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Total Synthesis of Pseudoionone and an Isomeric Ketone

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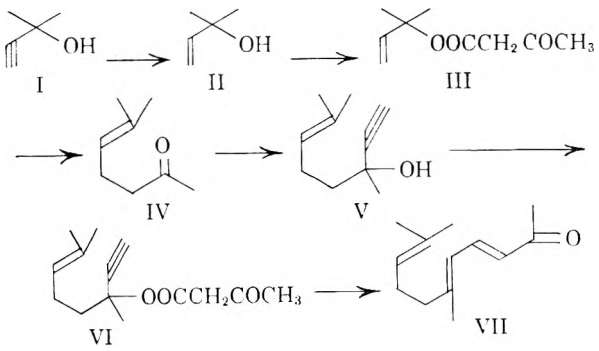
A practical total synthesis of pseudoionone, from acetone, is described. The key step is a pyrolytic rearrangement of a disubstituted propargyl acetoacetate (dehydrolinalyl acetoacetate) to pseudoionone. In addition, an isomeric ketone is obtained, which has been identified as 4-(5-isopropenyl-2-methylcyclopenten-1-yl)butanone-2. A mechanism is suggested for the novel rearrangement.

A key starting material for the commercial production of vitamin A[1] (and of various carotenoids) is pseudoionone (VII), which is ordinarily prepared by the condensation of acetone with citral.[2] The source of the latter, a C-10 unsaturated aldehyde, is lemon grass oil, a natural product which varies widely in purity, availability, and price. In an attempt to eliminate this dependence on a natural product, a program was initiated to obtain a reasonably inexpensive synthesis for citral or pseudoionone. We now wish to report a practical synthesis for the latter, starting from acetone, and employing a novel rearrangement of a propargylic acetoacetate.



Synthesis of pseudoionone. 2-Methyl-3-butyn-2-ol (I) was obtained by condensation of acetone with sodium acetylide,[3] and was hydrogenated to the vinyl carbinol (II) in the presence of Lindlar catalyst.[4] 2-Methyl-3-buten-2-yl acetoacetate (III) was prepared by the reaction of diketene with II. This reaction was effected, in virtually quantitative yield, at 25–30° in the presence of catalytic quantities of the sodium salt of II or sodium methoxide.[5] Pyrolysis of III at 140–160° caused rearrangement to 6-methyl-5-hepten-2-one (IV), with simultaneous evolution of carbon dioxide. This allylic rearrangement represents an application of the reaction reported by Kimel and Cope in 1943.[5] We have found that the yields of γ,δ-unsaturated ketones produced in this type of reaction may be increased by conducting the pyrolysis of the acetoacetate in the presence of small amounts of an aluminum alkoxide. In this instance, IV was obtained from III in 83% yield.

Ethynylation of IV afforded the acetylenic carbinol, dehydrolinalool (V).[6] This was converted to dehydrolinalyl acetoacetate, VI, by reaction with diketene. On pyrolysis of VI at 170–190°, carbon dioxide was evolved and a mixture of ketones was produced. The chief product was pseudoionone

(1) O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

(2) A. Russell and R. L. Kenyon, *Org. Syntheses*, **23**, 78 (1943).

(3) (*a*) J. F. Froning and G. F. Hennion, *J. Am. Chem. Soc.*, **62**, 653 (1940); (*b*) *cf.* also H. S. Taylor and W. J. Shenk, *J. Am. Chem. Soc.*, **63**, 2756 (1941).

(4) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(5) W. Kimel and A. C. Cope, *J. Am. Chem. Soc.*, **65**, 1992 (1943).

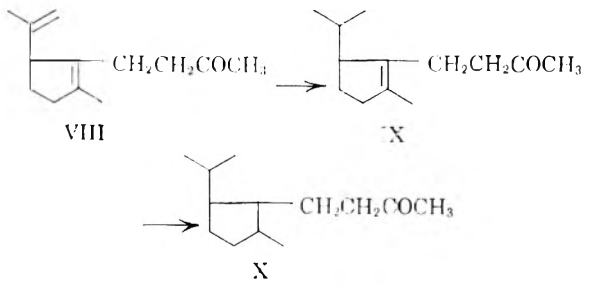
(6) L. Ruzicka and V. Fornasir, *Helv. Chim. Acta*, **2**, 182 (1919); *cf.* also H. Rupe and G. Lang, *Helv. Chim. Acta*, **12**, 1933 (1929).

(VII) and there was obtained also another ketone of the same empirical formula. The over-all yield of pseudoionone from acetone was about 35%. Considering the ready availability of inexpensive starting materials, this yield is sufficient to make the method attractive as a source of pseudoionone.

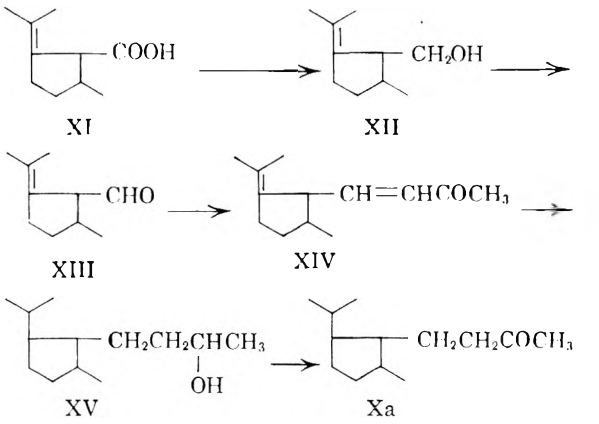
Structure of the isomeric ketone. Pyrolysis of dehydrolinalyl acetoacetate afforded, in addition to pseudoionone, another ketone, $C_{13}H_{20}O$, in appreciable quantities. The product was a methyl ketone, since iodoform was obtained on treatment with hypoiodite. Total hydrogenation disclosed the presence of two double bonds, in addition to the ketone function. One double bond was easily hydrogenated, while the second was reduced with more difficulty. Further, the absence of any characteristic absorption in the ultraviolet indicated that the double bonds were neither conjugated with each other nor with the carbonyl group.

Ozonolysis of the ketone produced formaldehyde–and no acetone–evidence of a methylidene double bond. This was confirmed by the infrared spectrum (absorption at 1640, 887, and 3060 cm.$^{-1}$). The absence of out-of-plane deformation frequencies in the 800 to 840 cm.$^{-1}$ range suggested that the second double bond was tetrasubstituted.[7]

These data (and the molecular refraction) were indicative of a monocyclic ketone. Numerous attempts at dehydrogenation (to an aromatic compound) of the hydrocarbon, $C_{13}H_{22}$, obtained by Wolff-Kishner reduction of the ketone, were unsuccessful. Thus, the possibility that the ketone was a cyclohexene derivative was rejected. From all the above-mentioned data, and in consideration of its formation from VI, formula VIII, with a cyclopentene ring, was deemed probable for the isomeric ketone.[8] Its di- and tetra-hydro derivatives would be IX and X, respectively.

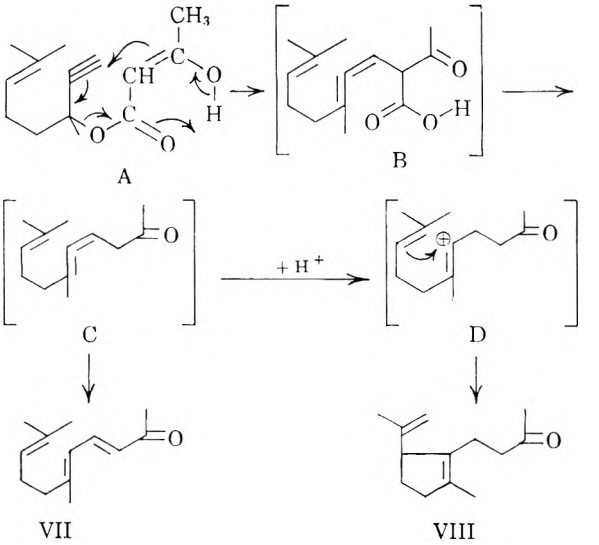


The structure for X, and thus, indirectly, for VIII, was confirmed by an independent synthesis of X starting with pulegenic acid, XI.[9]



Pulegenic acid (XI) was reduced with lithium aluminum hydride to the corresponding alcohol (XII), and the latter was oxidized by chromic acid to the aldehyde (XIII). Condensation of XIII with acetone in the presence of alkali afforded the C-13 ketone (XIV). Hydrogenation of XIV with Pt-C at elevated pressure caused formation of the saturated carbinol (XV). Oxidation of XV gave the saturated ketone (Xa). This was proved identical with our tetrahydroketone (X) by mixed melting point of a derivative,[10] and by identity of the infrared curves.

Mechanism of the reaction. Pyrolysis of dehydrolinalyl acetoacetate (as well as other substituted propargyl acetoacetates[11]) results in formation of products in which inversion of the original propargyl group has occurred. This conforms with the findings for the corresponding allylic compounds,[5] and hence the reaction is visualized as occurring by an intramolecular cyclic mechanism analogous to that proposed for the allylic rearrangement.



(7) We are indebted to Dr. F. Forrester of these laboratories for help in interpretation of infrared data.

(8) The presence of a cyclopentenyl ring and the nature of the ketonic side chain were demonstrated by G. Saucy *et al.*, Roche Labs., Basle, Switzerland, from physical data and degradation experiments; to be published independently.

(9) H. Rupe and K. Schafer, *Helv. Chim. Acta*, **11**, 463 (1928).

(10) It is worth noting that semicarbazones of the optically active Xa and racemic X have the same melting point.

(11) W. Kimel and N. W. Sax, U. S. Patent **2,661,368** (Dec. 1, 1953), and other unpublished results; *cf.* also R. N. Lacey, *J. Chem. Soc.*, 827 (1954); G. I. Samokhvalov, M. A. Miropolskaya, and N. A. Preobraghenskii, *Doklady Akad. Nauk U.S.S.R.*, **107**, 103 (1956).

In this sequence, the starting material is represented in its enolic form (A). Under the influence of heat, the α-carbon atom of the substituted propargyl group becomes detached from the ester oxygen atom, and the propargylic γ-carbon atom becomes attached to the central methylene carbon atom of the acetoacetic ester. Simultaneously, electron pairs shift as illustrated to produce the substituted acetoacetic acid (B). The latter immediately decarboxylates to the allenic ketone (C). Presumably, this allenic compound is quite labile and rearranges, for the most part, to the more stable conjugated configuration represented by pseudoionone (VII).

Formation of the cyclopentene derivative (VIII) may commence with addition of a proton to the allenic intermediate C to give a carbonium ion D. This cyclizes, in a concerted fashion, with loss of a proton, whereby the isomeric ketone, VIII, is obtained.

Such a cyclic mechanism accounts well for the inversion of the substituted propargyl group which occurs. However, we have no assurance that such a mechanism is a necessary requisite for the reaction, especially since no allenic compounds were isolated.

Formation of pseudoionone from dehydrolinalyl acetoacetate is representative of a general reaction whereby unsaturated ketones are produced by pyrolysis of disubstituted propargyl acetoacetates.[11] Similar results are obtained by heating the corresponding propargyl-type alcohols with acetoacetic ester.[12] However, we would interpret this latter reaction as proceeding first by a trans-esterification to the propargyl acetoacetate, and then rearrangement of the ethynyl carbinyl ester.

EXPERIMENTAL[13]

2-Methyl-3-butyn-2-ol (I). This compound was prepared as described by Froning and Hennion.[3] It was obtained in 90% yield; b.p. 104°; n_D^{25} 1.4182.

2-Methyl-3-buten-2-ol (II).[14] To a solution of I (336 g., 4.0 moles) in an equal volume of petroleum ether were added quinoline (16.8 g.) and Lindlar catalyst[4] (30 g.). The mixture was cooled to 10° and was shaken in a hydrogen atmosphere until four moles of hydrogen were consumed (about 3–5 hr.). Absorption of hydrogen had declined markedly at that point. The product was isolated by fractional distillation from a Fenske-type column packed with glass helices. II was obtained in yield of 323.3 g. (94%); b.p. 97–98°; n_D^{25} 1.4141; d_{25}^{25} 0.8200.

2-Methyl-3-buten-2-yl acetoacetate (III).[15] To a solution of II (430 g., 5.0 moles) in an equal volume of toluene was added sodium methoxide (5.0 g.). Diketene (462 g., 5.5 moles) was added, dropwise, during 2 hr. The reaction temperature was maintained at 25–30° by external cooling. The solution was stirred until there was no further evidence of heat evolution (about 5 hr.). Then the mixture was worked up by washing successively with dilute sulfuric acid, saturated sodium bicarbonate solution, and finally with water until neutral. Distillation at diminished pressure afforded III in yield of 825 g. (97%); b.p. 82–84° (8 mm.); n_D^{25} 1.4372; d_{25}^{25} 0.9850; M_D calcd. (keto form) 44.96, (enol form) 46.01, found 45.27.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.55; H, 8.24. Found: C, 63.50; H, 8.24.

6-Methyl-5-hepten-2-one (IV).[16] A 2-l. three necked flask, equipped with mechanical stirrer, thermometer, and condenser connected at the top to a gas meter *via* a Dry Ice trap, was charged with III (510 g., 3.0 moles) and aluminum isopropoxide (8.7 g.). The mixture was stirred vigorously and was heated to 140–160° for 5 hr., during which time 2.14 cu. ft. (90%) of carbon dioxide was evolved. Distillation of the residue afforded 314 g. (83%) of IV, b.p. 58–59° (10 mm.); n_D^{25} 1.4372; d_{25}^{25} 0.8610; 2,4-dinitrophenylhydrazone, m.p. 86–87°; semicarbazone, m.p. 135–136°. These physical constants are in agreement with those previously reported for this ketone.[17]

Dehydrolinalool (V). This compound was prepared essentially as described by Ruzicka and Fornasir;[6] yield from IV, 95%; b.p. 88–90° (14 mm.); n_D^{25} 1.4608.

Dehydrolinalyl acetoacetate (VI). By the same procedure described above for the preparation of III, there was obtained from V (760 g., 5.0 moles) and diketene (462 g., 5.5 moles) a quantitative yield (1180 g.) of VI. The undistilled product was of sufficient purity for use in the next step. However, it could be distilled, in high vacuum, as a colorless liquid; 43–46° (0.007 mm.); n_D^{25} 1.4652; d_{25}^{25} 0.9785; M_D calcd. (keto form) 66.07, (enol form) 67.11, found 66.78.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.32; H, 8.74.

Pseudoionone (VII). In an apparatus similar to that described for the preparation of IV, a mixture of VI (236 g., 1.0 mole), decalin (250 cc.), acetic acid (3.0 g.), and aluminum isopropoxide (0.2 g.) was heated to 175–190° for 2.5 hr. During that time, 0.666 cu. ft. of carbon dioxide (84%) was evolved. The residue was allowed to cool and was washed with dilute sulfuric acid, several times with saturated sodium bicarbonate solution, and finally with water until neutral. The organic portion was dried over calcium sulfate and the decalin was removed by concentration *in vacuo*. Fractionation of the residue gave 105.7 g. (55%) of VII; b.p. 90–95° (0.5 mm.); n_D^{25} 1.5272. Identity of the product was confirmed by preparation of its semicarbazone, m.p. 142°, and the 2,4-dinitrophenylhydrazone, m.p. 149.5°. There was no depression in m.p. of these derivatives on admixture with authentic samples prepared from pseudoionone obtained by condensation of citral with acetone.[2]

The pseudoionone obtained by the pyrolytic method was cyclized to β-ionone, using a mixture of sulfuric and acetic acids.[18] From 200 g. of VII, there was obtained 152 g. of β-ionone, b.p. 91–93° (0.7 mm. ; n_D^{25} 1.5187. The good yield of β-ionone attests to the high quality of pseudoionone employed.

4-(5-Isopropenyl-2-methylcyclopenten-1-yl)butanone-2 (VIII). Redistillation of the foreruns obtained from the preparation of VII gave 27.0 g. (14%) of VIII, b.p. 59–61° (0.3 mm.); n_D^{25} 1.4810; d_{25}^{25} 0.9213; semicarbazone (from 50% alcohol), m.p. 136°. M_D calcd. 59.13, found 59.38.

Anal. of the ketone. Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 80.77; H, 10.39.

(12) Y. R. Naves, *Compt. rend.*, **240**, 1437 (1955); Y. R. Naves, *Bull. soc. chim. France*, 672 (1956); Y. R. Naves and P. Ardizio, *Bull. soc. chim. France*, 1479 (1955); P. Teisseire, *Recherches*, **5**, 3 (1955).

(13) Boiling and melting points are uncorrected.

(14) For previous preparations of this compound see A. E. Favorskii and A. I. Lebedeva, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 879 (1938); (3, *b*); Commercial Solvents Corp., Brit. Patent **595,459** (Dec. 5, 1947); E. F. Smith, U. S. Patent **2,516,826** (July 25, 1956).

(15) W. Kimel, U. S. Patent **2,628,250** (Feb. 10, 1953).

(16) W. Kimel, U. S. Patent **2,638,484** (May 12, 1953).

(17) E. Guenther, *The Essential Oils*, D. Van Nostrand Co., Inc., New York, New York, 1949, Vol. II, p. 382.

(18) E. Royals, *Ind. Eng. Chem.*, **38**, 546 (1946).

Anal. of the semicarbazone. Calcd. for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.29; N, 16.86. Found: C, 67.50; H, 9.12; N, 16.70.

A solution of VIII (19.2 g.) in acetic acid (58 g.) was ozonized several hours at 0°. The ozonide was decomposed by warming with water (150 cc.), zinc dust (20 g.), and a trace of hydroquinone. A portion of the solution was distilled and from the distillate a dimedone derivative was prepared;[19] m.p. and mixed m.p. with formaldehyde dimedone 188°.

4-(5-Isopropyl-2-methylcyclopenten-1-yl)butanone-2 (IX). A solution of VIII (192.2 g.) in an equal volume of petroleum naphtha (60–80°) was hydrogenated at 25° at atmospheric pressure in the presence of Lindlar catalyst (19.2 g.). Uptake of hydrogen decreased sharply after consumption of 0.986 mole (about 4 hr.). Distillation, after removal of catalyst and solvent, gave IX, b.p. 94° (3 mm.); n_D^{25} 1.4681; d_{25}^{25} 0.9023. M_D calcd. 59.58, found 59.65.

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.84; H, 11.37.

The semicarbazone melted at 142°.

Anal. Calcd. for $C_{14}H_{25}N_3O$: C, 66.85; H, 10.02; N, 16.71. Found: C, 67.07; H, 9.73; N, 17.13.

4-(5-Isopropyl-2-methyl-1-cyclopentyl)butanone-2 (X). A mixture of VIII (250 g.), hexane (2000 cc.), and 5% palladium-calcium carbonate (25 g.) was hydrogenated in an autoclave at 500 lb. per sq. in. at 125° for 4 hr. The mixture was worked up in the usual manner, affording X, b.p. 75° (1 mm.), n_D^{25} 1.4536; d_{25}^{25} 0.8873; M_D calcd. 59.87, found 60.03.

Anal. Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.61; H, 12.28.

The product, X, gave a mixture of semicarbazones, which could be separated by fractional crystallization from 70% isopropyl alcohol. The more soluble derivative (which predominated) melted at 123°, while the less soluble derivative had m.p. 156°. However, melting points of mixtures of the two fractions were not depressed, suggesting that the semicarbazones were derivatives of different stereoisomeric forms of X.[20]

Anal. of the 123° semicarbazone. Calcd. for $C_{14}H_{27}N_3O$: C, 66.36; H, 10.74; N, 16.58. Found: C, 66.65; H, 10.38; N, 16.43.

Anal. of the 156° semicarbazone. Calcd. for $C_{14}H_{27}N_3O$: C, 66.36; H, 10.74; N, 16.58. Found: C, 66.31; H, 10.99; N, 16.79.

2-Butyl-3-isopropenyl-1-methylcyclopentene. VIII (400 g.) was dissolved in diethylene glycol (1500 cc.) and was reduced in the presence of hydrazine hydrate (200 cc.) and potassium hydroxide (336 g.) according to the method of Huang-Minlon.[21] The hydrocarbon, 2-butyl-3-isopropenyl-1-methylcyclopentene was obtained in yield of 261 g. (70%), b.p. 76–78° (7 mm.); n_D^{25} 1.4661; d_{25}^{25} 0.8312; M_D calcd. 59.12, found 59.42.

Anal. Calcd. for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.85; H, 12.07.

Numerous attempts were made to dehydrogenate the hydrocarbon, $C_{13}H_{22}$, to an aromatic compound. Among the conditions employed were: (1) refluxing with palladinized barium sulfate;[22] (2) heating in the vapor phase over palladinized charcoal;[23] (3) treatment with N-bromsuccinimide;[24] (4) heating with iodine;[25] (5) refluxing with sulfur or selenium. In all trials, either no reaction or extensive decomposition occurred; in no case was an aromatic compound obtained.

Pulegenic Acid (XI). The source of pulegone was commercial pennyroyal oil. XI was prepared from pulegone by the method described by Rupe and Schafer,[9] and had b.p. 95–97° (0.45 mm.); n_D^{25} 1.4780.

2-Hydroxymethyl-3-isopropylidene-1-methylcyclopentane (XII). A solution of XI (336 g.) in ether (600 cc.) was added dropwise, during 2 hr., to a stirred suspension of lithium aluminum hydride (91.2 g.) in ether (2000 cc.). The mixture was heated to reflux for an additional hour and then was cooled to room temperature. Excess reducing agent was destroyed by the cautious addition of alcohol (400 cc.) and water (200 cc.). Then 15% aqueous sulfuric acid (1000 cc.) was added, with ice cooling. The ether layer was separated and was washed with 5% aqueous sodium bicarbonate solution and with water until neutral. Concentration *in vacuo* gave crude XII, which was purified by fractional distillation. It was obtained as a colorless liquid in yield of 260 g. (84.5%) with b.p. 76–77° (0.9 mm.); n_D^{25} 1.4830.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.46; H, 11.54.

The *p-nitrobenzoate* melted at 90°.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.25; H, 7.02; N, 4.72.

5-Isopropylidene-2-methylcyclopentanecarboxaldehyde (XIII). To a well stirred mixture of XII (154 g.), benzene (500 cc.), acetic acid (750 cc.), and water (1,000 cc.) was added, in 100 cc. increments, a solution of potassium dichromate (294 g.) and sulfuric acid (245 g.) in water (1000 cc.). Addition was made at a rate such that the reaction temperature did not exceed 40°. Stirring was continued for 30 min. after addition was complete; then the benzene layer was separated and was washed with sodium bicarbonate solution and water until neutral. The product, XIII, was obtained by fractional distillation as a colorless liquid with b.p. 74–77° (8 mm.); n_D^{25} 1.4632; yield, 50.0 g. (33%); semicarbazone (needles from 50% ethanol), m.p. 202°.

A satisfactory C and H analysis was not obtained for XIII. The values observed for C were invariably too low. However, no difficulty was experienced with the *semicarbazone.*

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.38; H, 9.00; N, 20.30.

4-(5-Isopropylidene-2-methylcyclopentan-1-yl)buten-3-one-2 (XIV). A solution of XIII (45 g.) in acetone (100 cc.) was added, dropwise, to 3*N* sodium hydroxide (50 cc.) in acetone (100 cc.), causing a temperature rise from 22° to 30°. Stirring was continued for 40 hr. at room temperature. The mixture was then diluted with several volumes of water and was extracted with petroleum ether. The organic layer was washed neutral, dried over calcium sulfate, and concentrated *in vacuo*. The crude ketone was purified *via* Girard's reagent and was distilled at diminished pressure. XIV was obtained in yield of 19.8 g. (34.8%); b.p. 73–76° (0.2 mm.); n_D^{25} 1.4960.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 80.79; H, 10.51.

The *4-phenylsemicarbazone*, crystallized from ethanol, melted at 149–150°.

Anal. Calcd. for $C_{20}H_{27}N_3O$: C, 74.04; H, 8.08; N, 12.95. Found: C, 73.76; H, 8.20; N, 13.23.

4-(5-Isopropyl-2-methylcyclopentyl)-butanol-2 (XV). A mixture of XIV (19.8 g.), acetic acid (150 cc.), and 5% platinum-charcoal (3 g.) was placed in autoclave and hydrogenated at 1000 lb. per sq. in. at 90° for 2 hr. Three moles of hydrogen were consumed. The catalyst was removed by filtration and the filtrate was diluted with several volumes of water and was extracted with petroleum ether. Distillation of the

(19) W. Weinberger, *Ind. Eng. Chem., Anal. Ed.*, **3**, 365 (1931).

(20) A more complete discussion of the stereochemical considerations involved here will be presented in a forthcoming publication of Dr. G. Saucy.

(21) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(22) H. E. Eschinazi and E. D. Bergmann, *J. Am. Chem. Soc.*, **72**, 5651 (1950).

(23) R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1134 (1940).

(24) R. A. Barnes and G. R. Buckwalter, *J. Am. Chem. Soc.*, **73**, 3858 (1951).

(25) V. N. Ipatieff, H. Pines and R. C. Olberg, *J. Am. Chem. Soc.*, **67**, 694 (1945).

residue afforded 17.8 g. of XV, b.p. 77–79° (0.1 mm.); n_D^{25} 1.4590.

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.46; H, 12.97.

4-(5-Isopropyl-2-methylcyclopentyl)butanone-2 (Xa). A solution of sodium dichromate (27 g.) and sulfuric acid (23 g.) in water (80 cc.) was added, dropwise, with vigorous stirring, to a solution of crude XV (17.8 g.) in benzene (50 cc.). The reaction temperature increased to 40°. Then the mixture was heated to reflux for 1 hr. The organic layer was separated, washed neutral, dried, and distilled. There were obtained 16 g. of Xa; b.p. 70–73° (0.6 mm.); n_D^{25} 1.4532. It formed a semicarbazone, m.p. 123°, which was unchanged on admixture with the lower melting derivative of X. Further, there was no depression on admixture with the 156° derivative of X. Infrared curves of X and Xa were identical.

Acknowledgment. All microanalyses were performed by Dr. A. Steyermark and his staff of these laboratories. Infrared spectra were recorded by Dr. A. Motchane, using a Perkin-Elmer Model 21 spectrophotometer.

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[CONTRIBUTION FROM THE TECHNICAL DEVELOPMENT DEPARTMENT OF HOFFMANN-LA ROCHE, INC.]

Synthesis of Carotene Homologs

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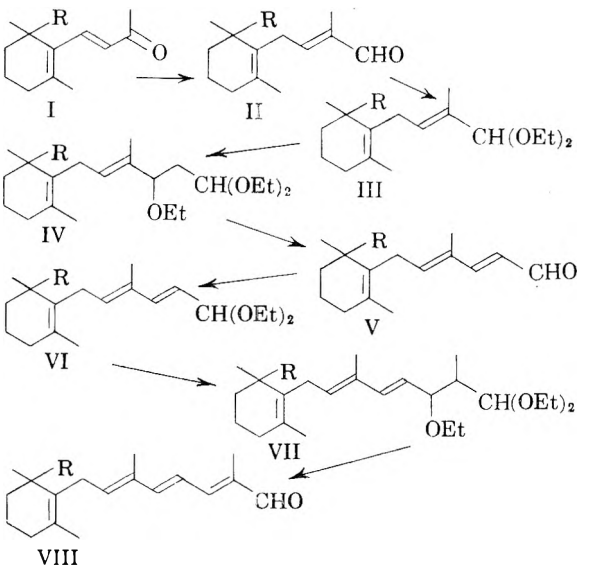
Three new carotene homologs were prepared by total synthesis. A C-41 hydrocarbon, 1-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XV) and a C-42 hydrocarbon, 1,18-bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,-17 (XIa) showed considerable vitamin A activity. A C-46 hydrocarbon, 1,18-bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XIb) resembled *trans* β-carotene in color and other physical properties but had no vitamin A activity.

In a recent publication by Eugster *et al.*,[1] it was disclosed that 2,2′-dimethyl-β-carotene had about half of the vitamin A activity of β-carotene. The result is rather surprising in view of the fact that other changes in the ionone ring of vitamin A cause almost complete loss of activity.[2] Further study of the carotenoids with respect to relationship of chemical constitution to vitamin A activity aroused our interest. Accordingly, we now wish to report the total synthesis of three such homologs, involving substitution at the geminal methyl groups of the ionone rings.

The new compounds are: a C-41 hydrocarbon, 1-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XV); a C-42 hydrocarbon, 1,18-bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XIa); and a C-46 compound, 1,18-bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,-11,13,15,17 (XIb). These compounds were prepared by a procedure reported by Isler *et al.*,[3] for the preparation of *trans*-β-carotene.

The appropriate substituted β-ionone[4] (I) was converted to the corresponding substituted C-14 aldehyde (II) by glycidation with ethyl chloroacetate followed by treatment of the glycidic ester with alkali.[5] The aldehyde (II) was converted to its acetal (III) in the conventional manner, and this was condensed with ethyl vinyl ether, in the presence of zinc chloride, to give an ether acetal (IV). When IV was heated with a solution of sodium acetate, water, and acetic acid, ethanol was eliminated from the α,β- position, the acetal was



a. R = C_2H_5
b. R = $CH_2CH(CH_3)_2$

(1) C. H. Eugster, A. H. Trivedi, and P. Karrer, *Helv. Chim. Acta*, **38**, 1359 (1955).

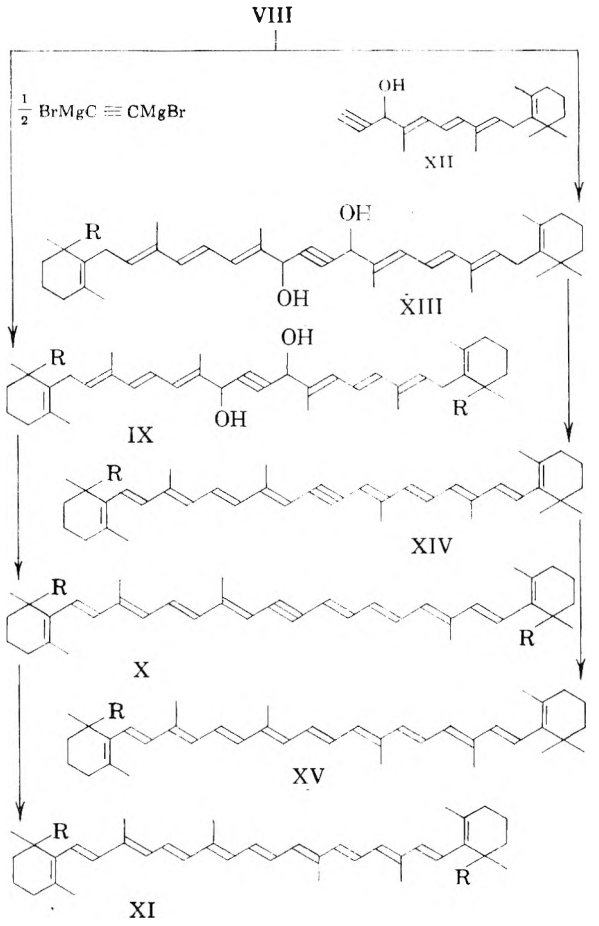
(2) W. Oroshnik, U. S. Patent 2,602,092, July 1, 1952; B. C. L. Weedon and R. J. Woods, *J. Chem. Soc.*, 2687 (1951).

(3) O. Isler, H. Lindlar, M. Montavon, R. Ruegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 249 (1956).

(4) Preparation to be described in a subsequent publication.

(5) See O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

hydrolyzed, and a crystalline substituted C-16 aldehyde (V) was isolated. Repetition of the sequence of acetalization, vinyl ether condensation, and hydrolysis, but employing ethyl propenyl ether in place of ethyl vinyl ether, resulted in formation of a substituted C-19 aldehyde (VIII).



a. R = C_2H_5
b. R = $CH_2CH(CH_3)_2$

The process for conversion of a substituted C-19 aldehyde (VIII) to a symmetrical carotene homolog (XI) commenced with condensation of two moles of VIII with acetylene dimagnesium bromide, whereby the acetylenic diol (IX) was obtained. Rearrangement and, simultaneously, dehydration of IX to the acetylenic hydrocarbon (X) was effected by means of hydrogen chloride in ethanol. Partial hydrogenation of X in the presence of a poisoned palladium catalyst[6] afforded the corresponding ethylenic compound in which the double bond at carbon atom 9 was *cis*. However, this was readily converted to the *trans*-β-carotene homolog (XI) by heating at reflux in normal hexane. Both XIa and XIb were obtained as well defined easily crystallized solid compounds resembling β-carotene in color and crystalline form.

The compounds were readily prepared free of the *cis* form by following the isomerization with a recrystallization from methylene chloride containing a trace of pyridine. These were then checked by ultraviolet absorption spectra. The presence of the *cis* isomer was easily noted by the typical "*cis* peak." Fig. 1 shows the ultraviolet absorption

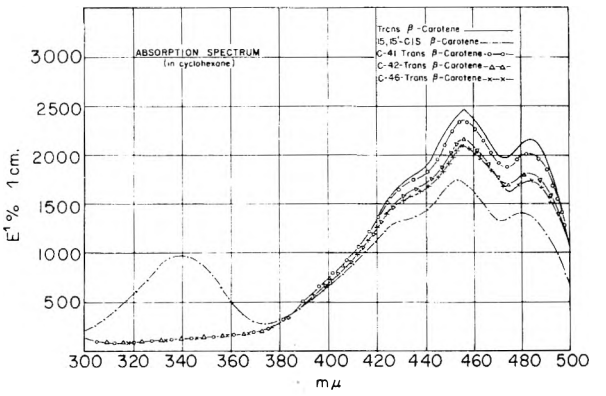


FIGURE 1

spectrum of the new compounds compared with *trans*-β-carotene and *cis*-β-carotene.[7]

The *cis* and *trans* forms of carotene can be also differentiated by the infrared spectrum in the

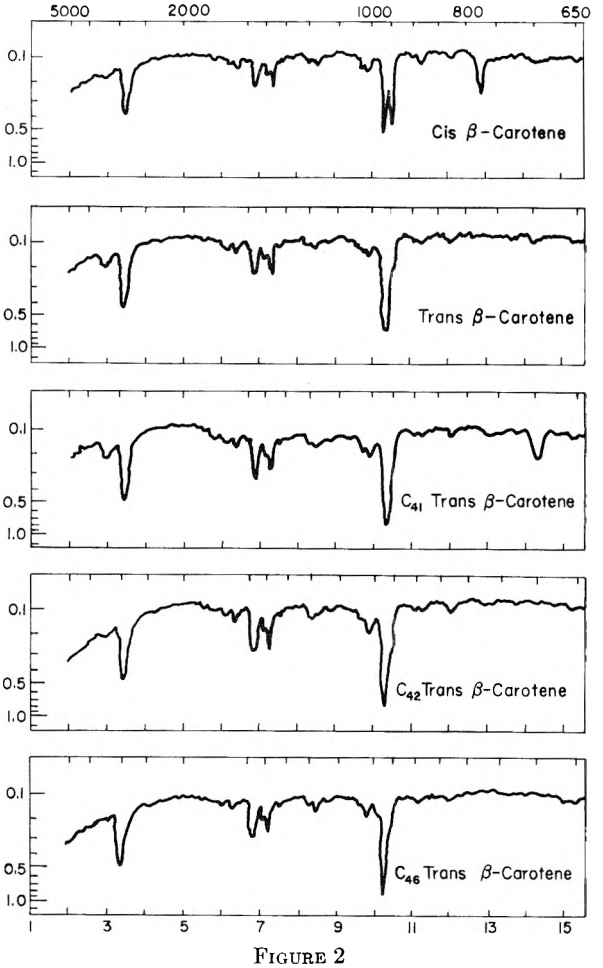
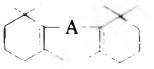
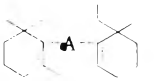
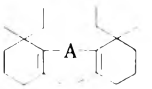
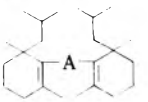
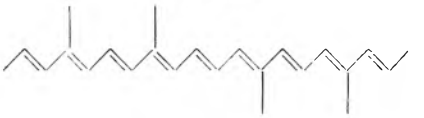


FIGURE 2

(6) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(7) The measurements were made with a Beckman spectrophotometer-Model DU.

TABLE I

Compound	Structure	Vitamin A Liver Storage Assay	Vitamin A Liver and Kidney Storage Assay	Curative Growth Assay
β-Carotene		100	100	100
1-Desmethyl-1-ethyl-β-Carotene (XV)		53	82	56
1,1′-Bisdesmethyl-1,1′-bisethyl-β-Carotene (XIa)		38	78	41
1,1′-Bisdesmethyl-1,1′-bisisobutyl-β-Carotene (XIb)		0	0	0
A =				

10.3–10.6 micron range. The infrared curves are shown by Fig. 2.[8]

The unsymmetrical carotene homolog (XV) was obtained from the substituted C-19 aldehyde (VIIIa) by a slightly different sequence. A C-21 acetylenic carbinol (XII)[3] (obtained by reaction of C-19 aldehyde with lithium acetylide) was treated with two moles of ethyl magnesium bromide, and to the resultant Grignard complex was added VIIIa, whereby the unsymmetrical acetylenic diol (XIII) was obtained. Conversion of the diol to the acetylenic hydrocarbon (XIV) and thence to the β-carotene homolog (XV) paralleled the preparation of the corresponding symmetrical homolog (XI). The unsymmetrical compound (XV) was also an easily crystallized relatively stable substance, with a color similar to that of β-carotene.

Solubility[9] *and biological activity.*[10] Samples of the C-41, C-42, and C-46 carotenoids were tested for biological activity by comparison to all-*trans*-β-carotene[11] using the rat liver storage[12,13] and curative growth assays. Kidney levels of vitamin A were also measured. Very similar results were obtained by the liver storage and curative growth methods. Although higher results were obtained using the combined liver and kidney vitamin A storage data, the biological activities must be assessed by the results of the curative growth test. The results are given in Table I.

Since the low solubility of *trans*-β-carotene, in edible oils, sometimes poses a problem for its application as a pigment, the solubilities of these carotene homologs in a variety of oils and solvents, were also determined.[14] The relative solubility in fifteen solvents are recorded in Table III.

It is interesting to observe that the vitamin A activity decreases with increasing substitution of the geminal methyl groups. Furthermore, this decrease in activity cannot be accounted for solubility characteristics because solubilities of our carotenoids increase with increasing substitution.

Dependence of vitamin A activity on chemical structure. The relative stability, crystalline nature, and ease of purification and characterization of synthetic carotenoids, compared with corresponding vitamin A homologs, make them attractive for study of the relationship between vitamin A activity and chemical structure. A comparison of the activities of the homologs reported in this paper with those previously reported for various other carotenoids, in which chemical changes have been introduced into the ionone rings, is presented in Table II.

3,4-Dehydro-β-carotene, 1-desmethyl-1-ethyl-β-carotene (XV) and cryptoxanthin would be expected to exhibit biological activity since the vitamin A moiety constitutes half of the molecule. However, even with compounds substituted in both ionone rings, such as 2,2′-dimethyl-β-carotene, and 1,1′-bisdesmethyl-1,1′-bisethyl-β-carotene (XIa), there is still considerable activity. This is true also of the compound containing an additional double bond in each ionone ring, 3,4,3′,4′-bisdehy-

(8) The infrared curves were made with potassium bromide disks by a Model 21 double beam spectrophotometer, Perkins–Elmer Corp.

(9) We are indebted to Dr. J. C. Bauernfeind for the solubility results.

(10) For determination of biological activities we are indebted to Mr. E. De Ritter of our Nutrition Department.

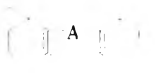
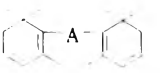
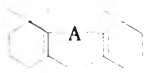
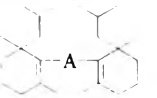
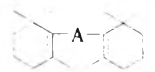
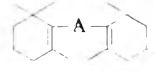
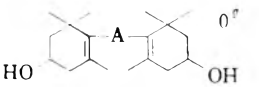
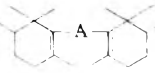
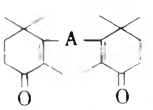
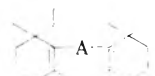
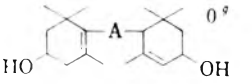
(11) Equimolar comparison to all *trans*-β-carotene.

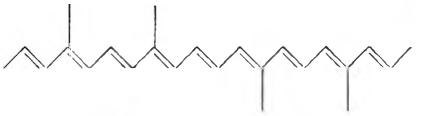
(12) J. R. Foy and K. Morgareidge, *Anal. Chem.*, **20**, 304 (1948).

(13) K. Guggenheim and W. Koch, *Biochem. J.*, **38**, 256 (1944).

(14) Details are given in the Experimental Part.

TABLE II

Name	Structure	Activity[a]	Name	Structure	Activity[a]
β-Carotene		100%	3,4,3′,4′-Bisdehydro-β-Carotene		38%[b,c,e]
3,4-Dehydro-β-Carotene		75%[b]	1,1′-Bis-desmethyl-1,1′-Bis-isobutyl-β-Carotene (XIb)		0
1-Desmethyl-1-Ethyl-β-Carotene (XV)		56%	Lycopene		0[f]
Cryptoxanthin		50%[f]	Zeaxanthin		0[g]
2,2′-Dimethyl-β-Carotene		50%[d]	Canthaxanthin		0[h]
1,1′-Bisdesmethyl-1,1′-Bisethyl-β-Carotene (XIa)		41%	Xanthophyll		0[g]

A = 

[a] Activity in rats compared with β-carotene. [b] *Helv. Chim. Acta*, **39**, 274 (1956). [c] *Arch. Biochem.*, **7**, 447 (1945). [d] Ref. (1). [e] *Ann.*, 594, 165 (1955). [f] *Helv. Chim. Acta*, **33**, 1349 (1950); *Helv. Chim. Acta*, **39**, 463 (1956). [g] *Helv. Chim. Acta*, **17**, 24 (1934). [h] *Biochem. J.*, **57**, 223 (1954).

dro-β-carotene. However, if the ionone rings are opened, as in lycopene, or if functional groups are introduced, as in zeaxanthin, canthaxanthin, or xanthophyll, there is complete loss of activity.

EXPERIMENTAL[15]

4-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-2-methylbuten-2-al-1 (IIa). 5-l. three-neck flask, equipped with an efficient stirrer, was charged with 4-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-buten-3-one-2 (Ia)[4] (576.1 g.), ethyl chloroacetate (685 g.) and methanol (216 cc.). The solution was cooled to −20° and sodium methylate (377 g.) was added in small portions during 2 hr. The reaction temperature was maintained at −5° to −10° during the addition, and stirring was continued for an additional hour at 0°. Then, a solution of sodium hydroxide (278 g.) in methanol (1980 cc.) was cooled to 15°, and was poured, with stirring, into the reaction mixture. This caused an increase in temperature to 20°. Water (5 l.) was added, and stirring was continued for 1 hr. Finally, the product was extracted with petroleum ether, washed neutral, and isolated by distillation. IIa was obtained at b.p. 110° (0.35 mm.); n_D^{25} 1.5112; yield, 514.8 g. (83.7%).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.77; H, 10.98. Found: C, 81.59; H, 10.60.

6-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-4-methylhexadien-2,4-al-1 (Va). IIa was converted to its acetal (IIIa) by stirring for 4 hr., at 20–25°, a solution of IIa (292 g.), ethyl orthoformate (240 g.), and *p*-toluenesulfonic acid (0.3 g.) in ethanol (40 cc.). The mixture was allowed to stand overnight, and then a solution of zinc chloride (4 g.) in acetic acid (240 cc.) was added. The reaction flask was cooled by an ice bath and ethyl vinyl ether (112 g.) was introduced at 5–10° during 1 hr. Stirring was continued overnight at the same temperature. The product, 6-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-4-methyl-1,1,3-triethoxyhexene-4 (IVa) was not isolated.

To the reaction mixture was added a solution of sodium acetate (160 g.) in water (120 cc.) and acetic acid (1000 cc.). The apparatus was arranged for distillation, and the solution was heated to 95–100° for 3 hr., whereby the low boiling components were eliminated. The residue was allowed to cool, and was diluted with water (1500 cc.). The oil layer was separated, dissolved in methanol (250 cc.), and was cooled to −10°, whereby the product crystallized. Recrystallization from petroleum ether afforded the aldehyde (Va) in yield of 189 g. (76%), as white crystals; m.p. 49–50°; ϵ = 29,480 at 284 mμ (95% ethanol).

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.88; H, 10.64. Found: C, 83.16; H, 10.28.

8-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-2,6-dimethyloctatrien-2,4,6-al-1 (VIIIa). The acetal 6-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-1,1-diethoxy-4-methylhexadiene-2,4 (VIa) was obtained by stirring a solution of Va (50 g.), ethyl orthoformate (38 cc.), and *p*-toluenesulfonic acid (0.15 g.) in ethanol (16 cc.) for 18 hr. at room temperature. The mixture was cooled to 5°, and a solution of zinc chloride (1 g.) in acetic acid (110 cc.) was added, followed by dropwise addition of ethyl propenyl ether (29 cc.) during 1 hr. The reaction mixture was maintained at 5–10° for 18 hr. The resultant ether acetal (VIIa) was not isolated, but was used directly for the next step.

A solution of sodium acetate (33 g.) in water (25 cc.) and acetic acid (200 cc.) was introduced into the reaction flask and the mixture heated at 90–95° for 3 hr. in a nitrogen

(15) Boiling and melting points are uncorrected. The melting points were determined in vacuum capillaries.

atmosphere. The solution was allowed to cool and was diluted with water, whereby an oil separated. It was washed with water, and was ultimately crystallized by dissolving in petroleum ether (100 cc.) and cooling to −20°. Repeated recrystallization afforded the C-20 aldehyde (VIIIa) as white crystals; yield, 25.8 g. (45%); m.p. 39–40°; ϵ = 43,420 at 329 mμ (95% ethanol).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.55. Found: C, 83.84; H, 10.30.

4,8-Dimethyl-10-(2,6,6-trimethylcyclohexen-1-yl)-decatrien-4,6,8-yne-1-ol-3 (XII). This compound was obtained by the action of lithium acetylide on 2,6-dimethyl-8-(2,6,6-trimethylcyclohexen-1-yl)-octatrien-2,4,6-al-1 (VIII, R = H) as described by Isler *et al.*[3]; yield, 80%; b.p. 100° (0.025 mm.); n_D^{25} 1.5750.

1-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecahexen-2,4,6,-12,14,16-yn-9-diol-8,11 (XIII). To ethylmagnesium bromide, prepared in the usual manner from magnesium turnings (5.0 g.), ethyl bromide (27 g.), and ether (100 cc.), was added, dropwise, a solution of XII (27 g.) in ether (50 cc.). The mixture was heated to reflux for 3 hr. Then, VIIIa (26.5 g.) in ether (100 cc.) was introduced, and refluxing was continued for 2 hr. The resultant Grignard complex was poured, cautiously, onto crushed ice (500 g.), and dilute (5%) sulfuric acid was added until the mixture was faintly acid. The ether solution of the diol was separated, washed to neutrality, and dried over calcium chloride. Removal of the solvent by distillation *in vacuo* afforded the C-41 diol, XIII, as a waxy, yellow solid, in quantitative yield. The crude product was of sufficient purity for use in the next step.

1-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecaocten-1,3,5,7,-11,13,15,17-yne-9 (XIV). The crude diol (XIII) was dissolved in ethyl acetate (400 cc.) and ethanol (80 cc.), and to it was added a solution (40 cc.) of 6*N* hydrogen chloride in ethanol. After several minutes, crystals of the acetylenic hydrocarbon (XIV) appeared. The mixture was stirred for about 30 min., and was then stored overnight at 0°. Finally, the product was filtered in an inert atmosphere, and was washed successively with cold alcohol, water, and cold alcohol again. There was obtained, in this manner, 34.8 g. (70%) of XIV, m.p. 136°. Recrystallization from ethyl acetate afforded a product of m.p. 142°.

Anal. Calcd. for $C_{41}H_{56}$: C, 89.72; H, 10.28. Found: C, 89.61; H, 10.34.

1-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,-7,9,11,13,15,17 (XV). A suspension of XIV (10 g.) in hexane (100 cc.) was hydrogenated in the presence of a poisoned palladium catalyst[6] until one molar equivalent of hydrogen was consumed. The suspension was heated to boiling before filtration of the catalyst, and the latter was washed thoroughly with additional portions of hot hexane. Finally, the filtrate was concentrated until a pasty mass remained. This was heated at 90° for 16 hr. in an inert atmosphere to effect a transformation to the *trans* compound. Filtration, and recrystallization from benzene-methanol, afforded 7.0 g. (70%) of XV, m.p. 168°.

λ_{max} 455–456 mμ ($E^{1\%}_{1\,cm}$ 2350); λ_{max} 484–486 mμ $E^{1\%}_{1\,cm}$ 2010). (Cyclohexane).

Anal. Calcd. for $C_{41}H_{58}$: C, 89.39; H, 10.61. Found: C, 89.17; H, 10.51.

1,18-Bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecahexen-2,4,6,12,14,16-yn-9-diol-8,11 (IXa). Ethynbis(magnesium bromide) was prepared[16] by bubbling dry acetylene for 20 hr. into the Grignard reagent from magnesium (12 g.), ethyl bromide (65 g.), and ether (250 cc.). A solution of VIIIa (60 g.) in ether (150 cc.) was added rapidly, and the mixture was heated to reflux for 2 hr. The resultant complex was decomposed by pouring onto ice and acidifying with dilute (5%) sulfuric acid. The ether layer was separated, was washed with sodium bicarbonate solution and then with water until neutral, and was dried over calcium chloride. Upon removal of the ether *in vacuo* there remained 63 g. of crude IXa, a white, waxy solid which was used in the next step without further purification.

1,18-Bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecaocten-1,3,5,7,11,13,15,17-yne-9 (Xa). By the same procedure described for the preparation of XIV, there was obtained from the crude diol, IXa, the acetylenic hydrocarbon, Xa, in yield of 37.7 g. (64%); m.p. (from ethyl acetate), 128°.

Anal. Calcd. for $C_{42}H_{58}$: C, 89.61; H, 10.39. Found: C, 89.84; H, 10.25.

1,18-Bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XIa). Xa was hydrogenated to the corresponding *cis* carotenoid as described for XV, and conversion to the *trans* compound, XIa, was effected by heat. XIa was obtained in yield of 75.8%, m.p. 162°.

λ_{max} 456 mμ ($E^{1\%}_{1\,cm}$ 2170); λ_{max} 483–484 mμ ($E^{1\%}_{1\,cm}$ 1800) (Cyclohexane).

Anal. Calcd. for $C_{42}H_{60}$: C, 89.29; H, 10.71. Found: C, 89.42; H, 10.47.

4-(2,6-Dimethyl-6-isobutylcyclohexen-1-yl)-2-methylbuten-2-al-1 (IIb). This was obtained, in the same manner as IIa, from 4-(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-buten-3-one-2 (Ib)[4] (542 g.) and chloroacetic ester (644 g.) in yield of 389 g. (67.7%); b.p. 117° (0.45 mm.); n_D^{25} 1.506.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.19; H, 11.36. Found: C, 82.02; H, 11.18.

6-(2,6-Dimethyl-6-isobutylcyclohexen-1-yl)-4-methylhexadien-2,4-al-1 (Vb). The acetal (IIIb) was obtained from IIb (160 g.) and orthoformic ester (120 g.), and was converted to the ether acetal IVb, and thence to the unsaturated aldehyde (Vb) in the same manner described for preparation of Va from IIa. The C-19 aldehyde (Vb) was obtained in yield of 139 g. (78.6%) with m.p. 48–52°. After repeated recrystallization from petroleum ether, the m.p. was 55–56°; ϵ 29,350 at 283–284 mμ (95% ethanol).

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.97; H, 10.68.

8-(2,6-Dimethyl-6-isobutylcyclohexen-1-yl)-2,6-dimethyloctatrien-2,4,6-al-1 (VIIIb). By the same procedure previously described for the preparation of VIIIa from Va, there was obtained from Vb (55 g.) using the processes of acetalization, condensation with ethyl propenyl ether (29 cc.) and hydrolysis, the C-22 unsaturated aldehyde (VIIIb). The product was crystallized from petroleum ether after long cooling in a Dry Ice–acetone bath. However, the crystals melted below room temperature. Therefore, the product was again cooled, and was filtered rapidly through a cooled sintered glass funnel. Then the crystals were allowed to melt, and the yellow oil was dried *in vacuo;* yield, 44 g. (70%). The product was purified further by distillation; b.p. 110° (0.025 mm.); n_D^{25} 1.5795; ultraviolet max. at 328–329 mμ (95% ethanol).

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 83.94; H, 10.68.

1,18-Bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecahexen-2,4,6,12,14,16-yn-9-diol-8,11 (IXb). In similar fashion to the preparation of IXa, there was obtained by the action of VIIIb (65 g.) on the ethynbis-(magnesium bromide) from 12 g. of magnesium, a yellow waxy product (IXb) in yield of 68 g. This crude diol was of sufficient purity for use in the next step.

1,18-Bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecaocten-1,3,5,7,11,13,15,17-yne-9 (Xb). The crude diol (IXb) (above), was dissolved in ethyl acetate (500 cc.) and ethanol (100 cc.), and was treated with 6*N* hydrogen chloride in ethanol (50 cc.). By working up in the

(16) R. Lespieau, *Bull. soc. chim. Belges*, **43**, 199 (1928); V. V. Shokina, O. V. Kil'disheva, and N. A. Preobrazhenskii, *J. Gen. Chem. (U. S. S. R.)*, 11, 425 (1941).

TABLE III

Solvent	Solubility, g./100 g. *Trans*-β-Carotene	C-41 *Trans*-β Carotene	C-42 *Trans*-β-Carotene	C-46 *Trans*-β-Carotene
Corn oil	0.053	0.064	0.071	0.177
Cottonseed oil	0.060	0.063	0.068	0.210
Olive oil	0.053	0.065	0.069	0.192
Safflower oil	0.049	0.063	0.067	0.175
Glyceryl trioleate	0.059	0.069	0.082	0.224
Preinoleyl alcohol	0.049	0.013	0.023	0.170
Aldol 40	...	0.013	0.034	...
Aldol 11	0.025	0.033	0.042	0.315
Ethyl laurate	0.180	0.180	0.199	0.250
Ethyl oleate	0.082	0.132	0.161	0.287
Ethyl myristate	0.096	0.174	0.177	...
Ethyl acetate	0.057	0.075	0.102	...
Propylene glycol	Trace	Trace	Trace	Trace
95% Ethanol	0.0021	0.0019	0.0018	...
Aldol 10	0.025	0.033	0.041	0.087
Solubility ratio	1.0	1.2	1.3	3.5

same manner as XIV, there was obtained Xb in yield of 39 g. (61%); m.p. (from ethyl acetate), 154°.

Anal. Calcd. for $C_{46}H_{66}$: C, 89.25; H, 10.75. Found: C, 89.12; H, 10.61.

1,18-Bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XIb). This compound was prepared in the same manner as XV in yield of 80%, m.p. 164° (from benzene methanol); λ_{max} 457 mμ ($E^{1\%}_{1cm}$ 2090); 485–486 mμ ($E^{1\%}_{1cm}$ 1650) in cyclohexane.

Anal. Calcd. for $C_{46}H_{68}$: C, 88.96; H, 11.04. Found: C, 88.73; H, 10.61.

Determination of carotenoid solubilities. The relative solubilities for our synthetic homologs and for carotene, in 15 different solvents, were compared. The solubilities were determined by agitating an excess of the crystalline compound with the desired solvent in a 5-cc. screwcap vial sealed under carbon dioxide for 5 days[17] in a rotating shaker (30 r.p.m.). The samples were then centrifuged, and the supernatant liquid was analyzed by ultraviolet spectroscopy. The results are given in Table III.

Acknowledgment. Microanalyses were made by Dr. A. Steyermark and his staff of these laboratories. Ultraviolet and infrared spectra were taken by Dr. F. Forrester of these laboratories.

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(17) A. A. Mikhailovinina and B. G. Savinov, *Ukrain. Khim. Zhur.*, 16, 183–7 (1950).

[CONTRIBUTION FROM BAKER LABORATORY, CORNELL UNIVERSITY]

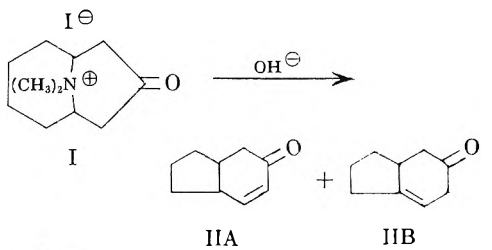
Derivatives of Homopseudopelletierine: Completely Enolic β-Ketoesters

ORVILLE L. CHAPMAN[1] AND JERROLD MEINWALD

Received August 19, 1957

Syntheses of the homopseudopelletierine derivatives IIIC, VIIIB, and VIIIC are described. The infrared spectra of these compounds show them to be completely enolized, both in the solid state and in solution. This conclusion is supported by ultraviolet spectral data.

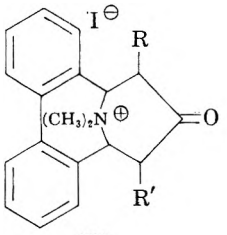
The degradative rearrangement of homopseudopelletierine methiodide (I) in base has been shown to yield the hydrindenone, IIA, along with an isomeric product, probably IIB.[2] Three types of mechanism have been suggested to rationalize this transformation.[2] None of these mechanisms could be operative in the case of the dibenzo derivative of I (IIIA), and it was therefore hoped that this compound might give rise to the unrearranged structure IV under elimination conditions. Efforts to prepare IIIA in order to test this reasoning have been unsuccessful and have now been discontinued. We wish, however, to report some incidental findings related to this problem.



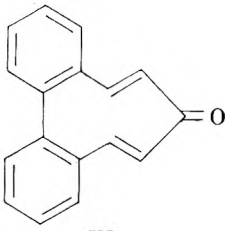
The synthesis of compounds of the type III *via* the Robinson-Schöpf biogenetic technique required

(1) American Viscose Corp. Fellow, Summer, 1956; Procter and Gamble Fellow, 1956–1957; Dow Chemical Co. Fellow, Summer, 1957. Present address: Department of Chemistry, Iowa State College, Ames, Iowa.

(2) J. Meinwald and M. Koskenkyla, *Chemistry & Industry*, 476 (1955).



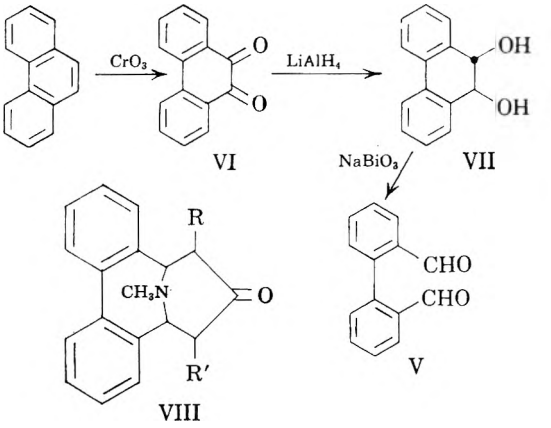
III



IV

A, R = R′ = H
B, R = R′ = $CO_2C_2H_5$
C, R = H; R′ = $CO_2C_2H_5$

a supply of diphenyl-2,2′-dialdehyde (V). Prior to our work, this aldehyde had been prepared from *o*-iodobenzaldehyde by treatment with copper powder at high temperatures.[3,4] In the course of this work, we have prepared V *via* phenanthrene-9,10-quinone (VI) and *trans*-9,10-dihydrophenanthrene-9,10-diol VII, as shown below.



VI VII V VIII

A, R = R′ = H
B, R = R′ = $CO_2C_2H_5$
C, R = H; R′ = $CO_2C_2H_5$

Since the development of this method, an even more convenient route to V, consisting of the direct ozonization of phenanthrene, has been described.[5]

The direct condensation of V with acetonedicarboxylic acid and methylamine in aqueous-organic solvent mixtures failed to give VIIIA, probably because of the insolubility of V in the media. The previously described diester VIIIB, however, was readily formed from V using diethyl acetonedicarboxylate and methylamine in ethanol.[3] Attempts to hydrolyze and decarboxylate VIIIB to VIIIA were uniformly unsuccessful. Furthermore, VIIIB itself could not be converted into the methiodide, IIIB, under a variety of conditions. Thus an impasse had been reached at this point.

In the course of studying the properties of VIIIB, it was discovered that treatment with two equivalents of sodium ethoxide in ethanol removed one carbethoxyl group, giving the monoester VIIIC in good yield. The decarbethoxylation of VIIIB is analogous to certain reactions of glutaconic[6] esters and nitromalonic esters.[7]

Attempts to hydrolyze and decarboxylate VIIIC were, however, no more successful than the previously described attempts to carry out these reactions on VIIIB. On the other hand, the monoester VIIIC formed a crystalline methiodide (IIIC) on treatment with methyl iodide. Base degradation of this methiodide gave only an amorphous solid which could not be characterized.

Examination of the infrared spectra of VIIIB, VIIIC, and IIIC led to an unexpected observation. The salient features of these spectra are summarized in Table I. VIIIB shows a band at 5.77–5.78 μ indicative of a normal, isolated ester grouping, while VIIIC is transparent in this region.

TABLE I

INFRARED SPECTRA

	VIIIB	VIIIC	IIIC
KBr pellet	2.92, 5.77, 6.02, 6.14 μ	2.98, 6.03, 6.20 μ	2.98, 6.03, 6.16 μ
$CHCl_3$ solution	5.78, 6.01, 6.14 μ	6.04, 6.17 μ	—

The total absence of normal ketonic absorption in the 5.80–5.90 μ region, together with the presence of 6.02 (6.03) μ absorption characteristic of a chelated, conjugated ester carbonyl group[8] and the 6.14 (6.20) μ absorption characteristic of the carbon-carbon double bond in a chelated, enolic β-ketoester[8,9] requires the assignment of the completely enolic structures IX and X to VIIIB and VIIIC, respectively. The case of IIIC is so similar to that of VIIIC that it will not be discussed in detail. This structural assignment is not without analogy. A completely enolic structure has been assigned to diethyl cyclohexanone-2,6-dicarboxylate (XI) on the basis of similar evidence.[8] Ethyl cyclohexanone-2-carboxylate (XII), however, is not completely eno-

(3) E. T. L. J. Anet, G. K. Hughes, D. Marmion, and E. Ritchie, *Australian J. Sci. Research, Ser. A*, **3**, 330 (1950).

(4) W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 487 (1941).

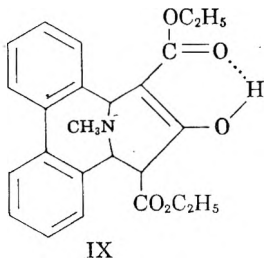
(5) W. J. Schmitt, E. J. Moriconi and W. F. O'Connor, *J. Am. Chem. Soc.*, **77**, 5640 (1955); P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956); J. P. Wibaut and T. J. de Boer, *Proc. Koninkl. Ned. Akad. Wetenschap.* **59**, B, 421 (1956).

(6) F. R. Goss, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc.*, **123**, 327 (1923) and references therein cited. The decarbethoxylation of VIIIB requires an excess over one mole of sodium ethoxide. It seems thus that the reaction takes place on the enolate anion. The enol form of VIIIB is actually a glutaconic acid derivative. It is interesting to note that this reaction violates the generalization suggested by Ingold and co-workers that only glutaconic esters which have no mobile hydrogen available for tautomerization will undergo reactions of this type.

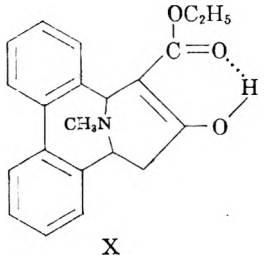
(7) C. Ulpiani, *Gazz. chim. ital.*, **35**, I, 273 (1905). W. Steinkopf and A. Supan, *Ber.*, **43**, 3239 (1910).

(8) N. Leonard, H. S. Gutowsky, W. Middleton, and E. Peterson, *J. Am. Chem. Soc.*, **74**, 4070 (1952).

(9) I. M. Hunsberger, R. Ketcham, and H. S. Gutowsky, *J. Am. Chem. Soc.*, **74**, 4839 (1952).

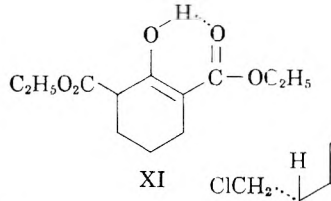


IX

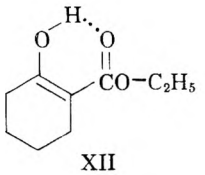


X

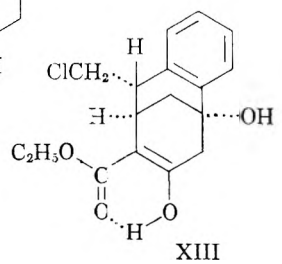
lic.[8] In the polycyclic series, Wenkert and Stevens have called attention to the completely enolic structure required by the infrared spectrum of XIII.[10]



XI

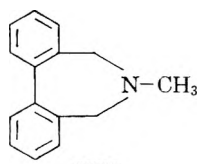


XII



XIII

Compounds VIIIB and VIIIC, if enolized would have two chromophores which should absorb in the ultraviolet, the diphenyl system and the enolic β-ketoester. Assuming that there is no interaction between these chromophores, it should be possible to isolate and examine the spectrum of the enolic β-ketoester chromophore by subtracting the spectrum of an appropriate model for the diphenyl system from the spectra of VIIIB and VIIIC. Examination of scale models shows that VIIIB, VIIIC, and XIV have approximately the same conformation of the diphenyl chromophore. Compound XIV was thus selected as a suitable spectral model. The ultraviolet spectra of VIIIB, VIIIC, and XIV are summarized in Table II. The results obtained by



XIV

subtracting the spectrum of XIV from the spectra of VIIIB and VIIIC are presented in Table III. The location of the absorption maxima of the resultant spectra is in good agreement with the 245 mμ absorption maximum reported for the enolic form of other β-ketoesters.[11] The ultraviolet spectra of VIIIB and VIIIC thus corroborate the enolic structures IX and X.

TABLE II

ULTRAVIOLET SPECTRA

	VIIIB	VIIIC	XIV
0.1*N* H_2SO_4/95% EtOH	248 mμ (29,200)	247 mμ (28,700)	248 mμ (16,600)
95% EtOH	248 mμ (29,800)	247 mμ (28,700)	248 mμ (15,500)
0.1*N* KOH/95% EtOH	255 mμ (23,700)	255 mμ (23,700)	—

TABLE III

ULTRAVIOLET SUBTRACTION SPECTRA

	VIIIB–XIV	VIIIC–XIV
0.1*N* H_2SO_4/95% EtOH	247 mμ (14,300)	245 mμ (12,000)
95% EtOH	248 mμ (13,000)	245 mμ (12,700)

It is difficult to account for the completely enolic structures IX, X, XI, and XIII while remembering that XII and a host of related β-ketoesters are only partially enolic. The difficulty is enhanced by the fact that comparison of scale models of VIIIB and IX or VIIIC and X reveals no steric preference for the enolic or ketonic form in either case. The explanation based on the dipole interactions of the carbonyl groups of a β-ketoester fixed in a rigid polycyclic system suggested by Wenkert and Stevens[10] to account for the enolic structure XIII seems to be the most plausible in the light of the limited data available.

EXPERIMENTAL

Diphenyl-2,2'-dialdehyde (V). Sodium bismuthate[12] (10.0 g.), *trans*-9,10-dihydrophenanthrene-9,10-diol[13] (1.34 g., 0.00632 mole), 10 ml. of 3.33*M* phosphoric acid, 10 ml. of water, and 10 ml. of dioxane were stirred in a 3-neck flask equipped with a reflux condenser. After approximately 2 min., the reaction mixture became very warm (solvent refluxed). In certain runs, the reaction did not proceed this rapidly; it was then necessary to add 5-ml. portions of 85% phosphoric acid until the reaction proceeded at an appreciable rate. When all the yellow-tan sodium bismuthate had been converted to the white bismuth phosphate, the reaction mixture was stirred for an additional hour. Extraction with ether followed by drying over anhydrous magnesium sulfate and evaporation of the ether gave V as an oil containing some dioxane and any unreacted starting material. The crude product could be used directly for condensations or purified by treatment with sodium bisulfite.

Absolute ethanol (3 ml.) was added to 12 ml. of 40% aqueous sodium bisulfite, and after filtration this solution was added to a solution of the crude product in 2 ml. of absolute ethanol. The resultant cloudy solution was filtered and then extracted with ether. The aqueous-alcoholic solution which contained the soluble bisulfite addition product

(10) E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, 78, 5627 (1956).

(11) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1954, 223 ff.

(12) For the use of this reagent see W. Rigby, *J. Chem. Soc.*, 1907 (1950).

(13) J. Booth, E. Boland, and E. Turner, *J. Chem. Soc.*, 1188 (1950).

was treated with 15 ml. of concentrated hydrochloric acid and 10 ml. of water. The acid solution was extracted thoroughly with ether. Evaporation of the ether, after washing with water and drying over anhydrous magnesium sulfate, gave V (0.7 g., 52.5%) as a yellow solid, m.p. *ca.* 50°. Recrystallization gave yellow crystals, m.p. 60–62° (reported m.p. 63°).[4]

Diethyl 10-methyl-2,3,4,5-dibenz-10-azabicyclo[4,3,1]deca-2,4-dien-8-one-7,9-dicarboxylate (VIIIB).[3] A solution of V (3.0 g., 0.0143 mole) and diethyl acetonedicarboxylate (3.0 g.) in 20 ml. of absolute ethanol, cooled to 10°, was treated with 1.6 ml. of 30% aqueous methylamine. Overnight, colorless crystals (4.14 g., 71%), m.p. 112–114°, were formed. Recrystallization from methanol gave colorless crystals m.p. 117–118° (reported 118°[3]).

Anal. Calcd. for $C_{24}H_{25}O_5N$: C, 70.76; H, 6.14; N, 3.44. Found: C, 70.54; H, 6.03; N, 3.39.

Attempts to hydrolyze VIIIB *and* VIIIC. A suspension of VIIIB in 5% sodium hydroxide was placed on a shaker for 4–5 hr. The solution was then made acidic with 10% sulfuric acid and refluxed. The time of reflux was varied from 2 to 48 hr. without significant change in the results. The acidic solution was extracted with ether to obtain the neutral and the acidic products. The solution was then made basic and extracted with ether. The only pure product which could be isolated from the mixed neutral and acidic products was a small amount of diphenyl-2,2′-dialdehyde[14] identified by comparison of its infrared spectrum with that of an authentic sample of V as well as by the undepressed mixed melting point of its bis-2,4-dinitrophenylhydrazone with the same derivative of V. The basic products which were obtained (5–20%) constituted a complex mixture from which no pure compound could be isolated.

Similar experiments with VIIIC gave identical results.

Attempts to prepare the methiodide of diethyl 10-methyl-2,3,4,5-dibenz-10-azabicyclo[4,3,1]deca-2,4-dien-8-one-7,9-dicarboxylate (VIIIB). Table IV summarizes the attempts to prepare the methiodide of VIIIB. The reactions were worked up by evaporating the reaction mixture to dryness and recrystallizing the solid thus obtained from ethanol; VIIIB was identified by its melting point and comparison of infrared spectra.

Ethyl 10-methyl-2,3,4,5-dibenz-10-azabicyclo[4,3,1]deca-2,4-dien-8-one-7-carboxylate (VIIIC). A solution of VIIIB (1.0 g., 0.0025 mole) in 50 ml. absolute ethanol was treated with a solution of sodium ethoxide prepared by dissolving 0.12 g. (0.005 mole) of sodium in 10 ml. of absolute ethanol. The solution, under an atmosphere of dry nitrogen, was stirred vigorously with a magnetic stirrer for 2 days. Aqueous hydrobromic acid (10 ml. of 0.5*N*) was added. The solution was diluted with approximately $^2/_3$ its volume of water and placed in the refrigerator for 11 days. The crystals which had formed were removed by filtration (0.71 g., 82%). These crystals in potassium bromide showed infrared maxima at 2.98, 6.03, and at 6.20 μ but not at 5.77 μ. The product (VIIIC) on recrystallization from methanol formed flat needles which melted at 130–131°; in ethanolic solution it gave a red color with 1% aqueous ferric chloride.

TABLE IV

ATTEMPTS TO PREPARE VIIIB METHIODIDE

Attempt No.	Conditions	Product
1	Methyl iodide in methanolic solution for 24 hr. at room temp.	VIIIB
2	Methyl iodide in ethanolic solution in glass bomb at 50–60° for 2 days	VIIIB
3	Methyl iodide in ethanolic solution at room temp. for 24 days	Red crystals m.p. <90°

Anal. Calcd. for $C_{21}H_{21}NO_3$: C, 75.23; H, 6.26; N, 4.18. Found: C, 75.40; H, 6.29; N, 3.95.

Ethyl 10-methyl-2,3,4,5-dibenz-10-azabicyclo[4,3,1]deca-2,4-dien-8-one-7-carboxylate methiodide (IIIC). A solution of VIIIC in absolute ethanol was cooled to 0° and then treated with excess methyl iodide. After standing for 2 days, crystals formed. These crystals had an infrared spectrum similar to that of VIIIC but with definite differences. The product was practically insoluble in water; in aqueous-ethanolic solution it gave an immediate precipitate with 5% aqueous silver nitrate. In ethanolic solution it gave an orange-red color with 1% aqueous ferric chloride. After recrystallization from ethanol, the product melted at 186–187°. A mixture melting point with VIIIC was depressed to 159–165°. The methiodide showed infrared maxima (KBr pellet) at 2.98, 6.03, and 6.16 μ.

Anal. Calcd. for $C_{22}H_{24}INO_3$: C, 55.34; H, 5.03; N, 2.94. Found: C, 54.89; H, 5.37; N, 3.09.

Degradation of IIIC. A solution of IIIC (1.0 g.) and sodium carbonate (0.53 g.) in 50 ml. of ethanol-water (1:3) was heated on a steam bath until the presence of dimethylamine could no longer be detected (7–8 hr.). The solution was acidified with 4*N* sulfuric acid and refluxed for a short time. Extraction of the acid solution gave 0.20 g. of a yellow amorphous solid. This material had a complex infrared spectrum with unresolved absorption between 5.77 μ and 6.10 μ. The solid could not be induced to crystallize. The product was converted in poor yield to an orange 2,4-dinitrophenylhydrazone. A chromatogram of this derivative on an alumina column failed to give a pure compound.

Acknowledgment. The authors wish to express their gratitude to The Research Corporation for the partial support of this work through a Frederick Gardner Cottrell grant and to Dr. Wilhelm Wenner of Hoffmann-LaRoche Inc., Nutley, N. J., for a sample of 6-methyl-6,7-dihydro-5*H*-dibenzo[c,e]azepine hydrobromide.

ITHACA, N. Y.

(14) This presumably is produced by the acid-catalyzed reversal of the Mannich condensation.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CORNELL UNIVERSITY]

The Structure of Thebainehydroquinone

GEORGE A. WILEY[1] AND JERROLD MEINWALD

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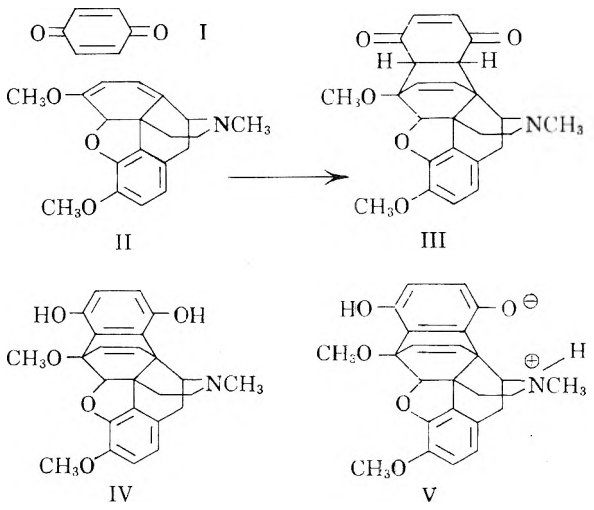
A reexamination of thebainehydroquinone and several of its derivatives indicates that structure IVa is to be preferred to the previously accepted "phenolbetaine" structure (V). This conclusion is based largely on ultraviolet and infrared absorption studies. In connection with this investigation, thebainehydroquinone-10-acetate (IX), thebainehydroquinone diacetate (X) and dehydrothebainequinone (XI) were prepared and characterized for the first time.

The reaction of *p*-benzoquinone (I) with the alkaloid thebaine (II) results in the formation of a yellow, crystalline, Diels-Alder adduct, thebainequinone (III).[2,3] When III is heated with acids or bases, or simply refluxed with high-boiling solvents, it is converted into a colorless, crystalline isomer, thebainehydroquinone. It would be natural to assume that this colorless product is simply the aromatized tautomer (IV) of III, and this was the first structure suggested for it by Schöpf.[3] However, some peculiarities in the chemistry of thebainehydroquinone led Schöpf to a subtle but significant modification of this proposal which resulted in the conclusion that the true structure of this substance is that of a "phenolbetaine" (which might be better termed a zwitterion), shown below as V.[4] Prior to our work on the structure of flavothebaone,[5] a simple rearrangement product of thebainehydroquinone, it was important to us to clarify the nature of its precursor. This was particularly necessary since the zwitterion formulation seemed intrinsically improbable. It was felt that if the properties of thebainehydroquinone could not be reconciled with expectations based on structure IV, there existed the serious possibility that some gross error had been made in assuming that the formation of thebainehydroquinone involved only aromatization. The results of our investigation of this problem are now presented.



The difference between IV and V is, of course, rather small, and not of the type one could hope to establish unequivocally by chemical means. The chief evidence sought was, therefore, physical. Our evaluation of the appropriate data has led us to the adoption of the internally hydrogen-bonded formula IVa as the most plausible representation for thebainehydroquinone. This conclusion serves to place subsequent speculation on the structure of flavothebaone[5] on firm ground.

To begin with, some key derivatives of thebainehydroquinone were required. Preparations of its monoacetate, monomethyl ether, and monomethyl ether monoacetate (presumably VI, VII, and VIII respectively) were carried out as described previously.[3] In addition, a new monoacetate (IX) and a diacetate (X) were prepared for the first time. The success in obtaining IX and X was of some preliminary importance, since one of the striking properties of thebainehydroquinone motivating the assignment of structure V was the presumed inability of the C_{10}-hydroxyl group to form a normal acetate ester.[3]

A summary of the functional group reactions and some of the salient properties of the thebainehydroquinone derivatives studied is given in Chart 1. It is interesting to note that acetylation of the C_7-hydroxyl group (of either IVa, VII, or IX) can be brought about in the usual way with acetic anhydride in pyridine, but not with acetyl chloride in dioxane. In sharp contrast, while the C_{10}-hydroxyl group (of IVa or VI) withstands acetylation by acetic anhydride in pyridine, it reacts readily with acetyl chloride (or in the case of IVa, acetic anhydride as well) in dioxane. It thus appears that one position is attacked only in the presence of an

(1) Opportunity Fellow, John Hay Whitney Foundation, 1955–1956; Allied Chemical and Dye Corp. Fellow, 1956–1957.

(2) W. Sandermann, *Ber.*, **71**, 648 (1938).

(3) C. Schöpf, K. von Gottberg, and W. Petri, *Ann.*, **536**, 216 (1938).

(4) A review of these arguments would be unnecessary and cumbersome at this point. They can be found in reference 3. The "phenolbetaine" formulation was accepted without further comment by K. W. Bentley, *The Chemistry of the Morphine Alkaloids*, Clarendon Press, Oxford, 1954.

(5) J. Meinwald and G. A. Wiley, *J. Am. Chem. Soc.*, **79**, 2569 (1957).

external base, while the other is attacked only in its absence.[6]

The ultraviolet spectra of thebainehydroquinone in both neutral [$\lambda_{max.}^{EtOH}$ 310 mμ (3.78), shoulder *ca.* 290 mμ] and acidic media [$\lambda_{max.}^{EtOH}$, 0.1*N* H^+, 311 mμ (3.83), shoulder 290 mμ] are strikingly similar. Furthermore, they are essentially the same as that of the monomethyl ether (VII) [$\lambda_{max.}^{EtOH}$, 0.1*N* H^+, 310 mμ (3.83), shoulder *ca.* 290 mμ], which from its mode of formation seems clearly to be the 10-methyl derivative. This would not be expected if the ionic structure V were correct, since then the neutral spectrum would represent the phenoxide species, which should differ significantly from both thebainehydroquinone in acid and from VII.

Further support for the assignment of the proton to the C_{10} oxygen rather than to the tertiary nitrogen is obtained from an examination of spectral shifts in alkali. IVa and VII suffer bathochromic shifts of 5 and 10 mμ respectively, when dissolved in tenth normal sodium hydroxide solution. Under similar conditions, hydroquinone monomethyl ether undergoes a bathochromic shift of 17 mμ, whereas hydroquinone itself shows a hypsochromic shift of 13 mμ. The fact that IVa undergoes a spectral shift toward *longer* wave lengths in base, and that it has a spectrum similar to that of VII under these conditions, indicates that a single hydroxyl group is ionizing, and that it is the first rather than the second ionization. In addition, the failure of IVa to ionize doubly under conditions where hydroquinone apparently does, suggests that one of the protons must be strongly hydrogen-bonded. Inspection of molecular models reveals that the tertiary nitrogen atom is very favorably situated for participation in a hydrogen bond with the C_{10}-hydroxyl group.[7] The zwitterion formula (V) would have predicted that any shift in alkali should have been to *shorter* wave lengths, in analogy with the behavior of hydroquinone.

The infrared spectra of IVa and its derivatives can be interpreted in a fashion consistent with the above conclusions. In IVa itself, the 2.99 μ band could be ascribed to the weakly hydrogen-bonded C_7-hydroxyl group, and the 3.99 μ band to the strongly hydrogen-bonded C_{10}-hydroxyl group. On the basis of these bands, structures could be allotted independently to the various derivatives of IVa discussed above. The results are in full accord with the earlier deductions. The pertinent data are included in Chart 1, and need no detailed discussion.

In the course of these studies, two new reactions of IVa which are, however, of no special structural significance were carried out, and it seems appropriate to append these findings at this point. IVa was found to react with potassium *t*-butoxide in *t*-butyl alcohol, to yield a small amount of an indicator (the chief reaction being simply the reversible ionization of IVa), which was not further investigated. Finally, silver oxide was found to transform IVa smoothly into a beautifully crystalline, ruby-red dehydro compound (XI), which

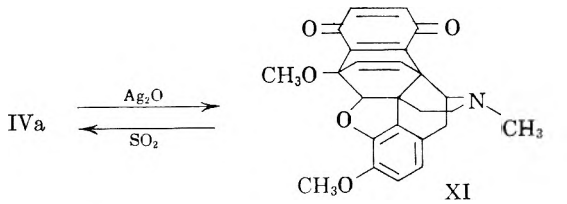
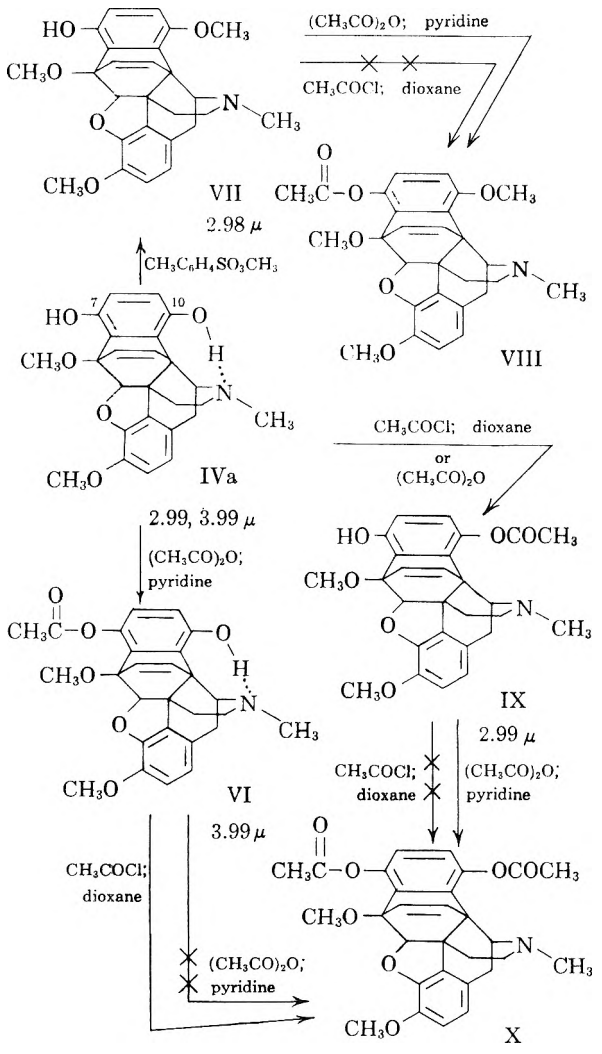


CHART I



(6) Although hypotheses can be constructed to rationalize this behavior, they will not be elaborated at this point in the interest of brevity.

Several unsuccessful efforts were made to prepare thebainehydroquinone dimethylether as described by Schöpf. The product seemed to be a flavothebaone derivative, on the basis of ultraviolet spectra, but no definite conclusions could be reached.

Attempts to prepare thebainehydroquinone-7-methylether using diazomethane were also fruitless (*cf.* ref. 4). Since the completion of this work, this ether has been prepared and characterized in a thorough study of the flavothebaone problem by K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 418 (1957).

