) J. J. Hlavka, A. Schneller, H. Krazinski, and J. H. Boothe, *J. Am. Chem. Soc.*, **84**, 1426 (1962).

(3) This photo rearranged product (II) still contains bromine but no longer has the bromo system [structure: O=C–CHBr–C=O] as evidenced by the lack of a positive starch iodide test and the absence of the isolated carbonyl (at carbon 12) stretching at 1739 cm.⁻¹ in the infrared. In addition this material was compared by infrared, ultraviolet, and paper strip chromatography in four different systems to authentic material.[2] It was identical in all cases.

(4)(a) An authentic sample of this material was prepared by treating [see J. Webb, R. Broschard, D. Cosulich, W. Stein, and C. Wolf, *ibid.*, **79**, 4563 (1957)] 6-demethyltetracycline with concentrated hydrochloric acid. This authentic sample was identical to the photo-product (III) in all respects, *i.e.*, ultraviolet, infrared, and paper strip chromatography in different solvent systems. (b) This type of dehydrohalogenation was reported by D. Kevill and N. Cromwell, *J. Am. Chem. Soc.*, **83**, 3812 (1961). They found that α-halo ketones undergo facile elimination reactions in acetonitrile using a variety of catalysts.

(5) (a) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *ibid.*, **82**, 3381 (1961); (b) C. R. Stephens, *et al.*, *ibid.*, **80**, 5324 (1958).

(6) We have found previously (see ref. 2) that electrophilic halogenation in concentrated sulfuric acid gave exclusively the 7-halo isomer.

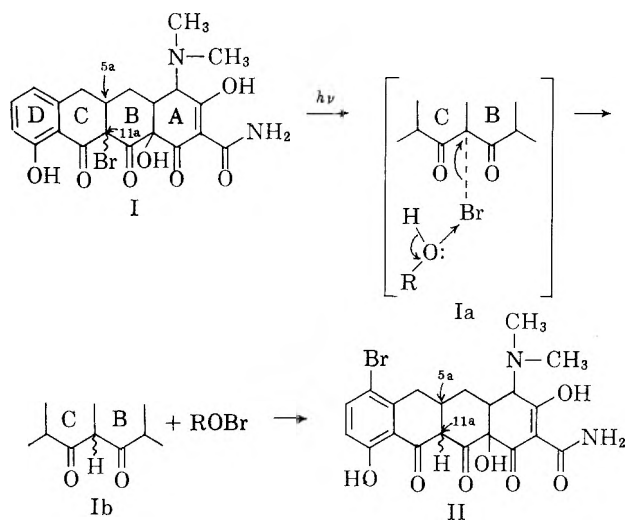(7) R. Meinel, *Ann.*, **510**, 129 (1934); **516**, 237 (1935).
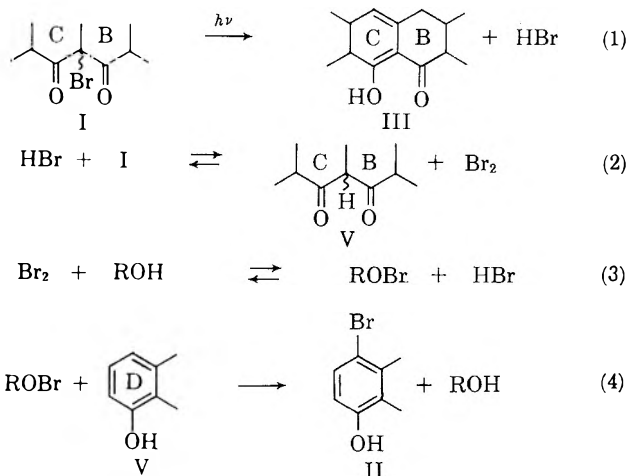
CHART I

CHART II

and convenient method for obtaining active halogen derivatives[2] in th 6-deoxytetracycline series.

**General Procedure for Irradiation of 11a-Bromo-6-demethyl-6-deoxytetracycline Hydrochloride (I).**—A solution of 100 mg. (0.19 mmole) of 11a-bromo-6-demethyl-6-deoxytetracycline hydrochloride in 50 ml. of solvent[11] was irradiated for 4 hr. in a double-walled immersion well.[10b] When either methanol or acetonitrile was used as the solvent, the reaction mixture was evaporated to dryness *in vacuo*. In the case of acetic acid the solvent was lyophilized.

The reaction product obtained from acetonitrile was pure enough to compare to an authentic sample of 6-demethylanhydrotetracycline.[4a]

The reaction product obtained from methanol or acetic acid was purified by partition column chromatography. The reaction product was dissolved in 15 ml. of the lower phase of the solvent system heptane–ethyl acetate–methanol–water (70:30:12:8) and 30 g. of Celite[12] was added to the solution. The mixture was placed on top of a column prepared from 300 g. of Celite which had been mixed with 50 ml. of the lower phase of the solvent system. The column [hold-back volume (h.b.v.)[13], 464 ml.] was eluted with the upper phase of the solvent system and the effluent was passed through a recording spectrophotometer (set at 265 m$\mu$). There were two major peaks, the first occurring at 0.7 h.b.v. and the second at 2.2 h.b.v. The first peak was evaporated to dryness and the residue obtained was identical in all respects to 6-demethylanhydrotetracycline[4] (10% yield), the second peak after evaporation of the solvent was identical in all respects to 7-bromo-6-demethyl-6-deoxytetracycline[3] (90% yield).

**Photolysis of 11a-Bromo-6-demethyl-6-deoxytetracycline Hydrochloride (I) in the Presence of $\alpha$-Naphthol.**—A solution of 100 mg. of I and 90 mg. of $\alpha$-naphthol in 15 ml. of methanol was irradiated for 4 hr. in a double-walled immersion well.[10b] The methanolic solution was evaporated to a volume of 2 ml. and diluted with 100 ml. of ether. The solid weighed 90 mg. This material was separated by fractional crystallization from methanol/ether. Paper strip chromatography showed the main fraction (90%) to be 6-demethyl-6-deoxytetracycline[5] and second fraction (10%) to be 7-bromo-6-demethyl-6-deoxytetracycline.[2,3]

**Reaction of 6-Demethyl-6-deoxytetracycline with Bromine.**—(1) A solution of 0.1 g. (0.24 mmole) of 6-demethyl-6-deoxytetracycline (free base) and 0.48 mmole of bromine in 0.75 ml. of methanol and 5 ml. of methylene chloride was stirred at room temperature for 2 hr. The solvents were evaporated *in vacuo* and the residue was dissolved in 2 ml. of methanol. This solution on dilution with ethyl ether yielded 90 mg. of solid.

Analysis of this reaction product by paper chromatography in five different solvent systems[14] as well as infrared and ultraviolet spectra showed both 7-bromo-6-demethyl-6-deoxytetracycline[3] (10%) and 11a-bromo-6-demethyl-6-deoxytetracycline[2] (90%) were formed.

(2) To a solution of 0.10 g. (0.24 mmole) of 6-demethyl-6-deoxytetracycline in 15 ml. of 1,2-dimethoxyethane was added 0.05 ml. (1.00 mmole) of liquid bromine. The solution was stirred at room temperature for 3 hr. and the solvent evaporated to dryness *in vacuo*. The residue was dissolved in a minimum amount of methanol and added to ethyl ether. The product that separated was identical in all respects to 11a-bromo-6-demethyl-6-deoxytetracycline[2] (*i.e.*, infrared and ultraviolet spectra and $R_f$ values in the system butanol–phosphate, pH 2).

hypobromite, prompted us to treat 6-demethyl-6-deoxytetracycline (V) with a bromine–methanol solution. Analysis of the reaction mixture by paper chromatography in a number of different solvent systems showed both 11a and 7-substituted products. In contrast, reaction of 6-demethyl-6-deoxytetracycline with bromine in the nonhydroxylic solvent, 1,2-dimethoxyethane, yielded no 7-halo derivative. These experimental results lend support to our suggestion that a transient hypobromite may be the effective halogenation agent in our photochemical process, but do not differentiate between the two alternative reaction pathways illustrated in Chart I and II. The mechanism in Chart II is consistent with the observed action of methanolic hydrogen bromide (in the dark) upon I. Examination of the reaction products by paper chromatography (four different systems) showed a small amount of the starting material and approximately equal amounts of II and V. The exact nature of hypobromite formation is under investigation.

Since both the preparation of the 11a bromo derivative, I, and the irradiations are carried out under mild conditions,[8] this reaction sequence provides a simple

(8) The previous method[2] involved the use of large quantities of concentrated sulfuric acid which resulted in rather tedious isolation procedures.

(9) We are indebted to C. Pidacks and co-workers for the purification of reaction products and to Miss Ruth Livant for paper chromatographic results.

(10) (a) All irradiations were carried out using a Hanovia lamp, Model #30,600, obtained from the Hanovia Lamp Division, Newark, N. J. (b) This reaction vessel was also obtained from the Hanovia Lamp Division.

(11) The solvents used were methanol, acetic acid, and acetonitrile.

(12) Celite is the trademark of the Johns-Manville Corp. for diatomaceous earth products.

(13) Hold-back volume is the volume of solvent necessary to fill the packed column.

(14) The solvent systems used were: (1) phosphate–versene, pH 3; (2) butanol–phosphate, pH 2; (3) isobutanol–isobutylacetate–versene, pH 7.7; (4) ethyl acetate; (5) nitromethane–benzene–pyridine, pH 3.4.
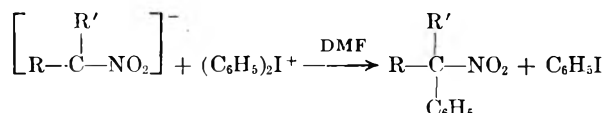
# The Phenylation of Nitroparaffins[1,2]

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*Received December 12, 1962*

The reaction of nitroparaffin salts with diphenyliodonium tosylate in N,N-dimethylformamide (DMF) takes place smoothly at room temperature and gives α-phenylnitroparaffins.

$$\left[ R-\overset{R'}{\underset{|}{\underset{|}{C}}}-NO_2 \right]^- + (C_6H_5)_2I^+ \xrightarrow{\text{DMF}} R-\overset{R'}{\underset{|}{\underset{C_6H_5}{C}}}-NO_2 + C_6H_5I$$

Since, thanks to the efforts of Beringer and his students,[3] a variety of diaryliodonium salts have now become accessible, this represents not only a new but also a useful reaction. The yields listed in Table I refer to pure products and, since no systematic study was made to arrive at optimum conditions, they are minimal. The salt of the only α-nitro ester studied, ethyl α-nitrocaproate, reacted less rapidly than any of the nitroparaffins and in this instance a temperature of 55° was employed.

## TABLE I
### REACTION OF DIPHENYLIODONIUM TOSYLATE AND NITROPARAFFIN SALTS IN DMF

| Salt of[a] | Product | Yield, % |
|---|---|---|
| 1-Nitropropane | 1-Phenyl-1-nitropropane | 62 |
| 2-Nitropropane | 2-Phenyl-2-nitropropane | 56 |
| 2-Nitrobutane | 2-Phenyl-2-nitrobutane | 69 |
| 2-Nitroöctane | 2-Phenyl-2-nitroöctane | 54 |
| Nitrocyclohexane | 1-Phenyl-1-nitrocyclohexane | 58 |
| Ethyl α-nitrocaproate | Ethyl α-phenyl-α-nitro-caproate | 58 |

[a] Sodium salts used in all instances except for the 2-nitropropane experiment; there the lithium salt was employed.

The salts of aliphatic nitro compounds are ambient anions and, therefore, phenylation at oxygen to give nitronic esters (I) is a real possibility, especially since alkylation usually occurs at oxygen.[4] It is of interest, then, that phenyl nitronic esters were not found.

$$R-\overset{R'}{\underset{|}{C}}=\overset{+}{N}\overset{O^-}{\underset{O-C_6H_5}{\diagdown}}$$
I
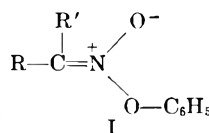
## Experimental[5]

**Preparation of Diphenyliodonium Tosylate.**—In a 1-l. flask cooled in an ice bath were placed 107 g. (0.50 mole) of potassium iodate, 90 ml. (0.50 mole) of benzene, and 200 ml. of acetic anhydride. A solution of 100 ml. of acetic anhydride and 225 ml. of concentrated sulfuric acid was added in the course of *ca.*

2 hr. to the stirred mixture while maintaining the temperature below 10°. The reaction mixture was stirred for *ca.* another hour and then the ice bath was removed and the mixture stirred for an additional 20 hr. The product was poured onto *ca.* 350 g. of ice and the resulting suspension was extracted twice with 100-ml. portions of ethyl ether. The aqueous phase was diluted with an equal volume of water and a solution of 80 g. (0.53 mole) of sodium iodide in 1 l. of water was added slowly. The precipitated diphenyliodonium iodide was removed by filtration.

The moist iodide was suspended in 750 ml. of methanol and to this was added, with vigorous stirring, 58.0 g. (0.25 mole) of silver oxide and 85.0 g. (0.50 mole) of p-toluenesulfonic acid monohydrate. After stirring overnight, the solids were removed by filtration and the filtrate vacuum evaporated (below 50°) to dryness. The residue was dissolved in 1.2 l. of chloroform and the solution was extracted with 5% aqueous sodium hydroxide until the aqueous phase remained alkaline. The chloroform layer was washed twice with water, dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo* (room temp.) to yield diphenyliodonium tosylate, m.p. 176–181°. The salt was recrystallized from 1.5 l. of hot acetonitrile giving 100 g. (44%) of material, m.p. 181–184° dec. (lit.,[6] m.p. 178–181°).

*Anal.* Calcd. for $C_{19}H_{17}IO_3S$: C, 50.45; H, 3.76; S, 7.08; I, 28.10. Found: C, 50.24; H, 3.97; S, 7.00; I, 27.99.

**Preparation of the Salts of Nitro Compounds.**—The alkali metal salts were prepared by addition of the nitro compounds in *ca.* 10% excess, to standardized absolute ethanolic solutions of the alkali ethoxide. When, as was usually the case, the salts were soluble in alcohol they were precipitated by dilution with either petroleum ether (b.p. 35–37°) or anhydrous ethyl ether. The salts, after collection on a sintered glass funnel, were dried in a vacuum desiccator over phosphorus pentoxide and paraffin wax. The neutralization equivalents, determined by potentiometric titration in absolute ethanol with standard ethanolic picric acid, agreed within 3% of the calculated values. Yields ranged from 75 to 90%. The salts were used within 24 hr. since dry alkali metal salts of nitro compounds are capable of decomposing explosively if heated or subjected to mild shock.[7]

**Preparation of 2-Phenyl-2-nitroöctane.**—This exemplifies the procedure for phenylating secondary nitro compounds. Diphenyliodonium tosylate (9.04 g., 20 mmoles) was added to a magnetically stirred suspension of 3.62 g. of the sodium salt of 2-nitroöctane in 15 ml. of dry DMF (distilled from calcium hydride) contained in a 50-ml. flask. After 22 hr.[8] the reaction was 95% complete as shown by titration of an aliquot for residual base. The reaction mixture was then poured into 100 ml. of ice–water and the aqueous phase was saturated with sodium chloride and extracted with five 40-ml. portions of petroleum ether (b.p. 35–37°). The combined petroleum ether layers were extracted twice with 10 ml. of 10% aqueous sodium hydroxide and then washed with four 25-ml. portions of water. The solution was dried over anhydrous sodium sulfate after which the solvent and most of the iodobenzene were removed *in vacuo* at room temperature. The residual liquid was dissolved in an equal volume of petroleum ether (b.p. 35–37°) and passed through a column of Merck's basic alumina. Elution with the petroleum ether washes the residual iodobenzene off the column and when this process is completed, elution with benzene–petroleum ether (1:4) washes the phenylated nitroöctane off the column. The pure nitro compound was obtained by vacuum evaporation of the benzene–petroleum ether solution at room temperature; yield 2.53 g. (54%) of a colorless liquid, $n^{20}D$ 1.5053, which is analytically pure (Table II) and which exhibits strong nitro absorption in the infrared at 6.50 μ.

**Preparation of 1-Phenyl-1-nitropropane.**—This, because it involves the salt of a primary nitroparaffin, required modified conditions. Preliminary experiments using equivalent amounts of nitroparaffin salt and iodonium salt gave relatively complex mixtures of products which presumably are derived from the salt of the monophenylated nitro compound. In keeping with this assumption it was found that these by-products were absent when 10 moles of 1-nitropropane were present.

To a suspension of the sodium salt of 1-nitropropane (2.22 g., 20 mmoles), 20 ml. of dry DMF and 1-nitropropane (18 ml., 203

(1) Paper XX in the series, "The Chemistry of Aliphatic and Alicyclic Nitro Compounds." For the previous paper in this series, see N. Kornblum, W. D. Gurowitz, H. O. Larson, and D. E. Hardies, *J. Am. Chem. Soc.*, **82**, 3099 (1960).

(2) Sponsored by the U. S. Army Research Office (Durham).

(3) F. M. Beringer, S. A. Galton and S. J. Huang, *J. Am. Chem. Soc.*, **84**, 2819 (1962), and earlier papers in that series.

(4) N. Kornblum and P. Pink, *Tetrahedron*, in press.

(5) Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and by Dr. C. S. Yeh and Mrs. T. M. Eikeri, Purdue University.

(6) F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner, and E. Sommer, *J. Am. Chem. Soc.*, **81**, 342 (1959).

(7) H. B. Hass, E. B. Hodge, and B. M. Vanderbilt, *Ind. Eng. Chem.*, **28**, 339 (1936).

(8) With the other secondary nitroparaffin salts reaction times of 1–3 hr. sufficed.

<div align="center">

TABLE II

PHENYLATED NITRO COMPOUNDS

</div>

| Compound | $n^{20}D$ | Carbon, % | | Hydrogen, % | | Nitrogen, % | |
|---|---|---|---|---|---|---|---|
| | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| 2-Phenyl-2-nitropropane | 1.5204 | 65.40 | 65.20 | 6.76 | 6.90 | 8.48 | 8.49 |
| 2-Phenyl-2-nitrobutane | 1.5206 | 67.04 | 66.91 | 7.26 | 7.30 | 7.82 | 7.82 |
| 2-Phenyl-2-nitroöctane | 1.5053 | 71.49 | 71.28 | 8.94 | 9.07 | 5.96 | 6.02 |
| 1-Phenyl-1-nitrocyclohexane | a | 70.24 | 70.04 | 7.32 | 7.28 | 6.83 | 6.73 |
| Ethyl 2-Phenyl-2-nitrocaproate | 1.5033 | 63.40 | 63.25 | 7.17 | 7.27 | 5.28 | 5.39 |
| 1-Phenyl-1-nitropropane | 1.5159 | 65.40 | 65.59 | 6.76 | 6.88 | 8.48 | 8.74 |

a M.p. 51.0–52.5°.

mmoles) in a 50-ml. flask was added diphenyliodonium tosylate (9.04 g., 20 mmoles). After 1 hr. the reaction mixture was poured into 150 ml. of ice–water saturated with sodium chloride. The suspension was extracted five times with 50-ml. portions of petroleum ether (b.p. 35–37°), the combined extracts were washed twice with water, dried over anhydrous sodium sulfate, and the drying agent removed by filtration. The solvent, the 1-nitropropane, and the major portion of the iodobenzene were removed *in vacuo* at room temperature. The residue was chromatographed on Merck's silicic acid[9] yielding 2.04 g. (62%) of 1-phenyl-1-nitropropane, $n^{20}D$ 1.5159, which is analytically pure (Table II) and which exhibits strong nitro group absorption at 6.45 μ.