(7) Schöpf and co-workers (ref. 3) have already called attention to the proximity of these centers.

could be reconverted to IVa by means of sulfur dioxide.

EXPERIMENTAL[3]

Thebainehydroquinone (IVa). The enolization of thebainequinone (II) was carried out using the Schöpf procedure calling for glacial acetic acid in xylene.[3] Quantitative yields of IVa were obtained. Recrystallization from absolute methanol, as suggested by Schöpf, was found to be superior to any other purification procedure, in spite of the remarkable insolubility of the compound (*ca.* 2.2 g./l. at reflux and *ca.* 0.7 g./l. at 7°). Colorless needles were obtained, m.p. 264–265.0° (lit. 270°).[3] Infrared spectrum (KBr): 2.99, 3.99, 6.13, 6.24 μ; ($CHCl_3$): 2.99, 3.94, 6.11 μ. Ultraviolet spectra: $\lambda_{max.}^{EtOH}$, 0.1*N* H^+, 311 mμ (3.83), shoulder *ca.* 290 mμ; $\lambda_{max.}^{EtOH}$, 310 mμ (3.78), shoulder *ca.* 290 mμ; $\lambda_{max.}^{EtOH-H_2O}$, 6*N* H^+, 306 mμ (3.83); $\lambda_{max.}^{EtOH}$, 0.1*N* OH^-, 315 mμ (3.23), shoulder 298 mμ (3.14).

Anal. Calcd. for $C_{25}H_{25}O_5N$: C, 71.57; H, 6.01; N, 3.32. Found: C, 71.46; H, 6.06; N, 3.58.

Thebainehydroquinone-7-acetate (VI). This derivative was prepared by treatment of IVa with acetic anhydride and pyridine as previously described.[3] Partial hydrolysis of the ester appeared to occur during work-up if the reaction mixture was poured into water instead of using the prescribed method. The product crystallized from absolute benzene or methanol-water as colorless prisms, m.p. 256–257° (lit. 259° dec.).[3] Infrared spectrum ($CHCl_3$): 3.99, 5.69 μ.

Thebainehydroquinone-10-methyl ether (VII). VII was prepared as described previously.[3] Recrystallization from methanol yielded rectangular plates, m.p. 238–240° (lit. 238°).[3] Infrared spectrum (KBr): 3.01 μ. Ultraviolet spectra: $\lambda_{max.}^{EtOH}$, 0.1*N* H^+, 310 mμ (3.83), shoulder *ca.* 290 mμ; $\lambda_{max.}^{EtOH}$, 0.1*N* OH^-, 320 mμ (3.63), shoulder *ca.* 294 mμ (3.45).

Thebainehydroquinone-7-acetate-10-methyl ether (VIII). VIII was prepared from VII using acetic anhydride and pyridine.[3] It crystallized from absolute methanol as colorless needles, m.p. 249–251° (lit. sinters 250°, m.p. 259°).[3] Infrared spectrum (KBr): 3.67, 5.73 μ.

Thebainehydroquinone-10-acetate (IX). *A.* A sample of 0.5 g. of IVa was mixed with 1 ml. of acetyl chloride in 5 ml. of purified dioxane. A visible reaction occurred which converted the needles into a white paste. After standing for 24 hr. the paste had transformed into a colorless glass. The solvent was stripped off, and the residue treated with 5% sodium bicarbonate solution and ethyl acetate. The organic layer was separated, a few drops of acetic anhydride were added, and the solution was concentrated until crystallization occurred.

IX, obtained in this way, crystallized from ethyl acetate containing a small amount of acetic anhydride as colorless prisms, m.p. 222.0–222.5°. Infrared spectrum ($CHCl_3$): 2.99, 5.70 μ.

Anal. Calcd. for $C_{27}H_{27}O_6N$: C, 70.25; H, 5.95; N, 3.04; acetyl, 9.33. Found: C, 70.33; H, 6.00; N, 3.08; acetyl, 9.98.

B. A 0.5 g. sample of finely ground IVa was dissolved in 5 ml. of acetic anhydride. After 2 hr. most of the thebainehydroquinone had dissolved and large, white crystals began to appear. After 48 hr. had elapsed, the reaction mixture was poured into dilute acetic acid. The free base (IX) was precipitated by addition of saturated sodium bicarbonate solution. After filtering, washing and drying, the precipitated IX recrystallized from ethyl acetate containing acetic anhydride as colorless prisms with melting point and infrared spectrum identical with those of the product obtained by procedure A.

Thebainehydroquinonediacetate (X). *A. From thebainehydroquinone-7-acetate* (VII). A 0.8 g. sample of VII was dissolved in 10 ml. of purified dioxane, and 2 ml. of acetyl chloride was added. After standing overnight at room temperature, a white precipitate had appeared. The solvent was evaporated to dryness in vacuum and the residue shaken with a mixture of saturated sodium bicarbonate solution and ethyl acetate. After separating layers, the ethyl acetate solution was dried over magnesium sulfate and evaporated. The infrared spectrum of the crude product contained neither the 2.99 μ nor the 3.99 μ hydroxyl bands. However, it could not be crystallized from dry benzene, and two recrystallizations from absolute ethanol-benzene yielded a crystalline material whose infrared spectrum showed a 3.94 μ band, indicating that the C_{10}-acetyl group was being cleaved.

B. From thebainehydroquinone-10-acetate (IX). A 0.5 g. sample of IX was dissolved in 5 ml. of pyridine containing 2 ml. of acetic anhydride. After standing for 24 hr. at room temperature, the solvent was evaporated under reduced pressure. A tan solid remained whose infrared spectrum was the same as that of the crude product obtained in procedure A. It crystallized as colorless rods, m.p. 187.0–187.7° from ethyl acetate containing a little acetic anhydride. Infrared spectrum ($CHCl_3$): 3.57, 5.69, 6.11, 6.12 μ.

Anal. Calcd. for $C_{29}H_{29}O_7N$: C, 69.00; H, 5.76; N, 2.79. Found: C, 69.01; H, 6.10; N, 2.68.

Ultraviolet spectra of hydroquinone and hydroquinone monomethylether. Hydroquinones $\lambda_{max.}^{EtOH}$, 0.1N H^+, 294 mμ (3.47); $\lambda_{max.}^{EtOH}$, 0.1N OH^-, 281 mμ (3.68). Hydroquinone monomethylether: $\lambda_{max.}^{EtOH}$, 0.1N H^+, 292 mμ (3.46); $\lambda_{max.}^{EtOH}$, 0.1N OH^-, 309 mμ (3.49).

Attempted preparation of methyl ethers using diazomethane. Unchanged starting material was recovered in all instances of attempts to cause IVa to react with diazomethane in ether, xylene, or methanol. Using trimethyl borate as a catalyst, the reaction also failed. Finally, attempts to replace the acetyl groups in VI and IX by methyl groups using diazomethane plus pyridine were abortive.

Action of potassium t-butoxide on thebainehydroquinone. A sample of IVa was dissolved in *t*-butyl alcohol containing potassium *t*-butoxide. The solution was deep red. Acidification with 6*N* hydrochloric acid gave an orange solution plus a white precipitate. The precipitate was readily identified as recovered IVa by its melting point, mixture melting point with an authentic sample, and infrared spectrum.

The orange mother-liquors were found to contain an indicator which was red-violet in base and orange in solutions more acidic than dilute acetic acid. On passing sulfur dioxide through the acidic solution, the color was changed to bright yellow. None of these species was isolated or characterized.

Dehydrothebainequinone (XI). A 0.25 g. sample of IVa was added to a stirred suspension of 1 g. of dry silver oxide and 1 g. of anhydrous sodium sulfate in absolute benzene. After 0.5 hr., the mixture was filtered, and the red-orange solution separated into two portions. One portion was saturated with sulfur dioxide. A white precipitate of recovered IVa (identified by m.p., mixture m.p., and infrared spectrum) was obtained.

The other portion of the filtrate was evaporated to dryness, and the solid recrystallized from ethyl acetate. XI formed ruby-red plates, m.p. 113–115°. Infrared spectrum ($CHCl_3$): 2.99, 6.01, 6.12, 6.22, 6.30 μ. Ultraviolet spectrum: $\lambda_{max.}^{EtOH}$, 2.94 mμ (3.73) plateau; 312 mμ (3.77). An equimolar mixture of XI and IVa shows a $\lambda_{max.}^{EtOH}$ at 312 mμ, with an intensity expected from a summation of the spectra of the two components.

Anal. Calcd. for $C_{25}H_{23}O_5N$: C, 71.93; H, 5.55; N, 3.36. Found: C, 72.02; H, 5.44; N, 3.30.

A suspension of IVa in water reduced periodic acid solution and was converted into a ruby-red solid, which appeared identical with that described above.

ITHACA, N. Y.

(8) All melting points were taken on a calibrated Fisher-Johns hot-stage. Ultraviolet spectra were recorded using a Beckman ultraviolet spectrophotometer, model DK. Infrared spectra were recorded using a Perkin-Elmer double-beam instrument, model 21.

[CONTRIBUTION FROM INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthesis of a Stereoisomer of the $C_{12}H_{18}O_6$ Tricarboxylic Acid from Abietic Acid*

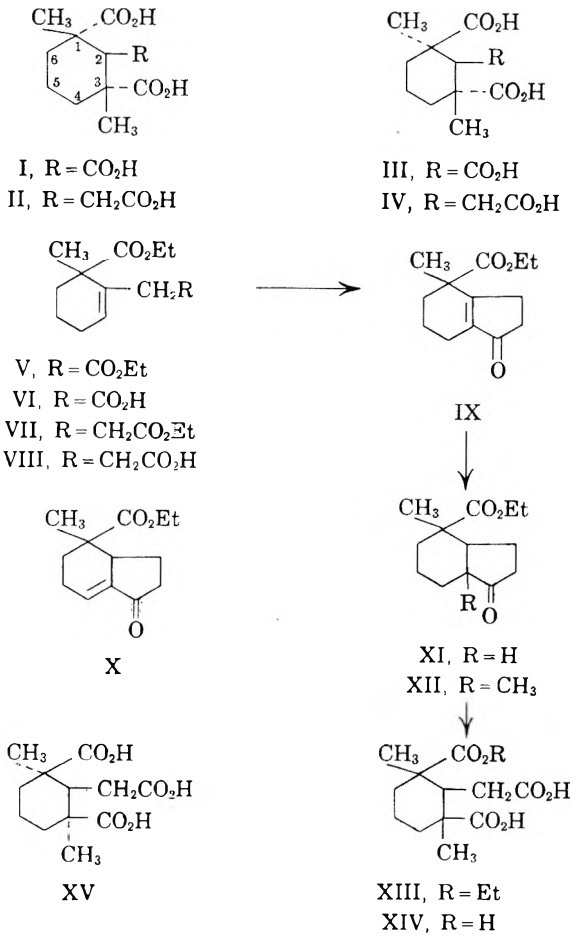
P. NARASIMHA RAO AND P. BAGCHI

Received June 7, 1957

A stereoisomer of the tricarboxylic acid $C_{12}H_{18}O_6$, obtained from the oxidation of abietic acid, has been synthesized. The synthetic product, although having the same melting point as the natural one, depressed its melting point and showed differences in infrared absorption spectrum.

Abietic acid on energetic oxidation with potassium permanganate, on vigorous ozonolysis,[1,2] and on oxidation with nitric acid,[3] gives two homologous tricarboxylic acids, $C_{11}H_{16}O_6$ of m.p. 219° and $C_{12}H_{18}O_6$ of m.p. 213°, which have been assigned structures I and II respectively.[4-7] The important part played by these acids in the elucidation of the structure and stereochemistry of the A/C ring junction of abietic and related resin acids is well known. The fact that these acids are optically inactive[8] settled the relative configurations of the two asymmetric carbon atoms 1 and 3 substituted by methyl and carboxyl groups. Determination of the configuration of the substituents at the carbon atom 2 in the C_{11}- and C_{12}-acids offered considerable difficulty. However, Barton and Schmeidler[7] from a study of the thermodynamic dissociation constants of the C_{11}-acid and its mono and dimethyl esters arrived at the conclusion that the C_{11}-acid has *trans-meso* structure I. Accordingly the C_{12} acid is assigned the *trans-meso* structure II.

Mention should also be made of optically active C_{11}- and C_{12}-acids which were obtained by Ruzicka and Bernold[9] as a mixture, by the oxidation of agathenedicarboxylic acid. Although these acids were not obtained in a pure state, the very fact that their ester mixture showed optical activity, along with the evidence that the stereochemistry of the A/C ring junction of agathenedicarboxylic acid is the same as that of abietic acid, led Ruzicka[9] to assign the stereostructures III and IV for the active C_{11}- and C_{12}-acids, respectively.



In view of the important part played by the C_{11}- and C_{12}-acids in the elucidation of the structures of diterpenoid resin acids, there have been attempts to provide confirmation of their structures by synthesis. Mention may be made of the unsuccessful attempts of Arbusov and Schapschinskaja[10] and of Mukherjee[11] for the synthesis of C_{11}- and C_{12}-acids, respectively.

2-Methyl-2-carbethoxycyclohexanone was subjected to a Reformatsky reaction with ethyl bromo-

* Taken from a thesis submitted by P. N. Rao for the degree of Doctor of Philosophy (Science) of the University of Calcutta, June 1953.

(1) L. Ruzicka, J. Meyer, and M. Pfeiffer, *Helv. Chim. Acta*, **8**, 632 (1925).

(2) L. Ruzicka, M. W. Goldberg, H. W. Huyser, and C. F. Seidel, *Helv. Chim. Acta*, **14**, 545 (1931).

(3) P. Levy, *Ber.*, **62**, 2497 (1929).

(4) L. Ruzicka and H. Waldmann, *Helv. Chim. Acta*, **16**, 842 (1933).

(5) F. Vocke, *Ann.*, **497**, 247 (1932).

(6) H. N. Rydon, *J. Chem. Soc.*, 257 (1937).

(7) D. H. R. Barton and G. A. Schmeidler, *J. Chem. Soc.*, 1197 (1948).

(8) L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, **21**, 565 (1938).

(9) L. Ruzicka and E. Bernold, *Helv. Chim. Acta*, **24**, 931 (1941).

(10) B. A. Arbusov and O. M. Schapschinskaja, *Ber.*, **68**, 437 (1935).

(11) S. M. Mukherjee, *J. Indian Chem. Soc.*, **24**, 495 (1947).

acetate[12,13] in benzene and the hydroxyester obtained in 70% yield was dehydrated in good yield by refluxing with phosphorus pentoxide in benzene. The product of dehydration should be considered as consisting of a mixture of α,β- and β,γ-isomers in which the latter predominates[14] and hence was assigned the structure V. The primary carbethoxyl group of the diester (V) was hydrolyzed by refluxing with one equivalent of sodium hydroxide in ethanol solution to give 6-methyl-6-carbethoxycyclohexenylacetic acid (VI) as a colorless viscous oil, which failed to crystallize. It may be recalled that Chwang, Tien, and Huang[12] prepared an acid by a similar sequence of reactions with the exception that the dehydration of the hydroxyester was effected with the help of thionyl chloride and pyridine and they obtained an acid of m.p. 93°, which perhaps represents the α,β-isomer, since the dehydrating agent employed by the Chinese workers is known to give a higher percentage of the α,β-isomer. Another evidence for the predominant β,γ-structure of our unsaturated acid is the fact that it could be homologated by the Arndt-Eistert method, whereas the method has been shown to fail in the case of α,β-unsaturated acids.[15] The ester-acid VI, on Arndt-Eistert homologation in the usual manner, gave ethyl β-(6-methyl-6-carbethoxycyclohexenyl) propionate (VII) in about 40% yield. The primary carbethoxyl group of the diethyl ester (VII) was hydrolyzed by refluxing with just one equivalent of sodium hydroxide in ethanol solution to furnish β-(6-methyl-6-carbethoxycyclohexenyl)propionic acid (VIII) as a colorless oil. This unsaturated acid was cyclized by refluxing in an atmosphere of nitrogen with a mixture of acetic anhydride and acetic acid containing catalytic quantities of zinc chloride.[16] The cyclized product obtained in about 50% yield was assigned the structure IX and not the alternative structure X since its ultraviolet absorption spectrum shows absorption maximum at 235 mμ (log ϵ = 3.98) which is expected for the $\Delta^{8,9}$-hydrinden-1-one, as against absorption maximum above 240 mμ for a $\Delta^{7,8}$-hydrinden-1-one.[17] Some lactonic product was invariably formed during this cyclization and could be separated by extracting with ice cold 5% sodium hydroxide solution. The unsaturated keto ester IX underwent smooth catalytic hydrogenation over palladium charcoal (5%) to give 4-methyl-4-carbethoxyhydrindan-1-one (XI).

In view of the well known fact that in the case of hydrindan-1-ones a *cis* fusion of the rings represents the energetically favored configuration, the compound XI should be assumed to have a *cis* structure at the ring junction. The stereochemical disposition of the groups at C_4, however, remains uncertain. Nevertheless, we believe that XI is essentially homogeneous since its semicarbazone, m.p. 206° (dec.), did not show any rise in melting point on repeated crystallization.

An angular methyl group was then introduced into XI by methylation with potassium *tert*-butoxide and methyl iodide in a nitrogen atmosphere, following the procedure of Birch and Robinson[18] by first protecting the active methylene group with an *N*-methylanilinomethylene group and subsequent removal of it by hydrolysis, giving an acid, which on esterification with ethanol and sulphuric acid furnished 4,8-dimethyl-4-carbethoxyhydrindan-1-one (XII), a colorless liquid with camphoraceous smell, in about 45% yield. Its semicarbazone obtained in 90% yield by the usual pyridine method was also subjected to fractional crystallization from ethanol to study whether the methylated keto ester XII was a mixture of stereoisomers. But there was absolutely no rise in the melting point of the semicarbazone from one crystallization to another. This suggests that the keto ester (XII) was a homogeneous product and there was no evidence of the formation of more than one stereoisomer in the methylation step. It has been shown by Birch, Jaeger, and Robinson[19] that angular methylation of *cis*-hydrindan-1-one according to the above procedure invariably leads to the *cis*-isomer. In analogy with the above observation keto ester XII should be considered to have a *cis*-hydrindan-1-one structure, with uncertain stereochemical disposition of groups attached to C_4. XII was then oxidized by warming under reflux with concentrated nitric acid (*d* 1.4)[20] to give 1,3-dimethyl-1-carbethoxy-3-carboxycyclohexane-2-acetic acid (XIII) which was not isolated but directly hydrolyzed with ethanolic potassium hydroxide solution to 1,3-dimethyl-1,3-dicarboxycyclohexane-2-acetic acid (XIV). This acid was at first obtained as a glass which subsequently crystallized from glacial acetic acid in small clusters of needles. The analytical sample melted at 213–214° (dec.) and analyzed correctly for $C_{12}H_{18}O_6$.

For direct comparison with the synthetic acid (XIV) an authentic specimen of Ruzicka's C_{12}-acid was prepared by oxidation of abietic acid. The oxidation was carried out with a mixture of concentrated

(12) C. K. Chuang, Y. L. Tien, and Y. T. Huang, *Ber.*, **68**, 866 (1935).

(13) W. E. Bachmann and S. Kushner, *J. Am. Chem. Soc.*, **65**, 1963 (1943).

(14) G. A. R. Kon and K. S. Nargund, *J. Chem. Soc.*, 2461 (1932).

(15) D. Barnard and L. Bateman, *J. Chem. Soc.*, 926 (1950).

(16) W. S. Johnson, H. C. E. Johnson, and J. W. Peterson, *J. Am. Chem. Soc.*, **67**, 1360 (1945).

(17) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1430 (1952).

(18) A. J. Birch and R. Robertson, *J. Chem. Soc.*, 501 (1944).

(19) A. J. Birch, R. Jaeger, and R. Robinson, *J. Chem. Soc.*, 582 (1945).

(20) G. A. R. Kon, R. P. Linstead, and C. Simons, *J. Chem. Soc.*, 814 (1937).

and fuming nitric acids in the presence of a catalytic quantity of vanadium pentoxide.[8] The crystalline C_{11}-acid from the oxidation product was separated, and the residue was then worked up exactly as recommended by Ruzicka[2] for the product of oxidation of abietic acid obtained by oxidation first with potassium permanganate and then with nitric acid. Ultimately a small quantity of C_{12}-acid of m.p. 213° (dec.) was isolated which analyzed correctly for $C_{12}H_{18}O_6$.

It is interesting to note that the synthetic acid (XIV) and Ruzicka's C_{12}-acid from abietic acid have identical melting points. But the mixed melting point of these two showed about 7° depression and melted at 206–208°. This suggests that the synthetic acid is not identical with the natural one, and must be a stereoisomer, a fact which has been confirmed from a study of their infrared spectra (in Nujol mull) shown in Figure 1, *A* and *B*.

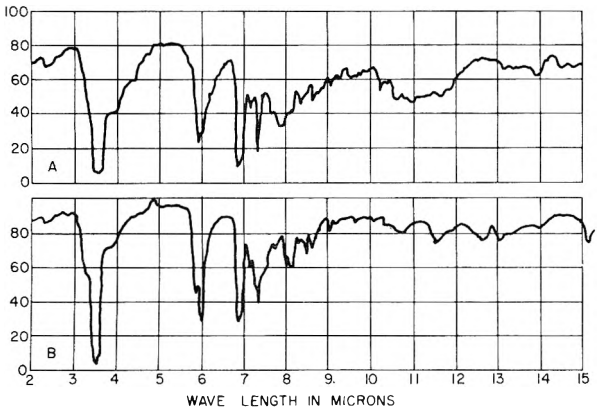


FIG. 1. INFRARED ABSORPTION SPECTRA: Curve A, natural C_{12}-acid from abietic acid: Curve B, synthetic C_{12}-acid.

From what has been previously said regarding the stereochemistry of the intermediate (XII) the acetic acid group and one of the carboxyl groups in the synthetic acid (XIV) must be related *cis* to each other, and the two possible stereostructures for the synthetic C_{12}-acid are *cis*-meso (XV) and racemic (IV). In the latter case, the synthetic acid should be capable of resolution into its antipodes one of which should correspond to the optically active C_{12}-acid obtained from agathenedicarboxylic acid.

The configuration of the other tertiary carboxyl group at C_1-position, however, could reasonably be guessed from a consideration of the theories of catalytic hydrogenation[21] of aromatic compounds which postulate that the hydrogen atoms preferably add to the site of reduction from the sterically less hindered side. In other words, the organic molecule will be adsorbed on the catalyst surface in such a way that the bulky groups are away from the catalyst surface and that the hydrogen atoms are added at the unsaturation from the same side. If we assume that similar phenomena had taken place during the reduction of the unsaturated keto ester (IX) it could be easily visualized that the more bulky carbethoxy group was away from the catalyst surface during hydrogenation and the entering hydrogen atoms took up the *cis*-position with respect to the methyl group at C_4-position with the result that the synthetic C_{12}-acid should have the *cis*-meso configuration (XV). It must be made clear, however, that the arguments put forward in favor of the configuration (XV) for the synthetic C_{12}-acid are based on analogy and hence the assigned configuration should be accepted only with a high degree of probability and not with certainty.

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EXPERIMENTAL

All melting points and boiling points are uncorrected.

Ethyl 1-hydroxy-2-methyl-2-carbethoxycyclohexylacetate was prepared according to the method recommended by previous workers[12,13] with the exception that thiophene-free dry benzene was employed as the solvent in the place of ether-benzene mixture and for one mole of the keto ester, two gram atoms of zinc wool and 1.3 mole of ethyl bromoacetate were used. We obtained consistently a little over 70% yield of the Reformatsky product.

Ethyl 6-methyl-3-carbethoxycyclohexenylacetate (V). To a mixture of the above mentioned Reformatsky ester (29.5 g.) and dry benzene (100 ml.), phosphorus pentoxide was added in three lots (15 g., 5 g., and 5 g.) at intervals of 15 min., and the contents were refluxed under anhydrous conditions on a steam bath for 3 hr. with occasional shaking. The contents were cooled, the benzene solution decanted from the phosphorus pentoxide, and crushed ice and water were added to decompose it. The aqueous solution was extracted with ether and the ether extract was added to the benzene solution. The combined extract was washed with water, sodium bicarbonate solution (5%), and again with water, and dried over anhydrous sodium sulfate. The solvent was then removed and the product distilled under reduced pressure. Ethyl 6-methyl-6-carbethoxycyclohexenylacetate (22 g., 88%) was obtained as a colorless oil, b.p. 132–138°/4 mm. [(lit.[15] b.p. 154–155°/10 mm.)] n_D^{28} 1.4656.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 65.84; H, 8.50.

A drop of the above dehydrated ester readily decolorized bromine in carbon tetrachloride solution.

6-Methyl-6-carbethoxycyclohexenylacetic acid (VI). To a solution of ethyl 6-methyl-6-carbethoxycyclohexenylacetate (22 g.) in ethanol (350 ml.), 1.1*N* aqueous sodium hydroxide solution (83.2 ml.) was added and the contents were refluxed on a water bath for 5 hr. Ethanol was removed under reduced pressure, the residue was dissolved in water, and the solution extracted with ether to remove the neutral material. The aqueous solution was cooled and acidified with dilute hydrochloric acid whereby a heavy oil separated. The mixture was saturated with salt and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, the solvent was removed, and the product was distilled in vacuum. 6-Methyl-6-carbethoxycyclohexenylacetic acid (18.1 g.) was obtained, b.p. 170–174°/3–4 mm., n_D^{27} 1.4820, as a colorless viscous oil. All attempts to induce crystallization were unsuccessful.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.71; H, 7.96. Found: C, 63.50; H, 8.20.

Ethyl β-(6-methyl-3-carbethoxycyclohexenyl)propionate (VII). (*a*) *Preparation of acid chloride of* (VI). To a solution of acid ester (9.1 g.) in thiophene-free dry benzene (10 ml.) cooled in ice water, two drops of dry pyridine and purified thionyl chloride (5.5 ml.) were added and the contents were

mixed intimately by swirling. Reaction took place immediately. The contents were left at room temperature for 4 hr. and then the mixture was warmed at 45° for 15 min. after which the solvent and excess thionyl chloride were removed under reduced pressure. Ten ml. of dry benzene were added to the residual acid chloride and removed again by a second evaporation to remove last traces of thionyl chloride.

(*b*) *Preparation of diazomethane solution.* An ethereal solution (300 ml.) of diazomethane was prepared from *N*-nitroso-*N*-methyl urea (30 g.), carefully distilled, and the distillate containing the diazomethane was dried over pellets of potassium hydroxide and then over sodium to remove last traces of moisture.

(*c*) *Preparation of the diazoketone and its conversion to the homologous ester.* The dried ethereal solution of diazomethane was taken in a round bottom flask and cooled in a freezing mixture. A solution of the acid chloride in dry ether (30 ml.) was then added dropwise with constant swirling to the diazomethane solution and the contents were left overnight at room temperature. Then the ether and excess of diazomethane were removed under reduced pressure (water pump) at room temperature. To the orange colored oily diazoketone in absolute ethanol (100 ml.) a slurry of silver oxide (obtained from 10% silver nitrate solution, 40 ml.) in absolute ethanol was added and the contents refluxed on a water bath. Brisk evolution of nitrogen took place and after 0.5 hr. another lot of silver oxide (0.2 g.) was added and the refluxing continued for 2 hr. more. The solution was then boiled with Norit, filtered, and the filtrate was evaporated under reduced pressure. The liquid diethyl ester left in the flask was then distilled in vacuum. Ethyl β-(6-methyl-6-carbethoxycyclohexenyl)propionate was obtained (4.3 g., 40%) as a colorless oil, b.p. 137–140°/3 mm., n_D^{29} 1.4715. [A low boiling product 70–80°/3 mm. (1.5 g.) was invariably obtained but this was not investigated.]

Anal. Calcd. for $C_{13}H_{24}O_4$: C, 67.16; H, 8.96. Found: C, 66.97; H, 9.04.

β-(6-Methyl-6-carbethoxycyclohexenyl)propionic acid (VIII). To a mixture of ethyl β-(6-methyl-6-carbethoxycyclohexenyl)propionate (25.3 g.) and ethanol (500 ml.) was added 1.109*N* aqueous sodium hydroxide solution (85.2 ml.) and the contents were refluxed on a steam bath for 5 hr. Ethanol was removed under reduced pressure, the residue dissolved in water and extracted with ether to remove any unhydrolyzed ester. The aqueous layer was separated, cooled, and acidified with ice cold dilute hydrochloric acid. The mixture was saturated with salt and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, the solvent was removed and the residue was distilled in vacuum. β-(6-Methyl-6-carbethoxycyclohexenyl)propionic acid (20 g.) distilled at 180–184°/4 mm., n_D^{22} 1.4860, as a colorless viscous oil. All attempts to induce crystallization were unsuccessful.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 64.70; H, 8.36.

4-Methyl-4-carbethoxyhydrind-Δ^{8,9}-en-1-one (IX). To a solution of β-(6-methyl-6-carbethoxycyclohexenyl)propionic acid (4.3 g.) in glacial acetic acid (17 ml.) were added freshly distilled acetic anhydride (70 ml.) and a solution of acetic acid containing zinc chloride (17 ml., fused zinc chloride 20 mg. per ml. of glacial acetic acid) and the contents were refluxed in an atmosphere of nitrogen for 5 hr. The solution gradually turned dark brown in color. After the refluxing was completed, excess acetic anhydride was decomposed with careful addition of water and the acetic acid was removed under reduced pressure. The dark brown residue left in the flask was taken up in ether, the ether extract was washed with water, and then with ice cold 5% sodium hydroxide solution to remove any lactone formed, and again with water until it was free from alkali, and dried over anhydrous sodium sulfate. The solvent was then removed and the residue distilled in vacuum. 4-Methyl-4-carbethoxyhydrind-Δ^{8,9}-en-1-one (2.4 g.) distilled at 144–150°/2–3 mm., n_D^{22} 1.5021.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.10; H, 8.34.

The ultraviolet absorption spectrum of the unsaturated keto ester (XI) showed λ_{max}^{alc} 235 mμ, log ε = 3.98.

Semicarbazone. To a mixture of semicarbazide hydrochloride (0.8 g.) and pyridine (1 ml.) in ethanol (10 ml.) 4-methyl-4-carbethoxyhydrind-Δ^{8,9}-en-1-one (0.45 g.) was added and the mixture was warmed at 70–75° (water bath) for 2 hr. Water was added to the mixture and the precipitated semicarbazone (0.4 g.) (crude m.p. 219–221°) crystallized from ethanol. The analytical sample melted at 220–222° (dec.).

Anal. Calcd. for $C_{14}H_{21}O_3N_3$: N, 15.05. Found: N, 14.80.

4-Methyl-4-carbethoxyhydrindan-1-one (XI). To palladium-charcoal (5% Pd, 1 g.) in ethanol (50 ml.) the above unsaturated keto ester (7 g.) was added and the contents were stirred under hydrogen at room temperature. After the theoretical amount of hydrogen had been consumed (15 hr. stirring), the alcoholic solution was filtered from the catalyst, the solvent was removed, and the product was distilled in vacuum. 4-Methyl-4-carbethoxyhydrindan-1-one distilled at 140–142°/3 mm., $n_D^{22.5}$ 1.4770, as a colorless oil with a sweet camphoraceous odor (6.3 g.).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.64; H, 8.93. Found: C, 69.25; H, 8.80.

The *semicarbazone* was prepared from 0.3 g. of the keto-ester as described above (crude m.p. 202–204°). After two crystallizations from ethanol, the analytical sample melted at 206° (dec.).

Anal. Calcd. for $C_{14}H_{23}O_3N_3$: C, 59.79; H, 8.19. Found: C, 59.88; H, 8.07.

4,8-Dimethyl-4-carbethoxyhydrindan-1-one (XII). (*a*) *Formylation.* Sodium ethoxide was prepared by slow addition of ethanol (3.5 ml.) to a cooled suspension of powdered sodium (1.25 g.) in dry benzene (50 ml.). After the reaction was complete the benzene was removed under reduced pressure. Twenty ml. of dry benzene were added to the sodium ethoxide and removed by a second evaporation. To the cooled suspension of sodium ethoxide in dry benzene (50 ml.) kept under nitrogen, were added ethyl formate (5 ml.) and 4-methyl-4-carbethoxyhydrindan-1-one (6 g.). The mixture was kept under nitrogen for 24 hr. with occasional shaking. The sodium ethoxide gradually disappeared and the solution became viscous and turned deep orange in color. The product was decomposed with ice water and the benzene layer was separated and washed twice with dilute sodium hydroxide solution (5%). The combined aqueous solution was acidified with cold dilute hydrochloric acid and the liberated oil was taken up in ether. The ether extracted was dried over anhydrous sodium sulfate and after removing the solvent the formyl derivative (crude 6.6 g.) was obtained. It gave a deep violet color with alcoholic ferric chloride solution.

(*b*) *N-methylanilino derivative.* To the aforementioned crude formyl compound (6.6 g.) in benzene (100 ml.) *N*-methylaniline (4 g.) was added and the mixture was refluxed on a steam bath for 2 hr. The water formed in the reaction was removed with the help of a Dean-Starke water separator. The solvent was then evaporated under reduced pressure and the residue was evaporatively distilled in high vacuum (from an air bath at 170° and pressure 0.4 mm.). The *N*-methylanilino compound was obtained as a very viscous gum, yellowish brown in color (7.6 g.).

(*c*) *Methylation.* To a cooled solution of potassium (5 g.) in *tert*-butyl alcohol in a 3-necked flask, fitted with a mechanical stirrer, reflux condenser, and a dropping funnel and filled with dry nitrogen, was added the solution of N-methylanilino compound (7.6 g.) in *tert*-butyl alcohol (10 ml.) and the contents were stirred. After 2 min. methyl iodide (25 ml.) was added and the stirring continued at room temperature for 2 hr. Gradually the dark brown color of the mixture disappeared and potassium iodide separated. The contents were refluxed for 2 hr., most of the solvent removed under reduced pressure and the residue diluted

with water, and extracted with ether and the solvent was removed.

(*d*) *Hydrolysis.* The above residue was refluxed for 2 hr. with a mixture of water (100 ml.), ethanol (60 ml.), and concentrated sulfuric acid (15 ml.). The product was extracted with ether, and the residue after the removal of the solvent was refluxed with 5% sodium hydroxide solution (150 ml.) for 4 hr. The reaction mixture was cooled and acidified with dilute hydrochloric acid and the liberated keto acid was taken up in ether. The solvent was removed and the residue was esterified by refluxing with a mixture of ethanol (30 ml.) and concentrated sulfuric acid (4 g., d. 1.84) for 10 hr. Crushed ice and water were added and the solution saturated with ammonium sulfate, and extracted with ether. After removing the solvent the residue was distilled in vacuum. 4,8-Dimethyl-4-carbethoxyhydrindan-1-one distilled at 145–150°/2–3 mm., n_D^{21} 1.4837, as a colorless mobile oil (3 g.) with a pleasant camphoraceous smell which was distinctly different from that of the unmethylated keto ester.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.70; H, 9.30.

The *semicarbazone* was prepared from 0.4 g. of the keto ester (XII) as described previously. The crude semicarbazone (0.47 g.) m.p. 230–232° (dec.) amounting to 90% was obtained. The derivative was fractionally crystallized from ethanol but it was observed that the melting point was practically the same after each crystallization. The analytical sample was obtained as small leaflets, m.p. 232–233° (dec.).

Anal. Calcd. for $C_{15}H_{25}O_3N_3$: C, 61.02; H, 8.47. Found: C, 61.03; H, 8.72.

1,3-Dimethyl-1,3-dicarboxycyclohexan-2-acetic acid (XIV). 4,8-Dimethyl-4-carbethoxyhydrindan-1-one (2 g.) was heated under reflux on a water bath with concentrated nitric acid (8 ml., d. 1.4) for 1 hr. and then 2 hr. more with the addition of water (6.5 ml.). The contents were cooled and the nitric acid and water were removed by keeping the flask in a vacuum desiccator over potassium hydroxide for 48 hr. The crystalline solid along with the adhering oil left in the flask was directly hydrolyzed by refluxing with a solution of potassium hydroxide (4 g.) in ethanol (20 ml.) for 5 hr. The alcohol was removed and the residue dissolved in water and acidified with 2*N* hydrochloric acid, and extracted with ether after saturating with ammonium sulfate. The solvent was removed and the residue which was obtained as a glass was dissolved in glacial acetic acid (5 ml.) when gradually clusters of stout needles began to separate after two days. They were filtered and washed with a little cold acetic acid. The first crop of crystals amounted to 0.3 g.; crude m.p. 211–213° (dec.). After some days another crop of crystals was obtained (0.15 g.) from the mother liquor. The analytical sample melted at 213–214° (dec.) after two crystallizations from glacial acetic acid.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 6.98. Found: C, 55.90; H, 7.26.

The melting point was determined according to the direction given by Ruzicka.[2]

Preparation of authentic $C_{12}H_{18}O_6$ tricarboxylic acid from abietic acid. Abietic acid was prepared from colophony according to the method of Palkin and Harris,[22] the acid sodium salt ($C_{19}H_{29}COONa \cdot 3C_{20}H_{30}O_2$) was crystallized from ethanol only once and the abietic acid liberated from it melted at 163–167°.

Abietic acid was oxidized with a mixture of concentrated and fuming nitric acids to which 0.2% (on the weight of abietic acid) of vanadium pentoxide was added as a catalyst as suggested by Barton.[8] After the oxidation was complete the nitric acid was removed by evaporation on a water bath, and the resinous residue was dissolved in acetone and kept in a refrigerator. The $C_{11}H_{16}O_6$-tricarboxylic acid crystallized out in nearly pure form and was further purified by recrystallization from acetone, m.p. 219° (dec.). Mixed melting point with an authentic specimen kindly supplied by Professor Ruzicka showed no depression. To the residue (250 g.) obtained after separation of the crystallized C_{11}-acid, was added a mixture of absolute methanol (500 ml.) and concentrated sulfuric acid (125 g., d. 1.84) and the contents were refluxed on a water bath for 10 hr. Half the quantity of methanol was removed under reduced pressure, water was added, and the product separated into acidic and neutral fractions with sodium carbonate solution and ether. The neutral fraction obtained from the ether extract was carefully fractionated in high vacuum and the fraction distilling at 135–155°/0.5 mm. (27.1 g.) was collected. The ester (27.1 g.) was hydrolyzed by heating under reflux at 130° with concentrated hydrochloric acid (250 ml.) for 20 hr. The crystalline product (12.2 g.) obtained after the hydrolysis was esterified by refluxing with a mixture of absolute methanol (100 ml.) and concentrated sulfuric acid (5 g.) for 40 hr. Again the reaction product was separated into acidic and neutral fractions, as described above. The neutral fraction was distilled in vacuum and the fraction distilling at 130–135°/0.1 mm. was collected (3.1 g.) and again hydrolyzed with concentrated hydrochloric acid. The acid so obtained (1.2 g.) was found to melt at 208–210°. This suggested that the acid was still a mixture of C_{11}- and C_{12}-acids and the pure C_{12}-acid was separated as the triester by re-esterifying the acid mixture (1.2 g.) of m.p. 208–210°, with 5% methanolic hydrochloric acid (30 ml.). The neutral fraction on hydrolysis with concentrated hydrochloric acid gave the C_{12}-acid (0.6 g.) and the analytical sample after two crystallizations from acetone melted at 213° (dec.). Mixed melting point with the authentic C_{11}-acid was found to be 205–207° (lit.[2] states mixed m.p. 205–207°). The melting point was determined as described by Ruzicka.[2]

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.81; H, 6.98. Found: C, 55.90, 56.01; H, 7.02, 6.99.

Acknowledgment. A preliminary communication on this subject appeared in *Science and Culture* (*India*).[23] We are grateful to Dr. P. C. Dutta, Head of the Dept. of Organic Chemistry, Indian Association for the Cultivation of Science, Calcutta—32, for his active interest during the course of this investigation. Our thanks are also due to Drs. P. Sen Gupta and H. Khastgir for the infrared spectra.

JADAVPUR, CALCUTTA 32

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[CONTRIBUTION FROM THE DIVISION OF STEROID METABOLISM AND BIOCHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Synthesis of 17α,20α-Dihydroxysteroids[1]

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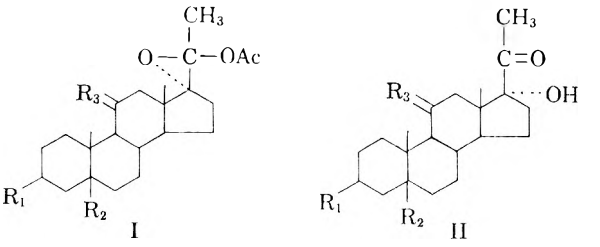
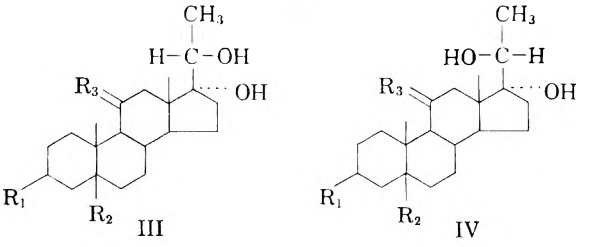
The preparation of 17α,20α-dihydroxysteroids by the lithium aluminum hydride reduction of 17α,20β-epoxy-20α-acetoxysteroids and the corresponding 17α-hydroxy-20-ketosteroids has been studied. Reduction of the epoxyacetates afforded the 17α,20α-glycols in higher yields.

The present study on the synthesis of 17α,20α-dihydroxysteroids was initiated because of the interest in the role of such glycols in the metabolism of adrenal steroid hormones.[2] There are a number of methods for the preparation of 17α,20-dihydroxysteroids but many of these yield the glycol with the β-orientated C-20 hydroxyl group as the principal product. Reduction of 17α-hydroxy-20-ketosteroids with lithium aluminum hydride affords the 17α,20α-dihydroxy epimer as the main product[3] but the yields are not so high as desired. Soloway and coworkers[4] reported that reduction of 17α,20β-epoxyallopregnane-3β,20α-diol diacetate (I B) with lithium aluminum hydride gave rise to a single product, allopregnane-3β,-17α,20α-triol (IV B) in 76% yield. Although the reduction of epoxyacetates with this reagent is highly stereoselective, it does not proceed with the formation of only a single α-glycol.[5] A study on the yields of the epimeric steroids obtained by the reduction of 17α,20β-epoxy-20-acetoxysteroids with lithium aluminum hydride has therefore been made. The corresponding 17α-hydroxy-20-ketosteroids were also reduced in order to evaluate the merits of the two methods for the synthesis of 17α,20α-dihydroxysteroids. It was found that the reduction of epoxyacetates with lithium aluminum hydride gave higher yields of 17α,-20α-glycols than the reduction of the corresponding ketols. Furthermore, since the 17α,20β-epoxyacetates are intermediates in the synthesis of 17α-hydroxy-20-ketosteroids, the direct reduction of the former is the method of choice for the preparation of 17α,20α-dihydroxysteroids.



A. R_1 = α-OAc R_2 = α-H R_3 = H_2
B. R_1 = β-OAc R_2 = α-H R_3 = H_2
C. R_1 = α-OAc R_2 = β-H R_3 = H_2
D. R_1 = α-OAc R_2 = β-H R_3 = O



A. R_1 = α-OH R_2 = α-H R_3 = H_2
B. R_1 = β-OH R_2 = α-H R_3 = H_2
C. R_1 = α-OH R_2 = β-H R_3 = H_2
D. R_1 = α-OH R_2 = β-H R_3 = H, β-OH
E. R_1 = α-OH R_2 = β-H R_3 = O

Chart 1

The following epoxyacetates, 17α,20β-epoxyallopregnane-3α,20α-diol diacetate (I A), 17α,20β-epoxypregnane-3α,20α-diol diacetate (I C), and 11-keto-17α,20β-epoxypregnane-3α,20α-diol diacetate (I D), and their corresponding 17α-hydroxy-20-ketosteroid analogs II A–D, were reduced with lithium aluminum hydride. The resulting epimeric 17α,20-glycols (III and IV) were separated as their 3,20-diacetates by a partition type chromatography on silica gel containing *tert*-butyl alcohol and elution with increasing amounts of *tert*-butyl alcohol in methylene chloride. In some cases the reduction products were directly separated on silica gel containing ethanol and eluted with increasing amounts of ethanol in chloroform. The 3,20α-diacetates were eluted first in the former system but the or-

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

(2) (a) A. M. Bongiovanni, W. R. Eberlein, and J. Cara, *J. Clin. Endocrinol. and Metab.*, **14**, 409 (1954). (b) E. C. Reifenstein, **16**, 1262 (1956). (c) J. P. Rosselet, J. W. Jailer, and S. Lieberman, *J. Biol. Chem.*, **225**, 977 (1957). (d) D. K. Fukushima and T. F. Gallagher, **226**, 725 (1957).

(3) (a) H. Hirschmann and F. B. Hirschmann, **187**, 137 (1951). (b) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).

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(5) (a) M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Compt. rend.*, **235**, 177 (1952). (b) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954). (c) W. Biggerstaff and T. F. Gallagher, *J. Org. Chem.*, **22**, 1220 (1957).

der was reversed for the alcohols in the latter system so that the 20β-hydroxy epimers were eluted before the 20α-hydroxy derivatives.

It was found that reduction of 17α,20β-epoxy-20α-acetoxysteroids resulted in about 70% yield of the 17α,20α-dihydroxysteroids whereas less than 10% of the epimeric 17α,20β-glycols was obtained (Table I). The yields of 17α,20α-glycols by the lithium aluminum hydride reduction of the 17α-hydroxy-20-ketosteroids in the present study were about 30–55% whereas the yields of the 17α,20β-epimers were from 30–45% (Table I). These yields are comparable with the results in the literature[3,6] although other investigators have reported only the 17α,20β-dihydroxy epimer from this reduction.[7]

TABLE I

REDUCTION OF STEROIDS WITH LITHIUM ALUMINUM HYDRIDE TO 17α,20-DIHYDROXYSTEROIDS

Epoxyacetates	17α,20α-Glycol, %	17α,20β-Glycol, %
17α,20β-Epoxyallopregnane-3α,20α-diol diacetate	68	3
17α,20β-Epoxyallopregnane-3β,20α-diol diacetate[a]	76	
17α,20β-Epoxypregnane-3α,20α-diol diacetate	70	8
3α,20α-Diacetoxy-17α,20β-epoxy-pregnane-11-one[b]	62[c]	8[c]
Ketols		
3α-Acetoxy-17α-hydroxyallopregnane-20-one	55	4[d]
3β-Acetoxy-17α-hydroxyallopregnane-20-one	45	29
3α-Acetoxy-17α-hydroxypregnane-20-one	41	31
3α,17α-Dihydroxypregnane-11,20-dione[b]	29[c]	45[c]

[a] A. H. Soloway, W. J. Considine, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2941 (1954). [b] Isolated as pregnane-3α,11β,17β,20-tetrol. [c] Includes the 11α-hydroxy epimer. [d] A mixture of the two epimers was obtained in 22% yield which was not resolved.

In contrast to lithium aluminum hydride, the metal borohydrides reduce 20-ketones predominantly to the 20β-hydroxy epimer. Thus the reduction of 3α,17α-dihydroxypregnane-11,20-dione (II D) with lithium borohydride or sodium borohydride in aqueous methanol overnight at room temperature gave 3α,17α,20β-trihydroxypregnane-11-one (IV E) in 71% yield, the 20α-hydroxy epimer (III E) in 5% yield and pregnane-3α,11β,17α,-20β-tetrol (IV D) in 8% yield. However, the use of a large excess of sodium borohydride under similar conditions has afforded only pregnane-3α,11β,17α,-20β-tetrol.[8] The large excess of the metal hydride is necessary for the reduction of the 11-ketone because the rate of reduction of this carbonyl group is slow[8c] and there is loss of the reagent by reaction with the solvent.

The assignment of the orientation of the C-20 hydroxy group in the heretofore undescribed 17α,-20-dihydroxysteroids, III A and D and IV A, was made by the application of molecular rotation differences (Table II). Further evidence was furnished by comparison of the order of elution in the partition chromatogram of the epimeric 17α,20-glycols, either as the aclohol or acetate, with that of known epimeric compounds. The molecular rotation differences resultant from acetylation of the 20-hydroxy epimers have been described by Sarett.[9] Since it would be tedious to prepare the necessary 3-acetoxy-17α,20-dihydroxysteroids[10] as reference compounds, the molecular rotation difference due to the conversion of 3-acetoxy-17α-hydroxy-20-ketosteroid to the epimeric 3,20-diacetoxy-17α-hydroxysteroid has been calculated (Table II). The differences for the compounds studied show good agreement. The ΔM is about −70 for the 17α,-20α-dihydroxysteroids (Δ^{α}) and about +125 for the 17α,20β-epimer (Δ^{β}) when the optical rotations were taken in chloroform. However, when the molecular rotation differences are calculated with optical rotation values obtained in acetone solution, the Δ^{α} is about −200 whereas the Δ^{β} is approximately 0. The discrepancy is primarily due to a solvent effect on the optical rotations of the 17α-hydroxy-20-ketosteroids since there is no solvent effect on the 17α-hydroxy-20-acetoxy derivatives. The effect of solvent on the optical rotations of α-ketols has previously been pointed out by Norymberski.[11]

After the reduction of 3α,17α-dihydroxypregnane-11,20-dione to the epimeric pregnane-3α,-11β,17α,20-tetrols with lithium aluminum hydride, two other isomeric pregnanetetrols were isolated in small amounts. These were pregnane-3α,11α,17α,-20α-tetrol and its 20β-hydroxy epimer; both were isolated as the 3,11,20-triacetates. The former was also obtained from the lithium aluminum hydride reduction of 3α,20α-diacetoxy-17α,20β-epoxypregnan-11-one and 11-ketopregnane-3α,17α,20α-triol-3,20-diacetate. That these two 11α-acetoxy compounds are epimeric at C-20 is borne out by the

(6) G. I. Poos, *J. Am. Chem. Soc.*, **77**, 4932 (1955).

(7) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, **73**, 1528 (1951).

(8) (a) H. Herzog, M. Jevnik, P. Perlman, A. Nobile, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 266 (1953). (b) E. P. Oliveto and E. B. Hershberg, **75**, 488 (1953). (c) J. I. Appleby, G. Gibson, J. K. Norymberski, and R. D. Stubbs, *Biochem. J.*, **60**, 453 (1955).

(9) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1175 (1949).

(10) In the acetylation of the reduction products of the allopregnane derivatives to the diacetate a small amount of 20-monoacetates was obtained. This fact indicates that it would be very difficult to isolate 3-monoacetylated products in large amount. The selective monoacetylation of the 20-hydroxyl group has also been observed by Sarett.[9]

(11) J. K. Norymberski, *J. Chem. Soc.*, 762 (1954).

TABLE II

MOLECULAR ROTATION DIFFERENCES IN THE REDUCTION OF 17α-HYDROXY-20-KETOSTEROIDS TO 17α-HYDROXY-20-ACETOXYSTEROIDS

	M_D		Δ^α		Δ^β		$\Delta^{\alpha-\beta}$	
	Chl	An	Chl	An	Chl	An	Chl	An
3α-Acetoxy-17α-hydroxypregnane-20-one	+102[a]							
Pregnane-3α,17α,20α-triol 3,20-diacetate	+ 12[b]		−90				+220	
Pregnane-3α,17α,20β-triol 3,20-diacetate	+232[b]				+130			
3β-Acetoxy-17α-hydroxyallopregnane-20-one	−60[a]	+60[c]						
Allopregnane-3β,17α,20α-triol 3,20-diacetate		−126[d]		−186				+239
Allopregnane-3β,17α,20β-triol 3,20-diacetate		+113[d]				+53		
17α-Hydroxypregnane-3,11,20-trione		+245[a]						
17α-Hydroxy-20α-acetoxypregnane-3,11-dione		+47[e]		−198				+185
17α-Hydroxy-20β-acetoxypregnane-3,11-dione		+232[f]				−13		
11β,17α-Dihydroxy-Δ⁴-pregnene-3,20-dione	+363[a]							
11β,17α-Dihydroxy-20α-acetoxy-Δ⁴-pregnene-3-one	+307[g]		−56				+356	
11β,17α-Dihydroxy-20β-acetoxy-Δ⁴-pregnene-3-one	+663[g]				+300			
3α-Acetoxy-17α-hydroxyallopregnane-20-one	+6[h]							
Allopregnane-3α,17α,20α-triol 3,20-diacetate	−66[b]		−72				+222	
Allopregnane-3α,17α,20β-triol 3,20-diacetate	+156[b]				+150			
3α-Acetoxy-17α-hydroxypregnane-11,20-dione	+196[i]	+328[j]						
3α,20α-Diacetoxy-17α-hydroxypregnane-11-one	+144[b]	+104[j]	−52	−224			+168	+207
3α,20β-Diacetoxy-17α-hydroxypregnane-11-one	+312[k]	+311[k]			+116	−17		
3α-Acetoxy-11β,17α-dihydroxypregnane-20-one	+156[a]	+324[l]						
Pregnane-3α,11β,17α,20α-tetrol 3,20-diacetate	+71[b]	+73[b]	−85	−251			+188	+222
Pregnane-3α,11β,17α,20β-tetrol 3,20-diacetate	+259[b]	+295[m]			+103	−29		

$\Delta^\alpha = \Delta M_D$ (20-C=O → 20α-OAc) $\Delta^\beta = \Delta M_D$ (20-C=O → 20β-OAc) $\Delta^{\alpha-\beta} = \Delta M_D$ (20α-OAc → 20β-OAc)
Chl = chloroform An = acetone

[a] This laboratory. [b] This investigation. [c] T. H. Kritchevsky and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951). [d] D. A. Prins and T. Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940). [e] L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1169 (1949). [f] E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 6113 (1954). [g] G. I. Poos, *J. Am. Chem. Soc.*, **77**, 4932 (1955). [h] D. K. Fukushima, A. D. Kemp, R. Schneider, M. B. Stokem, and T. F. Gallagher, *J. Biol. Chem.*, **210**, 129 (1954). [i] E. P. Oliveto and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 5167 (1954). [j] L. H. Sarrett, *J. Am. Chem. Soc.*, **70**, 1690 (1948). [k] M. Finkelstein, J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **36**, 1266 (1953). [l] E. P. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 486 (1953). [m] E. P. Oliveto and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 488 (1953).

molecular rotation difference of the triacetates. This value is +172, in good agreement with +200 for $\Delta^{\alpha-\beta}$ found in the present study (Table II). The production of an 11α-hydroxy isomer is quite general for adrenal steroids and is reported by Poos[6] in the reduction of 3-ethylenedioxy-17α-hydroxy-Δ⁵-pregnene-11,20-dione.

It has been recently postulated that the lithium aluminum hydride reduction of an epoxyacetate proceeded *via* the intermediate formation of a ketol (Fig. 1).[12] However, from the present study it is quite apparent that this mechanism does not apply. This follows from the fact that the yield of 17α,20α-glycols differs between the reduction of 17α,20β-epoxy-20-acetoxy- and 17α-hydroxy-20-ketosteroids. From this it is presumed that the reduction of the epoxyacetate proceeds in part by a mechanism similar to the one proposed by Gaylord for the reduction of the –N–C–O grouping.[12]

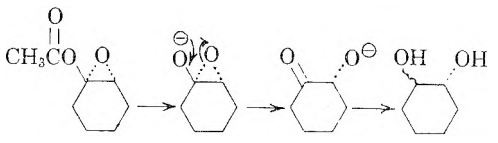

FIGURE 1

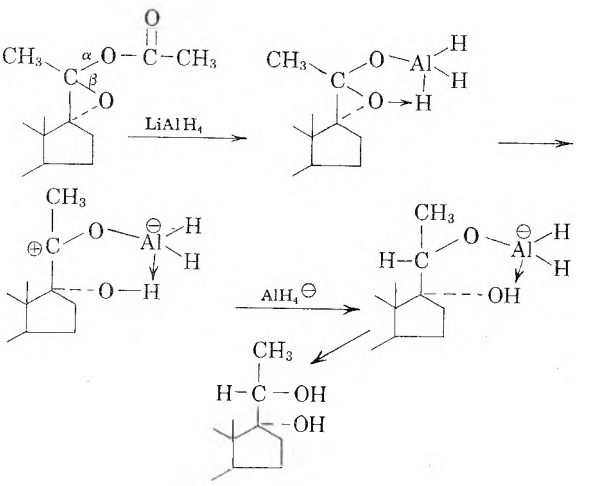

FIGURE 2

(12) N. G. Gaylord, *Experientia*, **10**, 351 (1954).

EXPERIMENTAL[13]

Allopregnane-3α,17α,20-triols. A. From 17α,20β-epoxyallopregnane-3α,20α-diol diacetate (I A). A solution of 2.2 g. of 17α,20β-epoxyallopregnane-3α,20α-diol diacetate[14] in 200 ml. of ether was added with stirring to a suspension of

(13) All melting points are corrected. The optical rotations were taken in chloroform solution unless stated otherwise.

(14) D. K. Fukushima, A. D. Kemp, R. Schneider, M. B. Stokem, and T. F. Gallagher, *J. Biol. Chem.*, 210, 129 (1954).

1.3 g. of lithium aluminum hydride in 250 ml. of ether. The mixture was then refluxed for 2 hr. and the excess reagent destroyed with ethyl acetate. After acidification with dilute sulfuric acid, the crude triol was extracted with ethyl acetate. The extract was washed with base and brine, dried, and the solvent evaporated to give 1.8 g. of crude reduction product. The epimeric triols were separated on 800 g. of silica gel containing 320 ml. of ethanol by elution with ethanol in chloroform at a rate of 15 ml./hr. With 5% ethanol in chloroform, 70 mg. of a substance judged to be allopregnane-3α,17α,20β-triol by infrared spectrometry was obtained. Recrystallization from ethyl acetate and from methanol gave 26 mg. of allopregnane-3α,17α,20β-triol (IV A), m.p. 226–229°; $[\alpha]_D^{25}$ −5.8°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.63; H, 10.89.

Elution with 6% ethanol in chloroform afforded 1.20 g. of the triol epimeric at C-20. Recrystallization from methanol gave 1.03 g. of allopregnane-3α,17α,20α-triol (III A), m.p. 224–228°; the analytical sample melted at 228–230°; $[\alpha]_D^{26}$ −13.2°. The mixture with the 20β-hydroxy epimer melted at 204–219°.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.45; H, 10.43.

Acetylation with acetic anhydride and pyridine at room temperature afforded allopregnane-3α,17α,20α-triol 3,20-diacetate which had a double m.p. 123–124° and 130–131°; $[\alpha]_D^{27}$ −15.7°.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.77.

B. From 3α-acetoxy-17α-hydroxyallopregnane-20-one (II A) *with lithium aluminum hydride.* A solution of 200 mg. of 3α-acetoxy-17α-hydroxyallopregnane-20-one[14] in 15 ml. of ether and 10 ml. of benzene was added with stirring to a suspension of 100 mg. of lithium aluminum hydride in 20 ml. of ether. The mixture was refluxed for 3 hr. and worked up in the manner described above. The crude reduction product (180 mg.) was acetylated with pyridine and acetic anhydride at room temperature for 2 hr., yielding 221 mg. of epimeric triol diacetates. The epimers were separated on 100 g. of silica gel containing 40 ml. of *tert*-butyl alcohol. Elution was started with 1% *tert*-butyl alcohol in petroleum ether-methylene chloride (1:1) at the rate of 10 ml./hr. With 1% *tert*-butyl alcohol in methylene chloride, 91 mg. of allopregnane-3α,17α,20α-triol 3,20-diacetate, as judged by infrared spectrometry, was obtained. Recrystallization from petroleum ether afforded 72 mg. of the 3α,20α-diacetate, m.p. 122–129°. The analytical sample had a double m.p., 123–124° and 130–131°; it was found that most of the samples had a melting point range between these two.[15]

Further elution with the same solvent gave 50 mg. of a mixture of the epimeric 3α,20α- and 3α,20β-diacetates of allopregnanetriol from which neither of the pure epimers could be obtained by recrystallization. A small amount of allopregnane-3α,17α,20β-triol 3,20-diacetate was then eluted from the chromatogram. Recrystallization gave 3,20-diacetate, m.p. 203–206°.

Elution with 5% *tert*-butyl alcohol in methylene chloride afforded 30 mg. of allopregnane-3α,17α,20α-triol 20-monoacetate. Recrystallization from acetone-petroleum ether gave the triol monoacetate, m.p. 213–216.5°; $[\alpha]_D^{28}$ −20.7°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 72.52; H, 10.27.

Acetylation with acetic anhydride and pyridine yielded allopregnane-3α,17α,20α-triol 3,20-diacetate. The triol monoacetate was recovered unchanged upon treatment with periodic acid. Oxidation with chromic acid yielded a substance which had an absorption band at 1716 cm.$^{-1}$ indicative of a ketone in a 6-membered ring (3-ketone).

C. From 3α,17α-dihydroxyallopregnane-20-one with sodium borohydride. A solution of 320 mg. of 3α,17α-dihydroxyallopregnane-20-one[14] in 13 ml. of methanol was reduced with 50 mg. of sodium borohydride in 6 ml. of methanol at room temperature overnight. The reduction mixture was diluted with equal volume of brine and extracted with ethyl acetate. The organic layer was washed with brine and dried and the solvent was evaporated to give 313 mg. of crude reduction product. The epimeric triols were acetylated (393 mg.) and chromatographed on silica gel containing *tert*-butyl alcohol in the manner described in *B*. Elution with 1% *tert*-butyl alcohol in methylene chloride afforded 264 mg. of crystalline material judged to be allopregnane-3α,17α,20β-triol 3,20-diacetate by infrared spectrometry. Recrystallization from acetone yielded 189 mg. of the 3α,20β-diacetate, m.p. 198–205°. The analytical sample melted at 203.5–206°; $[\alpha]_D^{28}$ +37.1°.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.52.

Elution with 5% *tert*-butyl alcohol in methylene chloride afforded 50 mg. of allopregnane-3α,17α,20β-triol monoacetate. Chromatography on silica gel and recrystallization from methanol gave prisms, m.p. 179.5–184°, clear at 192°. Acetylation yielded allopregnane-3α,17α,20β-triol 3,20-diacetate. The compound was proved to be the 20-monoacetate since it was recovered unchanged after treatment with periodic acid and afforded 3-ketoallopregnane-17α,20β-diol 20-monoacetate on oxidation with chromic acid.

Pregnane-3α,17α,20-triols. A. From 17α,20β-epoxypregnane-3α,20α-diol diacetate (I C). 17α,20β-Epoxypregnane-3α,20α-diol diacetate[16] (108 mg.) was reduced with 300 mg. of lithium aluminum hydride in the manner described above to give 87 mg. of crude pregnane-3α,17α,20-triols, m.p. 247–250.5°. Recrystallization from ethyl acetate gave 56 mg. of triol, m.p. 250–253°. Further recrystallization from methanol gave 31 mg. of pregnane-3α,17α-triol (III C), m.p. 253–254.5°.

The combined mother liquors (52 mg.) were acetylated and chromatographed on silica gel containing *tert*-butyl alcohol. Elutions with 1% *tert*-butyl alcohol in methylene chloride afforded 37 mg. of pregnane-3α,17α,20α-triol 3,20-diacetate. Recrystallization from methanol gave 29 mg. of the diacetate, m.p. 157.5–160.5°; $[\alpha]_D^{26}$ +3.4°.

Further elution yielded 9 mg. of the epimeric triol diacetate. Recrystallization from methanol gave 3 mg. of pregnane-3α,17α,20β-triol 3,20-diacetate, m.p. 186–188.5°; $[\alpha]_D^{27}$ +57.5°.

B. From 3α-acetoxy-17α-hydroxypregnane-20-one (II C). 3α-Acetoxy-17α-hydroxypregnane-20-one (209 mg.)[16] was reduced with 400 mg. of lithium aluminum hydride as described in method *B* above to give 184 mg. of pregnane-3α,17α,20-triols. Acetylation with acetic anhydride and pyridine for 3 hr. yielded 224 mg. of triol diacetate. Chromatography on silica gel containing *tert*-butyl alcohol and elution with 1% *tert*-butyl alcohol in methylene chloride yielded 72 mg. of pregnane-3α,17α,20α-triol 3,20-diacetate. Recrystallization from benzene gave 54 mg. of the diacetate, partial melt at 144° with transformation of prisms to needles and final melt at 157.5–158.5°. Further elution gave 24 mg. of compound judged to be pregnane-3α,17α,20α-triol diacetate by infrared spectrometry. Recrystallization gave 19 mg. of the triol diacetate, m.p. 140–147°, no depression of the m.p. when mixed with the above sample.

Continued elution with 1% *tert*-butyl alcohol in methylene chloride gave 72 mg. of pregnane-3α,17α,20β-triol 3,20-diacetate as judged by infrared spectrometry. Recrystallization from acetone-petroleum ether gave 60 mg. of the triol diacetate, m.p. 186–188°.

Allopregnane-3β,17α,20-triols. From 3β-acetoxy-17α-hydroxyallopregnane-20-one (II B). 3β-Acetoxy-17α-hydroxyallopregnane-20-one (570 mg.)[3b] was reduced with 600 mg. of lithium aluminum hydride as described in method *B*

(15) Many of the steroids in this investigation exhibited polymorphism and therefore the m.p. of a compound was not a good criterion of its purity.

(16) T. H. Kritchevsky and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951).

above to give 484 mg. of triol. Acetylation afforded 572 mg. of diacetate. Chromatography on silica gel containing *tert*-butyl alcohol afforded 284 mg. of allopregnane-3β,17α,20α-triol 3,20-diacetate as judged by infrared spectrometry. Recrystallization from ethyl acetate–methanol afforded 225 mg. of triol diacetate, m.p. 245–247°.

Further elution gave 54 mg. of a mixture of the diacetates of the epimeric 3β,17α,20-triols with the 20β epimer predominating as judged by infrared spectrometry. Following the mixture, 96 mg. of allopregnane-3β,17α,20β-triol 3,20-diacetate was obtained. Recrystallization from methanol gave 69 mg. of prisms, m.p. 151–159°. Further recrystallization from methanol gave 33 mg. of triol diacetate, m.p. 158–160°.

Pregnane-3α,11β,17α,20-tetrols. A. From 3α,20α-diacetoxy-17α,20β-epoxypregnane-11-one (I D). 3α,20α-Diacetoxy-17α,20β-epoxypregnane-11-one (170 mg.)[17] was reduced with 400 mg. of lithium aluminum hydride as described in method *A* above to give 153 mg. of pregnane-3α,11β,17α,-20-tetrols. Acetylation with acetic anhydride and pyridine at room temperature afforded 181 mg. of the 3,20-diacetate which was chromatographed on silica gel containing *tert*-butyl alcohol.

Elution with 2% *tert*-butyl alcohol in methylene chloride gave 11 mg. of substance judged to be pregnane-3α,11α,17α,-20α-tetrol 3,11,20-triacetate by infrared spectrometry. Further elution with the same solvent yielded 96 mg. of pregnane-3α,11β,17α,20α-tetrol 3,20-diacetate (III D diacetate). Recrystallization from methanol gave 70 mg. of the diacetate, m.p. 211–219°. The analytical sample melted at 214.5–219.5°; $[\alpha]_D^{26}$ +16.2°, +16.7° (acetone).

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 69.09; H, 9.44.

The diacetate III D had two crystalline forms, prisms and needles, melting at the same temperature. Some samples of pure pregnane-3α,11β,17α,20α-tetrol 3,20-diacetate which melted at 209–217° melted at 216.5–222° when pulverized. Chromic acid oxidation of the tetrol diacetate afforded 11-ketopregnane-3α,17α,20α-triol 3,20-diacetate, m.p. 225–227° (III E diacetate).

Saponification of III D diacetate and recrystallization from acetone–benzene gave pregnane-3α,11β,17α,20α-tetrol which had a double m.p. 133–136° and 200–201°; $[\alpha]_D^{29}$ +10.2°.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.45; H, 10.28.

Elution with 3% *tert*-butyl alcohol in methylene chloride afforded 13 mg. of crystalline substance judged to be pregnane-3α,11β,17α,20β-tetrol 3,20-diacetate by infrared spectrometry.

B. From 3α,17α-dihydroxypregnane-11,20-dione. 3α,17α-Dihydroxypregnane-11,20-dione (8.0 g.)[17] was placed in a Soxhlet thimble and continuously extracted into a flask containing 4 g. of lithium aluminum hydride in 500 ml. of benzene and 300 ml. of ether. The excess reagent was destroyed with ethyl acetate. Acidification of the mixture with dilute sulfuric acid gave insoluble crystalline material. Filtration of the solid and several washings with brine, base and water afforded 2.18 g. of pregnane-3α,11β,17α,20β-tetrol, m.p. 274–281°. Ethyl acetate was added to the aqueous filtrate and the organic layer was separated. It was washed successively with brine, base and water. After drying and concentrating the ethyl acetate solution, an additional 1.33 g. of pregnane-3α,11β,17α,20β-tetrol, m.p. 274–278°, was collected by filtration. The two crystalline fractions were combined and recrystallized from methanol to give 2.95 g. of pregnane-3α,11β,17α,20β-tetrol, m.p. 278–283°, reported m.p. 275–282°[8a] and 282–284°.[8c]

The solvent from the ethyl acetate filtrate was removed *in vacuo* to give 4.50 g. of yellow oil. Acetylation with acetic anhydride and pyridine at room temperature for 2 hr. afforded 5.22 g. of pregnanetetrol diacetate. Chromatography on 1.5 kg. of silica gel containing 600 ml. of *tert*-butyl alcohol in methylene chloride afforded 500 mg. of pregnane-3α,11α,17α,20α-tetrol 3,11,20-triacetate, m.p. 202–215.5°. Recrystallization from methanol gave 390 mg. of triacetate, m.p. 228–229°. The analytical sample from acetone melted at 229.5–230.5°; $[\alpha]_D^{30}$ −29°, M_D −140.

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.80; H, 8.94.

The α-orientation of the C-20 hydroxyl group has been assigned since this compound was also a side product of lithium aluminum hydride reduction of the known 11-keto-pregnane-3α,17α,20α-triol 3,20-diacetate to pregnane-3α,-11β,17α,20α-tetrol.

Further elution with the same solvent gave 2.41 g. of pregnane-3α,11β,17α,20α-tetrol 3,20-diacetate, m.p. 218–223°. Recrystallization from methanol gave 2.00 g. of tetrol diacetate, m.p. 212–219.5°.[15]

A mixture (618 mg.) of pregnane-3α,11β,17α,20α- and 20β-tetrol 3,20-diacetate and pregnane-3α,11α,17α,20β-tetrol 3,11,20-triacetate was then eluted.

Elution with 4% *tert*-butyl alcohol in methylene chloride gave 243 mg. of material judged to be pregnane-3α,11β,17α,-20β-tetrol 3,20-diacetate by infrared spectrometry. Recrystallization from methanol gave 72 mg. of the tetrol diacetate, partially melted from 120° and all clear at 189°; $[\alpha]_D^{27}$ +59.3°; reported m.p. 111–112.5° and 186–187°.[2b] An additional 90 mg. of tetrol diacetate, m.p. 128°, clear at 165°, was obtained from the mother liquor.

The mixture (618 mg.) obtained above was oxidized with chromic acid in acetic acid. Upon chromatography 11-keto-pregnane-3α,17α,20-triol 3,20-diacetate was separated from a new substance, pregnane-3α,11α,17α,20β-tetrol 3,11,20-triacetate (86 mg.), m.p. 264–266°, $[\alpha]_D^{27}$ +7.0, M_D +32.

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.83; H, 8.58.

11-Ketopregnane-3α,17α,20-triols. A solution of 200 mg. of lithium borohydride in 15 ml. of methanol was added to a solution of 500 mg. of 3α,17α-dihydroxypregnane-11,20, dione (II D) in 35 ml. of methanol. The reaction mixture was allowed to stand at room temperature overnight and then diluted with equal volume of brine. The solution was acidified to destroy the excess reagent and then neutralized with base. The reduction product was extracted with ethyl acetate and washed with brine. The extract was dried and the solvent was evaporated to give 500 mg. of triolone. Recrystallization from benzene gave 446 mg. of 11-ketopregnane-3α,17α,20β-triol (IV E), m.p. 222–226°. The crystals and the mother liquor were combined and acetylated with pyridine and acetic anhydride at room temperature for 2 hr. to give 658 mg. of triolone diacetate. Chromatography on silica gel containing *tert*-butyl alcohol and elution with 3% *tert*-butyl alcohol in methylene chloride yielded 29 mg. of 11-ketopregnane-3α,17α,20α-triol 3,20-diacetate. Recrystallization from methanol gave 17 mg. of diacetate-m.p. 220–224°. Further recrystallization gave 11-keto-pregnane-3α,17α,20α-triol 3,20-diacetate, m.p. 225–227°; $[\alpha]_D^{27}$ +32.2°, reported m.p. 227–228°.[18] Saponification and recrystallization from benzene gave 11-ketopregnane-3α,-17α,20α-triol (III E), m.p. 184–188°. The triolone had a tendency to gel from this solvent as Sarett[18] noted. Recrystallization from acetone gave needles, m.p. 193.5–194.5°; 7 months later the same samples melted at 203.5–206°. Concentration of the mother liquor yielded prisms, m.p. 205–209°. Sarett[18] reported m.p. 189–191° (from ether) and 210–212° (from benzene) for 11-ketopregnane-3α,17α,20α-triol. The infrared spectra of the two crystalline forms were identical in chloroform solution but differed when taken in potassium bromide disc. This work will be reported elsewhere.

Further elution with the same solvent gave 441 mg.

(17) H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan, and J. H. Hogg, *J. Am. Chem. Soc.*, **76**, 743 (1954).

(18) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1690 (1948).

of 11-ketopregnane-3α,17α,20β-triol 3,20-diacetate, m.p. 240–246°. Recrystallization from methanol gave the diacetate, m.p. 243–245.5°; $[\alpha]_D^{26}$ +72.1°; reported m.p. 244–246°; $[\alpha]_D^{24}$ +71.9°[19]; m.p. 249–250°.[20] Saponification and recrystallization from acetone gave 11-ketopregnane-3α,17α,20β-triol, m.p. 218–220.5°; reported m.p. 179° and 220°.[20] A small amount (50 mg.) of pregnane-3α,11β,17α,20β-tetrol 3,20-diacetate was eluted from the chromatogram. The reduction of 3α,17α-dihydroxypregnane-11,20-dione with sodium borohydride under the same conditions gave essentially the same result.

Acknowledgment. We wish to express our appreciation to Dr. T. F. Gallagher for his interest throughout this investigation and to Dr. G. Roberts and Friederike Herling for the determination and interpretation of the infrared spectra. We are indebted to Merck and Co., Inc., Rahway, N. J. and Schering Corp., Bloomfield, N. J., for their generous gifts of steroids.

NEW YORK, N. Y.

(19) M. Finkelstein, J. v. Euw and T. Reichstein, *Helv. Chim. Acta*, **36**, 1266 (1953).

(20) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1169 (1940).

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Liriodendrin, a New Lignan Diglucoside from the Inner Bark of Yellow Poplar (*Liriodendron tulipifera* L.)

EDGAR E. DICKEY

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A new di-β-D-glucoside was isolated from an alcohol extract of the inner bark of yellow poplar, *Liriodendron tulipifera* L., in yields of 0.05–0.08% of the fresh bark. The glucoside was colorless, odorless, tasteless, crystalline, m.p. 269–270°, and was hydrolyzed by dilute acids to D-glucose and a new lignan. The name "liriodendrin" is suggested for the glucoside and "lirioresinol" for the lignan. Liriodendrin octaacetate and octamethyl ether were prepared as crystalline substances. Lirioresinol was obtained in two forms, lirioresinol-*A* and -*B* from which the corresponding crystalline dimethyl and dibromodimethyl ethers were prepared. The dibromodimethyl ethers were degraded to 4-bromo-5,6-dinitropyrogallol trimethyl ether and bis(hydroxymethyl)succinic acid dilactone to establish lirioresinol as a tetrahydro-1,4-bis(4-hydroxy-3,5-dimethoxyphenyl)furo[3,4-*c*]furan, stereoisomeric with syringaresinol, and liriodendrin the corresponding di-β-D-glucoside. A diastereoisomeric form, lirioresinol-*C*, was obtained upon hydrolysis of liriodendrin with crude almond emulsin.

Introduction. The yellow poplar or tulip tree, *Liriodendron tulipifera* L., is ranked among the most beautiful and valuable of the hardwoods which are native to the North American continent.[1] The Indians made canoes from its strong, light wood. The colonists used the tree extensively for lumber, and developed the use of its bark for medicinal purposes. Morel and Totain[2] stated that without extracts of yellow poplar bark as a substitute for quinine, the War of Independence might have been lost!

During the 19th century, European scientists studied the extractives of the yellow poplar's wood and bark, but the isolation of specific substances was rarely reported.[3] In 1831, Emmet[4] isolated 2–3% of a bitter principle, from the fresh, winter-gathered root bark. He named the substance "liriodendrine," but it has not been reported by later investigators. Bouchardat[5] isolated a crystalline material which was alkaloidal in character but which was not further described. The Lloyds[6] named a material "tulipiferin" which, though not crystalline, was apparently an alkaloid. Since then the extractives of this tree have remained essentially uninvestigated, but the increasing utilization of yellow poplar along with other hardwoods for pulp and paper has renewed interest in its chemistry.

Studies in progress at The Institute of Paper Chemistry indicate that alcoholic extracts of fresh yellow poplar bark consist largely of sugars, and of lesser amounts of unknown phenolic substances, coloring matter, and an essential oil with a distinctive pleasant odor. In addition to these materials, a new colorless substance was crystallized from the extracts in amounts of 0.05–0.08% based on the fresh bark. This substance has been characterized as a di-β-D-glucoside of a new lignan built on a nucleus of tetrahydrofurofuran. *Liriodendrin* is proposed for the name of the glucoside, and *lirioresinol* for the lignan.

Lignans derived from tetrahydrofurofuran. A group of naturally occurring phenylpropane dimers which are linked through the beta-carbon atoms of the side chains are known as lignans, a compre-

(1) C. D. Mell, *Textile Colorist*, **63**, 349 (1941).

(2) P. Morel and P. Totain, *Assoc. franc. avance. sci. Congrès Nîmes, 41 Session*, 810 (1912).

(3) C. Wehmer, *Die Pflanzenstoffe*, p. 336, Jena, G. Fischer, 1929; J. von Wiesner, *Die Rohstoffe des Pflanzenreichs*, Vierte auflage, p. 146. Leipzig, W. Engelmann, 1927.

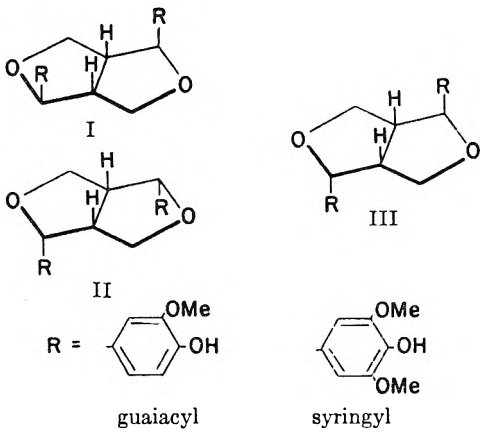
(4) J. P. Emmet, *J. pharm. chim.*, **17**, 334, 400 (1831).

(5) A. Bouchardat, *Bull. de therapeut.*, **19**, 243 (1842).

(6) J. U. Lloyd and C. G. Lloyd, *Pharm. Rundsch.*, **4**, no. 8, 169–72 (1886); *Jahresber. Pharm.*, **46**, 61 (1886); *Am. Druggist*, **15**, no. 6, 101 (June, 1886).

hensive review of which was prepared in 1955 by Hearon and MacGregor.[7]

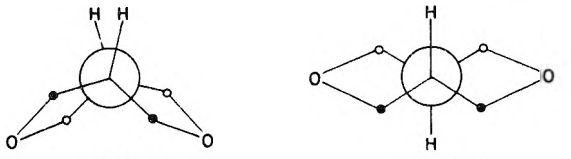
Among the several types of lignans, one group is built on a tetrahydrofuro[3,4-*c*]furan nucleus. (+)-Pinoresinol (I or II), tetrahydro-1,4-bis(4-hydroxy-3-methoxyphenyl)furo[3,4-*c*]furan, was the first guaiacyl type to be elucidated,[8,9] and several others with the same nucleus are now known. The first syringyl derivative of this type, syringaresinol, tetrahydro-1,4-bis(4-hydroxy-3,5-dimethoxyphenyl)furo[3,4-*c*]furan, I, II, or III, was described by Freudenberg and Dietrich.[10] It was synthesized from syringin in the presence of a crude almond emulsin, possibly through the action of accompanying dehydrogenases. The lignan analyzed as a dehydrodisinapyl alcohol and was found to be optically inactive.[10] The procedure was repeated in our laboratory and the product was also optically inactive. Freudenberg and Schraube[11] obtained



Pinoresinol (R = guaiacyl), and Syringaresinol and Lirioresinol (R = syringyl).

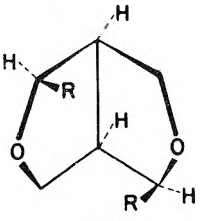
amorphous syringaresinol by a chemical synthesis and possibly identified the product through crystalline derivatives.

The central nucleus, tetrahydrofurofuran, on which these lignans are built, may be satisfactorily represented by the projection formulas, IV and V, as adapted from Newman.[12] The comparatively



Tetrahydrofurofuran nucleus

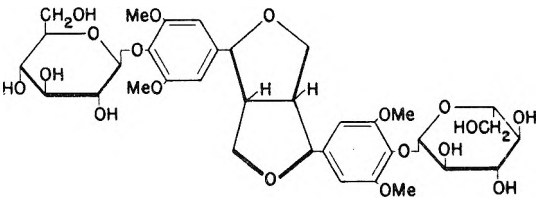
strainless *cis*-form (IV) would appear to be more probable than the puckered and very strained *trans*-form (V). This probability is strongly supported by the fact that all tetrahydrofurofuran lignans thus far elucidated have been derived from the *cis*-form. The spatial character of the *cis*-form may be even more realistically shown by the perspective formula VI (corresponds to formula II above), adapted from Cope and Shen.[13]



Tetrahydrofurofuran nucleus, *cis*-form

When the tetrahydrofurofuran nucleus is diagonally substituted, four asymmetric centers result which furnish two possible *meso*-structures and one *d,l*-pair for the *trans*-form (not shown), and three *d,l*-pairs for the *cis*-form (I, II, III).

The structure of liriodendrin. The new diglucoside was isolated from yellow poplar bark as a colorless, tasteless, crystalline solid. It was hydrolyzed in aqueous acid to D-glucose and the optically active aglucon, lirioresinol, which was diastereoisomeric with syringaresinol. Also the glucoside was hydrolyzed in the presence of a β-D-glucopyranosidase (crude almond emulsin) but not α- or β-anylase to establish that liriodendrin was probably a β-D-glucopyranoside. Liriodendrin was Mäule-positive,[14] and formed a crystalline octa-



Liriodendrin

acetate and a crystalline octamethyl ether. Hydrolysis of the ether and chromatography of the products on paper indicated the presence of a tetramethylglucose and unmethylated lirioresinol. Oxidation of the glucoside with nitrobenzene in alkali followed by chromatographic analysis yielded 13.2%

(7) W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957–1068 (1955).

(8) H. Wedtman, *Svensk Kem. Tidskr.*, **48**, 236–41 (1936).

(9) H. Erdtman and J. Gripenberg, *Acta Chem. Scand.*, **1**, 71–75 (1947).

(10) K. Freudenberg and H. Dietrich, *Chem. Ber.*, **86**, 4–10 (1953).

(11) K. Freudenberg and H. Schraube, *Chem. Ber.*, **88**, 16–23 (1955).

(12) M. S. Newman, *J. Chem. Educ.*, **32**, 344–347 (1955).

(13) A. C. Cope and T. Y. Shen, *J. Am. Chem. Soc.*, **78**, 5912, 5916 (1956).

(14) The chlorination of pyrogallol derivatives followed by treatment with alkali results in the formation of a red to purple color; C. Mäule, *Beitr. wiss. Botanik*, **4**, 166 (1900).

TABLE I

STUDIES ON THE HYDROLYSIS OF THE DIGLUCOSIDE IN ACID

Acid	Time and Temp.	Crude Lirioresinol Yield, %	Crude Lirioresinol Melting Range, °C.
10% Aqueous formic acid	25 min., steam bath	1st crop 51	170–197
		2nd crop 19.5	173–195
		Total 70.5	
10% Aqueous formic acid	25 min., steam bath	55	173–175
Diglucoside dissolved in concd. hydrochloric acid, 0°; then diluted to 7% acid	2 min., steam bath	89	175–195
Diglucoside dissolved in concd. hydrochloric acid, diluted after 3 min. to 7% acid	10 min., room temp.	93	180–200
5% Sulfurous acid	30 min., steam bath	—	174–190
0.5*N* Hydrochloric acid	30 min., steam bath	82	168–197
0.5*N* Hydrochloric acid in 40% aq. ethanol	30 min., steam bath	75	168–202

of syringaldehyde and established the presence of syringyl groups.[15]

In an effort to improve the yield and quality of aglucon from the hydrolysis of the diglucoside, several different acids were tried. The results are summarized in Table I. The lirioresinol from the several hydrolyses melted over a considerable range and varied in yield.

By fractional crystallization of the crude lirioresinol from mixtures of ethanol and chloroform, two purified materials were obtained. The properties of these forms and some of their derivatives are summarized in Table II. To differentiate these forms, the higher melting one was designated as lirioresinol-*A* and the other, lirioresinol-*B*. The variations in yield and melting point of the crude lignan and the subsequent isolation of two forms are consistent with the known lability of such lignans in acid.[1]

TABLE II

SOME PROPERTIES OF LIRIORESINOL AND RELATED COMPOUNDS

	M.P., °C.	$[\alpha]_D$ (In Chloroform), Degrees	Molecular Rotation, [M], Degrees
Lirioresinol-A	210–211	+127	+53,100
Dimethyl ether	118–120	+119	+52,800
Dibromodimethyl ether	124–126	+ 64.4	+38,900
Lirioresinol-B	172–177	+ 62.2	+26,000
Dimethyl ether	121–123	+ 46.2	+20,300
Dibromodimethyl ether	152–155	− 61.9	−39,600
Lirioresinol-C	185–186	+ 48.9	+20,200
D-*Pinoresinol*[a]	120–121	+ 84.4	+30,200
Dimethyl ether	107–108	+ 64.5	+24,900
Dibromodimethyl ether	172–173	− 69.1	−35,700
Epipinoresinol	—	—	—
Dimethyl ether[b]	130–131	+141.1	+54,400

[a] Ref. 9. [b] J. Gripenberg, *Acta Chem. Scand.* **2**, 82 (1948).

Because of the acid sensitivity of lirioresinol, an attempt was made to hydrolyze liriodendrin in the presence of crude almond emulsin. After 23 days at 37°, a product, lirioresinol-*C*, was obtained in a yield of 55% (Table II).

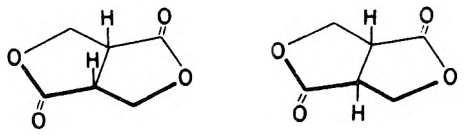
Through an elegant series of reactions Erdtman and Gripenberg[9] determined the structure of the central carbon skeleton of pinoresinol, and in a similar way syringaresinol was established by Freudenberg and Dietrich[10] as a bis(syringyl) tetrahydrofurofuran. Through the same series of reactions, the lirioresinols were converted to their dimethyl ethers from which the dibromodimethyl ethers were readily formed upon direct bromination in chloroform (Table II). The dibromolirioresinol dimethyl ethers were then cleaved in nitric acid to yield 34% of 4-bromo-5,6-dinitrotrimethyl pyrogallol and a very small amount of bis(hydroxymethyl)succinic acid dilactone; their properties are summarized in Table III. The isolation of the optically active dilactone (VIII), rather than the *meso*-form (IX), establishes the presence of the *cis*-form of the diagonally substituted tetrahydrofurofuran ring in lirioresinol. The new lignan is, therefore, tentatively identified as a diastereoisomer of syringaresinol, and its di-β-D-glucoside, liriodendrin, may be represented by formula VII.

(15) J. E. Stone and M. J. Blundell, *Anal. Chem.*, **23**, 771–774 (1951).

TABLE III

DEGRADATION PRODUCTS OF PINORESINOL, SYRINGARESINOL, AND LIRIORESINOL

	Yield, %	M.P., °C.	$[\alpha]_D$, Degrees
4-Bromo-5,6-dinitropyrogallol trimethyl ether			
Freudenberg[10]	38	134–135	—
This work	34	133–134	—
Bis(hydroxymethyl)succinic acid dilactone			
Erdtman[8,9]	—	137–138	Racemic
	65	160–161	+206 (water)
Freudenberg[10]			
From syringaresinol	63	136–137	Racemic
From pinoresinol	48	161	+203 (water)
This work	Very small	158–160	+253 (water)



VIII IX

cis-form *d,l* *trans*-form *meso*

bis(hydroxymethyl)-succinic acid dilactone

From the relative values of the molecular rotations as listed in Table II it would appear that lirioresinol-*B* may have the same configuration as (+) pinoresinol, and that lirioresinol-*A* dimethyl ether may possibly correspond with *epi*-pinoresinol dimethyl ether.[16]

As shown in Fig. 1, the infrared spectra of the

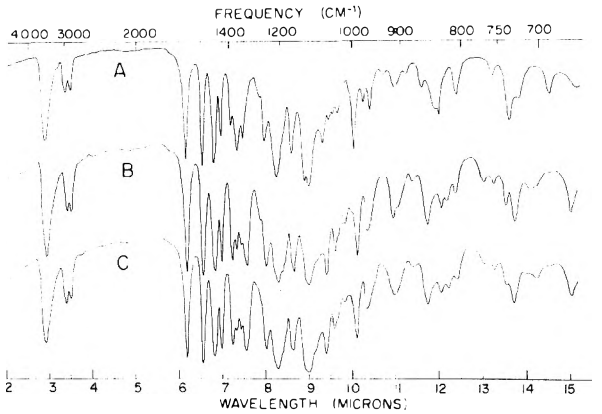


FIG. 1. INFRARED SPECTRA OF SYRINGYL LIGNANS. A. LIRIORESINOL-*A* AND -*B*. B. LIRIORESINOL-*C*. C. SYRINGARESINOL.

optically active lirioresinol-*C* and the inactive syringaresinol, both prepared in the presence of the same enzyme, are nearly identical which indicates no significant difference in structure. Syringaresinol, therefore, may be a single *d,l* pair and lirioresinol-*C* may be the dextrorotatory form. Proof of these possible relationships must await further chemical evidence, and a comparison of infrared spectra and other properties of the appropriate guaiacyl and syringyl compounds. Also, because of the acid sensitivity of lirioresinol, the stereoisomeric form of the lignan present in liriodendrin (VII) cannot yet be fixed.

The work on liriodendrin and the lirioresinols is being continued.

(16) J. Gripenberg, *Acta Chem. Scand.*, 2, 82 (1948).

EXPERIMENTAL

Isolation of liriodendrin. An amount of 20 kg. of fresh whole bark was peeled in 1-inch strips from saplings, 2–3 inches in diameter,[17] and was covered with 95% ethanol. After standing at room temperature for 4–6 weeks, the alcoholic extract, 30 l., was evaporated at reduced pressure, the aqueous concentrate was mixed with filter aid, filtered, and the combined filtrate and washings were extracted with chloroform. An excess of basic lead acetate was added and the heavy yellow precipitate was removed by filtration. The excess lead was then precipitated with hydrogen sulfide, the solution was filtered, and the filtrate was concentrated to a thin sirup at reduced pressure. After standing at room temperature for several days, a heavy deposit of colorless crystals of liriodendrin formed. The crystals were separated by filtration and washed on the funnel with water and absolute ethanol; yield of crude liriodendrin, 10 g. or about 0.05% based on the fresh bark, m.p. 262–265°.[18] The crude diglucoside was recrystallized from hot 50% aqueous ethanol; yield of purified material, 8.1 g., m.p. 269–270°. Liriodendrin was slightly soluble in hot ethanol, acetone, and ethyl acetate, and somewhat more soluble in water, glacial acetic acid, and quite soluble in hot 50% aqueous ethanol (3 g./100 ml. of boiling solvent).

Anal. Calcd. for $C_{34}H_{46}O_{18}$: C, 54.98; H, 6.24; CH_3O, 16.71. Found: C, 54.54; H, 6.35; CH_3O, 16.2.

Liriodendrin octaacetate. Liriodendrin, 1.02 g., was dissolved in a mixture of 5 ml. of pyridine and 10 ml. of acetic anhydride after heating on a steam bath for 45 min. After standing overnight, the clear, colorless reaction mixture was poured into 150 ml. of ice and water. The gummy precipitate gradually became friable, was collected on a tared funnel, and dried; yield 1.53 g. (103%). The acetate was crystallized from 30 ml. of boiling 95% ethanol; yield, 1.37 g. (92%), m.p. 124–125° to form a very viscous melt, $[\alpha]_D^{20}$ +7.2° (c, 4.7, chloroform).

Anal. Calcd. for $C_{50}H_{62}O_{26}$: C, 55.65; H, 5.79; CH_3O,

(17) The yellow poplar saplings were obtained through the courtesy of Dr. J. G. Leech, West Virginia Pulp and Paper Co., Luke, Md.

(18) All melting points were observed in Pyrex capillaries and are uncorrected.

TABLE IV

HYDROLYSIS OF LIRIODENDRIN AND THE RECOVERY OF LIRIORESINOL

Amount of Liriodendrin, G.	Yield of Lirioresinol						
	Crystalline Precipitate			Chloroform Extract		Total Recovered	
	G.	%	M.P., °C.	G.	%	G.	%
1.056	0.349	58.6	185–202	0.234	39.4	0.583	98
1.000	0.407	74.6	168–202	—	—	—	—
2.000	0.672	59.7	—	0.468	—	1.140	101
3.000	1.389	82.2	168–197	—	—	—	—

11.50; CH_3CO, 31.91; mol. wt., 1079. Found: G, 55.46; H, 5.80, CH_3O, 11.38; CH_3CO, 32.1; mol. wt. (Rast), 938.

Liriodendrin octamethyl ether. An amount of 2.0 g. of liriodendrin was suspended in 30 ml. of dioxane in a 1-l. 3-necked flask under efficient mechanical stirring. Sodium hydroxide, 160 ml. of 30%, and 80 ml. of dimethyl sulfate were each added in ten equal portions at 10-min. intervals. The temperature was held at 30° with a water bath. When half the reagents had been added, white crystalline material began to form. It was partly dissolved by the addition of 20 ml. of acetone. After the alkali and dimethyl sulfate were added, the temperature was raised to 75° for 30 min. The mixture was quickly cooled and the crystalline, partly methylated product was collected by filtration. To complete the methylation the general procedure of Freudenberg and Dietrich[10] was used. The material was dissolved in 150 ml. of boiling methanol and 20 ml. of dimethyl sulfate and 40 ml. of 40% potassium hydroxide were added in five portions over a period of 30 min. The heating was continued for an additional 30 min. After dilution with a liter of water, the reaction mixture was allowed to stand overnight and the crystalline precipitate was collected by filtration and dried; yield, 1.23 g., m.p. 165–169°. Two crystallizations from methanol yielded pure material, m.p. 177–178°, $[\alpha]_D^{20}$ +8.6°. Paper chromatograms of an acid hydrolyzate indicated the presence of a tetramethylglucose and the aglucon as the only products.

Anal. Calcd. for $C_{42}H_{62}O_{18}$: C, 59.00; H, 7.32; CH_3O, 43.56. Found: C, 59.05; H, 7.27; CH_3O, 43.48.

Preliminary hydrolysis of liriodendrin. An amount of 50 mg. of liriodendrin was suspended in 5 ml. of 0.25*N* hydrochloric acid and the mixture was heated on a steam bath. Samples were withdrawn at intervals and chromatographed on paper in a developer of ethyl acetate–acetic acid–water (9:2:2 v/v) for 3 hr. The sugar was located by the aniline hydrogen phthalate spray reagent,[19] and the syringyl substances were located on a separate paper by the Mäule test.[20]

The unchanged glucoside, R_f 0.2, disappeared after five minutes' heating; another spot, R_f 0.6, appeared at the 2-min. interval, passed through a maximum, and disappeared after 15 minutes. The aglucon, lirioresinol, R_f 0.9, appeared at 2 min. and was the only Mäule-positive spot after 25 min. The only sugar spot was glucose which appeared at 2 min. and followed the same pattern as lirioresinol.

Hydrolysis of liriodendrin (VII). (A) *Preparation of lirioresinol* (*I*, *II*, or *III*). An amount of 5.28 g. of the glucoside was suspended in 400 ml. of hot water, 80 ml. of 1.0*N* hydrochloric acid was added, and the mixture was heated on a steam bath. Within 10 min. the solution was clear and colorless, and after 12 min., the aglucon began to crystallize. The heating was stopped at 20 min., the mixture was cooled and stored at 5° overnight. The crystalline precipitate was collected by filtration, washed, and dried; yield, 2.114 g. (66.8%), m.p. 170–200°. This material was triturated with 2–3 ml. of chloroform and the slurry was filtered, washed with chloroform and dried; yield, 1.767 g. (55.8%), m.p. 204–207°. After standing overnight, the hydrolysis filtrate yielded an additional 0.313 g., m.p. 164–170°, for a combined yield of 2.427 g. (76.6%). The aqueous filtrate was then extracted with chloroform, amount recovered, 0.5815 g., for a total yield of 3.008 g. (95%). Fractional crystallization from chloroform-ethanol (1:1) yielded two materials in purified form designated as lirioresinol-A, m.p. 210–211°, $[\alpha]_D^{20}$ +127° (chloroform) and lirioresinol-B, m.p. 172–177°, $[\alpha]_D^{21}$ = +32.2° (chloroform).

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26; CH_3O, 29.67; Mol. wt. 418. Found: C, 63.30 (A), 63.16 (B); H, 6.26 (A), 6.23 (B); CH_3O, 29.68 (A), 29.46 (B); Mol. wt. (Rast) 362 (A). [(A) and (B) refer to lirioresinol-*A* and -*B*, respectively.]

(B) *Identification of* D-*glucose.* The aqueous solution from part (A) was deionized with Amberlite IR-4B (acetate form), and concentrated at reduced pressure to a thin sirup. After standing for several days, a colorless crystalline deposit formed. The substance was crystallized from aqueous alcohol and identified as anhydrous α-D-glucose, m.p. 146–150° upon very slow heating, $[\alpha]_D^{20}$ +52.3 (*c*, 5, water) constant after 24 hr., and by the preparation of *N*-*p*-nitrophenyl-D-glucosylamine, m.p. (dec.) 186–187°. An authentic specimen of anhydrous α-D-glucose melted at 146–150°, and the corresponding *p*-nitroaniline derivative melted (dec.) at 186–187°; the accepted equilibrium rotation of D-glucose in water is $[\alpha]_D^{20}$ = +52.6°.

Derivatives of lirioresinol. The procedures reported by Freudenberg and Dietrich[10] in their studies on syringaresinol were used with lirioresinol without significant modification. Although we have described experiments in the lirioresinol-*B* series only, analyses are given for derivatives in both the *A* and *B* series.

(A) *Methylation.* Lirioresinol-*B*, 1.093 g., m.p. 172–177°, was dissolved in 125 ml. of boiling methanol under a reflux condenser. The solution was treated portionwise with 15 ml. of dimethyl sulfate and 30 ml. of 40% potassium hydroxide over a period of thirty minutes. The mixture was boiled for an additional thirty minutes and was poured into 800 ml. of cold water. After standing for thirty minutes, colorless crystals formed in the cloudy solution. The product was extracted from the mixture with chloroform, and crystallized from methanol; the purified lirioresinol dimethyl ether was recovered as glistening, colorless plates, 0.534 g., m.p. 121–123°, $[\alpha]_D^{22}$ = 46.2°. A less pure lot of material was obtained from tailings, m.p. 117–119°, $[\alpha]_D^{25°}$ +44.4°.

Anal. Calcd. for $C_{24}H_{30}O_8$: CH_3O, 41.71. Found: CH_3O, 41.89 (A), 40.85 (B).

(B) *Bromination.* Lirioresinol-*B* dimethyl ether, 0.1973 g., was treated with an excess of bromine dissolved in chloroform (1:10) at room temperature. The reaction mixture was washed once with water and then with an excess of aqueous sodium sulfite. The product was crystallized from 95%

(19) The spray reagent was composed of 1.67 g. of *o*-phthalic acid and 1.02 g. of aniline dissolved in 100 ml. of water-saturated 1-butanol [S. M. Partridge, *Nature*, 164, 443 (1949)].

(20) The air-dry chromatogram was placed in an atmosphere of chlorine gas for ten minutes and then sprayed with 10% aqueous sodium sulfite. Syringyl substances form cerise or purple spots.

ethanol in tufts of colorless needles; m.p. 152–155°, $[\alpha]_D^{25°}$ −61.9°.

Anal. Calcd. for $C_{24}H_{28}O_8Br_2$: C, 47.70; H, 4.67; Br, 26.45; CH_3O, 30.81. Found: C, 47.64 (A), 47.65 (B); H, 4.64 (A), 4.60 (B); Br, 26.42 (A), 26.02 (B); CH_3O, 30.76 (A), 30.46 (B).

(C) *Oxidation with nitric acid.* Dibromodimethyl lirioresinol-*B*, 140 mg., was added in small portions to 1.4 ml. of nitric acid (d. 1.42) at room temperature. The solution became dark violet in color and turned to an orange red after one hour. The mixture was then heated for an hour on a steam bath. Upon cooling, crystalline material separated, 2 vol. of water were added, and the mixture was filtered; yield of crude material, 53.3 mg. (34%) of 4-bromo-5,6-dinitropyrogallol trimethyl ether, m.p. 126–129°. After crystallization from 95% ethanol, the very light yellow needles melted at 133–134°.

The aqueous filtrate was combined with a corresponding filtrate obtained from lirioresinol-*A*, was neutralized with sodium bicarbonate, the solution was evaporated to dryness and extracted with ether to recover the bis(hydroxymethyl)-succinic acid dilactone. A very small yield was obtained, m.p. 158–160°, $[\alpha]_D^{26}$ +253° (water). The rotation was observed on 0.0029 g. of material in 3.0 ml. of solution and must be regarded as an approximation.

Preparation of syringaresinol. (A) *Crude almond emulsin.* Using the general procedure of Bourquelot,[21] 10.6 g. of crude emulsin was prepared from 340 g. of sweet almonds.

(B) *Enzymic synthesis of syringaresinol from syringin.* Using the general procedure of Freudenberg and Dietrich[10] 2.5 g. of syringin[22] was dissolved in 125 ml. of water, 0.1 g. of thymol and 0.25 g. of crude enzyme were added, and the mixture was incubated at 37°. An additional amount of 0.25 g. of the enzyme was added daily until a total of 2.0 g. had been added. Colorless crystals, m.p. 172–174°, began to form after five days, and the reaction was stopped after eleven days. The mixture was treated with 2–3 g. of "Fibra-Flo-C"[23] and filtered, the filter cake was washed with water, air dried, and extracted with chloroform at room temperature. Upon evaporation of the chloroform, crude syringaresinol was obtained; yield, 0.85 g. (60.2%). After two crystallizations from 95% ethanol, 0.57 g. of purified material was obtained, the main portion melted at 170–172° with a small amount melting at 176–178°. The product was optically inactive. In a second experiment the yield of crude syringaresinol after 17 days was 0.958 g. (68%). Freudenberg and Dietrich[10] obtained syringaresinol, m.p. 174–175° in a 66% yield after seven weeks.

The aqueous filtrate from the reaction mixture was extracted three times with chloroform; yield of oily material believed to be crude sinapyl alcohol, 0.46 g. (32.6%). The combined yield of syringaresinol and sinapyl alcohol was 92.8%.

Syringaresinol diacetate. The acetate was prepared from the lignan, acetic anhydride, and pyridine; colorless crystals m.p. 179–181°, from 95% ethanol. Freudenberg and Dietrich[10] reported the m.p. 181–183° for this derivative.

Hydrolysis of liriodendrin with crude almond emulsin. Using the above procedure, 0.5 g. of liriodendrin was dissolved in 125 ml. of water, 0.1 g. of thymol and 0.25 g. of the crude enzyme were added, and the mixture was incubated at 37°. More enzyme, 0.25 g., was added on the second, third, sixth, and fifteenth days; the reaction was stopped after twenty-three days. Filter aid was added, the filter cake was air dried and extracted with chloroform; yield of crude lirioresinol-*C*, 0.1565 g. (55%). After two crystallizations from 95% ethanol the lirioresinol-*C* melted 185–186°, $[\alpha]_D^{28}$ +48.9° (in chloroform). The infrared spectrum was nearly identical with that of syringaresinol (Fig. 1).

APPLETON, WIS.

(21) E. Bourquelot, *Archiv. Pharm.*, **245**, 172–180 (1907).

(22) Syringin was isolated from the bark of the common lilac by the general procedure of K. Freudenberg, R. Kraft, and W. Heimberger, *Chem. Ber.*, **84**, 472–476 (1951).

(23) Filter aid manufactured by Johns-Manville.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Racemic 2-Hydroxymethyl-2,3-dihydro-4*H*-pyran, a Model Carbohydrate[1]

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Received June 25, 1957

2-Hydroxymethyl-2,3-dihydro-1,4*H*-pyran, a racemic dideoxyglucal, has been converted to 2,3,4-trideoxyaldohexose and its derivatives.

It has been demonstrated that 2,3-dihydro-4*H*-pyran can readily be converted to polydeoxyaldopentoses by hydration[3] and hydroxylation.[4] In similar manner, these glycal-like properties have now been extended to the formation of polydeoxyaldohexoses from 2-hydroxymethyl-2,3-dihydro-4*H*-pyran (II) with the ultimate, but as yet unrealized object, of synthesizing these in optically active forms of the D- or L-series.

The preparation of the precursor II, a racemic 3,4-dideoxyglucal, by reduction of 2,3-dihydro-4*H*-pyran-2-carboxaldehyde (I)[5] with aluminum alk-

(1) Abstracted from the senior thesis of Anthony Verbiscar (1951) and the master's thesis of Herman J. Eichel (1956). Part of this material has been reported at the Student Affiliate Symposium of the American Chemical Society, Chicago Section, in May 1951.

(2) Present address: 1653 S. Elm Avenue, Bartlesville, Okla.

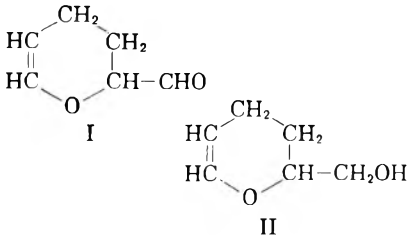
(3) L. E. Schniepp and H. H. Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946).

(4) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **70**, 1484 (1948); C. D. Hurd and O. E. Edwards, *J. Org. Chem.*, **14**, 680 (1949); and C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

(5) K. Alder and E. Rüden, *Ber.*, **74**, 320 (1941); K. Alder, H. Offermans and E. Rüden, *Ber.*, **74**, 905 (1941). A sample of this compound, acrolein dimer, was generously supplied by the Shell Development Co., Emoryville, Calif.

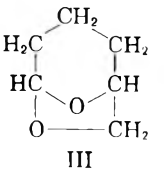
oxide has been reported,[6] but a better laboratory procedure was desired. Accordingly, satisfactory procedures for the reduction of the carboxaldehyde (I) in 61–63% yield were devised with lithium aluminum hydride or, more conveniently and safely, with sodium borohydride as the reducing agent.

The 2-hydroxymethyldihydropyran (II) was stable in the absence of acid[7] but upon heating under reflux for an hour, half of it polymerized to undistillable material. The expected product was 6,8-dioxabicyclo[3.2.1]octane (III).[8]



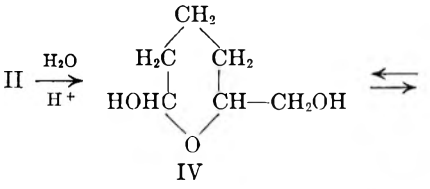
I

II

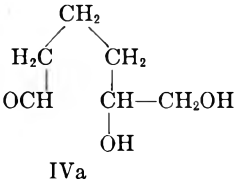


III

Compound II was stable in neutral or alkaline water solutions which failed to give a positive Benedict test. However, its sensitivity to acid was demonstrated by its ready reaction with 2,4-dinitrophenylhydrazine hydrochloride in 95% alcohol to form 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone, probably *via* intermediate hydrolysis to a tautomeric mixture of racemic 5,6-dihydroxyhexanal and 2-hydroxymethyltetrahydropyran-2-ol (IV).



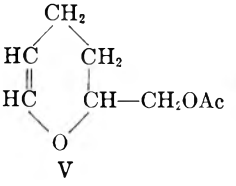
IV



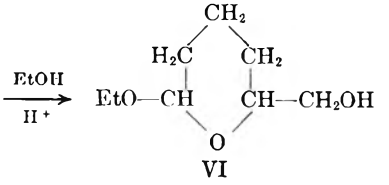
IVa

Dihydropyran is known to hydrolyze readily in dilute acid to a tautomeric mixture of tetrahydropyran-2-ol and 5-hydroxypentanal which either neat or in solution contains these substances in a ratio of about 95:5.[3,9] In like manner, 2-hydroxymethyltetrahydropyran almost immediately dissolved in very dilute acid to form a tautomeric mixture of 2-hydroxymethyltetrahydropyran-2-ol (IV) and 5,6-dihydroxyhexanal (IVa). As expected, infrared scanning of the hydrolysis product after neutralization and removal of water showed the presence of only a small carbonyl concentration. Although the tautomeric mixture could not be distilled, neturalization of the hydrolyzate and reduction with sodium borohydride gave 1,2,6-hexanetriol.[10] Both the hydrolysis mixture and the residue left by vacuum drying gave immediate Benedict and Schiff tests. With 2,4-dinitrophenylhydrazine both formed the compound we choose to call 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone.

The racemic 3,4-dideoxyglucal (II) was readily acetylated in pyridine to the acetate V, racemic 6-*O*-acetyl-3,4-dideoxyglucal. Treatment with absolute ethanol and a trace of acid rapidly formed a mixture of 2-ethoxy-6-hydroxymethyltetrahydropyrans (VI) which may be described as racemic forms of ethyl 2,3,4-trideoxyaldohexopyranosides.



V



VI

EXPERIMENTAL[11]

2-Hydroxymethyl-2,3-dihydro-4H-pyran (II). A mixture of 4.0 g. (0.11 mole) of lithium aluminum hydride and 90 ml. of anhydrous ethyl ether was stirred under nitrogen for 1 hr. A solution of 33.6 g. (0.30 mole) of 2,3-dihydro-4*H*-pyran-2-carboxaldehyde[5] in 25 ml. of ether was added dropwise with stirring in 2 hr. Fifteen minutes after addition was completed, 7.6 ml. (0.42 mole) of water was added, the first 0.5 ml. being introduced cautiously. The resultant gelatinous mixture was diluted somewhat with benzene, mixed with Super Cel or Celite and filtered. The filtrate was dried over sodium sulfate and distilled to give 20.7 g. (61 per cent) of II, b.p. 92–93°/25 mm., n_D^{25} 1.4757, n_D^{21} 1.4775 (lit.[4] b.p. 81–82°/13 mm., n_D^{20} 1.4848).

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.03; H, 8.52.

A safer and more convenient route to II involved the addition of a solution of 5.0 g. (0.18 mole) of sodium borohydride in 100 ml. of methanol to a chilled solution of 11.2 g. (0.10 mole) of the carboxaldehyde I in 150 ml. of methanol. Reaction temperature was allowed to rise to 30° during the 15-min. addition and was maintained there during 1 hr. of stirring. Most of the methanol was removed on the steam bath and 10 ml. of water was added to the residue which was then extracted with two 100-ml. portions of ether and one of benzene. The combined extract was dried and distilled to give 6.9 g. (62 per cent) of II, b.p. 100–103°/47 mm., n_D^{25} 1.4764. The infrared spectrum was

(6) H. Schulz and H. Wagner, *Angew. Chem.*, 62, 105 (1950).

(7) A sample stored three years remained unchanged and had the same infrared spectrum as a freshly prepared sample.

(8) R. R. Whetstone, U. S. Patent 2,511,891 (June 20, 1950).

(9) C. D. Hurd and W. H. Saunders, *J. Am. Chem. Soc.*, **74**, 5324 (1952).

(10) R. Zelinski and H. J. Eichel, to be published.

(11) Analyses by Micro Tech Laboratories, Skokie, Ill.

identical to the product obtained by means of lithium aluminum hydride.

When II was boiled under reflux for 1 hr., 57 per cent was recovered as a fraction boiling at 182–189°/750 mm., n_D^{20} 1.4761. The remainder was an orange-amber viscous sirup which could not be distilled.

Treatment of II with 2,4-dinitrophenylhydrazine hydrochloride in 95% ethanol gave 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone, m.p. 119–121°, a compound described more completely in a succeeding section.

2-Acetoxymethyl-2,3-dihydro-4H-pyran (V). A solution of 20 g. (0.175 mole) of II in 40 ml. of pyridine was allowed to stand overnight with 54 g. (0.53 mole) of acetic anhydride before the pyridine was distilled and the residue was hydrolyzed in ice and water. Ether extraction and distillation of the extract gave 14 g. (54 per cent) of racemic 6-*O*-acetyl-3,4-dideoxyglucal (V), b.p. 101–104°/14 mm., n_D^{20} 1.4578.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.30; H, 7.85.

Attempted preparation of 6-hydroxymethyltetrahydropyran-2-ol (IV). When 20 g. (0.175 mole) of II was dissolved in 80 ml. of 0.2*N* hydrochloric acid, heat was immediately evolved. A portion of the hydrolysis mixture was neutralized to the phenolphthalein end point and an attempt was made to fractionate at 1-mm. pressure. However, except for water no distillate was obtained at less than 250°. A second portion of the hydrolysis mixture was made basic and extracted with ten portions of ether. These were combined, dried, and evaporated under vacuum at room temperature to give a 25% recovery of a mixture of unidentified solid and liquid. The water was distilled from a third portion to leave a viscous orange liquid which was treated with acetic anhydride and pyridine in an exothermic reaction. However, distillation at 1 mm. pressure of the washed, ether extract of the ice water hydrolysate from that mixture resulted in decomposition.

Addition of one drop of 6*N* hydrochloric acid to a turbid mixture of 3.4 g. of the hydroxymethyl compound II and 5 ml. of water almost immediately resulted in a clear solution. This was made slightly basic and vacuum-dried at room temperature and finally vacuum dried over phosphorus pentoxide. The clear viscous residue was obtained in quantitative conversion. It was examined by infrared.

5,6-Dihydroxyhexanal 2,4-dinitrophenylhydrazone. A portion of the above sirupy mixture of 5,6-dihydroxyhexanal (IVa) and 6-hydroxymethyltetrahydropyran-2-ol (IV) was dissolved in alcohol and treated with alcoholic 2,4-dinitrophenylhydrazine in the usual way[12] to give long, orange needles of 5,6-dihydroxyhexanal 2,4-dinitrophenylhydrazone, m.p. 122–123°.

The same compound with an identical melting point was obtained by addition of 2,4-dinitrophenylhydrazine to a solution of II in alcohol-water containing a few drops of hydrochloric acid.

Anal. Calcd. for $C_{12}H_{16}O_6N_4$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.13; H, 5.13; N, 17.80.

2-Ethoxy-6-hydroxymethyltetrahydropyran (VI). A solution of 20 g. (0.175 mole) of 2-hydroxymethyl-2,3-dihydro-4*H*-pyran (II) in 100 ml. of absolute alcohol containing a drop of dilute hydrochloric acid was allowed to stand over night. Distillation from several pellets of solid sodium hydroxide gave 68% of the mixture of ethyl 2,3,4-trideoxyaldohexopyranosides (VI), b.p. 90–94°/7 mm., 151–154°/98 mm., n_D^{20} 1.4510.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.11; H, 10.12.

CHICAGO 14, ILL.

(12) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, Third Edition, John Wiley and Sons, Inc., New York, 1948, p. 171.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

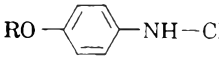
Tuberculostatic *N*-Arylglycines and Derivatives

N. B. TIEN, N. P. BUU-HOÏ, AND N. D. XUONG

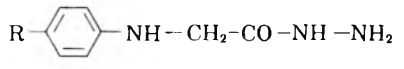
Received June 25, 1957

A large number of *N*-arylglycines, especially *para*-substituted *N*-phenylglycines, have been synthesized, along with their esters, hydrazides, and other derivatives, for biological evaluation as potential tuberculostatic agents.

Primary arylamines with substitutions in *para* position have repeatedly been found to show notable inhibitory activity against tubercle bacilli in *in vitro* tests;[1] their high toxicity, however, has limited both *in vivo* studies and practical application, and several attempts have therefore been made to prepare less toxic derivatives (anils, glucosides, etc.)[2] Recently, Bersch and Döpp[3] found that conversion of certain *p*-alkyloxyanilines to the corresponding *N*-arylglycines leads to compounds possessing very high *in vivo* tuberculostatic activity, such as *N*-(4-ethoxyphenyl)- (I; R = C_2H_5) and *N*-(4-butoxyphenyl)glycine (I; R = *n*-C_4H_9), but no *in vivo* studies were made with these substances.



I



II

In the framework of a general investigation on the relationship between chemical structure and tuberculostatic activity,[4] a large number of new *N*-arylglycines, especially those bearing an alkyl, alkyloxy, or halogen substituent in the *para*

(1) M. Kuroya, *Japan J. Exp. Med.*, **7**, 255 (1929); J. P. Jouin and N. P. Buu-Hoï, *Ann. Inst. Pasteur*, **72**, 580 (1946); B. L. Freedlander *et al.*, *Am. Rev. Tuber.*, **56**, 360 (1947); *Stanford Med. Bull.*, **12**, 33 (1954).

(2) H. Erlenmeyer, *et al.*, *Helv. Chim. Acta*, **28**, 1406 (1945); **30**, 2058 (1947); **32**, 605 (1949).

(3) H. W. Bersch and W. Döpp, *Arzneimittel-Forsch.*, **5**, 183, 335 (1955).

(4) N. P. Buu-Hoï, N. D. Xuong, *et al.*, *Experientia*, **10**, 169 (1954); **11**, 97 (1955); **12**, 102, 474 (1956); *Compt. rend.*, **236**, 635 (1953); **237**, 498 (1953); **238**, 295 (1954).

TABLE I

NEW *N*-ARYLGLYCINES

Aryl Radical	Formula	M.P., °C.	Analyses			
			Calcd.		Found	
			C	H	C	H
4-Fluorophenyl	$C_8H_8FNO_2$	140	56.8	4.7	57.0	4.9
3-Chloro-2-methylphenyl	$C_9H_{10}ClNO_2$	169	54.2	5.0	54.5	5.4
5-Chloro-2-methoxyphenyl	$C_9H_{10}ClNO_3$	182	50.1	4.6	50.4	4.6
2,3-Dimethylphenyl	$C_{10}H_{13}NO_2$	176	67.0	7.3	66.7	7.2
2,6-Dimethylphenyl	$C_{10}H_{13}NO_2$	154	67.0	7.3	67.4	7.5
3,4-Dimethylphenyl	$C_{10}H_{13}NO_2$	149	67.0	7.3	66.9	7.1
4-Ethylphenyl	$C_{10}H_{13}NO_2$	142	67.0	7.3	66.7	7.0
4-Propylphenyl	$C_{11}H_{15}NO_2$	136	68.4	7.8	68.2	7.8
4-Butylphenyl	$C_{12}H_{17}NO_2$	139	69.6	8.2	69.8	8.4
4-Cyclohexylphenyl	$C_{14}H_{19}NO_2$	178	72.1	8.2	72.0	8.2
4-Propoxyphenyl	$C_{11}H_{15}NO_3$	135	63.2	7.2	63.2	6.9
4-Isopropoxyphenyl	$C_{11}H_{15}NO_3$	141	63.2	7.2	62.9	7.4
4-Isoamyloxyphenyl	$C_{13}H_{19}NO_3$	119	65.8	8.0	65.8	8.2
4-Heptyloxyphenyl	$C_{15}H_{23}NO_3$	122	67.9	8.7	67.6	8.7

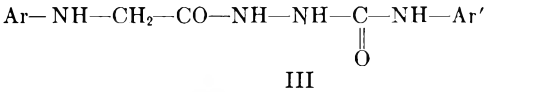
TABLE II

ETHYL ESTERS $ArNHCOOC_2H_5$ OF *N*-ARYLGLYCINES

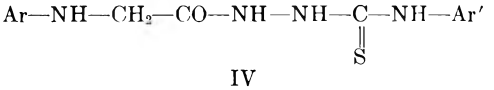
Aryl Radical	Formula	B.P., °C./Mm.	M.P., °C.	Analyses			
				Calcd.		Found	
				C	H	C	H
4-Fluorophenyl	$C_{10}H_{12}FNO_2$		72	60.9	6.1	60.6	6.1
3-Chloro-2-methylphenyl	$C_{11}H_{14}ClNO_2$	185/30		58.0	6.2	57.7	6.5
4-Ethylphenyl	$C_{12}H_{17}NO_2$	165/17		69.6	8.2	69.3	8.3
4-Propylphenyl[a]	$C_{13}H_{19}NO_2$	175/20		70.6	8.6	70.5	8.4
4-Butylphenyl[b]	$C_{14}H_{21}NO_2$	180/17		71.5	8.9	71.2	8.6
4-Heptylphenyl[c]	$C_{17}H_{27}NO_2$	180/13		73.7	9.8	73.6	9.9
4-Propoxyphenyl	$C_{13}H_{19}NO_3$	175/14		65.8	8.0	65.7	8.0
4-Isopropoxyphenyl	$C_{13}H_{19}NO_3$	180/17		65.8	8.0	65.6	8.1
4-Butoxyphenyl	$C_{14}H_{21}NO_3$	195/18		66.9	8.4	66.8	8.5
4-Isoamyloxyphenyl[d]	$C_{15}H_{23}NO_3$	190/16		67.9	8.7	67.7	8.5
4-*p*-Diphenylyl	$C_{16}H_{17}NO_2$		96–97	75.3	6.7	75.2	6.8
4-Cyclohexylphenyl	$C_{15}H_{23}NO_2$		65	73.6	8.8	73.4	8.9

[a] n_D^{22} 1.5365. [b] n_D^{22} 1.5359. [c] n_D^{22} 1.5253. [d] n_D^{22} 1.5223.

position, have been prepared by condensation of various primary arylamines with chloroacetic acid in the presence of sodium acetate.[5] The *N*-arylglycines thus obtained in good yields, except in the case of sterically hindered arylamines, are listed in Table I. In view of the known tuberculostatic activity of numerous hydrazides,[6] a large number of hydrazides (general formula II) derived from *N*-arylglycines, have been synthesized by hydrazinolysis of the corresponding ethyl esters, which were prepared by condensation of primary arylamines with ethyl chloroacetate in the presence of sodium acetate; these new esters are listed in Table II, and the new hydrazides in Table III. The reaction of hydrazides II with various aryl isocyanates and isothiocyanates[7] readily afforded the corresponding 1-acyl-4-arylsemicarbazides (III) and 1-acyl-4-arylthiosemicarbazides (IV).



III



IV

Biological studies on these compounds showed that several *N*-arylglycines bearing a bulky *p*-substituent (especially a higher alkyloxy group) are tuberculostatic *in vitro* at a concentration of 10γ per ml. Dubos culture medium (*Mycobacterium tuberculosis* var. *hominis*, strain $H_{37}RvD$), while the corresponding hydrazides are inactive. Unfortunately, all the *N*-arylglycines tested showed such a high degree of toxicity that no *in vivo* activity could be detected.[8]

(5) A. Hausdörfer, *Ber.*, **22**, 1799 (1889).

(6) H. A. Offe, W. Siefken, and G. Domagk, *Naturwissenschaften*, **39**, 118 (1952); see literature in E. Krüger-Thiemer, *Jahresber. Tuberkulose-Forschungsinstituts Borstel*, **3**, 192 (1956).

(7) N. P. Buu-Hoï, N. D. Xuong, and N. H. Nam, *J. Chem. Soc.*, 2160 (1956).

(8) N. P. Buu-Hoï, N. D. Xuong, N. B. Tien, J. M. Gazave, J. Pillot, and G. Dufraisse, *Experientia*, **13**, 235 (1957).

TABLE III

HYDRAZIDES DERIVED FROM *N*-ARYLGLYCINES

Aryl Radical	Formula	M.P., °C.	Analyses, N % Calcd.	Found
4-Fluorophenyl	$C_8H_{10}FN_3O$	115	22.9	22.5
4-Chlorophenyl	$C_8H_{10}ClN_3O$	140	21.1	21.3
4-Bromophenyl	$C_8H_{10}BrN_3O$	161	17.2	17.4
4-Tolyl	$C_9H_{13}N_3O$	152	23.5	23.1
4-Ethylphenyl	$C_{10}H_{15}N_3O$	148	21.8	22.2
4-Propylphenyl	$C_{11}H_{17}N_3O$	140	20.3	20.6
4-Butylphenyl	$C_{12}H_{19}N_3O$	145	19.0	18.7
4-Heptylphenyl	$C_{15}H_{25}N_3O$	146	16.0	15.6
4-Diphenylyl	$C_{14}H_{15}N_3O$	167	17.4	17.1
4-Cyclohexylphenyl	$C_{14}H_{21}N_3O$	160	17.0	16.9
3-Chloro-2-methylphenyl	$C_9H_{13}ClN_3O$	159	19.7	19.4
4-Ethoxyphenyl	$C_{10}H_{15}N_3O_2$	132	20.1	20.4
4-Propoxyphenyl	$C_{11}H_{17}N_3O_2$	135	18.8	18.8
4-Isopropoxyphenyl	$C_{11}H_{17}N_3O_2$	114	18.8	18.6
4-Butoxyphenyl	$C_{12}H_{19}N_3O_2$	135	17.7	17.5
β-Naphthyl	$C_{12}H_{13}N_3O$	152	19.5	19.0

EXPERIMENTAL

Preparation of intermediates. *p*-Alkylanilines and *p*-cyclohexylaniline were prepared by Beckmann rearrangement of the oximes of the corresponding *p*-substituted acetophenones. *p*-Alkyloxyanilines were prepared by alkylation of *p*-benzalaminophenol with alkyl halogenides and sodium hydroxide in aqueous ethanol, and subsequent hydrolysis of the aldimines with hydrochloric acid.

Preparation of N-arylglycines. A mixture of 1.5 moles of the primary arylamine, 1 mole of chloroacetic acid, and 2 moles of sodium acetate (dissolved in a minimum of water) was heated at 50–60° on a water bath for one hour; the solid obtained on cooling was washed with water, treated with a 10% aqueous solution of ammonium carbonate, and the filtrate acidified with hydrochloric acid. The precipitate formed was washed with ether to remove the imino derivative $ArN(CH_2CO_2H)_2$, and the residue recrystallized from benzene or a mixture of ethanol and benzene, giving colorless prisms in every instance. The yields varied from 65% for the *p*-substituted anilines, to 25% for the sterically hindered 2,6-dimethylaniline and 15% for the even more hindered 2,6-diethylaniline.

The same procedure was applied, with similar results, to α-bromobutyric acid; for example, α-(*p*-tolylamino)butyric acid, thus obtained in 60% yield, crystallized from benzene in shiny colorless needles, m.p. 158°; Bischoff and Mintz[9] gave m.p. 153–156° for a sample prepared by alkaline hydrolysis of the corresponding ethyl ether. α-(2-Naphthylamino)butyric acid, prepared from β-naphthylamine (7 g.), α-bromobutyric acid (5 g.) and sodium acetate (12 g.), crystallized from benzene in shiny colorless prisms (3.5 g.), m.p. 157°; Bischoff and Mintz[9] gave m.p. 158°. This compound is similar to the tuberculostatic β-(2-naphthylamino)-dihydrohydnocarpic acid.[10]

Preparation of ethyl esters of N-arylglycines. A mixture of 1 mole of the primary arylamine, 1 mole of redistilled ethyl chloroacetate, and 2 moles of sodium acetate (dissolved in a minimum of water) was heated on a water bath for one hour; after cooling, water was added, and the precipitate formed was taken up in benzene. The benzene solution was then dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated and if solid, crystallized from petroleum ether. The yields varied from 50 to 70%.

Preparation of hydrazides derived from N-arylglycines. A solution of 1 mole of the ethyl ester of the corresponding *N*-arylglycine and 2 moles of 95% hydrazine hydrate in ethanol was refluxed for 5 to 6 hr. on a water bath, the solvent distilled off *in vacuo*, and the solid residue recrystallized several times from ethanol, to give shiny colorless needles, in 85–90% yield.

Preparation of 1-acyl-4-arylsemicarbazides (III). To a solution of 1 mole of the hydrazide of the appropriate *N*-arylglycine in dry benzene, 1 mole of the aryl isocyanate was added, and the mixture warmed for a few minutes at 50–60°; after cooling, the precipitate obtained was recrystallized from benzene. Yield: 80–90%. For example, *1-(β-naphthylaminoacetyl)-4-p-chlorophenylsemicarbazide* was thus obtained as shiny colorless prisms, m.p. 213°.

Anal. Calcd. for $C_{19}H_{17}ClN_4O_2$: N, 15.2. Found: N, 14.9.

1-(p-Phenetylamino)acetyl-4-p-bromophenylsemicarbazide was shiny colorless needles, m.p. 219°.

Anal. Calcd. for $C_{17}H_{19}BrN_4O_3$: N, 13.8. Found: N, 13.5.

Preparation of 1-acyl-4-arylthiosemicarbazides (IV). These compounds were prepared as above, with aryl isothiocyanates.

1-(p-Phenetylamino)acetyl-4-phenylthiosemicarbazide crystallized from ethanol in shiny colorless prisms, m.p. 172°.

Anal. Calcd. for $C_{17}H_{20}N_4O_2S$: N, 16.3. Found: N, 16.4.

1-(p-Phenetylamino)acetyl-4-p-chlorophenylthiosemicarbazide crystallized from ethanol in colorless prisms, m.p. 189°.

Anal. Calcd. for $C_{17}H_{19}ClN_4O_2S$: N, 14.8. Found: N, 14.7.

1-p-(Cyclohexylphenyl)aminoacetyl-4-phenylthiosemicarbazide crystallized from ethanol in colorless leaflets, m.p. 196°.

Anal. Calcd. for $C_{21}H_{26}N_4OS$: N, 14.7. Found: N, 14.6.

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(9) C. A. Bischoff and N. Mintz, *Ber.*, 25, 2319, 2324 (1892).

(10) N. P. Buu-Hoï and P. Cagniant, *Ber.*, 76, 1269 (1943).

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Synthesis of Two Fluorinated 1-Naphthylacetic Acids

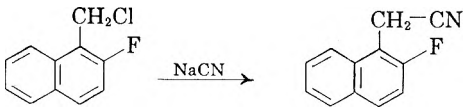
N. P. BUU-HOÏ, V. Q. YEN, AND N. D. XUONG

Received July 17, 1957

It is shown that 1- and 2-fluoronaphthalene readily undergo chloromethylation with paraformaldehyde and hydrochloric acid to give 4- and 2-fluoro-1-chloromethylnaphthalene respectively. These chloromethyl compounds served for the synthesis of 4- and 2-fluoro-1-naphthylacetic acid, compounds with biological interest as potential plant growth regulators. Friedel-Crafts cyclization of 2-fluoro-1-naphthylacetyl chloride afforded 3-fluoroacenaphthen-1-one, which was reduced to 3-fluoroacenaphthene.

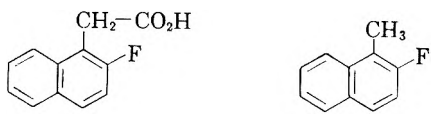
As 1-naphthylacetic acid on the one hand, and several halogenated phenoxyacetic acids on the other hand, are powerful regulators of growth in plants, it was of interest to synthesize a number of still untested halogenated 1-naphthylacetic acids, especially the fluorine-containing ones.

2-Fluoro-1-naphthylacetic acid (III) was prepared by hydrolysis of 2-fluoro-1-naphthylacetonitrile (II), itself obtained by reaction of sodium cyanide on 2-fluoro-1-chloromethylnaphthalene (I); chloromethylation of 2-fluoronaphthalene was effected in good yield, although experimental



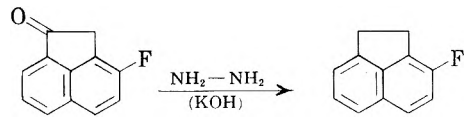
I II

conditions notably more drastic than with naphthalene were required. The constitution of the chloromethyl derivative (I), assumed on grounds of analogy with 2-methylnaphthalene which was chloromethylated in position 1,[1] was rigidly proven by the aluminum chloride-catalyzed cyclization of 2-fluoro-1-naphthylacetyl chloride to 3-



III

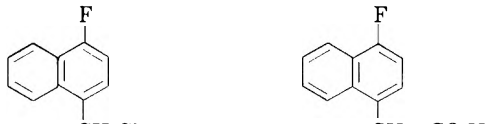
fluoroacenaphthene-1-one (V). Kishner-Wolff reduction of this ketone readily yielded 3-fluoroacenaphthene (VI), a compound also potentially



V VI

interesting in plant biology in view of the known mitoclastic activity of acenaphthene itself[2] and the growth-accelerating effects of certain substituted acenaphthenes on the roots of cereal seedlings.[3] Of similar interest (in view of the polyploidogenic activity of 1-fluoro- and 1-methylnaphthalene[4]) is 2-fluoro-1-methylnaphthalene (IV), prepared by reduction of compound I with zinc powder in ethanol.

Chloromethylation of 1-fluoronaphthalene was also successfully performed, and 4-fluoro-1-chloromethylnaphthalene (VII) thus obtained was converted into 4-fluoro-1-naphthylacetic acid (VIII), *via* 4-fluoro-1-naphthylacetonitrile. In the present case, the structure of the chloromethyl derivative (VII) was not rigidly proven, but was assumed on the grounds of the known directing influence of the fluorine atom[5] and because 1-methylnaphthalene is known to undergo chloromethylation in position 4.[6] 4-Fluoro-1-naphthylacetonitrile readily



VII CH_2Cl VIII $CH_2—CO_2H$

underwent alkali-catalyzed condensation with various aromatic aldehydes, to give a series of α-(4-fluoro-1-naphthyl)-β-arylacrylonitriles, listed in the Table. 2-Fluoro-1-naphthylacetonitrile failed to react in similar conditions.

Results of the plant tests will be published elsewhere.

EXPERIMENTAL

Chloromethylation of 2-fluoronaphthalene. A mixture of 58 g. of 2-fluoronaphthalene, 22 g. of paraformaldehyde, 52 ml. of acetic acid, 73 ml. of hydrochloric acid, and 33 ml. of phosphoric acid was heated for 12 hr. at 80–85° with stirring, hydrogen chloride being added at frequent intervals. After cooling and dilution with water, the solid product obtained was taken up in benzene, and the benzene solution washed, and dried over sodium sulfate. The solvent was then removed, and the residue vacuum-fractionated to yield 50

(1) See N. P. Buu-Hoï and P. Cagniant, *Compt. rend.*, **214**, 315 (1942).

(2) P. and N. Gavaudan and T. F. Durand, *Compt. rend.*, **208**, 593 (1939).

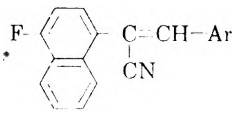
(3) R. Garrigues, N. P. Buu-Hoï, and P. Cagniant, *Compt. rend.*, **234**, 553 (1952).

(4) M. Simonet and M. Guinochet, *Compt. rend. Soc. biol.*, **132**, 455 (1939).

(5) See N. P. Buu-Hoï and P. Jacquignon, *J. Chem. Soc.*, 4173 (1952); N. P. Buu-Hoï and N. D. Xuong, *J. Chem. Soc.*, 386 (1953).

(6) G. Darzens and G. Levy, *Compt. rend.*, **202**, 73 (1936).

α-(4-FLUORO-1-NAPHTHYL)-β-ARYLACRYLONITRILES



Aryl group	Formula	M.P., °C.	Color with H_2SO_4	Analyses Calcd. N	Analyses Found N
p-Fluorophenyl	$C_{19}H_{11}F_2N$	170	Pale yellow	4.8	4.5
p-Methoxyphenyl	$C_{20}H_{14}FNO$	170	Green	4.6	4.5
3,4-Dimethoxyphenyl	$C_{21}H_{16}FNO_2$	182	Green	4.2	4.0
3,4-Dioxymethylenephenyl	$C_{20}H_{12}FNO_2$	180	Greenish brown	4.4	4.2
2-Thienyl	$C_{17}H_{10}FNS$	162	Deep green	5.0	4.9

g. of a product boiling at 150–151°/15 mm., and crystallizing from petroleum ether in colorless needles, m.p. 63°.

Anal. Calcd. for $C_{11}H_8ClF$: C, 67.9; H, 4.1. Found: C, 67.7; H, 3.9.

2-Fluoro-1-naphthylacetonitrile (II). A solution of 38.8 g. of 2-fluoro-1-chloromethylnaphthalene and 12 g. of sodium cyanide in 100 ml. of ethanol and 50 ml. of water was refluxed for 6 hr. The ethanol was distilled off, the reaction product taken up in ether, and the ether solution washed with water and dried over sodium sulfate. The solvent was then removed, and the residue vacuum-fractionated to yield 21 g. of a nitrile, b.p. 189–190°/17 mm., crystallizing from ethanol in silky colorless prisms, m.p. 82°.

Anal. Calcd. for $C_{12}H_8FN$: N, 7.6. Found: N, 7.3.

2-Fluoro-1-naphthylacetic acid (III). A mixture of 50 g. of the foregoing nitrile and 225 ml. of a 20% solution of potassium hydroxide in ethanol was refluxed for 6 hr. The ethanol was distilled off, and water was added to the residue; the aqueous solution was treated with ether to remove the neutral impurities, then acidified with dilute hydrochloric acid. The yield was 45 g. of an acid, crystallizing from aqueous ethanol in colorless needles, m.p. 154°.

Anal. Calcd. for $C_{12}H_9FO_2$: C, 70.6; H, 4.4. Found: C, 70.9; H, 4.7.

The corresponding *acid chloride*, prepared with thionyl chloride, was a pale yellow oil, b.p. 142–143°/1 mm., n_D^{21} 1.5986.

Anal. Calcd. for $C_{12}H_8OClF$: Cl, 16.0. Found: Cl, 15.6.

Reaction of this chloride with ice cooled, concentrated aqueous ammonia afforded *2-fluoro-1-naphthylacetamide*, crystallizing from aqueous ethanol in fine colorless prisms, m.p. 185°.

Anal. Calcd. for $C_{12}H_{10}FNO$: N, 6.9. Found: N, 6.8.

3-Fluoroacenaphthen-1-one (V). To a water cooled solution of 23 g. of 2-fluoro-1-naphthylacetyl chloride in 100 ml. of dry nitrobenzene, 16 g. of finely powdered aluminum chloride was added portionwise with stirring, and the mixture left overnight at room temperature. After decomposition with water, the nitrobenzene was distilled off with steam, and the residue was taken up in ether. The ethereal solution was washed first with 5% aqueous sodium hydroxide, then with water, and dried over sodium sulfate. The solvent was then removed, and the residue vacuum-fractionated. The portion boiling at 166–168°/1 mm., was recrystallized from ethanol, giving 2 g. of shiny colorless prisms, m.p. 155°.

Anal. Calcd. for $C_{12}H_7FO$: C, 77.4; H, 3.8. Found: C, 77.7; H, 3.9.

The corresponding *semicarbazone* crystallized from ethanol in fine colorless prisms, m.p. 236°.

3-Fluoroacenaphthene (VI). Reduction of 1 g. of ketone V with 1 g. of 95% hydrazine hydrate and 1 g. of potassium hydroxide in diethylene glycol[7] afforded 0.6 g. of a product, crystallizing from ethanol in silky colorless needles, m.p. 98°.

Anal. Calcd. for $C_{12}H_9F$: C, 83.7; H, 5.2. Found: C, 83.5 H, 5.4.

The corresponding *picrate* crystallized from ethanol in silky orange needles, m.p. 136°.

Anal. Calcd. for $C_{18}H_{12}FN_3O_7$: C, 53.9; H, 3.0. Found: C, 53.5; H, 3.2.

2-Fluoro-1-methylnaphthalene (IV). Into a warm suspension of 20 g. of 2-fluoro-1-chloromethylnaphthalene in 100 ml. of 80% aqueous ethanol, 25 g. of zinc powder was stirred portionwise, and the mixture refluxed on a water bath for one hour. After cooling, the zinc in excess was filtered off and washed with ethanol, the ethanol was distilled off from the filtrate, and the residue taken up in benzene. The benzene solution was washed with water and dried over sodium sulfate, the solvent was removed, and the residue vacuum-fractionated. The portion, b.p. 122–128°/18 mm., was redistilled, yielding 11 g. of the reduction product, a colorless liquid, b.p. 241°, or 126–128°/20 mm.

Anal. Calcd. for $C_{11}H_9F$: C, 82.5; H, 5.6. Found: C, 82.2; H, 5.8.

The corresponding *picrate* crystallized from ethanol in silky yellow needles, m.p. 101°.

As a by-product of the above reduction, some *α,β-di(2-fluoro-1-naphthyl)ethane* could be isolated. It crystallized from ethanol in colorless needles (1 g.), m.p. 167°.

Anal. Calcd. for $C_{22}H_{16}F_2$: C, 83.0; H, 5.0. Found: C, 82.8; H, 4.9.

4-Fluoro-1-chloromethylnaphthalene (VII). The chloromethylation of 50 g. of 1-fluoronaphthalene was performed as for the 2-fluoro isomer. The yield was 45 g. of *4-fluoro-1-chloromethylnaphthalene*, b.p. 157–158°/18 mm., crystallizing from ethanol in silky colorless prisms, m.p. 56°. Like its isomer, this compound possesses pronounced skin irritating and lachrymatory properties.

Anal. Calcd. for $C_{11}H_8ClF$: C, 67.9; H, 4.1. Found: C, 67.9; H, 3.9.

4-Fluoro-1-naphthylacetonitrile. This compound, prepared by refluxing the foregoing chloromethyl derivative for 24 hr. with a slight excess of sodium cyanide in acetone, crystallized from ethanol in silky colorless needles, m.p. 87°.

Anal. Calcd. for $C_{12}H_8FN$: N, 7.6. Found: N, 7.5.

4-Fluoro-1-naphthylacetic acid (VIII). Prepared by alkaline hydrolysis of the foregoing nitrile, this acid crystallized from aqueous ethanol in shiny colorless needles, m.p. 162°.

Anal. Calcd. for $C_{12}H_9FO_2$: C, 70.6; H, 4.4. Found: C, 70.8; H, 4.5.

The corresponding acid chloride, prepared with thionyl chloride, was a pale yellow oil, b.p. 127–129°/0.5 mm., n_D^{22} 1.6043, which could not be cyclized to 5-fluoroacenaphthen-1-one by means of aluminum chloride in nitrobenzene.

Preparation of 1-(4-fluoro-1-naphthyl)-2-arylacrylonitriles. A solution of equimolar amounts of 4-fluoro-1-naphthylacetonitrile and the appropriate aromatic or heterocyclic aldehyde in warm ethanol was shaken with a few drops of 25% aqueous sodium hydroxide, and the precipitate obtained on cooling was recrystallized from ethanol.

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(7) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW MEXICO HIGHLANDS UNIVERSITY]

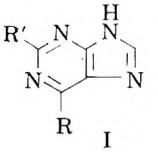
Potential Purine Antagonists VII. Synthesis of 6-Alkylpyrazolo-[3,4-*d*]pyrimidines[1,2a]

C. C. CHENG AND ROLAND K. ROBINS[2b]

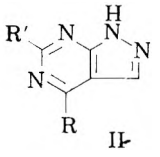
Received June 24, 1957

A synthesis of 6-alkyl-4-hydroxypyrazolo[3,4-*d*]pyrmidines (VI) has been devised from the corresponding 5-acylamino-4-cyanopyrazoles (IV) which were in turn prepared from 5-amino-4-cyanopyrazoles (III). Evidence is presented to show that the 5-acylaminopyrazole-4-carboxamide is an intermediate in this cyclization. Chlorination of the various 6-alkyl-4-hydroxypyrazolo[3,4-*d*]pyrimidines yielded the corresponding 6-alkyl-4-chloropyrazolo[3,4-*d*]pyrimidines (XI). Nucleophilic displacement of the chlorine atom in XI resulted in the preparation of a large number of 6-alkylpyrazolo[3,4-*d*]pyrimidines substituted in position 4.

The discovery[3,4] of 6-amino-2-methylpurine (I, R = NH_2, R′ = CH_3) and 6-hydroxy-2-methylpurine (I, R = OH, R′ = CH_3) as degradation products of pseudovitamin B_{12} prompted the investigation of the preparation of the corresponding analogs in the pyrazolo[3,4-*d*]pyrimidine series (II, R = NH_2, R′ = CH_3, and R = OH, R′ = CH_3).



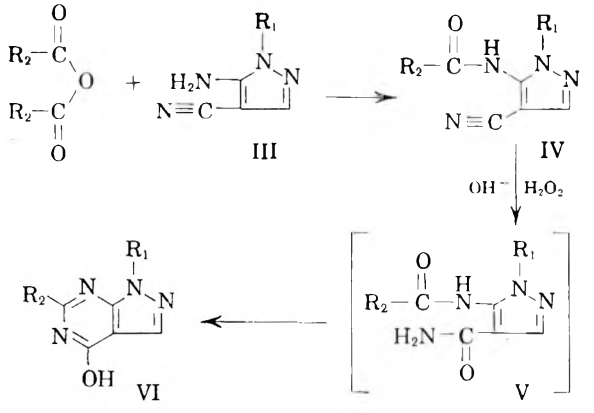
I



II

The general synthesis of the pyrazolo[3,4-*d*]pyrimidine system previously developed in this laboratory[5,6] proceeds *via* the appropriate 5-amino-4-cyanopyrazole (III). The ready accessibility of the corresponding 5-acylaminopyrazole led to a study of the use of this compound in an effort to find a general synthesis of 6-alkyl-4-substituted pyrazolo-[3,4-*d*]pyrimidines.

Bogert and Hand reported that the preparation of 2-methyl-4-hydroxyquinazoline could be accomplished by the action of warm alkaline peroxide solution upon acylanthranilic nitriles.[7] Following this lead it was found that when the 5-amino-4-cyanopyrazoles[5,6] (III) were acylated by either acetic or propionic anhydride to give the corresponding 5-acylamino-4-cyanopyrazoles (IV), these derivatives (IV) when treated with hydrogen peroxide in alkaline solution at 70–80° gave the desired 6-alkyl-4-hydroxypyrazole[3,4-*d*]pyrimidines (VI) in excellent yield.



III IV V VI

In succeeding reactions it proved unnecessary to isolate and purify the 5-acylamino-4-cyanopyrazole (IV). The crude syrupy residue (IV) remaining after distillation of the excess anhydride gave VI directly when treated with hydrogen peroxide in alkaline solution.

The over-all yield of the desired 6-alkyl-4-hydroxypyrazolo[3,4-*d*]pyrimidines (VI) obtained in this manner was even improved.

In the case of acetylation of 5-amino-4-cyano-1-β-hydroxyethylpyrazole(III, R_1 = CH_2CH_2OH), the acetylated product obtained was 1-β-acetoxyethyl-5-acetylamino-4-cyanopyrazole (IV, R_1 = $CH_2CH_2OCOCH_3$). It is interesting to note that when his product was cyclized in the base-peroxide medium, the original R_1 group was regenerated and 4-hydroxy-1-β-hydroxyethyl-6-methylpyrazolo[3,4-*d*]pyrimidine was the product obtained.

The probable intermediate, 5-acylaminopyrazole-4-carboxamide (V), could not be isolated during the process of cyclization. An attempt to prepare 5-acetylamino-1-phenylpyrazole-4-carboxamide (V, R_1 = C_6H_5, R = CH_3) from 5-acetylamino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5, R_2 = CH_3) and concentrated sulfuric acid at 15–20° was unsuccessful. The product isolated was identified as 5-amino-1-phenylpyrazole-4-carboxamide (VII). VII has previously been reported, prepared by the action of concentrated sulfuric acid on 5-amino-4-cyano-1-phenylpyrazole.[6]

(1) This investigation was supported by research grant C-2105 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) (a) Presented in part before the Division of Medicinal Chemistry, 128th Meeting of the American Chemical Society, Minneapolis, Minn., September 1955. (b) Present address: Dept. of Chemistry, Arizona State College, Tempe, Arizona.

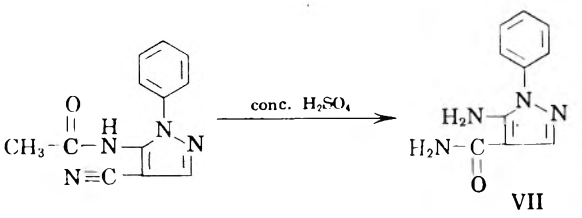
(3) Dion, Calkins and Pfiffner, *J. Am. Chem. Soc.*, **76**, 948 (1954).

(4) Brown and Smith, *Biochem. J.*, **56**, 34 (1954).

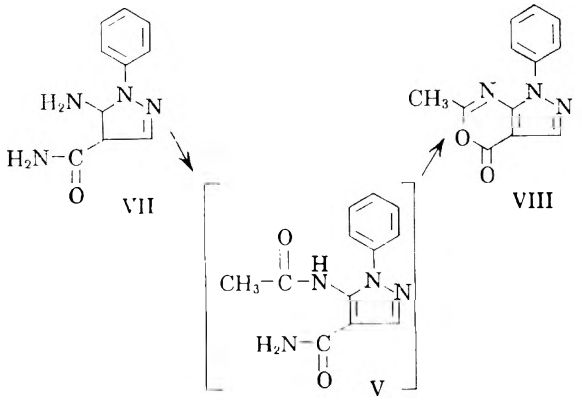
(5) Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

(6) Cheng and Robins, *J. Org. Chem.*, **21**, 1240 (1956).

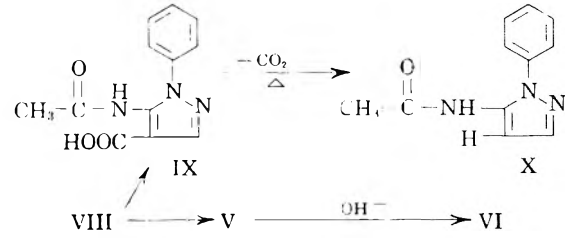
(7) Bogert and Hand, *J. Am. Chem. Soc.*, **24**, 1048 (1902).



Another attempt to prepare the suspected intermediate 5-acetylamino-1-phenylpyrazole-4-carboxamide from the acetylation of 5-amino-1-phenylpyrazole-4-carboxamide (VII) resulted in the formation of 6-methyl-4-keto-1-phenylpyrazolo[3,4-*d*]-5,7-oxazine (VIII). The formation of VIII is not entirely unexpected since benzoxazines can be prepared by heating anthranilic acid, substituted anthranilic acids and *N*-acetyl or *N*-benzoyl derivatives with acetic anhydride.[8]



The desired intermediate, 5-acetylamino-1-phenylpyrazole-4-carboxamide (V), was finally prepared from VIII and alcoholic ammonia on the steam bath. Treatment of V with 10% potassium hydroxide cyclized the acetylated amide almost immediately to 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (VI, $R_1 = C_6H_5$, $R_2 = CH_3$).



The oxazone ring in 6-methyl-4-keto-1-phenylpyrazolo[3,4-*d*]5,7-oxazine is not very stable and is ruptured easily in basic solution to form 5-acetylamino-1-phenylpyrazole-4-carboxylic acid (IX) which loses carbon dioxide readily on heating. It is interesting to note that the 5-acetylamino group was retained in warm alkaline solution but hydrolyzed quite readily in the cold acidic medium.

Justoni and Fusco[9] prepared "1',3'-diphenyl-6-hydroxy-2-methyl(pyrazolo-5',4':4,5-pyrimidine)" which is the only 6-alkylpyrazolo[3,4-*d*]pyrimidine reported prior to this work, from the dehydration of 5-acetylamino-1,3-diphenylpyrazole-4-carboxamide by heating with a direct flame. In this regard it is noteworthy that in the case of 5-acetylamino-1-phenylpyrazole-4-carboxamide a definite melting point could not be obtained on the Fisher-Johns melting point apparatus since thermal cyclization took place in a similar manner to give 1-phenyl-6-methyl-4-hydroxypyrazolo[3,4-*d*]pyrimidine.

The preparation of the pyrazolo[3,4-*d*]pyrimidine ring system by the fusion of formamide with the corresponding 5-amino-4-cyanopyrazoles of 5-aminopyrazole-4-carboxamide has been employed quite extensively.[5,6] Several attempts under various conditions to utilize acetamide or *p*-nitrobenzamide in place of formamide in the fusion reaction to give the corresponding 6-methyl or 6-*p*-nitrophenylpyrazolo[3,4-*d*]pyrimidine were unsuccessful. In both cases the unreacted pyrazoles were recovered.

A methyl group substituted on the pyrazolo[3,4-*d*]pyrimidine ring at the position "3"[6] was also prepared in the 6-alkyl series by acylation of the corresponding 3-methyl-5-amino-4-cyanopyrazole followed by base-peroxide cyclization.

Chlorination of the 4-hydroxy-6-alkyl-1-alkyl-(aryl)pyrazolo[3,4-*d*]pyrimidines was carried out under conditions similar to those employed for compounds having no alkyl substituent at the 6-position.[6] However, for the chlorination of 4-hydroxy-6-methylpyrazolo[3,4-*d*]pyrimidine (where the substituent at the 1- position is hydrogen) a considerable amount of *N*,*N*-dimethylaniline was required in addition to phosphorus oxychloride to effect successful chlorination. A similar situation has been found with 4-hydroxypyrazolo[3,4-*d*]pyrimidine[5] as compared to the case of the 1-alkyl (aryl)-4-hydroxypyrazolo[3,4-*d*]pyrimidines.[6]

The compound, 4-amino-6-methylpyrazolo[3,4-*d*]pyrimidine, an analog of 6-amino-2-methylpurine, was prepared by heating XI with alcoholic ammonia in a bomb. Various substituted amino derivatives were prepared by the reaction of XI with various primary and secondary amines, heated in aqueous or alcoholic solution on the steam bath, as shown in the reaction scheme. These compounds are listed in Table III.

The 4-mercapto-6-alkylpyrazolo[3,4-*d*]pyrimidines (XII) were prepared by two methods—either by the thiation of the corresponding 4-hydroxy compound (VI) with phosphorus pentasulfide in tetralin or by the reaction of the 4-chloro compound (XI) with thiourea in alcoholic solution. Samples

(8) (a) Bredy and Hof, *Ber.*, **33**, 29 (1900); (b) Bogert and Seil, *J. Am. Chem. Soc.*, **29**, 517 (1907); (c) Lothrop and Goodwin, *J. Am. Chem. Soc.*, **65**, 363 (1943); (d) Zentmyer and Wagner, *J. Org. Chem.*, **14**, 967 (1949); (e) Tomisek and Christensen, *J. Am. Chem. Soc.*, **70**, 2423 (1948).

(9) Justoni and Fusco, *Gazz. chim. ital.*, **68**, 66 (1938).

of products which were prepared by both methods were identical.

4-Alkoxy-6-alkyl derivatives (XIV) (Table II) were prepared from XI and sodium alkoxide at comparatively low temperatures. The sulfur analogs, 4-alkylmercapto-6-alkyl derivatives (XIII), were prepared by either the reaction of XI and potassium alkyl mercaptide or by the alkylation of XII in basic media with methyl iodide.

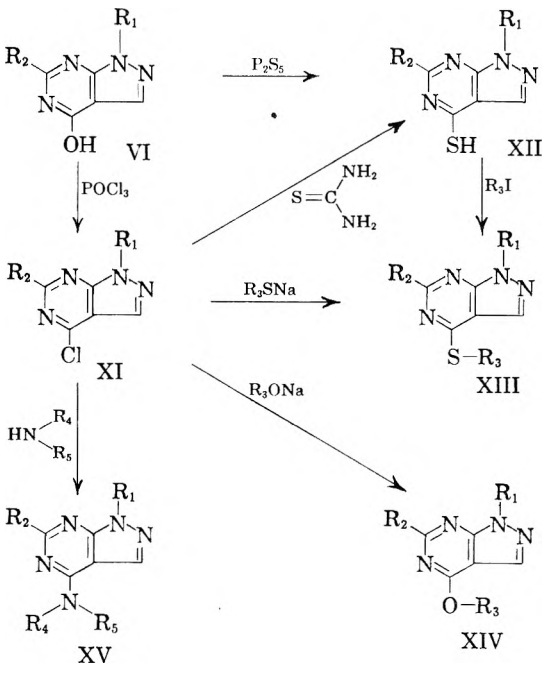
The presence of an alkyl group at the 6 position caused a definite hypsochromic shift in the absorption spectra in the ultraviolet region of the order of 2 to 10 mμ.

In the 6-alkyl-4-substituted pyrazolo[3,4-*d*]pyrimidines, ortho substitution of the aromatic ring at position 1 appears to cause interference to the conjugation of the pyrazole and the benzene ring. This was indicated by the ultraviolet absorption measurements as illustrated by strong absorption in ethanol for 4-chloro-6-methyl-1-phenylpyrazolo-[3,4-*d*]pyrimidine (λ_{max} 238 mμ, ϵ = 28,200), 4-chloro-6-ethyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 239 mμ, ϵ = 30,000), 4-chloro-6-methyl-1-*p*-tolylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 249 mμ, ϵ = 35,200), 4-chloro-6-methyl-1-*p*-chlorophenylpyrazolo[3,4-*d*] pyrimidine (λ_{max} 249 mμ, ϵ = 60,000) and 4-chloro-6-methyl-1-*p*-bromopyrazolo[3,4-*d*]-pyrimidine (λ_{max} 251 mμ, ϵ = 40,400); whereas the corresponding 4-chloro-6-methyl-1-(*o*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine exhibited a weak absorption peak at 264 mμ (ϵ = 7500). The latter compound showed rather closely the ultraviolet absorption characteristic of the 1-alkyl series. Thus the absorption spectra for 4-chloro-6-methylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 265 mμ, ϵ = 5050) and 4-chloro-1,6-dimethylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 266 mμ, ϵ = 5470) are typical. The absorption spectra of 4-chloro-6-methyl-1-(*o*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine is probably due to the hypsochromic shift of the interfered conjugated absorption caused by the ortho substitution, thus revealing the original absorption due to the nucleus, which exhibits a rather low optical intensity.

The screening of these compounds against tumors in mice thus far has not revealed any significant antitumor agents in this series. A full report of this testing has appeared.[10] Some interesting observations of these compounds in inhibiting the growth of *Neurospora crassa* has been observed.[11] The compound 4-dimethylamino-6-methyl-1-(*p*-tolyl)pyrazolo[3,4-*d*]pyrimidine at a low dosage showed relatively pronounced inhibition, however at larger dosages growth was supported by the same compound. Further microbiological testing is in progress.

(10) Skipper, Robins, Thomson, Cheng, Brockman, and Schabel, *Cancer Research*, **17**, 579 (1957).

(11) Fuerst, Somers, and Hsu, *J. Bacteriol.*, **72**, 387 (1956).



EXPERIMENTAL

All melting points are uncorrected and, unless otherwise stated, were taken on a Fisher-Johns melting point apparatus.

Preparation of 1-alkyl(aryl)-5-acetylamino-4-cyanopyrazoles. See Table I. *Example (1) 5-Acetylamino-4-cyanopyrazole*[6] (IV, R_1 = H, R_2 = CH_3). A mixture of 250 ml. of acetic anhydride and 80 g. of 5-amino-4-cyanopyrazole[6] (III, R_1 = H) was refluxed for 10 hr. Excess acetic anhydride was distilled off under reduced pressure. The syrupy substance was poured into 30 ml. of benzene. The mixture was stirred for several minutes, and the product crystallized slowly. The solid was filtered and recrystallized from water to give 89 g. (76%) of white crystals, m.p. 214–218°. A second recrystallization from water gave a m.p. of 221–222°.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.02; N, 37.3. Found: C, 47.9; H, 4.36; N, 37.4.

Example (2) 5-Acetylamino-4-cyano-1-methylpyrazole (IV, R_1, R_2 = CH_3). The procedure was similar to that for the acetylation of 5-amino-4-cyanopyrazole. The crude product (yield 90%) was recrystallized from water to give a white powder, m.p. 210–211°.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.1; H, 4.91. Found: C, 51.1; H, 4.91.

Example (3) 5-Acetylamino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5, R_2 = CH_3). One hundred fifty g. of 5-amino-4-cyano-1-phenylpyrazole[6] (III, R_1 = C_6H_5) was treated with 200 ml. of acetic anhydride and refluxed for 19 hr. Excess solvent was taken off under reduced pressure. To the syrupy residue was added a small amount of benzene and skellysolve (b.p. 60°). The product crystallized gradually. It was filtered and washed with a little benzene and was recrystallized from water to give 171 g. (92%) of a white crystalline compound which melted at 171–172°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 63.6; H, 4.45. Found: C, 63.2; H, 4.44.

Preparation of 5-amino-1-phenylpyrazole-4-carboxamide (VII) *by the action of concentrated sulfuric acid on 5-acetylamino-4-cyano-1-phenylpyrazole.* To 120 ml. of concentrated sulfuric acid cooled in icebath was gradually added, with continuous stirring, 30 g. of finely powdered 5-acetylamino-4-cyano-1-phenylpyrazole. The inside temperature was maintained at 15–20°. After the reaction was complete, the clear solution was allowed to stir for 30 min. It was then

TABLE I

5-ACYLAMINO-4-CYANOPYRAZOLES

R_1	R_2	R_3	M.P., °C.	Yield, %	U.V. Absorption				Recrystallization Solvents	Analyses					
					pH = 1, λ_{max}	ϵ	pH = 11, λ_{max}	ϵ		Calcd.			Found		
										C	H	N	C	H	N
H	H	CH_3	221°–222°[a]	76			234	7,050	Water	48.0	4.02	37.3	47.9	4.36	37.4
CH_3	H	CH_3	210–211	72	228	8,800	231	5,900	Water	41.2	4.91		51.2	4.91	
C_6H_5	H	CH_3	155–156	92	248	15,100	215	16,300	Water	63.6	4.45	24.8	63.2	4.44	24.1
o-ClC_6H_4	H	CH_3	175–175.5	82					ethanol, water	55.3	3.48	21.5	54.5	3.45	21.5
p-ClC_6H_4	H	CH_3	173–175	96	238	20,800	246	21,300	ethanol, water			21.5			21.3
p-BrC_6H_4	H	CH_3	175–175	98	238	22,300	237	26,500	ethanol, water	47.3	2.97		47.0	3.57	
p-$NO_2C_6H_4$	H	CH_3	198–200	95	286	12,400	290	11,100	ethanol, water	53.2	3.34		52.8	3.34	
p-$CH_3C_6H_4$	H	CH_3	128	96	238	13,900	239	17,800	ethanol, water			23.3			23.4
CH_3—C(=O)—O—CH_2—CH_2	H	CH_3	155–157	81	226	7,300			ethanol	50.9	5.12	23.7	51.1	5.04	24.0

poured, with vigorous stirring, onto 1 kg. of crushed ice. The solution was then neutralized with concentrated ammonium hydroxide. A white precipitate which formed instantly was filtered and washed with water, dried, and recrystallized from benzene and methanol to give 20 g. (78%) of a white solid, m.p. 171–172°. Recrystallization from ethanol and water raised the melting point of the product to 172–175°.

Anal. Calcd. for $C_{10}H_{10}N_4O$: N, 27.7. Found: N, 27.9.

A mixture of this compound and the compound prepared from the hydrolysis of 5-amino-4-cyano-1-phenylpyrazole[6] showed no depression in melting point.

6-Methyl-4-keto-1-phenylpyrazolo[3,4-d]-5,7-oxazine (VIII). A mixture of 20 g. of 5-amino-1-phenylpyrazole-4-carboxamide and 200 ml. of acetic anhydride was refluxed for 15 hr. Excess anhydride was distilled under reduced pressure. The residue solidified on cooling. It was recrystallized from a mixture of benzene and heptane to give 15 g. (67%) of a yellow solid, m.p. 184.5–185.5° (sublimed at 145°).

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.6; H, 4.00; N, 18.5. Found: C, 63.3; H, 4.11; N, 18.6.

5-Acetylamino-1-phenylpyrazole-4-carboxylic acid (IX). Two and one-half g. of 6-methyl-4-keto-1-phenylpyrazolo-[3,4-*d*]-5,7-oxazine were mixed with 200 ml. of water containing 2 g. of potassium hydroxide. The mixture was kept at room temperature for 2 hr. and then heated on a steam bath for 10 hr. and finally acidified with glacial acetic acid. A white precipitate gradually formed. The compound was filtered and reprecipitated from base with acetic acid to give 2 g. (74%) of white needles, m.p. 201–202[c] (with evolution of gas).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.9; H, 4.52; N, 17.2. Found: C, 58.7; H, 4.37; N, 17.1.

Preparation of 5-acetylamino-1-phenylpyrazole-4-carboxamide (V). Two g. of 6-methyl-4-keto-1-phenylpyrazolo[3,4-*d*]-5,7-oxazine were added to 100 ml. of alcoholic ammonia. The mixture was allowed to stand at room temperature for 30 min. with occasionally shaking. It was then heated briefly on a steam bath until a solid product precipitated from the alcoholic solution. The product was filtered, and, the product dried at 100° for 5 hr. The m.p. was 301–302°. Owing to the relative instability of this compound, it was analyzed without further purification.

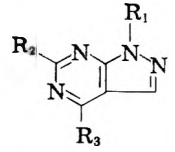
Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.1; H, 4.94; N, 22.0. Found: C, 59.6; H, 5.06; N, 23.0.

The melting point of this compound was the same as that for 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine. A mixed melting point indicated no depression. However, the ultraviolet absorption spectra for the carboxamide (in neutral solution, λ_{max} 230 mμ) and that for the cyclized pyrazolo[3,4-*d*]pyrimidine (in neutral solution, λ_{max} 233 mμ, 269 mμ) were different. So were the analyses of these two compounds. This indicated that the carboxamide cyclized at elevated temperature during the melting point determination. The thermal cyclization was further confirmed by the determination of ultraviolet absorption spectra of the acetylated carboxamide after heating at 350° for 30 min. The spectra were found to be identical to that of 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine.

Preparation of 1-alkyl(aryl)-4-hydroxy-6-methylpyrazolo-(3,4-d) pyrimidines (VI). See Table II. *4-Hydroxy-6-methylpyrazolo[3,4-d]pyrimidine* (VI, R_1 = H, R_2 = CH_3). A mixture of 1.5 g. of 5-acetylamino-4-cyanopyrazole, 7 ml. of 10% potassium hydroxide, and 15 ml. of 3% hydrogen peroxide was warmed on a water bath for 30 min. The temperature of the bath was kept at 70–75°. The mixture was then acidified with glacial acetic acid. A white precipitate was formed gradually from the clear solution. It was filtered and reprecipitated from dilute potassium hydroxide and acetic acid to give 1.1 g. (74%) of white powder, m.p. 336–338° (dec.). The melting point was determined on a copper block.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.00; N, 37.3. Found: C, 48.3; H, 3.98; N, 37.4.

TABLE II. 6-ALKYL 1,4-DISUBSTITUTED PYRAZOLO[3,4-*d*]PYRIMIDINES



R_1	R_2	R_3	M.P., °C.	Yield, %	U.V. Absorption *p*H 1, λ_{max}	*p*H 1, ϵ	*p*H 11, λ_{max}	*p*H 11, ϵ	Recrystallization Solvents	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3	OH	336–338	73.5	252	8,550	259	8,850	Acetic acid	48.0	4.30	37.3	48.3	3.98	37.4
H	CH_3	Cl	140 (dec.)	70.0	256	5,700	265	4,700	Benzene	42.7	2.97	33.3	42.5	2.91	33.6
H	CH_3	SH	>300	80.0	232	8,150			Repptd.			33.8			34.1
					323	20,400	315	18,000							
H	C_2H_5	OH	>300	82.0	253	10,200	259	10,300	Ethanol, water	51.4	4.87	34.1	51.1	4.78	33.8
CH_3	CH_3	OH	277–278	72.5	253	10,300	268	10,800	Ethanol, water	51.4	4.87	34.1	51.7	4.88	34.2
CH_3	CH_3	Cl	74	70.2	267	8,650	268	9,150	Heptane	46.1	3.84	30.7	45.9	4.01	30.6
CH_3	CH_3	SH	264–265	98.0	236	7,100	232	12,100	Repptd.			31.1			31.0
					322	21,200	318	16,600							
CH_3	CH_3	OCH_3	107.5–108.5	67.5	252	5,500	252	7,500	Methanol	53.9	5.66	31.4	54.0	5.91	31.4
CH_3	CH_3	SCH_3	74–75	90.2	251	6,800	261	8,150	Methanol, water			28.8			28.7
CH_2CH_2OH	CH_3	OH	265–266	54.8	253	9,100	253	10,100	Water	49.5	5.18	28.9	49.7	5.18	29.0
C_6H_5	CH_3	Cl	85–86	83.5					Heptane	58.9	3.72	23.0	59.0	3.54	23.4
C_6H_5	CH_3	SH	268.5	83.3	226	19,360	238	26,000	Repptd.	59.5	4.16	23.1	59.4	4.16	23.4
					259	12,800	319	20,300							
					320	21,000									
C_6H_5	CH_3	OCH_3	121.5–122						Methanol	65.0	5.04	23.3	64.5	5.00	23.6
C_6H_5	CH_3	OC_2H_5	95–95.5						Ethanol	66.2	5.51	22.0	66.2	5.64	22.5
C_6H_5	CH_3	SCH_3	135–137						Methanol, water			21.9			21.7
C_6H_5	CH_3	SC_2H_5	86–88						Ethanol, water			20.7			20.9
C_6H_5	C_2H_5	OH	295	88.5	229	28,300	275	14,400	Ethanol, water			23.3			23.5
C_6H_5	C_2H_5	SH	248–249	91.6	231	12,300	239	26,400	Repptd.	69.9	4.72	21.9	60.4	5.05	21.7
					275	13,600	319	18,200							
					320	15,600									
p-$CH_3C_6H_4$	CH_3	OH	298–300	93.6	230	35,700	275	15,400	Ethanol, water			23.4			23.5
p-$CH_3C_6H_4$	CH_3	Cl	89–91	78.1					Heptane			21.6			21.6
p-$CH_3C_6H_4$	CH_3	OCH_3	121–122	81.2					Methanol			22.0			21.7
p-$CH_3C_6H_4$	CH_3	OC_2H_5	93–94	53.0					Ethanol			20.9			20.8
o-ClC_6H_4	CH_3	Cl	121	77.8					Hexane			20.1			20.1
p-BrC_6H_4	CH_3	OH	>315	86.6	239	37,200	240	32,000	Ethanol, water			18.4			18.3
							277	18,300							
p-BrC_6H_4	CH_3	Cl	130.5–131	88.7					Hexane			17.3			17.3
p-ClC_6H_4	CH	OH	>310	94.5	240	36,400	240	41,700	Ethanol, water	55.4	3.46	21.5	55.1	3.37	21.2
							278	17,400							
p-ClC_6H_4	CH_3	Cl	129	82.6					Heptane	51.7	2.89	20.1	52.2	2.99	19.9
p-ClC_6H_4	CH_3	SH	>305	75.2					Repptd.			25.3			25.2
p-$NO_2C_6H_4$	CH_3	OH	>310	90.0	248	14,350	256	16,000	Repptd.	53.1	3.34	25.8	53.7	2.76	25.3
					306	14,900	321	13,800					52.4	3.26	
p-$NO_2C_6H_4$	CH_3	Cl	184	82.0					Toluene			24.2			24.2

4-Hydroxy-1,6-dimethylpyrazolo[3,4-d]pyrimidine (VI, R_1, R_2 = CH_3). One hundred twenty-one g. of 5-acetylamino-1-methyl-4-cyanopyrazole were added to a mixture of 1500 ml. of 3% hydrogen peroxide and 400 ml. of 10% potassium hydroxide. The mixture was warmed at 70° for 10 hr. It was then filtered and acidified to yield light yellow crystalline precipitate. The crude product was recrystallized from ethanol to give 103 g. (73%) of needles, m.p. 277–278° (sublimed at 180°).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.90; N, 34.2. Found: C, 51.2; H, 4.88; N, 34.2.