**Preparation of Ethyl 2-Phenyl-2-nitrocaproate.**—Diphenyliodonium tosylate (18.04 g., 40 mmoles) was added to a magnetically stirred solution of the sodium salt of ethyl 2-nitrocaproate (8.36 g., 40 mmoles) in 30 ml. of DMF at 55°. The reaction is 96% complete after 6 hr. at this temperatre. The reaction mixture was then poured into 150 ml. of ice–water. The water layer was saturated with sodium chloride and extracted with five 50-ml. portions of petroleum ether (b.p. 35–37°). The extracts were each washed with 25 ml. of water, combined, and dried over anhydrous sodium sulfate. The solvent and a portion of the iodobenzene were removed *in vacuo* at room temperature. The residue was dissolved in petroleum ether (b.p. 35–37°) and chromatographed on Merck's silicic acid. The residual iodobenzene was eluted with petroleum ether. Ethyl 2-phenyl-2-nitrocaproate, 6.16 g. (58% yield), was obtained on elution with 30% benzene–70% petroleum ether. Last traces of solvent were removed at *ca.* 1 mm. giving analytically pure material (Table II). The infrared spectrum shows strong nitro group absorption at 6.45 μ.

Preliminary experiments[10] using diphenyliodonium chloride and the lithium salt of 2-nitropropane in methanol, and in water, showed that these solvents are much less useful than DMF. In DMF these salts reacted to give 2-phenyl-2-nitropropane in *ca.* 50% yield.

**Acknowledgment.**—We thank Dr. Paul Haberfield for several preliminary experiments and the Commercial Solvents Corporation for generous gifts of several nitroparaffins.

(9) The product is decomposed by chromatographing on basic alumina.
(10) By Dr. Paul Haberfield.

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# Catalytic Hydrogenolysis of Hydroxamic Acids to Amides

ROBERT M. GIPSON,[1] FLORA H. PETTIT, CHARLES G. SKINNER, AND WILLIAM SHIVE

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Metallic reduction of various hydroxamic acids to yield the corresponding amide derivatives has been reported[2]; however, controlled catalytic hydrogenolysis

of hydroxamic acids to yield the corresponding amides has not been described adequately in the available literature.[3] Recently, as a part of a structural study of a reaction product formed by the interaction of glutamic acid and hydroxylamine in the presence of an enzyme from *Escherichia coli*, a reaction product, which appeared to be a hydroxamate of glutamic acid on the basis of elemental analysis, was found to undergo hydrogenolysis in the presence of Raney nickel catalyst to form glutamine.[4] Although the utility of such a conversion may not be of wide spread interest since the amides usually are more easily obtained through other routes, it was considered desirable to determine the scope of this type of hydrogenolysis reaction. Accordingly, a number of hydroxamic acids were prepared by conventional means and treated with hydrogen gas in the presence of Raney nickel catalyst. It was observed that, in each of the examples studied, the desired amide could be obtained directly from the corresponding hydroxamic acid in good yield. The variety of substituent groupings studied is indicated in Table I, and range from simple aliphatic analogs to cycloaliphatic, aromatic, and heterocyclic derivatives. The yields of the amides produced varied from 76 to 96%, even though no effort was made to determine optimum reaction conditions in each case.

<div align="center">

TABLE I

SYNTHESIS OF AMIDES FROM HYDROGENOLYSIS OF HYDROXAMIC ACIDS

</div>

$$R-\overset{\displaystyle O}{\overset{\|}{C}}-NHOH \xrightarrow{H_2} R-\overset{\displaystyle O}{\overset{\|}{C}}-NH_2 + H_2O$$

| R Amide produced | Time required for reaction, hr. | Yield, % |
|---|---|---|
| Acetamide | 1.25 | 96 |
| Capramide | 1.0 | 85 |
| Lauramide | 3.0 | 97 |
| Adipamide | 1.5 | 76 |
| L-Glutamine | 3.0 | 80[a] |
| Cyclohexanecarboxamide | 3.0 | 81 |
| Benzamide | 18.0 | 78 |
| o-Aminobenzamide | 12.0 | 82 |
| Nicotinamide | 20.0 | 84 |

a Yield determined by microbial assay using *Streptococcus lactis*, unpublished technique, J. M. Ravel and W. Shive.

(2) C. Gastaldi, *Gazz. chim. ital.*, **54**, 512 (1924).
(3) F. Mathis, *Bull. soc. chim. France*, D9 (1953), refers to a study of the reduction of gluconohydroxamic acid in the presence of nickel catalyst to yield a mixture of gluconamide and ammonium gluconate which was described by F. Mathis, *These Sciences* (Paris) (1952).
(4) F. Pettit and W. Shive, unpublished data.

## Experimental[5]

**Hydroxamic Acids.**—All of these intermediates were prepared by the usual method of treating the methyl or ethyl ester of the appropriate organic acid with salt-free hydroxylamine and were identified through their reported melting points which are indicated in parentheses: acetohydroxamic acid, m.p. 87–88° (88°[6]); caprohydroxamic acid, m.p. 63–64° (64°[7]); laurohydroxamic acid, m.p. 93–94° (94°[7]); adipohydroxamic acid, m.p. 164–165° (165–165.5°[8]); γ-glutamohydroxamic acid, m.p. 151–152° (155°[9]); cyclohexanecarbohydroxamic acid, m.p. 132–133° (132°[10]); benzohydroxamic acid, m.p. 127–128° (from 124° to 131°[11]); o-aminobenzohydroxamic acid, m.p. 147–149° (148°[12]); and nicotinohydroxamic acid, m.p. 164–165° (165°[13]).

**Catalytic Hydrogenolysis of Hydroxamic Acids (Table I).**—All of the hydroxamic acids indicated in the preceding paragraph were converted to the corresponding amide by the same general procedure. The hydrogenolysis of laurohydroxamic acid will be described as a representative example. A mixture of 4.0 g. of laurohydroxamic acid and about 1 g. of Raney nickel in 75 ml. of ethanol was shaken in a Parr hydrogenation apparatus under 50 p.s.i. of hydrogen pressure for a total of about 3 hr. The time required for essentially complete hydrogenolysis of the different compounds varied as indicated in Table I. The course of the reaction was determined by examining an aliquot sample of the reaction mixture for its ability to produce a visible violet color with ferric chloride reagent.[14] When the ferric chloride test became negative, the catalyst was filtered and the filtrate was reduced to about one-third volume *in vacuo*. Upon addition of water, the amide which precipitated was dried *in vacuo* over sodium hydroxide pellets to yield 3.24 g. of product, m.p. 101–102°. The identity of the compound was determined by a mixture melting point using a 50:50 mixture of the isolated material and a sample of lauryl amide to give a mixture which melted at 101–102°.

(5) All melting points are uncorrected and were determined using the capillary technique in a liquid bath. The authors are indebted to J. T. Lee for the elemental analysis.

(6) C. Hoffmann, *Ber.*, **22**, 2855 (1889).

(7) Y. Inoue and Y. Hanzaburo, *J. Agr. Chem. Soc., Japan.* **16** 504 (1940).

(8) C. Hurd and D. Botterton, *J. Org. Chem.*, **11**, 207 (1946).

(9) J. A. Roper and H. McIlwain, *Biochem. J.*, **42**, 485 (1948).

(10) F. Winternitz and C. Wlotzka, *Bull. soc. chim. France*, 509 (1960).

(11) The most generally accepted values appear to lie in the range of about 130°; B. Prager and P. Jacobson, ed., "Beilsteins Handbuch der Organischen Chemie," Vol. IX, 4th ed., Julius Springer, 1920, p. 301.

(12) A. Scott and B. Wood, *J. Org. Chem.*, **7**, 508 (1942).

(13) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Juaregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955).

(14) F. Feigl, "Spot Tests," Vol. II, Organic Applications, 4th rev. Engl. ed., Elsevier Publishing Company, Amsterdam, 1954, p. 170.

## The Acid-catalyzed Hydrolysis of (−)-2-Octyl Ethyl Methylphosphonate

LEONARD KEAY[1]

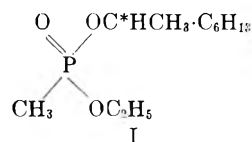*Department of Chemistry, Queen Mary College, London, E. 1, England*

The hydrolysis of esters of alkylphosphonic acids has been studied in some detail,[2] and, although the alkaline hydrolysis undoubtedly proceeds by a nucleophilic attack on the phosphorus atom with subsequent P—O fission, the mechanism of acid-catalyzed hydrolysis is less clearly defined. The O[18] studies on trimethylphosphate[3] are not entirely unambiguous and in any case, the mechanisms for phosphate and phosphonate

(1) Present address: Research and Engineering Division, Monsanto Chemical Co., St. Louis 66, Mo.

(2) R. F. Hudson and L. Keay, *J. Chem. Soc.*, 2463, 3269 (1956).

(3) E. Blumenthal and J. B. M. Herbert, *Trans. Faraday Soc.*, **41**, 611 (1945).

hydrolysis are not necessarily the same. The acid-catalyzed hydrolysis of optically active di(2-octyl) ethylphosphonate has been studied[4] and the alcohol produced shown to be mainly racemic with a slight retention of configuration, in agreement with the postulated alkyl–oxygen fission mechanism.

Unfortunately, the actual rates of hydrolysis and optical activity change were not determined, but the optical activity of the octanol-2 measured after extraction at the end of a prolonged hydrolysis and the rate of racemization of optically active octanol-2 under the hydrolysis conditions is not stated. Furthermore, in acid solution both alkyl groups are hydrolyzed, the alcohol could be produced in either reaction, and the mechanisms need not necessarily be the same.

Since the rate of hydrolysis of secondary alkyl ester groups is about 25-fold faster than that of primary alkyl ester groups,[2] a mixed ester could overcome this problem and so (−)-2-octyl ethyl methylphosphonate (I) was prepared by the reaction of (−)-2-octyl methylphosphonochloridate[5] with ethanol in the presence of a base.

$$\underset{\text{I}}{\underset{\displaystyle CH_3 \quad\quad OC_2H_5}{\overset{\displaystyle O \quad\quad OC{*}HCH_3 \cdot C_6H_{13}}{\diagdown\!\!\!\diagup\;P\;\diagdown\!\!\!\diagup}}}$$

The rate of acid-catalyzed hydrolysis was measured acidimetrically and the change in optical activity determined simultaneously. The optical activity of the octanol-2 liberated was also determined after extraction and distillation. The rate of racemization of (−)-octanol-2 was measured under the conditions used in the hydrolysis experiment and shown to be only one fifth the rate of the ester hydrolysis, so that changes in configuration subsequent to hydrolysis can be ignored. The results (Table I and Fig. 1) show that the rate of

### TABLE I

THE HYDROLYSIS OF (−)-2-OCTYL ETHYL METHYLPHOSPHONATE IN N PhSO₃H IN 50% DIOXANE AT 100°

| Time, hr. | $N_t^a$ | $k_1$ (acid production) | $\alpha\alpha^a$ | $k_1$ (racemization) |
|---|---|---|---|---|
| 0 | 20.62 | . . . | −1.20 | . . . |
| 0.5 | 20.78 | 0.188 | . . . . | . . . |
| 1 | 20.90 | .176 | −1.10 | 0.100 |
| 2 | 21.15 | .180 | −0.85 | .173 |
| 3 | 21.32 | .172 | . . . . | . . . |
| 4 | 21.52 | .180 | − .49 | .220 |
| 7 | . . . | . . . | − .35 | .177 |
| 11 | . . . | . . . | − .16 | .183 |
| 96 (∞) | 22.37 | . . . | 0 | . . . |

average $k_1 = 0.179$    average $k_1 = 0.171$

[a] See Experimental for explanation of symbols.

acid production and rate of change of optical activity are equal and the alcohol isolated is almost racemic with a slight retention of configuration. This confirms the view of Gerrard, Green, and Nutkins[4] that alkyl-oxygen fission occurs without simultaneous attack on the carbon atom by a water molecule, which would give inversion of configuration. The mechanism must involve a carbonium ion, unless both P—O and C—O

(4) W. Gerrard, W. J. Green, and R. A. Nutkins, *J. Chem. Soc.*, 4076 (1952).

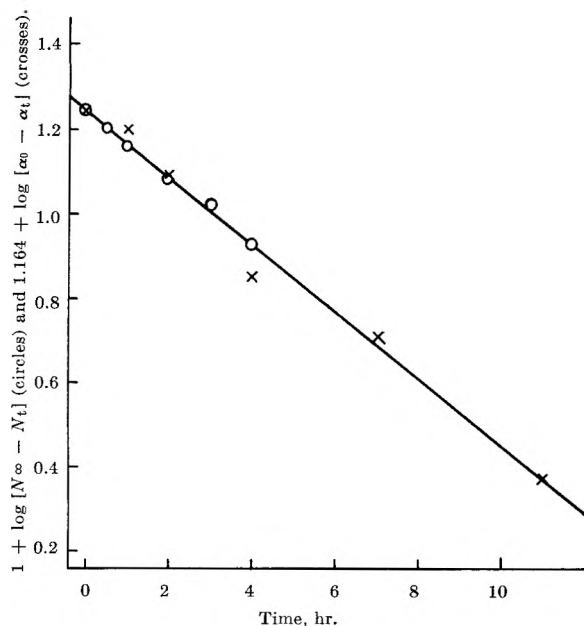(5) R. F. Hudson and L. Keay, *ibid.*, 1865 (1960).

Fig. 1.—First-order kinetic plot of titrimetic and polarimetric data for acid-catalyzed hydrolysis of ( −)-2-octyl ethyl methylphosphate. From the slope of the graph, $k_1 = 0.183$ hr.$^{-1}$.

fissions can occur, the latter reaction involving nucleophilic assistance from a water molecule (the $A_{AL}2$[6] or $A''2$[7] mechanism), which seems unlikely.

### Experimental

**Materials.**—Dioxane was purified by refluxing with hydrochloric acid to hydrolyze any acetals, adding an excess of solid potassium hydroxide, decanting, drying over sodium, and finally distilling from over fresh sodium.

Optically active octanol-2 was prepared by fractional crystallization of the brucine salts of the phthalic acid monoester, followed by hydrolysis and distillation.[8]

( −)-2-Octyl methylphosphonochloridate was prepared in 79% yield by the reaction between ( −)-octanol-2 and methylphosphonic dichloride in the presence of triethylamine in ether at 0°.[4] Specific gravity, 1.036; $[\alpha]^{18}D$ −12.65° (from octanol-2, $[\alpha]^{20}D$ −9.95°.)

*Anal.* Calcd. C, 47.7; H, 8.8; Cl, 15.7. Found: C, 48.1; H, 8.6; Cl, 15.7.

( −)-2-Octyl **Ethyl Methylphosphonate.**—A 22.6-g. sample (0.1 mole) of ( −)-2-octyl methylphosphonochloridate was added slowly with agitation to 16.0 ml. (0.1 mole) of diethylaniline and 30.0 ml. (0.5 mole) of anhydrous ethanol. The reaction mixture was then heated on a boiling water bath for 0.5 hr. The semi-solid pasty mass was allowed to cool and then shaken with 300 ml. of dry petroleum ether (b.p. 40–60°). The solid was removed by filtration and washed with more petroleum ether. The solvent was removed from the combined filtrate and washings and the residual oil distilled under reduced pressure; yield, 20.0 g. (85%), b.p. 73–74°/(0.2 mm.); specific gravity, 0.945; $[\alpha]^{18}D$ −11.87° (from alcohol $[\alpha]^{20}D$ −9.95°).

*Anal.* Calcd. C, 55.7; H, 10.5. Found: C, 54.8; H, 10.5.

An attempt to prepare the same compound by the reaction of octanol-2 with ethyl methylphosphonochloridate in the presence of a tertiary base was unsuccessful, probably due to the slow reaction with the octanol-2 which was recovered unchanged.

**Kinetic and Optical Activity Measurements.**—The ester (2.36 g.) was dissolved in 100 ml. of $N$ benzenesulfonic acid in 50% aqueous dioxane (v./v.) to give a 0.1 $M$ solution of ester. Five-milliliter aliquots were removed with pipets and placed in glass ampoules and sealed. The ampoules were placed in an agitated oil bath maintained at 100.2°, and ampoules were removed for

(6) C. A. Bunton, E. D. Hughes, C. K. Ingold, and D. F. Meigh, *Nature*, **166**, 680 (1950).

(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 318.

(8) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 2nd ed., Longmans Green and Co., London, 1951, p. 489.

analysis at suitable time intervals. The formation of acid was determined by rapidly cooling the ampoule and titrating the contents against 0.25 $N$ sodium hydroxide using methyl red indicator. The change in optical activity was determined by placing the cooled contents of ampoules in the 2-dm. polarimeter tube and measuring the rotation at the sodium "D" line.

The velocity constants for the acid production and optical activity change were determined using the equations,

$$k_1 = \frac{2.303}{t} \cdot \log\left\{\frac{N\infty}{N\infty - N_t}\right\} \quad \text{and} \quad k_1 = \frac{2.303}{t} \cdot \log\left\{\frac{\alpha_0}{\alpha_0 - \alpha_t}\right\}$$

where $N_t$ is the volume of 0.25 $N$ sodium hydroxide required to neutralize a 5-ml. reaction mixture at time $t$, and $\alpha_t$ is the optical rotation of the reaction mixture observed in a 2-dm. tube at time $t$, and also from the graph of log $(N\alpha − N_t)$ or log $(\alpha_0 − \alpha_t)$ vs. time, $k_1 = −2.303 \times$ slope of the graph.

The optical activity of the alcohol produced was also measured after isolation; 10 g. of ester was heated with 50 ml. of 1 $N$ benzenesulfonic acid in 50% aqueous dioxane at 100° for 6 hr. in a large sealed ampoule. The ampoule was cooled; the contents made slightly alkaline with sodium hydroxide and immediately extracted twice with ether. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed. The residue was distilled in a microfractionation unit to give 3.0 g. (55%) of octanol-2, b.p. 175–180° (lit. b.p. 178–179°), $[\alpha]^{20}D$ −0.84° (the octanol-2 used in the ester preparation had $[\alpha]^{20}D$ −9.95°).

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### The Addition of Phosgene to Carbodiimides

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It is well known that carboxylic acids add to carbodiimides[2] and recently acetyl chloride was shown to do so,[3] although the products are unstable and tend to decompose to the starting compounds. We have found that phosgene, which has not previously been reported as taking part in addition reactions with cumulative double bonds,[4] also adds readily to aliphatic and aromatic carbodiimides to give N,N′-disubstituted chloroformamidine-N-carbonyl chlorides (I), which are remarkably stable as illustrated by their distillation in vacuum without decomposition.

$$R-N=C=N-R + COCl_2 \longrightarrow$$
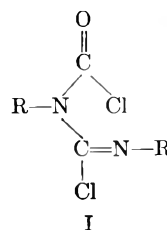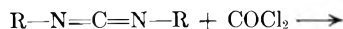


a.  R = *n*-butyl
b.  R = cyclohexyl
c.  R = *o*-tolyl

The structure of the 1:1 addition products was established by elementary analysis and infrared spectroscopy. The infrared spectra of I show C=O absorption at 5.73–5.75 $\mu$ and a C=N absorption at 5.98–6.0 $\mu$.
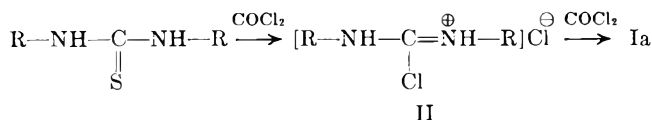
(1) To whom inquiries should be directed.

(2) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(3) K. Hartke and J. Bartulin, *Angew. Chem.*, **74**, 214 (1962).