4-Hydroxy-6-methyl-1-phenylpyrazolo(3,4-d)pyrimidine (VI, R_1 = C_6H_5, R_2 = CH_3). *Method (1)*: 5-Acetylamino-4-cyano-1-phenylpyrazole (14.5 g.) was dissolved in a solution of 5 g. of potassium hydroxide and 200 ml. of 3% hydrogen peroxide. The mixture was warmed at 70–75° for 5 hr. It was then acidified with glacial acetic acid to give a white precipitate. The product was recrystallized from ethanol to give 14 g. (97%) of white needles which melted at 298–300°. Another recrystallization raised the melting point to 301–302°.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 64.0; H, 4.42; N, 24.8. Found: C, 63.7; H, 4.33; N, 24.6.

Method (2): One g. of 5-acetylamino-1-phenylpyrazole-4-carboxamide was added to 100 ml. of 10% potassium hydroxide solution. The mixture was heated on a water bath (70°) for 20 min. and then acidified with glacial acetic acid. The white precipitate which formed immediately was filtered and washed with water. Recrystallization from ethanol gave 0.8 g. of white needles which melted at 301°. The mixed melting point of this product and that prepared by Method (1) showed no depression. The ultraviolet absorption spectra of this compound and the compound made from Method (1) were identical.

Preparation of 1-alkyl(aryl)-4-chloro-6-methylpyrazolo[3,4-d]pyrimidines (XI). See Table II. *4-Chloro-6-methylpyrazolo[3,4-d]pyrimidine* (XI, R_1 = H, R_2 = CH_3). Fifty g. of finely powdered 4-hydroxy-6-methylpyrazolo[3,4-*d*]pyrimidine were added to a mixture of 140 ml. of *N*,*N*-dimethylaniline (mono-free) and 1 l. of phosphorus oxychloride. The mixture was refluxed for 2 hr. until all the solid went into solution. Excess phosphorus oxychloride was distilled under reduced pressure, and the syrupy residue was poured onto crushed ice with vigorous stirring. The aqueous suspension was extracted with ether (6 l. required). The ethereal extract was washed well with water until absolutely free from acid. The ether extract was dried over magnesium sulfate for 12 hr. and finally distilled slowly from a water bath. The last trace of ether was removed with a stream of air. This procedure was necessary to avoid the decomposition of the chloro- compound by overheating. The crude compound was recrystallized from dry benzene to give 35 g. (62%) of the product which decomposed without melting at 135–140°.

Anal. Calcd. for $C_6H_5N_4Cl$: C, 42.7; H, 2.70; N, 33.3. Found: C, 42.5; H, 2.91; N, 33.6.

4-Chloro-1,6-dimethylpyrazolo[3,4-d]pyrimidine (XI, R_1, R_2 = CH_3). Twenty-five g. of 4-hydroxy-1,6-dimethylpyrazolo[3,4-*d*]pyrimidine and 400 ml. of phosphorus oxychloride were refluxed for 2 hr. Excess solvent was distilled from the clear solution. The syrup, which contained a small amount of phosphorus oxychloride so that it could be poured out easily, was poured slowly onto 1 kg. of crushed ice with vigorous stirring. The cold aqueous suspension was allowed to stand for 15 min. and then extracted with chloroform. The extract was dried over anhydrous sodium sulfate overnight. Chloroform was distilled at room temperature and a brownish yellow liquid resulted which solidified on cooling. The product was recrystallized from *n*-heptane to give 24 g. (87%) of white needles, m.p. 74°.

Anal. Calcd. for $C_7H_7N_4Cl$: C, 46.1; H, 3.84; N, 30.7. Found: C, 45.9; H, 4.01; N, 30.6.

4-Chloro-6-methyl-1-(p-nitrophenyl)pyrazolo[3,4-d]pyrimidine (XI, R_1 = *p*-$NO_2C_6H_4$, R_2 = CH_3). To 250 ml. of phosphorus oxychloride were added 20 g. of powdered 4-hydroxy-6-methyl-1-(*p*-nitrophenyl)pyrazolo[3,4-*d*]pyrimidine. The mixture was refluxed for 3 hr. Excess phosphorus oxychloride was then distilled at reduced pressure, and the syrupy residue was added cautiously, a little at a time, onto finely crushed ice with vigorous stirring. The resulting solid product was filtered and washed well with ice water followed by ether. It was recrystallized from toluene to give 17.5 g. (82%) of light yellow powder, m.p. 184°.

Anal. Calcd. for $C_{12}H_8N_5O_2Cl$: N, 24.2. Found: N, 24.2.

Preparation of 1-alkyl(aryl)-6-alkyl-4-mercaptopyrazolo[3,4-d]pyrimidines (XII). See Table II. *4-Mercapto-6-methyl-1-1-phenylpyrazolo(3,4-d)pyrimidine* (XII, R_1 = C_6H_5, R_2 = CH_3). *Method (1)*. A mixture of finely powdered, intimately mixed 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (11 g.) and phosphorus pentasulfide (50 g.) was added portionwise to 400 ml. of tetralin, preheated to 165°. During the addition, which required 45 min., the temperature was allowed to rise to 185°. The reaction mixture was then heated to 190–195° for 6 hr., with continuous stirring. The solution was then cooled overnight and filtered. The product was washed with Skellysolve "B," and finally dissolved in dilute potassium hydroxide solution. Precipitation of the product with acetic acid gave 5.5 g. (46.6%), m.p. 266–268°.

For analytical purposes part of the product was recrystallized from ethanol to give a light yellow solid, m.p. 268.5°.

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.5; H, 4.16; N, 23.1. Found: C, 59.4; H, 4.16; N, 23.4.

Method (2). A mixture of 14 g. of 4-chloro-6-methyl-1-phenylpyrazolo [3,4-*d*]pyrimidine and 14 g. of C.P. thiourea in 120 ml. of absolute ethanol was refluxed for 4 hr. A light yellow solid separated on cooling. The product was filtered and washed well with cold ethanol and water. The product was further purified by precipitation from a hot basic solution with acetic acid to give 11.5 g. (83.3%) of a white solid, m.p. 268.5°. A mixed melting point of the product and the one prepared by method (1) indicated no depression. Their ultraviolet absorption spectra were identical.

All the other 4-mercapto derivatives were prepared by essentially the same procedure as Method (2).

Preparation of 1-alkyl(aryl)-6-alkyl-4-alkylmercaptopyrazolo[3,4-d]pyrimidines (XIII). See Table II. *1,6-Dimethyl-4-methylmercaptopyrazolo(3,4-d)pyrimidine* (XIII, R_1, R_2, R_3 = CH_3). A mixture of 13 g. of 1,6-dimethyl-4-mercaptopyrazolo[3,4-*d*]pyrimidine, 40 ml. of 4*N* potassium hydroxide, 18 g. of methyl iodide, and 30 ml. of methanol was shaken vigorously in a separatory funnel for 30 min. The contents were allowed to stand overnight at 40°. The white solidwas filtered and recrystallized from dilute methanol. The yield was 12.5 g. (90.2%), m.p. 74–75°.

Anal. Calcd. for $C_8H_{10}N_4S$: N, 28.8. Found: N, 28.7.

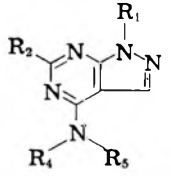
4-Ethylmercapto-6-methyl-1-phenylpyrazolo[3,4-d]pyrimidine (XIII, R_1 = C_6H_5, R_2 = CH_3, R_3 = C_2H_5). Nine g. of 4-mercapto-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine was added to 200 ml. of water containing 15 g. of potassium hydroxide and 21 g. of ethyl iodide. To this mixture was added 100 ml. of ethanol to make the solution homogeneous. The mixture was refluxed for 5 hr. It was then reduced in volume until an oily product appeared which solidified slowly on standing. The product was filtered, washed well with water, and recrystallized from dilute ethanol. The yield of slightly yellow needles was 3 g. (30%), m.p. 86–88°.

Anal. Calcd. for $C_{14}H_{14}N_4S$: N, 20.7. Found: N, 20.9.

Preparation of 4-alkoxy-1-alkyl(aryl)-6-methylpyrazolo[3,4-d]pyrimidines (XIV). See Table II. *4-Ethoxy-6-methyl-1-p-tolylpyrazolo[3,4-d]pyrimidine* (XIV, R_1 = *p*-CH_3-C_6H_4, R_2 = CH_3, R_3 = C_2H_5). To a solution of 100 ml. absolute ethanol and 5.5 g. of 4-chloro-6-methyl-1-(*p*-tolyl)pyrazolo-[3,4-*d*]pyrimidine was added, slowly, with shaking, a solution prepared by dissolving 2 g. of sodium in 70 ml. of ethanol. The mixture was allowed to stand at room temperature for 2 hr., with occasional shaking. It was then heated on a steam bath for 40 min. and sodium chloride

TABLE III

6-ALKYL-4-*N*-SUBSTITUTED PYRAZOLO[3,4-*d*]PYRIMIDINES



R_1	R_2	R_4	R_5	M.P., °C.	Method of Prepn.	U.V. Absorption Yield, %	pH 1, λ_{max}	pH 1, ϵ	pH 11, λ_{max}	pH 11, ϵ	Recrystallization Solvents	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3	H	H	>300	A	73.0	259	8,650	265	8,800	Ethanol, water	48.3	4.60	47.0	48.4	4.95	46.7
H	CH_3	H	CH_3	>300	B	60.0	265	7,650	275	9,950	Ethanol, water			42.9			42.7
H	CH_3	H	C_2H_5	273–274	B	56.0	269	10,100	275	12,600	Ethanol			39.5			39.7
H	CH_3	H	CH_2—CH_2—CH_3	220–222	B	49.1	270	10,700	276	12,700	Ethanol			34.2			34.5
H	CH_3	H	CH_2—C_6H_5	241	B	87.2					Ethanol			29.3			29.1
H	CH_3	H	Furfuryl	243–244	C	59.0			275	12,900	Ethanol	57.7	4.83	30.6	57.5	4.75	30.4
CH_3	CH_3	H	H	251–252	A	90.0	260	9,450	262	9,300	Ethanol, water			42.9			42.8
CH_3	CH_3	H	CH_3	136–138	B	77.2	265	11,700	279	13,500	Water			39.5			39.5
CH_3	CH_3	H	C_2H_5	131.5–132	C	66.9	266	21,000	279	22,000	Toluene, heptane	56.5	6.85	36.6	57.0	7.10	
CH_3	CH_3	H	CH_2—C_6H_5	180–182	B	83.0					Ethanol			27.7			27.4
CH_3	CH_3	H	Furfuryl	140–141.5	C	54.6					Ethanol			28.8			28.6
CH_3	CH_3	H	*o*-Cl—C_6H_4	223.5–224	B	60.0					Ethanol	57.1	4.33	25.6	57.2	4.37	25.9
CH_3	CH_3	H	*p*-Cl—C_6H_4	231.5	B	67.0					Ethanol, water			25.6			25.5
CH_3	CH_3	H	*o*-CH_3—C_6H_4	224–225.5	B	60.0	270	15,400	282	16,000	Ethanol			27.7			27.6
CH_3	CH_3	H	*p*-CH_3—C_6H_4	225–227	B	74.7					Ethanol	66.5	5.98	27.7	66.7	5.97	27.3
CH_3	CH_3	H	2,6-Diethylphenyl	218–218.5	B	48.5	215 269	24,800 13,000	279	13,000	Ethanol	69.2	7.17	23.7	68.8	7.00	23.9
CH_3	CH_3	H	NH_2	259–260	B	87.3	223 265	22,000 13,200	278	11,100	Ethanol	47.1	5.65		47.5	5.83	
C_6H_5	CH_3	H	H	287–289	A	82.5	238	25,200	236 278	18,700 9,000	Ethanol, water	64.0	4.92	31.1	64.0	4.73	30.9
C_6H_5	CH_3	H	CH_3	162–163	B	80.2	242	36,000	238 286	26,000 16,200	Ethanol, water	65.3	5.48	29.3	65.7	5.47	29.7
C_6H_5	CH_3	CH_3	CH_3	117–117.5	C	82.5	247	30,600	236 288	24,300 18,200	Ethanol	66.5	5.94	27.7	66.4	5.82	27.2
C_6H_5	CH_3	H	C_2H_5	87	B	87.2	232	29,400	235	23,000	Ethanol			27.7			27.9
C_6H_5	CH_3	C_2H_5	C_2H_5	66–68	C	83.0					Ethanol			25.0			24.8
C_6H_5	CH_3	H	$CH(CH_3)_2$	143–144	B	86.0	243	30,800	238 286	23,400 16,700	Ethanol, water	67.4	6.37	26.2	66.8	6.34	26.4
C_6H_5	CH_3	H	$C(CH_3)_3$	175–177	C	61.0					Ethanol, water	68.4	6.81	25.0	67.7	6.68	25.2
C_6H_5	CH_3	H	CH_2—CH_2—$N(C_2H_5)_2$	159–160	C	49.1	243	22,300	238 286	21,000 13,900	Heptane			25.9			25.5
C_6H_5	CH_3	CH_2—C_6H_5		187–188	B	92.0	245	29,000	237 282	16,800 11,300	Ethanol	72.4	5.44	22.2	71.7	5.10	22.4

TABLE III (*Continued*)

R_1	R_2	R_4	R_5	M.P., °C.	Method of Prepn.	U.V. Absorption: Yield, %	pH 1, λ_{max}	pH 1, ϵ	pH 11, λ_{max}	pH 11, ϵ	Recrystallization Solvents	Analyses: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	CH_3	H	Furfuryl	153–154.5	C	56.2	243	39,400	238 284	28,800 17,200	Toluene, heptane	67.0	4.96	23.0	67.3	4.87	23.1
C_6H_5	CH_3	H	C_6H_5	262–263	B	50.5	246 300	9,600 7,200	247	26,500	2-Ethoxy-ethanol			23.3			23.4
C_6H_5	CH_3	H	*m*-Br—C_6H_4	215–127	B	68.0					Ethanol	57.0	3.71	18.4	56.7	3.93	18.3
C_6H_5	CH_3	H	*o*-Cl—C_6H_4	175–176	B	51.3					Ethanol			20.9			21.1
C_6H_5	CH_3	H	*m*-Cl—C_6H_4	192–193	B	90.0	247	28,800	238 305	17,400 16,400	Ethanol	64.6	4.21	20.9	64.2	4.60	20.9
C_6H_5	CH_2	H	*p*-Cl—C_6H_4	226–226.5	B	82.0	248	25,800	252	73,500	Ethanol, water	64.6	4.21	20.9	64.0	4.33	20.7
C_6H_5	CH_3	H	2,6-Diethylphenyl	189–190	B	71.2					Ethanol			19.6			19.8
C_6H_5	CH_3	H	NH_2	243–244	B	80.1	242	25,200	239 283	19,200 11,300	Pyridine	60.0	5.00	35.0	60.2	5.12	35.4
C_6H_5	CH_3	H	NH—C_6H_5	240–241	B	47.5					Pyridine	67.3	5.10	26.6	67.7	5.05	26.5
C_6H_5	C_2H_5	CH_3	CH_3	90.5–91	B	55.5					Ethanol	67.5	6.41	26.2	67.7	6.62	26.3
C_6H_5	C_2H_5	H	$C(CH_3)_3$	148–148.5	C	73.3	238	15,900	240 286	2,950 3,250	Ethenol, sublimed	69.2	7.17	23.7	69.4	7.07	23.7
C_6H_5	C_2H_5	H	CH_2—C_6H_5	129–129.5	C	48.5	245	24,300	239 287	9,530 6,250	Benzene, ethanol			21.3			21.3
C_6H_5	C_2H_5	H	*o*-Cl—C_6H_5	168–168.5	B	71.5					2-Ethoxy-ethanol	65.5	4.62	20.0	66.0	4.71	19.9
C_6H_5	C_2H_5	H	*m*-Cl—C_6H_5	187–189	B	74.0					Ethanol			20.0			19.9
C_6H_5	C_2H_5	H	*p*-Cl—C_6H_5	208.5–209.5	B	87.8					2-Ethoxy-ethanol			20.0			19.8
C_6H_5	C_2H_5	H	*o*-CH_3—C_6H_5	175–176	B	75.5	247	29,800	242 291	19,600 16,300	Ethanol			21.3			21.0
C_6H_5	C_2H_5	H	*m*-CH_3—C_6H_5	169.5	B	58.0					Ethanol			21.3			21.3
C_6H_5	C_2H_5	H	*p*-CH_3—C_6H_5	199–200	B	78.6					Ethanol			21.3			21.1
C_6H_5	C_2H_5	H	2,5-Dichlorophenyl	181–183	B	42.1					Ethanol			18.2			18.4
C_6H_5	C_2H_5	H	2,6-Diethylphenyl	191–191.5	B	38.0	244	28,200	252 304	25,600 18,500	Ethanol			18.7			18.9
C_6H_5	C_2H_5	H	NH_2	198–199	B	87.5					Ethanol	61.5	5.55	33.1	61.4	5.29	33.2
p-CH_3—C_6H_4	CH_3	H	H	296.5–298	A	75.7	233	7,650			Ethanol			29.3			29.4
p-CH_3—C_6H_4	CH_3	H	CH_3	181–182.5	B	86.0	244	29,600	239 283	22,500 14,200	Methanol, water			27.6			27.7
p-CH_3—C_6H_4	CH_3	CH_3	CH_3	149–151	B	82.2	248	24,800	239 289	22,200 16,300	Ethanol			26.2			26.2
p-CH_3-C_6H_4	CH_3	H	C_2H_5	144–146	B	80.0					Ethanol, water			26.2			26.0
p-CH_3—C_6H_4	CH_3	H	CH_2—CH_2—$N(C_2H_5)_2$	165	C	62.8	244	25,700	239 283	23,300 14,900	Toluene, heptane			24.8			24.8
p-CH_3—C_6H_4	CH_3	H	*o*-Cl—C_6H_4	219–221	B	76.5					Pyridine	65.4	4.62	20.0	65.2	4.44	20.2
p-CH_3—C_6H_4	CH_3	H	*m*-Br—C_6H_4	218–220	B	63.5	253	30,000	241 315	23,200 19,300	Ethanol			17.8			18.0
o-Cl—C_6H_4	CH_3	H	H	294.5–295.5	A	71.8					Ethanol			27.0			27.1
o-Cl—C_6H_4	CH_3	CH_3	CH_3	152–153	C	77.7					Ethanol			24.4			24.4

TABLE III (*Continued*)

R_1	R_2	R_4	R_5	M.P., °C.	Method of Prepn.	Yield, %	U.V. Absorption pH 1, λ_{max}	ϵ	pH 11, λ_{max}	ϵ	Recrystallization Solvents	Analyses Calcd. C	H	N	Found C	H	N
o-Cl—C_6H_4	CH_3	H	*o*-Cl—C_6H_4	196–198	B	63.0					Ethanol			18.9			19.0
p-Br—C_6H_4	CH_3	C_2H_5	C_2H_5	123–124	B	51.6					2-Ethoxyethanol, water			19.4			19.5
p-Cl—C_6H_4	CH_3	H	H	>300	A	36.0					Ethanol			27.0			27.3
p-Cl—C_6H_4	CH_3	H	CH_3	218–219	B	57.2					Ethanol, water			25.6			25.3
p-ClC_6H_4	CH_3	H	CH_2—CH_2—CH_2—O—$CH(CH_3)_2$	109–110	B	51.1					Methanol, water	60.2	6.14	19.5	60.3	6.08	19.3
p-ClC_6H_4	CH_3	CH_2—CH_2—CH_2—CH_2		127.5–128.5	B	61.3					Ethanol, water	62.5	5.55		62.0	5.28	
p-ClC_6H_4	CH_3	H	CH_2—C_6H_5	214	B	93.3					2-Ethoxyethanol	65.4	4.61	20.0	65.5	4.50	20.1
p-ClC_6H_4	CH_3	H	CH_2—CH_2—C_6H_5	175–176	B	60.1			246 294	46,000 24,600	Ethanol	66.0	4.98	19.3	65.7	5.12	19.7
p-ClC_6H_4	CH_3	H	*o*-Cl—C_6H_4	221–222	B	62.0					Pyridine	58.5	3.54		58.2	3.58	
p-ClC_6H_4	CH_3	H	*m*-ClC_6H_4	222–223	B	85.5					2-Ethoxyethanol			18.9			18.6
p-ClC_6H_4	CH_3	H	*p*-ClC_6H_4	239–239.5	B	88.0					Pyridine	58.5	3.54	18.9	59.0	3.84	18.7
p-ClC_6H_4	CH_3	H	*m*-BrC_6H_4	230–232	B	74.2					Pyridine	52.2	3.17	16.9	51.8	3.44	16.6
p-ClC_6H_4	CH_3	H	2,5-Dichlorophenyl	200	B	71.5					2-Ethoxyethanol			17.4			17.3
p-$NO_2C_6H_4$	CH_3	H	CH_3	248–249	B	69.0	269 319	15,600 13,300	267	19,600	Ethanol			24.2			24.1
p-$NO_2C_6H_4$	CH_3	CH_3	CH_3	196	B	51.2	273	11,600	271	12,200	Ethanol, water			28.2			28.0
p-$NO_2C_6H_4$	CH_3	H	$CH(CH_3)_2$	190–192	B	81.1	232 281	21,200 21,800	271 316	17,800 14,400	Ethanol			26.9			26.7
p-$NO_2C_6H_4$	CH_3	H	CH_2—CH_2—CH_2—CH_3	147	B	66.6	239 270 327	10,800 12,100 9,450	269	21,200	Ethanol	58.8	5.53	25.8	59.0	5.68	25.6
p-$NO_2C_6H_4$	CH_3		[CH_2—CH_2—CH_2—CH_2—CH_2]	189–191	B	96.0	237 279	15,200 25,400	240 292 344	13,900 12,500 13,400	Pyridine	60.5	5.35	24.8	61.0	5.50	23.4
p-$NO_2C_6H_4$	CH_3	H	CH_2—CH_2—$N(C_6H_5)_2$	145	B	91.7	269 315	17,000 14,000	272	22,500	Ethanol, water			26.5			26.1
p-$NO_2C_6H_4$	CH_3	H	*o*-ClC_6H_4	227–228	B	43.2	276	21,300	238 285	18,200 13,300	Ethanol			22.1			22.2
p-$NO_2C_6H_4$	CH_3	H	*p*-ClC_6H_4	278	B	87.0					Acetic acid			22.1			22.4

filtered from the hot reaction mixture. To the filtrate was added 50 ml. of water, and the clear solution was cooled overnight. White, fluffy long needles were formed the second day, which were filtered and recrystallized from dilute ethanol to give 3.1 g. (53%) of the desired product, m.p. 93–94°.

Anal. Calcd. for $C_{15}H_{16}N_4O$: N, 20.0. Found: N, 20.8.

The other 4-alkoxy compounds were prepared by essentially the same method.

Preparation of 6-alkyl-4-N-substituted aminopyrazolo[3,4-d]pyrimidines (XV). See Table III. *General Method* (*A*). This method is illustrated by the following example. *4-Amino-6-methylpyrazolo[3,4-d]pyrimidine* (XV, R_1, R_4, R_5 = H, R_2 = CH_3). A mixture of 10 g. of 4-chloro-6-methylpyrazolo[3,4-*d*]pyrimidine (XI, R_1 = H, R_2 = CH_3) and 120 ml. of alcoholic ammonia was heated in a bomb at 160° for 8 hr. The reaction product was evaporated on a steam bath to dryness. The residue was boiled with dilute hydrochloric acid. The solution was treated with charcoal and filtered. The product was reprecipitated by the addition of ammonium hydroxide. The product was then filtered and recrystallized from dilute ethanol to give 6.5 g. (73%) of light yellow needles, m.p. > 300°.

Anal. Calcd. for $C_6H_7N_5$: C, 48.3; H, 4.60; N, 47.0. Found: C, 48.4; H, 4.95; N, 46.7.

General Method (*B*). This method is illustrated by the following specific examples. *4-n-Butylamino-6-methylpyrazolo[3,4-d]pyrimidines* (XV, R_1, R_4 = H, R_2 = CH_3, R_5 = CH_2—CH_2—CH_2—CH_3). Five g. of 4-chloro-6-methylpyrazolo(3,4-*d*)pyrimidine was added to a mixture of 7 g. of *n*-butylamine and 120 ml. of absolute ethanol. The mixture was refluxed on a steam bath for 7 hr., light yellow needles formed in the hot solution. The product was filtered and recrystallized from ethanol to give 3 g. (49.1%) of white needles, m.p. 220–222°.

Anal. Calcd. for $C_{10}H_{15}N_5$: N, 34.2. Found: N, 34.5.

4-(p-Chloroanilino)-6-methyl-1-phenylpyrazolo[3,4-d]pyrimidine (XV, R_1 = C_6H_5, R = CH_3, R_4 = H, R_5 = *p*-Cl-C_6H_4). Five g. of 4-chloro-6-methyl-1-phenylpyrazolo[3,4-*d*]-pyrimidine was added to a mixture of 8 g. of *p*-chloroaniline and 75 ml. of absolute ethanol. The mixture was refluxed on a water bath for 40 min., and a yellow solid separated from the hot solution. The mixture, after cooling in an ice bath for 3 hr., was filtered. The crude product, 6.2 g., m.p. 220–223°, was recrystallized from dilute ethanol to give 5.6 g. (82%) of white needles, m.p. 226–226.5°.

Anal. Calcd. for $C_{18}H_{13}N_5Cl$: C, 64.4; H, 4.21; N, 20.9. Found: C, 64.0; H, 4.33; N, 20.7.

1-(p-Chlorophenyl)-6-methyl-4-(p-phenylethylamino)pyrazolo[3,4-d]pyrimidine (XV, R_1 = *p*-Cl-C_6H_4, R_2 = CH_3, R_4 = H, R_5 = CH_2—CH_2—C_6H_5). Nine g. of 4-chloro-1-(*p*-chlorophenyl)-6-methylpyrazolo[3,4-*d*]pyrimidine was added to 160 ml. of absolute ethanol containing 10 g. of β-phenylethylamine. The mixture was boiled gently on a steam bath to near dryness. To the residue was added 20 ml. of methanol. The solid produce was filtered and recrystallized from ethanol to give 11 g. (94%) of white needles, m.p. 175–176°.

Anal. Calcd. for $C_{20}H_{18}N_5Cl$: C, 66.0; H, 4.98; N, 19.3. Found: C, 65.7; H, 5.12; N, 19.7.

General Method (*C*) is illustrated by the following examples. *4-Furfurylamino-1,6-dimethylpyrazolo[3,4-d]pyrimidine* (XV, R_1, R_2 = CH_3, R_4 = H, R_5 = CH_2—C_4H_3O). A mixture of 5.5 g. of 4-chloro-1,6-dimethylpyrazolo[3,4-*d*]pyrimidine, 5.5 g. of furfurylamine, and 200 ml. of absolute ethanol was heated on a steam bath for 8 hr. The mixture was then evaporated, and the syrupy residue was stirred with 30 ml. of 10% potassium hydroxide solution so as to neutralize the hydrochloride salt. The alkaline solution was decanted, and the syrup was boiled with 100 ml. of benzene for 2 hr. The hot benzene solution was filtered and evaporated to dryness. The light yellow solid remaining was recrystallized twice from ethanol to give 4 g. (54.6%) of white needles, m.p. 140–141.5°.

Anal. Calcd. for $C_{12}H_{13}N_4O$: N, 28.8. Found: N, 28.6.

4-Benzylamino-6-ethyl-1-phenylpyrazolo[3,4-d]pyrimidine (XV, R_1 = C_6H_5, R_2 = C_2H_5, R_4 = H, R_5 = CH_2—C_6H_5). To a solution of 13 g. of 4-chloro-6-ethyl-1-phenylpyrazolo-[3,4-*d*]pyrimidine in 150 ml. of absolute ethanol was added slowly, with stirring, a solution of 13 g. of benzylamine in 50 ml. of absolute ethanol. The mixture was refluxed for 12 hr. Excess ethanol was evaporated, and the syrupy product was treated with benzene and several drops of methanol. The compound solidified slowly after refrigeration. The product was recrystallized from a mixture of ethanol and benzene to give 8 g. (48.5%) of white crystals, m.p. 129–129.5°.

Anal. Calcd. for $C_{20}H_{19}N_5$: N, 21.3. Found: N, 21.4.

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A New Method for Preparation of Dialkylaminostyryl Derivatives of Pyridine and Quinoline and Their *N*-Oxides[1]

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Ten new nitrogen heterocyclic dialkylaminostyryl derivatives have been prepared by condensing the appropriate *p*-dialkylaminobenzaldehyde with the active methyl group of picoline, quinaldine, or 2-methylquinoxaline. In five cases the heterocyclic starting material was an *N*-oxide. These condensations, conducted in toluene solution, were catalyzed by piperidinium acetate; neither acidic nor basic catalysts alone were effective. In two of the five *N*-oxide condensations a side reaction occurred resulting in a deoxy product. The ultraviolet spectra of the ten styryl derivatives are recorded, and the infrared spectra of the *N*-oxide derivatives briefly discussed.

Preparation of styrylquinolines from 2- or 4-methylquinolines and aromatic aldehydes, using a number of Lewis acids to effect condensation, has previously been reported.[3,4] These reactions required relatively long periods of heating at 140–160°, and the yields in most cases were only fair (40–80%).

As would be predicted, quaternization of the heterocyclic compound facilitated condensation. Using piperidine as a catalyst, styryl derivatives of the alkiodides of pyridine and quinoline were prepared[5,6] in yields exceeding 90% by refluxing the reactants for short times in methanol or isopropyl alcohol.

Neither acid catalysts nor piperidine in alcohol would promote condensation of the *N*-oxides of quinaldine or 2- or 4-picoline with the dialkylaminobenzaldehyde. Only starting materials plus tars were obtained after heating the 2-methyl heterocyclic *N*-oxide for long periods of time with *p*-dimethylaminobenzaldehyde, using zinc chloride, acetic anhydride, or concentrated hydrochloric acid as the condensation catalyst. We were unable to repeat the work of Takahashi and Satake,[7] who reported the isolation of 2-(*p*-dimethylaminostyryl)quinoline *N*-oxide after heating the reactants in concentrated aqueous hydrochloric acid for 16 hours. Nor could condensation be effected by piperidine in alcohol, after periods much longer than required by the quaternary alkiodide compounds.

However, by using piperidinium acetate as catalyst, we have now prepared 2-(*p*-dimethylaminostyryl)- and 2-(*p*-diethylaminostyryl)quinoline *N*-oxides in fair yields (40–60%) by refluxing the reactants together in toluene under a Stark-Dean trap. It was found necessary to remove the water formed, since only starting materials were recovered when the reactants were refluxed together in ethanol with piperidinium acetate.

When this piperidinium acetate method was applied to certain picoline *N*-oxide derivatives, unexpected products were obtained, and *N*-oxide styryl derivatives were isolated with difficulty. 2-(*p*-Dimethylaminostyryl)pyridine *N*-oxide was isolated in only 13% yield after the heterocyclic compound and the aldehyde were refluxed under a Stark-Dean trap for two days; if the refluxing was continued two days longer the only product isolated (hereafter called "compound *A*") corresponded in analysis to $C_{23}H_{27}N_3$. Compound *A* was also the only product isolated when 2-picoline replaced the *N*-oxide derivative, or when the picoline compound was completely eliminated. Thus compound *A* was obtained in 21% yield when a mixture of piperidine and acetic acid was refluxed for two days in toluene with excess *p*-dimethylaminobenzaldehyde. At first it seemed that a reaction between piperidine and acetic acid took place since compound *A* also corresponded in analysis to $C_{16}H_{20}N_2$. This possibility was eliminated because compound *A* was also obtained (in 30% yield, with no other isolated products) when propionic acid was used instead of acetic acid. Hence the acid acted as a co-catalyst and was not incorporated in the product. That formation of compound *A* cannot be attributed to an impurity in the piperidine[8] originally used was demonstrated by isolation of compound *A* in 21% yield, when specially purified piperidine[8] was used. Similarly, when *p*-diethylaminobenzaldehyde, 2-picoline *N*-oxide, piperidine, and acetic acid were refluxed in toluene for 2.5 days, the only product isolated, hereafter called

(1) The research was supported by Grant No. C2798(C) from the U. S. Public Health Service, National Cancer Institute.

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(8) The piperidine originally used was Eastman "Practical" grade. It was subsequently separated by careful fractionation through a 2 × 64 cm. column packed with single-turn glass helices into only two fractions: piperidine-water azeotrope (b.p. 92°, 6% by volume), and pure piperidine (b.p. 106°, 92% by volume). There remained only 2% of higher boiling material.

"compound *B*," (20% yield based on piperidine) corresponded in analysis to $C_{27}H_{35}N_3$. The formula $C_{18}H_{24}N_2$ was also considered, but appeared improbable since (as noted above) the carboxylic acid catalyst used was not incorporated into the product.

When the reaction was stopped after 30 hours and the resulting thick dark sirup was chromatographed over alumina, over 95% of the starting materials was recovered, in addition to a very small proportion of a product not the same as compound *B*, as apparent from comparison of infrared spectra. This material may have been the desired *N*-oxide styryl derivative, but was never obtained in sufficient quantity for characterization.

The unidentified reaction products *A* and *B* were colorless solids, m.p. 135° and 102°, respectively, with very similar ultraviolet spectra. Compound *A* had λ_{max} 215 mμ, ϵ_{max} 28,000; λ_{max} 258.5 mμ, ϵ_{max} 37,000, and a shoulder at 314 mμ. Compound *B* had λ_{max} 215.5 mμ, ϵ_{max} 28,000; λ_{max} 266.5 mμ, ϵ_{max} 49,000 and a shoulder at 318 mμ. Compound *A* on oxidation by chromic acid or permanganate (acid, alkaline, or neutral) gave only polymeric material.

These unidentified reaction products were *not* isolated when 4-picoline *N*-oxide was refluxed with either of the aldehydes mentioned, plus piperidinium acetate in toluene, for periods of time varying between 2.5 and 7 days. In both cases, *mixtures* of two products were obtained: the 4-(*p*-dialkylaminostyryl)pyridine *N*-oxide and the corresponding styryl derivative without the *N*-oxide group. The nature of the reduction leading to formation of the deoxy products is not yet clear, for attempts to isolate *p*-dialkylaminobenzoic acids from the reaction mixtures were not successful. In the case of *p*-dimethylaminobenzaldehyde, the reactants were refluxed together for 4.5 days to give a 12% yield of *N*-oxide styryl derivative and an 18% yield of deoxygenated styryl derivative. Decreases in the yields of both products were noted when the mixtures were refluxed for shorter periods of time. The two styryl derivatives were separable by fractional recrystallization from ethanol. The deoxygenated styryl derivative crystallized first under the conditions used. In the case of *p*-diethylaminobenzaldehyde, a seven-day reflux period afforded a 55% yield of *N*-oxide styryl derivative, along with only 3% of deoxygenated styryl derivative. This mixture was separated by chromatography on alumina. If the reflux period was shortened to 3.5 days, 83% of the starting 4-picoline *N*-oxide was recovered; no styryl derivatives appeared to be present.

Certain other styryl derivatives, not *N*-oxides, were also made by the piperidinium acetate method. These included 2-(*p*-dimethylaminostyryl)quinoxaline, a previously unreported compound, which could not be prepared by any other method described in the literature.[3-6] Also made were 2-(*p*-dimethylaminostyryl)-8-hydroxyquinoline and 2-(*p*-diethylaminostyryl)pyridine. The analog, 2-(*p*-dimethylaminostyryl)pyridine, could not be made by this procedure owing to the preferential formation of compound *A* described above; nor was it possible to make this styryl compound using either zinc chloride or acetic anhydride as the condensing agent.

Table I summarizes our data on the preparation of the styryl derivatives. The piperidinium acetate method described here gives yields which at best are only fair. The optimum reflux times are seen to vary greatly with the identity of the reactants. Nevertheless, the method deserves consideration in condensation reactions where neither acidic catalysts nor basic catalysts alone promote the reaction.

Table I also lists the ultraviolet spectra of the new styryl derivatives. The previously reported bathochromic effect of quaternization of heterocyclic nitrogen[5] was also observed here, though to a much smaller degree, in the *N*-oxide styryl derivatives. This was to be expected on the basis of greater stabilization of ionic, excited state forms by the ability of the *N*-oxide oxygen atom to bear the negative charge.

Both 2-(*p*-diethylaminostyryl) pyridine tertiary base and 2-(*p*-dimethylaminostyryl)pyridine *N*-oxide absorbed at shorter wave lengths than did the corresponding 4-styryl derivatives. This may be attributable to some small steric hindrance to coplanarity in the excited state of the 2-styryl derivatives.

Bands between 7.3 mμ and 8.2 mμ in the infrared spectra of quinoline *N*-oxide and certain 4-substituted quinoline *N*-oxides have previously been attributed to N—O stretching.[9] 4-(*p*-Dimethylaminostyryl)pyridine *N*-oxide and the corresponding diethyl analog had strong bands at 7.97 μ and 8.00 μ, respectively, which the corresponding deoxygenated products did not show. 2-(*p*-Dimethylaminostyryl)pyridine *N*-oxide had a strong band at 8.14 μ, and its diethyl analog had a strong band at 8.10 μ. 2-(*p*-Diethylaminostyryl)pyridine did not absorb in this region. 2-(*p*-Dimethylaminostyryl)-quinoline *N*-oxide had a band at 7.76 μ not shown by its deoxy analog.

EXPERIMENTAL

General procedure for preparation of p-dialkylaminostyryl derivatives of heterocyclic free bases or N-oxides. To a solution of 0.020 mole of the active methyl heterocyclic base (or its *N*-oxide) and 0.027 mole of dialkylaminobenzaldehyde in 35 ml. of dry toluene was added one ml. of piperidine and about 0.8 ml. of glacial acetic acid. The mixture was refluxed under a Stark-Dean trap until no more water was collected, or for the optimum number of hours. The toluene

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TABLE I

STYRYL DERIVATIVES PREPARED BY PIPERIDINIUM ACETATE-CATALYZED CONDENSATIONS

Compound[a]	Reflux Time, Hr.	Yield, %	M.P.[b]		Anal.[c] C	H	N	Ultraviolet Spectral Data[d] λ_{max}	ϵ_{max}
2-(*p*-Dimethylaminostyryl)-pyridine *N*-oxide	47	13	200–201.5°	Calcd.	74.97	6.71	11.66	253	20,000
				Found	75.50	6.98	11.82	282	11,000
								400	33,000
quinoline *N*-oxide	17	60	213–214°	Calcd.	78.59	6.25	9.65	230.5[e]	35,000
				Found	78.64	6.13	9.7	264.5	38,000
								307	16,000
								336	16,000
								428	31,000
quinoxaline	116	32	166.1–166.9°	Calcd.	78.51	6.22	15.26	224.5	22,000
				Found	78.16	6.34	15.1	261.5	17,000
								306	23,000
								429	44,000
8-hydroxyquinoline[f]	6	62	164.3–165.1°	Calcd.	78.59	6.25	9.65	217	19,000
				Found	78.18	6.17	9.61	266	25,000
								294	16,000
								328	23,000
								390	>40,000
pyridine	69	12	142.8–143.6°	Calcd.	80.91	7.99	11.10	255	9,800
				Found	81.12	8.17	10.76	377	40,000
quinoline *N*-oxide	22	42	178.7–179.6°	Calcd.	79.21	6.96	8.80	234	21,000
				Found	79.05	6.74	8.54	269	27,000
								313	19,000
								340	20,000
								449	42,000
4-(*p*-Dimethylaminostyryl)-pyridine[g]	108	18	239.4–240°	Calcd.	80.32	7.03	12.65	253	16,000
				Found	80.14	7.20	12.56	377	28,000
				Found	80.17	7.23	12.65		
pyridine *N*-oxide	108	12	238–239°	Calcd.	74.97	6.71	11.66	221	14,000
				Found	75.00	6.80	11.58	279.5	12,000
								295	11,000
								403	33,000
4-(*p*-Diethylaminostyryl)-pyridine	168	3	188–188.6°	Calcd.	80.91	7.99	11.10	255.5	13,000
				Found	80.76	7.87	10.89	387	36,000
pyridine *N*-oxide	168	55	195–196.5°				10.44	223	15,000
							10.06	281	21,000
								299	15,000
								416	38,000

[a] All compounds have infrared bands in the 10.2–10.6 μ region and are unchanged on exposure to ultraviolet or visible light. On this basis they may tentatively be assigned the *trans* configuration. [b] Melting points were taken using an electrically heated block with Anschuetz thermometers. [c] Analyses were performed by Drs. Weiler and Strauss, Oxford, England, and Microchemical Specialties Co., Berkeley, Calif. [d] Spectra were determined on a Beckman Model DK-2 ratio-recording spectrophotometer. [e] 2-(*p*-Dimethylaminostyryl)quinoline[3] had λ_{max} 219.5, 253.5, 293, 392; ϵ_{max} 28,000, 23,000, 13,000, 34,000. [f] Prepared by the method of Tipson[3] using acetic anhydride. [g] Also prepared in 12% yield by the method of Tipson[3] using acetic anhydride.

was then removed by distillation, about the last 10 ml. under reduced pressure. The dark sirupy residues were cooled to induce crystallization and the crude solids washed with ether to remove the adherent dark oils. The crude solids were purified by recrystallization from 95% ethanol or benzene. In only two cases was more than a single product obtained.

Separation of N-oxide products from deoxy products. The mixture of 4-(*p*-dimethylaminostyryl)pyridine *N*-oxide and 4-(*p*-dimethylaminostyryl)pyridine obtained from reaction of 4-picoline *N*-oxide and *p*-dimethylaminobenzaldehyde was separated by fractional recrystallization from 95% ethanol.

The mixture of 4-(*p*-diethylaminostyryl)pyridine was separated on a 2 × 25 cm. column packed with *Alco F* 20 mesh alumina. One gram of the mixture (dissolved in benzene) was put on the column. Unreacted aldehyde was eluted by benzene, then the deoxygenated styryl derivative by benzene-ether mixtures and finally ether, and last the *N*-oxide styryl derivative by ether-methanol mixtures. The two products were then each purified by recrystallization from acetone.

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Identification of Scopoletin in Cigarette Tobacco and Smoke

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Scopoletin (6-methoxy-7-hydroxycoumarin) has been identified after isolation in chromatographically pure form from the flowers, stems, and leaves of oven-dried, healthy, greenhouse-grown One-Sucker tobacco. Examination of the tobacco in 29 brands of cigarettes commonly used in the U. S. has shown that every one contained scopoletin. The mainstream smoke from every cigarette sample tested also was found to contain scopoletin.

A fluorescent substance accumulating in the roots of decapitated tobacco plants infected with virus of spotted tomato wilt, was isolated and identified by Best[1] as scopoletin (6-methoxy,7-hydroxycoumarin). Best[2] determined the histological distribution of blue-fluorescing material in the healthy tobacco plant and reported that this fluorescence was markedly brighter in the endodermis of the root-stock, stem, and leaf veins than in the other tissues of these organs, while the small roots were fluorescent throughout. Goodwin and Kavanagh[3] point out, however, that the blue fluorescence which Best reported in his later paper may not all be due to the presence of scopoletin.

Yang[4] found that oven-dried tobacco from healthy, One-Sucker tobacco plants, *Nicotiana tabacum*, grown either in the greenhouse or in an open field at the Argonne National Laboratory contained, in addition to scopoletin, more than eight different blue-fluorescing compounds. From this complex mixture of blue-fluorescing substances, Yang isolated in pure form and identified scopoletin from the dried leaves, stems, and flowers of this tobacco.

The scopoletin was identified, after purification, by comparison with an authentic sample prepared by synthesis, according to the procedure of Aghoramurthy and Seshadri,[5] and also with another authentic sample obtained by isolation of the scopoletin from oat roots, using cellulose powder and mass paper chromatographic techniques. Goodwin and Kavanagh[3] had previously identified scopoletin in oat roots.

Pollock, Goodwin, and Greene[6] in a study of external applications of scopoletin to *Avena* and *Phleum* roots have shown that scopoletin inhibits root growth.

It also appeared important to learn by experimentation whether scopoletin is present in tobacco after curing and incorporation into cigarettes, and, if so, whether any scopoletin, m.p. 204°, survives the smoking process to persist in the mainstream smoke from the cigarette. We have examined tobacco in 29 brands of cigarettes commonly used in the U. S. and have found that every one tested contained scopoletin. These included regular size, filter, "denicotinized," menthol, and king size cigarettes. We have discovered also that the mainstream smoke from every cigarette sample tested contained scopoletin. This was the case under every different smoking condition used. The amounts of scopoletin present in the smoke, however, are apparently different, and quantitative studies are now in progress.

EXPERIMENTAL

Scopoletin from cigarette tobacco. Each qualitative analysis on the tobacco was performed separately on approximately 2 g. of cigarette tobacco obtained from cigarettes in a freshly opened pack or box, purchased locally on the open, retail market. The paper from each cigarette was removed before extraction of the tobacco. In the case of filter cigarettes, the tobacco was separated from both the filter and paper. Each 2-g. extraction was carried out in a separate Soxhlet extractor, using 200 ml. of 85% isopropyl alcohol for approximately 3 hr. on a steam bath. A second extraction was made on each sample, using 200 ml. of 85% isopropyl alcohol for 3 hr. The two extracts of the 2-g. tobacco sample were combined, reduced to approximately 150 ml. *in vacuo*, and the volume was then adjusted with 85% isopropyl alcohol to the mark in a 200 ml. volumetric flask. Aliquots of this solution were then taken for one-dimensional and two-dimensional paper chromatographic analyses in comparison with authentic scopoletin, and also for additional paper chromatographic purification for further study on the scopoletin identification.

For the one-dimensional paper chromatograms, 0.5-ml. samples of each cigarette tobacco extract concentrate were spotted on Schleicher and Schuell No. 589 red ribbon chromatographic paper next to a similar amount of an authentic sample of scopoletin. Solvent systems used were 15% acetic acid–water; 60% acetic acid–water; *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.); *n*-butyl alcohol–benzene-pyridine-water (5:1:3:3 v./v.); and nitromethane-benzene-water (2:3:5 v./v.). Typical R_f values for scopoletin in these solvent systems, respectively, using the S & S No. 589 red ribbon paper for chromatography and a temperature of 28° ± 3° were: 0.47; 0.74; 0.82; 0.82; and 0.69. After chromatography, the papers were examined under ultraviolet "black light" (3660 Å). A bright blue fluorescence is exhibited by scopoletin.

Although a one-dimensional chromatogram of the various cigarette tobacco extract concentrates prepared as just

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described showed many spots when viewed by ultraviolet light, the scopoletin spot thereon could be readily detected and tentative identification made by cochromatography with authentic scopoletin.

Two-dimensional paper chromatograms of the cigarette tobacco extract concentrates also were made, using in one group the *n*-butyl alcohol–acetic acid–water system in the first direction, then 15% acetic acid–water in the second direction.

In the second group of experiments on two-dimensional chromatograms, we used the nitromethane-benzene-water system in the first direction, then 15% acetic acid water in the second direction. After chromatography, the scopoletin spot could be easily located in every case, even though other spots could be seen on the chromatogram under the ultraviolet light.

By the methods described, the tobacco from 29 brands of cigarettes was examined, and every one was found to contain scopoletin. Cigarettes studied were Camel, Cavalier, Chesterfield (both regular and king size), Dunhill, Encore, Herbert Tareyton (both king and filter), Hit Parade, Kent, Kool (both regular and filter), L & M, Lucky Strike, Marlboro, Oasis, Old Gold (both regular and filter), Pall Mall, Parliament, Philip Morris (both regular and king), Raleigh (king), Regent (filter), Salem, Sano (regular), Spud, Viceroy, and Winston.

Scopoletin in cigarette smoke. Each cigarette was smoked on a standard smoking apparatus (Phipps & Bird, Inc., Richmond, Va.) based on a design of the American Tobacco Co.

Our experiments on representative brands and types of cigarettes indicated that scopoletin was readily detectable in the smoke, when 10 individual cigarettes were smoked under all varying smoking machine conditions tested. (With practice scopoletin can be recognized on a chromatogram of the smoke from one individual cigarette.) Tried were a faster smoking rate (3.3-sec. duration; 54 ± 4 ml. volume; 60-sec. interval); a medium speed (2-sec. duration; 35 ± 4 ml. vol.; 60-sec. interval); and a slower speed (1-sec. duration; 16 ± 1 ml. vol.; 60-sec. interval). Also varied were the cigarette butt lengths; regular size cigarettes (2, 3.5, and 5 cm.) and king size and filters (3, 4, and 6.5 cm.) All combinations of the above showed the presence of scopoletin in the smoke. Judged by gross observation of the size and intensity of the scopoletin on the paper chromatograms of the smoke obtained under different smoking conditions, quantitative differences occurred. The quantitative studies are in progress in our laboratory. In that *qualitatively*, scopoletin was present under all the conditions tried for the selected representative cigarettes, the following conditions were arbitrarily selected for smoking all 29 brands: butt length of 2 cm. for regular size cigarettes and 3 cm. for king size and filters; volume, 54 ± 4 ml.; puff duration, 3.3 ± 0.2 sec. at 60-sec. intervals; and one pack or box of 20 cigarettes per sample for study.

The smoke from each 20 cigarettes of one brand was trapped, in part, in a 300-ml. Kjeldahl flask, immersed in a salt-ice mixture (av. temp., −18°). Some scopoletin was found to escape into a second and into a third trap, even when a "Dry-Ice"–acetone bath was used for cooling the first two traps. For the identification of scopoletin as reported in this paper, however, a sufficient amount was obtained in the first Kjeldahl flask, even with a salt-ice mixture, for clear-cut *qualitative* analysis.

The trapped smoke, in each case, was dissolved in dry acetone. To analyze for the presence of scopoletin, the acetone solution of the smoke was then subjected to both one-dimensional and two-dimensional chromatography according to the procedure already described for the extract from cigarette tobacco. In the case of every one of the 29 brands of cigarettes smoked, a bright blue fluorescent spot coinciding in color and R_f values with authentic scopoletin was observed. Additional spots, often 10 or more, usually could be found under the ultraviolet light. Two additional blue fluorescent compounds present on the chromatograms from the smoke are now being investigated.

In order to obtain a pure sample of scopoletin from the smoke for further identification studies, the acetone solution of the smoke was subjected to extended paper chromatographic separation. For this purpose, the acetone solution of the smoke was streaked across a sheet of S & S No. 589 red ribbon chromatography paper, size 19 × 58 cm., and first developed in a 15% acetic acid–water solution for 9 hr. by descending chromatography. The developed chromatograms were air-dried. The zone which contained scopoletin and fluoresced a bright blue color under ultraviolet light was cut from the chromatogram and sewed onto a new sheet of the S & S No. 589 paper, 19 × 58 cm. The *n*-butyl alcohol–acetic acid–water system was used for 30 hr. during this second chromatographic step. The resulting scopoletin zone (R_f of approximately 0.82) was cut from this chromatogram and sewed onto still another sheet of the S & S No. 589 paper. The third chromatographic run involved the use of 15% acetic acid–water as the developing solvent. The resulting scopoletin zone (R_f of about 0.47) was cut, sewed onto yet another new sheet of the chromatographic paper, and the *n*-butyl alcohol–acetic acid–water system was used for this fourth chromatographic step. After this extended chromatographic separation, the scopoletin zone appeared to be completely free of other compounds. It was, therefore, eluted off the paper with methyl alcohol in an elution chamber. This eluted scopoletin cochromatographed with authentic scopoletin in the solvent systems already described.

Acknowledgment. This work and some previous research on which these findings are based were supported in part by the Tobacco Industry Research Committee and by the Atomic Energy Commission.

We also sincerely thank Dr. Norbert Scully, Mr. Will Chorney, and Mr. Ronald Watanabe of the Argonne National Laboratory for their cooperation with the oat seeds and One-Sucker tobacco.

NORMAN, OKLA.

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Preparation of 3-Arylthianaphthenes[1,2]

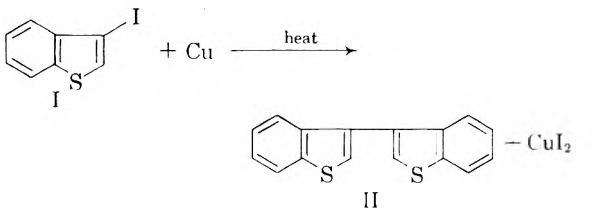
ROBERT D. SCHUETZ AND LEON CIPORIN[3]

Received June 30, 1957

The synthesis of 3,3′-dithianaphthyl was accomplished by utilizing the Ullmann reaction with 3-iodothianaphthene. The preparation of 3-phenylthianaphthene and 3-(1′-naphthyl)thianaphthene was successfully realized by the reaction of 3-thianaphthylmagnesium bromide with the appropriate cyclic ketone followed by hydrolysis, dehydration, and dehydrogenation. Five previously unreported *o*-aroyl-*p*-chlorophenyl methyl sulfides were prepared by the Friedel-Crafts acylation of *p*-chlorophenyl methyl sulfide and the yields in the acylation reactions were correlated with the amount of steric hindrance involved in the formation of the sulfides. The ring closure, with chloroacetic acid, of three of the five *o*-aroyl-*p*-chlorophenyl methyl sulfides was carried out to yield the corresponding 5-chloro-3-aryl-2-thianaphthenecarboxylic acids which were previously unknown.

A study of restricted rotation in thianaphthene compounds containing an aryl group in the 3-position have recently been initiated in these laboratories. This paper is concerned with an investigation of the methods for the preparation of such compounds.

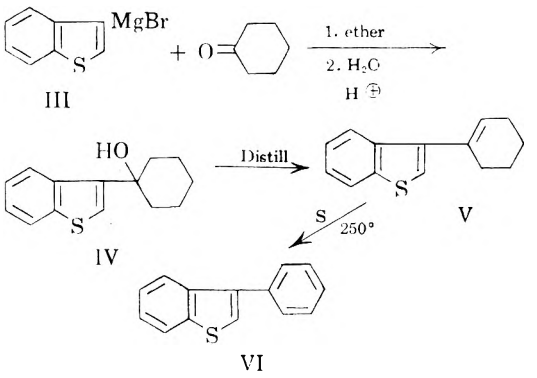
The symmetrical compound, 3,3′-dithianaphthyl (II) was prepared by the Ullmann procedure from 3-iodothianaphthene (I) and copper bronze. A small amount of a crystalline byproduct was isolated during the formation of 3,3′-dithianaphthyl (II) from 3-iodothianaphthene (I).



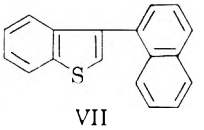
Although no structural studies were made on this substance, elementary analysis indicated that it is probably a polymer of thianaphthene. Steinkopf[4] has observed similar polymer formation when halothiophenes were submitted to the Ullmann reaction.

Attempts to effect the coupling of 3-thianaphthylmagnesium bromide (III) with metallic salts,[5] such as cupric chloride or nickel bromide, failed to yield 3,3′-dithianaphthyl (II).

The synthesis of 3-phenylthianaphthene (VI) was successfully accomplished by the reaction of 3-thianaphthylmagnesium bromide (III) with cyclohexanone followed by hydrolysis, dehydration, and dehydrogenation.



The same method, substituting α-tetralone for cyclohexanone, was used in the synthesis of 3-(1′-naphthyl)thianaphthene (VII).



The 3-arylthianaphthenes, obtained for the first time, during the course of this work are summarized in Table I.

The three, previously unreported, 5-chloro-3-aryl-2-thianaphthenecarboxylic acids (XI) listed in Table II, were prepared from the appropriate *o*-aroyl-*p*-chlorophenyl methyl sulfide (IX) by treatment with chloroacetic acid. The sulfonium salt (X) has been proposed as an intermediate for this reaction by Krollpfeiffer and co-workers.[6,7]

The five, heretofor undescribed, *o*-aroyl-*p*-chlorophenyl methyl sulfides (IX) were prepared by the acylation of *p*-chlorophenyl methyl sulfide (VIII) with the appropriate aroyl chloride. An examination of the yields of the *o*-aroyl-*p*-chlorophenyl methyl sulfides (IX) reported in Table III confirms the observations of other investigators[6,7] concerning

(1) Abstracted from part of a dissertation submitted by Leon Ciporin to the Graduate School of Michigan State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Presented, in part, at the 130th meeting of the American Chemical Society, Atlantic City, N. J., Sept. 16–21, 1956.

(3) Present address: E. I. du Pont de Nemours & Co., Inc., Greenville, N. C.

(4) W. Steinkopf, R. Leitsmann, and K. H. Hofmann, *Ann.*, **546**, 180 (1951).

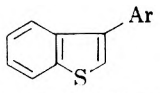
(5) J. Krizewsky and E. E. Turner, *J. Chem. Soc.*, **115**, 559 (1919).

(6) F. Krollpfeiffer, H. Hartmann, and F. Schmidt, *Ann.*, **563**, 15 (1949).

(7) F. Krollpfeiffer, K. L. Schnider, and W. Wissner, *Ann.*, **566**, 139 (1950).

TABLE I

3-ARYLTHIANAPHTHENES[a]

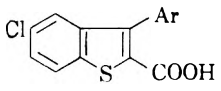


Ar	Formula	M.P., °C.	Yield, %	Analyses			
				Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found
Phenyl	$C_{14}H_{10}S$	172–173	17	79.9	79.3	4.8	4.9
1′-Naphthyl	$C_{18}H_{12}S$	90–92	38	83.0	82.8	4.7	4.9
3′-Thianaphthyl	$C_{16}H_{10}S_2$	>370	56	72.1	71.9	3.8	3.5

[a] All melting points are uncorrected.

TABLE II

5-CHLORO-3-ARYL-2-THIANAPHTHENECARBOXYLIC ACIDS

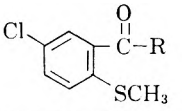


Ar	Formula	M.P., °C.[a]	Yield, %	Analyses					
				Neut. Equiv.		Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
Phenyl	$C_{15}H_9ClO_2S$	263–265	16	288	287	62.4	62.2	3.1	3.4
α-Thienyl	$C_{13}H_8ClO_2S_2$	267–268	53	294	292	52.9	52.7	2.4	2.9
o-Carboxyphenyl[b]	$C_{15}H_{12}ClO_4S$	282–284	61	179	177	60.3	60.2	3.1	3.3

[a] These compounds decompose at their melting points. [b] Analysis is for a compound with one-third mole of benzene of crystallization.

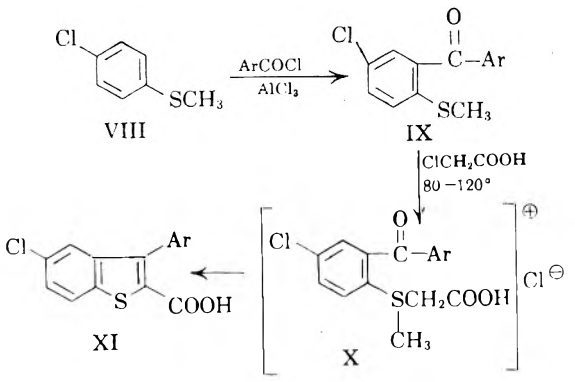
TABLE III

o-AROYL-p-CHLOROPHENYL METHYL SULFIDES



R	Formula	M.P., °C.	Yield, %	Analyses			
				Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found
Phenyl	$C_{14}H_{12}ClOS$	101–103	38	64.0	64.1	4.2	4.1
α-Naphthyl	$C_{18}H_{14}ClOS$	115–117	4	69.1	68.5	4.2	3.9
β-Naphthyl	$C_{18}H_{14}ClOS$	120–121	25	69.1	68.6	4.2	4.0
α-Thienyl[a]	$C_{11}H_9ClOS_2$	77–78	35	51.9	51.9	2.8	2.7
o-Carboxyphenyl	$C_{15}H_{13}ClO_3S$	183–185	13	58.7	58.7	3.6	3.8

[a] Isolated as the thiophenol rather than as the methyl sulfide.



the steric hindrance offered by a thiomethyl group to acylation in the ortho position with respect to such a group in the benzene series. The acyl groups, listed in order of decreasing yield of the sulfides are,

benzoyl ≥ α-thenoyl > β-naphthyl > o-carboxybenzoyl > α-naphthoyl

This is the order to be expected on the basis of increasing steric hindrance, due to the size of the attacking carbonium or potential carbonium ion in the acylation reaction.

In the Friedel-Crafts acylation of *p*-chlorophenyl methyl sulfide with 2-thenoyl chloride, cleavage of the thioether occurred and *o*-(2-thenoyl)-*p*-chlorothiophenol was obtained as the product of the acylation reaction. There is ample precedent for the cleavage of a thioether with anhydrous aluminum

chloride. Alkyl aryl ethers are dealkylated by warming with aluminum chloride to yield the free phenol.[8] However, we are unable to explain the absence of thioether cleavage in the acylations carried out with acylhalides other than 2-thenoyl chloride.

All attempts to effect the ring closure of *o*-(1-naphthoyl)-*p*-chlorophenyl methyl sulfide or its 2-naphthoyl isomer failed. Instead, ketonic cleavage occurred yielding α-naphthoic and β-naphthoic acids from the 1-naphthoyl and 2-naphthoyl isomers, respectively, as the only isolable products. The sulfide, *o*-benzoyl-*p*-chlorophenyl methyl sulfide, which did yield a ring closure product, also underwent some ketonic cleavage to yield benzoic acid.

EXPERIMENTAL

3,3'-Dithianaphthyl. 3-Iodothianaphthene was prepared from thianaphthene and iodine according to the method of Gaertner.[9] Commercial copper bronze was activated by the method of Kleiderer and Adams[10] immediately prior to its use.

3-Iodothianaphthene, 0.50 g. (0.019 mole), was placed in a Pyrex test tube and heated to 150° in an oil bath. As the temperature was gradually raised to 270° over a period of 20 min., 2.5 g. (0.039 mole) of copper bronze was added in small portions to the reaction mixture while stirring it with a thermometer. After the addition of the copper bronze was complete, the temperature was maintained in the range 270–280° for 2 hr. The cooled reaction mass was extracted with two 25-ml. portions of cold chloroform and on evaporation of the solvent 0.2 g. of a light tan polymeric substance was obtained which melted at 258–259°, after two recrystallizations from benzene.

Anal. Calcd. for $(C_8H_6S)_x$: C, 71.6; H, 4.5. Found: C, 71.0; H, 4.4.

The residue from the chloroform extraction was placed in a Bailey-Walker type extractor and extracted with 30 ml. of hot chloroform for 2 hr. Filtration of the cooled solution yielded 0.4 g. (0.0015 mole; 17%) of crude 3,3'-dithianaphthyl melting above 370°. The analytical sample was recrystallized from benzene.

3-Arylthianaphthenes. 3-(1'-Cyclohexenyl)thianaphthene and 3-(3',4'-dihydro-1'-naphthyl)thianaphthene were prepared by the method of Szmuskovicz and Modest.[11] Aromatization of the cycloalkenylthianaphthenes was accomplished by the following procedure. An intimate mixture of the compound and the required quantity of powdered sulfur was heated in an oil bath maintained in the temperature range 240–250° until hydrogen sulfide evolution ceased. The cooled reaction mass was dissolved in hot benzene and the unreacted sulfur was removed by filtration. The cooled filtrate was washed with 10% aqueous sodium sulfite and dried in contact with anhydrous sodium sulfate. After evaporating the benzene, the solid residue was sublimed in the temperature range of 230–240° under a pressure of 10 mm. The crystalline product was recrystallized from 95% ethanol.

p-Chlorophenyl methyl sulfide. A 100 g. (0.69 mole) quantity of *p*-chlorothiophenol was dissolved in 350 ml. of 10% aqueous sodium hydroxide. While stirring the alkaline solution, 177 g. (1.40 mole) of dimethyl sulfate were added dropwise over a 0.5-hr. period. During the course of the reaction, an additional 150 ml of 10% aqueous sodium hydroxide were added to the reaction mixture to maintain its alkalinity. The oily product was extracted with ether, dried, and the ether was evaporated. Distillation of the residue yielded 94.7 g. (0.60 mole; 87%) of a product; b.p. 107° (14 mm.), n_D^{30} 1.5997. The reported[12] b.p. is 170° (760 mm.) for *p*-chlorophenyl methyl sulfide.

o-Aroyl-p-chlorophenyl methyl sulfides. Equimolar quantities of the aroyl chloride and anhydrous aluminum chloride were brought to a temperature approximately 5° above the melting point of the aroyl chloride by immersion of the mixture in an oil bath. Then, one-sixth to one-third of the required quantity of *p*-chlorophenyl methyl sulfide was added dropwise, during 0.5 hr., to the reaction mixture which was held at the original temperature for 10 hr. after the addition of the aroyl chloride was complete. The cooled reaction complex was poured into a slurry of dilute hydrochloric acid and crushed ice and extracted with ether. The ether extract was washed with 10% aqueous sodium hydroxide and dried in contact with anhydrous magnesium sulfate. After removing the drying agent by filtration and evaporating the ether, the residue was distilled.

o-(2-Carboxyphenyl)-p-chlorophenyl methyl sulfide. A mixture of 10 g. (0.062 mole) of *p*-chlorophenyl methyl sulfide, 4.6 g. (0.031 mole) of phthalic anhydride, and 10.5 g. (0.065 mole) of anhydrous aluminum chloride was maintained at a temperature of 80° for 4 hr. The reaction mixture was cooled, decomposed with water, and steam distilled to remove the unreacted *p*-chlorophenyl methyl sulfide. The residual solid was collected by filtration and extracted with hot chloroform in which the unreacted phthalic anhydride is insoluble. After evaporating the chloroform, the solid residue was washed with petroleum ether and recrystallized from aqueous acetic acid.

Anal. Calcd. for $C_{15}H_{13}ClO_3S$: *Neut. equiv.* 307. Found: 302.

5-Chloro-3-aryl-2-thianaphthenecarboxylic acids. The *o*-aroyl-*p*-chlorophenyl methyl sulfide was added to a four to six mole excess of chloroacetic acid. The resulting solution was kept in the temperature range of 80–130°, for periods of time varying from 10 to 72 hr. The addition of water to the cooled reaction solution precipitated the thianaphthenecarboxylic acid which was collected and recrystallized from benzene.

EAST LANSING, MICH.

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(11) J. Szmuskovicz and E. J. Modest, *J. Am. Chem. Soc.*, **72**, 571 (1950).

(12) K. Brand and W. Groehe, *J. prakt Chem.*, **108**, 1 (1924).

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Ultraviolet Absorption Spectra of 3-Arylthianaphthenes[1,2]

ROBERT D. SCHUETZ AND LEON CIPORIN[3]

Received June 30, 1957

The ultraviolet absorption curves of six 3-arylthianaphthenes have been determined and interpreted according to a theory of steric hindrance to free rotation about the pivot bond of the two aromatic rings.

In a previous communication from this laboratory,[4] the preparation of a series of 3-arylthianaphthenes was recorded. The purpose of the work described here was to determine the extent to which rotation was restricted about the pivot bond in 3-arylthianaphthenes by an examination of their ultraviolet absorption spectra.

The initial investigation of the effect of restricted rotation in biphenyl compounds on the ultraviolet absorption spectra of such substances was made by Pickett, Walter, and France.[5] Since then, other investigators[6] have determined the absorption spectra of biaromatic compounds exhibiting restricted rotation and similar studies have been extended to biaromatic compounds containing herterocyclic nuclei.[7] These studies have shown that a biaromatic compound exhibits a more intense ultraviolet absorption at longer wave lengths than the uncoupled nucleus because coplanarity gives full extension to the conjugated system. Biaromatic derivatives substituted in the ortho positions with respect to the pivot bond should have difficulty in assuming a coplanar structure and, therefore, show absorption approximately equivalent to the single ring structure.

The 3-arylthianaphthenes for which ultraviolet absorption curves were determined in this investigation are listed in Table I together with the wave length and molar absorptivity of their absorption maxima. The curves of the compounds studied have been graphed in Fig. 1. The logarithms of the molar absorptivity has been used to permit inclusion of all the absorption curves on the same scale.

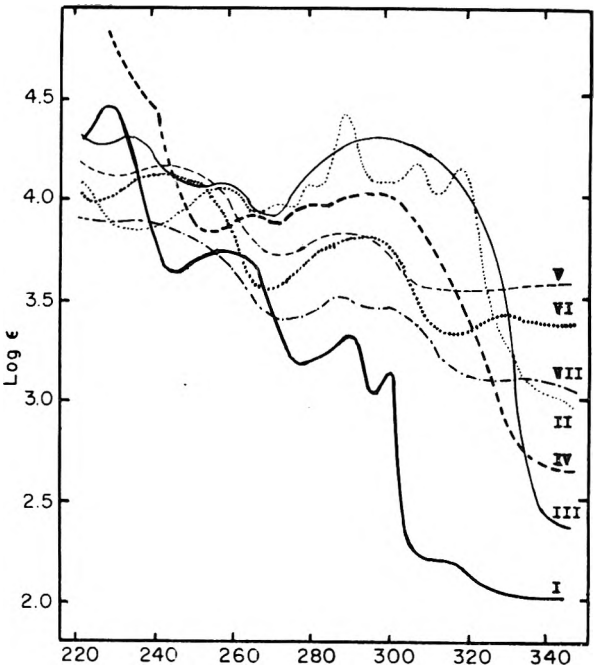


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA of 3-Arylthianaphthenes. I, Thianaphthene; II, 3,3′-Dithianaphthyl; III, 3-Phenylthianaphthene; IV, 3-(1′-Naphthyl)thianaphthene; V, 5-Chloro-3-(2′-thienyl)-2-thianaphthenecarboxylic Acid; VI, 5-Chloro-3-phenyl-2-thianaphthenecarboxylic Acid; VII, 5-Chloro-3-(*o*-carboxyphenyl)-2-thianaphthenecarboxylic Acid.

Before proceeding with a discussion of these absorption spectra, it is necessary to assess the effect of the chlorine and carboxyl groups in the 5-chloro-3-aryl-2-thianaphthenecarboxylic acids (V, VI, VII) on the ultraviolet absorption curves of these compounds. This information is needed in order to make an interpretive comparison with the absorption spectra of the 3-arylthianaphthenes containing neither a carboxyl or halogen substituent. With regard to the chlorine substituent, it has been shown[6b] that chlorine exhibits negligible resonance interaction with the aromatic ring in chlorobenzene. Padhye and Desai[8] have compared the absorption spectrum of 5-chlorothianaphthene

(1) Abstracted in part from a dissertation submitted by Leon Ciporin to the Graduate School of Michigan State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Presented, in part, at the 130th meeting of the American Chemical Society, Atlantic City, N. J., Sept. 16–21, 1956.

(3) Present address: E. I. Du Pont de Nemours & Co., Inc., Greenville, N. C.

(4) R. D. Schuetz and L. Ciporin, *J. Org. Chem.*, **23**, 206 (1958).

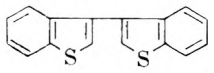
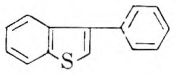
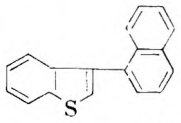
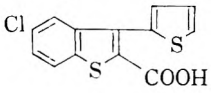
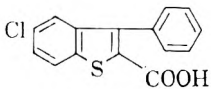
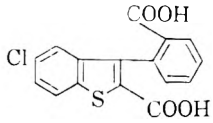
(5) L. W. Pickett, G. F. Walter, and H. France, *J. Am. Chem. Soc.*, **58**, 2296 (1936).

(6) (a) M. Calvin, *J. Org. Chem.*, **4**, 256 (1939). (b) M. T. O'Shaughnessy and W. H. Rodebush, *J. Am. Chem. Soc.*, **62**, 2906 (1940). (c) B. Williamson and W. H. Rodebush, *J. Am. Chem. Soc.*, **63**, 3018 (1941). (d) D. W. Sherwood and M. Calvin, *J. Am. Chem. Soc.*, **64**, 1350 (1942). (e) L. W. Pickett, M. Groth, S. Duckworth, and J. Cunliffe, *J. Am. Chem. Soc.*, **72**, 44 (1950).

(7) (a) A. Crawford and I. F. B. Smyth, *J. Chem. Soc.*, 4133 (1952). (b) G. N. Jean and F. F. Nord, *J. Org. Chem.*, **20**, 1370 (1955).

(8) M. R. Padhye and S. R. Desai, *Trans. Faraday Soc.*, **49**, 1386 (1953).

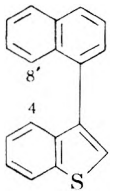
TABLE I

	Compound	λ_{max} Mμ	$\epsilon \times 10^{-3}$	Max, Mμ	$\epsilon \times 10^{-3}$
I		227	28.4		
II		256	12.5	288	27.8
III		233	21.2	297	22.4
IV		225	76.5	295	10.9
V		239	14.6	288	7.1
VI		236	13.1	294	7.0
VII		236	7.7	286	3.3

with that of thianaphthene (I). Their results show that the absorption spectra of these compounds are quite similar and that, therefore, chlorine must interact with the thianaphthene (I) nucleus only to a minor degree.

On the other hand, the carboxyl function, due to the double bond character in its structure, can interact with the aromatic ring and extend the resonance of the aromatic structure. The ortho or para carboxyl function shifts the characteristic absorption maximum of biphenyl to longer wave lengths and enhances its absorption intensity.[6b] The same effect should be operative in a 2-thianaphthenecarboxylic acid. The absorption spectra of several 2-thianaphthyl ketones have been shown to have enhanced absorption intensities.[9] It is reasonable to assume that the carbonyl group of the ketone and carboxylic acid will affect absorption spectra in a similar manner.

The absorption curve (curve I) for thianaphthene (I) has the fine structure which is characteristic of an unsubstituted aromatic compound. When the conjugated system is extended by substitution of a phenyl group in the 3-position of the thianaphthene nucleus, there is an increase in absorption intensity and a smoothing out of the fine structure (curve III). The same phenomenon is observed in the spectrum of biphenyl as compared to benzene.[5] However, 3-(1′-naphthyl)-thianaphthene (IV) (curve IV) has a considerably lower absorption intensity than 3-phenylthianaphthene (III) (curve III). If steric hindrance were not operative, and thus were not preventing coplanarity of the naphthyl and thianaphthyl parts of the molecule, the naphthyl group would be expected to extend the total resonating system by a larger factor than a phenyl group and, as a result, enhance the absorption intensity to a greater degree. The reduction in absorption intensity can be attributed to the hindrance to free rotation about the pivot bond imposed by the hydrogen atoms in the 4- and 8′-positions, thus inhibiting coplanarity of the naphthyl and thianaphthyl groups with a resulting loss in resonance.



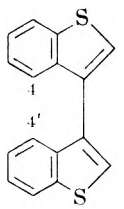
Inspection of the absorption spectra of 5-chloro-3-(2′-thienyl)-2-thianaphthenecarboxylic acid (V) (curve V) and 5-chloro-3-phenyl-2-thianaphthenecarboxylic acid (VI) (curve VI) reveal a very close similarity. The isoelectronic relationship between benzene and thiophene would predict such a similarity in the spectra of these compounds. Both absorption curves show a re-

(9) P. Ramart-Lucas and M. Martynoff, *Compt. rend.*, 2247 (1953).

duced intensity compared to those compounds which are not substituted in the 2-position with respect to the pivot bond. This undoubtedly is a result of the steric inhibition to free rotation supplied by the carboxyl group which prevents coplanarity of the thienyl or phenyl group with the thianaphthyl group thereby reducing the resonance of the systems. As previously noted, the carboxyl group tends to enhance absorption due to its interaction with the aromatic ring. That the opposite occurs is a further indication that the carboxyl group is sterically inhibiting full resonance in these structures.

When a second carboxyl group is placed adjacent to the pivot bond, as in 5-chloro-3-(*o*-carboxyphenyl)-2-thianaphthenecarboxylic acid VII (curve VII), the absorption maximum almost disappears. Thus, resonance through the pivot bond appears to be virtually nonexistent due to the lack of coplanarity of the thianaphthyl and phenyl groups; such coplanarity being prevented by steric hindrance of the two carboxyl groups.

The absorption spectrum of 3,3′-dithianaphthyl (II) (curve II) is somewhat more difficult to fully explain in that while there is an increase in the absorption intensity as compared to that of thianaphthene (I) (curve I) the fine structure of the thianaphthene (I) (curve I) has been retained. However, the many-fold increase of intensity in the 290 mμ region of the dimer compound II (curve II) strongly suggests that a very considerable resonance exists between the two halves of 3,3′-dithianaphthyl (II) (curve II). Except for the fine structure of 3,3-dithianaphthyl (II) (curve II) it is closely comparable to that of the naphthalene (IV) (curve IV) and the phenyl (III) (curve III) analogs. In fact, the main envelope of the absorption curve for 3,3-dithianaphthyl (II) (curve II) corresponds more closely to the phenyl analog (III) (curve III) than to the naphthalene analog (IV) (curve IV) which indicates that the two thianaphthyl rings interfere less with each other in being coplanar than do the two naphthalene rings in 1,1′-binaphthyl.



In conclusion, it can be stated, with a reasonable degree of certainty, that 5-chloro-3-(*o*-carboxyphenyl)-2-thianaphthenecarboxylic acid (VII) and very probably 3,3-dithianaphthyl (II) exist in a noncoplanar structure and should therefore be capable of optical resolution. However, it is not to be inferred that evidence for noncoplanarity is sufficient by itself for predicting the possibility of resolution in compounds where optical activity is due to restricted rotation.

EXPERIMENTAL

The ultraviolet absorption spectra were determined employing a Beckman Model DU Spectrophotometer equipped with equally matched, one-centimeter, fused quartz cells. The solvent used in every case was Eastman Kodak C.P. grade cyclohexane which was further purified by passage through a column of silica gel. The matching of the quartz cells was frequently checked by comparing readings taken with cyclohexane alone in the cells.

The solutions were prepared by the volume dilution method and were all of the order of $10^{-5}M$. The procedure used in preparing the solutions was as follows. A sample of 2×10^{-5} mole was accurately weighed out on an analytical balance and dissolved in 100 ml. of cyclohexane measured in a calibrated volumetric flask. A 5-ml. aliquot of this solution was then diluted to 100 ml. in a calibrated volumetric flask. An aliquot of the latter solution was transferred to a quartz cell.

Absorbance readings were taken over a range of wave lengths from 220 to 340 mμ. The values for the absorbance readings were converted to molar absorptivity by means of the equation,

$$\epsilon = \frac{A}{bc}$$

where ϵ is the molar absorptivity, A is the absorbance, c is the concentration of the light absorbing species in moles per liter, and b is the length in centimeters of the light path in the absorbing solution. Values for the logarithms of the molar absorptivity were then tabulated.

EAST LANSING, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE VIRGINIA POLYTECHNIC INSTITUTE]

Unsaturated Cyclic Sulfones. III. Some Halogen-Containing Derivatives

ROBERT C. KRUG, GEORGE R. TICHELAAR,[1] AND FRANCOIS E. DIDOT[2]

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Hydrogen bromide, hydrogen chloride, nitrosyl chloride, and iodine monochloride add to the carbon-carbon double bond in 3-methyl-2,5-dihydrothiophene 1,1-dioxide; however, only hydrogen bromide was found to add to the isomeric 4-methyl-2,3-dihydrothiophene 1,1-dioxide. Hydrogen bromide and hydrogen chloride fail to add to 2,5-dihydrothiophene 1,1-dioxide and to its isomer, 2,3-dihydrothiophene 1,1-dioxide. The preparation of 3-iodo- and 3-chloro-2,3-dihydrothiophene 1,1-dioxides is described.

In the continuation of the study of the chemistry of the five-membered unsaturated cyclic sulfones[3] emphasis in the present work is placed upon the preparation of halogen derivatives by reactions at the carbon-carbon double bond together with the two halogen derivatives obtained from displacement reactions on 3-bromo-2,3-dihydrothiophene 1,1-dioxide.

An intensive study of the addition of hydrogen bromide and of hydrogen chloride to 2,5- and to 2,3-dihydrothiophene 1,1-dioxides (I and II, respectively) and to 3-methyl-2,5- and 4-methyl-2,3-dihydrothiophene 1,1-dioxides (III and IV, respectively) was undertaken in this laboratory. It is of considerable interest that no evidence of the addition of hydrogen bromide or hydrogen chloride was found in the case of I or II. The starting sulfones were recovered; however, the weight recoveries of I at temperatures above 75° were low because of the reverse Diels-Alder reaction which evolved sulfur dioxide and 1,3-butadiene during the attempted reactions. Parenthetically, it should be recalled that mercaptans, alcohols, and water have been found to add to I in the presence of bases, presumably *via* a nucleophilic attack.

Hydrogen bromide adds to III in 55% yield in the presence of zinc bromide and hydrobromic acid with an excess of hydrogen bromide at 60°, whereas no adduct is found under similar conditions in the absence of hydrogen bromide. The structure of the adduct corresponds to 3-bromo-3-methyltetrahydrothiophene 1,1-dioxide (V). Under similar conditions hydrogen bromide adds to IV in 35% yield to give an adduct which is identical with that obtained from III. The action of hydrogen bromide on III, as described above, at 50° gave 25% of V.

Hydrogen chloride adds to III in 35% yield in hydrochloric acid-zinc chloride solution in the presence of hydrogen chloride, whereas the yield of adduct is 4% when the reaction is performed in benzene with hydrogen chloride in the presence of tin (IV) chloride. The structure of the adduct is assigned as 3-chloro-3-methyltetrahydrothiophene, 1,1-dioxide (VI) on the basis of the excellent agreement of its infrared spectrum with that of V. Addition of hydrogen bromide to III failed to occur in benzene in the presence of tin(IV) bromide. At temperatures above 50°, namely 60° and 75°, no hydrogen chloride adduct was isolated from III; however, IV was isolated in yields up to 60%. Thus, it is suspected that addition occurred followed by the elimination of hydrogen chloride at these higher temperatures. No acid catalyzed isomerization of III to IV has been reported in the literature.

The above-mentioned addition reactions are seen to follow the expected Markownikoff rule. Of particular interest is the tremendous effect of the methyl group whose inductive and/or hyperconjugative effects apparently overcome the strong electron withdrawing effect of the sulfone group thus making addition possible in III as compared with the result obtained with I.

With carbon tetrachloride as the solvent, iodine monochloride was found to add to III at room temperature in 91% yield. The adduct is assigned the structure corresponding to 3-chloro-4-iodo-3-methyltetrahydrothiophene 1,1-dioxide (VII). It seems quite reasonable to suggest that addition occurred in the manner claimed in view of the work of Ingle[4] with styrene and of Ingold and Geoffrey[5] with ethylenesulfonic acid. From the observations of the addition of the hydrogen halides to III and of nitrosyl chloride to III as will be discussed later, it should be expected that ionic addition will occur here with the positive iodine attacking at the 4-position, the more electron dense of the two carbon atoms in the double bond.

In the presence of sodium borohydride VII is quantitatively converted to III while the use of lithium aluminum hydride gives only 22% of III with some degradation of the molecule. Hydriodic acid converts VII to III in 100% yield, and the action of sodium thiosulfate solution on VII gives

(1) A portion of this work was taken from the Ph.D. dissertation of George R. Tichelaar, March 1957. Present address: Standard Oil Company (Ind.), Whiting, Ind.

(2) A portion of this work was taken from the M.S. thesis of Francois E. Didot, June 1957. Present address: Sun Oil Company, Marcus Hook, Pa.