(4) While phosgene does not react with isocyanates, F. S. Fawcett, C. W. Tullock, R. D. Smith, and D. D. Coffman, Second International Symposium on Fluorine Chemistry, Estes Park, Colo., 1962, have observed that carbonyl fluoride adds to phenyl isocyanate.

The aliphatic members of the series were also obtained from N,N'-dialkylthioureas and excess phosgene. When this reaction is carried out with molar ratios of reactants, the products were reported to be N,N'-disubstituted chloroformamidine hydrochlorides (II),[5] which, therefore, can be invoked as intermediates in the reaction involving excess phosgene. This is supported by the fact that II (R = n-butyl) reacts with phosgene to give a high yield of Ia. Furthermore, Ia can also be

$$R-NH-\underset{\underset{S}{\|}}{C}-NH-R \xrightarrow{COCl_2} [R-NH-\underset{\underset{Cl}{|}}{C}\overset{\oplus}{=}NH-R]Cl \overset{\ominus}{\phantom{X}}\overset{COCl_2}{\longrightarrow} Ia$$
$$II$$

obtained from N,N'-di-n-butylurea and phosgene in the presence of triethylamine,[6] the intermediate in this case being the carbodiimide.

$$R-NH-\underset{\underset{O}{\|}}{C}-NH-R \xrightarrow[Et_3N]{COCl_2} R-N=C=N-R \xrightarrow{COCl_2} Ia$$

$$R = n\text{-butyl}$$
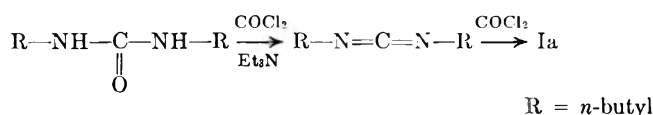
We investigated the reaction of amines and hydrazine with Ic. When it reacted with four equivalents of o-toluidine, the products were di-o-tolylcarbodiimide (84.7%) and some o-tolyl isocyanate; both could arise from the decomposition of a common four-membered ring intermediate.[7]

$$RN=C=N-R + RNCO \longleftarrow$$
$$R = o\text{-tolyl}$$
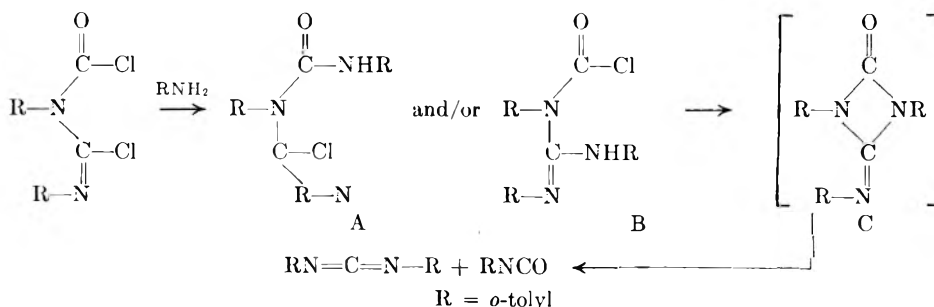
Similarly, di-o-tolylguanidine (III) was obtained from the reaction of Ic and alcoholic ammonia. Most likely, but not necessarily, III is formed by the addition of ammonia to di-o-tolylcarbodiimide.

When hydrazine hydrate and Ic reacted, 3-o-tolylamino-5-hydroxy-4-o-tolyl-1,2,4,4H-triazole (IV) was formed.

IV.   R = o-tolyl
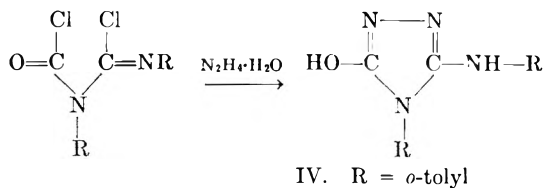
At 180° Ic, slowly generated phosgene but no carbodiimide could be detected. However, at 80° in the presence of hydrogen chloride, dissociation into carbodiimide (strong infrared absorption at 4.7 μ), isocyanate (weak infrared absorption at 4.4 μ), and isocyanide dichloride (weak infrared absorption at 11 μ) was observed.

(5) H. Eilingsfeld, M. Seefelder, and H. Weidinger, Angew. Chem., 72, 836 (1960).

(6) H. Ulrich, J. N. Tilley, and A. A. R. Sayigh, in print.

(7) One of the referees prefer not to involve the four-membered ring intermediate (C) but to decompose intermediates A and/or B concertedly to the products. However, we prefer to involve C in view of the tendency of similar derivatives (A, B) to form four-membered rings.

$$R = o\text{-tolyl}$$
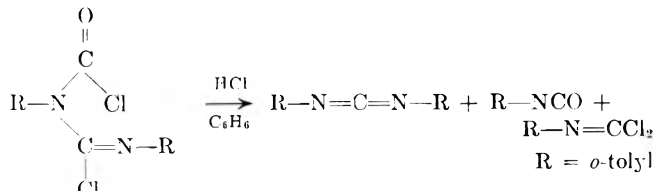
## Experimental[8]

**N,N-Dibutylchloroformamidine-N-carbonyl Chloride (Ia). A. From Di-n-butylcarbodiimide.**—Phosgene was added to a solution of 3.08 g. (0.02 mole) of di-n-butylcarbodiimide in 50 ml. of toluene at room temperature. The temperature of the mixture rose to 45°. The unchanged phosgene was removed in a stream of nitrogen, and the solvent was evaporated to give 4.4 g. (98%) of Ia, b.p. 86° (0.5 mm.), $n^{23}D$ 1.4718, $\lambda_{max}^{CHCl_3}$ (infrared): 3.43, 5.73, 5.98, 6.80, 7.35, and 8.05 μ.

*Anal.* Calcd. for $C_{10}H_{18}Cl_2N_2O$: C, 47.45; H, 7.16; N, 11.06. Found: C, 47.60; H, 7.40; N, 11.17.

**B. From N,N'-Di-n-butylthiourea.**—Phosgene was added to a solution of 30.2 g. (0.16 mole) of N,N'-di-n-butylthiourea in 600 ml. of benzene until the exothermic reaction stopped. The excess phosgene was removed in nitrogen and the solvent evaporated to give 39 g. (96.3%) of Ia. The infrared spectrum was superimposable on that of the Ia obtained, according to method A.

**C. From N,N'-Di-n-butylchloroformamidine Hydrochloride.** —Hydrogen chloride was bubbled into a solution of 7.7 g. (0.05 mole) of di-n-butylcarbodiimide in 77 ml. of benzene until the infrared spectrum of the mixture indicated the complete reaction of the carbodiimide. Then excess phosgene was added to the refluxing reaction mixture. After purging with nitrogen, 10.4 g.

(91.6%) of Ia was obtained. The infrared spectrum was identical with that of the material prepared according to method A.

**N,N'-Dicyclohexylchloroformamidine-N-carbonyl Chloride (Ib).**—Phosgene was added to a solution of 4.12 g. (0.02 mole) of dicyclohexylcarbodiimide in 50 ml. of ethylene dichloride at 2°. When the excess phosgene was removed with nitrogen and the solvent evaporated, 6.1 g. (100%) of Ib was obtained, b.p. 140–142° (0.8 mm.), $n^{23}D$ 1.5132, $\lambda_{max}^{CHCl_3}$ (infrared): 3.43, 5.73, 5.98, 6.88, 7.40, 7.83, 8.52, 9.45, 9.85, and 10.42 μ.

*Anal.* Calcd. for $C_{14}H_{22}Cl_2N_2O$: C, 55.05; H, 7.26; N, 9.17. Found: C, 54.99; H, 7.20; N, 9.40.

**N,N'-Di-o-tolylchloroformamidine-N-carbonyl Chloride (Ic).**—Phosgene (15 g., 0.15 mole) was added to a solution of 22.2 g. (0.1 mole) of di-o-tolylcarbodiimide in 200 ml. of ethylene dichloride at 2°. The excess phosgene and the solvent were removed to give 31.7 g. (98.8%) of Ic, $n^{21}D$ 1.5851, $\lambda_{max}^{CHCl_3}$ (infrared): 5.73, 6.00, 6.72, 6.85, 8.50, and 9.00 μ.

*Anal.* Calcd. for $C_{16}H_{14}Cl_2N_2O$: N, 8.72. Found: N, 8.98.

**Reaction of Ic with-o-Toluidine.**—A 21.4-g. sample (0.2 mole) of o-toluidine in 21 ml. of dry benzene was added dropwise over a period of 30 min. to a stirred solution of 16.05 g. (0.05 mole) of Ic in 110 ml. of benzene. The mixture was stirred for an additional 45 min. at room temperature and the precipitated solid was filtered off. The infrared spectrum of the benzene solution had a strong absorption band at 4.7 μ and a weak band at 4.4 μ. The benzene was evaporated and the residue distilled to give 9.4 g. (84.7%) of di-o-tolylcarbodiimide, b.p. 134–141° (0.4 mm.). The filtered solid was separated into o-toluidine hydrochloride,

(8) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared absorption spectra were determined using a Perkin-Elmer Model 21 spectrophotometer.

and the water-insoluble di-*o*-tolylurea, m.p. 270° dec. The infrared spectrum of the isolated urea was identical with that of an authentic sample.

**Reaction of Ic with Ammonia.**—A 3.2-g. sample (0.01 mole) of Ic was added to methanolic ammonia. When the solvent was evaporated, the hydrochloride of N,N'-di-*o*-tolylguanidine was obtained. From this, on treatment with aqueous sodium hydroxide, was isolated di-*o*-tolylguanidine (III), m.p. 183–185° (lit., m.p. 179°). A solution of 1 g. of di-o-tolylcarbodiimide in 10 ml. of benzene was saturated with ammonia in the presence of 10 mg. of cupric chloride to give 74.5% of III, m.p. 186–187°. No depression of the melting point was caused when samples of III prepared by the above methods were mixed. The infrared spectrum was identical with that of an authentic sample.

**Reaction of Ic with Hydrazine Hydrate.**—A 2.2-g. sample (0.007 mole) of Ic was added to 1.44 g. (0.03 mole) hydrazine hydrate in a mixture of 20 ml. of tetrahydrofuran and 20 ml. of water. An immediate reaction took place. After the mixture had been stirred, with ice-cooling, 1.4 g. (73%) of 3-o-tolylamino-5-hydroxy-4-o-tolyl-1,2,4,4H-triazole (IV) had separated. It crystallized from benzene in white crystals, m.p. 198–199°; $\lambda_{max}^{CHCl_3}$ (infrared): 2.96, 3.20, 3.30–3.40, 5.84, 6.17, 6.28, 6.48, 6.84, 7.27, 7.62, and 11.61 $\mu$.

*Anal.* Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.72; H, 5.96; N, 19.92.

In a similar experiment, using benzene as the solvent, IV was obtained in 83% yield. IV is soluble in dilute sodium hydroxide and it could be reprecipitated by acid.

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## The Structure of Nidulin

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Nidulin,[1] the chief chlorine-containing metabolite of a non-ascosporic strain of *Aspergillus nidulans*, has been allocated[2,3] structure I. Shortly after the publication of our last paper,[3] Beach and Richards claimed[4] that nidulin should be represented by structure II. Although we still maintain that the evidence which we have already presented[2,3] is sufficient to establish the correctness of our structure, we present the following additional arguments in favor of structure I.

(1) F. M. Dean, A. Robertson, J. C. Roberts, and K. B. Raper, *Nature* (London), **172**, 344 (1953).

( ) F. M. Dean, J. C. Roberts, and A. Robertson, *J. Chem. Soc.*, 1432 (1954).

(3) F. M. Dean, D. S. Deorha, A. D. T. Erni, D. W. Hughes, and J. C. Roberts, *ibid.*, 4829 (1960).

(4) W. F. Beach and J. H. Richards, *J. Org. Chem.*, **26**, 1339, 3011 (1961).
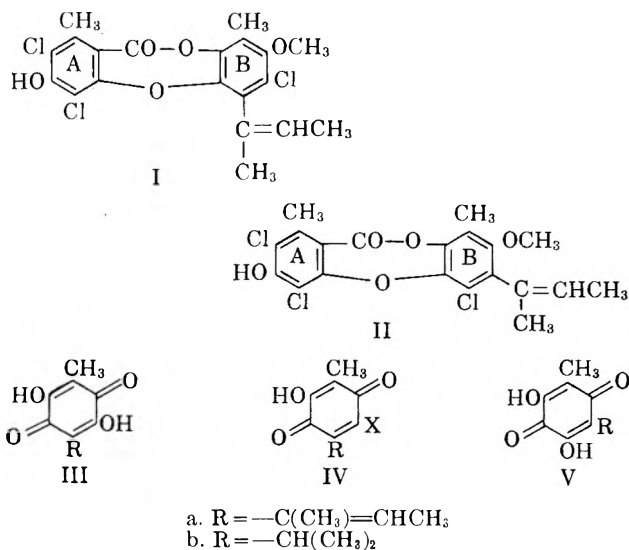


Degradation of nidulin under strictly defined conditions[3] yielded nucleus B as a dihydroxybenzoquinone which we have formulated,[3] on the basis of analysis, color reactions, and ultraviolet absorption spectrum,[5] as IIIa. If nidulin had possessed structure II, then the degradation product would have had structure Va. We have now compared (see Table I) the ultraviolet and infrared absorption spectra of the degradation product IIIa with the corresponding spectra of dihydroxythymoquinone[6] (IIIb) and of 3,5-dihydroxy-2,6-dimethylbenzoquinone[7] (V; R = CH₃). We also record (see Table I) the spectra of monohydroxythymoquinone[6] (IVb; X = H) and of the chloroquinone (IVa; X = Cl) which is obtainable[3] as a degradation product of nidulin. The three last-mentioned quinones, as expected,[8] show two carbonyl bands in their infrared spectra. (The two bands are not clearly resolved in the solution spectra of the chloroquinone and of 3,5-dihydroxy-2,6-dimethylbenzoquinone.)

Information from the ultraviolet absorption spectra does not differentiate clearly between the two possibilities for the nidulin degradation product (IIIa or Va). However, the evidence from the infrared absorption spectra establishes unequivocally that the degradation product has structure IIIa. Hence the chloroquinone has structure IVa (X = Cl). We maintain, therefore, that nidulin is correctly represented by structure I.

(5) *Cf.* W. Flaig, T. Ploetz, and A. Küllmer, *Z. Naturforsch.*, **10B**, 668 (1955).

(6) T. Zincke, *Ber.*, **14**, 92 (1881).

(7) H. Brunnmayr, *Monatsh.*, **21**, 9 (1900).

(8) *Cf.* P. Souchay, F. Tatibouët, and P. Barchewitz, *J. Phys. Radium*, **15**, 533 (1954).

TABLE I

| Compound | Ultraviolet absorption spectrum[a] (EtOH), $\lambda_{max}$ in m$\mu$ (log $\epsilon$) | Infrared absorption spectrum[b] (O—H and C=O stretching vibrations), $\nu_{max}$ in cm.⁻¹ Disk (KBr) | Solution (CHCl₃) |
|---|---|---|---|
| IIIa | 287 (4.24), 436 (2.40) | 3310, 1617 | 3365, 1642 |
| IIIb | 293 (4.31), 435 (2.36) | 3319, 1616 | 3327, 1640[c] |
| IVb (X = H) | 267 (4.16), 404 (3.01) | 3252, 1668, and 1643 | 3431, 1662, and 1645 |
| IVa (X = Cl) | 278 (4.15), 334 (3.24) 405 (2.77)[d] | 3411, 1665, and 1655 | 3431, 1662, and 1654[d] |
| V (R = CH₃) | 297 (4.26), 426 (2.26) | 3417, 1660, and 1641 | 3476, 1653, and 1645[d] |

[a] Taken on a Unicam S. P. 500. [b] Taken on a Unicam S. P. 100. [c] Compound IIIb is only sparingly soluble in chloroform. It is more soluble in bromoform and a solution in this solvent showed a single carbonyl peak at 1637 cm.⁻¹. [d] Shoulder.

**Acknowledgment.**—We thank Dr. J. H. Richards (personal communication) for drawing our attention to the existence of the quinone V (R = CH₃).

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# The Anomalous Behavior of
# *m*-Trifluoromethylnitrosobenzene Dimer[1]

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*Contribution No. 244 from the Central Research Laboratories of
Minnesota Mining and Manufacturing Company,
St. Paul 19, Minnesota*

It is well known that most aromatic nitroso compounds exist as colorless or pale yellow dimers in the crystalline state but dissociate to intensely green-colored monomers in the liquid state.[2,3]
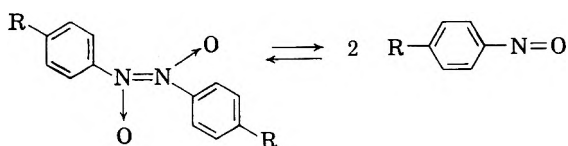
*para*-Substituents such as R₂N—, I, Cl, and CH₃ increase the tendency for dissociation owing to electronic interaction with the aromatic system, thereby weakening the N–N bond.[3] In fact, the effect is so great with *p*-nitrosodimethylaniline and with *p*-iodonitrosobenzene that these compounds are monomeric even in the solid state. When electronic interaction is prevented by *ortho* substituents that preclude formation of a planar configuration, the nitroso molecule exists mostly as a dimer even in solution. Thus, in a 1% benzene solution, nitrosomesitylene is dimerized 77%[4,5] whereas *p*-nitro-, *p*-bromo-, *p*-methylnitrosobenzene, and nitrosobenzene are dimerized less than 4%.[4,5] *m*-Substituents are reported[5] to have little or no effect on the N–N bond.

In view of these generally accepted properties of aromatic nitroso compounds, we wish to report the anomalous stability of the *m*-trifluoromethylnitrosobenzene dimer. This dimer is a white crystalline compound that melts at 48.5–49.0° forming a light amber oil. It dissolves in organic solvents giving water white to light amber solutions. The compound can be distilled at atmospheric pressure (b.p. 295°). The vapor is light green and the distillate when recrystallized from methyl alcohol is obtained as light yellow needles (m.p. 44–46°). Unlike nitrosobenzene dimer, which must be stored in a refrigerator, *m*-trifluoromethylnitrosobenzene dimer is air and light stable at room temperature and can be kept on the shelf for at least ten years without decomposition. This nitroso compound could not be reoxidized to the nitro compound using potassium permanganate in acetone, potassium dichromate in sulfuric acid, or hydrogen peroxide in acetic acid. Neither could it be reduced with ferrous ammonium sulfate in aqueous hydroxide. Much stronger reducing systems such as zinc or tin in aqueous hydrochloric acid were required for reduction to the corresponding amine.
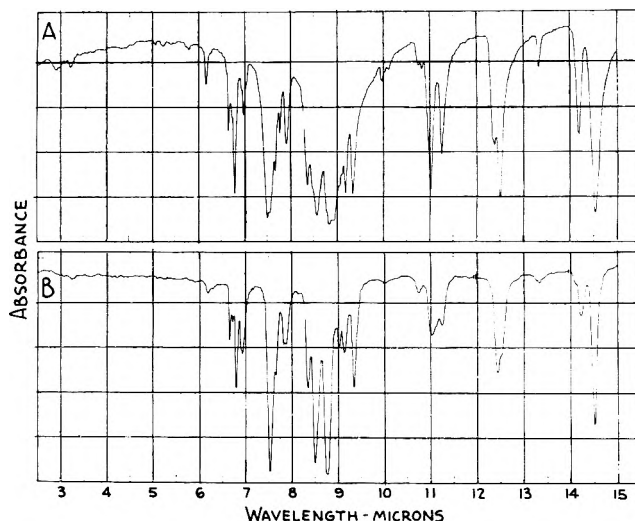
Fig. 1.—Infrared spectra of *m*-trifluoromethylnitrosobenzene dimer (A) in potassium bromide mull and (B) in carbon tetrachloride solution, 3–12 μ and 14–15 μ; in carbon bisulfide solution, 12–14 μ.