(3) For the previous paper in this series see R. C. Krug and T. F. Yen, *J. Org. Chem.*, 21, 1441 (1956).

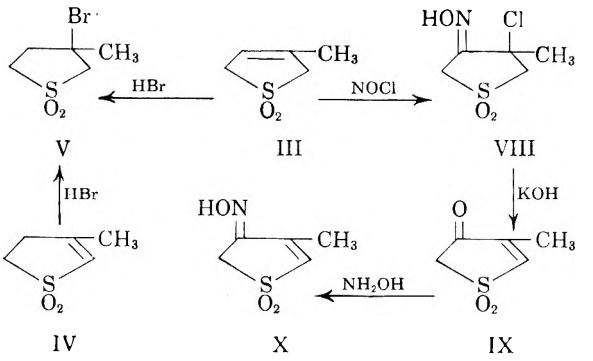
(4) H. Ingle, *J. Soc. Chem. Ind.* (*London*), 21, 591 (1902).

(5) C. K. Ingold and H. Goeffrey, *J. Chem. Soc.*, 2742 (1931).

III as the only isolable product. Aqueous potassium hydroxide on VII gives tars and a small amount of III. The action of weaker bases such as pyridine and *N,N*-dimethylaniline causes the formation of tars and resinous substances from VII.

Under conditions similar to those employed for the addition of iodine monochloride to III, no addition product could be isolated or detected in the attempts to form the corresponding adduct from IV. In each case IV was recovered.

In the studies involving the reaction of nitrosyl chloride and the sulfones, copper (I) chloride was employed as suggested by Beckham.[6] In the present study moisture was found to be a necessary component of the reaction system. In the presence of chloroform as the solvent, nitrosyl chloride reacted with III to give a quantitative yield of an adduct whose structure is assigned as 3-chloro-4-oxo-3-methyltetrahydrothiophene 1,1-dioxide oxime (VIII).



In the presence of alcoholic potassium hydroxide VIII was converted in 34% yield to IX which melted at 164–165° as compared with the value of 163° reported by Backer and Strating[7] for IX prepared by a different method. In order to establish the structure assigned to IX, this compound was treated with hydroxylamine according to the procedure of Backer and Strating[7] and X was obtained in 36% yield. The reported melting point for this oxime was *circa* 146–148° as compared with the presently found value of *circa* 143–145°. Thus, the structure of the nitrosyl chloride adduct is definitely established. Nitrosyl chloride failed to add to IV under similar or slightly modified conditions employed with III.

The free radical-catalyzed addition of hydrogen bromide to I and III was extensively studied, with the greater number of experiments having been performed with III. Although solvents such as benzene, carbon tetrachloride, ethylbenzene, anhydrous sulfur dioxide, and chloroform were used at temperatures from −20° to 95° and peroxides such as benzoyl peroxide and acetyl peroxide were employed, no evidence for the peroxide effect in the addition of hydrogen bromide was obtained. A small amount of V was isolated in one case as was a small amount of 3,4-dibromo-3-methyltetrahydrothiophene 1,1-dioxide. The latter compound was obtained when large amounts of peroxide were employed. These substances were identified by means of mixed melting point determinations with authentic samples. The use of ultraviolet light with or without peroxide likewise failed to effect addition of hydrogen bromide to III in a Vycor tube. Except as noted, when addition failed the starting sulfone was recovered unchanged. This failure of the peroxide effect is rather strange since other free radical-catalyzed additions with I and III have been observed.[8,9] The dehydrobromination of 3,4-dibromotetrahydrothiophene 1,1-dioxide in the presence of pyridine to give 3-bromo-2,3-dihydrothiophene 1,1-dioxide (XI) was first reported by Backer and Blaas[10] and more recently studied by Bailey and Cummins[11] in an attempt to prepare thiophene 1,1-dioxide. In addition to XI polymer was formed in the dehydrobromination. In the present study it was found that no polymer was formed if the reaction solution was first acidified before the removal of the solvent. This procedure increased the yield of XI 20–25% above the previous y reported values.

In the presence of sodium iodide in anhydrous acetone, XI was converted to 3-iodo-2,3-dihydrothiophene 1,1-dioxide (XII). The bromide XI was so reactive that at room temperature the immediate precipitation of sodium bromide was realized in 94% yield. Pure XII was obtained in 53% yield. Upon standing in air XII gradually decomposes. The structure of XI has been established[10] and the comparison of the infrared spectra of XI and XII clearly demonstrates the structural similarities of these two compounds.

The 3-chloro-2,3-dihydrothiophene 1,1-dioxide XIII was obtained by the action of mercury(II) chloride in absolute ethanol on XII in 42% yield. Again, a comparison of the infrared spectra of XI, XII, and XIII definitely establishes the common structural relationship of these compounds. Compound XII gives an immediate reaction with silver nitrate solution while the bromide XI requires several seconds and the chloride XIII does not give a positive test after standing for 15 hours at room temperature.

(6) L. T. Beckham (To Solvay Process Co.), U. S. Pat. 2,417,675, Mar. 18, 1947.

(7) H. J. Backer and J. Strating, *Rec. trav. chim.*, **54**, 170 (1935).

(8) M. S. Kharasch, M. Freeman, and W. H. Urry, *J. Org. Chem.*, **13**, 570 (1948).

(9) R. C. Krug and T. F. Yen, *J. Org. Chem.*, **21**, 1082 (1956).

(10) H. J. Backer and Th. A. H. Blaas, *Rec. trav. chim.*, **61**, 785 (1942).

(11) W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, **76**, 1932 (1954).

EXPERIMENTAL[12]

2,5-Dihydrothiophene 1,1-dioxide (I). Anhydrous sulfur dioxide and 1,3-butadiene (The Matheson Co., Inc.) were used. The procedure was that of Grummitt, Ardis, and Fick[13]; however, contact time was reduced to 4 hr. at 100–105°. Crude I was purified by recrystallization from water to give pure I; m.p. 64–65° (lit.,[13] 64.5–65.0°), 85–93% yields.

2,3-Dihydrothiophene 1,1-dioxide (II). A modification of the procedure described by Bailey and Cummins[11] was employed. A solution of 50.0 g. (0.423 mole) of I in 1 liter of 0.5*N* potassium hydroxide was irradiated at room temperature with ultraviolet light for 20 hr. The resulting solution was submitted to continuous extraction with chloroform for 2 days, and upon the evaporation of the chloroform from the extract 35.4 g. of light brown-colored oil was obtained. This oil was heated to 180° at 15–20 mm. to remove unchanged I. The residual oil was purified by crystallization from benzene–petroleum ether or by distillation at reduced pressure. The latter procedure is recommended since 3-hydroxytetrahydrothiophene 1,1-dioxide, an impurity, is difficult to remove by the former procedure. The yield of pure II b.p. 114–116°, m.p. 49–50° (lit.,[14] 48.5–49.5°) was 24.6 g. (49%). It was found that acidification of the basic, irradiated solution prior to the extraction with chloroform gave only 24% of pure II.

4-Methyl-2,3-dihydrothiophene 1,1-dioxide (IV). To 1000 ml. of 0.5*N* potassium hydroxide was added 60 g. (0.45 mole) of 3-methyl-2,5-dihydrothiophene 1,1-dioxide (III),[3] and the solution was stirred for 20 hr. at 30°. This solution was then extracted with 6 portions of chloroform, and the removal of solvent from the combined extracts gave a solid. This solid was recrystallized from ethanol to yield 42 g. (79%) of long, needle-shaped crystals, m.p. 77–78° (lit.,[10] 79°). Upon reducing the volume of the ethanolic mother liquor, 5.0 g. (8%) of III was obtained.

Addition of hydrogen bromide to 3-methyl-2,5-dihydrothiophene 1,1-dioxide (III). Zinc bromide was prepared by dissolving 32.7 g. (0.50 mole) of zinc in 171 ml. of 48% hydrobromic acid. After all of the zinc had reacted 10 g. (0.076 mole) of III was added. For 2 hr. hydrogen bromide was passed into the stirred solution which was heated to 50°. Heating was continued for 2 more hours and the solution was allowed to stand overnight at room temperature. The contents of the flask was then poured into 100 ml. of water, and this solution was extracted with 4 portions of chloroform. The extracts were combined and the chloroform was removed under reduced pressure to give an oil which was then dissolved in ethanol. Upon cooling the ethanolic solutions, 9.0 g. (55%) of small, white, needle-shaped crystals of 3-bromo-3-methyltetrahydrothiophene 1,1-dioxide (V), m.p. 95–96°, were obtained.

Anal. Calcd. for $C_5H_9BrO_2S$: C, 28.18; H, 4.25; Br, 37.50; S, 15.05. Found: C, 28.38; H, 4.18; Br, 37.72; S, 15.21.

The infrared spectrum of V showed the following principal frequencies: 2930, 1445, 1415, 1400, 1378, 1310, 1275, 1185, 1150, 1118, 1095, 1035, 913, 860, 790, and 765 cm.$^{-1}$

Addition of hydrogen chloride to III in the presence of zinc chloride. To 42 ml. of concentrated hydrochloric acid was added 68 g. (0.50 mole) of zinc chloride, followed by the addition of 10 g. (0.076 mole) of III, and solution of the components was effected at 50°. Hydrogen chloride was slowly passed into the solution for 2 hr. at 50° with stirring. After 22 hr. at 50° the liquid was poured into 150 ml. of water. The aqueous solution was extracted 3 times with 50-ml. portions of chloroform. The extracts were combined and the chloroform was removed under reduced pressure to give an oil. The oil was dissolved in ethanol, and upon cooling the solution crystals appeared which were recrystallized from ethanol to give 4.5 g. (35%) of small, white needle-shaped crystals of 3-chloro-3-methyltetrahydrothiophene 1,1-dioxide (VI); m.p. 95–96°.

Anal. Calcd. for $C_5H_9ClO_2S$: C, 35.61; H, 5.38; Cl, 21.02; S, 19.01. Found: C, 35.34; H, 5.25; Cl, 21.16; S, 19.17.

The infrared spectrum of VI showed the following principal frequencies: 2930, 1445, 1405, 1395, 1370, 1300, 1270, 1190, 1150, 1118, 1095, 1038, 910, 863, 791, and 767 cm.$^{-1}$

Addition of hydrogen chloride to III in the presence of tin(IV) chloride. To 100 ml. of anhydrous benzene were added 10 g. (0.076 mole) of III and 8.9 g. (0.029 mole) of freshly prepared tin(IV) chloride. Anhydrous hydrogen chloride was passed into the solution for 1 hr. at room temperature. After allowing the solution to stand for 72 hr., with the occasional passage of hydrogen chloride to keep the solution saturated, the benzene phase was separated and washed with water to remove the tin(IV) chloride. The aqueous phase was extracted once with benzene and this extract was combined with the original benzene layer, and the volume of benzene was reduced under vacuum. Crystals formed upon cooling the residual liquid. By fractional crystallization from ethanol, 9.5 g. (95%) of III and 0.5 g. (4%) of 3-chloro-3-methyltetrahydrothiophene 1,1-dioxide, VI (m.p. 95–96°) were obtained.

Addition of hydrogen bromide to 4-methyl-2,3-dihydrothiophene 1,1-dioxide (IV). Zinc bromide was freshly prepared by dissolving 16.4 g. (0.25 mole) of zinc in 85 ml. of 48% hydrobromic acid. After all of the zinc had reacted 5.0 g. (0.038 mole) of IV was dissolved in the solution. For 2 hr. hydrogen bromide was passed into the stirred solution which was heated to 50°. Heating was continued for 11 hr. After 7 hr. at room temperature the solution was poured into 100 ml. of water, and this aqueous solution was extracted 4 times with chloroform. The chloroform was removed from the combined extracts under reduced pressure, and the residual oil was dissolved in ethanol. Upon cooling the ethanolic solution, 4.5 g. (55%) of small, white, needle-shaped crystals of V, m.p. 95–96°, were obtained. A mixed melting point determination of this solid with that from the addition of hydrogen bromide to III showed no depression.

3-Chloro-4-iodo-3-methyltetrahydrothiophene 1,1-dioxide (VII). To a solution of 20 g. (0.15 mole) of III in 100 ml. of carbon tetrachloride was added dropwise approximately 8 ml. (slight excess) of iodine monochloride. To prevent the contents from overheating, the flask was immersed in cold water. After addition was complete, the solution was brought to reflux for 2 hr. Upon cooling the solution the heavy precipitate which formed was filtered, washed with petroleum ether to remove most of the purple color, and recrystallized from absolute ethanol. A total of 40 g. (91%) of VII, m.p. 107–108°, was obtained.

Anal. Calcd. for $C_5H_8ClIO_2S$: C, 20.39; H, 2.74; Cl, 12.04; I, 43.09; S, 10.88. Found: C, 20.08; H, 2.95; Cl, 11.86; I, 42.87; S, 10.80.

Alcoholic potassium hydroxide and VII. To a solution of 3.0 g. (0.010 mole) of VII in absolute ethanol was added dropwise a solution of 0.57 g. (0.010 mole) of potassium hydroxide in 50 ml. of absolute ethanol. After 2 hr. the yellow-colored mixture was filtered to remove inorganic salts (potassium chloride and iodide). The volume of the filtrate was reduced under vacuum and the residual oil was crystallized and purified to give 0.10 g. (8%) of III. In this and other experiments the identity of III was established by means of mixed melting point determination with an authentic sample. No other organic substance was isolated.

Sodium thiosulfate and VII. To a solution of 4.0 g. (0.014 mole) of VII in 200 ml. of 50% ethanol was added a solution of 4.3 g. (0.027 mole) of sodium thiosulfate in a small amount of water. After 2 min. the solution turned dark

(12) All melting and boiling points are uncorrected. Analyses performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(13) O. Grummitt, A. E. Ardis, and J. Fick, *J. Am. Chem. Soc.*, 72, 5167 (1950).

(14) E. de Roy van Zuydewijn, *Rec. trav. chim.*, 57, 445 (1938).

suddenly. The solution was found to be acidic and aqueous potassium hydroxide was added to *p*H 7. The resulting colorless solution was extracted with chloroform, and upon removal of the chloroform under reduced pressure a solid remained. The solid was recrystallized from ethanol to give 1.3 g. (70%) of III.

Sodium borohydride and VII. The procedure of Brown and Subba Rao[15] was followed with certain modifications. To 1.0 g. (0.0034 mole) of VII in 15 ml. of methanol was slowly added a solution of 0.15 g. (0.0040 mole) of sodium borohydride in 100 ml. of methanol. After 15 min. the solution turned dark brown in color. The solvent was removed under vacuum, the remaining oil was taken up in chloroform, and the chloroform solution was washed with 5% aqueous sodium thiosulfate. The chloroform phase was separated, and the chloroform was removed at reduced pressure. The residue was recrystallized from ethanol to give 100% of III.

Hydriodic acid and VII. Three grams (0.010 mole) of VII was dissolved in 75 ml. of colorless 50% hydriodic acid. After 3–4 hr. the solution was extracted with several portions of chloroform. The extracts were combined and washed with 5% aqueous sodium thiosulfate. The chloroform was removed under vacuum leaving a solid which upon recrystallization from ethanol gave a quantitative yield of III.

3-Chloro-4-oxo-3-methyltetrahydrothiophene 1,1-dioxide oxime (VIII). In a flask equipped with a stirrer was placed 20 g. (0.15 mole) of III dissolved in 100 ml. of chloroform. As the solution was stirred at room temperature approximately 0.5 g. of copper (I) chloride was added followed by a few drops of water, and nitrosyl chloride was passed into the solution for 2 hr. A precipitate appeared 6 hr. later. The experiment was continued for 1 week, with daily passage of gas to keep the solution saturated with nitrosyl chloride, and a few drops of water were added at least once a day. After 1 week the mixture was filtered. The solid was recrystallized from absolute ethanol and subsequently from chloroform. A quantitative yield of VIII, m.p. *circa* 148–152°d, was obtained.

Anal. Calcd. for $C_5H_8ClNO_2S$: Cl, 17.94; N, 7.09; S, 16.23. Found: Cl, 17.31; N, 6.87; S, 15.70.

Alcoholic potassium hydroxide on VIII. To a solution of 8.0 g. (0.040 mole) of VIII in 180 ml. of absolute ethanol at 30° a solution of 2.3 g. (0.040 mole) of potassium hydroxide in 200 ml. of absolute ethanol was added dropwise with vigorous stirring. Six hours after the addition was complete a precipitate appeared. This solid, which was identified as potassium chloride, was filtered and the filtrate was reduced in volume under vacuum. The residual alcoholic solution was cooled, and crystals formed which upon recrystallization from 95% ethanol gave 2.0 g. (34%) of 3-oxo-4-methyl-2,3-dihydrothiophene 1,1-dioxide (IX) as white needles; m.p. 164–165° (lit.,[7] 163°).

The oxime from IX was prepared according to the procedure described by Backer and Strating.[7] The crude oxime was recrystallized from water, then from chloroform to give 0.2 g. (36%) of X melting *circa* 143–145° (lit.,[7] 146–148°).

Attempted free radical addition of hydrogen bromide to 3-methyl-2,5-dihydrothiophene 1,1-dioxide (III). In a typical experiment, 10 g. (0.076 mole) of III (previously dried over sulfuric acid *in vacuo*) was dissolved in the selected solvent (anhydrous benzene in this case), and 1.2 g. (0.0050 mole) of benzoyl peroxide was added. Dry hydrogen bromide was passed into the solution for 2 hr. at the desired temperature (room temperature here). The solution was allowed to stand for 46 hr. or a shorter period. The solvent (benzene) was removed under reduced pressure and the residual oil was crystallized from ethanol. The recovered III weighed 9.0 g. (90%). The compound was identified by a mixed melting point determination with an authentic sample.

Under similar conditions the attempted peroxide catalyzed addition of hydrogen bromide to I was unsuccessful.

3-Bromo-2,3-dihydrothiophene 1,1-dioxide (XI). The procedure described here, based on the work of Backer and Blaas[10] and of Bailey and Cummins,[11] was found to give XI an improved yield. In a 1-liter round-bottomed flask was placed a solution of 60 g. (0.22 mole) of 3,4-dibromotetrahydrothiophene 1,1-dioxide[16] in 250 ml. of dry acetone. To this solution was added 33 g. (0.42 mole) of dry pyridine and the system was protected with a drying tube. Within 20 min., at room temperature, crystals of pyridinium bromide began to appear. After 14 hr. the mixture was filtered to give 35.4 g. of pyridinium bromide. The filtrate was acidified with concentrated hydrochloric acid and the resulting aqueous phase removed. The acetone-rich phase was subjected to reduced pressure to remove the acetone. The residue (oil and small amount of water) was extracted with 50 ml. of benzene from which 24.7 g. of a white solid was obtained. Extraction of the combined aqueous phases with three 25-ml. portions of benzene gave an additional 12.3 g. of white solid. The solids were combined and purified by recrystallization from ethanol to give 33.1 g. (76%) of white crystals; m.p. 63–64° (lit.,[10] 64–65°).

The infrared spectrum of XI showed the following principal frequencies: 3050, 3000, 2930, 1600, 1400, 1285, 1218, 1130, 1103, 1030, 950, 920, 895, 883, 762, and 715 cm.$^{-1}$

3-Iodo-2,3-dihydrothiophene 1,1-dioxide (XII). To a solution of 9.9 g. (0.05 mole) of XI in 50 ml. of dry acetone was added a solution of 11.3 g. (0.075 mole) of sodium iodide in dry acetone. A precipitate formed immediately and the solution turned a light yellow color. After 15 min. the solution began to darken and the solid was filtered. The solid, 4.8 g. (94%), was sodium bromide and was found to be free of iodide. The filtrate was shaken with a saturated solution of sodium thiosulfate and was dried over magnesium sulfate. The acetone was removed at room temperature under reduced pressure and the residue (oil plus a small amount of water) was extracted with chloroform. Removal of the chloroform gave 9.9 g. of crude oil which solidified upon standing. Recrystallization from methanol–petroleum ether gave 6.5 g. (53%) pure XII; m.p. 72.0–72.5°.

Anal. Calcd. for $C_4H_5IO_2S$: C, 19.68; H, 2.07. Found: C, 19.85; H, 1.93.

The infrared spectrum of XII showed the following principal frequencies: 3110, 3000, 2955, 1580, 1395, 1290, 1218, 1135, 1100, 1020, 955, 915, 895, 865, 747, and 710 cm.$^{-1}$

3-Chloro-2,3-dihydrothiophene 1,1-dioxide (XIII). To 3.9 g. (0.016 mole) of XII in 50 ml. of hot, absolute ethanol was added a solution of 4.4 g. (0.016 mole) of mercury (II) chloride in 50 ml. of hot, absolute ethanol. The resulting solution was allowed to stand overnight at room temperature after which time the solution was heated to reflux for 8 hr. Distillation of about two thirds of the ethanol caused the precipitation of 2 g. of mercury (II) iodide which was removed by filtration. The removal of the remainder of the ethanol gave a mixture of mercury (II) iodide, mercury (II) chloride, and XIII. Fractional crystallization of this mixture from ethanol gave 1.0 g. (42%) pure XIII; m.p. 82.5–83.0°.

Anal. Calcd. for $C_4H_5ClO_2S$: C, 31.48; H, 3.30. Found: C, 31.30; H, 3.33.

The infrared spectrum of XIII showed the following principal frequencies: 3070, 3000, 2950, 1610, 1400, 1285, 1230, 1130, 1105, 1030 955, 920, 900, 885, 765, 715 cm.$^{-1}$

BLACKSBURG, VA.

(15) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956).

(16) This compound was prepared by the bromination of I in chloroform, a modification of the method of Bailey and Cummins.[11]

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Cyclic Sulfides. I. Ultraviolet Spectra of Ethylene Sulfides

ROBERT EARL DAVIS[1]

Received June 26, 1957

The ultraviolet spectra of several ethylene sulfides have been measured in solution and in the gas phase. The spectra have been compared with those of the corresponding oxygen compounds. Several possible explanations of the origin of the absorption are discussed.

The first ethylene sulfide[2] was synthesized by Delépine[3] and was characterized by marked reactivity, ease of polymerization, and ease of ring opening. The chemical properties of this ring system have been reviewed by Schönberg.[4] In many respects the chemistry resembles that of the ethylene oxides.

The physical properties of ethylene sulfide have been subject to the investigation of several groups of workers. The infrared spectrum, vapor pressure, and some thermodynamic properties were measured as part of the American Institute Research Project 48A on sulfur compounds.[5] The dipole moment[6] has been reported and the structures of the sulfide and ethylene oxide have been compared on the basis of their microwave spectra.[7] The heats of combustion[8] of ethylenimine, ethylene oxide, ethylene sulfide, and cyclopropane have been compared in consideration of the strain energies of various three-membered rings. The present study has centered upon the ultraviolet spectra of several ethylene sulfides having various degrees of alkyl substitution.

EXPERIMENTAL

Materials. Ethylene oxide[9] was dried over calcium sulfate and fractionally distilled through a twenty-plate helix column. Propylene oxide[9] was purified in the same manner. Cyclohexene oxide was synthesized from 2-chlorocyclohexanol[10] and purified by careful fractionation.

Ethylene oxide was prepared from ethylene oxide and aqueous potassium thiocyanate.[11] The material was dried over sodium sulfate and then over calcium sulfate and fractionally distilled through a seventeen plate column, b.p. 54.6–54.8° at 756 mm., into glass bulbs. The bulbs were then opened in a vacuum line and purified by repeated bulb-to-bulb distillations.

Propylene sulfide, b.p. 74.5–74.6°, was prepared from propylene oxide and aqueous thiourea[12] and purified in the same manner as ethylene sulfide. Cyclohexene sulfide was prepared from cyclohexene oxide and potassium thiocyanate[13] and purified by fractionation *in vacuo*, b.p. 73–74.5° at 22 mm. The sulfide was then purified by repeated bulb-to-bulb distillations on a vacuum line.

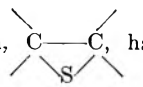
Solvent. ASTM iso-octane (Phillips) was repeatedly shaken with dilute sulfuric acid and then washed with water and dried over potassium carbonate. The iso-octane was fractionally distilled from phosphorus pentoxide. Further samples were purified by passage through active silica gel.

Spectra. The spectra were measured on a Beckman DU spectrophotometer and on a Model 11 Cary. The gas spectra were recorded using 5.00-cm. silica cells while the solution spectra were measured using 1.00-cm. cells. The spectrophotometers were calibrated against the benzene vapor spectrum. The extinction coefficients were expressed as $\epsilon_m = A/cl$ for the solution spectra and $e = A/pl$ for the gas spectra where A is the optical density, c the concentration in moles/liter, l is the optical path in centimeters, and p is the pressure in millimeters of mercury.

DISCUSSION

The ultraviolet absorption of the ethylene sulfide ring system is characterized by one band in the region of 2600 Å (38460 cm.$^{-1}$) which is present in both the solution and gas phase spectra. The solution spectra have inflections in the region of 2450 Å (40820 cm.$^{-1}$) while the gas phase spectra reveal a distinct second transition. Table I and Figures 1 and 2 present the data. The corresponding oxides are transparent in the ultraviolet and can be used as solvents in the range above 2100 Å. However, spectra are observed in the vacuum ultraviolet below 2000 Å. Liu and Duncan[14] measured the spectrum of ethylene oxide in the gas phase. Two electronic transitions at 1713.4 Å (58362 cm.$^{-1}$) and at 1572.4 Å (63597 cm.$^{-1}$) were observed and each was coupled to a vibrational mode such that transitions were observed at 1690.4 Å (59157 cm.$^{-1}$) and 1545.0 Å

(1) National Science Foundation predoctoral fellow, 1955–1957.

(2) The system,  , has been called: ethylene sulfide, thiacyclopropane, and thiirane.

(3) M. Delépine, *Compt. rend.*, **171**, 36 (1920).

(4) A. Schönberg, *Houben-Weyl, Methoden der Organischen Chemie*, Vol. 9, Verlag, Stuggart, 1955, pp. 148–169.

(5) G. B. Guthrie, D. W. Scott, and G. Waddington, *J. Am. Chem. Soc.*, **74**, 2795 (1952).

(6) H. H. Gunthard and T. Gaumann, *Helv. Chim. Acta*, **33**, 1985 (1950).

(7) G. L. Cunningham, Jr., A. W. Boyd, R. J. Myers, W. D. Gwinn, and W. I. Le Van, *J. Chem. Phys.* **19**, 676 (1951).

(8) R. A. Nelson, and R. S. Jessup, *J. Research Nat. Bur. Standards*, **48**, 206 (1952).

(9) Eastman Organic Chemicals.

(10) A. E. Osterburg, *Org. Syntheses*, Coll. Vol. I, 185 (1932).

(11) Ref. 4, p. 154.

(12) W. Davies and W. E. Savige, *J. Chem. Soc.*, 317 (1950).

(13) E. E. van Tamelen, *Org. Syn.*, **32**, 39 (1952).

(14) T. Liu and A. B. F. Duncan, *J. Chem. Phys.*, **17**, 241 (1949).

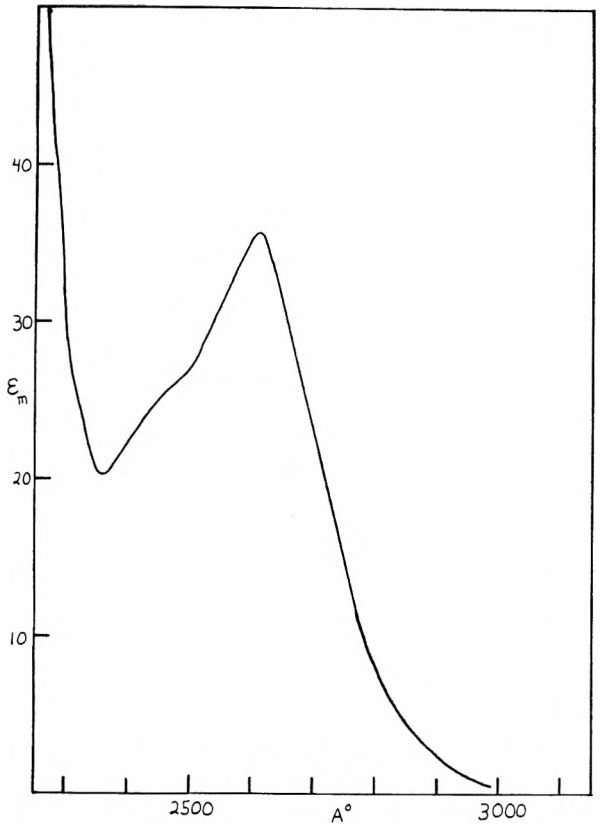


FIG. 1. ETHYLENE SULFIDE IN ISOOCTANE.

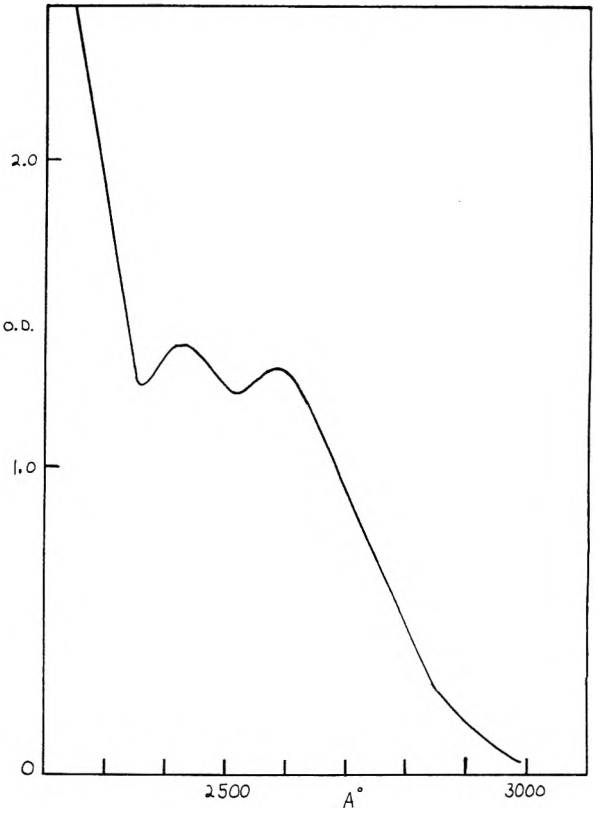
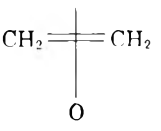


FIG. 2. OPTICAL DENSITY OF ETHYLENE SULFIDE ABSORPTION IN THE GAS PHASE AT 250 MM. PRESSURE.

(64722 cm.$^{-1}$). Below 1435 Å the Rydberg transitions were observed.

The nature of the electronic transitions in the ethylene oxide system and in the sulfide is not completely understood. The bonding in the oxide has been disputed.[15–18] The molecule of ethylene oxide has been considered by Walsh[18] to be represented as a π-bond of ethylene binding the three nuclei (I).



I

Formula I is meant to imply that each carbon atom is trigonal forming three planar hybridized sp^2 bonds and the remaining carbon valency is a pure $2p_z$ orbital overlapping the $2p_x$ of the other carbon and the $2p_x$ of oxygen. The construction of a semi-localized bonding molecular orbital in LACO form has been given[14] and the observed transitions of ethylene oxide in the region of 1700–1500 Å have been considered as due to excitations to the anti-bonding forms of the orbital. This could be used as an explanation of the present data. Using the C_{2v} symmetry of the ethylene sulfide ring and taking the z-axis normal to the plane of the ring, the orbital would be described (without subscripts or normalization) as

$$\psi_{CCS} = z_1 + z_2 + 3p(S)$$

where $(z_1 + z_2)$ represents the ethylenic contribution overlapping with the $3p_z$ orbital on the sulfur atom. The excited states would then be transitions from $[z_1 + z_2 + 3p(S)]^2$ to forms of $[z_1 \pm z_2 \pm 3p(S)]^2$. The sulfur atom having 3s and 3p electrons in contrast to oxygen's 2s and 2p electrons has its excited states at lower levels than those of oxygen. This is observed in the oxygen atom spectrum[19] compared to that of the sulfur atom spectrum. Thus it is expected and observed that sulfur compounds absorb at higher wavelengths. This explanation based upon the treatment of ethylene oxide by Walsh[15,18] and used for the ultraviolet discussion by Liu and Duncan[14] may be satisfactory for these systems and by analogy to the ethylene sulfides. However, doubts exist.

The absorption bands have weak intensities (20–40) which means that the oscillator strengths[20] are low. Low strengths or weak bands are generally "forbidden" transitions which are observed because

(15) A. D. Walsh, *Nature*, **159**, 165 (1947).
(16) R. Robinson, *Nature*, **159**, 400 (1947).
(17) C. A. McDowell, *Nature*, **159**, 508 (1947).
(18) A. D. Walsh, *Nature*, **159**, 712 (1947).
(19) *Atomic Energy Levels*, Nat. Bur. of Standards, Cir. No. 467, Vol. I, 1949.
(20) W. Kauzmann, *Quantum Chemistry*, Academic Press, New York, 1957, pp. 573, 644–666.

TABLE I

ULTRAVIOLET SPECTRA IN ISOOCTANE SOLUTIONS AT 25°

Compound	Maxima Å	ϵ_m	Minima Å	ϵ_m
Ethylene sulfide	2610	34.3[b]	2370	20.4
	(2450)[a]	24.6		
Propylene sulfide	2624	35.0	2373	19.7
	(2450)[a]	25.0		
Cyclohexenesulfide	2625	39.3	2370	19.7

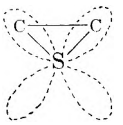
ULTRAVIOLET SPECTRA IN THE GAS PHASE

Compound	Maxima Å	e × 10^3	Minima Å	e × 10^3
Ethylene sulfide	2592	1.13[c]	2521	1.06
	2430	1.16	2364	1.09
Propylene sulfide	2611	1.72	2500	1.41
	2450	1.47	2360	1.07

[a] Inflection. [b] Units: A liter mole^{-1} cm.$^{-1}$ [c] Units: A mm.$^{-1}$ cm.$^{-1}$

of perturbation effects. Thus the benzene bands in the region of 2600 Å are forbidden by selection rules based on the C_2 symmetry of benzene but vibrations of the atoms cause the absorption bands to appear with ϵ_m in the range of 100. These bands are called "partially forbidden".

Another explanation for the origin of the spectra can be built using the C_{2v} symmetry of the three membered ring compounds and some of the geometric requirements of some *d* orbitals. In this case the spectra would be considered as excitation from an unbonded pair on the sulfur (*p* orbital) to a *d* orbital. The excited state would then appear as



Unfortunately it is difficult to describe the complete electronic states of these polyatomic sulfur compounds. Even hydrogen sulfide has not been analyzed with respect to the electronic spectrum. At least there are suggestive reasons why the ethylene sulfide system should exhibit some type of ultraviolet absorption above 2000 Å though the spectra might not be predicted before hand.

There is evidence in the literature of ultraviolet spectra of sulfur compounds that the degree of electronic charge on the sulfur atom in divalent sulfur compounds is related to the position of the absorption band. This will be considered in the following paper in this series on the effect of ring size upon the spectra of cyclic sulfides.

The author wishes to express his appreciation to Prof. W. E. Lyons for helpful discussions during the course of this investigation and to Prof. P. D. Bartlett for permission to publish this report.

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF LOYOLA UNIVERSITY]

Skeletal Rearrangement of β,β,β-Triphenylpropionic Acid in the Hunsdiecker Reaction[1,2]

JAMES W. WILT AND DONALD D. OATHOUDT

Received June 17, 1957

The reaction of silver β,β,β-triphenylpropionate with bromine under conditions normally employed for the Hunsdiecker degradation proceeds anomalously to give the phenyl esters of β,β-diphenylacrylic and α-bromo-β,β-diphenylacrylic acids in moderate yield, with little bromodecarboxylation. Evidence is presented that this skeletal transformation proceeds by an ionic process probably involving 1,4-phenyl migration *via* a five-membered ring intermediate.

Introduction. Curtin and Hurwitz[3] in their preparation of a number of related radicals by decarbonylation of the appropriate aldehyde found evidence that the β,β,β-triphenylethyl radical $(C_6H_5)_3CCH_2\cdot$ gives 100% rearrangement under these conditions to the α,α,β-triphenylethyl radical $(C_6H_5)_2\dot{C}CH_2C_6H_5$ by migration of a phenyl group. This rearrangement is appreciably faster than the identically engendered transformation of the neophyl radical $C_6H_5C(CH_3)_2CH_2\cdot$ to the β-phenyl-*t*-butyl radical $\cdot C(CH_3)_2CH_2C_6H_5$,[4] and presumably might occur even in the presence of an active substrate such as bromine.[5]

(1) Abstracted in part from the thesis of Donald D. Oathoudt presented to the faculty of the Graduate School of Loyola University in partial fulfillment of the requirements for the degree of Master of Science, February, 1957.

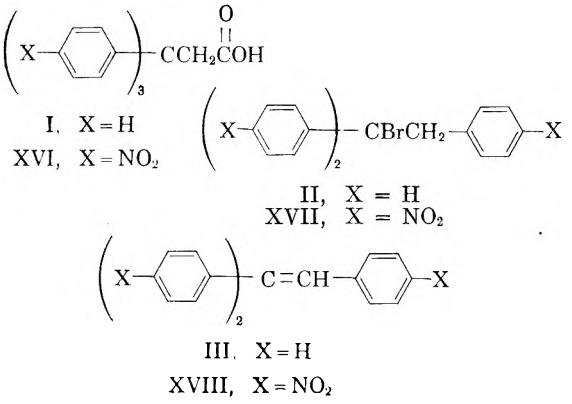
(2) A preliminary report of this work appeared in *J. Org. Chem.*, **21**, 1550 (1956).

(3) D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952).

(4) W. H. Urry and M. S. Kharasch, *J. Am. Chem. Soc.*, **66**, 1438 (1944); S. Winstein and F. Seubold, *J. Am. Chem. Soc.*, **69**, 2916 (1947); F. Seubold, *J. Am. Chem. Soc.*, **75**, 2532 (1953). In the last reference, the neophyl rearrangement is deduced to possess an activation energy of about 8 kcal./mole.

(5) The neophyl rearrangement is apparently absent or at best present to the extent of 5–10% in such a reactive medium. *Cf.* (a) C. E. Berr, Ph.D. thesis, University of California at Los Angeles (1952); (b) J. W. Wilt, *J. Am. Chem. Soc.*, **77**, 6397 (1955); (c) W. T. Smith, Jr., and J. T. Sellas, *Trans. Kentucky Acad. Sci.*, **16**, 72 (1955).

Because of this work it was thought that an investigation of β,β,β-triphenylpropionic acid (I) in the Hunsdiecker reaction[6] would be of interest.



I, X = H
XVI, X = NO_2

II, X = H
XVII, X = NO_2

III, X = H
XVIII, X = NO_2

Were this reaction homolytic in nature, as is commonly believed,[6b] it would be likely to yield a halide or olefin, *viz.*, II or III, rearranged in accordance with the above observation, inasmuch as the same radicals would be involved. The detection of such rearranged substances would furnish needed support for the free radical interpretation of the Hunsdiecker reaction.

Results. The reaction of silver β,β,β-triphenylpropionate with dry bromine in anhydrous carbon tetrachloride was found not to proceed as expected from the above considerations. Rather, an anomalous reaction superceded the usual one of bromodecarboxylation. Indeed, carbon dioxide, normally evolved readily in such reactions, was not even detected in several of the reactions performed. When, however, a nitrogen gas sweep was used, the presence of carbon dioxide (about 3%) was determined in the effluent by precipitation in saturated barium hydroxide solution.

Treatment of the reaction mixture in the customary manner[7] gave, in addition to much *original acid* (44%), a refractory semisolid material which resisted all conventional methods of purification. This crude product contained *halogen* (Beilstein test) and was shown to contain a phenyl ester function by the hydroxamic acid test and by the isolation of phenol (as tribromophenol) upon hydrolysis.

Eventually the crude material was separated by chromatography on alumina and vacuum fractional sublimation into two colorless solids, a halogen-free substance *A* in 17% yield (m.p. 123.5–124.5°) with an analysis corresponding to $C_{21}H_{16}O_2$, and a material *B* in 36% yield containing bromine (m.p. 90.5–91.5°) with an analysis corresponding to $C_{21}H_{15}BrO_2$. Evidence for the presence in the crude material of a *halide* in less than 4% yield was obtained *via* dehydrobromination with alcoholic alkali and argentometric determination of bromide ion in the precipitated salt.[8] Since a mass balance was achieved with the detection of these products and recovered acid, it seems no other significant products are formed.

Both *A* and *B* were phenyl esters and both possessed ultraviolet maxima of 285 mμ (in 95% ethanol), indicating similarly activated carbonyl excitation (see Figures 1 and 2). The infrared

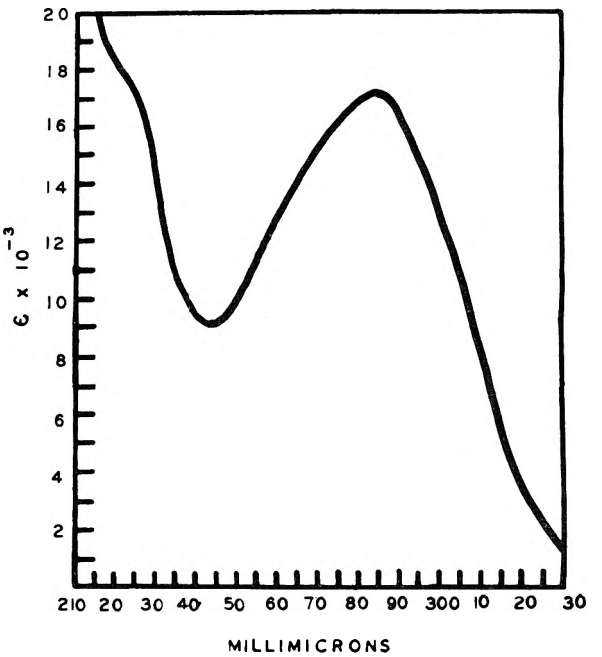


FIG. 1. THE ULTRAVIOLET SPECTRUM (in 95% ethanol) of phenyl β,β-diphenylacrylate, VI (*A*).

spectrum of *A* (bands at 1736, 1618, 1594, and 1579 cm.$^{-1}$) was clearly that of an *α,β-unsaturated aromatic ester*, while that of *B* (bands at 1740, 1594, and 1494 cm.$^{-1}$) failed to show unsaturation beyond that expected for aromatic nuclei.

In accord with these findings, *A* was quickly oxidized by dilute potassium permanganate while *B* was much more resistant. In addition, *A* when treated with bromine under reaction conditions was converted to *B* in an amount dependent on time of reflux. The halogenated substance *B* remained unaffected upon prolonged reflux with alcoholic silver nitrate.

Consideration of all the preceding information as well as possible subversions of the usual path of the Hunsdiecker reaction led us to speculate that *β,β-diphenylacrylate esters* had been produced in this reaction. This speculation was proved to be correct

(6) (a) H. Hunsdiecker and C. Hunsdiecker, *Ber.*, **75**, 295 (1942); (b) R. G. Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956).

(7) *Cf.* the references given in footnote 5.

(8) Unfortunately this halide could not be isolated. Because of the ready dehydrobromination under nonsolvolytic conditions, however, we believe this substance to be the partly expected II, since the non-rearranged halide (IV) would not be expected to lose hydrogen bromide under these conditions.

$(C_6H_5)_3CCH_2Br$
IV

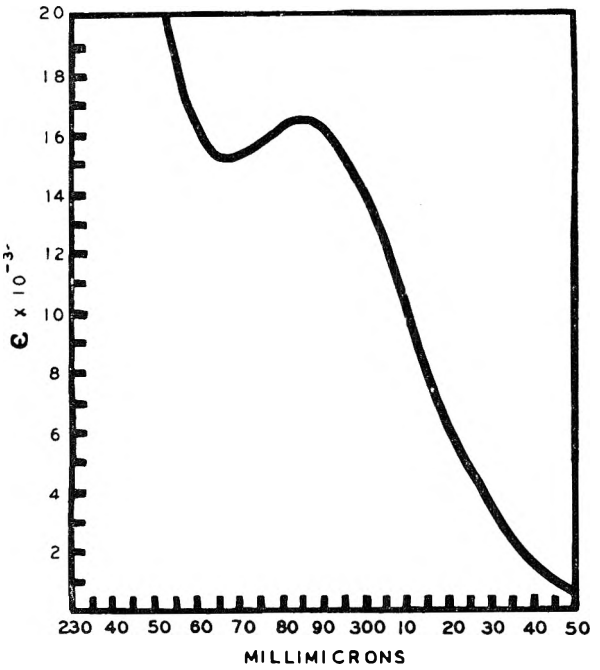


FIG. 2. THE ULTRAVIOLET SPECTRUM (in 95% ethanol) of phenyl α-bromo-β,β-diphenylacrylate, VIII (*B*).

by independent syntheses of both *A* and *B* by unequivocal routes.

β,β-Diphenylacrylic acid[9] (V) was converted to its acid chloride and thence directly to the previously unreported *phenyl β,β-diphenylacrylate*[10] (VI) using standard techniques. Compound VI thus prepared was identical in every detail with *A* isolated from the reaction mixture. The finding of Newman and Owen[9c] that β,β-diphenylacrylic acid derivatives are converted on treatment with bromine to dibromo addition products which readily lose hydrogen bromide to form α-bromo substituted compounds seemed to verify our suspicion, reached prior to knowledge of their work, that *B* was in fact *phenyl α-bromo-β,β-diphenylacrylate* (VIII), produced from *A* by bromine at the reflux temperature of carbon tetrachloride. This substance was therefore synthesized from α-bromo-β,β-diphenylacrylic acid[9c] (VII) *via* the acid chloride and phenol.

$$(C_6H_5)_2C{=}CHCO_2H \xrightarrow{PCl_5} \underset{V}{} (C_6H_5)_2C{=}CHCOCl \xrightarrow[95\%]{\phi OH} (C_6H_5)_2C{=}CH{-}CO_2{-}C_6H_5$$

VI, *A*

$$(C_6H_5)_2C{=}CBrCO_2H \xrightarrow{SOCl_2} (C_6H_5)_2C{=}CBrCOCl \xrightarrow[OH^-,\ 48\%]{\phi OH}$$

VII

$$(C_6H_5)_2C{=}CBrCO_2C_6H_5$$

VIII, *B*

The independently synthesized ester VIII and *B* were found to be identical.

In the light of its proven structure, the infrared spectrum and chemical behavior of *B* upon attempted characterization (*vide supra*) warrant some discussion. The absence of non-aromatic unsaturation in the infrared spectrum is not unexpected for *B* since tetrasubstituted ethylenes often exhibit such behavior.[11] Also, permanganate oxidation of such a compound might reasonably be expected to be slow.[12] The vinylic bromine, as is well known, resists displacement or solvolytic reactions.

Discussion. An interesting feature of this reaction is the overall *1,4-phenyl migration* observed, presumably by an intramolecular process. Such rearrangements have been observed previously in ionic reactions such as the solvolysis of certain bromobenzenesulfonates,[13a] and in homolytic processes such as the peroxide-induced decarbonylation of 5-phenylpentanal,[13a] the Kolbe electrolysis of β,β,β-triphenylpropionic acid,[13b] and the thermal conversion of 2-phenoxybenzoyl peroxide to phenyl salicylate.[13c] While ester formation is common in Hunsdiecker reactions,[14] *intramolecular* ester formation apparently has been previously observed but once[15] and *intramolecular ester formation accompanied by rearrangement* of the carbon skeletal system seems to be unreported previously.

Since *B* can be produced from *A* under reaction conditions, it is simpler to discuss the conversion of the silver salt of I to *A* alone. In this fashion, the formation of *B* may be viewed as a simple addition of bromine to the double bond of *A* followed by thermal dehydrobromination (perhaps assisted by the silver bromide and/or the unreacted silver salt of I present in the mixture). The rather large

(9) (a) H. Rupe and A. Busolt, *Ber.*, **40**, 4537 (1907); (b) M. S. Kharasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.*, **64**, 333 (1942); (c) D. Newman and L. Owen, *J. Chem. Soc.*, 4726 (1952).

(10) Independently, this ester has been recently synthesized by S. Patai and R. Ikan, *J. Org. Chem.*, **21**, 1379 (1956).

(11) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 32.

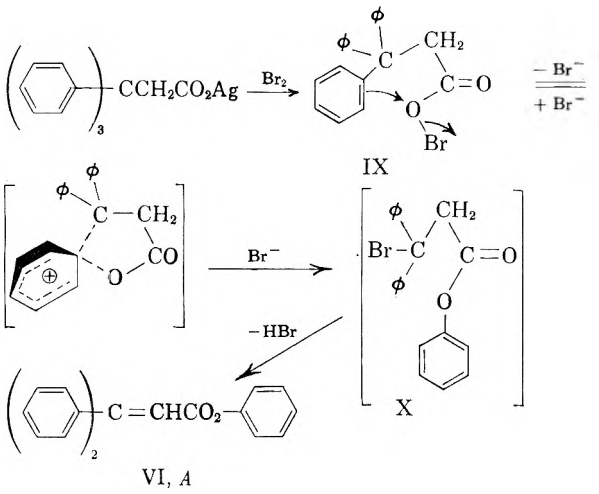
(12) (a) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., Englewood Cliffs, N. J., 1954, p. 330; (b) *Cf.*, however, R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 134.

(13) (a) S. Winstein, *et al.*, *Experientia*, **12**, 138 (1956); (b) E. C. Kooyman and H. Breederveld, *Rec. trav. chim.*, **76**, 297 (1957). This reaction yields phenyl β,β-diphenyl-β-methoxypropionate and is closely allied to that described herein since the carbon skeletal changes are identical. (c) D. F. DeTar and A. Hlynsky, *J. Am. Chem. Soc.*, **77**, 4411 (1955).

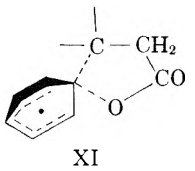
(14) Ester formation under these conditions is known as the Simonini reaction (*cf.* reference 6b, p. 259). Generally *intermolecular* ester formation is observed.

(15) C. E. Berr (reference 5a) obtained a lactone from silver β-phenylisovalerate in a Hunsdiecker reaction, probably by an "internal" Simonini reaction.

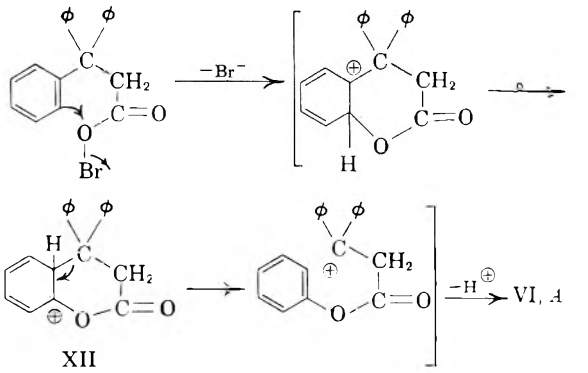
amount of recovered acid may be attributed in part[16] to the reaction *in situ* of the silver salt with the two moles of hydrogen bromide stoichiometrically liberated in this reaction. There are three mechanisms for the conversion of the silver salt of I to *A* that find analogy or precedent in the literature. The first of these, Mechanism 1, involves a five-membered ring intermediate with phenonium-ion characteristics,[17] an *ionic mechanism* similar to that proved useful in the interpretation of certain solvolyses.[13a] As applied to the present case, this mechanism would be the following:



The formation of an acyl hypobromite, such as IX, is generally accepted as the first stage in Hunsdiecker reactions.[18] Mechanism 2 utilizes the free radical analog of the above and resembles the mechanism proposed for the Kolbe electrolysis of β,β,β-triphenylpropionic acid.[13b] Applied to the present reaction, this mechanism would be the same as Mechanism 1, except that the entity XI

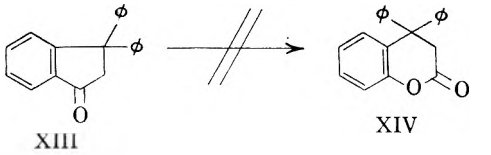


would be the cyclic intermediate, attacking bromine to give the unstable bromoester X. A final mechanism, Mechanism 3, has direct precedent in Hunsdiecker reactions. It employs a six-membered ring intermediate produced by the attack of an adjacent phenyl group at its *ortho* position upon the hypobromite function:

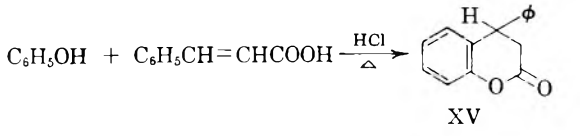


A similar mechanism (here shown as ionic, though a free radical analog is also possible) served to explain the formation of a 4,4-dimethyl-3,4-dihydrocoumarin derivative in the reaction of silver β-phenylisovalerate and bromine.[5a,15] Presumably proton loss from an intermediate akin to XII, rather than carbon-carbon cleavage, accounts for the formation of this lactone.

Certain considerations lead us to reject Mechanism 3. For example, repeated and varied attempts to oxidize 3,3-diphenylindanone-1 (XIII) to 4,4-diphenyl-3,4-dihydrocoumarin (XIV) by the Baeyer-Villiger ring expansion[19] gave only trace amounts of lactone material, indicating serious resistance to the formation of the as yet unknown ring system of 4,4-diphenyl-3,4-dihydrocoumarin.



In this regard the recent synthesis of 4-phenyl-3,4-dihydrocoumarin[20] (XV) by treatment of phenol and cinnamic acid with hot concentrated hydrochloric acid is of interest. Work performed in this present study indicates that this technique *fails* with β,β-diphenylacrylic acid (V).



$$C_6H_5OH + (C_6H_5)_2C{=}CHCOOH \xrightarrow{Ibid.} \text{N. R.}$$

These reactions undoubtedly proceed through intermediates just like or closely related to those in Mechanism 3, involving electrophilic attack upon a phenolic ring. Furthermore, examination of molecular models of the intermediates (such as XII) in Mechanism 3 reveals serious steric crowding at the 4-position. The possibility, therefore, of

(16) Original acid is often recovered from Hunsdiecker reactions, anhydrous though the system may be. How this occurs is as yet not fully known.

(17) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3863 (1949).

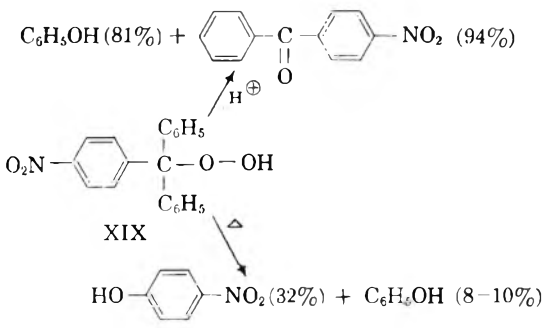
(18) Reference 6b, pp. 260 ff.

(19) (a) A. Baeyer and V. Villiger, *Ber.*, **32**, 3625 (1899); (b) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(20) J. Simpson and H. Stephen, *J. Chem. Soc.*, 1382 (1956).

the acyl hypobromite IX proceeding to VI (*A*) *via* such a ring system is considered unlikely if other, less crowded, paths are possible.[21]

In order to investigate the polar or radical nature of this reaction, use was made of a proposal first advanced by Bartlett and Cotman.[22] From a variety of earlier data, and particularly from their own study of mono-*p*-nitrotriphenylmethyl hydroperoxide (XIX), they proposed that a criterion of ionic *vs.* free radical mechanisms may be found in the relative rearrangement ability of the *p*-nitrophenyl group and the unsubstituted phenyl group. Thus, in their study,



the *ionic* (acid catalyzed) rearrangement gave migration of the phenyl group to the *exclusion* of the *p*-nitrophenyl group, while the *free radical* (thermally induced) rearrangement gave a migration ratio of *p*-nitrophenyl/phenyl ~ 4. Such a reversal of the "normal" migration ability ratios may be taken as evidence for a homolytic process. To this end, β,β,β-tris(*p*-nitrophenyl)propionic acid (XVI) was prepared from I and its silver salt treated with bromine under the same conditions used previously. *Carbon dioxide evolution increased nearly tenfold* (3 -> 27%) over that from I. No ester product was detected and the halide and olefin (probably XVII and XVIII, respectively) isolated indicate that the reaction here is the usual one of bromodecarboxylation. Apparently the two processes of ester formation by rearrangement and bromodecarboxylation are in competition, the former occurring with the unsubstituted system, the latter occurring with the nitrated system. Since, as has been noted above, *radical* rearrangement processes in so far as they have been studied are somewhat faster with the *p*-nitrophenyl group than with the unsubstituted phenyl group, while the analogous *ionic* rearrangements are just the reverse, the evidence points to a *polar* path for the ester formation observed in this work. From these considerations, Mechanism 1 seems favored.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Ultraviolet spectra were determined in previously scanned 95% ethanol with a manually operated Beckman DU spectrophotometer equipped with an 1P28 photo tube using 1-cm. silica cells. The infrared spectra were determined in potassium bromide pellets on a Perkin-Elmer Model 21 spectrophotometer. Analyses were performed by the Galbraith Laboratories, Knoxville, Tenn.

Preparation of β,β,β-triphenylpropionic acid (I). The procedure of Hellerman[23] gave an average 50% yield of the acid, m.p. 180–181° (reported[23] 180°), as white needles from ethanol.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.4; H, 6.00. Found: C, 83.24; H, 6.11.

The infrared spectrum of I (chloroform) showed peaks at 3049s cm.$^{-1}$ (aromatic C—H), 1718m cm.$^{-1}$ (saturated acid C=O), 1215s cm.$^{-1}$ (broad) (C_3—C), 929m cm.$^{-1}$ (confirmatory —COOH).

The silver salt of I was prepared in 80% yield in the usual fashion and dried in an oven at 70° for two days.

Reaction of the silver salt of I with bromine. This reaction was carried out seven times and the following is a representative description of the procedure.

To silver β,β,β-triphenylpropionate (66.0 g., 0.161 mole), dispersed in dry carbon tetrachloride (100 ml., stored over phosphorus pentoxide for one week and azeotropically freed from water by distillation), was added dropwise with stirring a solution of bromine (27.7 g., 0.173 mole, dried over phosphorus pentoxide for three days) in further dry carbon tetrachloride (15 ml.) at a temperature of 25–50° over a period of 20 min. A gentle nitrogen gas sweep was employed to carry any evolved gas through a condenser into a trap containing saturated barium hydroxide solution. When all the bromine had been added, the mixture was refluxed (77°) with continued stirring for a further 0.5 hr. The evolved carbon dioxide (collected as barium carbonate) amounted to 0.0042 mole (2.6% yield).

Filtration of the rust colored mixture gave silver bromide (30.3 g., 0.161 mole, 100% yield, washed *thoroughly* with hot ethanol). The filtrate was washed once with successive portions (100 ml.) of 5%, 2.5%, and 1.25% sodium hydroxide solutions. Acidification of the aqueous alkaline extracts with dilute hydrochloric acid yielded original βββ-triphenylpropionic acid (18.5 g., m.p. 165–170°, raised to 180° with one recrystallization from ethanol). Further acid (2.9 g.) was obtained from the alcohol washings of the crude silver bromide. Total I recovered was 21.4 g. (44%). The carbon tetrachloride layer from the alkaline wash was dried over sodium sulfate and freed from solvent by distillation under reduced pressure. The golden, semisolid residue (about 30 g.) was then treated as described below.

Chromatographic separation of A and B. When the residue from the Hunsdiecker reaction was dissolved in various solvents, in attempted fractional crystallizations, or sublimed in a vacuum, oils, semisolids, or wide-range melting substances were obtained. Separation into sharp-melting materials was achieved by chromatography on alumina (Fisher Chromatographic Alumina, 80–200 mesh) in a 65 cm. tube (a converted Jones reductor). Elution of the crude residue (about 30 g.) with petroleum ether (b.p. 30–60°)-benzene fractions (twenty fractions, 30 ml. each), followed by vac-

(21) The useful technique of testing for *ortho* attack by phenyl by placing substituents on the benzene rings and noting whether isomerization occurs during the phenyl migration is at present under study and will be reported at a later date. NOTE ADDED IN PROOF: Recent work by Mr. J. Finnerty and one of the authors (J.W.W.) indicates that the rearrangement of β,β,β-tris(*p*-*t*-butylphenyl)propionic acid (I, X = *t*-butyl) in this reaction yields the *p*-*t*-*butylphenyl ester* of α-bromo-β,β-di(*p*-*t*-butylphenyl) acrylic acid *exclusively*. Such a result renders Mechanism 3 an unlikely path for these rearrangements, and supports either Mechanism 1 or 2. Details of this and of other related xperiments will be reported at a later date.

(22) P. D. Bartlett and J. D. Cotman, Jr., *J. Am. Chem. Soc.*, **72**, 3095 (1950).

(23) L. Hellerman, *J. Am. Chem. Soc.*, **49**, 1738 (1927).

uum sublimation (100°, <1 mm.) of the crystalline material so obtained, gave a colorless solid (*B*) which contained halogen (Beilstein test) (m.p. 90.5–91.5°, 22.2 g., 36.4%).

Anal. Calcd. for $C_{21}H_{15}BrO_2$: C, 66.6; H, 3.99; Br, 21.05. Found: C, 66.42; H, 4.07; Br, 20.8.

Further elution of the column with benzene (eight fractions, 30 ml. each), followed by vacuum sublimation as before (125°, <1 mm.) gave a colorless solid (*A*) which was halogen-free (Beilstein test) (m.p. 123.5–124.5°, 7.4 g., 16.7%).

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 84.15; H, 5.38.

Characterization of A and B. The ultraviolet spectrum of *A* (see Fig. 1) possessed λ_{alc}^{max} 285 mμ (ε 17,180), λ_{alc}^{min} 245 mμ (ε 9130). Its infrared spectrum (KBr pellet) had peaks at 1736s cm.$^{-1}$ (ester C=O), 1618s–1594s–1579s cm.$^{-1}$ (aromatic with conjugated —C=CH—). *A* quickly (5 min.) decolorized potassium permanganate solution (0.5%) and gave a positive ester test in the hydroxamic acid reaction.[24] The ultraviolet spectrum of *B* (see Fig. 2) possessed λ_{alc}^{max} 285 mμ (shoulder) (ε 16,500), λ_{alc}^{min} 267 mμ (ε 15,160). Its infrared spectrum (KBr pellet) had peaks at 1740s cm.$^{-1}$ (ester C=O), 1594w–1494m cm.$^{-1}$ (aromatic). *B* slowly (overnight) decolorized potassium permanganate solution (0.5%) and was positive in the hydroxamic acid test for esters.[24] Extended reflux (3 hr.) of *B* with alcoholic silver nitrate (5%) gave no reaction. The phenyl ester nature of the crude reaction material was established by a procedure similar to that described here for the examination of *B*. *B* (0.05 g.) was saponified by refluxing with an excess of alcoholic potassium hydroxide and then treated with solid carbon dioxide chunks. Microsteam distillation of the mixture and collection of the distillate in bromine water gave tribromophenol (0.04 g., m.p. 93–94°, 92% yield).

Conversion of A to B under reaction conditions. *A* (1.0 g., 3.3 millimoles, m.p. 123.5–124.5°) dissolved in dry carbon tetrachloride was treated at reflux with excess bromine in the presence of silver bromide for one hour. Conventional work-up and recrystallization from alcohol gave a white solid, m.p. 72–80°. The ultraviolet spectrum of this material exhibited λ_{alc}^{max} 285 mμ and λ_{alc}^{min} 262 mμ and matched that of crude *B* isolable from the chromatographic column (m.p. 75–78°). The shift in λ^{min} here is 17 mμ. Longer reaction times (2 hr.) produced further λ^{min} shifts, but some bromophenol also was detectable (odor) under these conditions.

Detection of halide in crude residue. Crude semisolid residue (5.4 g.) was refluxed (1 hr.) with absolute ethanolic potassium hydroxide (1.86 g. in 100 ml.). The precipitated salts were collected, dissolved in distilled water, and treated with aqueous silver nitrate. Gravimetric determination of silver bromide (characteristic pale yellow solid) showed 0.55 millimole of bromide ion present. With the assumption that the crude material contains about 33% *A* and 67% *B* (the values found by chromatography), the bromide ion found is 3.5 mole %. The close agreement (within the error of the measurements) of the carbon dioxide and bromide percentages indicates that dehydrobromination and not some spurious reaction occurred here.

Preparation of phenyl β,β-diphenylacrylate (VI). β,β-Diphenylacrylic acid (V, 2.24 g., 0.01 mole, m.p. 161–162°, reported[9b] 161°), prepared according to the method of Rupe and Busolt,[9a] or by that of Kharasch, *et al.*,[9b] and benzene (60 ml.) were refluxed for 10 min. to effect solution. Phosphorus pentachloride (2.61 g., 0.0125 mole) was added and the mixture refluxed for 1 hr. To the slightly cooled solution phenol (1.18 g., 0.0125 mole) was then added and reflux again initiated and continued until no further hydrogen chloride evolution was noticed (another hour). A wash of the cooled material with aqueous sodium carbonate (40 ml., 10%), and separation, drying, and evaporation of the benzene phase left a crystalline residue which crystallized from ethanol as a colorless solid (m.p. 123.5–124.5°, 2.8 g., 95% yield, λ_{alc}^{max} 285 mμ (ε 17,150), λ_{alc}^{min} 245 mμ (ε 9100)). A mixture melting point determination of this substance with *A* showed no depression and their spectra were identical.

Preparation of phenyl α-bromo-β,β-diphenylacrylate (VIII). α-Bromo-β,β-diphenylacrylic acid (VII, 1.0 g., 3.3 millimoles, m.p. 150–152°, reported[9c] 150°), prepared by the method of Newman and Owen[9c] in 56% yield, and thionyl chloride (1.8 g., 15 millimoles) were refluxed for 15 min. Excess thionyl chloride was codistilled from the solution with benzene and the residual benzene removed by aspiration. To the oil remaining was added water (10 ml.), phenol (0.94 g., 100 millimoles), and sodium hydroxide solution (20%, 10 ml.), the last in portions. The mixture was vigorously shaken for an extended time and allowed to stand overnight. The crystalline precipitate (0.6 g., 48% yield) was washed with water, chromatographed on alumina to remove a small amount of colored impurity (petroleum ether–benzene eluant), and finally vacuum sublimed to a colorless solid (m.p. 91–92°, λ_{alc}^{max} 285 mμ (ε 16,450), λ_{alc}^{min} 267 mμ (ε 15,000)). This substance was identical with *B* from mixture melting point determinations and identity of spectra.

Attempted oxidation of 3,3-diphenylindanone-1 (XIII). XIII, prepared by the cyclization of the acid chloride of I[25] as a colorless solid (m.p. 130–131°, reported[25] 130–131°, 88% yield), was treated under several different sets of conditions with peroxyacetic, perbenzoic, and trifluoroperoxyacetic acids with little evidence of reaction. Since the latter acid has proven to be the most efficient reagent for the Baeyer-Villiger reaction,[19b,26] an illustrative experiment with this acid is described here. Trifluoroperoxyacetic acid [prepared from trifluoroacetic anhydride (0.018 mole) and hydrogen peroxide (90%, 0.015 mole) in cold methylene chloride (10 ml.)] was added in small portions to a solution of XIII (0.01 mole) in further methylene chloride (10 ml.) under reflux. A self-sustaining reaction commenced with the mixture deepening in color, after which the solution was refluxed further for fifteen minutes. After neutralization with sodium carbonate solution (10%), separation, drying, and evaporation of the organic phase, a small amount of a tan solid remained, m.p. 92–102°, which was primarily still ketonic since the material was positive to 2,4-dinitrophenylhydrazine reagent. Workup of the alkaline washings gave only intractable gums. Lactone material was present in traces in the tan solid as evidenced by very weak hydroxamic acid results.

Attempted synthesis of 4,4-diphenyl-3,4-dihydrocoumarin (XIV) *from β,β-diphenylacrylic acid* (V). V (1.8 g., about 8 millimoles, m.p. 160°, reported[9b] 161°), phenol (0.78 g., about 8 millimoles), and concentrated hydrochloric acid (42 ml.) were treated as described by Simpson and Stephen.[20] The isolated material was completely bicarbonate soluble and gave a negative hydroxamic acid test for lactones. The acidic nature of the product implies that no reaction of consequence occurred here.

Preparation of β,β,β-tris(p-nitrophenyl)propionic acid (XVI). I (1.9 g., 5.3 millimoles, m.p. 180°) was added in portions to a stirred mixture of nitric acid (concentrated, 12 g.) and sulfuric acid (concentrated, 18.5 g.) held at 0–2°. Slow solution of the solid occurred and a brown color developed. The mixture was allowed to warm to room temperature by stirring in a melting ice bath. When completely homogeneous, the solution was poured into a large volume of cold water. The white solid was collected and dried (2.6 g., 95% yield, m.p. 220–223°). This material gave a positive test for the nitro group with ferrous hydroxide[27] and dissolved

(24) Reference 12b, pp. 122–23.

(25) C. F. Koelsch and C. D. LcClaire, *J. Org. Chem.*, 6, 516 (1941).

(26) W. F. Sager and A. Duckworth, *J. Am. Chem. Soc.*, 77, 188 (1955).

(27) Reference 12b, p. 113.

in alkali to give a yellow solution. Two recrystallizations of this solid from ethanol gave XVI as pale yellow, short needles, m.p. 248–250° decomposing to a red liquid.

Anal. Calcd. for $C_{21}H_{15}N_3O_8$: N, 9.61. Found: N, 9.55.

The infrared spectrum of XVI (chloroform) showed peaks at 3049s cm.$^{-1}$ (aromatic C—H), 1730w cm.$^{-1}$ (saturated acid C=O), 1527s–1351s cm.$^{-1}$ (C—NO_2), 1215s cm.$^{-1}$ (broad) (C_3—C), 929m cm.$^{-1}$ (confirmatory —COOH).

The silver salt was prepared in the usual way and dried at 80° for two days.

Reaction of the silver salt of XVI with bromine. The silver salt of XVI (3.0 g., 5.5 millimoles) was suspended in dry carbon tetrachloride (30 ml.) and treated with dry bromine (1.0 g., 6 millimoles) in further solvent (10 ml.) under a nitrogen gas sweep as described previously for the silver salt of I. Carbon dioxide evolution commenced in about five minutes at room temperature and was completed at the reflux temperature (77°) in thirty minutes. The carbon dioxide evolved (measured as barium carbonate) was 1.47 millimole (26.8% yield). Treatment of the reaction mixture as described before gave recovered XVI (70%) and a yellow solid (about 25–30%), m.p. 70–85°. This solid gave a precipitate of silver bromide *readily* in alcoholic silver nitrate (5%) and developed acidity when refluxed in aqueous alcohol. Potassium permanganate in acetone (0.5%) was quickly decolorized by the solid. While the alkaline conditions required for the hydroxamic acid test for esters appeared to affect the substance, a negative ester test was obtained.

The ready solvolytic loss of hydrogen bromide from the substance suggests that it contains XVII, while the unsaturation evident implies the presence of at least some olefin, probably XVIII.[28]

Acknowledgment. The authors wish to thank Professor C. E. Moore for certain technical assistance and Miss E. Godar for some of the infrared spectra.

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(28) While the purpose of using XVI in this study was strictly the comparison of the carbon dioxide percentage (bromodecarboxylation percentage) with I, the reaction of XVI is of great interest in itself, perhaps being the first reported instance of appreciable rearrangement, not caused by side reactions, in the Hunsdiecker reaction series. A more detailed investigation of this point is under way in this laboratory and will be reported separately.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

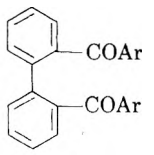
Steric Interactions in the Absorption Spectra of 2,2′-Diaroylbiphenyls

WILLIAM F. FORBES,[1] FRIEDRICH T. WALLENBERGER, WILLIAM F. O'CONNOR, AND EMIL J. MORICONI

Received July 29, 1957

The electronic absorption spectra of 2,2′-biphenyldialdehyde, (+) 6,6′-dinitro-2,2′-di(2,4-dimethylbenzoyl)biphenyl, and a series of 2,2′-diaroylbiphenyls in which the 2,2′-diaroyl substituents increase in bulk (Aroyl = 4-methylbenzoyl, 2,4-dimethylbenzoyl, 1-naphthoyl, 2,4,6-trimethylbenzoyl, and 2,3,5,6-tetramethylbenzoyl) are discussed in terms of current theories.

As part of a configurational study of *cis*- and *trans*- 9,10-diaryl-9,10-dihydro-9,10-phenanthrenediols in which the 9,10-diaryl substituents increase in bulk, five 2,2′-diaroylbiphenyls (I) have been prepared as intermediates.[2] The structures of these diketones, synthesized by a Friedel-Crafts reaction between diphenoyl chloride and the appropriate arene, have been previously established by unequivocal methods.[3]



I

Ia, Ar = 4-methylphenyl
Ib, Ar = 2,4-dimethylphenyl
Ic, Ar = 2,4,6-trimethylphenyl
Id, Ar = 2,3,5,6-tetramethylphenyl
Ie, Ar = 1-naphthyl

Compounds of this type should also be of special interest since they provide examples in which steric effects are known to cause changes in the light absorption properties. In particular, steric effects in electronic spectra of organic compounds have been classified into two types: Type I steric effects, which give rise to intensity changes only, and Type II steric effects, which normally also cause appreciable wavelength displacements.[4] Acetophenones show steric effects of the former type, whereas biphenyls show steric effects of the latter type. Consequently, it would be a matter of interest to determine which type of steric effect occurs in the compounds under investigation. With this in mind, a spectral analysis of the compounds Ia to Ie and of a suitable reference compound, 2,2′-biphenyldialdehyde (II), has been carried out.

(1) Memorial University of Newfoundland, St. John's, Newfoundland, Canada.

(2) (a) E. J. Moriconi, F. T. Wallenberger, L. P. Kuhn, and W. F. O'Connor, *J. Org. Chem.*, **22**, 1651 (1957); (b) E. J. Moriconi, F. T. Wallenberger, and W. F. O'Connor, *J. Am. Chem. Soc.*, in press.

(3) W. E. Bachmann, *J. Am. Chem. Soc.*, **54**, 1969 (1932); W. E. Bachmann and E. J. Chu, *J. Am. Chem. Soc.*, **57**, 1095 (1935); D. Nightingale, H. E. Heiner, and H. E. French, *J. Am. Chem. Soc.*, **72**, 1875 (1950); R. C. Fuson and C. Hornberger, *J. Org. Chem.*, **16**, 637 (1951); R. C. Fuson and R. O. Kerr, *J. Org. Chem.*, **19**, 373 (1954).

(4) E. A. Braude, F. Sondheimer, and W. F. Forbes, *Nature*, **173**, 117 (1954); E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

Compound III, (+) 6,6′-dinitro-2,2′-di(2,4-dimethylbenzoyl)-biphenyl, is also included to compare the effect of molecular rigidity on absorption spectra. Results are summarized in Table I.

TABLE I

ABSORPTION SPECTRA OF 2,2′-DIAROYLBIPHENYLS

Compound	Ultraviolet[a] B-band λ_{max} mμ	B-band ϵ_{max}	C-band λ_{max} mμ	C-band ϵ_{max}	Infrared[b] Carbonyl Band ν_{max} cm.$^{-1}$
II	252	18,500	*284*	*3,100*[c]	1699
			294	4,200	
Ia	262	31,600	*287*	*13,400*[c]	1661
Ib	260	23,400	*289*	*10,400*[c]	1664
Ic	252	16,800	287	5,800	1673
Id	250	16,900	300	5,700	1674
Ie	*259*	*21,800*[c]	285	9,500	1660
			312	12,700	
III	257	13,700	*288*	*8,100*[c]	1671
	243	16,000			

[a] Values of ethanolic solution; the band designation is the same as the one used by Forbes *et al.* in *Can. J. Chem.*, **35**, 1049 (1957) and preceding papers of that series. [b] Values in chloroform solution; this band, due to the infrared carbonyl stretching frequency, will be referred to as the "carbonyl band" throughout this paper. [c] Values in italics in this and the subsequent table represent inflections.

The simplest 2,2′-diaroylbiphenyl is compound II, which may be regarded as a di-*ortho*-substituted biphenyl where both *o*-substituents are fairly small. It is also known that two *o*-substituents in a biphenyl system normally destroy most of the 1,1′-biphenylic conjugation.[5] Therefore the spectrum of II may be anticipated to resemble the spectrum of benzaldehyde; or perhaps that of an orthosubstituted benzaldehyde, which also absorbs in a similar wave length range as biphenyl, that is near 250 mμ. Since the benzaldehyde and biphenyl spectra absorb closely to each other, no definite assignment can be made on the basis of location of maximal absorption alone. However, the following three factors enable us to ascribe the absorption band of II at 252 mμ, ϵ = 18,500 primarily to benzaldehyde absorption:

(i) In ethanol, II shows an absorption band at 252 mμ; in cyclohexane solution this splits into a maximum at 248 mμ and an inflection at 255 mμ. This, as well as the general shape of the B-band, is characteristic of benzaldehyde absorption. By contrast, the biphenyl band does not exhibit any such fine structure.[5] Table II lists the B-band of II together with the B-bands of two ortho-substituted benzaldehydes.

(ii) If the absorption band of II at 252 mμ corresponds to benzaldehyde absorption, the absorption bands in Ia to Id should, by analogy, correspond to benzophenone absorption. It would be anticipated that steric effects in the series Ia to Id cause essentially type I steric effects, since the system then resembles an acetophenone system. This is found to be so (Table I). If biphenyl absorption were chiefly responsible for the observed absorption band, one would expect steric effects essentially of type II in Ia to Id similar to those observed in biphenyl.

TABLE II

ABSORPTION MAXIMA (B-BANDS) OF *Ortho*-SUBSTITUTED BENZALDEHYDES IN HEXANE SOLUTION[6]

Compound	λ_{max}, mμ	ϵ_{max}
2,2′-Biphenyldialdehyde (II)	248	19,300
	255	*17,300*
o-Chlorobenzaldehyde	246	10,800
	252	8,500
o-Methoxybenzaldehyde	246	10,600
	253	*8,500*

(iii) Scale models indicate that the biphenyl system in compound II is nonplanar.[7]

Two additional points concerning the spectrum of II may also be noted. First, although the absorption intensity of II is almost exactly twice the intensity of the two *o*-substituted benzaldehydes listed in Table II, this does not imply that biphenyl absorption will not contribute to the observed absorption. In fact, biphenyl conjugation quite probably contributes to the observed absorption intensity, because ortho-substituted benzaldehydes normally absorb with a smaller extinction coefficient than the parent compound.[6] Secondly, the carbonyl band of II at 1699 cm.$^{-1}$ lies within the expected absorption range for aryl aldehydes, that is between 1715 and 1695 cm.$^{-1}$ [8] It also absorbs closely to the reported absorption bands of 1- and 2-naphthaldehyde which in 0.02 molar carbon tetrachloride solution occur at 1700 and 1702 cm.$^{-1}$ respectively.[9]

In the next example, Ia, steric inhibition of 1,1′-biphenylic conjugation has presumably increased. Consequently, as mentioned above, we would expect this system to absorb essentially as two molecules of *p*-methylbenzophenone. This hypothesis is supported by the data. Benzophenone absorbs maximally in ethanol at 252 mμ (ϵ = 17,400)[10] and a *p*-methyl substituent would be expected to cause a bathochromic wave length displacement of about 9 mμ (benzaldehyde to *p*-methylbenzaldehyde and acetophenone to *p*-

(5) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 3776 (1955).

(6) W. F. Forbes and J. C. Dearden, unpublished information.

(7) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **34**, 1542 (1956).

(8) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen and Co. Ltd., London, 1954, p. 114–119.

(9) I. M. Hunsberger, *J. Am. Chem. Soc.*, **72**, 5626 (1950).

(10) L. J. Andrews and W. W. Kaeding, *J. Am. Chem. Soc.*, **73**, 1007 (1951).

methylacetophenone both afford shifts of 9 mμ[4]). In this way, an expected maximal absorption at 261 mμ is obtained, in excellent agreement with the experimentally obtained value of 262 mμ. It may be noted that the absorption of benzophenone may be related to the spectrum of acetophenone by assuming the non-planarity of the two benzene rings (*cf.* ref. 11) and this tends to justify the assumed bathochromic shift of 9 mμ for the *p*-methyl substituent. Jones[11] also noted a "suggestion of an inflection" near 280 mμ for benzophenone and this may correspond to the inflection observed for compound Ia at 287 mμ. The carbonyl band of Ia at 1661 cm.$^{-1}$ corresponds with the expected infrared absorption for a diaryl ketone, which is reported to occur between 1670 and 1660 cm.$^{-1}$[8]

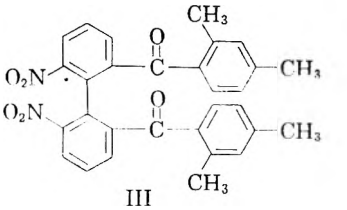
In compound Ib a type I steric effect, namely a reduced absorption intensity without appreciable wave length displacement, is observed (Table I). It should be compared with the change from *p*-methylacetophenone (λ_{max} 252 mμ, ϵ = 15,100) to 2,4-dimethylacetophenone (λ_{max} 251 mμ, ϵ = 14,000).[4] The greater intensity decreases in the series Ia, Ib may be ascribed either to further reduced biphenylic absorption, or more generally to secondary steric interactions caused by the introduction of two additional methyl groups into an already crowded system. The carbonyl band at 1664 cm.$^{-1}$ again lies between the limits as stated for Ia; the shift of 3 cm.$^{-1}$ relative to Ia may be compared with a similar shift occurring between *p*-methylacetophenone (1687 cm.$^{-1}$) and *o*-methylacetophenone (1690 cm.$^{-1}$),[12] and may be indicative of steric interaction.

Compound Ic also exhibits a pronounced steric effect (a wave length displacement of 8 mμ relative to Ib and a definite decrease in absorption intensity) on introducing a second ortho-substituent in the benzophenone system. The change should be compared with a similar wave length displacement occurring between 2,4-dimethylacetophenone (λ_{max} 251 mμ, ϵ = 14,100) and 2,4,6-trimethylacetophenone (λ_{max} 242 mμ, ϵ = 3600).[4] It may be noted that the spectral change from Ib to Ic can be regarded as a type II steric effect. Alternatively, the spectrum of Ic compared to that of compound II (Table I) does not show a wave length displacement of the B-band, and the change may consequently also be regarded as a type I steric effect. This illustrates a general principle: namely that a steric effect, apparently type II, may actually represent a type I steric effect. In the particular example of the 2,2′-diaroylbiphenyls a possible explanation comes readily to mind; that is, in compound Ic transitions involving the phenyl ring of the biphenyl system are preferred for steric reasons to transitions involving the 2,2′-disubstituted phenyl ring. In this way, the spectrum of Ic reverts to the spectrum of compound II. In the acetophenone series also, acetophenone, *o*-methylacetophenone, and 2,4,6-trimethylacetophenone are reported to absorb at 242 ± 1 mμ.[4] However, the explanation there is less readily obvious and the relevant discussion will be deferred for the present.

For the compound Id, the B-band is similar to that of Ic. This is in agreement with the hypothesis that for compounds Ic and Id transitions occur preferentially which involve the phenyl ring of the biphenyl system. Transitions involving the phenyl ring of the biphenyl system may also account for the somewhat greater residual absorption intensity of the B-band in the present series (Ic and Id), compared to the absorption intensities of 2,4,6,-trimethyl-[4] and 2,3,5,6-tetramethylacetophenones.[12] On the other hand, there is some evidence that transitions involving the other phenyl rings also contribute to the observed absorption. This is indicated by the C-band which shows the characteristic shift to longer wave length (Table I) and this relates with the known sensitivity of this band to *meta*-substituents. (*Cf.*, for example, the C-bands of 2,4-dimethyl- and 2,5-dimethylacetophenones which are reported to absorb maximally at 282 and 296 mμ respectively.)[4] The carbonyl bands for compounds Ic and Id at 1673 and 1674 cm.$^{-1}$, not unexpectedly, now also occur outside the limits recorded for diaryl ketones (1670–1660 cm.$^{-1}$),[8] and approach the values found for compound II (1699 cm.$^{-1}$).

The absorption of compound Ie, by analogy with the other compounds, would be anticipated to be similar to that of 1-naphthophenone or to that of a PhCOR entity as in Ic or Id. The infrared carbonyl band for Ie at 1660 cm.$^{-1}$ indicates a resemblance with compound Ia (1661 cm.$^{-1}$) rather than with 1-acetonaphthone, which in 0.02 molar carbon tetrachloride solution is reported to occur at 1685 cm.$^{-1}$.[9] Since, however, the B-band occurs only as an inflection, no definite assignment seems warranted.

Compound III is an *o,o*′-tetrasubstituted biphenyl in which the blocking 6,6′-nitro groups ensure optical stability. It would be expected therefore that in III, the two phenyl rings of the biphenyl system become electronically independent, and the absorption spectra of the system would revert to a 1,2-disubstituted nitrobenzene chromophore.



III

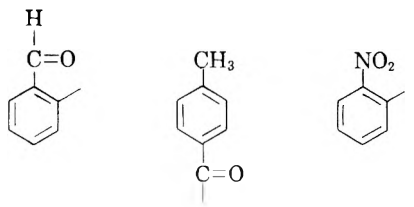
(11) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(12) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **35**, 488 (1957).

It was observed that the band shape of compound III differs from that of compounds in the I series. A maximal absorption occurs in ethanol at 257 mμ. Nitrobenzene and a number of ortho-substituted nitrobenzenes similarly absorb maximally in ethanolic solution. For example, 2-carboxy-4,5-dimethoxy-2′-nitrobiphenyl absorbs maximally at 256 mμ (ϵ = 16,000), and 2-carboxy-4,5-dimethoxy-2′-nitro-3′-methylbiphenyl, which is slightly more sterically hindered because of the buttressing effect of the additional methyl group, still absorbs at 256 mμ (ϵ = 10,700).[13] Therefore this maximal absorption of compound III is ascribed to nitrobenzene absorption.

Further, since compound III is also a meta-substituted nitrobenzene, it would be anticipated to afford an absorption spectrum of a meta-disubstituted benzene. That is, no appreciable resonance interaction occurs between the two substituents, and the molecule absorbs essentially as two monosubstituted benzenes. It follows that the electronic spectrum would include nitrobenzene absorption. It also follows that the maximal absorption due to the 2,4-dimethylbenzoyl moiety, which in Ib is located at 260 mμ, should occur in the absorption spectrum of III. Now, it is known that a nitro group in the meta position gives rise to an interaction which often causes an appreciable hypsochromic shift.[14] For example, in ethanolic solution the acetophenone band at 240 mμ occurs in *m*-nitroacetophenone at 226 mμ and a similar hypsochromic shift is observed in hexane solution. Therefore, we would anticipate in the spectrum of III a second maximal absorption near 260 mμ − 14 mμ = 246 mμ, and the observed maximal absorption at 243 mμ presumably corresponds to this band.

The 2,2′-diaroylbiphenyls have in this way been shown to give rise to B-bands corresponding to the following chromophoric systems within the molecule:



Depending on the substituents, absorptions corresponding to any one of these chromophoric systems may predominate, and the steric effects arising in the electronic spectra are classified as mainly type I steric effects.

Nitrobenzene, as will be shown elsewhere,[14] therefore provides a good illustration of type I steric effects, and may also, because of the large effective interference radius of the nitro group, be used to illustrate secondary steric interactions such as the buttressing effect. The carbonyl band of III at 1671 cm.$^{-1}$ lies between that of compound Ib (1664 cm.$^{-1}$) and that of compound Ic (1673 cm.$^{-1}$). Since the change in the carbonyl bands from Ib to Ic has been tentatively ascribed to increased steric inhibition of resonance, the value of 1671 cm.$^{-1}$ for compound III may also correspond to increased steric interactions in the 2,4-dimethylbenzophenone chromophores because of the nitro groups. The hypothesis receives support since III is an optically stable biphenyl isomer. The hypothesis of increased steric interaction may also explain the slight discrepancy (3 mμ) between the calculated and observed values for the second B-band at 243 mμ in compound III.

Finally, Braude, and Sondheimer[4] have indicated that electronic absorption spectra are a less sensitive index of steric effects than reaction rates. It is perhaps significant, then, that the indicated order of increasing steric interference Ia, Ib, Ie, Ic, and Id (B-bands, Table I) based on ultraviolet measurements is inversely related to the rates of lead tetraacetate cleavage of the cis-9,10-diaryl-9,10-dihydro-9,10-phenanthrendiols,[2b] obtained, respectively, from these diketones.[2a]

EXPERIMENTAL[15]

Infrared absorption spectra. Carbonyl absorption measurements were made by Dr. Lester P. Kuhn at the Ballistics Research Laboratory, Aberdeen Proving Ground, Md., with a Perkin-Elmer Model 12B Spectrometer equipped with LiF optics; Concn., 10 mg./ml., cell thickness, 0.1 mm., $CHCl_3$ solvent.

Ultraviolet absorption spectra. Ultraviolet absorption measurements were made in a Beckmann Quartz Spectrophotometer Model DU or in a Unicam Spectrophotometer Model SP 500 using 1-cm. quartz cells.

Preparation of compounds. Details of preparation and properties of compounds Ia, Ib, Ic, Id, Ie, and II, may be found in ref. 2.

(+)*6,6′-Dinitro-2,2′-di(2,4-dimethylbenzoyl)biphenyl* (III), m.p. 222–224°, $[\alpha]_D^{25}$ +145.8 (c = 0.60, acetone), was prepared in 85% yield from a Friedel-Crafts reaction between *m*-xylene and (+)6,6′-dinitro-2,2′-diphenoyl chloride.

Anal. Calcd. for $C_{30}H_{24}O_6N_2$: C, 70.85; H, 4.75. Found: C, 70.74; H, 4.64.

(+)*6,6′-Dinitro-2,2′-diphenoyl chloride,* m.p. 155–157°, $[\alpha]_D^{25}$ +55.0 (c = 1.10, $CHCl_3$) was prepared in 96% yield from $SOCl_2$ and (+)6,6′-dinitro-2,2′-diphenic acid,[16] m.p. 230–231°, $[\alpha]_D^{25}$ +132.0 (c = 0.50, methanol).

Acknowledgment: The authors wish to thank the Research Corp. for grants supporting this work, and Dr. Lester P. Kuhn for the infrared absorption data.

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(13) W. F. Forbes and W. A. Mueller, *J. Am. Chem. Soc.*, **79**, 6495 (1957).

(14) W. F. Forbes, *et al.*, unpublished information.

(15) All melting points are uncorrected. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(16) This compound was generously supplied to us by Professor Kurt Mislow, New York University, University Heights, N. Y.

[CONTRIBUTION NO. 1015 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Reaction of 1-Alkynes with Organometallic Compounds. VII.[1] Rate of Reaction of Hexyne-1 with Methyl- and Ethylmagnesium Halides in the Presence of Triethylamine

JOHN H. WOTIZ,[2] C. A. HOLLINGSWORTH, R. E. DESSY,[2a] AND LUNG CHING LIN[3]

Received August 7, 1957

The addition of triethylamine to ether solutions of Grignard reagents increases their reactivity toward hexyne-1. The increased reactivity is a function of the amount of the added amine, and the nature of the alkyl group and the halogen of the Grignard reagent. Triethylamine has no effect upon the rate of reaction of halogen-free diethylmagnesium with hexyne.

The rate of reaction of equivalent quantities of RMgX (R = CH_3, C_2H_5; X = Cl, Br, I) with hexyne-1, $C_4H_9C{\equiv}C{-}H$, in the presence of various amounts of triethylamine cosolvent was determined. Fig. 1 represents the dependence of the relative reactivities[4] of such reactions as determined from their half lives, upon the triethylamine concentration.

EXPERIMENTAL

The Grignard reagents were prepared and purified as previously described.[4,5] *Diethylmagnesium* was the same as previously described.[6] *Ethylmagnesium bromide in triethylamine* was prepared by the addition of freshly distilled ethyl bromide in purified[5] triethylamine to a suspension of magnesium in triethylamine. After the exothermic reaction ceased, the solution was decanted into a nitrogen-filled bottle which was sealed with a serum cap. When the solution had remained at room temperature for a day, a precipitate formed. The clear supernatant liquid was forced into a smaller amber-colored storage bottle capped with a serum stopper. The concentration was determined by the Zerewitinoff method and found to be 0.38 molar. *The apparatus and the rate determinations* were the same as previously described.[5] In order to minimize the solubility of the evolved hydrocarbon, R—H, the reaction mixture was kept refluxing throughout the reaction. The reflux temperature increased proportionately with an increase in the concentration of amine. The increase was less than three degrees when the amine concentration was less than one molar. The increase was four and seven degrees when the amine concentration was two and three molar, respectively. The relative reactivities were not corrected for these differences in temperature of the refluxing mixture. The reaction in the absence of ether was kept at 36° ± 2 by thermostating the reaction flask. Duplicate measurements showed a precision of ±3.0% (average deviation from the mean) provided the relative reactivity was not greater than 800. In faster reactions it was more difficult to maintain the pressure of 1 atm. during the reaction. In these cases the data are only good estimates of the rate of the reaction.

The observed rates are not a function of the time lapse[6] between the addition of the triethylamine to the Grignard reagent and the start of reaction brought about by the addition of hexyne. Thus in reactions where 30 sec., 5 min., or 4 hr. were permitted to elapse between the addition of triethylamine and the hexyne-1, the same values for the half lives were obtained.

DISCUSSION

Examination of the data in Table I and Fig. 1 reveals several important facts. The changing of

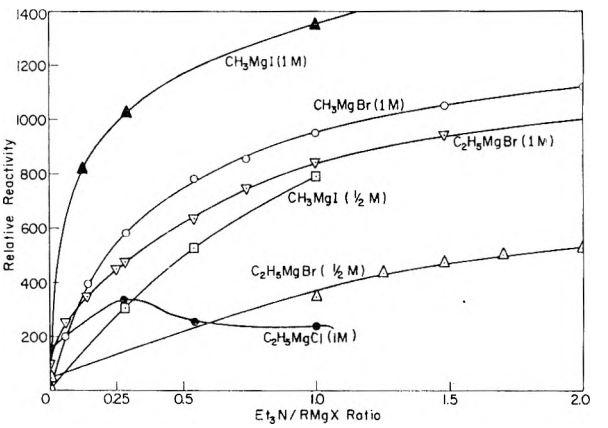

FIG. 1 RELATIVE REACTIVITIES AS A FUNCTION OF THE MOLE RATIO OF $(C_2H_5)_3N$ TO RMgX.

TABLE I

RELATIVE REACTIVITY OF EQUIVALENT QUANTITIES RMgX AND $C_4H_9C{\equiv}C{-}H$ IN THE PRESENCE OF $(C_2H_5)_3N$

RMgX	Molar Conc. of Solution	Relative Reactivity $(C_2H_5)_3N$, Molar Conc. 0	0.25	0.5	1.0	19.0[a]
CH_3MgI	1.0	7	1000	1170	1350	...
CH_3MgI	0.5	3	500	790	...	...
CH_3MgBr	1.0	7	560	750	950	...
C_2H_5MgBr	1.0	100[b]	450	620	840	...
C_2H_5MgBr	0.5	48	210	340	520	...
C_2H_5MgBr	0.38	...	...	...	...	469[c]
C_2H_5MgCl	1.0	160[d]	...	...	240[d]	...
$(C_2H_5)_2Mg$	0.5	300	...	...	300	...

[a] No ether present. [b] Standard of reference.[4] [c] A saturated solution of C_2H_5MgBr in $(C_2H_5)_3N$ is 0.38 molar. [d] Reacting mixture was heterogeneous.

(1) Part VI, *J. Am. Chem. Soc.*, 79, 358 (1957).

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(3) Abstracted from thesis of L. C. L. presented in partial fulfillment of the requirement for the degree of Master of Science, 1957. (Present address: Department of Chemistry, National Taiwan University, Taipei, Formosa, China).

(4) J. H. Wotiz, C. A. Hollingsworth and R. E. Dessy, *J. Am. Chem. Soc.* **77**, 103 (1955).

(5) J. H. Wotiz, C. A. Hollingsworth and R. E. Dessy, *J. Org. Chem.* **20**, 1545 (1955).

(6) J. H. Wotiz, C. A. Hollingsworth and R. E. Dessy, *J. Am. Chem. Soc.* **78**, 1221 (1956).

the halogen in a given alkylmagnesium halide produces a difference in the rate of reaction. The iodide is more affected by the presence of amine than the bromide and chloride. There is a reversal in the order of reactivity in case of CH_3MgBr and CH_3MgI brought about by triethylamine cosolvent. However, the addition of amine does not change the rate of reaction of a halogen-free solution of diethylmagnesium.

Triethylamine increases the rate of reaction of hexyne with methylmagnesium halides more than with ethylmagnesium halides. Thus the order of reactivity of methyl- and ethylmagnesium bromides (1 molar solution) is reversed if at least 0.1 mole-equivalent of triethylamine is present.

Because of the variation of the temperature during the reaction, it is not possible to determine accurately the rate laws from the individual gas evolution curves. However, casual inspection of the data indicates that the reactions are approximately second order. Thus, it can be seen from Table I that the relative reactivities are approximately doubled when the concentrations of the alkylmagnesium halide and the hexyne are both doubled, the molarity of amine being constant.

The influence of triethylamine upon the rate of reaction of the Grignard reagent with hexyne cannot be the result of a shift in the Schlenk equilibrium[6,7] since the relative reaction of halogen-free diethylmagnesium

$$2\ RMgX \rightleftharpoons R_2Mg\cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2$$

is independent of the amine concentration. This is likely due to the existence of a different mechanism of reaction. However the coordination of the amine with the magnesium atom of reacting species is not an important factor in determining the rate of reaction.

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(7) J. H. Wotiz, C. A. Hollingsworth, and R. E. Dessy, *J. Org. Chem.*, 21, 1063 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Conjugate Addition Condensations of Diphenylmethane Involving Methylene Hydrogen by Potassium Amide. Cyclizations of Products by Polyphosphoric Acid[1]

MARVIN T. TETENBAUM AND CHARLES R. HAUSER

Received August 12, 1957

Potassium diphenylmethide, prepared from diphenylmethane and potassium amide, was condensed through conjugate addition with ethyl cinnamate, and the resulting ester was cyclized by means of polyphosphoric acid to form a cyclic ketone. Potassium diphenylmethide also underwent conjugate addition with benzalacetophenone and α-phenylcinnamonitrile but these products failed to be cyclized by polyphosphoric acid. Potassium diphenylmethide underwent with ethoxymethylenemalonic ester conjugate addition accompanied by elimination to form an ester that yielded an aromatic product on cyclization.

Diphenylmethane has previously been shown to enter into several types of carbon-carbon condensations through the metalation of its α-hydrogen by means of sodium or potassium amide in liquid ammonia. Thus, this hydrocarbon has been alkylated,[2] acylated,[3] carbethoxylated,[3] carbonated,[3] and condensed with the carbonyl group of ketones or aldehydes.[4] An example of the alkylation that has been realized quantitatively is represented by Equation 1.[2]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{NaNH_2} (C_6H_5)_2CHNa \xrightarrow{C_6H_5CH_2Cl} (C_6H_5)_2CHCH_2C_6H_5 \quad (1)$$

In the present investigation, diphenylmethane was found to undergo through its potassium or sodium derivative still another type of condensation, involving conjugate addition with α,β-unsaturated carbonyl compounds or nitriles. This type of condensation is of special interest since certain of the products obtained were cyclized by means of polyphosphoric acid. These reactions will be considered on the basis of the α,β-unsaturated compound empolyed.

Reaction with ethyl cinnamate. Potassium diphenylmethide, prepared from molecular equivalents of diphenylmethane and potassium amide in liquid ammonia containing some ether, underwent conjugate addition with an equivalent of ethyl cinnamate in this medium to form ester I, which was saponified to give acid II in 84% overall yield (Equation 2).

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) C. R. Hauser and P. J. Hamrick, Jr., *J. Am. Chem. Soc.*, 79, 3142 (1957).

(3) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, 69, 2325 (1947).

(4) P. J. Hamrick, Jr., and C. R. Hauser, unpublished results.

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{KNH_2} (C_6H_5)_2CHK \xrightarrow[2.\ HCl]{1.\ C_6H_5CH{=}CHCOOC_2H_5}$$

$$C_6H_5CHCH_2COOC_2H_5 \xrightarrow[2.\ HCl]{1.\ KOH} C_6H_5CHCH_2COOH \quad (2)$$
$$(C_6H_5)_2CH \qquad\qquad (C_6H_5)_2CH$$
$$\text{I} \qquad\qquad \text{II}$$

Under similar conditions, sodium diphenylmethide produced a lower yield of ester I. These conjugate additions, especially that with sodium diphenylmethide, might have been accompanied by some 1,2 addition leading to the formation of ketone III but neither this ketone nor condensation products with the alkali diphenylmethide were isolated. A small amount of a solid besides ester I was obtained with sodium diphenylmethide, but it was not identified.

$$C_6H_5CH{=}CH{-}C{=}O$$
$$\qquad\qquad |$$
$$\qquad (C_6H_5)_2CH$$
$$\qquad\quad \text{III}$$

Bergmann[5] has observed that sodium diphenylmethide, prepared from benzhydrylmethyl ether and metallic sodium underwent mainly conjugate addition with methyl or ethyl cinnamate (Equation 3) although some 1,2-addition also appeared to take place. No yields were reported.

$$(C_6H_5)_2CH{-}OCH_3 \xrightarrow[\text{ether}]{Na}$$
$$(C_6H_5)_2CHNa \xrightarrow[\text{ether}]{C_6H_5CH{=}CHCOOC_2H_5} \text{I} \quad (3)$$

The present method starting with diphenylmethane (Equation 2) is more convenient than that of Bergmann since not only is this hydrocarbon more available than benzhydrylmethyl ether, but the cleavage of this ether by sodium has been somewhat tedious.[6]

The mechanism for the conjugate addition presumably involves the attack of the diphenylmethide ion at the β-carbon of ethyl cinnamate to form anion IV from which ester I is obtained on acidification (Equation 4).

$$C_6H_5CH{=}\overset{\curvearrowright}{CH}{-}\overset{\curvearrowright}{C}{=}O \xrightarrow[\text{liq. } NH_3]{(C_6H_5)_2CH}$$
$$\qquad\qquad |$$
$$\qquad\quad OC_2H_5$$

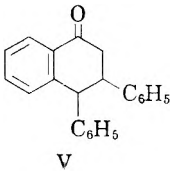
$$C_6H_5CH{-}CH{=}C{-}O^- \xrightarrow{HCl} \text{I} \quad (4)$$
$$(C_6H_5)_2CH \qquad\quad OC_2H_5$$
$$\text{IV (one resonance form)}$$

Although the related Michael type of condensation of malonic ester or other active methylene carbonyl compound with ethyl cinnamate is known to require only a catalytic amount of base such as ethoxide ion,[7] the conjugate addition of diphenylmethane with this ester was not realized satisfactorily when a catalytic amount of potassium amide was employed. Thus, whereas an equivalent of potassium amide gave within 15 minutes an 84% yield of acid II (after hydrolysis of ester I), twenty mole percent of this base produced during five hours only a 24% yield of acid II through ester I. Since the conversion of diphenylmethane to potassium diphenylmethide by potassium amide is essentially complete,[8] twenty mole percent of this hydrocarbon was first converted to potassium diphenylmethide which underwent conjugate addition with the corresponding amount of ethyl cinnamate to form anion IV (Equation 4). However, the ionization of the remaining diphenylmethane by anion IV, which would presumably be required for further conjugate addition to occur, evidently proceeded very slowly under the conditions employed. This may be ascribed to an unfavorable acid-base reaction, the equilibrium of which is probably far on the side of unchanged diphenylmethane and anion IV (Equation 5). It is to be noted that whereas the conjugate addition stops at anion IV when an equivalent of potassium amide is employed, this anion is converted to the neutral

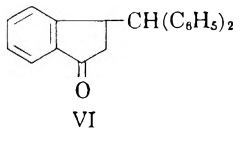
$$(C_6H_5)_2CH_2 + C_6H_5CH{-}CH{=}C{-}O^- \rightleftharpoons$$
$$\qquad\qquad\quad (C_6H_5)_2CH \qquad\quad OC_2H_5$$
$$\qquad\qquad\qquad\quad \text{IV}$$
$$(C_6H_5)_2\bar{C}H + C_6H_5CHCH_2C{=}O \quad (5)$$
$$\qquad\qquad\quad (C_6H_5)_2CH \qquad OC_2H_5$$
$$\qquad\qquad\qquad\quad \text{I}$$

ester I when a catalytic amount of the base is successful.[7]

The conjugate addition represented by equation 2 is of interest not only as a convenient method of synthesis of ester I and acid II, but also because this ester or acid underwent cyclization with polyphosphoric acid, involving the loss of ethanol or water to form a ketone that analyzed for tetralone V or hydrindone VI. The presence of the ketone group was indicated by conversion of a sample of the product to the corresponding 2,4-dinitrophenylhydrazone. The over-all yield of the ketone from diphenylmethane through ester I was about 50%.



V



VI

This acid-catalyzed cyclization of ester I or acid II seems likely to have produced tetralone V rather than hydrindone VI, since the related Friedel-

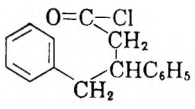
(5) E. Bergmann and O. Blum-Bergmann, *J. Chem. Soc.*, 727 (1938).

(6) E. Bergmann, *J. Chem. Soc.*, 412 (1936).

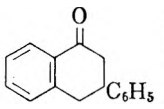
(7) See E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, pp. 791, 792.

(8) This conclusion is based on the earlier observation (ref. 2) that diphenylmethane undergoes essentially complete metalation with sodium amide in liquid ammonia.

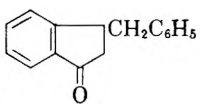
Crafts type cyclizations of similar acid chlorides have been shown to yield six membered rings in preference to five.[9] For example, acid chloride VII has given tetralone VIII rather than the possible hydrindone IX.[10]



VII

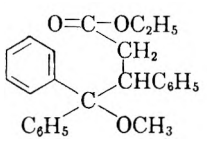


VIII

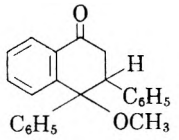


IX

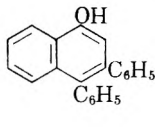
Moreover, ether-ester X has been cyclized by polyphosphoric acid to form the ether-ketone XI which was aromatized by hydrogen fluoride to give naphthol XII.[11]



X



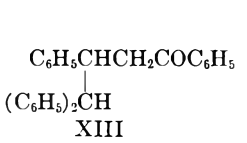
XI



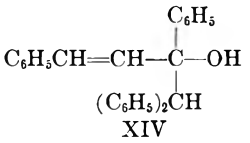
XII

Since the present product, presumably tetralone V, was readily isolated as a sharp melting solid, it evidently consisted largely of only one of the two possible diastereoisomers.

Reactions with benzalacetophenone and α-phenylcinnamonitrile. Under the conditions employed with ethyl cinnamate, potassium diphenylmethide reacted with benzalacetophenone to form a compound that analyzed for either the conjugate addition product or the 1,2-addition product, XIII or XIV, respectively.



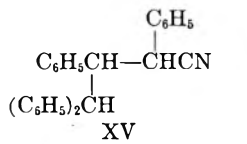
XIII



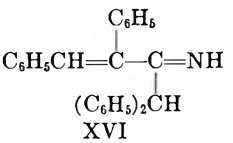
XIV

That the product was ketone XIII and not the isomeric carbinol XIV was shown by its infrared absorption spectrum which gave a strong band for the carbonyl group but none for the hydroxyl group. Moreover, the product was stable toward acid as might be expected for ketone XIII but not for carbinol XIV which should readily undergo dehydration.

Similarly potassium diphenylmethide reacted with α-phenylcinnammonitrile to form a compound that analyzed for either the conjugate addition product or the 1,2-addition product, XV and XVI respectively.



XV



XVI

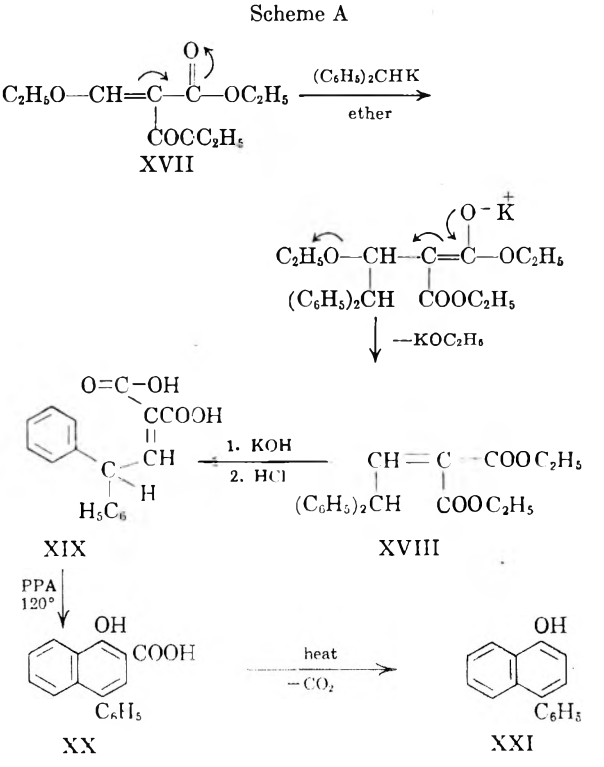
That the product was nitrile XV and not the isomeric imine XVI was indicated by its infrared absorption spectrum which showed a definite (although weak) band for the nitrile group but none for the imine group.

Attempts to hydrolyze the nitrile group of XV with concentrated sulfuric acid or with aqueous or alcoholic potassium hydroxide were unsuccessful. Had the product been imine XVI, it might be expected to have undergone hydrolysis under these conditions to form the corresponding ketone, but the original compound was recovered.

In contrast to ester I from the conjugate addition with ethyl cinnamate, ketone XIII and nitrile XV failed to undergo cyclization with polyphosphoric at 125–130°, or even at 200° (in the case of ketone XIII), the starting compounds being recovered.

Reaction with ethoxymethylenemalonic ester. Besides the ordinary α,β-unsaturated carbonyl compounds employed in the experiments described above, ethoxymethylenemalonic ester (XVII) was used with potassium diphenylmethide after the liquid ammonia had been replaced by ether. The reaction that resulted evidently involved conjugate addition accompanied by elimination of ethoxide ion to form ester XVIII, which possesses sufficient unsaturation to produce an aromatic ring on cyclization. Such a cyclization was realized with the corresponding carboxylic acid XIX by means of polyphosphoric acid (PPA) to given naphthol-acid XX in an overall yield of 47% from diphenylmethane or ester XVII. These reactions are represented in Scheme A.

Scheme A



(9) See W. S. Johnson, *Org. Reactions*, II, 116 (1944).
(10) J. v. Braun and G. Manz, *Ann.*, **468**, 258 (1929).
(11) C. R. Hauser and M. T. Tetenbaum, *J. Org. Chem.*, **23**, 233 (1958).

These reactions furnish a convenient method for the synthesis of naphthol-acid XX which appears not to have been described previously. The structure of this product was established as XX by decarboxylation to form the corresponding naphthol XXI which is a known compound (see Scheme A).

EXPERIMENTAL[12]

Conjugate addition with ethyl cinnamate to form ester I and acid II. To a stirred solution of 0.2 mole of potassium amide in 300 ml. of anhydrous liquid ammonia[3] was added 33.6 g. (0.2 mole) of diphenylmethane in an equal volume of anhydrous ether, and the resulting dark orange solution of potassium diphenylmethide was stirred for 15 min. A solution of 35.2 g. (0.2 mole) of ethyl cinnamate in an equal volume of anhydrous ether was added with stirring. The color was discharged and a heavy white precipitate formed. The ammonia was evaporated on the steam bath as an equal volume of anhydrous ether was added, and the resulting ether suspension was refluxed for 15 min. Excess iced hydrochloric acid was added, and the two layers were separated. The aqueous layer was extracted three times with ether, and the ether extracts combined with the ether layer. The ethereal solution was dried over Drierite, and the solvent removed. The oily residue was cooled in the refrigerator for three days to give 66 g. of ethyl 3,4,4-triphenylbutyrate (I) as a white, amorphous solid which resisted satisfactory recrystallization.

A sample (10 g.) of ester I was saponified with aqueous potassium hydroxide, and the resulting mixture acidified with iced hydrochloric acid. The precipitate was collected on a funnel, and recrystallized from 50% acetic acid to give 8 g. (84% based on diphenylmethane) of 3,4,4-triphenylbutyric acid (II) m.p. 174–177°. After another recrystallization this acid melted at 178–179° (reported m.p. 178°).[5]

When the conjugate addition reaction was repeated on a 0.1 molar scale employing sodium amide[13] instead of potassium amide, there were obtained 23 g. of ester I, 1 g. of an unidentified solid, m.p. 148–149°, and 6 g. of a recovered mixture of diphenylmethane and ethyl cinnamate.

When the conjugate addition reaction was carried out in a similar manner employing 0.2 mole each of diphenylmethane and ethyl cinnamate, and only 0.02 mole of potassium amide (refluxed 5 hours in the liquid ammonia-ether mixture), there were obtained 23 g. of ester I, and 33 g. of a mixture of recovered diphenylmethane and ethyl cinnamate. Saponification of an 8 g. sample of ester I gave 2.6 g. of acid II, m.p. 174–177°, which corresponds to a 24% yield of the conjugate addition product based on diphenylmethane.

Cyclization of ester I and acid II. A mixture of 8 g. of crude ester I and excess of polyphosphoric acid[14] was stirred and heated at 125–130° for 30 min. After cooling, ice water was added, and the resulting mixture extracted with ether. The ethereal solution was dried over Drierite, and the solvent removed, to leave 3 g. (50% based on diphenylmethane, of slightly colored cyclic ketone (V or VI), m.p. 157–160). This product was recrystallized twice from ether to give a white powder, m.p. 164.5–165°.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.72; H, 6.07.

In a similar manner, 3 g. of pure acid II was cyclized to give 1.6 g. (57%) of the cyclic ketone, m.p. 157–160°.

A sample of the cyclic ketone (V or VI) was converted to the corresponding 2,4-dinitrophenylhydrazone in the usual manner. The derivative melted at 290° after recrystallization from glacial acetic acid.

Anal. Calcd. for $C_{28}H_{22}N_4O_4$: N, 11.71. Found: N, 11.65.

Conjugate addition with benzalacetophenone to form ketone XIII. To a stirred solution of potassium diphenylmethide, prepared from 0.1 mole each of potassium amide and diphenylmethane in 300 ml. of liquid ammonia and about 50 ml. of ether, was added 20.8 g. (0.1 mole) of solid benzalacetophenone. Most of the color was discharged. After stirring for 1 hr., the liquid ammonia was replaced by ether, and the resulting brown ether suspension was refluxed for 15 min. Iced hydrochloric acid was added, and the resulting white precipitate of 2,3,3-triphenylbutyrophenone (XIII) was collected on a funnel. More of this ketone was recovered from the aqueous-ethereal filtrate. The total yield was 30 g. (80%), m.p. 181–183°. After two recrystallizations from a mixture of chloroform and petroleum ether (b.p. 30–60°), the ketone melted at 187–188°.

Anal. Calcd. for $C_{25}H_{24}O$: C, 89.32; H, 6.43. Found: C, 89.11; H, 6.40.

An infrared absorption spectrum of this ketone gave a strong band at 5.94 μ showing the presence of the carbonyl group. Attempts to convert samples of this compound to the oxime or the 2,4-dinitrophenylhydrazone under the usual conditions were unsuccessful.

Also, this ketone was recovered after treatment with polyphosphoric acid at 125–130° or at 200° for 30 min., or with concentrated sulfuric acid at room temperature for 1 hr.

Reaction with α-phenylcinnamonitrile. To a stirred solution of potassium diphenylmethide, prepared from 0.1 mole each of potassium amide and diphenylmethane in 300 ml. of liquid ammonia and 50 ml. of ether, was added 20.5 g. (0.1 mole) of solid α-phenylcinnamonitrile. The greenish mixture was stirred for 15 min., and the liquid ammonia then replaced by ether. The resulting tan colored ether suspension was refluxed for 15 min., and iced-hydrochloric acid then added. The resulting mixture (which contained much solid) was extracted three times with ether, and the combined ether extracts dried over Drierite. The solvent was removed, leaving 23 g. (62%) of white nitrile XV (or immine XVI) m.p. 210–211°. Two recrystallizations from a mixture of chloroform and ether gave white needles, m.p. 211–211.5° (softening slightly at 175°).

Anal. Calcd. for $C_{28}H_{23}N$: C, 90.05; H, 6.21; N, 3.75. Found: C, 89.92; H, 6.34; N, 3.84.

An infrared absorption spectrum of this product gave a weak band at 4.48 μ indicating the presence of the nitrile group.

This product was recovered when treated with polyphosphoric acid at 125–130° for 30 min., liquid hydrogen fluoride at room temperature, aqueous and alcoholic refluxing potassium hydroxide solution for 5 hr., and concentrated sulfuric acid for 1 hr. on the steam bath.

Reaction with ethoxymethylenemalonic ester and cyclization. A solution of potassium diphenylmethide was prepared from 0.1 mole each of potassium amide and diphenylmethane in 300 ml. of liquid ammonia, and the liquid ammonia was replaced by anhydrous ether. After refluxing for 15 min., 21.6 g. (0.1 mole) of ethoxymethylenemalonic ester in an equal volume of anhydrous ether was added with stirring and the resulting ether suspension refluxed for 1 hr. After hydrolysis with iced hydrochloric acid, the ether layer was separated and combined with three ether extracts of the aqueous layer. The ethereal solution was dried over Drierite, and the solvent removed. The oily residue was distilled in vacuo until 9 g. of a mixture of diphenylmethane and ethoxymethylenemalonic ester were recovered, leaving a residue of ester XVII which was saponified with aqueous potassium hydroxide. The resulting acid XIX, obtained on acidification with hydrochloric acid, was stirred and heated with excess polyphosphoric acid at 120° for 30 min. After cooling, iced hydrochloric acid was added and the precipitate was recrystallized three times from a mixture of chloroform and

(12) Melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(13) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions* VIII, 122 (1954).

(14) We are indebted to the Victor Chemical Works, Chicago, Ill., for a generous sample of polyphosphoric acid.

ligroin (b.p. 60–90°) to give 12.5 g. (47% overall yield) of 1-hydroxy-4-phenyl-2-naphthoic acid (XX), m.p. 227–228° dec.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.02; H, 4.47.

This compound gave a greenish-blue coloration with aqueous-alcoholic ferric chloride.

Decarboxylation of naphthol-acid XX. An 0.18 g. sample of naphthol-acid XX was heated above its melting point in a covered crucible. The resulting tarry material was recrystallized from a mixture of chloroform and ligroin (b.p. 60–90°) to produce 0.10 g. (67%) of 4-phenyl-1-naphthol (XXI) as a brownish powder, m.p. 139–140° (lit. value 140°).[15] This compound gave a dark blue coloration with aqueous alcoholic ferric chloride.

DURHAM, N. C.

(15) W. Borsch, S. Kettner, M. Giles, H. Kuhn, and R. Manteuffel, *Ann.*, 526, 21 (1936).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensations of Benzhydryl Methyl Ether Involving α-Hydrogen by Potassium Amide. Cyclization of Conjugate Addition Product by Polyphosphoric Acid[1]

CHARLES R. HAUSER AND MARVIN T. TETENBAUM

Received August 12, 1957

The α-hydrogen of benzhydryl methyl ether was metalated by means of potassium amide, and the resulting potassium derivative then condensed with benzyl chloride and ethyl cinnamate. The product from the latter condensation was cyclized by means of polyphosphoric acid to form a methoxytetralone which was subsequently aromatized by means of hydrogen fluoride to give a naphthol. Some other reactions were also effected.

It is well known that one of the methylene hydrogens of diphenylmethane can be metalated readily by means of sodium amide or potassium amide in liquid ammonia, and that the resulting alkali diphenylmethide can serve as the carbanion component in several useful types of carbon-carbon condensations. One of these types of reaction involves alkylation, certain of which have been effected quantitatively (Equation 1).[2]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{NaNH_2} (C_6H_5)_2CHNa \xrightarrow{C_6H_5CH_2Cl} (C_6H_5)_2CHCH_2C_6H_5 \quad (1)$$

Another type of condensation involves conjugate addition such as that with ethyl cinnamate, which has been realized in good yield (Equation 2).[3]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{KNH_2} (C_6H_5)_2CHK \xrightarrow[2.\ HCl]{1.\ C_6H_5CH{=}CHCOOC_2H_5} \underset{\displaystyle (C_6H_5)_2CH}{\overset{\displaystyle C_6H_5CHCH_2COOC_2H_5}{|}} \quad (2)$$

It has now been found that the α-hydrogen of benzhydryl methyl ether (I) can be metalated similarly with potassium amide, and that the resulting potassium derivative can enter into the two analogous condensations with benzyl chloride and ethyl cinnamate to form ether II and ether-ester III in yields of 63% and 62%, respectively (Equations 3a and 3b).

$$(C_6H_5)_2CH{-}OCH_3 \xrightarrow[\text{liq. } NH_3]{KNH_2} \underset{\text{K}}{(C_6H_5)_2C{-}OCH_3} \xrightarrow{C_6H_5CH_2Cl} \underset{\text{II}}{(C_6H_5)_2C(CH_2C_6H_5){-}OCH_3} \quad (3a)$$

$$\xrightarrow[2.\ HCl]{1.\ C_6H_5CH{=}CHCOOC_2H_5} \underset{\text{III}}{C_6H_5CHCH_2COOC_2H_5 \text{ on } (C_6H_5)_2C{-}OCH_3} \quad (3b)$$

The conjugate addition with ethyl cinnamate (Equation 3b) might have been accompanied by some 1,2 addition to form α,β-unsaturated ketone IV, but neither this product nor products that might have arisen from its further reaction with the potassium derivative of benzhydryl methyl ether were isolated.

$$\underset{\text{IV}}{C_6H_5CH{=}CH{-}C(=O){-}C(C_6H_5)_2{-}OCH_3}$$

The reactions represented by equations 3a and 3b, in which the ether group remains intact, are to be distinguished from those reported by Bergmann[4] who cleaved benzhydryl methyl ether (I) by means of metallic sodium, and then employed the resulting sodium diphenylmethide in corresponding condensations. Such a cleavage, followed by alkylation, is illustrated by equation 4, the end result of which is analogous to that represented in Equation 1.

$$(C_6H_5)_2CH{-}OCH_3 \xrightarrow[\text{ether}]{Na} (C_6H_5)_2CHNa \xrightarrow{RX} (C_6H_5)_2CHR \quad (4)$$

(1) Supported by the Office of Ordnance Research, U. S. Army.

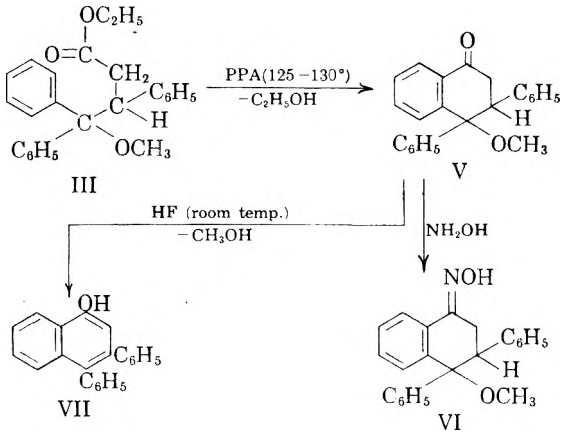
(2) C. R. Hauser and P. J. Hamrick, Jr., *J. Am. Chem. Soc.*, 79, 3142 (1957).

(3) M. T. Tetenbaum and C. R. Hauser, *J. Org. Chem.*, 23, 229 (1958).

(4) E. Bergmann, *J. Chem. Soc.*, 412 (1936); E. Bergmann and O. Blum-Bergmann, *J. Chem. Soc.*, 727 (1938).

The conjugate addition of the potassium derivative of benzhydryl methyl ether with ethyl cinnamate (Equation 3b) is of particular interest, since the resulting ester was cyclized by means of polyphosphoric acid (PPA) to form ether-ketone V in 90% yield. This cyclic product (V) was not only converted to the corresponding oxime (VI) but it was also aromatized by means of hydrogen fluoride to form a known naphthol (VII). These reactions are summarized in Scheme A.

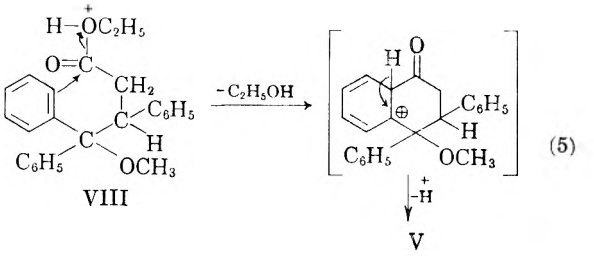
Scheme A



That the cyclization product from ether-ester III was ether-ketone V was established not only by the reactions shown in Scheme A but also by its infrared absorption spectrum which gave a strong band for the carbonyl group and none for an hydroxyl group. On the other hand, the infrared absorption spectrum of the product subsequently obtained on treatment with hydrogen fluoride showed a strong band for the hydroxyl group and none for a carbonyl group, in agreement with structure VII.

Since ether-ketone V was readily isolated as a sharp melting product, it appeared to consist largely of only one of the two possible diastereoisomers.

The mechanism for the cyclization of ether-ester III may be considered to involve the protonated intermediate VIII (Equation 5).



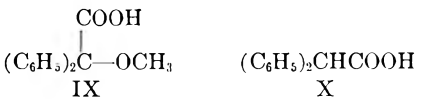
(5)

It seems rather remarkable that this cyclization of the protonated ether-ester VIII, involving the loss of ethanol, was not accompanied by the elimination of methanol (from the β,γ-position) to form naphthol VII since the methoxy group in both the starting ether-ester III and the product ether-ketone V was presumably also protonated by the excess of polyphosphoric acid employed.

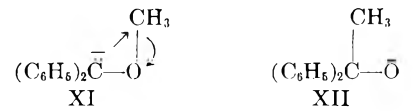
It should be mentioned that concentrated sulfuric acid at room temperature converted ether-ketone V to water soluble material which was presumably a sulfonated product. Boiling concentrated hydrochloric acid and potassium amide (two equivalents) in refluxing ether failed to affect ether-ketone V which was largely recovered. The latter reagent has been shown to effect the trans β-elimination of methanol from certain ethers having β-hydrogen activated by one or two phenyl groups.[5] Ether-ketone V was also recovered after being heated above its melting point.

It is noteworthy that, whereas strong acids failed to effect the aromatization of ether-ketone V to form naphthol VII, hydrogen fluoride brought about this reaction even at room temperature. Incidentally, an attempt to effect the overall cyclization and aromatization of ether-ester III to form naphthol VII by means of hydrogen fluoride produced only an alkali insoluble tar.

Other reactions of benzhydryl methyl ether. Besides the condensations in liquid ammonia described above, benzhydryl methyl ether (I) was carbonated through its potassium derivative, after replacing the ammonia by ether, to form ether-acid IX but the yield was low (10%). The corresponding carbonation of potassium diphenylmethide in ether to form acid X has been realized in 90% yield.[6]



It is possible that the reaction in ethyl ether was accompanied by the Wittig type of rearrangement (indicated in XI) to form the anion of diphenylmethylcarbinol (XII), but none of this carbinol was isolated



Certain benzyl ethers, for example, dibenzyl ether, have been observed to undergo such 1,2 shifts with potassium amide in ethyl ether.[7]

EXPERIMENTAL[8]

Benzhydryl methyl ether. This ether was prepared by a modification of the method of Bergmann.[9] A solution of 100 g. of

(5) P. J. Hamrick, Jr., S. W. Kantor, and C. R. Hauser, unpublished result.

(6) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 2325 (1947).

(7) C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

(8) Melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(9) E. Bergmann and J. Hervey, *Ber.*, **62**, 915 (1929).

benzhydryl bromide in 333 ml. of commercial absolute methanol was stirred overnight and an aqueous solution of potassium hydroxide was then added. The heavy organic layer was separated, and combined with several ethyl ether extracts of the aqueous layer. After drying over Drierite, the solvent was removed under reduced pressure on the steam bath, and the residual brown oil distilled *in vacuo* to give 77 g. (97%) of the colorless ether I, b.p. 129° at 5 mm. (reported b.p. 125° at 5 mm.;[10] 147–148° at 17 mm.).[9]

Alkylation of ether I to form ether II. To a stirred suspension of 0.1 mole of potassium amide[11] in 500 ml. of liquid ammonia was carefully added 19.8 g. (0.1 mole) of benzhydryl methyl ether in an equal volume of anhydrous ethyl ether. The resulting dark orange suspension of the potassium derivative was stirred for 15 min., and 12.7 g. (0.1 mole) of benzyl chloride in an equal volume of anhydrous ethyl ether then added. The color was discharged, and a white precipitate was formed. After stirring one hour, the liquid ammonia was evaporated on the steam bath as an equal volume of anhydrous ethyl ether was added. The resulting white suspension was refluxed 15 min., cooled, and decomposed with iced hydrochloric acid. The yellow ether layer was separated, and combined with several ether extracts of the aqueous layer. After drying over Drierite, the ethyl ether was evaporated under reduced pressure on the steam bath. The residual red-brown oil was worked up to give, after recrystallization from a mixture of methanol and benzene, 18 g. (63%) of white crystals of methyl 1,1,2-triphenylethyl ether (II), m.p. 90–91°. A second recrystallization raised the melting point to 93° in agreement with the literature value.[12]

Conjugate addition with ethyl cinnamate to form ether-ester. III. To the stirred dark orange suspension of the potassium derivative of benzhydryl methyl ether prepared from 0.1 mole each of potassium amide and ether I in 500 ml. of liquid ammonia and 50 ml. of ethyl ether, was added 17.6 g. (0.1 mole) of ethyl cinnamate in an equal volume of anhydrous ethyl ether. The color was mostly discharged. The liquid ammonia was replaced by anhydrous ethyl ether and the resulting suspension was refluxed on the steam bath for 30 min. The mixture was hydrolyzed with iced hydrochloric acid, and the yellow ether layer, after being combined with several ether extracts of the aqueous layer, was dried over Drierite. The solvent was removed to leave 23 g. (62%) of ethyl 3,4,4-triphenyl-4-methoxybutyrate (III) as a white crystalline compound, m.p. 130–133°. Three recrystallizations from ethyl ether raised the melting point to 139–140°.

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 80.18; H, 7.00. Found: C, 79.99; H, 7.07.

Cyclization of ether-ester III to form cyclic ketone V. A mixture of 7 g. of ethyl 3,4,4-triphenyl-4-methoxybutyrate (III) and excess of polyphosphoric acid[13] was stirred and heated at 125–130° for 30 min. The resulting brown solution was cooled, ice water added, and the mixture extracted with ethyl ether. The yellow ethereal solution was dried over Drierite, and the solvent removed under reduced pressure. There was obtained 6 g. (98%) of pale yellow 3,4-diphenyl-4-methoxy-1-tetralone (V) m.p. 104–106°. Three recrystallizations from ethanol gave white crystals, m.p. 106.5–107.5°.

Anal. Calcd. for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 84.17; H, 6.33.

An infrared absorption spectrum of this ether-ketone V gave a strong carbonyl band at 5.76 μ. A sample of this compound was converted to the corresponding oxime following the general directions of Shriner and Fuson.[14] After recrystallization from ethanol-water, the oxime (VI) was obtained as a white powder that softened at 140° and melted at 178°.

Anal. Calcd. for $C_{23}H_{21}O_2N$: C, 80.44; H, 6.16. Found: C, 80.69; H, 5.93.

Aromatization of ether-ketone V to form naphthol VII. To 138 g. of anhydrous liquid hydrogen fluoride contained in a polyethylene bottle was added one gram of 3,4-diphenyl-4-methoxy-1-tetralone (V) and the resulting dark solution allowed to evaporate in the hood at room temperature overnight. The dark residue was extracted with ether, and the ethereal solution was dried over Drierite. The solvent was removed, and the residual solid was taken up in potassium hydroxide solution. Iced-hydrochloric acid was added to precipitate 0.9 g. (98%) of yellowish pink 3,4-diphenyl-1-naphthol (VII) m.p. 143–144°, in agreement with the reported melting point.[15] This compound was almost white after being washed with petroleum ether (b.p. 30–60°). A recrystallization from ligroin (b.p. 60–90°) did not change the melting point. An infrared absorption spectrum gave a strong hydroxyl band at 2.77 μ.

This naphthol (0.9 g.) was boiled for one minute with 6 ml. of acetic anhydride and three drops of concentrated sulfuric acid essentially as described by Smith and Hoehn.[15] The solution was poured onto ice and the product was recrystallized twice from ethanol to give 0.8 g. (78%) of an almost colorless powder of the acetyl derivative of VII, m.p. 165–166°, (reported m.p. 162.5–163°).[15]

Carbonation to form ether-acid IX. The potassium derivative of benzhydryl methyl ether (0.1 mole) was prepared in liquid ammonia as above, and stirred for 15 min. The liquid ammonia was then replaced by anhydrous ethyl ether, and the resulting suspension refluxed for 30 min. The mixture was cooled, and excess crushed Dry Ice carefully added with stirring. When the excess Dry Ice had evaporated, water and ethyl ether were added, and the brown layers separated. The aqueous alkaline layer was combined with an alkali extract of the ether layer, and, after filtration to remove tarry material, the cooled solution was acidified with iced-hydrochloric acid. The resulting precipitate was collected on a funnel to give 7 g. of crude, tan carboxylic acid. A solution of this product in aqueous potassium hydroxide was boiled with Norit. Acidification with hydrochloric acid precipitated a white solid from which 0.3 g. of benzilic acid was removed by washing with hot water. The methyl ether of benzilic acid (IX) was obtained in about 10% yield melting at 108.5–109.5 (reported m.p. 111–112°;[16] 100°).[17]

Evaporation of the original ether layer produced a dark brown oil that partially solidified. The mixture was filtered. The solid (1.5 g.) melted at 138–140°, and at 142–143° after two recrystallizations from ethyl ether. The filtrate obtained on removing the 1.5 g. of solid was distilled to give 5 g. (25%) of recovered ether I.

DURHAM, N. C.

(10) P. S. Skell, Thesis, Duke University, 1942, p. 54.

(11) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, 69, 2325 (1947).

(12) K. Ziegler and B. Schnell, *Ann.*, **437**, 248 (1924).

(13) We are indebted to the Victor Chemical Works, Chicago, Ill., for a generous sample of polyphosphoric acid.

(14) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202 (B).

(15) L. I. Smith and H. H. Hoehn, *J. Am. Chem. Soc.*, 61, 2619 (1939).

(16) See Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, Vol. I, p. 252.

(17) S. A. Setlur, A. N. Kothare, and V. V. Nadkarny, *J. Univ. Bombay*, 12A, Pt. 3, 68–70 (1943).

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

Reaction of Nitroparaffins with Alicyclic Ketones. III. The Solid By-Product from Nitromethane and Cyclohexanone

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Received July 8, 1957

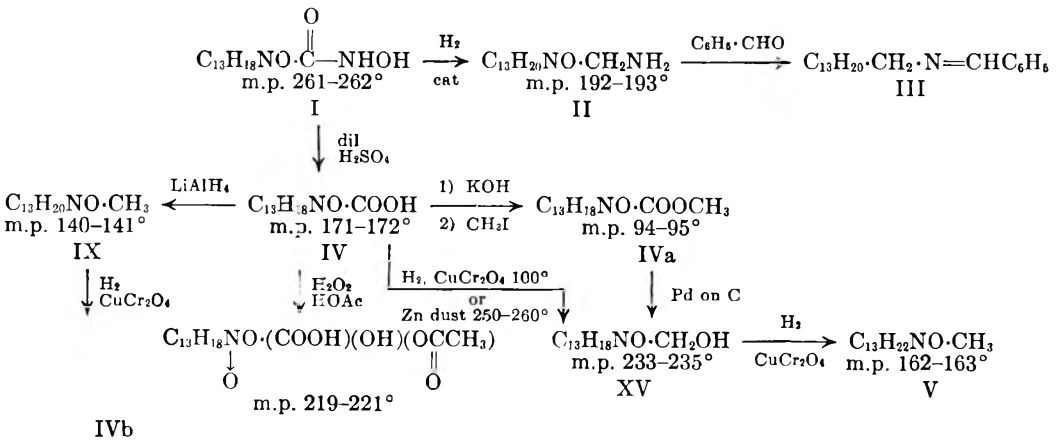
The solid by-product from the reaction of nitromethane with cyclohexanone in the presence of piperidine or *sec*-aliphatic amine catalysts may be a heterocyclic hydroxamic acid containing nitrogen and oxygen in the heterocyclic system. Other functional groups believed to be present are —C=C— and —C=N—, not conjugated. The chemical reactions and infrared absorption spectra of this solid and compounds derived from it are consistent for the most part with a structure containing these functional groups.

In this laboratory, the formation of a solid by-product, I, $C_{14}H_{20}N_2O_3$, m.p. 261–262° (dec.) in 8% yield from the reaction of nitromethane and cyclohexanone in the presence of piperidine or of di-*n*-propylamine had been noted in 1941.[2] Lambert and Lowe[3] reported this same solid when the condensation was catalyzed by diethylamine and stated that its constitution was unknown. In the present investigation, the yield of I was increased to 14% by the use of benzene as a solvent and removing the water as it was formed by azeotropic distillation. Analogous solids were obtained from 3- and 4-methylcyclohexanone[4] and cyclopentanone (XIX) but no solid was obtained from 2-methylcyclohexanone or cycloheptanone. No solid was obtained from nitroethane, nitropropane, or phenylnitromethane under the same experimental conditions. No solid was formed from nitromethane and cyclohexanone in the presence of sodium ethoxide.

I is slightly soluble in ether, benzene, and the petroleum ethers; slightly soluble in nitrobenzene, cold ethanol, and cold ethoxyethanol, but soluble enough in hot ethanol and hot ethoxyethanol to permit use of these solvents for cystallization. These solubilities, the high melting point, and the presence of one nitrogen and one oxygen which appear to be unaffected by most reagents, suggested that I may be heterocyclic and that it contained a polar group. I was insoluble in water and 10% hydrochloric acid but was soluble in sodium and potassium hydroxide and in concentrated sulfuric acid. Nitrogen containing groups which could confer solubility in base would be a nitro group with at least one alpha hydrogen, an oxime group, or an hydroxamic acid group. I was recovered unchanged either after boiling for twenty-four hours in 20% aqueous potassium hydroxide or after standing overnight in concentrated sulfuric acid. Upon treatment with nitrous acid I gave a reddish brown to orange solution.

The principal compounds obtained from I and compounds derived from them are shown in Charts I and II. Molecular weight determinations of II, the anil of II, Va and XV by the Rast method agree with the molecular formulas of these compounds.

CHART I



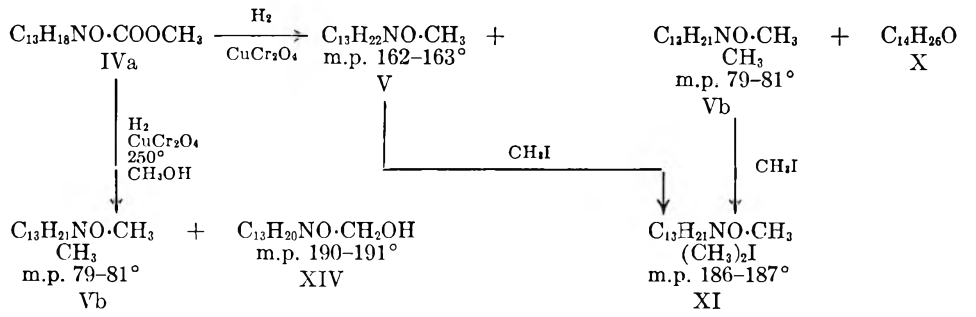
(1) Abstracted from the Ph.D. dissertations of D. A. Reich, June 1956 and F. B. Erickson, August 1949. Presented in part at the American Chemical Society Meeting, Kansas City, Mo., March 1954.

(2) N. C. Knight, Master's dissertation, University of Missouri, 1943.

(3) A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947).

(4) D. V. Nightingale, F. B. Erickson, and J. M. Shackelford, *J. Org. Chem.*, 1005 (1952).

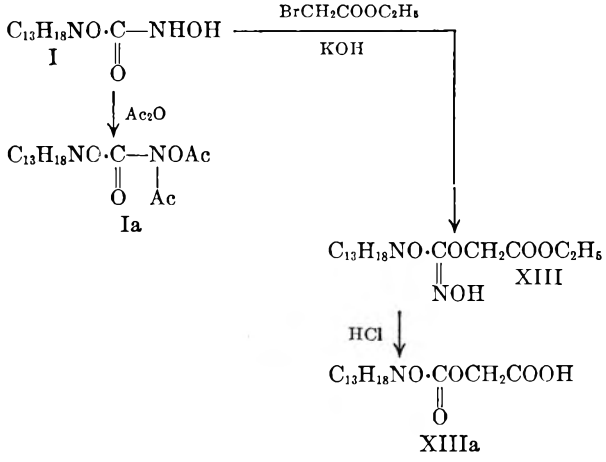
CHART II



When I was pyrolyzed at 280–290°, extensive decomposition occurred with the formation of cyclohexyl cyanide, ammonium carbonate and ammonia. I reacted vigorously when added rapidly to 85% sulfuric acid at 110° to yield some benzoic acid, accompanied by the evolution of sulfur dioxide and charring. This reaction and the formation of cyclohexyl cyanide by pyrolysis suggested that the unit $C_{13}H_{18}NO$ contained the group $C_6H_{11}C{=}N{-}$ or possibly $C_6H_9C{=}N{-}$.

Hydrolysis of I with dilute sulfuric acid yielded the base soluble compound IV, $C_{13}H_{18}NO\cdot COOH$ in 90–95% yields, and hydroxylamine. The neutral equivalent of IV agreed closely with the calculated value for the monocarboxylic acid, and the potassium salt of IV reacted with methyl iodide to form the methyl ester IVa, $C_{13}H_{18}NO\cdot COOCH_3$. Either a nitromethyl group or an hydroxamic acid group would form a carboxyl group and hydroxylamine, but both the chemical reactions and spectroscopic evidence favor the hydroxamic acid group. It may be written $C_{13}H_{18}NO\cdot CONHOH$.

Reactions of the hydroxamic group in I in addition to its hydrolysis include the formation of a diacetyl derivative Ia and the reaction with ethyl bromoacetate:



Lossen rearrangements attempted with I yielded intractable dark oils.

Bromination of I in refluxing carbon tetrachloride formed a monobromo compound Ib, $C_{13}H_{17}NOBr\cdot CONHOH$. This compound could be formed by direct substitution or by addition to a double bond followed by the loss of hydrogen bromide. I did not react with aqueous bromine.

When I was hydrogenated over Raney nickel or copper chromium oxide, II, $C_{13}H_{20}NO\cdot CH_2NH_2$, was the principal product. With acetic anhydride, II formed a monoacetyl derivative IIa after heating for ten minutes and a diacetyl derivative IIb after three hours. The presence of a primary amino group was indicated by the reaction of II with benzaldehyde to form III, presumably a Schiff's base, which would not react with acetic anhydride. No further reaction took place when II was heated with hydrogen and fresh catalyst at 220° and 5490 p.s.i. for one hour. There was no odor of ammonia or of a volatile amine when the bomb was opened.

Treatment of the acid IV with 30% hydrogen peroxide in glacial acetic acid yielded IVb. The molecular formula ($C_{15}H_{22}NO_5\cdot COOH$) of the latter suggested that a tertiary amine oxide and a monoacetyl derivative of a diol were formed during the oxidation.

Hydrogenation of IV at 100° over copper chromium oxide in ethanol yielded XV, $C_{13}H_{18}NO\cdot CH_2OH$ which on further hydrogenation formed V, $C_{13}H_{22}NO\cdot CH_3$. When XV was analyzed in the Grignard machine, one mole of methane was liberated per mole of XV and one mole of reagent was added, presumably to a carbon to nitrogen double bond.

Reduction of IV with excess lithium aluminum hydride in refluxing ether yielded acid-soluble IX,[5] $C_{13}H_{20}NO\cdot CH_3$, and an intractable oil. This reagent should have reduced the carbon to nitrogen double bond but not the olefinic double bond.

Hydrogenation of IX over copper chromium oxide yielded V as the main product, along with a small amount of a nitrogen free oil, X, $C_{14}H_{26}O$.

Hydrogenation of the ester IVa in methylcyclohexane or in methanol led to a mixture of products which included those which would result from partial or complete reduction of the carbomethoxy group, the unsaturated groups, and cleavage products. The odor of ammonia or a volatile amine was usually noticeable when the bomb was opened.

(5) Under forcing conditions, reduction of the carboxyl group with lithium aluminum hydride may be carried beyond the primary alcohol stage to the hydrocarbon. W. G. Brown, *Org. Reactions*, VI, 477 (1951).

In methylcyclohexanone at a final temperature of 250°, the compounds isolated were V, $C_{13}H_{22}NO{\cdot}CH_3$, and Vb, $C_{13}H_{21}(CH_3)NO{\cdot}CH_3$, both acid soluble. The formation of Vb may be accounted for by the methylation of V with the methanol formed during hydrogenolysis of IVa. With methyl iodide, V and Vb formed the same quaternary salt, XI, $C_{13}H_{21}(CH_3)_2INO{\cdot}CH_3$. V readily formed a monoacetyl derivative, Va. Compound Vb did not react with acetic anhydride but it did form a hydrochloride.

When the final temperature for the hydrogenation of IVa was raised to 270–280° in an effort to cleave completely a hetero nucleus, the main products were V, Vb, and some X. Hydrogenation of IVa in methanol at a final temperature of 230° yielded Vb as the main product and some acid in soluble XIV, $C_{13}H_{20}NO{\cdot}CH_2OH$, in which the olefinic double bond was presumably reduced but not the carbon to nitrogen double bond.

Compound X did not contain nitrogen. Carbon and hydrogen percentages found for X, m.p. 56–57°, and for its phenylurethane Xa, m.p. 155–156°, agreed well for $C_{14}H_{26}O$ and $C_{21}H_{31}NO_2$ for these respective compounds. The hydrogenation of IVa was repeated several times at 270–280° in an effort to accumulate enough of pure X for a series of structure determination reactions, but only variable smaller amounts were isolated.

A survey of all of the hydrogenation products isolated from IV and IVa in this study and their structural implications suggested that a 2-methyl-6-(cyclohexanemethyl)cyclohexanol, $C_{14}H_{28}O$, was a possible cleavage product. This cyclohexanol was synthesized by the hydrogenation of 2-hydroxy-3-methylbenzophenone over Raney nickel,[6] but this compound melted at 42–44° and its phenylurethane melted at 138–139°. The mixed melting point of this phenylurethane and the same derivative of X was 118–121°.

The infrared spectrum of X and of 2-methyl-6-(cyclohexanemethyl)-cyclohexanol both have the strong —OH band at 3.00 microns and are similar in many respects, but there are bands occurring at 9.35 microns and 10.15 microns in X which are not present in the spectrogram of the synthetic compound.

3 - Phenyl - 7 - methylbenzisoxazole was synthesized[6] and hydrogenated over Raney nickel at 220° to yield an oil which contained no nitrogen, the phenylurethane of which melted at 99–105° during several recrystallizations. The carbon and hydrogen percentages found for this derivative agreed with those calculated for $C_{21}H_{31}NO_2$. This product may be a mixture of stereoisomers of 2-methyl-6-(cyclohexanemethyl)cyclohexanol.

The fact that the carbomethoxy group of IVa was reduced to methyl without difficulty, suggested that a second oxygen should be on the carbon beta to the carbomethoxy group or to the hydroxymethyl group of the possible intermediate XIV. Adkins[7] states that a hydroxyl group in the 3-position with respect to a second hydroxyl group facilitates the cleavage of the latter. For example, 1,3-cyclohexanediol is quantitatively converted to cyclohexanol at 200° while the 1,4-isomer is stable at 250°.

If IVa should have a heterocyclic nucleus containing oxygen, the oxygen in the hetero system could be in the 3-position with respect to the hydroxyl group of XIV, $C_{13}H_{20}NO{\cdot}CH_2OH$, and could conceivably facilitate the conversion of the hydroxymethyl group to methyl.

The action of palladium on IVa, the distillation of IV with zinc dust, and the hydrogenation of IV over copper chromium oxide all yielded XV. Hydrogenation of XV from each of these reactions yielded V.

Reactions which gave results of little or no value included the oxidation of I, IV, and V with sodium dichromate and sulfuric acid or with postassium permanganate, the reaction of II with nitrous acid in 10% acetic acid, the reaction of V with 50% hydriodic acid, efforts to dehydrogenate IV with chloranil and to decarboxylate IV with copper and quinoline, ozonolysis of IV, and the reaction of the silver salt of IV with bromine. I, Ib, IV, and IVa were the only compounds in this study which gave a purple color with ferric chloride.

A study of the papers of Dunstan and Goulding,[8] Lippincott,[9] and Stork[10] which deal with reactions of nitromethane or cyclohexanone in the presence of amine catalysts and mechanisms for the formation of the principal products and some by-products leads to no simple explanation for the formation of I. The experimental conditions used in this study are similar to those used in a Michael reaction or a Stork alkaylation.[10] Increasing the amount of catalyst did not increase the yield of I.

Other compounds[3] which have been obtained from the reaction of cyclohexanone and nitromethane in the presence of *sec*-amine catalysts are 1-nitromethylcyclohexene, 1-nitromethylcyclohexanol, and 1,1-bis(nitromethyl)cyclohexane. Any of these compounds (or possibly cyclohexylidenecyclohexanone) could be considered as an intermediate in the formation of I. In this laboratory, I was obtained in smaller yields from both 1-nitromethylcyclohexene and 1-nitromethylcyclohexanol in the presence of the amine catalysts, and oc-

(6) D. A. Reich and D. V. Nightingale, *J. Org. Chem.*, **21**, 825 (1956).

(7) H. B. Adkins, *Reactions of Hydrogen with Organic Compounds Over Copper Chromium Oxide and Nickel Catalysts*, The University of Wisconsin Press, Madison, Wis., 1937, p. 104.

(8) W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **77**, 1262 (1900).

(9) S. B. Lippincott, *J. Am. Chem. Soc.*, 62, 2604 (1940).

(10) G. Stork, R. Terrel, and J. Szumzkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

casionally I separated slowly from 1-nitromethylcyclohexene which had been purified by distillation. Lambert and Lowe[3] also obtained some I from 1-nitromethylcyclohexanol and nitromethane in the presence of diethylamine.

The formation of I from the primary reactants may be written

$$2C_6H_{10}O + 2CH_3NO_2 \longrightarrow C_{14}H_{20}N_2O_3 + 3H_2O$$

or from nitromethylcyclohexene

$$2C_7H_{11}NO_2 \longrightarrow C_{14}H_{20}N_2O_3 + H_2O$$

The presence of nitrite ion in the azeotroped water suggests that secondary reactions are involved. It is generally recognized that intramolecular oxidation-reduction reactions are not uncommon with aliphatic nitro compounds or with phenylnitromethane, and the allylic system —C=C—CH_2NO_2 in 1-nitromethylcyclohexene should be reactive.

A variety of heterocyclic structures having the formula $C_{14}H_{20}N_2O_3$ can be devised from reactions of various components of the reaction mixture, including the self-condensation of 1-nitromethylcyclohexene either by a Michael reaction or a diene synthesis. Most of these structures, however, contain a secondary nitro group or an $=\overset{|}{N} \rightarrow O$ group, and they do not account for most of the observed reactions of I or of IV.

The infrared absorption spectra of these compounds were helpful to the extent that bands present in the spectra agreed qualitatively with functional groups thought to be present in the compounds. The significant bands are as follows:

I. The strong bands at 3.25 microns and 5.9 microns may be due to the —OH group and C=O group, respectively, of the hydroxamic group. The two bands at 6.05 and 6.10 microns may be due to the —C=N— and —C=C—. The ultraviolet spectrum of I indicates that these double bonds are not conjugated.

II. The two bands in the 3.0–3.25 region are characteristic of the $-NH_2$ groups and the strong band at 5.94 may be caused by the —C=N—.

V. Only one band is observed at 3.2 microns, characteristic of the —N—H, and there is no absorption characteristic of unsaturation.

XV. The band at 10.02 may be due to an —OH group and the two bands near 6 microns indicate unsaturation probably due to —C=C— and —C=N—.

IX. The bands at 3.20 and 3.29 microns may be due to a vinyl hydrogen and the —N—H, while the weak bands at about 6 microns could be caused by —C=C—.

There are two or three strong bands between 12 and 13 microns present in I, II, and XV but absent in V and IX which may be characteristic of a ring structure of these compounds.

The solids from nitromethane and 3-methylcyclohexanone, 4-methylcyclohexanone, and cyclopentanone gave the same purple color with ferric chloride as did I. On hydrolysis with dilute sulfuric acid they formed base soluble compounds analogous to IV.

EXPERIMENTAL[11]

The melting points were determined in a capillary tube in a copper block and are uncorrected.

Compound I. In a flask equipped with a Stark and Dean trap were placed 180 ml. (1.74 moles) of cyclohexanone, 102 ml. (1.90 moles) of nitromethane, 200 ml. of benzene, and 12 ml. of piperidine. The mixture was refluxed gently for 30 hr., then allowed to cool and the solid which separated was collected on a filter. Compound I was recrystallized from 2-ethoxyethanol, m.p. 262–263° (dec.), literature[3] value 270–271°, yield 33 g. (14.8%).

Anal. Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63. Found: C, 63.61; H, 7.78.

The water in the trap had a *p*H of 8–9 (Hydrion universal indicator paper). When this water was acidified with hydrochloric acid and tested with starch iodide paper, the purple color characteristic of nitrous acid developed. Evaporation of the water left a white solid which gave a positive brown ring test with ferrous sulfate solution and sulfuric acid, and which liberated ammonia when treated with sodium hydroxide solution.

The diacetyl derivative of I was obtained by warming it with acetic anhydride for 10 min., m.p. 128–129°, the literature value.[3] Long boiling of I with acetic anhydride yielded a dark, viscous oil.

Reaction of I *with ethyl bromoacetate.* The procedure was that of Kitagawa and Takis[12] for benzhydroxamic acid. Compound I (10 g., 0.04 mole), 75 ml. of absolute ethanol, and 4.5 g. (0.08 mole) of potassium hydroxide were placed in a 100-ml. flask fitted with a condenser, stirrer, and dropping funnel. The ester (6.7 g., 0.04 mole) was added dropwise to the refluxing solution. After refluxing for 6 hr., the cooled solution was diluted with water, the solid product was collected on a filter and washed with dilute base. The solid, XIII, was recrystallized from aqueous ethanol, m.p. 163–165°, yield, 10 g. (71%).

Anal. Calcd. for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48. Found: C, 62.01; H, 7.52.

Hydrolysis of XIII with 5% hydrochloric acid yielded XIIIa, m.p. 137–138°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88. Found: C, 62.46; H, 6.95.

Bromination of I. When a solution of 2 g. of I in 50 ml. of carbon tetrachloride was refluxed on a steam bath with excess bromine, a monobromo compound Ib was obtained, m.p. 184–185°.

Anal. Calcd. for $C_{14}H_{19}N_2O_3Br$: C, 48.98; H, 5.83. Found: C, 48.66; H, 5.59.

Pyrolysis of I. Compound I (5 g.) was pyrolyzed in a small distilling flask in a metal bath at 280–290°. The receiver was connected to a barium hydroxide trap in which a white precipitate formed. A white solid and a brown liquid which collected in the receiver were extracted with ether and the white solid collected on a filter. The solid reacted with benzenesulfonyl chloride in basic solution to form benzenesulfonamide, m.p. 150.5–152.5°, mixture melting point with an authentic sample, 151.5–153°. When an aqueous

(11) The carbon and hydrogen analyses were by Mr. R. A. Carpenter, Mr. P. D. Strickler, Mr. R. L. Elliott, Mr. R. E. Bolin, and Mr. A. Mendel. The Dumas nitrogen determinations were by Mr. D. A. Reich.

(12) M. Kitagawa and A. Takis, *J. Agr. Chem. Soc. Japan*, **11**, 1007 (1936); *Chem. Abstr.*, **30**, 3409 (1936).

solution of the solid was treated with hydrochloric acid, the evolved gas formed a precipitate with barium hydroxide. These reactions identified the solid as ammonium carbonate.

When the ether extract was dried and the solvent removed on a steam bath, the residue (7 g. collected from five runs) was fractionated to yield 2.2 g. of cyclohexyl cyanide, b.p. 65–66° (10 mm.), n_D^{30} 1.4575, which was hydrolyzed in concd. sulfuric acid to yield the amide of cyclohexanecarboxylic acid, m.p. 184.5–186°.[13] Carbon and hydrogen percentages found for both the cyanide and the amide agreed with the calculated values.

Hydrogenation of I. *A. Over Raney nickel.* Compound I (13.2 g., 0.05 mole) in 100 ml. of ethanol was hydrogenated in conventional high pressure hydrogenation equipment over 3 g. of Raney nickel at an initial pressure of 2900 p.s.i. After heating began, there was a large pressure drop at 105–130° and heating was continued until the temperature reached 160° and 4240 p.s.i. The catalyst was removed from the solution by filtration and the solvent evaporated to yield 10.9 g. (92%) of II, m.p. 192–193°, after recrystallization from petroleum ether (86–100°).

Anal. Calcd. for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85; mol. wt. 236. Found: C, 71.49; H, 10.29; N, 11.74; mol. wt. 213, 238, 223 (Rast).

B. Over copper chromium oxide. Hydrogenation of 16 g. of I in 170 ml. of ethanol over 20 g. of copper chromium oxide at 90–110° and 3400 p.s.i. yielded 12 g. (85%) of II.

The monoacetyl derivative IIa of II was prepared by refluxing it with acetic anhydride for 10 min.; m.p. 271–272°.

Anal. Calcd. for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41. Found: C, 68.79; H, 9.60.

The diacetyl derivative of II was prepared by refluxing it with acetic anhydride for 3 hr.; m.p. 224.5–226°.

Anal. Calcd. for $C_{18}H_{28}N_2O_3$: C, 67.43; H, 8.88. Found: C, 67.72; H, 8.62.

Compound II formed an anil III when heated with benzaldehyde at 150–160° for 30 min.; m.p. 239–240° (from ethanol).

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.70; H, 8.96; mol. wt. 324. Found C, 77.04; H, 8.78; mol. wt. 300, 298 (Rast).

Reaction of I *with hot sulfuric acid.* When 19 g. of I was added all at once to 50 ml. of 85% sulfuric acid at 100°, there was a violet reaction accompanied by charring and the evolution of sulfur dioxide, and the temperature rose rapidly to 170°. The cooled reaction mixture was extracted continuously with ether, and the ether extract was washed and dried. Removal of the solvent yielded 3 g. of benzoic acid, m.p. 119–120°, mixture melting point with an authentic sample 121–122°.

Hydrolysis of I *with dilute sulfuric acid.* Compound I 5 g.) was refluxed for 53 hr. with 400 ml. of dilute sulfuric acid (1:4). After the solution had cooled over night, the separated acid IV was collected on a filter and recrystallized from aqueous ethanol. Yield, 4.3 g. (91%), m.p. 170–172°.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.69; Neut. equiv. 249. Found: C, 67.55; H, 7.81; Neut. equiv., 246, 249, 242.

The methyl ester of IV. In a 250-ml. flask fitted with a reflux condenser were placed 20 g. (0.08 mole) of IV, 4.55 g. (0.08 mole) of potassium hydroxide and 150 ml. of methanol. Methyl iodide (11.4 g., 0.08 mole) was added through the condenser and the mixture was refluxed for 3 hr. When the contents of the flask were cooled and diluted with water, the solid which separated was collected on a filter and washed with water. After recrystallization from aqueous methanol, the ester IVa melted at 94–95°, yield 17 g. (80%).

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04. Found: C, 68.75; H, 8.20.

(13) E. H. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds*, New York, John Wiley and Sons, 1946.

Reaction of IV *with hydrogen peroxide in acetic acid.*[14] In a 50-ml. flask were placed 5 g. (0.02 mole) of IV, 8 ml. (0.06 mole) of 30% hydrogen peroxide and 50 ml. of glacial acetic acid. The mixture was heated on a steam bath for 5 hr., then diluted with 50 ml. of water and the water and acid removed under reduced pressure. The oily residue was dissolved in methanol and on cooling, crystals of IVb separated and were recrystallized from methanol. Yield, 2.1 g. (30%), m.p. 219–221°.

Anal. Calcd. for $C_{16}H_{23}NO_7$: C, 56.29; H, 6.79. Found: C, 56.04; H, 6.67.

Reduction of IV *with lithium aluminum hydride.* In the conventional apparatus were placed 3 g. (0.07 mole) of lithium aluminum hydride and 150 ml. of dry ether. A solution of 15 g. (0.06 mole) of IV in 1 l. of dry ether was added as rapidly as possible. After addition was complete, the mixture was refluxed for 5 hr. The complex was decomposed in the usual manner. The oily residue from the ether solution slowly crystallized, and after recrystallization from benzene and petroleum ether (60–70°), 2.3 g. of acid soluble IX was obtained, m.p. 140–141°.

Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47. Found: C, 76.28; H, 10.42.

Reaction of IV *with zinc dust.* In a 125-ml. distilling flask were placed 25 g. of IV and 20 g. of zinc dust. The flask was placed in a metal bath preheated to 140° and the temperature of the bath was slowly raised. At 250–260°, there was vigorous bubbling in the melted mixture and at 275° some sublimation began. A water aspirator was attached to the receiver and the pressure reduced to 24 mm., but the refluxing material would not distill at a bath temperature of 340°.

The charred, tarry mixture was extracted with acetone. The acetone was then evaporated leaving a solid residue (14 g.) which was washed with dilute base and recrystallized, first from aqueous ethanol, then from petroleum ether (86–100°) and finally from 95% ethanol to yield XV, m.p. 232–234°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; mol. wt. 235. Found: C, 71.48; H, 9.09; mol. wt. 248, 246, 247 (Rast).

Hydrogenation of 6 g. of XV in 100 ml. of methylcyclohexane over 20 g. of copper chromium oxide catalyst at 220–235° yielded 4 g. of V, m.p. and mixture m.p. with V from the hydrogenation of IVa, 162–163°. The acetate Va of this sample of V did not depress the melting point of Va from the hydrogenation of IVa.

Hydrogenation of IV *over copper chromium oxide.* Compound IV (15 g.) in 150 ml. of ethanol was hydrogenated over 20 g. of catalyst. The initial pressure was 2500 p.s.i. and the temperature was raised to 100° and held there until no more hydrogen was absorbed. The slightly soluble reduction product and catalyst were extracted in a Soxhlet extractor with acetone to yield 10.5 g. (75%) of XV, m.p. and mixture m.p. with XV from the zinc dust reaction, 233–234°.

Hydrogenation of IVa *over copper chromium oxide in methylcyclohexane.* Compound IVa (5.2 g., 0.02 mole) in 100 ml. of methylcyclohexane was hydrogenated over 23 g. of catalyst, at an initial pressure of 2500 p.s.i. There was a small drop in pressure at 65° and a large drop at 125–130°. The final temperature was 250° at 4200 p.s.i. The catalyst and liner were washed with ether and the washings added to the methylcyclohexane solution. The ether was removed from the mixture of solvents by distillation. As the remaining methylcyclohexane cooled, compound V separated and after recrystallization from aqueous ethanol it melted at 162–163°.

Anal. Calcd. for $C_{14}H_{25}NO$: C, 75.28; H, 11.28. Found: C, 75.50; H, 11.28.

The acetate Va of V melted at 142–143°.

(14) E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, 19, 1633 (1954).

Anal. Calcd. for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.26; mol. wt. 265. Found: C, 72.41; H, 10.34; mol. wt. 287, 289 (Rast).

The methylcyclohexane filtrate from V was concentrated to less than 5 ml. and petroleum ether (60–70°) was added. Compound Vb separated and was collected on a filter. After recrystallization from petroleum ether (28–38°) it melted at 79–80°.

Anal. Calcd. for $C_{15}H_{27}NO$: C, 75.87; H, 11.47. Found: C, 75.74; H, 11.39.

The hydrochloride of Vb melted at 212–214°.

Anal. Calcd. for $C_{15}H_{28}NOCl$: C, 65.45; H, 10.23; N, 5.15. Found: C, 65.70; H, 10.31; N, 5.14.

Another hydrogenation of 12 g. of IVa in methylcyclohexane at a final temperature of 270–280° and 4000 p.s.i. yielded 3.4 g. of V, 1.5 g. of Vb, 2 g. of an acid soluble oil which was not identified, and 2 g. of a nitrogen-free oil X which became semi solid on standing. Compound X was purified by distillation through a short column at 122–123° (2 mm.) and melted at 56–57°.

Anal. Calcd. for $C_{14}H_{26}O$: C. 79.93; H, 12.46. Found: C, 79.79; H, 12.32.

The phenylurethane Xa of X melted at 155–156°.

Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48. Found: C, 76.29; H, 9.44.

A mixture of Xa and the phenylurethane of authentic 2-methyl-6-(cyclohexanemethyl)cyclohexanol (m.p. 138–139°) melted at 118–121°.

Preparation of the quaternary salts of V *and* Vb. Compound V (6.7 g., 0.03 mole), 9 g. (0.06 mole) of methyl iodide, and 1.5 g. of potassium hydroxide were added to 200 ml. of absolute ethanol and the mixture allowed to stand for two days at room temperature. The separated potassium iodide was removed and the filtrate concentrated to precipitate the quaternary salt XI, m.p. 186–187° after recrystallization from absolute ethanol and ether.

Anal. Calcd. for $C_{16}H_{30}NOI$: C, 50.66; H, 7.91. Found: C, 50.97; H, 8.13.

The quaternary salt XI of Vb was obtained in the same way, m.p. and mixture m.p. with XI from V, 186–187°.

Hydrogenation of IVa *over copper chromium oxide in methanol.* Compound IVa (17 g., 0.06 mole) in 150 ml. of methanol was hydrogenated over 60 g. of catalyst and an initial pressure of 2600 p.s.i. There was a large drop in pressure at 110°, and the final temperature was 230°. The alcohol solution was diluted to 4 l. with ether and the solution extracted with dilute hydrochloric acid. When the acid extract was made basic with dilute sodium hydroxide solution, 9.3 g. of Vb was obtained. When the ether layer was evaporated, 1.5 g. of acid insoluble XIV was obtained, m.p. 190–191° (from ethanol).

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77. Found: C, 70.80; H, 10.09.

Reaction of IVa *with palladium on carbon.* Compound IVa (9 g.) and 0.4 g. of 5% palladium on carbon were introduced into a nitrogen filled 50-ml. Claisen distilling flask equipped with a nitrogen inlet tube, thermometer, and receiver. The flask was heated in a metal bath to 200° while nitrogen was passed in. Then the nitrogen tube was replaced with a stopper, the receiver was placed in a dry ice bath and attached to a barium hydroxide trap. At 275° the evolution of gas was vigorous and some barium carbonate separated in the trap. When gas was no longer evolved, the temperature was raised to 210° and held there for 6 hr.

The dark, solid residue in the reaction flask was extracted with ethanol and the solution decolorized with Norite. Compound XV, insoluble in acid and base, was obtained by removal of the solvent and melted at 233–234°, after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.28; H, 9.01.

The melting point of a mixture of this sample of XV with a sample of XV from the reaction of IV and zinc dust was 233–234°.

Reaction of cyclopentanone with nitromethane. In a 500-ml. flask equipped with a Stark and Dean trap were placed 89 ml. (1 mole) of cyclopentanone, 55 ml. (1 mole) of nitromethane, 6 ml. of piperidine, and 200 ml. of dry benzene. The mixture was refluxed for 24 hr., and after cooling some solid separated. The solution was diluted with an additional 300 ml. of benzene and allowed to stand several days. The solid (6.5 g., yield 8%) which separated was collected on a filter and after recrystallization from ethanol, XIX melted at 242–245° (dec.).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83. Found: C, 61.13; H, 7.90.

This compound gave a purple color with ferric chloride solution, and its solubilities were the same as those of I.

Hydrolysis of XIX. In a 250-ml. flask were placed 100 ml. of 1:4 sulfuric acid and 2.5 g. of XIX. After refluxing the mixture for one hour all of XIX had dissolved and the solution was allowed to cool. The needles which separated were collected on a filter and recrystallized from absolute ethanol and petroleum ether (60–70°). The yield of XX was 1.7 g. (72%), m.p. 157–158°.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 64.99; H, 7.00.

Reaction of 4-methylcyclohexanone with nitromethane. A benzene solution of 61 g. (1 mole) of nitromethane, 112 g. (1 mole) of 4-methylcyclohexanone, and 6 ml. of piperidine was refluxed for 30 hr. Compound XXI which separated was recrystallized from 2-ethoxyethanol. The yield of XXI, m.p. 257–258° (dec.) was 10.5 g. (9%) as compared with a 4.5% yield obtained by Erickson[4] without solvent.

Hydrolysis of XXI. Compound XXI (2 g.) was refluxed 50 hr. with 160 ml. of 1:4 sulfuric acid. The acid XXII was isolated as described for the hydrolysis of I. Compound XXII sintered at 153° and melted at 160–162°, yield, 1.5 g. (81%).

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.55. Found: C, 69.90; H, 8.48.

Absorption spectra. The absorption spectra were determined and interpreted by Prof. E. E. Pickett of the spectrographic laboratory of the University of Missouri. The ultraviolet spectra were determined on alcoholic solutions of the samples by means of a Cary Recording Spectrophotometer, Model 11, Serial 36. The infrared spectra were determined on a Beckman Infrared Spectrophotometer, Model IR-2A, with automatic slit adjustment. Nujol mulls of the solids were used for the infrared measurements.

COLUMBIA, MO.

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

Oxidation and Characterization of α,α'-Dichloro-*p*-xylene

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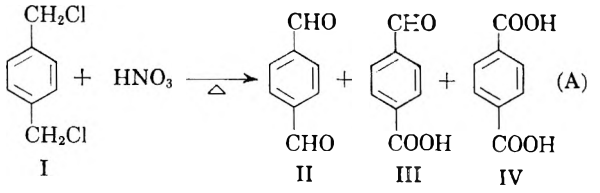
The major products of the oxidation of α,α'-dichloro-*p*-xylene (DCX) with dilute nitric acid at atmospheric pressure, are terephthalaldehyde and terephthalaldehydic acid; only small amounts of terephthalic acid are produced. An attempt to oxidize DCX with an alkaline three per cent hydrogen peroxide solution resulted in hydrolysis to the glycol, α,α'-dihydroxy-*p*-xylene. The characterization of DCX and terephthalaldehyde is described in detail.