The empirical formula for *m*-trifluoromethylnitrosobenzene was established by elemental analysis. The molecular weight was determined cryoscopically using naphthalene and ebulloscopically using benzene. Both methods indicated that the compound was a dimer. The infrared spectra of this compound in its crystalline state and in solution are very similar as shown in Fig. 1, supporting the premise that no dissociation occurs at room temperature in solution. The ultraviolet absorption spectrum in ethanol [0.21 g./l.; peaks at 3150 Å., ε (l./g.-cm.) 42.9; at 2540 Å., ε 23.6; at 2320 Å., ε 30.8] also showed no evidence for the presence of the monomer. Dissociation in solution, however, begins to occur at temperatures above 100°.

N.m.r. data for this compound, summarized in Table I, are consistent with that anticipated for the symmetrical dimer as represented by the azodioxide structure.

Reduction of the dimer with zinc in aqueous hydrochloric acid gave *m*-trifluoromethylaniline which was identified by infrared analysis, and by conversion to its acetyl derivative.

*m*-Trifluoromethylnitrosobenzene dimer is prepared easily by reduction of *m*-trifluoromethylnitrobenzene with mild reducing systems such as ethylmercaptan in aqueous alkali, zinc in aqueous ammonium chloride, and even alcoholic sodium hydroxide. The reaction gives a mixture of reductive dimerization products from which the desired azodioxide can be isolated in 30–40% yield as described in Experimental.

## Experimental

**Reduction with Ethylmercaptan.**—Ethylmercaptan (1.2 moles) was added dropwise to a chilled mixture of *m*-trifluoromethylnitrobenzene (0.3 mole), water (400 cc.), and sodium hydroxide

(1) Part of this work was completed in the laboratories of the M. W. Kellogg Co. The data were acquired by the Minnesota Mining and Manufacturing Co. with the purchase of the Chemical Division of the M. W. Kellogg Co. in March, 1957.

(2) N. V. Sidgwick, "Organic Chemistry of Nitrogen," Oxford Press, London, 1942, p. 204.

(3) B. G. Gowenlock and W. Lüttke, *Quart. Rev.*, **12**, 321 (1958).

(4) N. Nakamoto and R. E. Rundle, *J. Am. Chem. Soc.*, **78**, 1113 (1956).

(5) D. L. Hammick, *J. Chem. Soc.*, 3105 (1931).

## TABLE I



N.M.R. DATA FOR

| H atom | $\tau^a$ | Mult. | $J^b$ |
|---|---|---|---|
| 2 | 1.57 | b | ... |
| 4 | 2.39 | s | ... |
| 5 | 2.38 | AB | 7.6 |
| 6 | 1.50 | AB | 7.6 |

$\phi^c$ for F atom of CF$_3$ = 63.62

b = broad
s = sharp
AB = type system[b]

[a] See ref. 6.   [b] See ref. 7.   [c] See ref. 8.

(2.5 moles) contained in a three-necked round-bottom flask fitted with a reflux condenser, stirrer, and dropping funnel. The dropping funnel was replaced by a thermometer and reaction was allowed to occur for an additional 24 hr. at 85°. The excess ethyl mercaptan and diethyl disulfide were removed by steam distillation. The residual aqueous alkaline mixture was extracted with benzene. The aqueous layer was discarded and the benzene layer was evaporated to dryness. The residue was dissolved in n-hexane and the solution passed through a 72 × 1 in. column filled with activated alumina. The column was developed with hexane. The first three 1-l. fractions contained 20 g. of sulfur-free white compound that melted at 48.5–49.0° after recrystallization from methanol. Fractions 4 and 5 contained 5 g. of a mixture of products, m.p. 45–60°. The infrared spectra of these fractions indicated that they were a mixture of the compound melting at 48.5–49.0° and the azoxy compound eluted next from the column. Fraction 6 contained 1.5 g. of a yellow compound (m.p. 127–129°). The compound was recrystallized from ethanol to give yellow crystals (m.p. 130–131°) that were identified as 4,4'-diethylmercapto-3,3'-ditrifluoromethylazoxybenzene by elemental analysis and by comparison of the infrared spectrum with those of similar azoxy compounds.[9] The compound gave a deep red-purple color when dissolved in concentrated sulfuric acid indicative of an aromatic azoxy containing alkyl mercapto-substituent in the para position.[9]

*Anal.* Calcd. for C$_{18}$H$_{16}$ON$_2$S$_2$F$_3$: C, 47.57; H, 3.55; S, 14.12. Found: C, 47.2; H, 4.0; S, 13.8.

Elemental analysis of the white compound melting at 48.5–49.0° indicated an empirical formula of C$_7$H$_4$ONF$_3$.

*Anal.* Calcd. for C$_{14}$H$_8$O$_2$N$_2$F$_6$: C, 47.98; H, 2.30; N, 8.00; O, 9.14; F, 32.55; mol. wt., 350. Found: C, 48.3; H, 2.49; N, 7.74; O, 8.98; F, 33.0; mol. wt., 356.

The molecular weight at 5° and at 80° was measured as 356 but the value decreased steadily when solvents of increasing boiling points were used, indicating that dissociation increased with temperature above 80°. The infrared spectrum and n.m.r. data for this compound are shown in Fig. 1 and Table I, respectively.

A sample of this compound (m.p. 48.5–49.0°) was distilled at atmospheric pressure (b.p. 295°) and showed no color formation in the vapor state or when melted. The distillate was crystallized from methanol in the form of long white thin needles (m.p. 44–46°), indicating that only little decomposition had occurred.

One gram of this compound (m.p. 48.5–49.0°) was reduced with zinc at reflux temperature for 4 hr. in 40 cc. of 10% aqueous hydrochloric acid. The solution was cooled to room temperature, made strongly alkaline, and then extracted with ether. The ether extract was dried with magnesium sulfate, separated by filtration, and evaporated to dryness. The residual oil was made

to react with acetic anhydride to give the corresponding amide. The product was crystallized from aqueous methanol and then from hexane in the form of white platelets (0.9 g., m.p. 102.5–103.5°). The compound was identified as m-trifluoromethylacetanilide (no depression in melting point when mixed with an authentic sample).

**Reduction with Zinc in Aqueous Ammonium Chloride.—**Powdered zinc (0.46 mole) was added slowly to a cold mixture of m-trifluoromethylnitrobenzene (0.16 mole), water (500 cc.), and ammonium chloride (0.28 mole) contained in a 1-l. three-necked round-bottom flask fitted with a stirrer, reflux condenser, and an adapter for addition of solids. The mixture was allowed to react at room temperature for 6 hr. A small amount of m-CF$_3$C$_6$H$_4$-NH$_2$·ZnCl$_2$ precipitated from solution, and was removed by filtration. The mother liquor was acidified with dilute aqueous hydrochloric acid and then extracted with ether. The ether extract was evaporated to dryness. The residual oil was crystallized from a methanol–water solution and 10 g. (36%) of m-trifluoromethylnitrosobenzene was isolated in the form of tiny slightly orange needles, m.p. 44–46°.

The aqueous acid layer from which m-trifluoromethylnitrosobenzene was removed by extraction with ether was made alkaline and re-extracted with ether. The ether layer was evaporated to dryness and the residue treated with acetic anhydride. The acetylated product was recrystallized from water. The compound (7 g., 22%) was isolated in the form of white platelets (m.p. 87–88°). The compound resolidified when a crystal of m-trifluoromethylacetamide, m.p. 102–103°, was added to the melt. This white solid remelted at 102–103°.

**Reduction with Alkaline Ethanol.—**A mixture of m-trifluoromethylnitrobenzene (0.18 mole), water (100 cc.), sodium hydroxide (0.6 mole), and ethanol (0.5 mole) was allowed to react at reflux temperature for 24 hr. to give a deep red solution. The solution was diluted with water and extracted with benzene. The aqueous layer was discarded and the organic layer was evaporated to dryness. The red crystalline residue was dissolved in hexane and separated by chromatography as described previously to give m-trifluoromethylnitrosobenzene in the form of orange tinted delicate needles (10.5 g., m.p. 48.0–48.5°).

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## On the Modified Oppenauer Oxidation

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The use of acidic reagents for oxidation of a hydroxyl group to a carbonyl function has sometimes failed with compounds containing basic nitrogen atoms,[2] particularly if the nitrogen is in the immediate vicinity of the hydroxyl. The difficulty is not necessarily circumvented by oxidation under the basic conditions of the Oppenauer procedure since the aluminum alkoxide is capable of complexing with the nitrogen[3,4a] and in some

(6) G. V. P. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(7) J. A. Pople, W. G. Schneider, and H. J. Bernstein. "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 119.

(8) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

(9) H. R. Davis, J. W. Copenhaver, W. E. Hanford, and H. F. Lederle, 121st National Meeting of American Chemical Society, Buffalo, N. Y., March, 1952, p. 66-K.

(1) Department of Chemistry, University of Western Ontario, London, Canada.

(2) *Inter alia* (a) quinine: P. Rabe, W. Naumann, and E. Kuliga, *Ann.* **364**, 345 (1909); (b) buphanamine: L. G. Humber and W. I. Taylor, *Can. J. Chem.*, **33**, 1268 (1955); codeine: F. Ach and L. Knorr, *Ber.*, **36**, 3070 (1903).

(3) (a) quinine: R. L. McKee and H. R. Henze, *J. Am. Chem. Soc.*, **66**, 2021 (1944); (b) 1,2-aminoalcohols: R. E. Lutz, R. H. Jordan, and W. L. Truett, *ibid.*, **72**, 4085 (1950); (c) *cis-* and *trans-*1-amino-2-indanols: R. E. Lutz and R. L. Wayland, *ibid.*, **73**, 1639 (1951).

TABLE I

THE MODIFIED OPPENAUER OXIDATION OF QUININE

| Reaction | Ketone, mole ratio to quinine | Base, mole ratio to quinine | Solvent | Temp. | Time, hr. | % Yield, crude product | % Quininone in product |
|---|---|---|---|---|---|---|---|
| 1 | Benzophenone, 5.0 | K–O–t-Bu, 2.5 | Benzene | R.t.[a] | 1 | 81 | 9–25 |
| 2 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | Benzene | R.t. | 0.5 | 82 | 82 |
| 3 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | Benzene | R.t. | 1 | 97 | 88 |
| 4 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | Benzene | R.t. | 12 | 88 | 96 |
| 5 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | Benzene | Reflux | 2 min. | 80 | 66 |
| 6 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | Benzene | Reflux | 10 min. | 85 | 100 |
| 7 | Fluorenone, 5.0 | K–O–t-Bu, 1.0 | Benzene | R.t. | 1 | 76 | 36 |
| 8 | Fluorenone, 5.0 | K–O–t-Bu, 0.1 | Benzene | R.t. | 1 | 73 | 2.7 |
| 9 | Benzophenone, 5.0 | K–O–t-Bu, 2.5 | t-BuOH | R.t. | 6 | 93 | 0 |
| 10 | Benzophenone, 5.0 | K–O–t-Bu, 2.5 | t-BuOH | Reflux | 0.5 | 92 | 1.8 |
| 11 | Benzophenone, 5.0 | K–O–t-Bu, 2.5 | t-BuOH | Reflux | 4.5 | 85 | 8 |
| 12 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | t-BuOH | R.t. | 4 | 93 | 2–3 |
| 13 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | t-BuOH | Reflux | 0.5 | 83 | 48 |
| 14 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | t-BuOH | Reflux | 4 | 92 | 91 |
| 15 | Quinone, 4.0 | K–O–t-Bu, 2.5 | Benzene | R.t. | 0.5 | 69 | 1.7 |
| 16 | Quinone, 4.0 | K–O–t-Bu, 2.5 | Tetrahydrofuran | R.t. | 1 | 72 | 0.8 |
| 17 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | Tetrahydrofuran | R.t. | 1 | 89 | 43 |
| 18 | Fluorenone, 5.0 | Al–(O–t-Bu)₃, 1.2 | Benzene | R.t. | 1 | 72 | 0 |
| 19 | Fluorenone, 5.0 | Al–(O–i-Pr)₃, 1.4 | Benzene | Reflux | 2 | 74 | 0 |
| 20 | Fluorenone, 5.0 | None | Benzene | R.t. | 1 | 78 | ... |
| 21 | Fluorenone, 5.0 | None | Benzene | R.t. | 1 | 80 | ... |
| 22 | Fluorenone, 5.0 | K–O–t-Bu, 2.5 | Me₂S → O | R.t. | 0.1 | 99 | 0 |

[a] R.t. = room temperature.

manner stabilizing the amino alcohol. To avoid these difficulties, Woodward substituted potassium t-butoxide for the aluminum alkoxide in the Oppenauer oxidation.[4] However, this modification, which is conducted at the reflux temperature of a benzene solution for several hours, is limited to the preparation of those carbonyl compounds not sensitive to heat and strong base.

Some time ago this problem arose in the course of work on amino alcohols among the *Amaryllidaceae* alkaloids. A study of the modified Oppenauer oxidation of quinine was made with the purpose of finding milder conditions for the reaction. Quinine was chosen because it is a typical amino alcohol not oxidized by the usual Oppenauer conditions[3a] but readily oxidized by the potassium t-butoxide–benzophenone modification,[4a] and because the yield of ketone, quininone, could be determined conveniently by ultraviolet spectroscopy (see Experimental). The results of the study are summarized in Table I.

The most significant finding was that use of the more rapid hydride acceptor, fluorenone,[5] permits the reaction time and temperature to be decreased considerably. Thus, oxidations can be carried out in benzene solution at room temperature in one-half to one hour (reactions 2 and 3) or within about five minutes at reflux temperature (reactions 5 and 6). With the more powerful but slower hydride acceptor, quinone,[5] no appreciable oxidation occurred at room temperature (reaction 15). As expected, attempts to use the weaker, complex-forming aluminum alkoxides at room temperature or at

reflux gave no oxidation (reactions 18 and 19). Furthermore, even with potassium t-butoxide, about 2.5 equivalents of base were required for rapid oxidation (compare reactions 7 and 8 with 3). The room temperature reactions were strongly inhibited by t-butyl alcohol (reaction 12), although the oxidation can be carried out in this solvent at reflux (reaction 14) if fluorenone is used. The rate of oxidation was faster in benzene (reaction 3) than in tetrahydrofuran (reaction 17) or dimethylsulfoxide (reaction 22).[6]

Since this work was completed, a number of oxidations have been done under these milder conditions, and some of these are listed in Table II. In spite of the strong base used there has been only one case of condensation to produce a fluorenylidene derivative (Table II, haemanthamine) and no case of ketone self condensation. Base-catalyzed β-elimination can take place as in the oxidation of montanine and coccinine, and some special ketonic systems (caranine) are oxidized further by fluorenone or air under the strongly basic conditions. The reactions are run in a nitrogen atmosphere in view of the ease of air oxidation of ketones in the presence of potassium t-butoxide.[7]

In general, good yields of oxidation products have been obtained (Table II). However, the large size of the fluorenone molecule, which must approach quite

(4) (a) R. B. Woodward, N. L. Wendler, and F. V. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945); (b) R. B. Woodward and E. C. Kornfeld, *ibid.*, **70**, 2513 (1948); (c) H. Rapoport, R. Naumann, E. R. Bissell, and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

(5) R. H. Baker and H. Adkins, *J. Am. Chem. Soc.*, **62**, 3305 (1940).

(6) D. J. Cram, M. R. V. Sahyun, and G. R. Knox [*J. Am. Chem. Soc.* **84**, 1734 (1962)] have found the use of dimethyl sulfoxide or tetrahydrofuran as solvent to increase the rate of several reactions. In the Oppenauer reaction benzene is superior to either of these solvents, probably for the same reason these authors suggest for the superiority of tetrahydrofuran over dimethyl sulfoxide in the Cope elimination; less solvation energy of the potassium quinine alkoxide has to be overcome in going to the transition state for hydride transfer to fluorenone.

(7) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

### TABLE II
#### OXIDATIONS BY THE MODIFIED OPPENAUER METHOD

| Compound Oxidized | Product | Yield, % |
|---|---|---|
| α-Dihydrocaranine | α-Dihydrocaranone | 65[a] |
| Caranine | a Phenanthridinium betaine | 86[b] |
| Dihydroundulatine | Epioxodihydroundulatine | 75[c] |
| Montanine | Dehydrococcinine | 60[d] |
| Coccinine | Dehydrococcinine | 35[d] |
| Dihydrobuphanamine | Oxodihydrobuphanamine | 58[e] |
| Dihydrohaemanthamine | Fluorenylideneoxodihydro-haemanthamine | ...[f] |
| Yohimbine | Yohimbinone | 51[g] |
| β-Yohimbine | Yohimbinone | 17[g] |
| Corynanthine | Yohimbinone | 18[g] |
| Deoxyajmaline | Deoxyajmalone | 85[h] |
| Dihydroambelline | Recovered starting material | 81[i] |
| Falcatine | Recovered starting material | ...[j] |
| Dihydrocrinine | Oxodihydrocrinine | 51[k] |
| Cholesterol | Δ[4]-3-Cholestenone | 44[l] |
| Crinamine | Recovered starting material | 45[i] |

[a] E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **79**, 2192 (1957). [b] H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *ibid.*, **77**, 5885 (1955). [c] E. W. Warnhoff and W. C. Wildman, *ibid.*, **82**, 1472 (1960). [d] Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960). [e] H. M. Fales and W. C. Wildman, *ibid.*, **26**, 881 (1961). [f] H. M. Fales, personal communication. [g] M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. LeHir, *Bull. soc. chim. France*, 637 (1961). [h] M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi, and E. Wenkert, *J. Am. Chem. Soc.*, **84**, 622 (1962). [i] E. W. Warnhoff, unpublished work. [j] W. C. Wildman, personal communication. [k] W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958). [l] Present work.

close to the hydroxyl bearing carbon for hydride transfer, makes the reaction subject to stringent steric requirements, and there are several examples of amino alcohols not oxidized under these conditions (Table II, dihydroambelline, crinamine, and falcatine). In some of these cases (crinamine[8] and dihydroambelline[9]) the chromic acid–pyridine reagent has proved a successful alternative.

The potassium *t*-butoxide need not be freshly prepared as long as it has been protected from moisture and carbon dioxide. Commercially available alkoxide[10] should meet these requirements. The use of sublimed potassium *t*-butoxide is indicated whenever the alcohol to be oxidized contains a group which might react with the hydroxide or carbonate invariably present in unsublimed material (yohimbine, β-yohimbine, corynanthine, Table II).

The method is most readily applied to amino alcohols which can be separated by acid extraction from the fluorenone–fluorenol mixture. However, nonbasic alcohols, *e.g.*, cholesterol, can be oxidized and purified by chromatography, distillation, or sublimation. During the reaction even at room temperature some fluorenone is cleaved by base to 2-biphenylcarboxylic acid and this must be taken into account in isolation of acidic oxidation products.

### Experimental

**Reagents.**—*t*-Butyl alcohol was distilled from sodium. Commercial fluorenone, benzophenone, and quinine were used without purification. Reagent grade benzene was dried over sodium.

(8) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960).
(9) P. Naegeli, E. W. Warnhoff, H. M. Fales, R. E. Lyle, and W. C. Wildman, *J. Org. Chem.*, **28**, 206 (1963).
(10) MSA Research Corporation, Callery, Pa.

**Typical Oxidation Procedure.**—Potassium metal (0.5 g., 0.012 g.-atom) was dissolved in 30 ml. of *t*-butyl alcohol. The excess alcohol was removed by distillation at atmospheric pressure and then at aspirator vacuum. The solid potassium *t*-butoxide was dried at 120–130° at aspirator vacuum for 15–30 min.

To the dry *t*-butoxide was added 1.62 g. (5.0 mmoles) of dry quinine, 40 ml. of dry benzene (tetrahydrofuran or dimethyl sulfoxide), 4.50 g. (25 mmoles) of dry fluorenone, and a magnetic stirring bar. The reaction mixture was immediately put under a nitrogen atmosphere and stirred (with or without heating) for the period specified in Table I. The reaction mixture turned an opaque brown on mixing. The oxidation was terminated by the addition of 30–50 ml. of water, whereupon the color lightened to an orange-yellow.

The reaction mixture was diluted with 30–50 ml. of ether, and the two phases were separated. The aqueous layer was washed with two portions of ether. The combined organic layers were extracted with four portions of 5% hydrochloric acid. The combined aqueous acid solutions were washed twice with ether and poured into a mixture of ice and concentrated ammonium hydroxide solution. The white precipitate was extracted with three portions of ether. The ether extract was washed three times with saturated sodium chloride when the last wash was neutral. The dried (magnesium sulfate) ether solution was evaporated at reduced pressure. The yield of product varied from 70–97%.

The per cent of quininone in the product was determined from the ultraviolet extinction coefficient in absolute ethanol at 360 mμ. At this wave length pure quinine had no absorption while quininone had ε 3760. This analytical procedure was shown to be accurate to ±1% by measurements on known mixtures of quinine and quininone.

In the case of the reactions run in *t*-butyl alcohol, most of the alcohol was evaporated at reduced pressure before addition of water and ether and work-up.

The product from reaction 4, Table I, was chromatographed on 30 g. of alumina. Benzene–hexane (1:1) and pure benzene eluted quininone, m.p. 99–104° (hot stage), after recrystallization from cyclohexane.

When a reaction was carried out for 1 hr. at room temperature exactly as described above except that the quinine was omitted, there was recovered from the basic aqueous layer after acidification 0.59 g. of 2-biphenylcarboxylic acid whose infrared spectrum in chloroform was identical with that of an authentic sample.

**Oxidation of Cholesterol.**—A mixture of the potassium *t*-butoxide prepared from 0.5 g. of potassium, 4.50 g. of dry fluorenone, 2.02 g. of dry cholesterol, and 40 ml. of dry benzene was put under nitrogen and stirred with a magnetic stirring bar for 1 hr. at room temperature. The reaction mixture was diluted with water and ether. The ether layer was separated, dried, and evaporated to leave 6.35 g. of yellow oil. Crystallization from cyclohexane removed 2.99 g. of fluorenone in three crops. The filtrate was then chromatographed on 100 g. of alumina. Pure benzene eluted Δ[4]-3-cholestenone which was recrystallized from cyclohexane to give 0.90 g. (44%), m.p. 80–82° undepressed on admixture with an authentic specimen.

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### Cleavage–Elimination of Diphenylmethane from 7,7-Diphenylbicyclo[3.2.0]hept-2-en-6-one in Base[1]

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During an investigation into the synthesis and chemistry of certain strained bicyclic and polycyclic systems, we had occasion to study various methods of removing the carbonyl group from the product of the cycloaddi-

(1) From the M. S. thesis of A. C. Kovelesky, Kansas State University, 1962.

tion of diphenylketene and cyclopentadiene.[2,3] The structure of this product has been established as 7,7-diphenylbicyclo[3.2.0]hept-2-en-6-one (I) by two independent degradative sequences.[3,4]

When the ketone I was subjected to the Huang-Minlon modification[5] of the Wolff–Kishner reduction, three compounds were isolated, a hydrocarbon along with a mixture of trans-3-benzhydrylcyclopentene-4-carboxylic acid (II) and a small amount of the hydrazide of II (III). The initial basic cleavage of the cyclobutanone portion of the bicyclic ketone undoubtedly results in the formation of the cis acid which under the conditions of the reaction is isomerized to the thermodynamically more stable trans acid II. II is the only acid isolated.
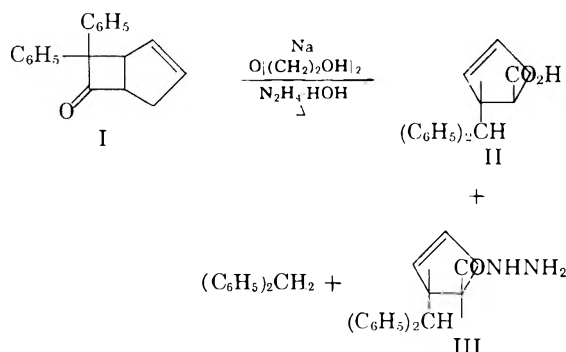


Identification of the hydrazide III was accomplished by elemental analysis, infrared and proton magnetic resonance[6] spectra. In the latter spectrum, the compound showed three exchangeable hydrogens when equilibrated with deuterium oxide at room temperature. III was also synthesized from the acid chloride of II or by refluxing the bicyclic ketone I with excess hydrazine hydrate, thereby establishing its stereochemistry and origin.

The hydrocarbon formed in 30–35% yield was found to be diphenylmethane by its boiling point, and infrared and proton magnetic resonance[6] spectra. The formation of diphenylmethane must result from a cleavage process, and it appeared reasonable that this might arise from a conjugate elimination[7] involving the trans acid II, or its carboxylate anion.

To test this proposal, trans-3-benzhydrylcyclopentene-4-carboxylic acid (II) was treated with alkali under conditions comparable to those employed in the modified Wolff–Kishner reduction. As the amount of diphenylmethane isolated in these experiments was small (See Table I in Experimental), it appears that a conjugate elimination from II or its anion is unlikely. Our efforts to prepare the pure cis isomer of acid II have

been unsuccessful.[8,9] It would have been of interest to examine the cis acid, cis-3-benzhydrylcyclopentene-4-carboxylic acid, to determine whether it might be the precursor to the diphenylmethane.[10]

## Experimental[11]

**7,7-Diphenylbicyclo[3.2.0]hept-2-en-6-one (I).**—This ketone was prepared according to the method of Smith and co-workers[3] by the cycloaddition of diphenylketene and cyclopentadiene, m.p. 86–88°, yield 75–88% (reported[3] m.p. 88–89°).

**Attempted Modified Wolff–Kishner Reduction of 7,7-Diphenylbicyclo[3.2.0]hept-2-en-6-one.**—To a solution of 4.9 g. (0.21 mole) of sodium in 200 ml. of diethylene glycol was added 18.3 g. (0.070 mole) of bicyclic ketone and 21 ml. of hydrazine hydrate. The mixture was refluxed for 10 hr. After cooling to room temperature, the reaction mixture was diluted with water, extracted with ether, and the combined extracts dried over sodium sulfate. Evaporation of the solvent and fractional crystallization of the residue from petroleum ether (b.p. 60–70°) gave 3.5 g. (30%) of diphenylmethane and 0.4 g. (2%) of trans-3-benzhydrylcyclopentene-4-carboxylic acid hydrazide. The diphenylmethane was identified by its infrared and n.m.r. spectra, and its b.p. of 131–135° (15 mm.) [reported[12] b.p. 141° (27 mm.)].

The trans-3-benzhydrylcyclopentene-4-carboxylic acid hydrazide was recrystallized from aqueous ethanol and sublimed at 130° (0.1 mm.), m.p. 159–160°. The n.m.r. spectrum indicated twenty protons with three labile ones as determined by equilibration at room temperature with deuterium oxide. The infrared spectrum had bands at 2.88, 3.0, and 6.1 $\mu$ attributable to the acylhydrazide structure IV.

*Anal.* Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.85; N, 9.59. Found: C, 78.31; H, 7.19; N, 9.70.

The basic aqueous layer remaining after ether extraction was acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were dried over sodium sulfate and the solvent evaporated to yield 12.0 g. (61%) of a colorless solid, m.p. 145–149°, whose infrared spectrum identified it as trans-3-benzhydrylcyclopentene-4-carboxylic acid. The trans acid could be purified by fractional crystallization from petroleum ether, followed by recrystallization from aqueous methanol, m.p. 148–149° (reported[13] m.p. 148–149°).

**trans-3-Benzhydrylcyclopentene-4-carboxylic Acid Hydrazide (IV). A.**—A solution of 3.6 g. (0.014 mole) of 7,7-diphenylbicyclo[3.2.0]hept-2-en-6-one in 25 ml. of 85% hydrazine hydrate was heated under reflux for 18 hr. After cooling to room temperature the solution was poured into water and extracted with ether. The combined ether extracts were washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 3.4 g. (86%) of the hydrazide. After recrystallization from aqueous ethanol and sublimation of 130° (0.05 mm.), the colorless solid melted at 157–159°. The infrared spectra of this and the material isolated from the Wolff–Kishner reduction was identical and mixture melting point showed no depression.

**B.** *trans*-3-Benzhydrylcyclopentene-4-carboxylic acid, 2.3 g. (0.008 mole), and thionyl chloride, 1.5 g. (0.012 mole), were allowed to stand at room temperature for 3 hr. and heated on a steam bath for 1 hr. Excess thionyl chloride was removed under reduced pressure and the residual acid chloride solidified. This was dissolved in 50 ml. of chloroform which was slowly added to 8.3 g. (0.017 mole) of hydrazine hydrate cooled in an

(2) H. Staudinger, *Ann.*, **356**, 94 (1907); H. Staudinger and E. Suter, *Ber.*, **53B**, 1092 (1920).

(3) L. I. Smith, C. L. Agre, R. M. Leekley, and W. W. Prichard, *J. Am. Chem. Soc.*, **61**, 7 (1939).

(4) J. R. Lewis, G. R. Ramage, J. L. Simonsen, and W. G. Wainwright, *J. Chem. Soc.*, 1837 (1937).

(5) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(6) The authors wish to express their appreciation to Dr. Donald P. Hollis, Varian Associates, for determination of the p.m.r. spectrum on the A-60 spectrometer.

(7) G. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955), have discussed a number of conjugate or 1,4-eliminations. Further examples of such eliminations are given by S. Searles, Jr., R. G. Nickerson, and W. K. Witsiepe, *J. Org. Chem.*, **24**, 1839 (1959), and examples cited therein.

(8) We wish to express our appreciation to Mr. Jerry Reed, a participant in a National Science Foundation Undergraduate Participation Program, for further efforts to obtain the cis acid II.

(9) We have not been able to duplicate the reported[3] hydroxide cleavage of 7,7-diphenylbicyclo[3.2.0]hept-2-en-6-one (I) in refluxing methanol to yield a mixture of acids II and III. Varying reaction times and amounts of reactants lead in almost every case to the isolation of only the trans acid III.

(10) The other possible conjugate elimination products, carbon dioxide and cyclopentadiene, have not been observed, probably due to the basic reaction medium. Efforts were made to find cyclopentadiene after acidification of the diluted reaction mixture but were without success.

(11) All melting points were taken on a Kofler hot stage. Boiling points are uncorrected. Infrared absorption spectra were determined on a Perkin-Elmer Model 137 double beam recording spectrophotometer.

(12) A. Klages and P. Allendorff, *Ber.*, **31**, 999 (1898).

(13) E. H. Farmer and M. O. Farooq, *J. Chem. Soc.*, 1925 (1938).

ice bath. After warming to room temperature, the two layers were separated, the aqueous layer extracted with chloroform, and the combined extracts dried over sodium sulfate. Evaporation of the chloroform yielded 2.1 g. (87%) of the hydrazide which after recrystallization from dilute ethanol and sublimation at 130° (0.1 mm.) gave colorless product, m.p. 157–159°.

*trans*-3-Benzhydrylcyclopentene-4-carboxylic Acid (III).—This acid was prepared by the hydrolytic fission of 7,7-diphenylbicyclo-[3.2.0]hept-2-en-6-one.[13] In the majority of experiments the melting points of the product indicated that almost pure *trans* acid was isolated rather than the mixture as reported by Farmer and Farooq.[13] Reducing the amount of base and reaction time did not alter the product melting point significantly. The pure *trans* acid was obtained by recrystallization once from petroleum ether then from methanol, m.p. 148–149°.

**Elimination Studies of** *trans*-3-Benzhydrylcyclopentene-4-carboxylic Acid.—The general procedure is exemplified by the following experiment. To a solution of 2.72 g. (0.0413 mole) of potassium hydroxide pellets in 50 ml. of diethylene glycol was added 4.5 g. (0.0162 mole) of *trans*-3-benzhydrylcyclopentene-4-carboxylic acid and the mixture heated at 180° for 2 days. After cooling and diluting with water the mixture was extracted with ether and the extracts dried over magnesium sulfate. Evaporation yielded the diphenylmethane.

The basic solution remaining after ether extraction was acidified with dilute hydrochloric acid, extracted with ether, and the combined extracts dried. Removal of the solvent yielded the residual starting *trans* acid.

The results of the elimination studies are given in Table I.

TABLE I

ELIMINATION STUDIES WITH *trans*-3-BENZHYDRYLCYCLOPENTENE-4-CARBOXYLATE SALTS

| Weight of acid, g. | Solvent | Reaction time, hr. | Temp. | Ph₂CH₂, g. (yield) | recovery acid, g. |
|---|---|---|---|---|---|
| 4.5[a] | Ethylene glycol | 48 | 180° | 0.1 (4%) | 4.2 |
| 4.2[a] | Diethylene glycol | 29 | 200–250° | .1 (4%) | 4.1 |
| 2.2[a] | Diethylene glycol | 8 | 250° | .05 (4%) | 2.0 |
| 5.4[a] | Diethylene glycol | 8 | 280–300° | .2 (6%) | 5.2 |
| 4.7[b] | Diethylene glycol | 9.5 | 200–250° | .2 (7%) | 4.3 |

[a] Reaction mixture contains an excess of potassium hydroxide (see Experimental). [b] Preprepared sodium salt.

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# Reaction of 1-Alkynes with Organometallic Compounds. XI. The Reactivity of Dialkylmagnesiums toward 1-Hexyne

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It was reported in the first paper[3] of this series that the relative reactivities toward 1-hexyne of diethyl ether solutions of alkylmagnesium halides (as deter-

mined from reaction half-lives) were in the order isopropyl > ethyl > *n*-propyl > methyl. This order was correlated with the number of β-hydrogens on the alkyl group, and it was suggested that this might be evidence for anionic hyperconjugation.[3,4]

The purpose of the present paper is to report results which show that the reactivities of diethyl ether solutions of some dialkylmagnesiums follow the same order as that observed for the Grignard reagents, and, therefore, the same correlation with the number of β-hydrogens applies. These dialkylmagnesium reactivities are in terms of rate constants corresponding to a two-step, competitive, consecutive, second-order mechanism. The agreement between this mechanism and the experimental data does not rule out the possibility that the mechanism is actually more complicated (for example, that dimers of the dialkylmagnesium may be present).

**Kinetic Theory.**—One would expect that the reaction of a dialkylmagnesium with 1-hexyne would involve at least two competitive, consecutive steps, and, if the dialkylmagnesium is dimerized in ether a four-step reaction would be involved. The nonlinear differential equations for any number of competitive, consecutive, second-order steps can be made linear and solved in terms of a time variable θ used by French.[5] For the reaction here under consideration, θ can be defined by

$$\theta = \int_0^t (b - P)\,dt \tag{1}$$

where $b$ is the initial concentration of 1-hexyne, and $P$ is the moles of hydrocarbon gas produced per liter of solution. $\theta$ can be calculated easily by graphical integration of the experimental curve for $P$ *vs.* $t$. For a single reaction of any number of competitive, consecutive, second-order steps the integrated rate law takes the form

$$P/a = f(\theta) \tag{2}$$

where, for the case here under consideration, $a$ is the initial concentration of alkyl groups (*i.e.*, twice the initial molarity of $R_2Mg$). According to equation 2, $P/a$ does not depend upon $a$ or $b$ explicitly. For the two-step reaction with rate constants $k_1$ and $k_2$, equation 2 is

$$\frac{P}{a} = \frac{1}{2(k_1 - k_2)}\,[(2k_2 - k_1)e^{-k_1\theta} - k_1 e^{-k_2\theta}] + 1 \tag{3}$$

Becker, *et al.*,[6] concluded, from vapor pressure data and from the kinetics of the reaction with benzonitrile, that diethylmagnesium dimerizes in tetrahydrofuran. If there are present in ethyl ether both monomers, $R_2Mg$, and dimers, $R_2Mg \cdot R_2Mg$, then the reaction with 1-hexyne would no longer be a single reaction. Equation 2, in general, would not hold, and $P/a$ could depend explicitly upon both $a$ and $b$.

## Results

The experimental results for the reactions of three dialkylmagnesiums with 1-hexyne in ethyl ether are shown as plots of $P/a$ *vs.* $\theta$ in Fig. 1 and 2. The values of $a$ and $b$ are given in Table I. Theoretical

(1) Parts IX and X, *J. Org. Chem.*, **27**, 760, 762 (1962).

(2) To whom inquiries should be sent.

(3) H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Am. Chem. Soc.*, **77**, 103 (1955).

(4) R. E. Dessy, J. H. Wotiz, and C. A. Hollingsworth, *ibid.*, **79**, 358 (1957).

(5) D. French, *ibid.*, **72**, 4806 (1950).

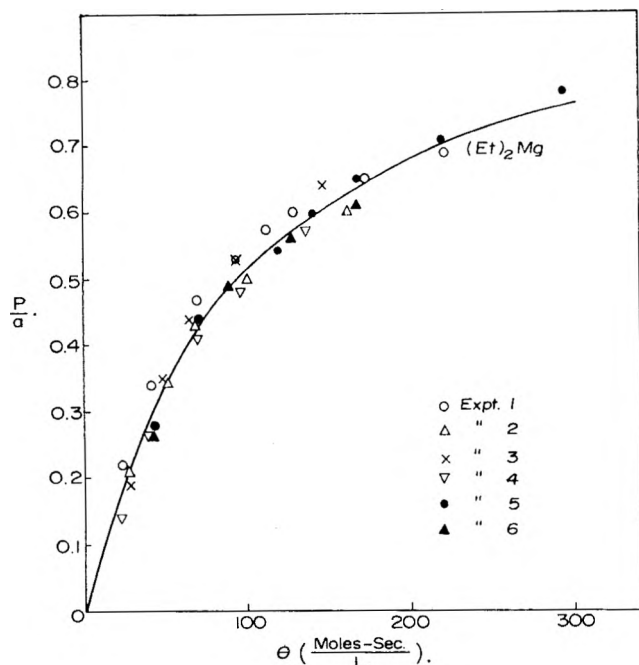(6) S. J. Storfer and E. I. Becker, *J. Org. Chem.*, **27**, 1868 (1962).