This paper deals with some reactions of α,α'-dichloro-*p*-xylene, p-$ClCH_2C_6H_4CH_2Cl$. For convenience, the work is divided into the two categories of oxidation and characterization.

DISCUSSION

The oxidation of DCX. The oxidation of *p*-xylene to terepthahlic acid can be accomplished by the use of dilute nitric acid at both high temperatures and pressures.[1] The hydrocarbon, however, is resistant to oxidative attack by the same reagent at the milder experimental conditions of reflux temperature and atmospheric pressure. The conversion of the two methyl groups of the *p*-xylene into methylene groups, *e.g.*, by a substitution reaction, yields a compound with a bisbenzyl structure; the latter should then be more susceptible to oxidation at the moderate experimental conditions. In addition, if the substitution is by chlorine atoms as in DCX, then the oxidation will be further facilitated because the alcohols derived by hydrolysis should be oxidized with ease.

This is found to be the case. At atmospheric pressure and at the reflux temperature, DCX (I) is oxidized by dilute nitric acid to a mixture of terephthalaldehyde (II), terephthalaldehydic acid (III), and terephthalic acid (IV).[2]



The absence of the glycol, p-$HOCH_2C_6H_4CH_2OH$, as a reaction product indicates that a hydroxymethyl group is more readily oxidized by nitric acid than is a corresponding aldehydic group. This substantiates the previous report that the oxidation of α,α'-dihydroxy-*p*-xylene with concentrated nitric acid gives an 80 per cent yield of terephthalaldehyde.[3]

The results of the dilute nitric acid oxidation of DCX are summarized in Table I. They are consistent with the expectation that the product representing the lowest state of oxidation, terephthalaldehyde, is produced in greatest amount at the lower concentrations of oxidizing agent. The inverse is true for the product of the highest state of oxidation, terephthalic acid.[4]

It can be seen from Table I that although the short time oxidation of DCX with dilute nitric acid can lead to satisfactory yields of terephthalaldehyde, this single-stage oxidation process produces terephthalic acid in poor yield.

The characterization and reactions of DCX. The DCX used in the instant study was prepared by the interaction of sulfuryl chloride with *p*-xylene, in the presence of benzoyl peroxide.[5] The dihalide was characterized by the preparation of derivatives which are analogous to those obtained from benzyl chloride. As compared to the latter compound,

(1) (a) E. B. Bengtsson, *Acta Chem. Scand.*, **7**, 774 (1953); (*b*) E. B. Bengtsson, *Iva.*, **25**, 121 (1954); (*c*) I. N. Nazarov, N. V. Kuznetsov, and A. V. Semenovskii, *Doklady Akad. Nauk*, **99**, 1003 (1954).

(2) E. Grimaux, *Compt. rend.*, **83**, 825 (1876) observed that terephthalaldehyde is produced by refluxing DCX with a lead nitrate solution. No qualitative data concerning the isolation of other products, or quantitative data with regard to the aldehyde, are mentioned. No further oxidative work with DCX is cited until 1954 when M. Kulka and R. H. F. Manske were issued U. S. Patent **2,666,786**, 19 January 1954, for its oxidation with concentrated nitric acid at super-atmospheric pressures. For a review and study of the oxidation of the dibromo analog, DBrX, one should consult the paper by R. Wegscheider and E. Suida, *Monatsh.*, **33**, 1006 (1912).

(3) B. Helferich, R. Streeck, and E. Gunther, *J. prakt. Chem.*, **151**, 251 (1938).

(4) After this work was completed, several recently published data concerning the nitric acid oxidation of DCX were discovered. J. Manka, J. Tomaszewski, and M. Wajnryb, *Zeszyty Naukowe Politechniki Lodzkiej*, No. 9, 31 (1955) concluded that the oxidation, in the presence of mercuric chloride as a catalyst, yielded a mixture of terephthalic acid and other oxidation products; the latter were not identified. The yields of terephthalic acid in this single-stage oxidation were poor and they finally evolved the following three-stage process for the oxidation of DCX to moderately good yields of terephthalic acid: (i) the hydrolysis of DCX to the glycol and other products, (ii) the oxidation of the hydrolysate with nitric acid, (iii) further oxidation of the product of (ii) with a fresh portion of nitric acid.

Independently of this paper, and the work of Manka, *et al.*, two patents were issued to Vereinigte-Glanzstoff-Fabriken (British Patent **724,921**, 23 February 1955 and U. S. Patent **2,740,811**, 3 April 1956) which also show that the single-stage oxidation of DCX with dilute nitric acid does not represent a feasible synthesis of terephthalic acid.

(5) M. Kulka, *Can. J. Research*, **23B**, 106 (1945).

TABLE I

OXIDATION OF DCX WITH DILUTE NITRIC ACID

Nitric Acid Conc., %	Temp.	Time, Hr.	Percentage Yield of		
			p-$OHCC_6H_4CHO$	*p*-$HOOCC_6H_4CHO$	*p*-$HOOCC_6H_4COOH$
10	106	7	56	23	15
15[a]	106	7	36	35	16
19	104	6	70[b]	23	5
40	107	4.2	3	63	29
50	106	8	2	43	49

[a] Used five mole per cent V_2O_5 as a catalyst. [b] The higher yield of terephthalaldehyde as compared to the 10 or 15 per cent nitric acid reaction is due to the shorter reaction time.

however, DCX exhibited a decreased reactivity towards displacement reactions. The use of more drastic experimental conditions (diethylene glycol monobutyl ether as solvent, and potassium iodide to effect halogen exchange) was necessary to prepare certain derivatives.

The reaction of sodium nitrite with DCX in methanolic solution was conducted in an attempt to prepare α,α'-dinitro-*p*-xylene. There is no recorded synthesis in the literature for this dinitro compound. It is of interest for it would lead to a novel synthesis of terephthalic acid.

$$p\text{-}O_2NCH_2C_6H_4CH_2NO_2 + 2H_2O \xrightarrow{H^+} p\text{-}HOOCC_6H_4COOH + 2NH_2OH$$

The infrared spectrum indicates that the small amount of reaction product isolated by distillation from a Hickmann micro still is *p*-chloromethylbenzyl alcohol with some *p*-chloromethylbenzaldehyde as an impurity. The fact that only one chloromethyl group of DCX was attacked indicates the slow reaction of DCX with sodium nitrite in methanol. Kornblum, *et al.*, has since reported that nitro compounds may be prepared from sodium nitrite and alkyl bromides or iodides, in dimethyl formamide as a solvent.[6] In corroboration of the experiment described above they also state that chlorides react too slowly to be satisfactorily employed in this reaction.

The treatment of DCX with sodium nitrate in aqueous solution yields *p*-hydroxymethylbenzaldehyde as a major reaction product. The DCX is apparently first hydrolyzed to the diol; one hydroxymethyl group is then oxidized by the nitrate salt to that of an aldehyde.

EXPERIMENTAL

General. All reagents are commercial chemicals which were used without further purification, unless otherwise noted. The 2,4-dinitrophenylhydrazone derivatives were prepared by a variation of Brady's method;[7] the reagent is prepared by dissolving 5 g. 2,4-dinitrophenylhydrazine in a solution of 37.5 ml. H_2SO_4 in 375 ml. methanol. The filtered reagent, when stored in a brown bottle, is stable for years. The derivative usually precipitates when the carbonyl compound is added at room temperature; slight warming is sometimes necessary. The preparation of other derivatives in the characterization of DCX and its oxidation products were carried out in standard manners.[8] All melting points are corrected unless otherwise noted.

Preparation of DCX. The dichloride was prepared by Kulka's method of the interaction of *p*-xylene and sulfuryl chloride in the presence of benzoyl peroxide;[5] this avoids impurities introduced by either multiple substitution (direct chlorination process) or the production of isomers (chloromethylation procedure). Kulka ran the reaction in sunlight for four hours using a molar ratio of xylene:chloride:peroxide of 1:2.5:0.006, and obtained a 58% yield of DCX. In diffuse room light for two hours and a respective molar ratio of 1:2.0:0.011, the instant experiment gave a 28% yield of DCX (white platelets from ethanol, m.p. 99–99.5°) and a 67% yield of *p*-methylbenzyl chloride (sweet-smelling liquid, b.p. 95–97°/20; lit. b.p. 92–94°/20[9]). Both materials are highly lachrymatory and should be manipulated in a hood.

Oxidation of DCX. All oxidations with dilute nitric acid were conducted in the following manner:

A suspension of DCX (3.5 g., 0.02 mole), in the appropriate concentration of nitric acid (molar ratio of HNO_3/DCX = 10) is refluxed for several hours at 106–108°. The solid DCX forms oily globules, at the reflux temperature, which gradually disappear as the hydrolysis and oxidation reactions proceed. Copious fumes of NO_2 are evolved and within two to three hours of reflux, a solid appears. On cooling to room temperature the reaction mixture deposits a mass of colorless crystals. The following scheme to separate the products (Fig. 1) was evolved after numerous tedious and unsuccessful separations were attempted by fractional crystallizations and sublimations, and by chromatographic techniques.

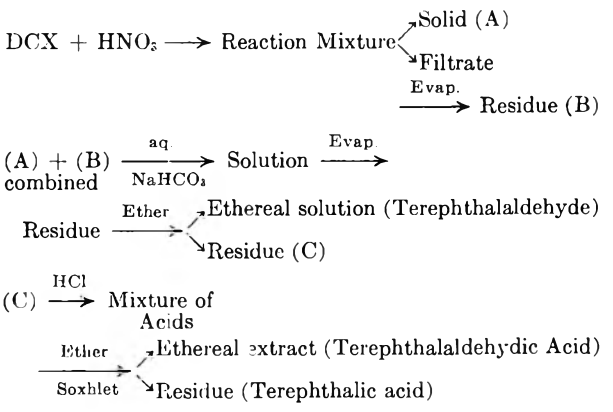


FIG. 1. SCHEME EMPLOYED TO SEPARATE DCX—HNO_3 REACTION PRODUCTS.

(6) N. Kornblum, H. O. Larson, D. D. Mooberry, R. K. Blackwood, E. P. Oliveto and G. E. Graham, *Chem. & Ind. (London)*, 443 (1955).

(7) O. L. Brady, *J. Chem. Soc.*, 756 (1931).

(8) R. L. Shriner, R. C. Fuson, D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Ed., John Wiley & Sons, Inc., New York (1956).

(9) H. Stephen, W. F. Short, G. Gladding, *J. Chem. Soc.*, **117**, 520 (1920).

TABLE II

ISOLATION AND IDENTIFICATION OF DCX-DILUTE HNO_3 PRODUCTS

Product or Derivative	Formula	M.P., °C.	% C		% H		Principal Infrared Bands ($Cm.^{-1}$)	Comments
			Calcd.	Obs.	Calcd.	Obs.		
Terephthalaldehyde	$C_8H_6O_2$	115–116	71.6	71.7	4.5	4.7	C=O at 1694 *p*-Subst. at 1198	Small white platelets. Positive Tollens' test
Terephthalaldehyde oxime	$C_8H_8N_2O_2$	211.5–212[a]	58.5	58.6	4.9	5.1	Broad OH at 3230 Weak C=N at 1652	Extremely water soluble colorless crystals
Terephthalal Dianiline	$C_{20}H_{16}N_2$	164–165	84.5	84.4	5.7	5.6	C=N at 1620 N=C—ArC=N at 1590[b]	% N calcd. 9.9; % N obsd. 10.1. Small yellow needles from ethanol
Terephthalal Di-*p*-toluidine	$C_{22}H_{20}O_2$	190–192	84.6	84.8	6.5	6.2	—	Yellow solid. Sublimed after recryst. from ethanol
Terephthalal Di-acetophenone	$C_{24}H_{18}O_2$	197–197.5[c]	85.2	84.7	5.4	5.4	—	Yellow tablets from ethanol
Terephthalaldehyde bis-*p*-nitrophenyl hydrazone	$C_{20}H_{16}N_6O_4$	294–295[d] (dec.)	59.4	59.4	4.0	3.8	—	Red crystals from ethanol
Terephthalaldehydic acid	$C_8H_6O_3$	Softens at 250, not molten at 320[e]	64.0	64.2	4.0	3.8	Broad OH in 3000 region C=O at 1680, 1698, 1728 COO— at 1616 C—O at 1248, 1292	Colorless, microcrystalline powder. Neut. equiv. calcd. 150; neut. equiv. obsd. 149
Terephthalaldehydic acid 2,4-dinitrophenylhydrazone	$C_{14}H_{10}N_4O_6$	326–327 (dec.) (uncorr.)[f]	50.9	50.5	3.1	2.6	—	Extremely insoluble orange solid. Analytical sample prepared by hot ethanol wash in Soxhlet extractor. % N calcd. 16.9; % N obsd. 16.4
Terephthalic acid	$C_8H_6O_4$	Not molten at 320	—	—	—	—	Broad OH in 3000 region —C=O at 1700 —COO at 1620 —C—O at 1285, 1292	Non-sublimeable solid. Purified by solution in base and reprecipitation with acid. Neut. equiv. calcd. 83.1; neut. equiv. obsd. 82.8. Prepared dimethyl terephthalate derivative, m.p. 140–141°

[a] K. W. Rosenmund, F. Zetzsche, and C. Flutsch, *Ber.*, **54**, 2888 (1921) list the m.p. 198°; B. Westenberger, *Ber.*, **16**, 2995 (1883) has m.p. 200°. [b] An authentic sample of benzalaniline (m.p. 50–51°) has the usual doublet at 1598 and 1587 $cm.^{-1}$ denoting Ar-conjugation. The replacement of these two bands by the singlet in the terephthalaldehyde derivative may be due to the symmetry of the *para*-conjugated groups. [c] H. V. Lendenfelt, *Monatsh.*, **27**, 969 (1906) lists m.p. 200–201°. [d] K. W. Rosenmund, *et al.* (*loc. cit.*) report m.p. 281° with sintering at 272°. [e] This behavior of the aldehyde-acid during a melting point determination had been observed previously by Wegscheider and Suida (*loc. cit.*). The use of a CO_2-filled, or an evacuated capillary tube leads to m.p. 248–250° [W. Davies, W. H. Perkin, and H. Clayton, *J. Chem. Soc.*, **121**, 2214 (1922) and N. V. Sidgwick and H. Clayton, *J. Chem. Soc.*, 2264 (1922)]. [f] J. B. Bowen and E. M. Wilkinson, *J. Chem. Soc.*, 750 (1950) observed m.p. 319.5–320.5° (uncorr.); J. W. Eustance, private communication recorded m.p. 322° (uncorr.).

TABLE III

CHARACTERIZATION AND REACTIONS OF DCX

Reagents	Product	Formula	M.P., °C.	% C		% H		% N		Comments
				Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.	
Sodium benzoate, KI (butyl carbitol–water)	α,α′-*p*-xylenediol dibenzoate[a]	$C_{22}H_{18}O_4$	87–88.5	76.3	76.1	5.2	4.9	—	—	Refluxed 2 hr. Small white needles from ethanol. Similar reaction with sodium *p*-nitrobenzoate, in absence of KI, failed to yield derivative
Sodium phenoxide (butyl carbitol–water)	α,α′-diphenoxy-*p*-xylene	$C_{20}H_{18}O_2$	142[b]	82.7	83.2	6.3	6.2	—	—	Refluxed 100 min. White needles from ethanol
Thiourea, picric acid (ethanol)	α,α′-di-*S*-isothiuronium-*p*-xylene dipicrate	$C_{22}H_{20}N_{10}O_{14}S_2$	251–252 (dec.)	—	—	—	—	19.6	19.3	Refluxed 1.5 hr. Bright yellow needles from a water-ethanol-acetone mixture
Sodium *o*-benzoyl sulfimide (saccharin), KI (butyl carbitol–water)	*N,N′*-*p*-xylene disaccharin	$C_{22}H_{16}N_2O_6S_2$	315 (uncorr.)	—	—	—	—	6.0	5.8	Refluxed one hr. Twice recrystallized from dimethyl formamide–ethanol mixture. Attempts to prepare diphthalimido derivative only gave phthalimide
Sodium nitrite (methanol)	*p*-Chloromethyl benzyl alcohol (*p*-chloromethyl benzaldehyde)	C_8H_9ClO	B.p. 100–130/0.5	61.3	61.1	5.8	5.8	—	—	Refluxed 3 hr. Small amount of product as brown oil from a Hickman micro still. Positive Beilstein test. Immediate ppt. with silver nitrate. Broad OH at 3390 CH_2 at 2920, 2860. Formyl H at 2735. Aryl-CHO at 1700. CH_2OH at 1270, 1042. No NO_2 group absorption
Sodium nitrate (methanol)	*p*-Hydroxymethyl benzaldehyde (as *p*-nitrophenyl hydrazone)	$C_{14}H_{13}N_3O_3$	189–191	—	—	—	—	15.5	15.4	Small amount of product isolated as yellow oil
Hydrogen peroxide (NaOH, water)	(*i*) Terephthalic acid as dimethyl ester	$C_{10}H_{10}O_4$	141–142	—	—	—	—	—	—	Refluxed 12 hr. Molar ratio of NaOH:-H_2O_2:DCX = 5:4:1
	(*ii*) α,α′-dihydroxy-*p*-xylene	$C_8H_{10}O_2$	118–119[c]	69.5	69.2	7.3	7.6	—	—	Broad OH at 3280. CH_2OH at 1290, 1025[d]

[a] The monobenzoate (m.p. 73–74°) was prepared by E. Grimaux, *Compt. rend.*, **70,** 1363 (1870) by heating an alcoholic solution of DCX and sodium benzoate for 48 hr. at 100°. [b] The only previous mention is by J. v. Braun and H. Reich, *Ann.*, **445,** 225 (1925) who record m.p. 142°. They indicate that they investigated the reaction of the ether with hydrochloric acid and that it had not been prepared previously. No preparative or analytical data are presented. [c] I. Wender, H. Greenfield, S. Metlin, and M. Orchin, *J. Am. Chem. Soc.*, **74,** 4079 (1952) report m.p. 118–119.4°. [d] The infrared spectrum is identical with that of the glycol prepared by the lithium aluminum hydride reduction of dimethyl terephthalate (R. E. Burnett and J. R. Ladd, personal communication).

After this separation scheme was adopted, a somewhat similar plan was found to have been used by Low;[10] he had used chloroform instead of ether in the Soxhlet extractor. The latter was found to be a more selective solvent in this step. The terephthalaldehyde and terephthalaldehydic acid were then further purified by microsublimation at reduced pressure. Because of the aqueous insolubility of the acids produced, neutralization equivalents were found to be valid only if the acids were first dissolved in warm, standard alkali.

A detailed composite of the results of the isolation and identification of the DCX–HNO_3 reaction products is presented in Table II.

(10) W. Low, *Ann.*, **231**, 361 (1885).

Characterization and reactions of DCX. Table III summarizes the various reactions which were investigated with DCX. The most satisfactory derivative is α,α'-diphenoxy-*p*-xylene, *p*-$C_6H_5OCH_2C_6H_4CH_2OC_6H_5$; it is easily prepared and purified, and has a convenient melting point range.

Acknowledgment. I wish to thank the following Research Laboratory personnel for their invaluable assistance: Mr. Carl Hirt and Mrs. Florence Crouse for their aid in the interpretation and determination of infrared spectra, and Mrs. Joyce Northrup and Miss Beatrice Fey for their combustion analyses.

SCHENECTADY, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE UNIVERSITY]

Oxidation of 3-Phenoxymesitol

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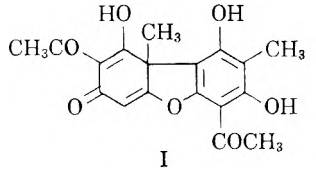
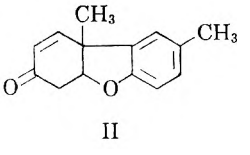
The synthesis of 3-phenoxymesitol (V) and the products of its alkaline ferricyanide oxidation are described.

The mold metabolite, usnic acid (I)[1,2] as well as the *p*-cresol oxidation product known as Pummerer's ketone (II)[2] are formed in one-electron

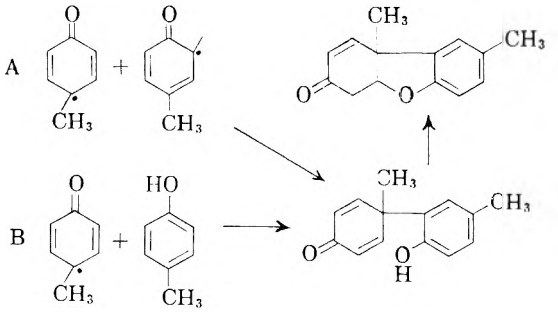


I

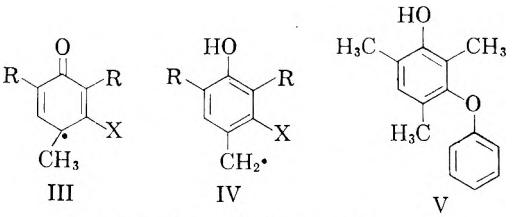


II

oxidation of methylphloracetophenone or *p*-cresol, respectively, by the pairing of radicals (A) or the substitution of one radical into a neutral phenol molecule followed by further oxidation (B).



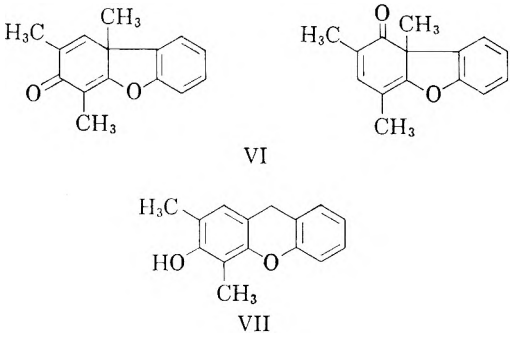
In the free radical oxidation of 2,6-dialkyl-4-methylphenols the nature of the products suggests the transient existence of radicals IIIa and IVa.[3] If in the one-electron oxidation of 3-phenoxymesitol (V) there occurred an internal condensation



III IV V

a, R = R = alkyl; X = H
b, R = R = CH_3; X = —OC_6H_5

of the radicals IIIb and IVb as in reaction B there would be formed analogs of I (*i.e.*, VI) or the dibenzopyran VII.



VI VII

The purpose of this study has been to ascertain whether the monomolecular ring closure of IIIb and or IVb could compete with the bimolecular dimerization and hydroxylation reactions which generally follow the formation of IIIa and IVa.

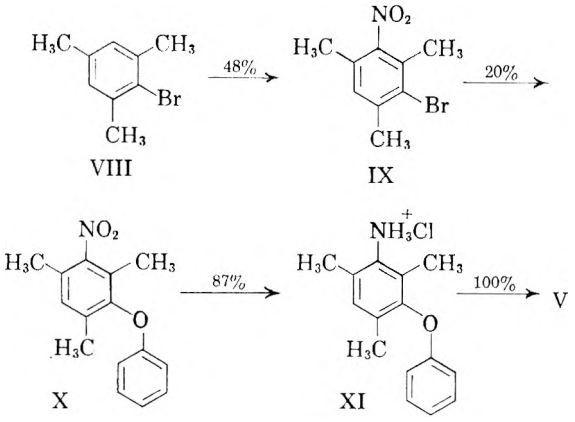
The synthesis of V was accomplished in the following manner. Bromonitromesitylene (IX), obtained by nitration of bromomesitylene,[4] was converted to nitrophenoxymesitylene by refluxing with sodium phenoxide and copper bronze in

(1) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Chem. Soc.*, 530 (1956).

(2) V. Arkley, F. M. Dean, A. Robertson, and P. Sidisunthorn, *J. Chem. Soc.*, 2322 (1956).

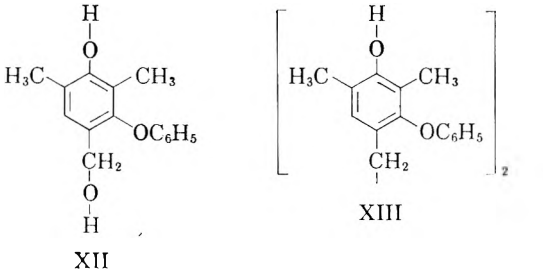
(3) For discussion and general references see H. E. Hey and W. A. Waters, *J. Chem. Soc.*, 2754 (1955).

(4) L. I. Smith, *Org. Syntheses*, **Coll. Vol. II** 95 (1943).



diethylene glycol diethyl ether. The period of reflux was found to be critical and the best yields were obtained when the reaction was run on a small scale. The nitrodiphenyl ether (X) was easily reduced to 3-phenoxymesidine (XI) by the general procedures of Furst[5] and XI converted to V by the general method of Lambooy.[6]

The oxidation of V by ferricyanide in water was found to occur only at high *p*H. When a 7% excess of ferricyanide was used and the reaction run in 5% aqueous potassium hydroxide solution at room temperature there was recovered 52% of the starting phenol (V), 14% of the pure benzyl alcohol XII, and 10% of the pure bibenzyl XIII. The



proposed structures XII and XIII are based on molecular weight and analytical data as well as infrared analysis. The positions of the —CH_2OH group in XII and of dimerization in XIII are assigned by analogy.[3]

Infrared analysis of the mixture of reaction products, prior to their fractionation, showed no absorbance between 4 and 7.7 μ, thus eliminating the presence of dienones (VI)[7] and there could not be isolated from the reaction mixture a fraction corresponding to VII. Thus, the internal condensation of the radicals IIIb and IVb does not appear to compete with the hydroxylation and pairing reactions which are the usual fate of IIIa and IVa.[3]

EXPERIMENTAL

Nitrobromomesitylene (IX). To 264 g. (1.33 mole) bromomesitylene[4] in 225 ml. acetic anhydride there was added, with constant stirring, a solution of 83 ml. (2.0 mole) fuming nitric acid (sp. gr. 1.51) in 160 ml. of a 50% acetic acid–acetic anhydride mixture (15–20°). When addition was completed the reaction mixture was allowed to warm to room temperature and stand for several hours. The reaction mixture was then warmed to 50° for 15 min., cooled, and poured into 2.5 l. of cold brine. The organic layer was separated and the aqueous phase thoroughly extracted with ether. The organic phase and washings were combined, washed thoroughly with 5% sodium bicarbonate solution and the solvent removed on the steam bath. The residue was then fractionated by use of a three-foot helices packed column, b.p. 127° at 3 mm. Hg and a bath temperature of 180–195°. The solid distillate was melted and poured into 175 ml. of hot 95% ethanol and allowed to crystallize; 152–156 g. (47–48%) of IX, m.p. 54–56°. (lit.[8] 54°).

Nitrophenoxymesitylene (X). Phenol (33.8 g.; 0.36 mole) and sodium metal (7.2 g; 0.31 mole) were allowed to react to completion in 75 ml. of anhydrous diethylene glycol diethyl ether contained in a 200-ml. round bottom flask equipped with an air condenser with a takeoff 8″ above the solvent surface. To the suspension of sodium phenolate there was then added 0.9 g. copper-bronze and 29.4 g. (0.12 mole) of IX. After refluxing for 6 hr. the reaction mixture was cooled and poured into 200 ml. of 5% aqueous potassium hydroxide solution. The suspension was thoroughly extracted with petroleum ether which was then washed with a little water and dried over anhydrous sodium carbonate. After removal of solvent, over steam, the residue was distilled *in vacuo* using a modified Claisen head with a 5″ Vigreaux column heated at 70°. The fraction containing the product distilled at 140–155° at 1.5 mm. Hg and a bath temperature of 190–200°.

In practice it was found most convenient to repeat the above procedure a dozen times and then to recrystallize the pooled distillates three times from 95% ethanol. When this procedure was followed, and when the mother liquors from the recrystallizations of the product were added to the following batch, prior to distillation, then there was obtained 6.2 g. (20%) of X per batch, m.p. 66–68°. For analysis the compound was sublimed *in vacuo* (100° at 1.0 mm. Hg), m.p. 66–68°.

Anal. Calcd., for $C_{15}H_{13}O_3N$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.78; H, 6.02; N, 5.38.

3-Phenoxymesidine hydrochloride (XI). The nitrophenoxymesitylene (25.7 g.; 0.10 mole) was dissolved in 250 ml. of 95% ethanol to which was added 15 ml. of 100% hydrazine hydrate and a small quantity of Raney nickel. The suspension was warmed on a steam bath to initiate the reaction and then allowed to stand at room temperature for 60 min. Additional catalyst was then added and the flask heated to 50°. When ebullition of gas had ceased the catalyst was removed by filtration and 13 ml. of concentrated hydrochloric acid added. After several hr. of refrigeration the amine hydrochloride was collected and dried *in vacuo* over $CaCl_2$. In this manner 22.2 g. (84%) of XI was obtained, m.p. 239–246°. For characterization the acetyl 3-phenoxymesidine was prepared and recrystallized from *n*-heptane and benzene and from ethanol and water, m.p. 168–169°.

Anal. Calcd. $C_{17}H_{19}O_2N$: C, 75.82; H, 7.11; N, 5.20. Found: C, 75.56; H, 7.17; N, 5.30.

3-Phenoxymesitol (V). By vigorous mechanical stirring, 5.27 g. (0.02 mole) of XI was dissolved in a solution composed of 80 ml. glacial acetic acid and 40 ml. *o*-phosphoric acid. The resultant clear solution was poured into a vigorously stirred solution of 800 ml. water and 64 ml. sulfuric acid. The fine suspension of the amine sulfate was then diazotized (0–5°) by the slow addition of a solution of sodium nitrite (2.75 g.; 0.04 mole) dissolved in 25 ml. water. When diazotization was completed (45 min.) excess nitrous acid was destroyed by addition of a solution of sulfamic acid.

(5) A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).
(6) J. P. Lambooy, *J. Am. Chem. Soc.*, **72**, 5327 (1950).
(7) G. M. Coppinger, *J. Am. Chem. Soc.*, **79**, 2758 (1957).
(8) R. Fittig and J. Storrer, *Ann.*, **147**, 7 (1868).

The solution of diazonium salt was then added dropwise to a boiling solution of 80 ml. sulfuric acid in 340 ml. water, the phenol being continuously removed by steam distillation after the method of Lambooy,[6] in all, about 3.5 to 4 l. of distillate being collected. After addition of ammonium sulfate the distillate was extracted four times with benzene, the benzene dried over anhydrous sodium carbonate and evaporated *in vacuo* to yield the 3-phenoxymesitol as a colorless oil (4.5 g; 98%) which could not be induced to crystallize.

The phenol was characterized through its α-naphthylurethane which, for analysis, was chromatographed on acid washed alumina (benzene and *n*-heptane) and recrystallized from the same solvents, colorless needles melting at 173° *in vacuo*.

Anal. Calcd. for $C_{26}H_{23}O_3N$: C, 78.7; H, 5.84; N, 3.53. Found: C, 78.89; H, 5.96; N, 3.53.

Oxidation of V. To 3.31 g. of V (0.0145 mole) dissolved in 200 ml. of 5% potassium hydroxide solution there was added over a period of 30 min. and with rapid stirring, 5.1 g. (0.0155 mole) of potassium ferricyanide dissolved in 25 ml. 5% KOH solution. During the addition the solution acquired a bright violet color and then became milky in appearance. After an additional 2.5 hr. stirring the solution became clear and colorless. At this time the reaction mixture was neutralized with acetic acid, the precipitated oil extracted with benzene and the benzene solution washed with a little water and dried over Na_2CO_3. The yellow, viscous oil obtained by removal of solvent *in vacuo* was taken up three times in 25-ml. aliquots of boiling *n*-heptane, each time the solution was allowed to cool and the supernatant decanted. The combined supernatants were allowed to pass through (slight suction) a 6″ × 0.5″ acid washed alumina column previously wetted with *n*-heptane. Evaporation of the column effluent yielded 1.7 g. (52%) of starting material (α-naphthyl urethane and infrared spectra). The oil remaining after extraction with *n*-heptane was dissolved in a minimum volume of benzene which was then passed through the column. The column was then washed with additional aliquots of benzene until a yellow band separated from the origin and traversed the length of the column. The benzene effluent when evaporated yielded a pale yellow glass which crystallized when stored at 40° under *n*-heptane (product A). The column was next washed with 25 ml. of a 10% ethanol-benzene mixture and the effluent evaporated to yield a yellow glass which also crystallized under *n*-heptane at 40° (product B).

On repeated recrystallization from benzene by addition of *n*-heptane, product A yielded 0.46 g. (14%) of 4,4′-dihydroxy-3,3′,5,5′-tetramethyl-2,2′-diphenoxybibenzyl (XIII) as buttons of white needles, m.p. 154–155°.

Anal. Calcd. for $(C_{15}H_{15}O_2)_2$: C, 79.4; H, 6.66. Found: 79.23; H, 6.38. A Rast molecular weight determination could not be performed because of the reactivity of the product with camphor. A molecular weight by the isothermal distillation method of Childs:[9] Calcd. 454, found 436.

Recrystallization of product B from benzene and *n*-heptane mixtures yielded 0.33 g. (10%) of flat colorless plates of 2,6-dimethyl-1-hydroxy-3-phenoxybenzyl alcohol, m.p. 131–132°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.7; H, 6.59; mol. wt., 244. Found: C, 73.95; H, 6.68; mol. wt., 288 (Rast).

NEW HAVEN, CONN.

(9) C. E. Childs, *Anal. Chem.*, 26, 1963 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

1-Ketolilolidine and Some of Its Reactions

HENRY RAPOPORT AND JAMES R. TRETTER

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Cyanoethylation of indoline gave 1-indolinepropionitrile which was cyclized directly to 1-ketolilolidine in very poor yield. However, hydrolysis to 1-indolinepropionic acid and heating this acid in polyphosphoric acid gave an excellent yield of cyclic ketone. Condensation with benzaldehyde or furfuraldehyde led to the α-ylidene ketone which was isomerized readily with alkali to the corresponding 4-quinolone.

As a possible entry to the difficulty prepared 7-substituted indoles and indolines, the synthesis of 1-ketolilolidine[1] (IV) was undertaken. Although its conversion to 7-substituted indolines as yet has not been achieved, a convenient preparation of the desired ketone (IV) and an account of some of its reactions are presented at this time.

Since acrylonitrile has been used to cyanoethylate numerous aromatic amines, the reaction of acrylonitrile and indoline was examined for the preparation of 1-indolinepropionitrile (I). Following the procedure which had been used successfully to cyanoethylate tetrahydroquinoline,[2] indoline and acrylonitrile were heated in acetic acid. Some 1-indolinepropionitrile was obtained, but a by-product of major proportions was 1-acetylindoline. Similar difficulty had been encountered in the cyanoethylation of *o*-toluidine[3] and since it had been overcome by the addition of cuprous chloride, a comparable addition was made in the present case. As a result the formation of 1-acetylindoline was eliminated almost completely and 1-indolinepropionitrile (I) was obtained in excellent yield.

Cyclization to the ketone (IV) was considered first directly from the nitrile (I). Several examples of closely-related ring-closures have been re-

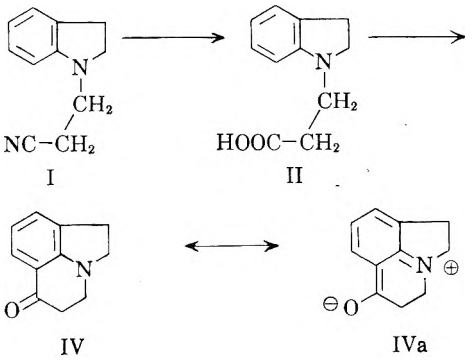
(1) The nomenclature proposed by C. Y. Almond and F. G. Mann, *J. Chem. Soc.*, 1870 (1952), based on liline, liloline, and lilolidine has been used throughout the discussion with the usual delta designation for the position of the double-bond in liloline except when it is 1,2. In the experimental part, alternative names have been given for most compounds, derived from the *Chem. Abstr.* name for lilolidine, 1,4,5,6-tetrahydro-2*H*-pyrrolo[3,2,1-*ij*]quinoline.

(2) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, *J. Am. Chem. Soc.*, 66, 725 (1944).

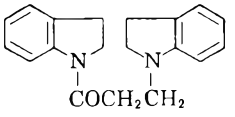
(3) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1817 (1953).

ported, *e.g.*, in which *N*,*N*-bis-2-cyanoethylaniline,[3,4] *p*-chloro-*N*,*N*-bis-2-cyanoethylaniline,[5] *N*-2-cyanoethyl-*N*-methylaniline,[6] 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline,[7] and 9-(2′-cyanoethyl)carbazole[7] have been converted to the corresponding ketones. Various combinations of aluminum chloride with hydrochloric acid in chlorobenzene and aluminum chloride, sodium chloride, and potassium chloride have been used, although it is interesting to note that attempts to repeat the cyclization of 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline[8] and 9-(2′-cyanoethyl)carbazole[9] have failed.

Numerous reactions were performed with 1-indolinepropionitrile (I) and aluminum chloride under conditions suggested by the above. Small amounts of 1-ketolilolidine (IV) were obtained, but the yields were quite poor and an appreciable proportion of the starting nitrile was converted to indoline as well as to polymeric material. For this reason, direct ring-closure of the nitrile was abandoned. It was hydrolyzed to the acid (II) and cyclization of the acid then was undertaken.



Three methods were investigated for cyclizing the propionic acid. The first, anhydrous hydrogen fluoride, led to no ketone, and the starting acid was recovered quantitatively. Trifluoroacetic anhydride in benzene[10] then was applied and although about a 20% yield of ketone (IV) was obtained, most of the propionic acid (II) was converted to indoline and 1′-indolinepropionyl-1-indoline (III).



The structure of 1′-indolinepropionyl-1-indoline was established by its analysis, the presence of a strong band at 1645 cm.$^{-1}$ in its infrared spectrum, and its ultraviolet spectrum which was almost exactly that of indoline plus 1-acetylindoline. Its formation had probably occurred through the mixed anhydride of II and trifluoroacetic acid which had in part eliminated indoline, and the latter then was acylated by the anhydride.

The best method for converting acid (II) to ketone (IV) was by the use of polyphosphoric acid which resulted in an 87% yield. 1-Ketolilolidine is bright yellow and in its color and ultraviolet absorption (Fig. 1) is very similar to the 1,2,3,4-

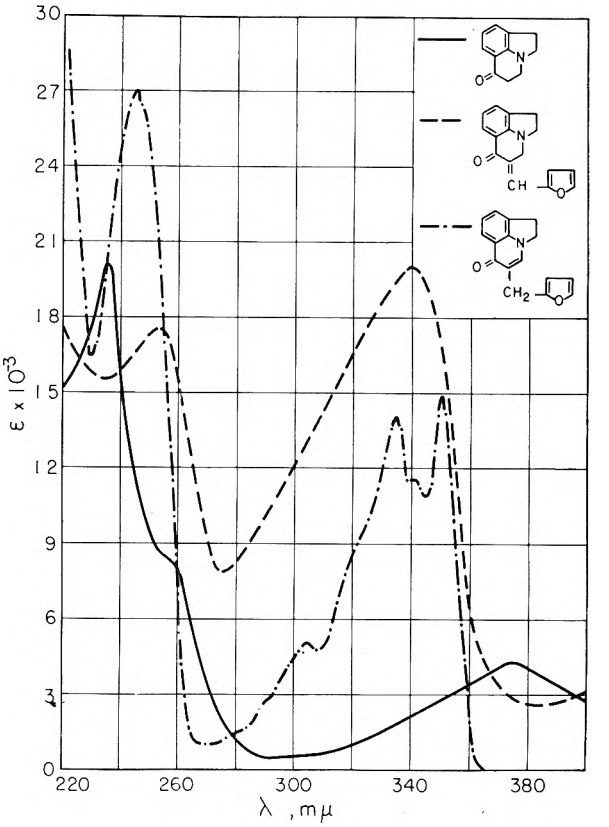


FIG. 1. ULTRAVIOLET SPECTRA IN ETHANOL: ——— 1-Ketolilolidine; - - - - 1-Keto-2-furfurylidenelilolidine; — · — · — 1-Keto-2-furfuryl-Δ²-liloline.

tetrahydro-4-oxoquinolines. The color of these compounds has been ascribed[6] to the contribution of the *o*-quinonimine form, and similarly the resonance form IVa undoubtedly is responsible for many properties of 1-ketolilolidine. In addition to the color, this should lead to a strong base-weakening effect as is the case. Spectral and distribution studies indicated the ketone (IV) had a pK_a' of 1 or less.

To prepare liloline (V), the method of Bamford and Stevens[11] was applied. This consists in heating the ketone *p*-toluenesulfonylhydrazone in ethylene

(4) R. C. Cookson and F. G. Mann, *J. Chem. Soc.*, 67 (1949).

(5) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 651 (1954).

(6) J. A. C. Allison, J. T. Braunholtz, and F. G. Mann, *J. Chem. Soc.*, 403 (1954).

(7) French Patent 806,715 (1936).

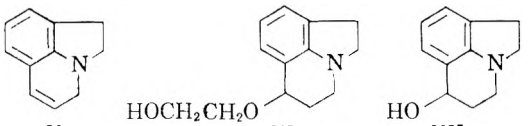
(8) F. G. Mann and B. B. Smith, *J. Chem. Soc.*, 1898 (1951).

(9) P. A. S. Smith and T. Yu, *J. Am. Chem. Soc.*, 74, 1096 (1952).

(10) R. J. Ferrier and J. M. Tedder, *J. Chem. Soc.*, 1435 (1947).

(11) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

glycol with sodium glycolate. However, instead of the olefin (V), the product was the ethylene glycol ether (VI).[12] An alternative approach to liloline was through the alcohol (VII). Reduction of 1-ketolilolidine with sodium borohydride gave 1-hydroxylilolidine in quantitative yield, but it could be converted neither to the chloride nor tosylate for subsequent elimination.



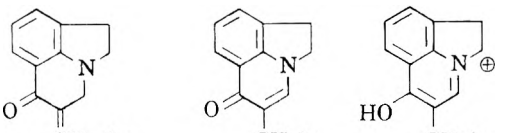
V VI VII

Condensation of 1-ketolilolidine with aromatic aldehydes offered a particularly promising path to 1,7-disubstituted indolines since such α-ylidene ketones have been successfully oxidized to the ring-opened dibasic acids.[13] The first stage of this method proceeded readily in the condensation of furfural and 1-ketolilolidine to the red 1-keto-2-furfurylidenelilolidine (VIII). When the latter compound was subjected to the action of alkaline hydrogen peroxide,[14] a rapid reaction took place as indicated by the fading of the red color and the appearance of a yellow substance. This yellow material was not an oxidation product but was isomeric with the red starting material (VIII), suggesting that an alkali-catalyzed isomerization rather than an oxidation had occurred.

This was proved to be the case by treating the furfurylidene ketone (VIII) with alkali and obtaining the same isomeric yellow material in excellent yield. In parallel experiments with benzaldehyde, the initial red benzylidene compound (IX) was observed, but it proved too unstable and the alkali used in the condensation was sufficient to cause isomerization to yellow material. It was also demonstrated that acid caused this isomerization to occur, but at a much decreased rate.

Although the possibility existed that the red and yellow isomers were cis-trans isomers about the double bond, this seemed unlikely in view of the accompanying gross changes in ultraviolet absorption (Fig. 1) and infrared absorption. In the infrared, the carbonyl band moved from 1660 cm.$^{-1}$ to 1630 cm.$^{-1}$, indicating even greater conjugation. In the ultraviolet, the peak at 340 mμ was replaced by a clear bifurcation in the 320-360 mμ region, and the absorption at 252 mμ underwent a 7 mμ hypsochromic shift while its extinction coefficient increased from 17,500 to 27,000. This spectrum is very characteristic of 4-quinolones[15] and provides sufficient evidence to assign structures X and XI to the yellow isomers. Actually, this type of condensation and isomerization offers an interesting alternative to the general methods for preparing 4-quinolones.[15]

The quinolone spectrum is only slightly effected by alkali, but in 1*N* hydrochloric acid, the bifurcation disappears and the short wavelength maximum increases tremendously in extinction coefficient to 64,500 and 75,000 for X and XI, respectively. This is probably due to acid stabilization of the highly conjugated form XII.



VIII, Ar = C_4H_3O X, Ar = C_4H_3O XII
IX, Ar = C_6H_5 XI, Ar = C_6H_5

EXPERIMENTAL[16]

1-Indolinepropionitrile (I). Indoline was prepared in 76% yield by hydrogenation of indole using Raney nickel[17] in absolute ethanol at 90 atmospheres and 100° for twelve hours.[18] For the cyanoethylation, 10 g. (.084 mole) of indoline, 3 ml. of acetic acid, 8 g. of acrylonitrile, and 0.8 g. of freshly prepared cuprous chloride were heated under reflux (bath temperature, 125°) for 12 hr. in a nitrogen atmosphere, with an additional 6 g. of acrylonitrile being added after the first seven hours had elapsed. The reaction mixture was then cooled, made alkaline with concentrated ammonium hydroxide, and extracted thoroughly with methylene chloride. Evaporation of the methylene chloride and distillation of the residue gave 2 g. of recovered indoline plus a fraction, b.p. 125–140°/1 mm., consisting of 1-indolinepropionitrile and a small amount of 1-acetylindoline. This fraction was dissolved in benzene, hexane was added almost to turbidity, and the organic phase was washed repeatedly with 3*M* sulfuric acid. Addition of ammonium hydroxide to the cooled aqueous solution then precipitated the nitrile which was crystallized from ethanol; yield, 11.0 g. (95%), m.p. 40–41°. Ultraviolet spectrum in ethanol: λ_{max} 253 mμ (ϵ 10,400), 299 (2400).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.7; H, 7.0; N, 16.3. Found: C, 77.0; H, 7.0; N, 16.0.

1-Indolinepropionic Acid (II). 1-Indolinepropionitrile (18 g., 0.1 mole) and 200 ml. of 3*N* potassium hydroxide were heated under reflux in a nitrogen atmosphere until solution was complete (about 3 hr.). The reaction mixture then was cooled, washed with methylene chloride, and acidified to *p*H

(12) Although the original reference (ref. 11) gives two examples of ethylene glycol mono ether formation in this reaction, these were all with compounds having no α-hydrogens. In the present case and also with two other 6-membered cyclic aromatic ketones each having two α-hydrogens, we have obtained glycol ethers as the sole products.

(13) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **78**, 6354 (1956).

(14) In other experiments with ozone, the entire material was oxidized to non-isolable, highly water soluble products.

(15) E. A. Steck, G. W. Ewing, and F. C. Nachod, *J. Am. Chem. Soc.*, **71**, 238 (1949).

(16) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley.

(17) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(18) F. E. King, J. A. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945). In some hydrogenations, as much as 5% of perhydrogenated material was formed, but this was easily removed by extraction with methylene chloride at pH 6. Under these conditions, indoline goes into the organic phase while the strongly basic perhydrogenated material stays in the water.

3–4, precipitating the acid. Crystallization from hexane gave 14.1 g. of 1-indoline propionic acid, and extraction of the aqueous acid solution with methylene chloride, evaporation of the methylene chloride, and crystallization of the residue gave an additional 4.1 g.; total yield, 18.2 g. (91%), m.p. 75–76°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.8; equiv. wt., 191. Found: C, 69.2; H, 6.8; equiv. wt., 192.

Cyclization of 1-indolinepropionic Acid (II) *to 1-ketolilolidine* (IV) (*6-oxo-1,4,5,6-tetrahydro-2H-pyrrolo [3,2,1-ij] quinoline*). *A. Using polyphosphoric acid.* 1-Indolinepropionic acid (100 g., 0.52 mole) and 3000 g. of polyphosphoric acid were heated at 100° with stirring in a nitrogen atmosphere for 24 hr. after which 12 l. of water was added and the pH was adjusted to 3.5 with concentrated sodium hydroxide. Continuous extraction with ether was carried on for 3 days and the ether extract then was washed with 2*N* potassium hydroxide to remove uncyclized acid. Acidification of this extract to pH 3.5, extraction with ether, and evaporation of the ether gave 30 g. of recovered 1-indolinepropionic acid. Evaporation of the ether that had been washed with alkali left a viscous residue which was distilled at reduced pressure, b.p. 151°/2.4 mm. This material solidified to yellow crystals and could be recrystallized from heptane, m.p. 55–56°; 55 g., 61% conversion, 87% yield based on recovered acid. Ultraviolet spectrum in ethanol: λ_{max} 236 mμ (ε 20,000), 376 (4,200), shoulder at 256 mμ (ε 8,200).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N, 8.1. Found: C, 76.4; H, 6.2; N, 8.2.

The dark red *p-nitrophenylhydrazone* was prepared in the usual way and was crystallized from ethanol, m.p. 245° (dec.).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.2; H, 5.2; N, 18.2. Found: C, 66.2; H, 5.1; N, 18.2.

On standing in ethanol for 24 hr., a solution of 1-ketolilolidine and *p*-toluenesulfonylhydrazine precipitated the yellow *p-toluenesulfonylhydrazone* which was recrystallized from aqueous acetone, m.p. 217° (dec.).

Anal. Calcd. for $C_{18}H_{19}N_3O_2S$: C, 63.3; H, 5.6; S, 9.4. Found: C, 63.1; H, 5.9; S, 9.6.

B. Using trifluoroacetic anhydride. After 20 ml. of benzene was distilled from a solution of 5 g. (.026 mole) of 1-indolinepropionic acid in 70 ml. of benzene, a solution of 4 ml. of trifluoroacetic anhydride in 4 ml. of benzene was added over 5 min. and the solution was heated under reflux for another 10 min. Excess, dilute potassium hydroxide then was added to the cooled solution, the aqueous phase was extracted with two additional portions of benzene, and acid was added to pH 4. Extraction of the aqueous acid solution with ether led to the recovery of 0.8 g. of 1-indolinepropionic acid. The combined benzene extracts were washed with water and evaporated leaving a residue which was distilled at reduced pressure. From the fraction boiling at 70–110°/0.3 mm., 0.95 g. of 1-ketolilolidine (IV) was isolated. The distillation residue was dissolved in ethanol, treated with decolorizing carbon, and crystallized from benzene to give 2 g. of *1'-indolinepropionyl-1-indoline* (III), m.p. 125–126°. Ultraviolet spectrum in ethanol: λ_{max} 255 mμ (ε 23,200), 282 (7600), 292 (7000).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.1; H, 6.9; N, 9.6. Found: C, 78.3; H, 6.8; N, 9.6.

Decomposition of 1-ketolilolidine p-toluenesulfonylhydrazone. To 0.3 g. of sodium dissolved in 10 ml. of ethylene glycol was added 1.5 g. of 1-ketolilolidine *p*-toluenesulfonylhydrazone prepared above and the solution was heated to 150° in a nitrogen atmosphere. After 24 hr., the solution was poured into 40 ml. of water and the oil which separated was extracted into benzene. Evaporation of the benzene and distillation (100°/0.1 mm.) of the residue onto a cold finger gave 0.7 g. of *ethylene glycol mono (1-lilolidinyl) ether* (VI) as an oil. Ultraviolet spectrum in ethanol: λ_{max} 252 mμ (ε 7100), 307 (2700).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.4; H, 8.0; N, 6.3.

1-Hydroxylilolidine (VII) (*6-oxy-1,4,5,6-tetrahydro-2H-pyrrolo[3,2,1-ij]quinoline*). A solution of 1 g. of 1-ketolilolidine in 200 ml. of methanol to which 4 g. of sodium borohydride in 25 ml. of water had been added was allowed to stand at room temperature for 24 hr. The methanol was then removed *in vacuo*, the aqueous residue was extracted with benzene, and the benzene was evaporated. Distillation (125°/0.1 mm.) of the residue onto a cold finger gave 0.95 g. of 1-hydroxylilolidine, m.p. 54–54.5°. Ultraviolet spectrum in ethanol: λ_{max} 251 mμ (ε 7400), 304 (2700).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0. Found: C, 75.5; H, 7.5; N, 8.1.

1-Keto-2-furfurylidenelilolidine (VIII) (*5-furfurylidene-6-oxo-1,4,5,6-tetrahydro-2H-pyrrolo[3,2,1-ij]quinoline*). A sodium hydroxide solution (10 ml. of 5*N*) was added to a cold solution of 1 g. of 1-ketolilolidine and 1 g. of furfural in 10 ml. of methanol, and the nitrogen filled flask was shaken for 6 hr. The mixture was filtered and the precipitated furfurylidene compound was washed well with cold water and crystallized from ethanol to give 0.9 g. (62% yield) of long, red needles, m.p. 148–149°. Ultraviolet spectrum in ethanol: λ_{max} 252 mμ (ε 17,500), 340 (20,000).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.2; H, 5.2; N, 5.6. Found: C, 76.1; H, 5.5; N, 5.8.

1-Keto-2-furfuryl-Δ²-liloline (X) (*5-furfuryl-6-oxo-1,6-dihydro-2H-pyrrolo [3,2,1-ij] quinoline*). 1-Keto-2-furfurylidenelilolidine (1 g.) was dissolved in 25 ml. of methanol and 5 ml. of 1*N* aqueous potassium hydroxide was added. After this solution was stirred overnight under nitrogen, removal of the methanol at reduced pressure and cooling gave pale yellow crystals of 1-keto-2-furfuryl-Δ²-liloline in quantitative yield, m.p. 177–178° after recrystallization from aqueous methanol. Ultraviolet spectra: in ethanol, λ_{max} 245 mμ (ε 27,000), 335 (14,200), 350 (14,800); in 1*N* ethanolic hydrochloric acid, λ_{max} 238 mμ (ε 64,500), 324 (7000).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 76.5; H, 5.2; N, 5.6. Found: C, 76.1; H, 5.1; N, 5.7.

1-Keto-2-benzyl-Δ²-liloline (X) (*5-benzyl-6-oxo-1,6-dihydro-2H-pyrrolo[3,2,1-ij]quinoline*). To a cold solution of 0.75 g. of 1-ketolilolidine and 0.92 g. of benzaldehyde in 10 ml. of methanol was added 5 ml. of 5*N* aqueous sodium hydroxide. The flask was flushed with nitrogen, stoppered, and shaken. Within a few minutes, the solution became red and shortly after this a red precipitate appeared. This gradually disappeared and was replaced by a yellow-orange precipitate. After 24 hrs. of shaking, the mixture was filtered and the precipitate was recrystallized from aqueous ethanol to give 0.8 g. of 1-keto-2-benzyl-Δ²-liloline, m.p. 171–172°. Ultraviolet spectra: in ethanol, λ_{max} 248 mμ (ε 32,000), 336 (14,600), 352 (15,400); in 1*N* ethanolic hydrochloric acid, λ_{max} 243 mμ (ε 75,000), 328 (8,000).

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.8; H, 5.8; N, 5.4. Found: C, 83.1; H, 6.0; N, 5.5.

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[CONTRIBUTION NO. 241 FROM THE JACKSON LABORATORY, E. I. DU PONT DE NEMOURS & CO., INC.]

Preparation and Properties of Esters of *N*-Substituted Peroxycarbamic Acids

C. J. PEDERSEN[1]

Received April 8, 1957

Nine *tert*-butyl and α-cumyl esters of *N*-substituted peroxycarbamic acids have been prepared by: (*a*) reacting isocyanates with hydroperoxides in the presence of a solvent and a tertiary amine; or (*b*) reacting *N*-substituted carbamoyl chlorides with hydroperoxides in the presence of 30% aqueous potassium hydroxide. Various properties of these products are described. They liberate iodine from acidified potassium iodide and initiate the polymerization of vinyl monomers. Polystyrene containing amino groups was prepared by initiating the polymerization with *tert*-butyl *N*-dimethylperoxycarbamate.

tert-Butyl peroxycarbamate and four of its *N*-monosubstituted derivatives (phenyl, α-naphthyl, *p*-xenyl, and (−)-methyl) were prepared by Davies and Hunter[2] by three methods: (*a*) R—N=C=O + *t*-C_4H_9—O—OH with pyridine as catalyst; (*b*) RNHCOCl + *t*-C_4H_9—O—OH with pyridine as acid acceptor; and (*c*) R—NH_2 + *t*-C_4H_9—O—O—COCl. They give little information on the thermal stability of these compounds, and their only reference to polymerization is the statement that *tert*-butyl *N*-phenylperoxycarbamate catalyzes the polymerization of styrene at 85°.

Some other peroxycarbamates were synthesized in order to investigate in greater detail their thermal stability and their ability to initiate polymerization. Two general methods were used for their preparation:

Method I

$$R{-}N{=}C{=}O + R''{-}O{-}OH + (\text{tertiary amine}) \longrightarrow R{-}NH{-}\overset{\overset{O}{\|}}{C}{-}O{-}O{-}R''$$

Method II

$$RR'N{-}\overset{\overset{O}{\|}}{C}{-}Cl + R''{-}O{-}OH + 30\%\ KOH \longrightarrow RR'N{-}\overset{\overset{O}{\|}}{C}{-}O{-}O{-}R'' + KCl + H_2O$$

The first method can be used for the preparation of only peroxycarbamates containing the —NH— group, but the second method is applicable to the synthesis of all types although it is less suitable for the *N*-monosubstituted compounds.

The peroxycarbamates, especially the liquid ones, possess a characteristic odor which is a disagreeable blend of the odors of peroxides and amines. They are colorless unless they contain groups which confer color, such as —N(—C$_6$H$_4$—)—NO_2. As expected, they are all oxidizing agents which liberate iodine quantitatively from acidified potassium iodide. The preparative conditions and some of the properties are given in Table I.

(1) Present address: Elastomer Chemicals Department.

(2) A. G. Davies and K. J. Hunter, *J. Chem. Soc.*, **18**, 1808 (1953).

DISCUSSION

tert-Butyl *N*-ethylperoxycarbamate, hexamethylene-*N*,*N*′-bis(*tert*-butyl peroxycarbamate), and *tert*-butyl *N*-(*p*-nitrophenyl)peroxycarbamate were the most stable compounds prepared, and their half-lives are estimated to lie between 600 and 800 days at 24–28°. At the same temperature the half-life of hexamethylene-*N*,*N*′-bis(α-cumylperoxycarbamate) is about 250 days; those of *tert*-butyl *N*,*N*-dimethylperoxycarbamate and *tert*-butyl *N*,*N*-diethylperoxycarbamate are 57–65 days; and that of α-cumyl *N*,*N*-dimethylperoxycarbamate is about 32 days. It will be noted that the α-cumyl ester is less stable than the corresponding *tert*-butyl ester. *tert*-Butyl *N*,*N*-pentamethyleneperoxycarbamate and *tert*-butyl *N*-methyl-*N*-(*p*-nitrophenyl)-peroxycarbamate were the least stable compounds synthesized, and their half-lives lie between 2 and 4 days at 30°.

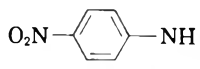
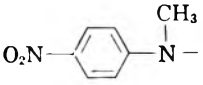
All these compounds begin to decompose rapidly between 80 and 140°, and all decompose violently when dropped on a hot plate at 140–180° except *tert*-butyl *N*-ethylperoxycarbamate which did not explode up to 220°. In no case was the decomposition accompanied by a flame. For possible hazards due to violent reaction see Experimental.

Aside from establishing the presence of carbon dioxide and basic substances among the decomposition products from peroxycarbamates, the products were not identified except those from *tert*-butyl *N*-(*p*-nitrophenyl)peroxycarbamate and *tert*-butyl *N*-methyl-*N*-(*p*-nitrophenyl)peroxycarbamate. The latter will be discussed in detail in another paper.

Peroxycarbamates initiate the polymerization of vinyl monomers as shown in Table II which compares *tert*-butyl *N*,*N*-pentamethyleneperoxycarbamate to benzoyl peroxide for the bulk polymerization of styrene at different temperatures. It will be observed that benzoyl peroxide is more effective at 82°, but the peroxycarbamate is the better initiator at lower temperatures. *tert*-Butyl *N*-ethylperoxycarbamate, *tert*-butyl *N*-(*p*-nitrophenyl)peroxycarbamate, *tert*-butyl *N*-methyl-*N*-(*p*-nitrophenyl)-peroxycarbamate, hexamethylene-*N*,*N*′-bis(*tert*-butyl peroxycarbamate), and hexamethylene-*N*,*N*′-bis(α-cumyl peroxycarbamate) also accelerated the bulk polymerization of styrene at 80°.

TABLE I

PREPARATION AND PROPERTIES OF A—C(=O)—O—O—R

No.	A	R[a]	Method	Solvent	Catalyst	Yield,[b] %	M.P., °C.[c]	Purity by KI, %	Nitrogen Content, % Calcd.	Nitrogen Content, % Found
1	C_2H_5NH—	R′	I	Benzene	Pyridine	18	39–40[d]	99	8.7	8.7
2	$(CH_3)_2N$—	R′	II	None	—	54	Liquid[e]	100	8.7	8.7
3	$(CH_3)_2N$—	R″	II	None	—	40	60[d]	100	6.3	6.3
4	$(C_2H_5)_2N$—	R′	II	None	—	43	Liquid[f]	100	7.4	7.4
5		R′	II	None	—	81	Liquid[g]	99	7.0	7.1
6		R′	I	Benzene	Triethylamine	59	93[h]	100	11.0	10.9
7		R′	II	Petrol. ether	—	68	66[h]	100	10.5	10.4
8	R′—O—O—C(=O)—NH—$(CH_2)_6$—NH—	R′	I	Benzene	Pyridine	6	64–5[d]	100	8.0	8.1
9	R″—O—O—C(=O)—NH—$(CH_2)_6$—NH—	R″	I	Benzene	Triethylamine	57	105[d]	98	5.9	6.3

[a] R′ is tertiary-butyl and R″ is alpha-cumyl. [b] Yields are based on isocyanate or carbamoyl chloride. They are approximate and no effort was made to secure maximum yields. [c] These points were determined on a bronze block and are uncorrected. In general the compounds decomposed on melting. [d] White crystals. [e] Colorless; boiling at 43–45°/0.1–0.2 mm. without decomposition. [f] Undistilled. [g] Undistillable at 0.005 mm. Pale yellow. [h] Yellow crystals.

The peroxycarbamates initiate the polymerization of other monomers. For example, in the solution polymerization (solvent: benzene) of chloroprene at 49°, 3.32 g. of polymer were obtained by using a given concentration of *N,N′*-azobis(α-isobutyronitrile), and 5.93 g. were obtained by using an equimolar quantity of *tert*-butyl *N*-pentamethyleneperoxycarbamate.

It was experimentally established that polystyrene prepared with *tert*-butyl *N,N*-dimethylperoxycarbamate contained amino groups: 0.9% nitrogen by Dumas' method; and 0.73% nitrogen by titrating the amino groups with perchloric acid in benzene solution. The polymer prepared with benzoyl peroxide contained no nitrogen. It is concluded, therefore, that the nitrogen-containing fragments from the peroxycarbamates participate in the formation of polymers, and that polymers incorporating amino groups can be produced by means of the esters of peroxycarbamic acids.

EXPERIMENTAL

Materials used. *tert*-Butyl hydroperoxide and α-cumyl hydroperoxide were commercial products used without purification; the former was 60% pure and the latter 72%. All other materials were either laboratory or commercial products, or were prepared by well known methods.

Quantitative analysis. The peroxycarbamates were analyzed for purity by adding a weighed quantity to an equivolume mixture of acetone and acetic acid containing potassium iodide, and warming under nitrogen at 45–50° from 10 to 70 min. depending on the stability of the peroxycarbamates. The equipment was protected from strong light during this period, and the liberated iodine was titrated with standard thiosulfate solution.

Preparation. The peroxycarbamates were prepared by two general methods. Method I is useful for the syntheses of compounds containing the —NH— group and Method II for the others.

Method I. tert-Butyl N-ethylperoxycarbamate (No. 1). Ethyl isocyanate, 2.57 g. (0.036 mole), dissolved in 10 ml. of benzene, *tert*-butyl hydroperoxide, 3 g. of 60% product (0.02 mole), and 5 drops of pyridine were mixed together at 5° in an Erlenmeyer flask. The flask was kept in an ice bath for 2 hr. and in the dark at room temperature for 5 days. At the end of this time the reaction mass was clear, colorless, and smelled of ethyl isocyanate and *tert*-butyl hydroperoxide. It was shaken with 25 ml. of water and left at room temperature for a day. The water layer was then separated and discarded. Ten ml. of benzene were added to the benzene portion and allowed to stand for 6 hr. in contact with 50 ml. of water containing 2.5 ml. of concentrated ammonium hydroxide. The ammonia layer was removed and replaced with 10 ml. of 10% aqueous sodium hydroxide, and the mixture was left overnight at room temperature. The benzene layer was separated, washed twice with 25 ml. of water, dried with anhydrous sodium sulfate and evaporated to dryness under reduced pressure.

The viscous oil which solidified shortly, 1.17 g., was 88% pure by KI analysis (yield: 18% based on the isocyanate). The product was purified by dissolving it in petroleum ether (30–60°) at 45° and cooling with a mixture of alcohol and solid carbon dioxide. White crystals were obtained melting at 39–40°.

Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.2; H, 9.3; N, 8.7. Found: C, 52.1; H, 9.3; N, 8.7. Infrared bands in Nujol solution: N—H at 3.01μ; C=O at 5.78μ; C—O at 8.73μ; and probably O—O at 11.80μ. Other properties of the compound are shown in Table I.

Hexamethylene-N,N′-bis(tert-butyl peroxycarbamate) (No. 8). This compound was made by the method used for the previous compound. Data concerning it are given in Table I.

Anal. Calcd. for $C_{16}H_{32}N_2O_6$: C, 55.2; H, 9.2; N, 8.0. Found: C, 55.9; H, 9.2; N, 8.1.

The above preparations were the first two attempted by Method I. Better yields would probably have been obtained if the simplified method used for the next compound had been employed.

Hexamethylene-N,N'-bis(α-cumyl peroxycarbamate) (No. 9). Hexamethylenediisocyanate, 1.25 g. (0.0074 mole), dissolved in 24 ml. of benzene, α-cumyl hydroperoxide, 3.2 g. of 72% product (0.015 mole), and 6 drops of triethylamine were mixed together at 5° in an Erlenmeyer flask. The charge was kept cool for 2 hr. and at room temperature for 22 hr. Fifty ml. of petroleum ether (30–60°) was added to the yellowish viscous reaction mixture, shaken vigorously, and allowed to settle. The precipitated paste, isolated by decantation, was dissolved in 30 ml. of benzene, filtered, and the filter washed with 20 ml. of benzene. The combined benzene solution was poured into 100 ml. of petroleum ether and mixed thoroughly. The solid which separated was collected, washed with petroleum ether, and dried on several layers of filter paper. The properties of the product, 2.01 g. (yield: 57% based on the diisocyanate), are shown in Table I.

tert-Butyl N-(p-nitrophenyl)peroxycarbamate (No. 6). This compound was prepared by the previous method using the appropriate intermediates. Its properties are given in Table I. It has an absorption maximum at 292 mμ (ϵ = 13,000 in isooctane).

Method II. tert-Butyl N,N-dimethylperoxycarbamate (No. 2). *N,N*-Dimethylcarbamoyl chloride, 21 g. (0.234 mole), and 30% aqueous potassium hydroxide, 43.4 ml. (0.3 mole) were separately but simultaneously added dropwise in the course of 45 min. with stirring to 35 g. of 60% *tert*-butyl hydroperoxide. The temperature was maintained throughout at 10–15° by external cooling. After complete addition the charge was permitted to come up to room temperature and stirred for 22 hr. The upper organic layer was separated and taken up in 300 ml. of petroleum ether and washed three times with 25 ml. of 30% aqueous sodium hydroxide to remove the unreacted hydroperoxide. The petroleum ether solution was filtered through a plug of glass wool and dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure at room temperature. The clear, nearly colorless oil, 34.6 g., was 73% pure by KI analysis (yield at this stage: 70% based on the carbamoyl chloride).

A colorless liquid product (20.3 g., 54%) was obtained by distillation under high vacuum, b.p. 43–45°/0.1–0.2 mm. (without decomposition), n_D^{25} 1.4303, d^{28} 0.935. Infrared bands without diluent: N—H band absent; C=O at 5.73μ; C—O at 8.75μ; and probably O—O at 12.08μ. Other properties of the compound are shown in Table I.

Safety tests. *tert*-Butyl *N,N*-dimethylperoxycarbamate, No. 2, was submitted to safety tests. Although it decomposes vigorously at elevated temperatures, it does not detonate like a true explosive. It must be emphasized, however, that peroxycarbamates should be handled with care, especially in large quantities, and stored in a cool place. It is also possible that some of them may be much more sensitive to disruptive influences than *tert*-butyl *N,N*-dimethylperoxycarbamate.

No decomposition was noted in 13 attempts to decompose this compound through impact by dropping a 5-kg. weight 55 in. Thermal decomposition tests were run with 7.5-ml. samples in a 75-ml. stainless steel cylinder in the absence of air, the temperature being raised 2.65°/min. It was found that the decomposition temperature was in the range of 60–63°, the maximum pressure was 1100 lb./sq. in. accompanied by a rapid rise in temperature to about 165°, and the maximum pressure development was 6140 lb./sq. in./sec. On the basis of this limited experience it has been concluded that the compound can be handled safely as far as impact alone is concerned, but that elevated temperatures should be carefully avoided especially when it is under confinement.

Although neither the pure compound nor 60% *tert*-butyl hydroperoxide ignited when dropped in the open on a bronze block heated to 158–160°, a mixture of the two products instantly burst into flame.

Alpha-cumyl N,N-dimethylperoxycarbamate (No. 3), *tert-butyl N,N-diethylperoxycarbamate* (No. 4), *tert-butyl N,N-pentamethyleneperoxycarbamate* (No. 5). These compounds were prepared by the same method as was used for the previous compound, and pertinent data are given in Table I. Unfortunately, *tert*-butyl *N,N*-diethylperoxycarbamate and *tert*-butyl *N,N*-pentamethyleneperoxycarbamate could not be purified by distillation even at 0.005 mm. because of thermal instability. They did not crystallize on cooling but formed glasses.

The *tert*-butyl esters of *N,N*-hexamethyleneperoxycarbamic and *N,N*-(3-oxapentamethylene)peroxycarbamic acids, and α-cumyl *N,N*-pentamethyleneperoxycarbamate were also prepared by this method. The products were liquids which could not be purified by distillation. Although the compounds were obtained their properties are not reported because of their low purity. The crude products decomposed vigorously at about 160°.

tert-Butyl N,N-pentamethyleneperoxycarbamate (No. 5). The pure product and equal volume mixtures with piperidine and glacial acetic acid, respectively, were stored at room temperature in the dark, and samples were analyzed at intervals. After 70 hr. of storage the pure compound had decomposed 37%, the acetic acid mixture 58%, and the piperidine mixture 78%.

The liberation of carbon dioxide during decomposition was established by passing the off-gases through protected aqueous barium hydroxide, and identifying the white precipitate as barium carbonate by x-ray diffraction. The gases coming off this peroxycarbamate contained a substance which was strongly alkaline to Brilliant Yellow test paper.

tert-Butyl N-methyl-N-(p-nitrophenyl)peroxycarbamate (No. 7). *N*-Methyl-*N*-(*p*-nitrophenyl)carbamoyl chloride, 6.32 g. (0.029 mole), dissolved in 650 ml. of petroleum ether was cooled in an ice bath to 5°, and 4.84 g. (0.032 mole) of 60% *tert*-butyl hydroperoxide was added. With vigorous agitation, 7.07 g. (0.037 mole) of 30% aqueous potassium hydroxide was added dropwise during 15 min., and stirring was continued for 2 hr. in the cold. Light yellow crystals, 3.5 g., were obtained by filtering the solids, washing four times with water, and drying in a vacuum desiccator containing anhydrous calcium chloride. By concentrating the petroleum ether solution 1.79 g. more of the product were recovered. Total quantity: 5.29 g. (yield: 68% based on the carbamoyl chloride). The compound was purified by recrystallizing from 600 ml. of petroleum ether warmed to 45° for a very short time. Data on this product are given in Table I. In order to maintain high purity, crystals of this compound must be kept cool at all times, around 0–5°. This compound has an absorption maximum at 295 mμ (ϵ = 12,000 in isooctane).

Polymerization. Polymerization tests were made with freshly distilled styrene containing no inhibitor and freshly distilled chloroprene containing 2 parts per million of phenothiazine. Styrene was polymerized in 30 ml. screw-capped glass vials under conditions given in the text and in Table II. The polymers were isolated by precipitating and washing with methanol, and drying overnight in a vacuum oven at 50°.

Polystyrene containing substituted amino groups was prepared in the following way: 41.6 g. (0.4 mole) of styrene, 100 ml. of benzene, and 8.05 g. (0.05 mole) of *tert*-butyl *N,N*-dimethylperoxycarbamate were refluxed (90–91° max. temp.) under nitrogen for 6 hr. The charge was steam-distilled until 900 ml. of water had come over, and the polymer was washed with water and dried to constant weight at 80°. The water condensate was titrated with standard

TABLE II

BULK POLYMERIZATION OF STYRENE[a]

Temp., °C.	Catalyst Concn., Molar	Polymer Obtained, Grams: Benzoyl peroxide	Polymer Obtained, Grams: Compound[b]
41	0	0.011	0.011
	2×10^{-4}	0.023	0.070
	2×10^{-3}	0.069	0.195
	2×10^{-2}	0.214	0.493
61	0	0.058	0.058
	2×10^{-4}	0.180	0.384
	2×10^{-3}	0.486	1.067
	2×10^{-2}	1.574	2.820
82	0	0.522	0.522
	2×10^{-4}	1.385	1.216
	2×10^{-3}	2.581	2.263
	2×10^{-2}	Solid	3.900

[a] Nine g. of freshly distilled styrene heated in the dark under nitrogen for 6 hr. [b] The compound is *tert*-butyl *N,N*-pentamethyleneperoxycarbamate.

hydrochloric acid to a phenolphthalein end point and found to contain 0.01 equivalent of base. The polymer, 32 g., was brittle and possessed the following properties: molecular weight by boiling point elevation of benzene, 2360; nitrogen by Dumas' method, 0.9%; nitrogen by titrating the amino groups with perchloric acid in benzene, 0.73%. The former value for the nitrogen content calculates to 1.5 amino groups per molecule, assuming that 2360 is the molecular weight of the polymer.

Since it was possible that amino-containing impurities had been occluded in the polystyrene, 12 g. of the polymer was dissolved in benzene and reprecipitated with methanol and this process was repeated three times in all. The final dry polymer weighed 5.6 g. and contained 0.85% nitrogen by Dumas method, indicating that the polymer molecules contained amino groups as substituents.

The polystyrene prepared under the same conditions without the initiator did not contain nitrogen.

Vigorous reactions. The following mixtures gave violent reactions: 1.8 g. ethyl isocyanate, 2.78 g. perbenzoic acid, 50 ml. benzene, and 4 drops triethylamine when most of the solvent had been removed under reduced pressure; 3.15 g. toluene-2,4-diisocyanate, 3.0 g. 60% *tert*-butyl hydroperoxide and 10 ml. benzene after standing at room temperature for 2 hr. Isolated products which spontaneously decomposed very rapidly at room temperature were obtained from the following reactions: 0.7 g. *p*-nitrophenyl isocyanate, 0.6 g. perbenzoic acid, 15 ml. benzene, and 1 drop triethylamine; 3.2 g. *p*-nitrophenyl isocyanate, 4.2 g. 72% α-cumyl hydroperoxide, 500 ml. petroleum ether, and 3 drops triethylamine. These mishaps did not cause any bodily harm because adequate protective measures had been taken ahead of time.

Acknowledgment. The author wishes to express his appreciation to: John Willister for preparing many of the compounds; Hamilton Lewis and B. W. Ricards for the safety tests; and H. E. Schroeder for his advice.

WILMINGTON, DEL.

[CONTRIBUTION FROM E. I. DU PONT DE NEMOURS AND COMPANY, INC. ORGANIC CHEMICALS AND ELASTOMER CHEMICALS DEPARTMENTS, RESEARCH DIVISIONS]

Thermal Decomposition of Crystalline *tert*-Butyl *N*-Methyl-*N*-(*p*-nitrophenyl)peroxycarbamate

C. J. PEDERSEN*

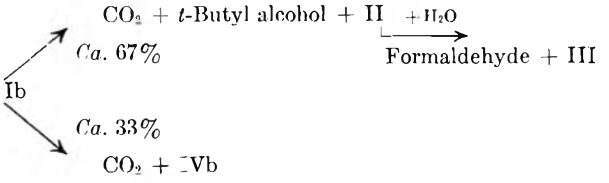
Received June 13, 1957

The decomposition of crystalline *tert*-butyl *N*-methyl-*N*-(*p*-nitrophenyl)peroxycarbamate at 30° proceeds by two different mechanisms: about 67% by an intramolecular concerted reaction giving carbon dioxide, *N*-methylene-*p*-nitroaniline, and *tert*-butyl alcohol; and the remainder by a homolytic scission followed by partial recombination of free radicals to give carbon dioxide and *O*-(*tert*-butyl) *N*-(*p*-nitrophenyl)hydroxylamine. The *N*-methylene-*p*-nitroaniline is rapidly converted to formaldehyde and *N,N'*-methylenebis(*p*-nitroaniline) by the moisture in the atmosphere.

This behavior is contrasted to that of crystalline *tert*-butyl *N*-(*p*-nitrophenyl)peroxycarbamate. The action of these compounds in aromatic solvents and styrene is briefly discussed.

During an investigation of the properties of the esters of *N*-substituted peroxycarbamic acids,[1] *tert*-butyl *N*-(*p*-nitrophenyl)peroxycarbamate, Figure 1, (Ia), and *tert*-butyl *N*-methyl-*N*-(*p*-nitrophenyl)peroxycarbamate, (Ib), were synthesized. Stability tests on the crystalline compounds stored in the open air at room temperature showed that Ia is rather stable, but Ib decomposes quietly and nearly completely to a yellow crystalline residue in about four days.

Identification of the products indicates that the decomposition of crystalline Ib at 30° may be represented as follows:



Every product was definitely identified except II, but its transient existence was suggested by the infrared spectrum (C=N band present) of the residue obtained by decomposing Ib in the absence of

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(1) C. J. Pedersen, *J. Org. Chem.*, **23**, 253 (1958).

TABLE I

THERMAL STABILITY OF PEROXYCARBAMATES

Compound	State	Stability
Ia	Crystalline	Rough estimate of half-life: 600 days at room temperature.[a]
	Cumene solution[b]	Decomposes at 50–80[c] to produce (VIa) free radicals in high yield.
Ib	Crystalline	Decomposes at 30° by two different mechanisms. Approximate half-life: 2 days at 30°.
	Cumene solution[b]	Decomposes at 50° to produce (VIb) free radicals in high yield.
$(CH_3)_2N-\overset{\overset{O}{\|}}{C}-O-O-C(CH_3)_3$	Liquid	Approximate half-life: 65 days at room temperature.[a]
$C_2H_5-\overset{H}{N}-\overset{\overset{O}{\|}}{C}-O-O-C(CH_3)_3$	Crystalline	Rough estimate of half-life: 800 days at room temperature.[a]

[a] 24–28°. [b] At 0.03 to 0.04 molar concentration.

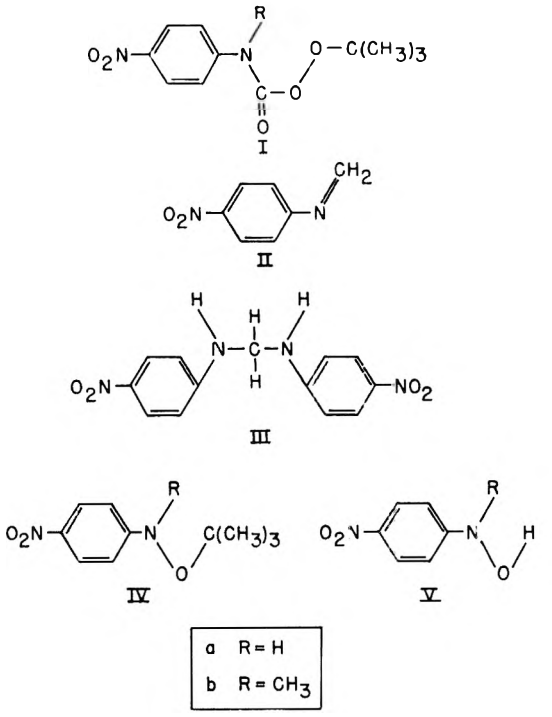


FIG. 1. STRUCTURES OF COMPOUNDS.

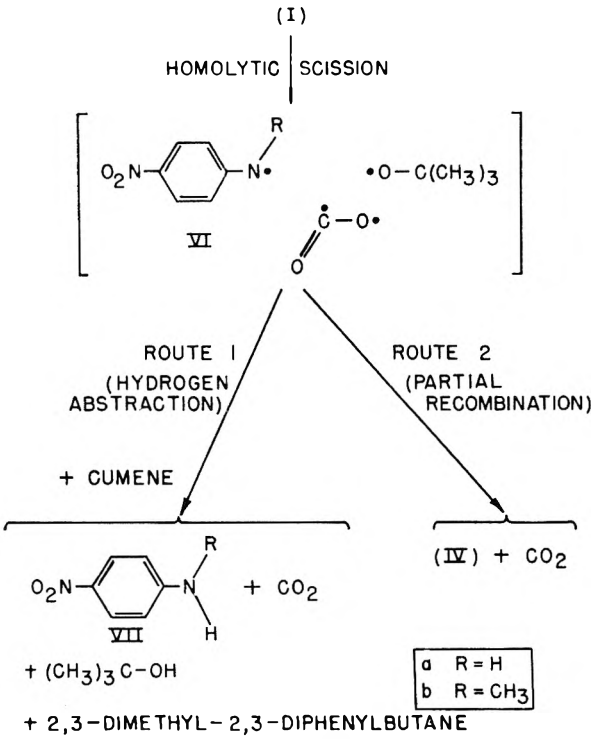


FIG. 2. FREE RADICAL DECOMPOSITION OF PEROXYCARBAMATES.

moisture. *N,N'*-Methylenebis(*p*-nitroaniline), (III) is formed by the following reaction:

$$2\ \text{II} + H_2O \longrightarrow \text{III} + H_2CO$$

No formaldehyde is released while Ib is decomposing in the absence of moisture.

In cumene solutions at 50–80°, however, both Ia and Ib decompose by homolytic scission as indicated by the formation in high yields of carbon dioxide and *p*-nitroaniline, (VIIa), and carbon dioxide and *N*-methyl-*p*-nitroaniline, (VIIb), respectively. These facts and some data from prior work[1] are summarized in Table I. The listed peroxycarbamates were obtained in high purity by crystallization or by distillation under reduced pressure.

Discussion. A satisfactory mechanism for the thermal decomposition of crystalline Ib will have to account for the facts given in Table I.

It seems likely that the decomposition of Ia and Ib in cumene solutions at 50–80° proceeds as shown in Figure 2, Route 1, the relatively weak O—O bond breaking first. The reactions in Route 2 occur to some extent as side-reactions and, in the case of Ib, a small amount of III is also formed (possibly from the crystals of Ib while they are dissolving). The expected products, except tertiary butyl alcohol, were isolated and identified. The fate of the *tert*-butoxy free radicals was not determined in these experiments, but they are presumed to have reacted with cumene to give tertiary butyl alcohol and 2,3-dimethyl-2,3-diphenylbutane. At least, no significant quantity of acetone was formed to suggest that the *tert*-butoxy radicals had decomposed into the ketone and methyl free radicals.

If the breaking of the O—O bond is the mainspring for the thermal decomposition of crystalline per-

oxycarbamates, there is no reason to conclude from structural considerations that Ia and Ib would differ greatly in stability. Since, however, the stability of these compounds is so widely different, some reaction besides homolytic scission must intervene in the crystals of Ib to render it so much less stable than crystalline Ia.

It is proposed that the cause of the decreased stability of Ib is the occurrence of an intramolecular concerted reaction resulting in the production of three stable[2] compounds as shown in Figure 3.

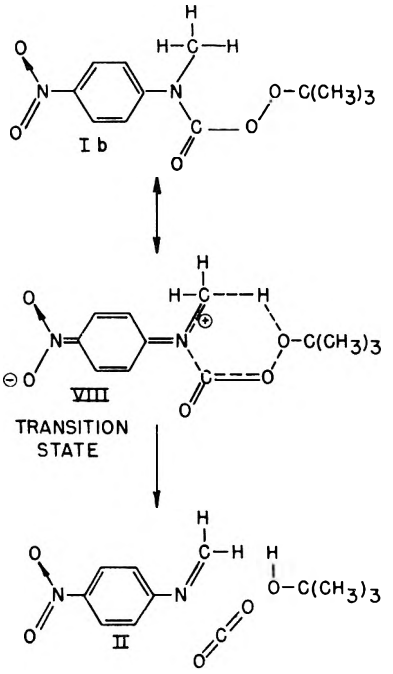


FIG. 3. DECOMPOSITION OF CRYSTALLINE Ib BY A CONCERTED REACTION.

This reaction is favored by three conditions: (*a*) the formation of "quasi six-membered ring;"[4,5] (*b*) the maintenance of this favorable configuration in the crystal; and (*c*) the relatively high electronegativity of the nitrogen atom linked to the methyl group because of its attachment to the *p*-nitrophenyl group. These conditions facilitate the attainment of the transition state and subsequent reaction in which the breaking of the O—O bond and the C—H bond of the methyl group, the binding of the hydrogen to the oxygen of the *tert*-butoxy group, and the elimination of carbon dioxide proceed simultaneously. Note that independent ions or free radicals are not formed during this process.