Fig. 1.—$P/a$ vs. $\theta$ for diethylmagnesium. Points, experimental. Curve, theoretical. Experiment numbers are those given in Table I.
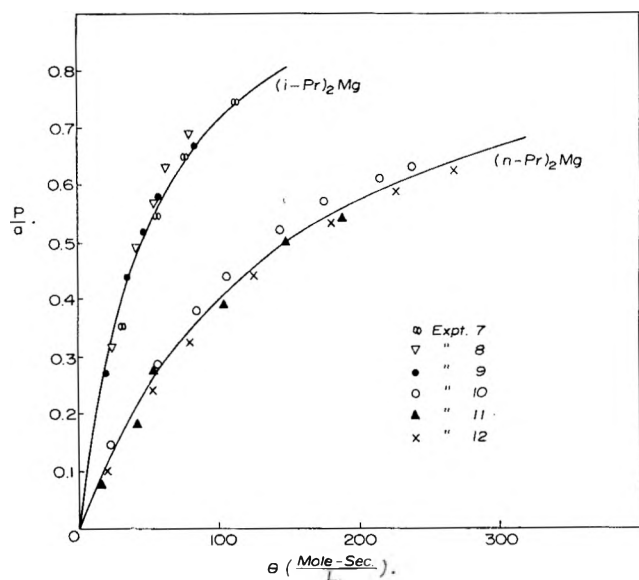


Fig. 2.—$P/a$ vs. $\theta$ for di-$n$-propylmagnesium and diisopropylmagnesium. Points, experimental. Curves, theoretical. Experiment numbers are those given in Table I.

curves given by equation 3 and with the values of $k_1$ and $k_2$ given in Table I are also shown in Fig. 1 and 2. There may be a small dependence on $a$ indicated, but in this respect the results are not conclusive. The results do show clearly that the order of reactivity is isopropyl > ethyl > $n$-propyl, in agreement with the order previously found for the corresponding Grignard reagents.[3] Also, it is clear that the reaction consists of at least two steps and that the first half of the alkyl groups are more reactive than the second half.

### Experimental

**Materials.**—1-Hexyne (Farchan) was passed over alumina and distilled [b.p. 68°, (745 mm.)].

#### TABLE I
INITIAL CONCENTRATIONS AND RATE CONSTANTS (33 ± 1°)

| Expt. | $R_2Mg$ | $a^a$ | $b^a$ | $k_1{}^b$ | $k_2{}^b$ |
|---|---|---|---|---|---|
| 1 | $Et_2Mg$ | 1.01 | 0.89 | $2.2 \times 10^{-2}$ | $3.0 \times 10^{-3}$ |
| 2 | $Et_2Mg$ | .57 | .52 | | |
| 3 | $Et_2Mg$ | .55 | .50 | | |
| 4 | $Et_2Mg$ | .46 | .41 | | |
| 5 | $Et_2Mg$ | .47 | .76 | | |
| 6 | $Et_2Mg$ | .17 | .76 | | |
| 7 | $(i\text{-}Pr)_2Mg$ | .44 | .60 | $4.0 \times 10^{-2}$ | $8.0 \times 10^{-3}$ |
| 8 | $(i\text{-}Pr)_2Mg$ | .55 | .50 | | |
| 9 | $(i\text{-}Pr)_2Mg$ | .39 | .39 | | |
| 10 | $(n\text{-}Pr)_2Mg$ | .88 | .74 | $1.3 \times 10^{-2}$ | $2.0 \times 10^{-3}$ |
| 11 | $(n\text{-}Pr)_2Mg$ | .54 | .50 | | |
| 12 | $(n\text{-}Pr)_2Mg$ | .70 | .65 | | |

$^a$ The value of $a$ is twice the initial molarity of $R_2Mg$ and $b$ is the initial molarity of 1-hexyne. $^b$ $k_1$ and $k_2$ are second-order constants expressed $1 \times mole^{-1} \times sec.^{-1}$.

The dialkylmagnesiums were prepared from the Grignard reagents by the addition of dioxane as described previously.[7] In all cases analysis showed that the resulting ethyl ether solution of dialkylmagnesium contained excess basic magnesium. In three separate preparations of diethylmagnesium the ratios of active dialkyl to total basic magnesium was 0.72, 0.73, and 0.77. The ratios of active dialkyl to total basic magnesium for the diisopropyl and the di-$n$-propyl were 0.85 and 0.90, respectively. Care was taken to keep moisture and oxygen from the starting materials and reagents. The alkyl bromides were freshly fractionally distilled; dioxane was fractionally distilled from sodium; the ether (Mallinckrodt, anhydrous, analytical reagent) was freshly opened and stored over sodium for several hours before use; the products were transfered under cover of prepurified nitrogen and stored in serum rubber capped bottles. Samples were removed by means of hypodermic syringes. All of the dialkylmagnesiums gave a negative bromide test with silver nitrate.

**Apparatus.**—The apparatus and method used to determine the rates by gas evolution were the same as those described in previous papers.[8,9] Special care was taken to prevent an increase in pressure within the apparatus when gas was evolving rapidly. This was a problem for reactions with a half-life of less than 4 min. An increase in pressure of 1 or 2 cm. was found to cause enough "hold up" of gaseous product (probably mostly in the condenser, which was charged with ice and alcohol or Dry Ice and acetone) to cause a significant decrease in the value obtained for $k_1$.

(7) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Am. Chem. Soc.* **78**, 1221 (1956).

(8) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Org. Chem.*, **20**, 1545 (1955).

(9) E. W. Smalley and C. A. Hollingsworth, *ibid.*, **27**, 760 (1962).

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## 3-Mercaptopropionamidine and
## S-2-Amidinoethyl Thiosulfuric Acid[1]

THOMAS P. JOHNSTON AND ANNE GALLAGHER

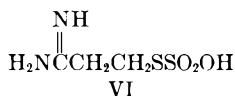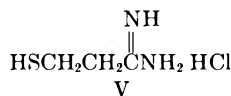*Southern Research Institute, Birmingham, Alabama*

Recently reported[2,3] syntheses of S-substituted mercaptoamidine derivatives attest interest in aminoalkane-

(1) This investigation was supported by the U. S. Army Research and Development Command under contract no. DA-49-193-MD-2028.

(2) L. Bauer and T. L. Welsh, *J. Org. Chem.*, **27**, 4382 (1962).

(3) G. Sosnovsky, P. Schneider, and E. Baltazzi, Abstracts of the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 3-O.

thiol analogs of this type as potential antiradiation drugs. This report concerns the conversion of 3-mercaptopropionitrile (I) in several steps to 3-mercaptopropionamidine hydrochloride (V) and S-2-amidinoethyl thiosulfuric acid (VI, inner salt).

$$\underset{V}{HSCH_2CH_2\overset{\overset{\displaystyle NH}{\|}}{C}NH_2\ HCl} \qquad \underset{VI}{H_2N\overset{\overset{\displaystyle NH}{\|}}{C}CH_2CH_2SSO_2OH}$$

Protection of the mercapto group was achieved by the immediate iodine oxidation of freshly distilled I to 3,3'-dithiobispropionitrile (II). The conversion of II to 3,3'-dithiobispropionamidine dihydrochloride (IV) was effected via uncharacterized diethyl 3,3'-dithiobispropionimidate dihydrochloride (III). Contamination of IV by partially changed bisnitrile as detected by CN absorption in the infrared was minimized by a prolonged reaction time for the formation of III in chloroform, a better solvent for this conversion than p-dioxane. The use of these solvents was suggested by a previously described bisamidine synthesis in which a mixture of the two was helpful.[4] The structure of IV was evident in the close resemblance of its infrared absorption spectrum to that of acetamidine hydrochloride.

An investigation of conditions for the catalytic hydrogenolysis of IV in neutral aqueous solution at 50 p.s.i. revealed that catalyst poisoning could be overcome by the use of an amount of 30% palladium on charcoal equal to at least 50% of the disulfide weight. Hydrogenolysis of IV under these conditions thus afforded the thiol V in high yield but was completely retarded or extremely slow when only 40% by disulfide weight of catalyst was used. A similar hydrogenolysis of the dimethyl ester of L-cystine dihydrochloride has been reported.[5] Hydrogenolytic reactions of other disulfides have been carried out by the use of "sulfactive" cobalt[6] and molybdenum[7] sulfide catalysts at elevated temperatures and relatively high pressures.

Sulfite cleavage of IV gave a mixture of products from which the nitroprusside-negative internal thiosulfate VI was separated by extraction with N,N-dimethylformamide. The structure of VI was confirmed by an infrared absorption spectrum showing thiosulfate bands typical of salts of this type.[8] The N,N-dimethylformamide-insoluble fraction, which was strongly nitroprusside-positive, apparently consisted mainly of salts of 3-mercaptopropionamidine and its oxidized form with sodium bisulfite. Treatment of these salts with hydrochloric acid and subsequent in vacuo evaporation gave a residue containing sodium chloride from which IV was extracted by concentrated hydrochloric acid in low yield.

### Experimental[9]

**3,3'-Dithiobispropionitrile.**—Freshly prepared and distilled 3-mercaptopropionitrile[10] (12.5 g., 0.143 mole) in 50 ml. of ethanol was titrated with 1 N iodine–potassium iodide solution (143 ml.). The solution was decolorized with sodium thiosulfate and brought to pH 6 with 10 N sodium hydroxide. The product

was extracted with chloroform (3 × 100 ml.), and the chloroform solution, washed with water (2 × 25 ml.) and dried over magnesium sulfate, was evaporated to dryness under reduced pressure. The residual oil, further dried in vacuo (oil pump) at 60° for 1 hr., quickly solidified to a hard, white, crystalline solid; yield of bisnitrile, 11.4 g. (92.5%); m.p. 49–51° (lit.[11] m.p. 48°). For analysis, a sample was recrystallized from ether as long, white needles with no change in melting point; $\bar{\nu}_{max}^{KBr}$ in cm.$^{-1}$: 2250 (s, CN).

*Anal.* Calcd. for $C_6H_8N_2S_2$: C, 41.83; H, 4.68; S, 37.22. Found: C, 42.08; H, 4.57; S, 37.5.

**3,3'-Dithiobispropionamidine Dihydrochloride.**—A cold (0°) solution of 3,3'-dithiobispropionitrile (2.18 g., 12.5 mmoles) in 10 ml. of chloroform containing 1.5 ml. (26 mmoles) of anhydrous ethanol was treated with anhydrous hydrogen chloride until 1.03 g. (28.0 mmoles) had been absorbed. This solution was refrigerated for 4 days. The solid that formed was collected by filtration under nitrogen, washed with ether (2 × 10 ml.), and dried in vacuo over phosphorus pentoxide and sodium hydroxide for 1 hr. The crude bisimidate dihydrochloride thus obtained was suspended in 15 ml. of anhydrous ethanol, and 5.2 ml. of a 9–10% solution of ammonia in ethanol was added. The resulting mixture was stirred at room temperature for 24 hr. The white solid was collected, washed with N,N-dimethylformamide (3 × 15 ml.) and then ethanol, and dried in vacuo over phosphorus pentoxide; yield of bisamidine dihydrochloride 2.21 g. (63%). Recrystallization of a small sample from ethanol gave white crystals for analysis; m.p. 182–183° dec.; $\bar{\nu}_{max}^{KBr}$ in cm.$^{-1}$: 1705 (s), 1685 (s), 1510 (m), 715 (m-s, broad) [—C(NH₂)(=NH₂)⊕].

*Anal.* Calcd. for $C_6H_{14}N_4S_2\cdot2HCl$: C, 25.79; H, 5.77; S, 23.00. Found: C, 26.12; H, 5.78; S, 23.0.

**3-Mercaptopropionamidine Hydrochloride (V).**—A solution of 3,3'-dithiobispropionamidine dihydrochloride (1.40 g., 5.00 mmoles) in water (25 ml.) was hydrogenated at an initial pressure of 50 p.s.i. in a Parr apparatus over 700 mg. of 30% palladium on charcoal, hydrogen absorption being complete within 4 hr. The catalyst was removed by filtration under nitrogen, and the colorless filtrate was evaporated to dryness in vacuo. The residual oil was dissolved in ethanol and the filtered solution evaporated to dryness in vacuo without heating. The white crystalline residue, further dried in vacuo over phosphorus pentoxide, weighed 1.38 g., melted at ca. 100° dec., and assayed 89% as V by iodometric titration; $\bar{\nu}_{max}$ in cm.$^{-1}$: 2540 (w, SH), 1680 (s), 1500 (m), 720 (s, broad) [—C(NH₂)(=NH₂)⊕]. (The somewhat low thiol content is attributed to oxidation of V during isolation and handling rather than incomplete hydrogenolysis.)

*Anal.* Calcd. for $C_3H_8N_2S\cdot HCl$: C, 25.62; H, 6.45; N, 19.76; S, 22.80. Found: C, 25.80; H, 6.48; N, 19.92; S, 22.3.

**S-2-Amidinoethyl Thiosulfuric Acid (VI).**—To a mixture of 3,3'-dithiobispropionamidine dihydrochloride (2.32 g., 8.30 mmoles) and sodium acetate trihydrate (2.25 g., 16.6 mmoles) was added 12.5 ml. of a 10% solution of sulfur dioxide in water. The resulting clear solution was stored in a stoppered flask at room temperature for 10 days and then evaporated to dryness under reduced pressure. The gummy residue was triturated in ethanol (3 × 5 ml.) and the resulting white solid dried in vacuo over phosphorus pentoxide. The dried solid (3.02 g.) was extracted with N,N-dimethylformamide (5 × 25 ml.), leaving an insoluble residue (1.36 g., after being dried). The extract was evaporated to dryness in vacuo, and the oily residue was reevaporated three times after successive additions of ethanol. The resulting white crystalline residue was further dried in vacuo over phosphorus pentoxide; yield of VI, 1.66 g. (54%). For analysis, a small sample was recrystallized from methanol with Norit treatment; m.p. 148–150° dec.; $\bar{\nu}_{max}^{KBr}$ in cm.$^{-1}$: 1685 (s), 1500 (m-w), 705 (m-s) [—C(NH₂)(=NH₂)⊕], 1235 (s), 1165 (s), 1010 (s), 640 (m-s) [—SSO₃⊖].

*Anal.* Calcd. for $C_3H_8N_2O_3S_2$: C, 19.55; H, 4.37; N, 15.26; S, 34.80. Found: C, 19.76; H, 4.56; N, 15.31; S, 35.1.

(4) S. M. McElvain and J. P. Schroeder, *J. Am. Chem. Soc.*, **71**, 40 (1949).

(5) L. Zervas and D. M. Theodoropoulas, *ibid.*, **78**, 1359 (1956).

(6) F. K. Signaigo, U. S. Patent 2,402,686 (1946).

(7) K. Itabashi, *Yūki Gōsei Kagaku Kyokai Shi*, **18**, 48 (1960) [*Chem. Abstr.*, **54**, 6611 (1960)] and subsequent papers.

(8) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **27**, 2452 (1962).

(9) Melting points are uncorrected.

(10) L. Bauer and T. L. Welsh, *J. Org. Chem.*, **26**, 1443 (1961).

(11) R. Stroh, German Patent 894,244 (1953).

## The Dipole Moments and Structure of Cyclic Compounds: Lactones, Lactams, Anhydrides, Carbonates, Carbamates, Ureides, and Imides

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The dipole moments of cyclohexane-1,3- and 1,4-lactone, cyclohexane-1,3-carbonate, and 1,3-ureide were measured to complete a series of moments of imides,[2-3] lactams,[4] and carbamates.[5] Comparisons between the $-\overset{H}{\underset{}{N}}-$ and $-O-$ analog and within groups between five- and six-membered ring compounds are given.

### Results and Discussion

Table I gives the results of the measurements and Table II lists the dipole moments for related compounds. With one exception, the six-membered ring compounds have higher moments than the five-membered ring compounds. Two reasons for this were discussed in previous papers,[1,4] namely, the larger angles between the main dipoles in the five-membered ring compounds and the opposition of the $N^+O^-$ dipoles to the carbonyl resultant in these compounds.

The difference between the dipole of the five- and the six-membered ring compounds is greatest in the case of anhydrides and imides, being around 1.1 D.; it is about 0.4 D. for carbonates, about 0.3 D. for lactams and ureides, and about 0.1 D. for lactones and carbamates. The larger values for anhydrides and imides as compared with the other five types of compounds is due to the fact that carbonyl groups have higher dipoles than ether, N–H, or N–C groups, so the difference in angle has a larger over-all effect. Another reason the difference is less in case of carbonates, carbamates, ureides, lactones, and lactams is that in these compounds the dipoles in the forms with a separation of charge augment the main carbonyl moment and they do it more in the five-membered ring compounds because the angle is more acute.

Lactones have higher moments than lactams and this does not result from a greater contribution of the forms with a separation of charge, for the carbonyl stretching frequencies are greater in lactones, indicating the C=O in these compounds has more double bond character and, therefore, less contribution from resonance forms with a separation of charge.

| Cyclohexane-1,3 | Infrared C=O in cm.$^{-1}$ (KBr) |
|---|---|
| Lactone | 1767 |
| Lactam | 1669 |
| Cyclohexane-1,4 | |
| Lactone | 1730 |
| Lactam | 1669 |

(1) Present address: School of Pharmacy, Chelsea College of Science and Technology, Chelsea, London. Requests for reprints should be addressed to W. D. Kumler at San Francisco.

(2)(a) C. M. Lee and W. D. Kumler, *J. Am. Chem. Soc.*, **83**, 4586 (1961); (b) C. M. Lee and W. D. Kumler, *ibid.*, **84**, 565 (1962).

TABLE I

DIPOLE MOMENTS IN DIOXANE AT 30°

**Cyclohexane-1,3-lactone**

| | $\omega_{12}$ | $\epsilon_{12}$ | $\nu_{12}$ |
|---|---|---|---|
| | 0.00 | | |
| | .0007332 | 2.22784 | 0.97427 |
| | .0010766 | 2.23341 | .97417 |
| $\mu = 4.37 \pm 0.04$ D. | .0026900 | 2.26499 | .97377 |
| | .0032037 | 2.27278 | .97362 |
| | .0041664 | 2.29204 | .97347 |

$\epsilon = 2.21376$  $\nu_1 = 0.97442$  $P_{2_0} = 415.05$  Mol. wt. =
$\alpha = 18.72711$  $\beta = -0.23851$  $P_E = 32.23$  126.16
calcd.

**Cyclohexane-1,4-lactone**

| | | | |
|---|---|---|---|
| | 0.00 | 2.20961 | 0.97442 |
| | .0009112 | 2.22741 | .97417 |
| | .0018368 | 2.24633 | .97397 |
| $\mu = 4.50 \pm 0.03$ D. | .0023417 | 2.25592 | .97377 |
| | .0029836 | 2.26996 | .97367 |
| | .0036619 | 2.28237 | .97357 |
| | .0043407 | 2.29453 | .97347 |

$\epsilon_1 = 2.20969$  $\nu_1 = 0.97439$  $P_{2_0} = 438.70$  Mol. wt. =
$\alpha = 19.78195$  $\beta = -0.22847$  $P_E = 32.23$  126.16
calcd.

**Cyclohexane-1,3-carbonate**

| | | | |
|---|---|---|---|
| | 0.00 | 2.21996 | 0.97391 |
| | .004128 | 2.21475 | .97385 |
| | .0009413 | 2.22904 | .97381 |
| $\mu = 6.14 \pm 0.03$ D. | .0026349 | 2.28408 | .97371 |
| | .0037361 | 2.32012 | .97357 |
| | .0040934 | 2.33133 | .97347 |

$\epsilon_1 = 2.20001$  $\nu_1 = 0.97391$  $P_{2_0} = 790.54$  Mol. wt. =
$\alpha = 32.05873$  $\beta = -0.09527$  $P_E = 34.02$  142.16
calcd.

**Cyclohexane-1,3-ureide**

| | | | |
|---|---|---|---|
| | 0.00 | 2.20353 | 0.97357 |
| | .0003070 | 2.20825 | .97328 |
| | .0006980 | 2.21200 | .97308 |
| $\mu = 3.69 \pm 0.05$ D. | .0020344 | 2.22896 | .97308 |
| | .0021452 | 2.22972 | . . . |

$\epsilon_1 = 2.20402$  $\nu_1 = 0.97336$  $P_{2_0} = 311.03$  Mol. wt. =
$\alpha = 12.26629$  $\beta = -0.30312$  $P_E = 37.66$  140.19
calcd.

This higher moment of lactones is due to the ether moment being in a direction which augments the carbonyl moment, while in lactams the $-NH$ moment to some extent opposes the carbonyl moment.

Carbonates have higher moments than ureides and the same reasons apply here. The infrared shows that the carbonates have higher carbonyl frequencies than the ureides,

| | |
|---|---|
| Cyclohexane-1,3-carbonate | 1724 cm.$^{-1}$ |
| Cyclohexane-1,3-ureide | 1669 cm.$^{-1}$ |

so there is more resonance and contribution of forms with a separation of charge in the ureides but the other effects mentioned above overcome this and the higher moments for carbonates result.

(3) C. M. Lee and W. D. Kumler, *ibid.*, **84**, 571 (1962).
(4) C. M. Lee and W. D. Kumler, *ibid.*, **83**, 4593 (1961).
(5) C. M. Lee and W. D. Kumler, *ibid.*, **83**, 4596 (1961).

TABLE II

| Anhydride | Lactone | Carbonate | Carbamate | Lactam | Ureide | Imide |
|---|---|---|---|---|---|---|
| **5-membered** | | | | | | |
| Succinic | Butyro | Ethylene | Ethylene | Butyro | Ethylene | Succinic |
| $4.22^a$ | $4.09^b$ | $4.80^c$ | $5.07^d$ | $3.55^f$ | $3.94^h$ | $1.47^i$ |
| **6-membered** | | | | | | |
| Glutaric | Valero | Trimethylene | Trimethylene | Valero | Trimethylene | Glutaric |
| $5.31^e$ | $4.22^b$ | $5.21^c$ | $5.10^d$ | $3.83^f$ | $4.22^h$ | $2.58^i$ |
| **6-membered** | | | | | | |
| Cyclohexane-1,3 | Cyclohexane-1,3 | Cyclohexane-1,3 | Cyclohexane-1,3 | Cyclohexane-1,3 | Cyclohexane-1,3 | Cyclohexane-1,3 |
| $4.97^e$ | 4.37 | 6.14 | $5.64^d$ | $3.73^g$ | 3.69 | $2.89^i$ |
| | Cyclohexane-1,4 | | Cyclohexane-1,4 | Cyclohexane-1,4 | | |
| | 4.50 | | $5.60^d$ | $4.24^g$ | | |

$^a$ G. Rau and N. Ansatanarayanan, *Proc. Indian Acad. Sci.*, **5A**, 185 (1937). $^b$ Benzene, 25°; R, Huisgen and H. Ott, *Tetrahedron*, **6** 253 (1959). $^c$ Benzene, 25°; R. P. Steward and E. C. Vierira, *J. Chem. Phys.*, **62**, 127 (1958). $^d$ C. M. Lee and W. D. Kumler, *J. Am. Chem. Soc.*, **83**, 4596 (1961). $^e$ C. M. Lee and W. D. Kumler, *J. Org. Chem.*, **27**, 2055 (1962). $^f$ Benzene, 25°; R. Huisgen and H. Walz, *Chem. Ber.*, **89**, 2616 (1956). $^g$ C. M. Lee and W. D. Kumler, *J. Am. Chem. Soc.*, **83**, 4593 (1961). $^h$ Unpublished data; Brian Loader, L. E. Sutton, and W. D. Kumler. $^i$ C. M. Lee and W. D. Kumler, *J. Am. Chem. Soc.*, **83**, 4586 (1961).

Anhydrides have higher moments than imides and here the same factors will be operating.

Compounds with nitrogen in the ring, namely, the imides, ureides, and lactams occupy the seventh, sixth, and fifth positions.

Five membered:
carbamate > carbonate > anhydride > lactone > ureide > lactam > imide

Six membered:
anhydride > carbonate > carbamate > lactone > ureide > lactam > imide

Six membered, 1,3-bridge:
carbonate > carbamate > anhydride > lactone > lactam > ureide > imide

Lactones are always in the fourth position with anhydrides third or first and carbonate second or first. Thus, in general, the compounds with oxygen in the ring have higher moments than those with nitrogen. The carbamate with both oxygen and nitrogen in the ring might be expected to be intermediate, but actually is near the front of the order being first, second, and third. The reason for this probably is that most of the plus charge in the forms with a separation of charge is confined to the nitrogen which augments the resultant of the ether and the carbonyl dipoles, giving rise to a high moment.

#### Experimental

All dipole moments were measured in dioxane at 30° and calculations were made using the equation and method of Halverstadt and Kumler.[6]

(6) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(7) H. K. Hall, Jr., M. K. Brandt, and R. M. Mason, *ibid.*, **80**, 6412 (1958).

## Diels–Alder Adducts of Hexachlorocyclopentadiene with Mono- and Divinyl Substituted Benzenes

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During the course of investigations aimed at developing a relationship between the structure and fire retardancy of halogen-containing compounds in polymeric systems, it was necessary to prepare several examples of the products derived from hexachlorocyclopentadiene by the Diels–Alder reactions with mono- and divinyl derivatives of substituted benzenes. This report describes the preparation of some of these compounds[1,2]; their use in polymeric systems is described in a previous publication.[3]

The Diels–Alder reaction proceeded with considerable ease in each of the cases studied; it was found that the styrene adduct previously described[4,5] is dimorphic. The reaction of commercial divinylbenzene with hexachlorocyclopentadiene gave rise to the two bis-adducts expected from the analysis of the starting isomeric divinylbenzenes. In addition, the commercial material contained isomeric ethylstyrenes, and from the bis-adduct reaction mixtures it was also possible to isolate the mixture of isomeric adducts of the ethylstyrenes. The pure bis-adduct from 1,2-divinylbenzene was prepared to determine the steric requirements imposed by the presence of two "norbornenyl" groups *ortho* to each other on the benzene ring. The yield of product indicates that the formation of the *ortho* product is not severely hindered.

(1) C. W. Roberts, U. S. Patent 2,952,711 (September 13, 1960).

(2) C. W. Roberts and D. H. Haigh, U. S. Patent 2,952,712 (September 13, 1960).

(3) C. W. Roberts, U. S. Patent 2,976,842 (January 10, 1961).

(4) P. B. Polen, M. Kleiman, and H. G. Fechter, U. S. Patent 2,673,172 (March 23, 1954).

(5) S. H. Herzfeld, R. E. Lidov, and H. Bluestone, U. S. Patent 2,606,910 (August 12, 1952).

## TABLE I

### DIELS-ALDER ADDUCTS OF HEXACHLOROCYCLOPENTADIENE WITH MONO- AND DIVINYL SUBSTITUTED BENZENES

| Substituent R | Starting compound | Yield, % | M.p., °C | Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|---|
| H | Styrene[a] | 80 | 58–59 71.5–72.5[b] | ... | ... | .. | .. | ... | ... |
| ar-CH₃— | Vinyltoluenes[c] | 94 | 163.5 (0.8[d] mm.) | 43.01 | 43.29 | 2.58 | 2.65 | 54.41 | 54.25 |
| ar-C₂H₅— | Ethylstyrenes[e] | 75 | 194 (2.2[f] mm.) | 44.48 | 44.62 | 2.99 | 2.90 | 52.53 | 52.42 |
| 4-t-C₄H₉— | 4-t-Butylstyrene[g] | 93 | 103.5–104 | 47.15 | 47.10 | 3.72 | 3.83 | 49.13 | 48.87 |
| 2,4-Cl₂— | 2,4-Cl₂-styrene[h] | 35 | 127–128 | 35.02 | 35.05 | 1.36 | 1.46 | 63.62 | 63.13 |
| 2-(C₇H₃Cl₆)[i] | 1,2-Divinylbenzene[j] | 82 | 121–121.5 | 35.54 | 35.64 | 1.49 | 1.54 | 62.96 | 62.45 |
| 3-(C₇H₃Cl₆)[i] | 1,3-Divinylbenzene[k] | 90 | 213–215 | 35.54 | 35.35 | 1.49 | 1.54 | 62.96 | 62.45 |
| 4-(C₇H₃Cl₆)[i] | 1,4-Divinylbenzene[k] | 85 | 291 | 35.54 | 35.72 | 1.49 | 1.51 | 62.96 | 62.20 |

[a] The Dow Chemical Co. [b] Ref. 4, reported m.p. 73.7–74.5°. The compound isolated here was shown to be dimorphic; the compound recrystallized from heptane showed the indicated melting points. After melting at the lower temperature the compound resolidified and melted again at the higher temperature. [c] The Dow Chemical Co., an isomeric mixture containing 35% meta and 65% para compounds. [d] B.p., $n^{25}D$ 1.5828. [e] Mixed ethylstyrenes contained to 30% in the isomeric mixture of divinylbenzene (see footnote k); 30% meta and 70% para isomer distribution. Yields based upon original available ethylstyrenes. [f] B.p., $n^{25}D$ 1.5750. [g] Prepared by dehydration of 1-(4-t-butylphenyl)ethanol; b.p. 65–70° (6 mm.), $n^{25}D$ 1.5245. D. T. Mowry, M. Renoll, and W. F. Huber, J. Am. Chem. Soc., 68, 1105 (1946), reported b.p. 77–100° (14 mm.), $n^{22}D$ 1.5245. [h] From a mixture of isomeric dichlorostyrenes; yield based upon available 2,4-dichlorostyrene (45% in original mixture). [i] C₇H₃Cl₆ represents the substituent (1,4,5,6,7,7-hexachloro-5-norbornen-2-yl). [j] Prepared according to the published procedure, J. O. Halford and B. Weissmann, J. Org. Chem., 17, 1646 (1952), b.p. 78–79° (16 mm.). [k] The Dow Chemical Co. divinylbenzene; contains 55% divinyl compounds of which 65% is the 1,3-isomer. Yields in the 1,3- and 1,4-divinylbenzene reaction are based on potential available isomer.

### Experimental[6]

Most of the preparations were run in a similar fashion; typical syntheses are described for the reaction of commercial divinylbenzene with hexachlorocyclopentadiene and 4-t-butylstyrene with hexachlorocyclopentadiene. Where isomeric mixtures of products were obtained or when a pure isomer was produced, infrared analysis was used for analysis of isomeric purity.

**Preparation of 5-(4-t-Butylphenyl)-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene.**—A solution of 273 g. (1 mole) of hexachlorocyclopentadiene (Hooker) in 500 ml. of n-heptane was heated to reflux and 160 g. (1 mole; purity 90–95%) of 4-t-butylstyrene was added dropwise during 1 hr. The resulting mixture was heated under reflux for 70 hr. and then chilled. The resulting precipitate was removed by filtration and recrystallized from n-hexane to give 333 g. of product, m.p. 103.5–104°. The combined filtrates, on evaporation, gave additional product which, when recrystallized from n-hexane, gave 73.5 g., m.p. 103.5–104°, a 93% yield based on 100% 4-t-butylstyrene or nearly a quantitative yield based on estimated purity of the 4-t-butylstyrene used.

**Preparation of 1,4-Bis(1,2,3,4,7,7-hexachlorobicyclo[2.2.1]-hept-2-en-6-yl)benzene and 1,3-Bis(1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-en-6-yl)benzene (Fractional Crystallization and Method I).**—A mixture of 900 g. (3.3 moles) of hexachlorocyclopentadiene, 264 g. (55% divinylbenzene, 45% ethylstyrene—70% para, 30% meta; approximately 3.3 moles of vinyl groups) and 1 l. of anhydrous toluene was allowed to stand at room temperature for 72 hr.; the mixture then was warmed and heated under reflux for 4 hr. and allowed to cool to room temperature and stand overnight. The precipitated solid was removed by filtration and the mother liquor partially evaporated at room temperature under vacuum; additional crops of crystalline products were obtained in this fashion. A total yield of solid product was obtained representing an 85% yield of bis-adducts of the isomeric divinylbenzenes. From this mixture was isolated a pure sample of each of the pure para and pure meta isomers (see Table I) by fractional crystallizations from mixtures of toluene and heptane; the pure isomers which resulted were recrystallized from 1,2-dibromoethane. The infrared spectra[6] of these pure isomeric compounds established the identity of the para and meta isomers, "using the well known correlation of the summation bands in the 1650–2000-cm.⁻¹ region.[7] The spectra were obtained as Nujol mulls. The isomer, m.p. 291°, showed weak absorption at 1910 cm.⁻¹, a very weak absorption at 1790 cm.⁻¹, and no other absorption in the 1700–200-cm.⁻¹ region; this is very typical of the para-disubstituted phenyl structure.

The isomer, m.p. 213–215°, showed three weak absorptions at 1940 cm.⁻¹, 1870 cm.⁻¹, and 1790 cm.⁻¹, and no other significant absorption in the 1700–200-cm.⁻¹ region; this is very typical of the meta-substituted phenyl structure or the 1,3,5-trisubstituted phenyl structure; in these examples the latter structure is ruled out."

The mother liquors from several preparations of the bis-adducts were combined and evaporated to dryness under reduced pressure. The oily residue was distilled under reduced pressure to give the adducts of the isomeric meta- and para-ethylstyrenes (see Table I).

The experimental procedure for the preparation of the other adducts listed in Table I varied primarily in the duration of reflux. In most instances the best yields of product are obtained after a 24- to 48-hr. reflux time.

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## Condensation Derivatives in Corticosteroid Side Chains. IV. Aldosterone 20,21-Cyclic Acetals[1,2]

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In order to account for the low intensity of the 20-ketone band in the infrared spectrum of aldosterone, Ham, et al.,[3] suggested at autometic 20,21-dihydroxy-11,18;18,20-bisepoxide form (I) in equilibrium with the ketol–aldehyde and ketol–hemiacetal forms. Others[4] proposed a hydrogen bond between the 18-hydroxyl and the 20-ketone.

Now we wish to report the preparation of aldosterone acetals doubtless recognized as derivatives of form I. Interchange reaction between aldosterone and acetone diethyl acetal, carried out in a suitable solvent in the

(1) Previous paper in this series, III, *Gazz. chim. ital.*, in press.

(2) This paper represents a part of the Round Table contribution by R. Gardi at the International Congress on Hormonal Steroids, Milan, May 14–19, 1962 (Excerpta Medica, International Congress Series No. 51, p. 57).

(3) E. A. Ham, R. E. Harmon, N. G. Brink, and L. H. Sarett, *J. Am. Chem. Soc.*, 77, 1637 (1955).

(4) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. Van Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, 37, 1163 (1954).
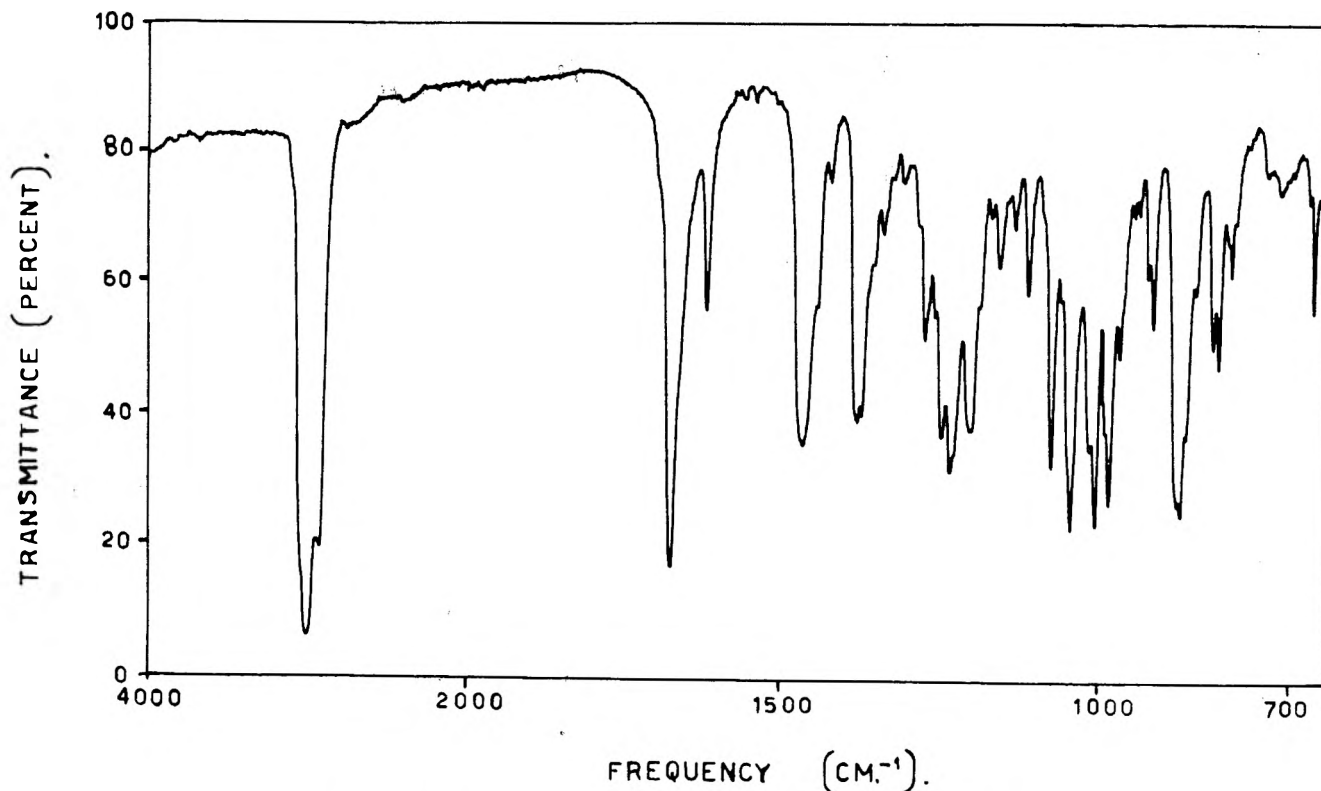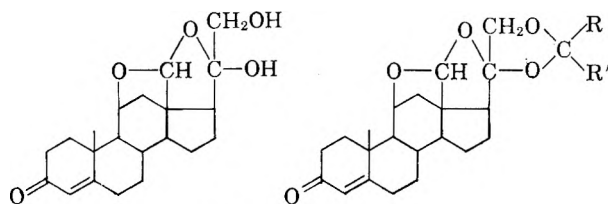
(6) Analytical data kindly supplied by S. Shrader. Infrared spectra and interpretations by W. J. Potts.

(7) C. W. Young, R. B. DuVall, and N. Wright, *Anal. Chem.*, 23, 709 (1951).

Fig. 1.—Infrared spectrum (Nujol mull) of aldosterone 20,21-acetonide (IIa).

IIa. R = R' = CH₃

b. R = R' = (CH₂)₄

c. R = H; R' = C₆H₅

presence of an acid catalyst,[5] gave in satisfactory yield a product, which afforded analytical data in agreement with the formula of an acetal $C_{24}H_{32}O_5$. Its infrared spectrum (Fig. 1) showed lack of hydroxyl and 20-carbonyl bands, clearly supporting the structure of 20,21-acetonide (IIa). In a similar manner we prepared the corresponding 20,21-cyclopentylidene and benzylidene derivatives (IIb and IIc).

The new acetals proved to be stable to base, remaining unchanged after refluxing in methanolic $N$ potassium hydroxide while, by hydrolysis with aqueous hydrochloric acid in dioxane, they readily regenerated aldosterone. The possible usefulness of such compounds in protecting both hemiacetal and ketol groups of aldosterone is apparent.

The results of the interchange reactions between aldosterone and trialkyl ortho esters[6] will be reported later.

### Experimental[7]

**Aldosterone 20,21-Acetonide (IIa).**—To an anhydrous boiling solution of 5 ml. of acetone diethyl acetal and 3 mg. of pyridine

(5) *Cf.* R. Gardi, R. Vitali. and A. Ercoli. *J. Org. Chem.*, **27**, 668 (1962).

(6) *Cf.* R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Letters.* 448 (1961).

$p$-toluenesulfonate in 300 ml. of benzene, 300 mg. of aldosteron was added and the mixture was heated with rapid solvent distillation for 20 min. After complete solvent evaporation under vacuum, digestion with ether–petroleum ether yielded 170 mg. of IIa, m.p. 227–232°. One crystallization from ethanol raised the melting point to 235–237°, $[\alpha]^{23}D$ +170° (di); $\lambda_{max}^{EtOH}$ 240–241 m$\mu$ ($\epsilon$ 16.000); $\nu_{max}^{Nujol}$ 1672, 1618, 1076, 1045, 1006, 985, 917, 871 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{32}O_5$; C, 71.97; H, 8.05. Found: C, 71.86; H, 8.03.

By reaction of aldosterone with cyclopentanone diethyl acetal and benzaldehyde diethyl acetal, carried out according to the above described procedure, and followed by chromatography on Florisil, we prepared the following compounds, respectively.

**Aldosterone 20,21-cyclopentanonide (IIb)**, m.p. 202–205°e $[\alpha]^{23}D$ +162° (di); $\lambda_{max}^{EtOH}$ 241 m$\mu$ ($\epsilon$ 15.9C0); $\nu_{max}^{Nujol}$ 1672, 1622, 1045, 1015, 985, 966, 928, 876, 865 cm.$^{-1}$.

*Anal.* Calcd. for $C_{26}H_{34}O_5$; C, 73.21; H, 8.04. Found: C, 72.94; H, 8.05.

**20,21-Benzylidenealdosterone (IIc)**, m.p. 224–226°, $[\alpha]^{23}D$ +115° (di); $\lambda_{max}^{EtOH}$ 240–241 m$\mu$ ($\epsilon$ 17.000); $\nu_{max}^{Nujol}$ 1675, 1619, 1090, 1052, 1011, 985, 965, 886, 867 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{32}O_5$; C, 74.94; H, 7.19. Found: C, 74.75; H, 7.21.

**Acid Hydrolysis.**—The following example is given to describe the acid hydrolysis of the acetals II. Aldosterone 20,21-acetonide (IIa) (50 mg.) was dissolved by stirring in 1 ml. of a mixture of dioxane–$N$ hydrochloric acid 10:1. After standing for 4 hr. at room temperature, ether was added and the solution washed with saturated natrium hydrogen carbonate solution and then with water. Evaporation of the dehydrated extract gave a residue (35 mg.) which crystallized from acetone–ether yielding 25 mg. of aldosterone, m.p. 112–115° to 160–162° $[\alpha]^{23}D$ +151° (chf.).

(7) Melting points are uncorrected. We are indebted to Dr. Sergio Cairoli for the microanalyses and to Dr. Cesare Pedrali for the infrared spectra.

# Studies on the Leaves of the Family Salicaceae. II.[1] Quercetin-3-glucosiduronic Acid from *Populus grandidentata* Leaves[2]

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In the continuing studies on the evaluation of the lead salts obtained during the purification of glucosides of *Populus* species leaves,[1] the precipitated lead salts obtained by treatment of the hot water extractives of *P. grandidentata* leaves were processed to yield a yellow crystalline compound. Upon hydrolysis with dilute sulfuric acid this compound yielded quercetin and glucuronic acid, and analysis corresponded with a monoglucosiduronic acid of quercetin. The compound is identical with querciturone, a quercetin-glucosiduronic acid of undetermined glycoside substitution, isolated from the leaves of the French bean, *Phaseolus vulgaris*, by Endres and co-workers[3] and by Marsh[4] and with purified miquelianin (quercetin-3-glucosiduronic acid) isolated in a somewhat impure state from the leaves of the Japanese evergreen shrub, *Gaultheria miqueliana*, by Sasaki and Watanabe.[5] Thus, the structure of the quercetin-monoglucosiduronic acids from the three botanical species is established as quercetin-3-glucosiduronic acid, and we suggest that this name be applied to all three products.

## Experimental[6]

**Quercetin-3-glucosiduronic Acid from *P. grandidentata* Leaves.** —An amount of 820 g. (oven-dry basis) of leaves freshly obtained from a bigtooth aspen (*P. grandidentata*) felled in Oneida County, Wisconsin, on June 14, 1962, was digested with 40 l. of boiling water, filtered through cloth, and processed with lead subacetate exactly as described earlier.[1] The filtered lead precipitate was suspended in 3 l. of water with vigorous stirring, saturated with hydrogen sulfide, heated to boiling, and filtered hot through a Celite pad. The dark red filtrate was concentrated to 200-ml. volume and allowed to stand at room temperature. Crystalline material separated after a few days. After several weeks, the reddish orange crystals were filtered. The yield was 3.03 g. This crude product was recrystallized several times from water in the presence of decolorizing carbon to give pale yellow needles (2.01 g.) shrinking at 135°, melting at about 170° with gas evolution, solidifying at about 190°, and finally decomposing to a black melt at about 260–265°. Paper chromatography in 4:1:5 butanol–acetic acid–water followed by spraying with 2% ethanolic sodium hydroxide indicated three materials which gave yellow spots fluorescing strongly under ultraviolet light. The crude product was dissolved in 25 ml. of boiling 95% ethanol, treated with decolorizing carbon, filtered hot, diluted with 10 ml. of chloroform, and allowed to stand in the refrigerator. Orange colored crystals separated after a short time and were filtered. These melted at 160°. The pale yellow filtrate was allowed to evaporate spontaneously, and the yellow residue was recrystallized from water to give 1.11 g. of pale yellow crystals. These were dehydrated *in vacuo* in a drying pistol at 100° over phosphorus pentoxide to yield 1.00 g. of light yellow crystals melting at 193–195° with gas evolution, resolidifying immediately to a yellow product which turned brown at 210° and finally melted with decomposition at 260–262°, $[\alpha]^{25}$D $-48.1°$ ($c$ 1.67 in 50% pyridine), $[\alpha]^{25}$D $-21°$ ($c$ 1.0 in absolute ethanol). The infrared absorption spectrum contained bands at 2.95, 5.62, 6.03, 6.23, 6.38, 6.68, 6.86, 7.36, 7.74, 8.30, 8.63, 8.90, 9.30, 9.50, 9.81, 10.05, 10.62, 11.42, 12.25, 12.50, and 12.70 $\mu$, and was identical with those of authentic querciturone[7] and authentic miquelianin[8] which had been purified further by the ethanol–chloroform procedure employed for our product. Marsh[4] reported $[\alpha]$D $-50°$ (in 50% pyridine), and Sasaki and Watanabe[5] reported $[\alpha]^{10}$D $-22.93°$ (in anhydrous ethanol) for their somewhat impure product.

Hydrolysis of the compound with $N$ sulfuric acid for 90 min. yielded yellow crystals melting at 309–310° and not depressing the melting point of a mixture with authentic quercetin. The infrared spectra of the yellow compound and of quercetin were identical. The aqueous filtrate from the quercetin was neutralized with excess barium carbonate and filtered. The filtrate was concentrated, and the concentrate gave a strong uronic acid test with naphthoresorcinol. Paper chromatography indicated glucuronic acid. The orginal quercetin-glucosiduronic acid liberated carbon dioxide from sodium bicarbonate solution.

**Infrared Spectra.**—Infrared absorption spectra were obtained with a Perkin-Elmer Model 21 recording spectrophotometer using a sodium chloride prism and potassium bromide pellets prepared by hand grinding with sample before pressing.

(1) For paper I of this series, see I. A. Pearl, S. F. Darling, and O. Justman, *J. Org. Chem.*, **27**, 2685 (1962).

(2) A portion of a paper presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., March 31–April 5, 1963.

(3) C. Endres, R. Huttel, and L. Kaufmann, *Ann.*, **537**, 205 (1939).

(4) C. A. Marsh, *Nature*, **176**, 176 (1955).

(5) T. Sasaki and Y. Watanabe, *J. Pharm. Soc. Japan*, **76**, 1893 (1956).

(6) All melting points are uncorrected. Infrared absorption spectra were determined by Mr. Lowell Sell of The Institute of Paper Chemistry Analytical Department.

(7) Kindly supplied by Dr. C. A. Marsh of Rowett Research Institute, Bucksburn, Aberdeen, Scotland.

(8) Kindly supplied by Dr. Toyosaku Sasaki, Hyogo University of Agriculture, Sasayama, Hyogo-ken, Japan.

## Diethyl 3-Ethoxyallylidenemalonate, a Versatile New Intermediate. A New Route to α-Pyrones and α-Pyridones

*Sir:*

We wish to report the preparation of diethyl 3-ethoxyallylidenemalonate (I), and some of its applications in heterocyclic synthesis.
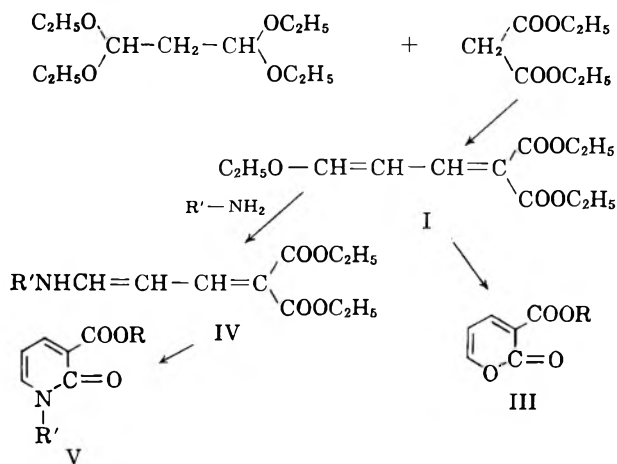
Heating 1,1,3,3-tetraethoxypropane with diethylmalonate in acetic anhydride for 2 hours at the reflux temperature in the presence of catalytic amounts of zinc chloride gave diethyl 3-ethoxyallylidenemalonate (I) in excellent yield, b.p. 128° (0.2 mm.) (Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49.). Found: C, 59.49; H, 7.49.); $\lambda_{max}^{MeOH}$ 300 mμ, ε 25.900; infrared $\lambda_{max}$ 5.85, 6.18 μ (neat).

In the absence of diethylmalonate, 1,1,3,3-tetraethoxypropane reacted with acetic anhydride and zinc chloride (or p-toluenesulfonic acid) under conditions identical with those above and, after distillation, gave 1,3,3-triethoxy-1-propylacetate $(C_2H_5O)_2CH—CH_2—CH(OC_2H_5)(OCO—CH_3)$ (II), b.p. 70–71° (2 mm.). (Calcd. for $C_{11}H_{22}O_5$: C, 56.39; H, 9.47. Found: C, 56.53; H, 9.17.), which has been previously obtained[1] by reacting ethyl orthoformate with vinylacetate. When II was heated with diethylmalonate in the presence of zinc chloride or p-toluenesulfonic acid as catalysts, I was again obtained, indicating that II may be an intermediate in the above reaction. This is reminiscent of the proposed[2] mechanism for diethyl ethoxymethylenemalonate formation[3] by the Claisen method.

Cyclization of compound I has led to a new synthesis of α-pyrones. Short heating of I in acidic medium (polyphosphoric or formic acid) produced a high yield of the heretofore unknown ethyl α-pyrone-3-carboxylate (III. R = $C_2H_5$), b.p. 122–123° (0.25 mm.) (Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.94; H, 4.92.); $\lambda_{max}^{MeOH}$ 309 mμ, ε 7450; $\lambda_{max}$ 5.65, 5.85, 6.15, 6.45, 8.10, 9.10 μ (neat). It was further characterized by its acidic hydrolysis to the corresponding α-pyrone-3-carboxylic acid (III. R = H), m.p. 127–128° (Calcd. for $C_6H_4O_4$: C, 51.44; H, 2.88. Found: C, 51.42; H, 2.96.); $\lambda_{max}^{MeOH}$ 313 mμ, ε 14.800; $\lambda_{max}$ 5.71, 6.02, 6.46, 8.08, 8.98 μ (nujol).

Reaction of an ethanolic solution of I with ammonia or benzylamine at room temperature, gave the corresponding 3-aminoallylidenemalonates (IV) in good yields. IVa (R′ = H), m.p. 126° (Calcd. for $C_{10}H_{15}O_4N$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.75; H, 7.06; N, 6.63.); $\lambda_{max}^{MeOH}$ 357 mμ, ε 46.430. IVb (R′ = $CH_2—C_6H_5$), m.p. 88° (Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.42; H, 6.64; N, 4.50.); $\lambda_{max}^{MeOH}$ 367 mμ, ε 53.320.

Cyclization of compounds of type IV, which con-



stitutes a new synthesis of α-pyridones, is accomplished most conveniently in an alcoholic solution of sodium ethoxide or piperidine. From IVa there was obtained ethyl α-pyridone-3-carboxylate[4] (Va. R = $C_2H_5$; R′ = H; m.p. 139°; $\lambda_{max}^{MeOH}$ 328 mμ, ε 14.960), which was hydrolyzed with concentrated hydrochloric acid to the corresponding acid[4] (Vc. R = H; R′ = H; m.p. 262°; $\lambda_{max}^{MeOH}$ 327 mμ, ε 17.500). Acid Vc was identified by infrared spectra and mixture melting point with a sample prepared by the hydrolysis of 3-cyano-α-pyridone, which was obtained by a different method.[5]

Cyclization of IVb gave the oily ethyl N-benzyl-α-pyridone-3-carboxylate (Vb. R = $C_2H_5$, R′ = $CH_2—C_6H_5$; $\lambda_{max}^{MeOH}$ 334 mμ, ε 8558), which was hydrolyzed directly to N-benzyl-α-pyridone-3-carboxylic acid (Vd. R = H, R′ = $CH_2—C_6H_5$; m.p. 130° (Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.41; H, 4.72; N, 6.27.); $\lambda_{max}^{MeOH}$ 331 mμ, ε 12.400.

The chemistry of I and other analogs is currently under further investigation.

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(4) A. Dornow, *Ber.*, **73**, 153 (1940).

(5) T. V. Protopopova and A. P. Skoldinov, *J. Gen. Chem. USSR*, **27**, 1360 (1957) (Eng. Transl.).

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## Conversion of Ketones to Olefins

*Sir:*

It has been found that dithioketals when refluxed with moderately active Raney nickel (W2) in ketonic solvents such as acetone and methyl ethyl ketone yield olefins as the main products of the reaction. The product can usually be isolated without difficulty and yields are generally satisfactory. The chief by-products

(1) Japanese Patent 3071 (1955); *Chem. Abstr.*, **51**, 16520ᵃ (1957).

(2) R. C. Fuson, W. E. Parham, and L. J. Reed, *J. Org. Chem.*, **11**, 194 (1946).

(3) L. Claisen, *Ber.* **26**, 2729 (1893); *Ann.*, **297**, 16 (1897).

are the unreacted starting material and in some instances the regenerated ketone.[1]

The results obtained with a number of steroid ketones are listed in Table I. The products are produced stereoselectively, i.e., in each instance only one of the possible geometrical isomers was isolated.[2] Thus the 3-ketone with the $5\alpha$-configuration yielded the $\Delta^2$-olefin, while the corresponding $5\beta$ ketone gave the $\Delta^3$-olefin. This is in accordance with the direction of enolization of these ketones[3] and the relative stability established for

TABLE I

| Starting material[a] | Product | Yield,[b] % |
|---|---|---|
| 3-Hydroxy-$\Delta$1,3,5(10)-estratrien-17-one | 3-Hydroxy-$\Delta$1,3,5(10),16-estratetraene[c] | 65 |
| $3\alpha$-Hydroxy-$5\alpha$-androstan-17-one | $\Delta$16-$5\alpha$-Androsten-3$\alpha$-ol[d] | 64 |
| $17\beta$-Hydroxy-$5\alpha$-androstan-3-one | $\Delta$2-$5\alpha$ Androsten-$17\beta$-ol[e] | 55 |
| $17\beta$-Hydroxy-$5\beta$-androstan-3-one | $\Delta$3-$5\beta$ Androsten-$17\beta$-ol[f] | 65 |
| $3\beta$-Hydroxy-$5\alpha$-pregnan-20-one | $\Delta$20-$5\alpha$ Pregnen-$3\beta$-ol | 70 |
| $3\beta$-Acetoxy-$\Delta$5-prenen-20-one | $3\beta$-Acetoxy-5,20-pregnadiene[g] | 75 |
| $17\beta$-Hydroxy-$\Delta$4-androsten-3-one | $17\beta$-Hydroxy-$\Delta$2,4-androstadiene[h] $17\beta$-hydroxy-$\Delta$3,5-androstadiene | 40 |

[a] In each instance the starting material was converted to the ethylenedithioketal which was then desulfurized without purification. [b] Based on starting ketone. [c] V. Prelog, L. Ruzicka, and P. Wieland, Helv. Chim. Acta, 28, 250 (1945). [d] V. Prelog, L. Ruzicka, and P. Wieland, ibid., 27, 66 (1945). [e] R. E. Marker, O. Kamm, D. M. Jones, L. W. Mixon, J. Am. Chem. Soc., 59, 1363 (1937). [f] J. McKenna, J. K. Norymberski, and R. D. Stubbs, J. Chem. Soc., 2502 (1959). [g] P. L. Julian, E. W. Meyer, and H. C. Printy, J. Am. Chem. Soc., 70, 887 (1948). [h] G. Rosenkranz, S. Kaufmann, and J. Romo, ibid., 71, 3689 (1949).

these olefin isomers.[4] The 20-ketone, however, yielded the terminal $\Delta^{20}$-olefin whereas the thermodynamically preferred enolization is towards C-17.[5]

The method is also applicable to diene synthesis from $\alpha,\beta$-unsaturated ketones. Testosterone dithioketal on brief desulfurization gave a mixture of dienes which by ultraviolet analysis consisted of the homoannular $\Delta$2,4-diene ($\lambda_{max}$ 266, 275, 284 m$\mu$) and the heteroannular $\Delta$3,5-diene ($\lambda_{max}$ 228, 235, 243 m$\mu$) in a ratio of 4 to 1. Prolongation of the reaction time increased the proportion of the heteroannular diene, indicating that it was produced by rearrangement from the homoannular precursor.

Both of the 17-keto compounds studied gave good yields of $\Delta^{16}$-steroids, with no evidence of any methyl shift or ring enlargement. It is noteworthy that this reaction represents the simplest synthesis of these biologically significant compounds. Furthermore, the mild and essentially neutral conditions employed in the reaction permit application to compounds containing acid or base sensitive groups. These and other aspects of this olefin synthesis will be reported in the near future.

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(1) Two recent reviews of Raney nickel desulfurization are: H. Hauptmann and W. F. Walter, Chem. Rev., 62, 347 (1962); G. R. Pettit and E. E. van Tamelen, Org. Reactions, 12, 356 (1962).

(2) The presence of small amounts of isomeric olefins in the product has not been rigidly excluded.

(3) Fieser and Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p. 276.

(4) R. B. Turner, W. R. Meador, and R. E. Winkler. J. Am. Chem. Soc. 79, 4122 (1957); R. B. Turner and W. R. Meador, ibid., 79, 4133 (1957); H. B. Henbest, G. D. Meakins, B. Nicholls, and R. A. L. Wilson, J. Chem. Soc., 997 (1957).

(5) C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, J. Am. Chem. Soc. 70, 1837 (1948); H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner, and T. F. Gallagher, ibid., 74, 2810 (1952).