The stability of *tert*-butyl *N*,*N*-dimethylperoxycarbamate at room temperature (Table I) is probably due to the higher electron density on the nitrogen atom attached to two methyl groups, and to its liquid state in which the configuration favorable for the concerted reaction is less readily attained and maintained.[6]

The concerted reaction discussed above must be exothermic, and possibly it is the heat generated by it that causes roughly one third of the molecules of Ib in the crystal to decompose by a free radical mechanism and proceed according to Figure 2, Route 2. The nearly quantitative yield of IVb is attributable to: (*a*) the production of *tert*-butoxy radicals of low energy content with a reduced tendency to decompose into acetone and methyl radicals; and (*b*) the super-"cage-effect"[7] of the crystal lattice which compels the combination of *tert*-butoxy and VIb radicals to form IVb. The *tert*-butoxy radicals, and also VIb, are of low energy content because the heat supplied for their production is delicately regulated by the balance between the heat given off by the spontaneous, exothermic, concerted reaction, and the heat taken up to initiate the induced, endothermic, free radical reaction.[8]

The contrasting stability of Ia must depend on something besides its physical state, since it is also crystalline. It is apparent from Figure 4 that only a five-membered ring can be formed in this case and

(2) *N*-Methylene-*p*-nitroaniline is not reported in the literature. In spite of this it is called a stable compound because its apparent nonexistence must be due to its extreme reactivity in regard to hydrolysis and polymerization, and not to thermodynamic instability. It is likely that *tert*-butyl *N*-benzyl-*N*-(*p*-nitrophenyl)peroxycarbamate would react like Ib and yield *N*-benzylidene-*p*-nitroaniline instead of II. Since *N*-benzylidene-*p*-nitroaniline is an isolable compound,[3] its formation would have provided direct evidence for the reaction mechanism proposed above. The preparation of the desired peroxycarbamate was prevented by the refusal of *N*-benzyl-*p*-nitroaniline to react with phosgene to give the carbamoyl chloride required for its synthesis.

(3) W. v. Miller, J. Plöchl, *et al.*, *Ber.*, **25**, 2020 (1892).

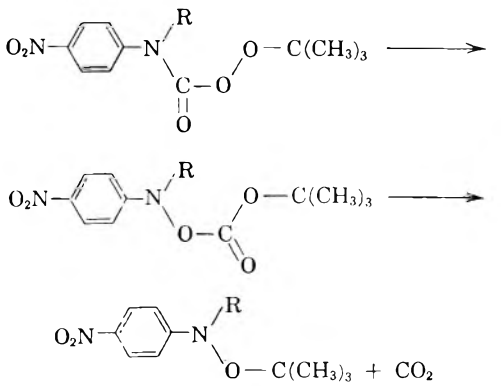
(4) R. T. Arnold and W. W. Lee, *J. Am. Chem. Soc.*, **75**, 5396 (1953).

(5) R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Am. Chem. Soc.*, **72**, 4359 (1950).

(6) In order to test the first point without involving the second, an attempt was made to prepare *tert*-butyl *N*-methyl-*N*-(*p*-tolyl)peroxycarbamate which should be a solid, but without success.

(7) J. Franck and E. Rabinowitsch, *Trans. Faraday Soc.*, **30**, 120 (1934).

(8) A referee has suggested an alternative mechanism for the production of (IV) in high yield. It involves the carboxy inversion of the peroxy compound,[9] followed by the elimination of carbon dioxide from the carbonic ester-anhydride.[10]



(9) J. E. Leffler, *J. Am. Chem. Soc.*, **72**, 67 (1950).

(10) R. Boschan, Abstr. Papers, ACS Meeting, September 1956, p. 10-O.

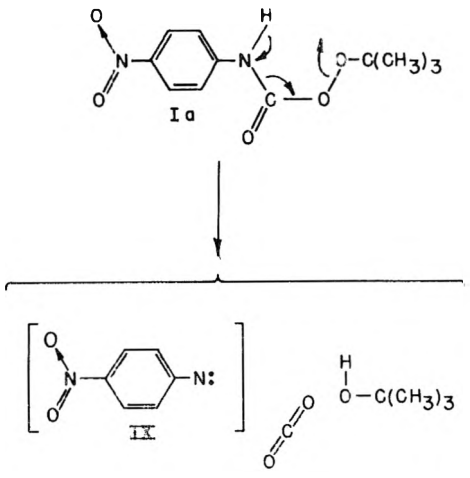


FIG. 4. HYPOTHETICAL REACTION FOR THE DECOMPOSITION OF CRYSTALLINE Ia.

not the six-membered ring which is favorable for the concerted reaction. Moreover, even if the reaction were to proceed, one of the products is IX which cannot be considered a stable entity. It might be suggested that two IX's could combine to form *p,p'*-dinitroazobenzene, but this compound was never found among the Ia decomposition products obtained under any condition.

There is another possibility, however, the formation within Ia crystal of intermolecular hydrogen-bonds between the hydrogen atom linked to the nitrogen and the oxygen atom of the carbonyl group. Such an arrangement will not only tend to prevent the occurrence of an intramolecular concerted reaction, but it would not weaken the O—O bond since these oxygen atoms are not involved in the hydrogen bond. This type of hydrogen-bonding might be thought to resemble that existing in amides or dimers of carboxylic acids.

It will be noted (Table I) that the two *N*-monosubstituted peroxycarbamates, even the one having the electron-releasing ethyl group, are much more stable than the *N,N*-dimethyl derivative. This probably indicates that hydrogen-bonding is an important factor contributing to the stability of the *N*-monosubstituted compounds.

It has been stated that the intramolecular, concerted reaction does not yield free radicals, hence, that portion of Ib decomposing by this mechanism should be incapable of initiating radical polymerization. If Ib behaved similarly in solution as in the crystalline state, the occurrence of the concerted reaction would be revealed by its low effectiveness as an initiator of polymerization at relatively low temperatures, and by the formation of III. Data from experiments on the bulk polymerization of styrene are shown in Table II. At the end of 211 hours at 30° the freshly distilled styrene containing no initiator was 1.3% polymerized; that containing Ia was 61% polymerized (molecular weight about 9,000);

TABLE II

BULK POLYMERIZATION OF STYRENE[a]

No.	Condition	Polymer Formed: g. per 10-ml. sample Control	(Ia)[b]	(Ib)[b]
1	Original samples	Nil	Nil	Nil
2	After 66 hr. at 30°	0.025	0.755	4.200
3	After 66 hr. at 30° followed by 24 hr. at 50°	0.110	4.510	4.660
4	After 211 hr. at 30°	0.114	5.500	4.610
5	After 211 hr. at 30° followed by 20 hr. at 80°	1.130	5.590	4.630

[a] Heated under nitrogen in the dark. [b] Concentration of additive: 0.02 mole per liter.

and that containing Ib was 51% polymerized (molecular weight about 4,500).

Three interesting points issue from all these facts: (*a*) that Ib is an effective initiator and does not undergo the concerted reaction in styrene solution (confirmed by the absence of the insoluble III in the system); (*b*) that Ia decomposes much faster in styrene solution than would be expected (from the relative stability of the crystalline compounds and cumene solution) to initiate polymerization at 30°; and (*c*) that both compounds decompose in styrene mainly by a free radical mechanism which appears to be autocatalyzed (the polymer radical induces the decomposition of a molecule of initiator and generates a single free radical to start another polymer chain).

At any rate, both Ia and Ib behave differently when dissolved in styrene than when in the crystalline state. The more random orientation of the molecules in solution: (*a*) hinders the formation of the hydrogen bonds which stabilize Ia; and suppresses the concerted reaction of Ib by making the attainment of the favorable configuration less likely. Hence, the decomposition of Ib by a combination of the mechanisms represented in Figure 2, Route 2, and Figure 3 is conditioned on its crystalline state and is an example of a topochemical reaction.[11]

EXPERIMENTAL

Decomposition of crystalline Ib in the absence of moisture. The material balance for the decomposition of crystalline Ib in a representative experiment is shown in Table III, and the corresponding experimental procedure is described below. Analytical results and other data concerning authentic compounds and recovered decomposition products are given in Table IV, nitrogen contents and melting points; Table V, ultraviolet absorption peaks; Table VI, infrared absorption bands; and Table VII, x-ray diffraction angles.

Crystalline *tert*-butyl *N*-methyl-*N*-(*p*-nitrophenyl)peroxycarbamate, (Ib), was placed in a vacuum-tight glass system (343 ml. free-space) in a constant temperature bath at 30°. The container was protected from light, evacuated, closed off from the atmosphere at 0.1 mm., and the rate of gas evolution was measured during the following 7 days by

(11) W. Feitknecht, *Fortschr. Chem., Physik. u. physik. Chem.*, 19, No. 2, 56 (1930).

TABLE III

MATERIAL BALANCE FOR THE DECOMPOSITION OF CRYSTALLINE Ib AT 30° IN THE ABSENCE OF MOISTURE

Products	Weight, g.	Mole × 10^3	Yield, %[a]	Remarks
Original (Ib)	2.000	7.46	...	Vol. of sample, 18 ml.
Carbon dioxide	0.297	6.74	90	Identified by mass spec. and x-ray pattern of resulting barium carbonate.
Tertiary butyl alcohol	0.343	4.64	62	Identified by mass spec.
Isobutylene[b]	0.0013	0.022	0.3	Identified by mass spec.
Residue after high evacuation	1.277	...	64[c]	Vol. of residue, 2 ml.[d] 5.98-μ band present in the infrared spectrum. No peroxide value.
Recovered from the residue after exposure to moisture for 3 days.				
Formaldehyde	...	...	...	Identified by smell and alkaline resorcinol test.[e]
III (Benzene insoluble)	0.719	2.50	33.5	Identified by analysis, melting point and x-ray diffraction.
IVb(Benzene soluble)	0.546	2.44	32.7	Structure established by analysis, physical properties, and conversion to Vb with concentrated sulfuric acid.

[a] 100 (mole of product)/[mole of (Ib)]. [b] This compound must have been produced by either dehydration of tertiary butyl alcohol or dehydroxylation of tertiary butoxy group, possibly during the main reaction. [c] 100 (weight of residue)/[weight of (Ib)]. [d] When a similar experiment was run under nitrogen at 50% relative humidity, the volume of the residue was 20.4 ml. although the yields of (III) and (IVb) remained nearly the same. Formaldehyde was formed during this experiment. [e] Ref. 12.

TABLE IV

NITROGEN CONTENTS AND MELTING POINTS[a] OF COMPOUNDS

Compound	Isolated Decomposition Product			Authentic Sample	
	M.P., °C.	% N, Found	% N, Calcd.	% N, Found	M.P.,° C.
Ia	...	...	11.0	10.9	93[b,c]
Ib	...	...	10.5	10.6	64–5[b,c]
p-Nitroaniline (VIIa)	147	...	20.3	20.5	147
N-Methyl-*p*-nitroaniline (VIIb)	151–2	...	18.4	18.6	151–2
III	230–2	19.6	19.5	19.7	230–2
IVb	138–40	12.6	12.5	...	...
N-(*p*-Nitrophenyl)hydroxylamine (Va)	...	...	18.2	18.2	107[b,d]
2-Hydroxy-4-nitroaniline	...	...	18.2	18.1	201–2[e]

[a] Determined on a bronze block and are uncorrected. [b] Melting with decomposition. [c] Ref. (1). [d] Ref. (13). [e] Ref. (14).

TABLE V

SPECTRAL ABSORPTION MAXIMA OF COMPOUNDS

Compound	Decomposition Product		Authentic Sample	
	mμ[a]	ε[b]	mμ[a]	ε[b]
Ia[c]	...	...	292	13,000
Ib[c]	...	...	295	12,000
p-Nitroaniline (VIIa)	370	14,000	368	16,000
N-Methyl-*p*-nitroaniline (VIIb)	382	18,000	381	18,000
III	...	...	380	66,000
IVb	352	12,000	...	...
N-(*p*-Nitrophenyl)hydroxylamine (Va)	...	...	356	12,000
IVa[d]	348	10,000	...	...
2-Hydroxy-4-nitroaniline	...	...	390	13,000

[a] Absorption peaks in methanol (unless otherwise noted) with a Cary Model 11 recording spectrophotometer. [b] Extinction coefficients. [c] In iso-octane instead of methanol. [d] Not pure.

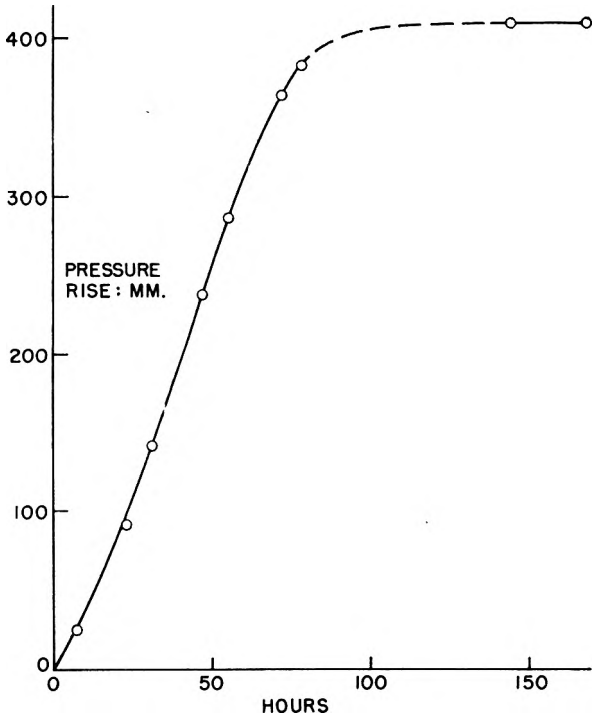


FIG. 5. EVOLUTION OF GAS FROM *t*-butyl *N*-methyl-*N*-(*p*-nitrophenyl)peroxycarbamate (Ib).

TABLE VI

INFRARED ABSORPTION BANDS OF COMPOUNDS AND PRODUCTS[a]

Compound	Absorption Band in Microns O—H	N—H	C=O	C=N
$(CH_3)_2N—\overset{\overset{O}{\|}}{C}—O—O—C(CH_3)_3$	...	...	5.73	...
$C_2H_5N(H)—\overset{\overset{O}{\|}}{C}—O—O—C(CH_3)_3$	...	3.01	5.78	...
Ia	...	2.99	5.75	...
Ib	...	...	5.75	...
Dry residue from Ib[b]	...	3.00	5.73	5.98
Moist residue from Ib[c]	...	3.00	5.73	...
IVb	2.99[d]	...	...	...
Vb from IVb with sulfuric acid	3.01	...	...	...
N-(*p*-Nitrophenyl)hydroxylamine (Va)	2.96	3.01	...	...
III	...	3.03	...	...
2-Hydroxy-4-nitroaniline	2.96	3.00	...	...

[a] Absorption bands in smear of Nujol mull with a Perkin-Elmer Model 21 spectrophotometer. The well known bands for alkyl, aromatic, and nitro groups, as well as many ambiguous bands have been omitted. [b] This was the residue obtained by decomposing crystalline (Ib) in the absence of moisture and pumping off to constant weight. The band at 6 μ indicates the presence of the C=N bond. No other sample had this band. Even with careful handling moisture caused the formation of some (III) as shown by a weak band at 3 μ. According to iodometric analysis (Ib) had been completely decomposed, but a weak band at 5.73 μ persisted. The compound responsible for this band was not identified. [c] This was the residue obtained by decomposing crystalline (Ib) in the presence of moisture and pumping off to constant weight. The 6-μ band was no longer present, the 3-μ band was stronger and the 5.73-μ band was weaker than for the dry residue. [d] This band was very weak and is thought to be due to the presence of a small amount of either (III) or (Vb) as an impurity.

TABLE VII

X-RAY DIFFRACTION PATTERNS OF COMPOUNDS

Compound	Bragg Angle[a]	Relative Intensity[b]
Ib	5.8	100
	11.7	46
	25.5	34
III	14.0	100
	19.3	55
	16.0	40
IVb	20.4	100
	21.3	83
	23.8	83

[a] With a Norelco Wide Range diffractometer using Cu K α radiation. [b] Three strongest.

periodically observing the internal pressure by means of a manometer. The resulting data are plotted in Figure 5. The composition of the evolved gases (185 ml. at 30° and 760 mm.) was determined with a mass spectrograph and found to consist of (in mole %): carbon dioxide, 90.8; *tert*-butyl alcohol, 8.9; and isobutylene, 0.3. No trace of methane, ethane, formaldehyde, or acetone was found in the gas mixture. It is assumed that all the carbon dioxide was in the gas mixture but that much of the *tert*-butyl alcohol was retained in the greasy-looking residue which smelled of the alcohol. The quantity of *tert*-butyl alcohol given in Table III was arrived at by adding the amount in the gas mixture (0.049 g.) to the weight lost by the residue under high evacuation to constant weight. The final residue no longer had the odor of *tert*-butyl alcohol. It is likely, however, that some carbon dioxide was dissolved in the residue, and some *tert*-butyl alcohol was condensed on the walls of the equipment, thus accounting for the deficiencies in the material balance.

The infrared spectrum of the residue at this stage (before exposure to moisture) had an absorption band at 5.98 μ indicating the presence of the C=N bond, and suggesting that (II) still persisted in the residue.

The residue was then submitted to a stream of nitrogen at 50% relative humidity for 3 days. During this time the sample became loosely crystalline and increased in volume about tenfold, and formaldehyde was evolved. The infrared spectrum of the residue at the end of the 3 days no longer had the band at 6 μ.

The moist residue was treated with cold benzene and separated into soluble and insoluble fractions. The yellow crystals insoluble in benzene were found to be *N,N'*-methylenebis(*p*-nitroaniline) (III), as shown by analysis and a comparison of their x-ray diffraction pattern with that of an authentic sample. The benzene soluble compound has been identified as the *O-tert*-butyl ether of *N*-methyl-*N*(*p*-nitro-

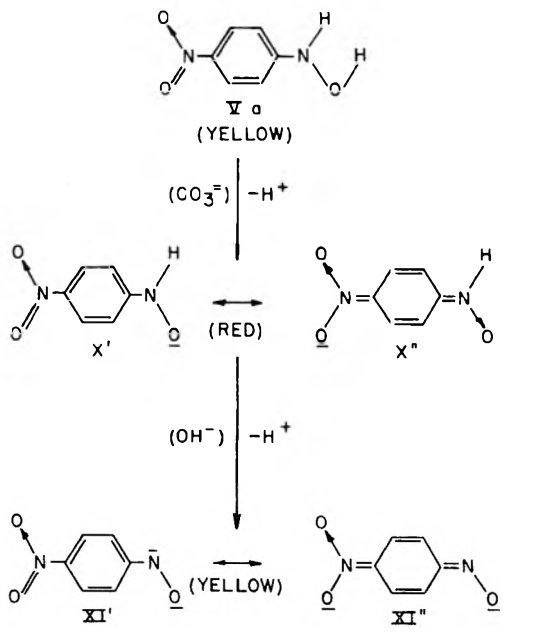


FIG. 6. STRUCTURES OF *N*-(*p*-NITROPHENYL)HYDROXYLAMINE AND ITS IONS.

phenyl)hydroxylamine, (IVb). This conclusion is based on the facts discussed below.

Structure of IVb. The benzene soluble portion, when evaporated to dryness, was an oil which gradually solidified. Orange crystals were obtained from petroleum ether (30–60°). They are soft and readily smeared with a spatula in spite of the fact that they melt at 138–140° on a bronze block. The odor of this compound is reminiscent of nitrobenzene and cinnamaldehyde. As seen in the tables, the analysis and the infrared spectrum are in agreement with the proposed structure. Its ultraviolet spectrum is similar to that of *N*-(*p*-nitrophenyl)hydroxylamine (Va), whose structure and those of its ions obtained by treatment with 2% aqueous sodium carbonate and 2% aqueous sodium hydroxide, respectively, are shown in Figure 6. Note that its univalent anion is red but its divalent anion is yellow, the latter due probably to the unfavorable charge distribution on resonance form XI′.

IVb is soluble in neither alkaline solution, since it has no readily ionizable hydrogen. When IVb was treated with cold concentrated sulfuric acid for 2 min. and poured on ice, a yellow solution was obtained which gave a red color with both alkaline solutions. The following reaction is thought to have occurred:

$$\text{IVb} + H_2SO_4 \longrightarrow \text{Vb} + (CH_3)_3C{-}O{-}SO_3H$$

The resulting *N*-methyl-*N*-(*p*-nitrophenyl)hydroxylamine, (Vb), gives a red color with both alkaline solutions because it can be converted to X-type ions but not to XI-type ions due to the absence of a hydrogen on the nitrogen atom.

It was thought remotely possible that sulfuric acid might have caused the rearrangement of Vb to *N*-methyl-2-hydroxy-4-nitroaniline. It is seen, however, that the ultraviolet spectrum of 2-hydroxy-4-nitroaniline, which should closely resemble that of the *N*-methyl derivative, is entirely different, and whereas the red color obtained by dissolving 2-hydroxy-4-nitroaniline in either sodium carbonate or sodium hydroxide persists for a long time, the red colored carbonate and hydroxide solutions of Va and Vb fade within an hour or so.

Decomposition of cumene solution of Ib at 51°. Seventy-five ml. of a 0.025 molar solution of Ib in purified cumene were heated for 72 hr. in a constant temperature bath at 51° while a slow stream of nitrogen was passed through it and a connected flask containing aqueous barium hydroxide. The latter was protected from the atmosphere with a tube of Ascarite. The barium carbonate formed during this time (identified by x-ray diffraction) accounted for 90% of theory of carbon dioxide. The yellow cumene solution was found to contain 0.02 g. of III, 0.251 g. of *N*-methyl-*p*-nitroaniline (89% of theory), 0.07 g. of IVb, and much less than the expected amount of 2,3-dimethyl-2,3-diphenylbutane (mixed melting point with an authentic sample: 115°).

Note that the decomposition in this case is mainly by Figure 2, Route 1.

Decomposition of cumene solution of Ia at 51° and 80°. One hundred ml. of a 0.037 molar solution of Ia in purified cumene were heated at 51° for 21 days in the same way as in the previous experiment. The barium carbonate formed during this period accounted for only 28% of theory of carbon dioxide. The temperature was then raised to 80° and heating was continued for 3 more days. The total evolution of carbon dioxide was 87% of theory. The clear red solution was found to contain 0.233 g. of *p*-nitroaniline (45% of theory), and a considerable amount of a material listed as IVa in Table V. It gave no red color with either sodium carbonate or sodium hydroxide solution, but on treatment with concentrated sulfuric acid, a yellow solution was obtained which became red in sodium carbonate and yellow in sodium hydroxide. This behavior is that of *N*-(*p*-nitrophenyl)hydroxylamine.

Ninety ml. of a 0.02 molar solution of Ia in purified ethylbenzene was found to decompose completely in 10 days at 30°. In this case, the yield of *p*-nitroaniline was 95% of theory.

The much faster rate of decomposition of Ia in ethylbenzene than in cumene may be due to the fact that whereas *alpha*-cumyl radical is relatively inert and dimerizes, *alpha*-phenethyl radical behaves like the polystyrene radical and induces the decomposition of Ia. The rate of decomposition in ethylbenzene is about one half that in styrene. This ratio holds also for the rates of decomposition of Ib in ethylbenzene and styrene.

Bulk polymerization of styrene. Freshly distilled styrene, 400 ml., containing 0.008 mole of Ia or Ib was placed in a 430-ml. brown glass bottle which was swept with nitrogen, stoppered with cork, and kept in a constant temperature bath at 30°. Samples (10 ml.) were taken periodically and analyzed for peroxide content iodometrically, and for degree of polymerization by the following method.

The sample was poured into 50 ml. of 95% alcohol and allowed to stand overnight at room temperature. The precipitated polymer was filtered through a tared asbestos-matted Gooch crucible, washed with 25 ml. of methanol, dried at 80°, and weighed. The molecular weights were determined by the elevation of the boiling point of benzene.

Some of the samples taken from the 30° reservoir were heated at a higher temperature before analysis for polymer formation, in order to show that if the extent of polymerization was low at this stage, it was due to the fact that all the initiator had not yet reacted rather than that the initiator had been decomposed without initiating polymerization.

As control, styrene containing no additive was treated in the same way. The data obtained are given in Table II and discussed in the text.

Acknowledgment. The author wishes to thank R. C. Ferguson and K. A. Kubitz for discussing the infrared spectra; T. E. Beukelman for interpreting the x-ray patterns; and H. E. Schroeder for his advice.

WILMINGTON, DEL.

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

The Chemistry of Oxamidines. I[1,2]

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Salts and metal complexes of oxamidines are described, and the behavior of oxamidines toward hydrolysis, aminolysis reduction, and the action of acylating agents and bifunctional compounds such as diamines, aminomercaptans, aminoalcohols, and aminophenols is discussed.

During our study of the reactions of cyanogen with organic compounds[4] a great many oxamidines, HN NH ‖ ‖ RNHC—CNHR, have been prepared. With the emphasis on cyanogen, however, scant attention has been paid to the chemistry of the products. The presence in oxamidines of amino and imino groups favorably located for mutual as well as independent action makes it desirable to learn how to take advantage of these reactive centers.

Aliphatic oxamidines are white, crystalline solids, stable at temperatures slightly above their melting points, or colorless liquids which decompose on distillation. Their solubility in water decreases with increasing molecular weight and becomes very small at C_4. They hydrolyze slowly in moist air.

Basic properties. (a) *Salt formation.* Salts having NH ‖ the general formula $(RNHC—)_2 \cdot 2HX$ were formed with hydrogen chloride,[5] hydrogen bromide, nitric,[5] nitrous, carbonic, picric, and oxalic acids. Acetic and sulfuric acids gave unsatisfactory results. Except for the carbonates all of the salts were stable.

Evidence that at least one of these salts exists as a hydrate was obtained during the preparation of dimethyloxamidine dihydrochloride which repeatedly separated first as $(CH_3NHC—)_2 \cdot 2HCl \cdot H_2O$ and formed the anhydrous material only on redissolving in ethanol and saturating with hydrogen chloride.

(b) *Formation of metal complexes.* From the admixture of ethanol solutions of nickelous or cupric chlorides with ethanol solutions of oxamidines, excellent yields of solid complexes having NH ‖ the general formula $(RNHC—)_2 \cdot MCl_2 \cdot 2H_2O$ were NH ‖ produced. Manganese appeared to form $(RNHC—)_2 \cdot MnCl_2 \cdot 4H_2O$ but attempts to obtain complexes of cobalt, chromium, and iron have thus far been unsuccessful. These reactions will be described more fully in a forthcoming paper.

Hydrolysis. Earlier work has shown that cold aqueous solutions of the free base, especially if small amounts of alkyl amine are present, hydrolyze to disubstituted oxamides. Refluxing, with or without amine, causes complete breakdown to unsubstituted oxamide and alkyl amine.

Aminolysis.[6] Woodburn, Morehead, and Chen studied the reaction of oxamidine hydrochlorides with alkyl amines. When the alkyl groups are the same in the oxamidine and in the amine, substitution of the imino hydrogens occurs resulting in tetraalkyloxamidines. If the alkyl group in the amine has a greater formula weight than the alkyl group in the oxamidine and steric effects are not predominant, an exchange occurs with the formation of a new disubstituted oxamidine. This is often followed by substitution of the imino hydrogens, the tetra substituted compound being the final product. No unsymmetrical oxamidine has yet been produced although a variety of methods has been studied in an attempt to produce one.

Acylation. One of the chemical reactions which oxamidines might be expected to undergo is that of acylation:

$$(RNHC—)_2 + 2R'COCl \longrightarrow (RNHC(NCOR')—)_2 + 2HCl$$

Our study indicates that this occurs only when the acylating agent is aromatic, such as benzoyl chloride or benzoic anhydride. If the acylating agent is aliphatic all oxamidines give the same product, namely a diacyloxamide:

$$(RNHC—)_2 + 2R'COCl \longrightarrow (R'CNHC(=O)—)_2 + 2RNH_3 \cdot HCl$$

(1) From the dissertation submitted by Warren E. Hoffman in partial fulfillment of the requirements for the Ph.D. degree, June 1955.

(2) Presented in part at the 50th Anniversary Celebration of the Western New York Section of the American Chemical Society, November 1955.

(3) Present address, National Aniline Division, Allied Chemical and Dye Corp., Buffalo, N. Y.

(4) Papers I–X of this series have appeared in *J. Org. Chem.* beginning with Volume 15 (1950).

(5) H. M. Woodburn, B. Morehead, and M. C. Chen, *J. Org. Chem.*, **15**, 535 (1950).

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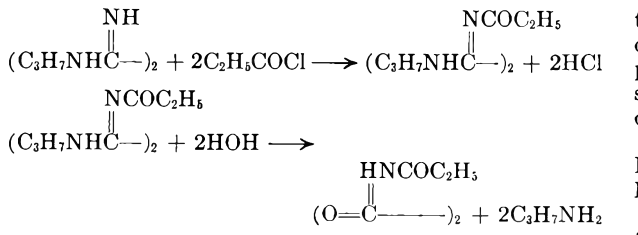
Dipropionyloxamide, for example, resulted from the action of either propionyl chloride or propionic anhydride on dimethyl-, diethyl-, di-*n*-propyl-, diisopropyl-, di-*n*-butyl-, or di-*n*-amyloxamidine, and butyryl chloride or butyric anhydride gave di-*n*-butyryloxamide in every case from the same series.

The isolation of the aroyl derivative suggests that the mechanism of diacyloxamide formation includes the two steps of acylation and hydrolysis:



That the mechanism is not hydrolysis of the oxamidine to oxamide followed by replacement of alkyl by acyl, was demonstrated by refluxing dimethyl- and di-*n*-butyloxamides with propionic anhydride for twenty-four hours. The oxamide was recovered unchanged.

The reaction of acetyl chloride was too vigorous to control and acetic anhydride gave inconsistent results. In the two cases where crystals were obtained they corresponded in analysis to diacetyloxamide. Often, however, only red-brown or black solutions were obtained which became tars on distillation.

Reduction. Every method of reduction so far attempted has failed. O'Gee[7] used hydrogen and a catalyst at greater than atmospheric pressure and recovered the oxamidine unchanged. We have had a similar experience with lithium aluminum hydride and with sodium and acetic acid in ether. The only statement that can be made with assurance is that oxamidines are strongly resistant to reduction.

Reactions with bifunctional compounds. Study of cyanogen reactions has shown that bicyclic compounds result from properly constituted diamines[8,9] and mercaptans.[10] The same, or similar compounds result from the interaction of oxamidines with many bifunctional compounds. Table I compares the result of direct cyanogenation with the oxamidine reaction for a number of cases.

The majority of the reactions described in this paper were carried out with di-*n*-butyloxamidine because a simple change in the preparative procedure (described in the Experimental Section) resulted in an increase in yield of this compound from the original 30%[6] to 70%.

(7) R. C. O'Gee, unpublished work, University of Buffalo.

(8) H. M. Woodburn and R. C. O'Gee, *J. Org. Chem.*, **17**, 1235 (1952).

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EXPERIMENTAL

sym-Dialkyloxamidines and their hydrochlorides were prepared by the method of Woodburn, Morehead, and Chen.[6] However, the existence of a hydrate of *sym*-dimethyloxamidine dihydrochloride was demonstrated for the first time and a marked improvement in the yield of di-*n*-butyloxamidine resulted from a change in procedure.

sym-Dimethyloxamidine dihydrochloride monohydrate. The free base, obtained in the prescribed manner[6] was dissolved in 95% ethanol and the solution saturated with dry hydrogen chloride. A white, curdy, non-crystalline solid separated, which was filtered, washed with ether, and recrystallized three times from ethanol. After drying in a vacuum desiccator it melted at 156–157°. The yield was 73%. The compound appeared to be perfectly stable, a two-year old sample having shown no signs of decomposition. The procedure was repeated four times with identical results.

Anal. Calcd. for $(C_4H_{10}N_4)_2 \cdot 2HCl \cdot H_2O$: C, 30.1; H, 7.5; N, 35.1; Cl, 22.3; molecular weight, 319. Found: C, 29.9; H, 8.2; N, 35.0; Cl, 22.2; molecular weight, 320.

If the monohydrate was dissolved in ethanol and the solution saturated with dry hydrogen chloride, a white, *crystalline* solid formed. After recrystallization from ethanol this melted at 289–291°C. and gave no melting point depression with a laboratory sample of *sym-dimethyloxamidine dihydrochloride.*

sym-Di-n-butyloxamidine. The following procedure gave greatly improved yields of this compound: A 33% aqueous solution of *n*-butylamine containing 73.1 g. (1.0 mole) of amine was placed in an ice bath and treated with purified cyanogen gas *until the solution started to turn milky* (slightly less than 0.5 mole). The reaction flask, still in the ice bath, was then closed with a mercury-sealed stirrer and the mixture thoroughly stirred for about one hour. During this time solid material separated and was filtered at the end of the process. Yields of 65–70% were obtained consistently. Stirring need not be commenced immediately after admission of the cyanogen but a delay of more than a few hours resulted in a decreased yield.

Effect of heat on sym-dibutyloxamidine. Three grams of di-*n*-butyloxamidine (m.p. 63°) in an open casserole was kept in an oven at 60–65° for several hours. The solid melted to a pale yellow liquid and solidified on cooling to a white solid melting at 62–63°. The recovered solid weighed 3.0 g.

Formation of salts. (*a*) *Picrates.* The hydrochloric acid salt of the oxamidine (0.1 g.) was dissolved in 10 ml. of water in an 8-inch test tube and the solution heated in a water bath to about 95°. Fifteen ml. of a saturated aqueous solution of picric acid was added, the tube shaken, and then left in the water bath for 15 min. The salt precipitated as the test tube cooled to room temperature. The product was filtered, washed several times with ether and dried in vacuo. Recrystallization was from ethanol. (The isopropyl derivative was too soluble to recrystallize well.) Table II lists the salts prepared.

The picric acid salts were soluble in hot ethanol and hot water and insoluble in ether, benzene, ligroin, and other common organic solvents.

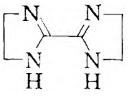
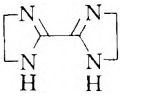
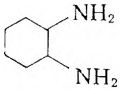
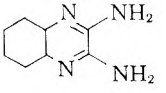
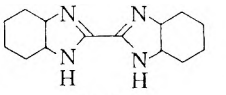
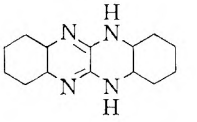
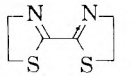
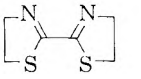
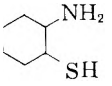
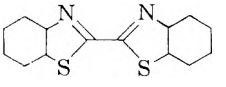
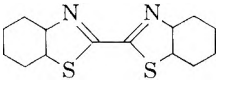
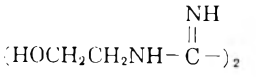
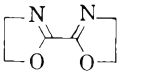
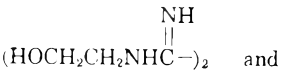
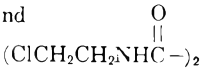
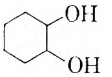
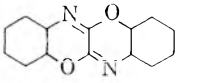
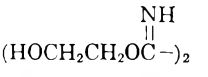
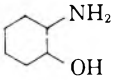
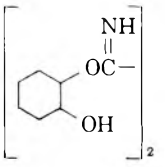
Additional salt-forming reactions were run with the purpose of proving the reaction rather than characterizing a long list of compounds. Only a few oxamidines were used and the salts were not analyzed.

Oxalates, hydrobromides, carbonates, and nitrites were formed from ether, ethanol or water solutions of the oxamidines, the precipitating agents being oxalic acid, hydrogen bromide, carbon dioxide, and sodium nitrite (followed by hydrogen chloride), respectively. All were white crystalline solids and stable in air, except for the carbonates which gradually decomposed to light brown liquids.

Several attempts with different oxamidines to produce acetates and sulfates were unsuccessful.

Reactions with acylating agents. (*a*) *With propionic anhydride.* Two grams of di-*n*-propyloxamidine dihydrochloride

TABLE I

Bifunctional Reagent	Product of Cyanogenation		Product of Oxamidine Reaction
$H_2NCH_2CH_2NH_2$		(ref.8)	
		(ref.11)	 and 
$HSCH_2CH_2NH_2$		(ref.10)	
		(ref.12)	
$HOCH_2CH_2NH_2$[a]		(ref.13)	  and 
	Unknown		 (?)[b]
$HOCH_2CH_2OH$		(ref. 14)	Unidentifiable mixture.
		(ref. 15)	Unidentifiable mixture.

[a] The bicyclic product could not be obtained from some lots of ethanolamine. We are searching for the catalyst or inhibitor which controls the process. [b] The product corresponded to a compound previously prepared by Kehrmann.[22] However, he failed to report the evidence on which he based the structure of his compound. The alternative possibility, bisbenzoxazole, has not been reported.

TABLE II

Properties of $RNHC(=NH)-C(=NH)NHR \cdot 2C_6H_3(NO_2)_3OH$

R	M.P., °C.	% Yield	% N Calcd.	% N Found
Methyl	226–228	73	24.5	24.3
Ethyl	210–213	71	23.3	23.1
n-Propyl	210–212	88	22.3	22.3
iso-Propyl	201–202	13	22.3	22.3
n-Butyl	208–210	70	21.3	21.3
n-Amyl	184–186	57	20.4	20.5
Phenyl	102	Very poor	—	—

was dissolved in water and neutralized with 0.1*N* sodium hydroxide. The free base was extracted by four 10-ml. portions of ether and the combined extracts placed in a flask in a hot water bath at 85–95°. An excess of propionic anhydride was added and the mixture shaken. In a few minutes the color of the liquid began to change, progressing through yellow to red, brown, and finally violet black. The flask was left in the water bath about one hour, then removed, covered, and allowed to come to room temperature. In about an hour crystals began to form. After standing overnight they were

(11) O. Hinsberg and E. Schwantes, *Ber.*, **36**, 4040 (1903).

(12) A. W. Hofmann, *Ber.*, **20**, 2251 (1887).

(13) E. L. Graminski, Ph.D. Thesis, University of Buffalo, June 1956.

(14) A. B. Whitehouse, unpublished work, University of Buffalo.

(15) G. Hahn and W. Leopold, *Ber.*, **68B**, 1976 (1935).

filtered, washed several times with ether, and recrystallized three times from ethyl acetate. They melted at 227–229° and gave no melting point depression with an authentic sample[16] of *dipropionyloxamide*. The solid was insoluble in water, ether, ethanol, benzene, ligroin, acetone, and cold ethyl acetate.

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.0; H, 6.0; N, 14.0; mol. wt., 200. Found: C, 48.1; H, 6.2; N, 14.0; mol. wt., 206.

The procedure was repeated for a series of oxamidines. The same product was isolated in every case. Mixed melting point determinations with the material obtained from di-*n*-propyloxamidine showed no depression nor did mixed melting points with an authentic sample of dipropionyloxamide. The product crystallized very slowly from the reaction mixtures of di-*n*-amyloxamidine (two days) and diisopropyloxamidine (one week). The yields for each oxamidine are given in Table III.

TABLE III

YIELD OF DIPROPIONYLOXAMIDE FROM VARIOUS OXAMIDINES

Oxamidine	% Yield	Oxamidine	% Yield
Dimethyl	30	Di-isopropyl	15
Diethyl	33	Di-*n*-butyl	38
Di-*n*-propyl	37	Di-*n*-amyl	34

It was also possible to obtain the product by adding propionic anhydride directly to the neutralized oxamidine salt, eliminating the ether extraction. Two layers formed. As soon as the top layer had become brownish red, it was separated and allowed to stand. Crystals of dipropionyloxamide (m.p. 227–229°) formed after an hour or two. Yields were approximately the same as those given above.

(*b*) *With propionyl chloride.* Substitution of propionyl chloride for the anhydride accelerated the reaction somewhat but gave slightly lower yields of the same product.

Mixing the reagents at a lower temperature slowed down the reaction. At 0° there was no perceptible color change and no crystals were obtained even after several days.

(*c*) *With butyric anhydride.* When butyric anhydride was reacted with di-*n*-propyloxamidine as in (*a*) above, the color change was considerably slower in coming and crystals required ten to twelve hours to appear. After two or three days the crystals were filtered and purified. They melted at 199–201° and gave no melting point depression with an authentic sample[17] of *di-n-butyryloxamide*. The yield was 25%.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.6; H, 7.1; N, 12.3; mol. wt., 228. Found: C, 52.2; H, 7.2; N, 12.0; mol. wt., 225.

The same product was produced from the action of butyric anhydride on dimethyl-, diethyl-, and di-*n*-butyloxamidines. It was observed that in cases where the free base was used as such rather than as liberated by neutralization of the hydrochloride, a drop or two of sodium hydroxide solution was needed to bring about the reaction.

(*d*) *Butyryl chloride* gave the same product as the anhydride. The rates of reaction were similar.

(*e*) *With acetic anhydride.* Because of the vigor of this reaction it had to be carried out near 0°. The usual change in color occurred with di-*n*-propyloxamidine but from several runs crystals were obtained in only one case. These melted at 222–228° and were too few to recrystallize. No crystals were obtained from any of the other oxamidines by the method used in (*a*).

When an excess of acetic anhydride was added at room temperature to di-*n*-butyloxamidine (the free base) and the mixture allowed to stand for two days, a red color developed but no crystals. Ten ml. of water and ten ml. of ether were added and the whole mixture shaken thoroughly. The ether layer became red and the water layer light yellow. The two layers were separated. After three weeks a small amount of pink solid appeared in the ether solution. After filtration and several washings with ether it melted at 231–235°. There appeared to be no melting point depression with the crystals from (*e*). Recrystallization twice from ethyl acetate raised the melting point to 236–238°. The yield of *diacetyloxamide* was 6%.

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.9; N, 4.7; N, 16.2. Found: C, 41.7; H, 4.8; N, 16.2.

(*f*) The use of *acetyl chloride* was prohibited because the reaction proceeded at an uncontrollable rate.

(*g*) *With benzoic anhydride.* Two grams of di-*n*-butyloxamidine was dissolved in 25 ml. of ether. A solution of 9 g. of benzoic anhydride and 2 drops of aqueous sodium hydroxide in ether was added with vigorous shaking. A white, feathery solid separated. It was filtered, washed with ether and ethanol, and recrystallized from ethyl acetate. It melted at 207–209° with decomposition and represented an 87% yield of *N,N'-dibenzoyldibutyloxamidine*, $(C_4H_9NHC(=NBz)—)_2$.

Anal. Calcd. for $C_{24}H_{30}N_4O_2$: C, 70.9; H, 7.4; N, 13.8; mol. wt., 407. Found: C, 70.8; H, 7.5; N, 13.9; mol. wt., 403.

(*h*) *With benzoyl chloride.* Two grams of diethyloxamidine dihydrochloride was dissolved in water, neutralized, and extracted with ether as in (*a*). Two drops of concentrated aqueous sodium hydroxide was added, followed by an excess of benzoyl chloride. After vigorous shaking for a few minutes a white solid separated. This was filtered, washed with cold ethanol, and recrystallized from ethyl acetate. White needles, melting at 199–202° with decomposition, represented a 78% yield of *N,N'-dibenzoyldiethyloxamidine*, $(C_2H_5NHC(=NBz)—)_2$.

Anal. Calcd. for $C_{20}H_{22}N_4O_2$: C, 68.6; H, 6.3; N, 16.0; mol. wt., 350. Found: C, 68.9; H, 6.5; N, 15.7; mol. wt., 357.

With di-*n*-butyloxamidine, benzoyl chloride gave the same product as was obtained in (*g*).

Reactions with bifunctional reagents. (*a*) *Ethylenediamine.* Fifty ml. of an ethanol solution containing 5.4 g. (0.02 mole) of di-*n*-butyloxamidine dihydrochloride and 2.4 g. (0.04 mole) of ethylenediamine was heated to reflux. The solution turned yellow almost immediately and after refluxing four hours a white solid began to form. The evolution of a gas basic to litmus was also noted. The mixture was allowed to reflux thirty minutes after the evolution of gas had subsided. The white solid was filtered and washed several times with ethanol. It melted at 290° and gave no melting point depression with an authentic sample[8] of *bis*(Δ²-*2-imidazolinyl*). The yield was almost quantitative.

The same compound was obtained from diethyloxamidine dihydrochloride and ethylenediamine[18] also in quantitative yield.

(*b*) *2-Mercaptoethylamine hydrochloride.* Fifty ml. of an ethanol solution containing 2.71 g. (0.01 mole) of di-*n*-butyloxamidine dihydrochloride and 2.27 g. (0.02 mole) of 2-mercaptoethylamine hydrochloride was refluxed for twenty-four hours. No solid had appeared, consequently water was added until a cloudiness remained. A brown solid settled out and was filtered and recrystallized from ethanol with Norite present as a decolorizer. The white product melted at 127–129° and gave no depression with an authentic sample[10] of bis(Δ²-2-thiazolinyl). The yield was almost quantitative.

Di-*n*-butyloxamidine (the free base) gave the same prod-

(16) Th. Figee, *Rec. trav. chim.*, **34**, 294 (1915).

(17) J. Th. Bornwater, *Rec. trav. chim.*, **35**, 126 (1916).

(18) M. C. Chen, Ph.D. Thesis, University of Buffalo, February 1950.

uct in nearly quantitative yield. The yield from diethyloxamidine dihydrochloride was 81%.

(c) *Ethanolamine.* (1) Fifty ml. of ethanol containing 5.4 g. (0.02 mole) of di-*n*-butyloxamidine dihydrochloride and an excess of ethanolamine was refluxed for twenty-four hours and the reaction mixture allowed to stand until the next day. A light-brown solid was filtered and washed with ether, becoming almost white. It was recrystallized by dissolving in 25% ethanol and adding ether to induce crystallization. Fine white needles separated which melted at 210–212°. A mixed melting point with some independently synthesized[19] *bis*(Δ^2-*2-oxazolinyl*) gave no depression.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 20.0. Found: N, 20.0.

Some lots of ethanolamine did not give this reaction. We are searching for the catalyst or the inhibitor which controls the process.

(2) When an excess of ethanolamine was avoided, a white crystalline solid melting at 203° was obtained. A mixed melting point with some independently synthesized *β,β'-dichlorodiethyloxamide* gave no depression.

(3) When the equivalent amount of the free base (di-*n*-butyloxamidine) rather than the hydrochloride was used, not only was the bicyclic compound isolated, but in one week another product came out of the filtrate in small amounts. After filtration and washing with ether it melted at 120–127° and was quite soluble in water and alcohol. It gave a melting point depression with the diethanoloxamide but no depression with bis(2-hydroxyethyl) oxamidine, $(HOCH_2CH_2NC(=NH)-)_2$, recently synthesized by Graminski.[13]

(d) *Ethylene glycol.* A mixture of 20 ml. of ethylene glycol and 6.4 g. (0.03 mole) of di-*n*-butyloxamidine was heated cautiously on a hot plate until the oxamidine dissolved. A yellow solution resulted. No change occurred on standing for 1 hr. On heating gradually to 115° the color became orange and later brown. After standing several days at room temperature a few crystals were noted. These disappeared before they could be filtered.

Refluxing the same reagents for 24 hr. gave a viscous mixture which could not be filtered. The hydrochloride gave the same results as the free base.

(e) *o-Phenylenediamine.* (1) A solution of 2.0 g. (0.01 mole) of di-*n*-butyloxamidine and 3.0 g. (0.027 mole) of *o*-phenylenediamine in 45 ml. of a 2:1 mixture of nitrobenzene and ethanol was refluxed for 24 hr. and then allowed to stand one day. Distillation of the solvents left a mass of orange needles. Four recrystallizations from boiling acetic acid produced golden yellow needles which did not melt up to 541° but showed signs of decomposition at about 410°. The yield of $C_{14}H_{10}N_4$, proved by ultraviolet spectrum analysis (see Figures 1–4) to be a mixture of bisbenzimidazole and fluoflavin, was 76%.

Anal. Calcd. for $C_{14}H_{10}N_4$: C, 71.9; H, 4.3; N, 23.9; mol. wt., 234. Found: C, 71.8; H, 4.3; N, 23.8; mol. wt., 234.

(2) A solution of 1.42 g. (0.01 mole) of diethyloxamidine and 3.0 g. (0.027 mole) of *o*-phenylenediamine in 45 ml. of a 2:1 mixture of nitrobenzene and ethanol was refluxed for 24 hr. After two days at room temperature, the solvents were stripped off leaving a black residue. This was dissolved

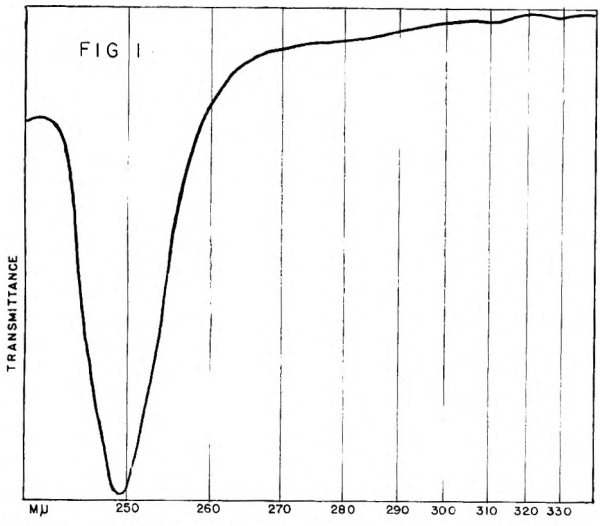


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRUM of pure fluoflavin. λ_{max} 249 mμ; ϵ_{max} 72,000.

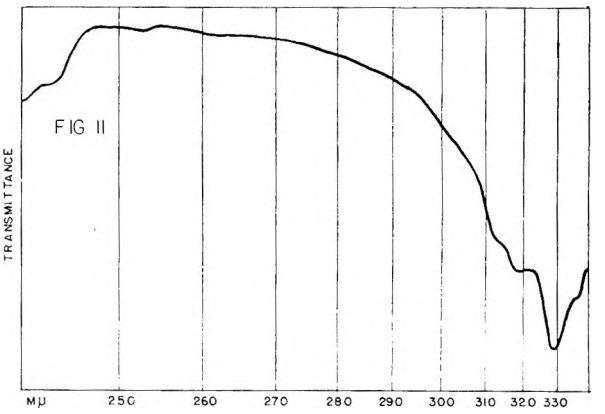


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRUM of pure bisbenzimidazole. λ_{max} 329 mμ; ϵ_{max} 42,000.

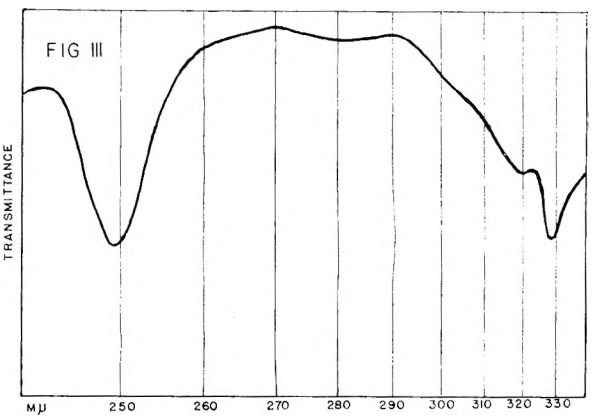


FIG. 3. ULTRAVIOLET ABSORPTION SPECTRUM of the product from the reaction of *o*-phenylenediamine and dibutyloxamidine.

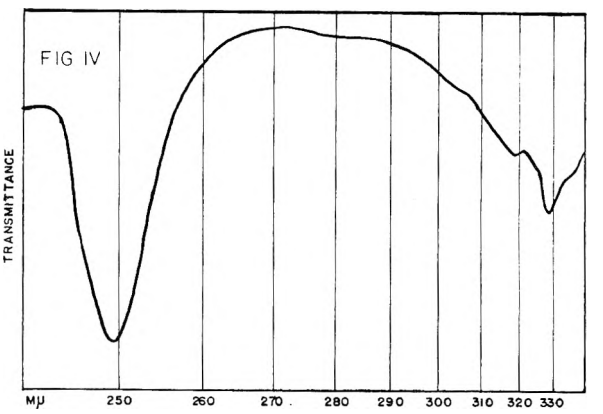


FIG. 4. ULTRAVIOLET ABSORPTION SPECTRUM of a 1:1 mixture of pure fluoflavin and pure bisbenzimidazole.

(19) H. Wenker, *J. Am. Chem. Soc.*, 60, 2152 (1938).

in boiling acetic acid, decolorized with Norite, and recrystallized twice from acetic acid. Golden-yellow needles of $C_{14}H_{10}N_4$ were obtained in 70% yield.

(*f*) *2-Aminobenzenethiol.* (1) A solution of 2.0 g. (0.01 mole) of di-*n*-butyloxamidine in an excess of 2-aminobenzenethiol was boiled in a covered beaker for 15 min. Shimmering crystals separated from the orange-brown solution. They were recrystallized from toluene with Norite present and melted at 303–306°. A mixed melting point with an authentic sample[12] of *bisbenzothiazole* gave no depression. The yield was 80%.

(2) The preparation was repeated using diethyloxamidine. A yield of 73% of bisbenzothiazole was obtained.

(*g*) *o-Aminophenol.* Fifty ml. of nitrobenzene containing 8.5 g. (0.042 mole) of di-*n*-butyloxamidine and 10.0 g. (0.091 mole) of *o*-aminophenol was refluxed for 24 hr. A white solid collected in the condenser. It weighed 1.7 g. and melted at 83–90°. It had the odor of butylamine but was not identified further. A mass of orange-brown crystals deposited in the reaction flask after cooling. These were filtered and washed several times with ether. The mother liquor from the reaction flask was evaporated to about one tenth its volume, producing more crystals. The combined yield was 90%. After two recrystallizations from ethanol the solid melted at 259–260°. A mixed melting point with an independently synthesized sample of Kehrmann's *diphendioxazine*[23] gave no depression.

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.2; H, 3.4; N, 11.9; mol. wt., 236. Found: C, 71.1; H, 3.4; N, 11.9; mol. wt., 233.

(*h*) *Catechol.* Fifty ml. of nitrobenzene containing 8.0 g. (0.04 mole) of di-*n*-butyloxamidine and 8.8 g. (0.08 mole) of catechol was refluxed for 24 hr. A very viscous mixture resulted which upon filtration (over 10 hr.), yielded a brownish solid which appeared crystalline but did not melt up to 365°. Upon standing, this solid turned black, resembling charred wood. None of the common organic solvents would dissolve it.

This experiment was repeated five times, varying the time of reflux, etc. The results were identical.

Dipropionyloxamide was prepared from propionamide and oxalyl chloride according to the method of Figee.[16] A 64% yield of white crystals melting at 226–229° was obtained. Figee recorded a melting point of 216°.

Anal. Calcd. for $C_8H_{12}N_2O_4$: N, 14.0. Found: N, 14.0.

Di-n-butyryloxamide was prepared from butyramide and oxalyl chloride according to the method of Bornwater.[17] White needles melting at 198–201° with decomposition were obtained in 57% yield.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: N, 12.3. Found: N, 12.4.

Diacetyloxamide. A solution of 4.72 g. (0.08 mole) of acetamide and 5.08 g. (0.04 mole) of oxalyl chloride in 100 ml. of pure, dry benzene was refluxed for 24 hr. No product could be isolated. The preparation was attempted three times without success.

Dibenzoyloxamide. Three attempts to prepare dibenzoyloxamide by refluxing benzamide and oxalyl chloride in benzene failed.

Bisbenzothiazole. Thirty ml. of ethanol containing 6.3 g. (0.05 mole) of 2-aminobenzenethiol was saturated with cyanogen at 0°.[12] The mixture was kept in the ice box overnight and then filtered. Two recrystallizations from toluene, using Norite for decolorization, produced shimmering white flakes which melted at 304°. The yield was 53%.

Bisbenzimidazole.[23] To a solution of 21.8 g. of *o*-nitroaniline in 200 ml. of ether was added 10 g. of oxalyl chloride. A yellow solid began to form almost immediately. The mixture was refluxed for several hours. Filtration gave a yellow solid which melted at 302–324° with decomposition compared to a literature value of 331° for 2,2′-dinitroörthooxanilide.[18] Without further purification, a mixture of 13.0 g. of this substance, 200 ml. of acetic acid, and a slight excess of finely granulated tin was refluxed for about 30 hr. Two yellow solids were isolated from the reaction mixture. Bisbenzimidazole, the main product, was recrystallized from acetic acid. Evaporation of the mother liquor from the reaction mixture gave additional solid which resulted in a final yield of 33%. The compound did not melt up to 365°. The ultraviolet spectrum of an acetic acid solution of the compound is shown in Figure 2.

The second yellow solid was identified through its picrate as *o-benzimidazole.* The picrate melted at 223° (lit. 225–226°).

Fluoflavin. A mixture of 10.8 g. of *o*-phenylenediamine and 4.5 g. of oxalic acid in 120 ml. of 4*N* HCl was refluxed for two hours.[24] The green solid which formed was filtered, washed with water, and dried *in vacuo.* It represented an almost quantitative yield of *2,3-dihydroxyquinoxaline.*

A mixture of 5.7 g. (0.036 mole) of 2,3-dihydroxyquinoxaline and an excess of phosphorus pentachloride was heated to 160° and held there for 15 min. The melt was allowed to crystallize to a brownish yellow solid. Recrystallized from ethanol, the *2,2′-dichloroquinoxaline* melted at 150°.

(1) Following the method of Hinsberg and Pollack[25] a 1:2 mole mixture of 2,2′-dichloroquinoxaline and *o*-phenylenediamine containing some rock salt as a dispersing medium was heated to about 125° and held at that temperature for about 15 min. The product was boiled in water and washed with ethanol and cold acetic acid. Recrystallization from boiling acetic acid gave golden yellow needles of *fluoflavin* in 5% yield.

(2) A second method of preparation was discovered in this work. To an ethanol solution of dichloroquinoxaline was added *o*-phenylenediamine in a 1:2 ratio. The mixture was heated to boiling for 15 min. Filtration, followed by recrystallization of the solid product gave golden yellow needles of fluoflavin.

(3) An ethanol solution of diaminoquinoxaline, prepared from *o*-phenylenediamine and cyanogen after the method of Bladin,[26] and *o*-phenylenediamine was refluxed for 24 hr. with agitation. After cooling, the mixture was filtered and the solid recrystallized from boiling acetic acid. A yield of 57% of fluoflavin resulted. The ultraviolet spectrum of an acetic acid solution of the compound is shown in Figure 1.

Diphendioxazine.[22] Kehrmann's method for the production of diphendioxazine was followed to the extent that his directions could be understood. A mixture of 6.3 g. (0.05 mole) of oxalic acid, 10.9 g. (0.10 mole) of *o*-aminophenol, and 10.0 g. of benzoic acid was heated at a maximum temperature of 200° for 15 min. The melt was poured into double its volume of ethanol, mixed thoroughly, and the solid filtered. This was washed with 0.1*N* NaOH, water, and ethanol. Recrystallization from ethanol with Nuchar gave a white solid melting at 258–260°.

Bis(Δ^2-2-oxazolinyl).[20] Twenty grams of diethanoloxamide, prepared from diethyloxalate and ethanolamine, was dissolved in 100 ml. of toluene and treated with 42 g. of thionyl chloride. The mixture was heated at 60° for 30 min. and at the boiling point for 90 min. more. White, crystalline β,β'-dichlorodiethyloxamide was filtered, washed with water and ethanol, and dried *in vacuo.* It melted at 200–203° (lit. 203°). The yield was 80%.

Following Wenker's method,[19] 10.6 g. (0.05 mole) of β,β'-dichlorodiethyloxamide was dissolved in 100 ml. of 1*N* methanolic KOH and boiled for 1 hr. The solution was fil-

(20) L. Knorr and P. Rössler, *Ber.*, **36**, 1278 (1903).

(21) The assistance of Mr. Richard Van Deusen in obtaining these curves is gratefully acknowledged.

(22) F. Kehrmann and C. Bener, *Helv. Chim. Acta*, **8**, 16 (1925).

(23) H. Hubner, *Ann.*, **209**, 370 (1881).

(24) M. A. Phillips, *J. Chem. Soc.*, (1928) 2393.

(25) O. Hinsberg and J. Pollack, *Ber.*, **29**, 784 (1896); O. Hinsberg, *Ann.*, **319**, 267 (1901).

(26) J. A. Bladin, *Ber.*, **18**, 672 (1885).

tered and the solid washed with cold methanol. The combined filtrates were evaporated to dryness and the residue taken up in water. Bis(Δ^2-2-oxazolinyl), melting at 210–213°, was obtained by adding sufficient alcohol to make the solution 25% and then ether to give a permanent cloudiness. An 87% yield of white needles resulted.

Ultraviolet absorption spectra were obtained with a Beckmann DK 2 Spectrophotometer. Acknowledgment is made of the gift of certain chemicals as follows:

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE AND THE BIOMEDICAL RESEARCH GROUP, LOS ALAMOS SCIENTIFIC LABORATORY, UNIVERSITY OF CALIFORNIA]

Substituted 4,7-Phenanthrolines and Benzo[*f*]quinolines as Scintillation Solutes

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A new synthesis for 4,7-phenanthroline based on *N,N'*-diacetyl-*p*-phenylenediamine has been developed. In reactions with aryllithium reagents it has been shown that 4,7-phenanthroline undergoes mono- and disubstitution reactions at positions 3 and 8. In this manner the 3,8-diphenyl, 3-phenyl, 3-(*p*-tolyl), and 3-*p*-dimethylaminophenyl derivatives of 4,7-phenanthroline have been prepared. In each case the intermediate dihydro compound was isolated. These compounds and the analogous benzo[*f*]quinolines have been evaluated as scintillation solutes. Their behavior as solutes in liquid scintillation systems is shown by calculation and actual light output to involve considerable self-quenching. The 650 cm.$^{-1}$ to 900 cm.$^{-1}$ region of the infrared spectrum has been analyzed for each of the benzo[*f*]quinolines and 4,7-phenanthrolines and is shown to be composed of vibrational frequencies due to the individual aromatic rings involved.

Those substances which have been shown to function most efficiently as solutes in liquid scintillation counting systems are structurally simple materials built up of aromatic rings in continuous conjugation. For example, *p*-terphenyl and 2-phenyl-5-(*p*-biphenylyl)oxazole are excellent solutes for liquid scintillation systems. In compounds like 4,7-phenanthroline and benzo[*f*]quinoline which possess phenanthrene-like structures there exists the possibility of building up molecules containing a similar arrangement of rings in continuous conjugation; however, such materials have thus far not been evaluated as scintillator solutes. In this report we wish to describe the preparation and discuss the relative pulse heights of a series of new mono and disubstituted 4,7-phenanthrolines and the corresponding 3-substituted benzo[*f*]quinolines.

Phenanthrolines containing the desired substituents in either or both the 3 and the 8 positions are theoretically available by a number of routes involving either the well-known ring formation reactions[1] of quinoline chemistry or by direct addition to the azomethine bond of the phenanthroline. In view of its generality of application to aromatic bromine compounds the addition of aryllithium reagents to 4,7-phenanthroline was considered to be the best synthetic approach to obtaining such structures. This necessitated a source of 4,7-phenanthroline which is reported to be available from *p*-phenylenediamine,[2] 6-nitroquinoline,[3,4] or 6-aminoquinoline[5] by the Skraup reaction. In our hands none of these methods were reproducible so the development of a synthesis was undertaken. Conditions have been devised for the use of *N,N'*-diacetyl-*p*-phenylenediamine in the Skraup reaction which give reproducible 60-75% yields of 4,7-phenanthroline. The most efficient oxidizing mixture was found to be nitrobenzene and 96% sulfuric acid with ferrous sulfate as a moderator. In the absence of ferrous sulfate, extensive decomposition of the product takes place. The crude 4,7-phenanthroline was isolated as a black, intractable solid from which the pure material could not be isolated by steam distillation or recrystallization. Purification was, however, readily effected by extracting the crude product with ligroin in a Soxhlet extractor. The procedure described in the experimental section has repeatedly given yields of 60% or over.

The addition of aryllithium reagents to 4,7-phenanthroline was found to proceed smoothly and in good yields as indicated in Table I to yield substituted phenanthrolines according to diagram 1. As in other addition reactions of aryllithium reagents[6] it was found necessary to exclude rigidly all

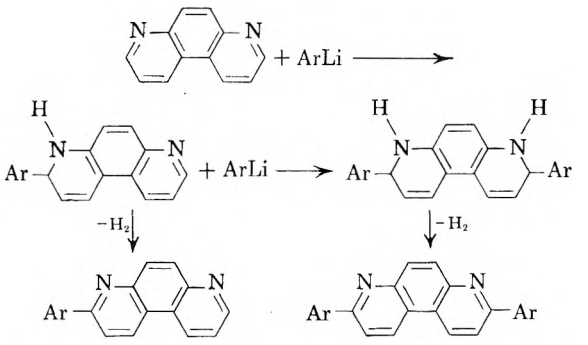
(1) E. H. Woodruff and Roger Adams, *J. Am. Chem. Soc.*, **54**, 1977 (1932).

(2) C. R. Smith, *J. Am. Chem. Soc.*, **52**, 397 (1930).

(3) L. Haskelberg, *J. Am. Chem. Soc.*, **69**, 1539 (1947).

(4) E. Bornemann, *Ber.*, **19**, 2377 (1886).

(5) A. Kaufmann and R. Radosevic, *Ber.*, **42**, 2613 (1909).



traces of water from the reaction mixture. It is especially important to dry the phenanthroline which is known to be hygroscopic.[2] The addition proceeds in discreet stages and yields either 3-substituted or 3,8-disubstituted 4,7-phenanthrolines. The initial reaction product in all cases was the dihydrophenanthroline. These materials are spontaneously dehydrogenated in dilute hydrochloric acid solution but show fair stability in basic solution. Both the phenanthrolines and the dihydrophenanthrolines have unusual fluorescent qualities. The fluorescence of the dihydrophenanthrolines is yellow and that of the phenanthrolines blue-white.

TABLE I

ARYL SUBSTITUTED 4,7-PHENANTHROLINES

Substituent	M.P., °C.	Yield[a]	Nitrogen Analysis Calcd.	Found
3,8-Diphenyl	278	22T	8.43[b]	8.52
3-Phenyl	188	95A	10.93	11.15
3-(*p*-Tolyl)	181	80A	10.36	10.49
3-(*p*-Dimethylaminophenyl)	282	62T	14.04	14.05

[a] Recrystallized from T, toluene; A, anisole. Yield in per cent. [b] Calcd. for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85. Found: C, 86.71; H, 4.88.

With the exception of 3-(*p*-tolyl)benzo[*f*]quinoline which was prepared by *p*-tolyllithium addition, the derivatives of benzo[*f*]quinoline evaluated here have been previously reported.[7-9] As with the dihydrophenanthrolines the intermediate dihydroquinolines show appreciable stability in basic solutions and are dehydrogenated in dilute hydrochloric acid solutions. The blue-white fluorescence of these compounds is even more pronounced than that of the analoguos phenanthrolines.

The infrared spectra of benzo[*f*]quinoline and 4,7-phenanthroline as well as their homologs are well defined in the C—H region ranging from 650 cm.$^{-1}$ to 900 cm.$^{-1}$ The data characterizing this portion of the spectrum is found in Table II. These compounds are structurally analogous to phenanthrene and their spectra should possess at least a qualitative resemblance to that of phenanthrene, which in the 700 cm.$^{-1}$ to 825 cm.$^{-1}$ region is simple and lends itself to the interpretation that each of the benzene rings is a separate vibrating unit. Thus, one finds in the spectrum of phenanthrene at 732 cm.$^{-1}$ a strong band which is characteristic of ortho-disubstituted benzene, a strong band at 815 cm.$^{-1}$ and a weaker band at 710 cm.$^{-1}$ which are both characteristic of a tetrasubstituted benzene ring with two adjacent C—H bonds. The band at 710 cm.$^{-1}$ has been noted[10] as not always occurring; however, in phenanthrene, the benzo[*f*]quinolines and the 4,7-phenanthrolines it is always present.

In extending the correlations developed for phenanthrene to the benzo[*f*]quinolines and 4,7-phenanthrolines, the C—H frequencies due to benzene rings are readily assigned. As shown in Table II these bands are shifted towards higher frequencies. Thus the band due to ortho-disubstituted benzene is shifted from 732 cm.$^{-1}$ to the range of 745 cm.$^{-1}$ to 752 cm.$^{-1}$ in the benzo[*f*]-quinoline series. The bands due to a tetrasubstituted benzene ring with two adjacent C—H bands are shifted from 815 cm.$^{-1}$ and 710 cm.$^{-1}$ to 865–869 cm.$^{-1}$ and 781–720 cm.$^{-1}$ in the benzo[*f*]-quinolines and to 845–855 cm.$^{-1}$ and 705–727 cm.$^{-1}$ in the 4,7-phenanthrolines. These assignments are based on the stability of the stronger band to substitution effects, a characteristic most clearly noted in the benzo[*f*]quinoline derivatives. These data are also presented in Table II.

The assignment of frequencies due to the pyridine rings is more difficult because of the lack of information available on the infrared spectra of substituted pyridine compounds. However, it is known that 2,3-lutidine absorbs at 787 cm.$^{-1}$ and 840 cm.$^{-1}$ and that other 2,3-disubstituted pyridines absorb in this general region.[11] The spectrum of benzo[*f*]quinoline has a strong band at 840 cm.$^{-1}$ and shoulder at 760 cm.$^{-1}$ on the 745 cm.$^{-1}$ disubstituted phenyl band. The 3-aryl derivatives of benzo[*f*]quinoline show alterations of this pattern and also contain a third strong band very close to the 840 cm.$^{-1}$ band. Thus the spectrum of 3-phenylbenzo[*f*]quinoline shows in addition to the appropriate benzene frequencies strong bands at 845 cm.$^{-1}$, 830 cm.$^{-1}$, and 800 cm.$^{-1}$

The spectrum of 4,7-phenanthroline contains a strong band at 835 cm.$^{-1}$ and a strong doublet with maxima at 783 cm.$^{-1}$ and 790 cm.$^{-1}$ showing a relationship to 2,3-lutidine similar to that of benzo-[*f*]quinoline. The 3-aryl and 3,8-diaryl substituted

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(7) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **72**, 2181 (1950).

(8) O. Doebner and J. Peters, *Ber.*, **23**, 1231 (1890).

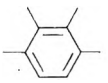
(9) J. Kalff, *Rec. trav. chim.*, **46**, 599 (1927).

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 67.

(11) E. Godar and R. P. Mariella, *J. Am. Chem. Soc.*, **79**, 1404 (1957).

TABLE II

C—H Out of Plane Deformation Frequencies[b]

Ring System	3-Substituent			
Phenanthrene	—	815(s), 710(m)	732(s)	—
Benzo[*f*]quinoline	H	865(s), 720(w)	745(s)	760(sh), 840(sh)
	C_6H_5[c]	869(m), 720(w)	750(s)	800(s), 830(s), 845(s)
	p-$CH_3C_6H_4$[d]	869(m), 718(w)	748(s)	792(s), 832(s), 840(s)
	p-$(CH_3)_2NC_6H_4$[e]	869(m), 718(w)	752(sh)	795(s), 820(s), 835(s)
4,7-Phenanthroline	H	852(s), 705(m)		783(s), 790(s), 835(s)
	C_6H_5[f]	845(s), 720(m)		785(s), 815(s), 835(s)
	C_6H_5[g]	855(sh), 727(m)		775(s), 825(s), 840(s)
	p-$CH_3C_6H_4$[h]	855(s), 720(w)		787(s), 832(s), 840(s)
	p-$(CH_3)_2NC_6H_4$[i]	845(s), 715(w)		785(s), 830(s), 840(sh)

[a] Also 8-phenyl. [b] All frequencies are expressed in cm.$^{-1}$ [c] Mono substituted phenyl absorption at 690(s) and 765(s). [d] *p*-Disubstituted phenyl absorption at 815(s). [e] *p*-Disubstituted phenyl absorption at 820(s). [f] Mono substituted phenyl absorption at 685(s) and 765(s). [g] Mono substituted phenyl absorption at 680(s) and 767(s). [h] *p*-Disubstituted phenyl absorption at 809(s). [i] *p*-Disubstituted phenyl absorption at 803(s).

4,7-phenanthrolines do not show the doublet, but rather one strong band at about 785 cm.$^{-1}$, a strong band at 830 cm.$^{-1}$ to 840 cm.$^{-1}$, and, as with the substituted benzo[*f*]quinolines, a third strong band at 815 cm.$^{-1}$ to 832 cm.$^{-1}$

In the light of these data it is apparent that the presence of a disubstituted pyridine ring in this sort of condensed ring system gives rise to two bands in the C—H out of plane deformation region of the infrared. These bands fall at about 840 cm.$^{-1}$ and from 760 cm.$^{-1}$ to 790 cm.$^{-1}$ The introduction of a third substitutent adjacent to the C=N bond causes the appearance of a third band which occurs between 815 cm.$^{-1}$ and 832 cm.$^{-1}$

TABLE III

Solute		Scintillation Data		Fluorescence Spectral Data[a]	
Ring system	3-Substituent	I_{max}[b]	c_{max}, g./l.	λ_{max}, mμ	$\bar{\lambda}$, mμ
Benzo[*f*]-quinoline	H	0.07	—	366	386
	C_6H_5	0.28	2.1	385	400
	p-$CH_3C_6H_4$[f]	0.33	2.3	388	404
	p-$(CH_3)_2NC_6H_4$	0.72	2.0[c]	432	444
4,7-Phenanthroline	H	0.07	—	[d]	[d]
	C_6H_5	0.11	1.2	[e]	[e]
	p-$CH_3C_6H_4$	0.13	1.3	378	416
	p-$(CH_3)_2NC_6H_4$	0.48	0.1[c]	433	448

[a] 314 mμ Hg-arc line excitation. [b] Measured relative to 3 g./l. 2,5-diphenyloxazole, as pulse heights[1] with a Ba^{137} electron source, an evaporated aluminum reflector and a photomultiplier having average S-11 spectral characteristics. [c] Concentration of saturated solution. [d] Response too weak for measurement. [e] Insufficient sample for measurement. [f] M.p. 156°, yield 90%, recrystallized from benzene. *Anal.* Calcd. for $C_{20}H_{15}N_2$: C, 89.18; H, 5.61 Found: C, 89.24; H, 5.55.

Toluene solutions of the benzo[*f*]quinolines and 4,7-phenanthrolines were subjected to conventional scintillation[12] and spectral[13] tests. The results are presented in Table III.

The parameters, I_{max} and c_{max}, are the maximum relative light output and the concentration at which this was obtained, respectively. The spectral quantities, λ_{max} and $\bar{\lambda}$, (obtained from corrected fluorescence spectra) are the most probable wave length and the mean wave length, respectively. The concentration curves for four of these compounds, all of which showed considerable self-quenching, were fitted to the Kallman equation,[14] $I = \frac{I_\infty Rc}{(Q+c)(R+c)}$, in order to obtain values for I_∞, the calculated ultimate light output if self-quenching were absent. Values for I_∞ of 0.70 and 0.75 were calculated for 3-phenyl- and 3-*p*-tolylbenzo[*f*]-quinoline, respectively, and 0.25 and 0.31 for the correspondingly substituted 4,7-phenanthrolines.

The 3-aryl derivatives of benzo[*f*]quinoline and 4,7-phenanthroline, can be considered as condensed ring analogs of *p*-terphenyl, a very efficient liquid scintillation solute whose value[12] of I_{max} is 1.00 (c_{max} = 8 g./l.). Inasmuch as carbocyclic analogs such as 2-phenylphenanthrene have not been tested for scintillation properties, it is inappropriate to try to comment at this time on the poor performance of these heterocyclic compounds. The marked improvement of the scintillation properties through substitution of a dialkylamino group on a poor scintillator, as noted in the comparison of 2-phenylbenzothiazole[13] and 2-(*p*-dimethylaminophenyl)benzothiazole,[15] is clearly evident here but it is unfortunate that limited solubility terminated the rise in the concentration curve of light output for these compounds.

(12) F. N. Hayes, D. G. Ott, V. N. Kerr, and B. S. Rogers, *Nucleonics*, **13**, No. 12, 38 (1955).

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EXPERIMENTAL

4,7-Phenanthroline. All of the operations in this synthesis were carried out in a well ventilated hood and behind a safety shield. A 12-l. flask equipped with a sealed stirrer and a 400-mm. jacket Allihin condenser is charged with 170 g. *N,N'*-diacetyl-*p*-phenylenediamine, 800 g. 96% sulfuric acid, 200 g. glycerol, 150 g. nitrobenzene, and 84 g. ferrous sulfate heptahydrate. The flask is heated with stirring until the heat of reaction is sufficient to maintain the mixture at steady reflux. After the reaction subsides the mixture is refluxed for 2 hr., diluted with 2 l. of water, and the excess nitrobenzene steam distilled. The strongly acid solution is treated twice with Norite and filtered while hot through an asbestos mat. The liquid is cooled and made basic with ammonium hydroxide. The crude phenanthroline is precipitated as a black, semicrystalline mass which is filtered and dried. The crude product is sewed into a cloth sack and extracted with ligroin (b.p. 66–75°) in a Soxhlet extractor to give 120 g. (75%) of white, crystalline 4,7-phenanthroline, m.p. 173°.

3-(p-Tolyl)-4,7-phenanthroline. A solution of 50 ml. anhydrous ethyl ether and 4.3 g. (0.025 mole) of freshly distilled *p*-bromotoluene is added very slowly from a dropping funnel to a stirred suspension of 0.4 g. (0.057 g.-atom) of finely chopped lithium ribbon in 100 ml. of anhydrous ether. The reaction is vigorous and the lithium is consumed in 1 hr. The *p*-tolyl lithium reagent thus formed is added dropwise to a stirred solution of 4.7 g. (0.025 M) of 4,7-phenanthroline in 50 ml. thiophene-free benzene. Initially a red complex is formed which after standing 24 hr. fades to orange. The suspension is shaken in a separatory funnel with 200 ml. water which causes the precipitate to pass into the ether-benzene phase. Evaporation of the solvent leaves the yellow dihydrophenanthroline which vigorously dehydrogenates upon the addition of 6*N* hydrochloric acid to 3-(*p*-tolyl)-4,7-phenanthroline. Two recrystallizations from anisole gave 5.3 g. (80%) of buff needles, m.p. 181°.

Anal. Calcd. for $C_{19}H_{14}N_2$: N, 10.36. Found: N, 10.49, 10.48.

The other products listed in the tables were prepared by the same procedure using the appropriate aryllithium reagent. The aryl bromides were distilled just prior to use and the reactions were run under oxygen-free nitrogen. The benzo[*f*]quinoline was prepared as previously described.[16]

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, INDIANA UNIVERSITY]

Nitration of 3-Phenylquinoline[1,2]

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Mononitration of 3-phenylquinoline gave as the only isolatable product, 3-(*p*-nitrophenyl)quinoline. Further nitration gave two products; the main dinitro compound was proven to be 5-nitro-3-(*p*-nitrophenyl)quinoline. The structure of this substance was proven by synthesis. A modified Skraup reaction using α-methylacrolein diacetate gave 3-methylquinoline which on nitration resulted in 5- and 8-nitro-3-methylquinoline. The former was oxidized to 5-nitro-3-quinolinecarboxylic acid which was converted to 5-nitro-3-aminoquinoline by way of the azide and urethan. Coupling 5-nitro-3-quinolinediazo hydroxide with dimethylamine gave the corresponding dimethyltriazeno compound which upon decomposition in benzene, produced 5-nitro-3-phenylquinoline. Nitration of the latter gave 5-nitro-3-(*p*-nitrophenyl)quinoline. The synthesis of many other quinoline compounds related to this work is described.

It has been reported by Koenigs and Nef[4] that the nitration of 4-phenylquinoline gave about 60% *p*-nitrophenyl-, 30% *m*-nitrophenyl- and 5% of the *o*-nitrophenyl-quinoline. These were called α-, β-, and γ-nitro compounds. LeFevre and Mathur[5] found that nitration of 2-phenylquinoline gave about 60% *p*-nitro- and 30% of the *m*-nitro-phenyl quinoline. The latter authors also reported a quantitative yield of 2-(*m*-nitrophenyl)quinolinium methosulfate by the nitration of 2-phenylquinolinium methosulfate. Similar ratios of meta and para substitution have been reported by Forsyth and Pyman[6] for the nitration of 2-phenyl- and 4-phenylpyridine. The meta substitution is explained on the basis of ammonium salt formation while the para orientation is explained by attack on the dissociated molecule. The similarity of behavior in the 2-phenyl- and 4-phenyl-quinoline and -pyridine may be attributed to resonance through the vinylogous position in the pyridine ring. A much smaller amount of meta substitution occurred on nitration[7] of 2-benzyl- and 4-benzylpyridine. However, on the basis of vinylogy, it was quite surprising not to

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(3) Present address: The American Agricultural Chemical Co., Carteret, N. J.

(4) W. Koenigs and J. U. Nef, *Ber.*, 20, 624 (1887).

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(6) R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 2912 (1926).

(7) F. Bryars and F. L. Pyman, *J. Chem. Soc.*, 549 (1929).

have meta substitution occurring in the nitration of 2-styrylpyridine.[8] Since it has been reported[6] that 3-phenylpyridine gave no meta nitration product, it was of interest to determine whether or not similar behavior might be shown by 3-phenylquinoline. It was also of interest to determine whether introduction of a second nitro group would occur in the phenyl group or in the quinoline portion of the molecule.

Of the several methods reported[9a-e] for the preparation of 3-phenylquinoline, the best one with respect to yield and the number of steps involved is the Pfitzinger reaction between isatin and phenylpyruvic acid.[9d] This gave consistently a yield of 68–70% of 3-phenyl-2,4-quinolinedicarboxylic acid which on decarboxylation gave 70–75% of purified 3-phenylquinoline. The preparation of β-phenylpyruvic acid by the acid hydrolysis of ethyl ethoxalylphenylacetate[10] according to the procedure of Wislicenus[11] proved to be much easier than the benzalazlactone method.[12]

The treatment of 3-phenylquinoline in sulfuric acid with one equivalent of concentrated nitric acid gave consistently a 78–80% yield of crude nitration product which on recrystallization yielded 64–68% of a pure mononitro compound. Some 3-phenylquinoline was always recovered. The *p*-nitrophenyl orientation was shown by oxidation of the mononitro compound from which only *p*-nitrobenzoic acid was isolated. It was not possible to show the presence of other nitrophenylquinolines; one can only say that the major product was 3-(*p*-nitrophenyl)-quinoline. The direct approach to the synthesis of 3-(*p*-nitrophenyl)quinoline from *p*-nitrophenylpyruvic acid by the Pfitzinger reaction failed. Only brown resinous polymer-like material was obtained. Another confirmatory structure proof was obtained by conversion of the mononitro compound to the *N*-oxide and this was rearranged in boiling acetic anhydride to 3-(*p*-nitrophenyl)carbostyril which had been reported by Pschorr.[13]

The nitration of 3-(*p*-nitrophenyl)quinoline in sulfuric acid with one equivalent of nitric acid gave two dinitro compounds, I and II. The lower melting compound, I, was obtained in a 63–65% yield and the higher melting isomer, II, was generally about a 10% yield. No other pure dinitro compounds could be isolated. Proof that in both I and II, the second nitro group was in the quinoline portion of the molecule came through oxidation studies. Both substances gave *p*-nitrobenzoic acid. All attempts at oxidation to isolate a nitroanthranilic acid were unsuccessful; either the unchanged dinitrophenylquinoline and *p*-nitrobenzoic acid or only *p*-nitrobenzoic acid were isolated. Even oxidation attempts with the carbostyril derived from I did not yield an anthranilic acid.

One obvious synthetic route to the structure proof is through the nitroisatins. 7-Nitroisatin was prepared according to the procedure of Buchman,[14] but it would not undergo the Pfitzinger reaction with phenylpyruvic acid. Another method involved the use of chloroisatins; 4- and 6-chloroisatin[15,16] were subjected to the Pfitzinger reaction with phenylpyruvic acid to yield 5- and 7-chloro-3-phenyl-2,4-quinolinedicarboxylic acids which were decarboxylated to the corresponding 5- and 7-chloro-3-phenylquinoline. Nitration of 5-chloro-3-phenylquinoline gave 5-chloro-3-(*p*-nitrophenyl)-quinoline. However, attempted reduction of one nitro group in I using sodium sulfide was not successful since a pure mononitro monoamino phenylquinoline could not be isolated. Thus, structure proof through use of the chloro compound was not possible.

On the assumption that perhaps I might be 5-nitro-3-(*p*-nitrophenyl)quinoline, proof of structure through synthetic means from a 5-nitroquinoline was attempted. 3-Methylquinoline was prepared according to the procedure of Untermohlen[17] and this was nitrated to give a 78% yield of mixed nitro-3-methylquinolines which were separated by means of the nitrate salts. One nitration product proved to be 8-nitro-3-methylquinoline[18] and the other one was shown to be the 5-nitro compound. Oxidation of this substance to the nitro-3-quinolinecarboxylic acid and then decarboxylation, gave 5-nitroquinoline. Conversion of 5-nitro-3-quinolinecarboxylic acid to the axide through the acid chloride and decomposition of the azide in ethyl alcohol gave the urethan which was hydrolyzed easily to 5-nitro-3-aminoquinoline. The Hofmann hypohalite method for preparing the 3-amino compound was not satisfactory. Also, the azide could not be prepared satisfactorily from 5-nitro-3-quinolinecarbohydrazide. When 5-nitro-3-aminoquinoline was diazotized then coupled with dimethylamine and the 5-nitro-3-(dimethyltriazeno)quinoline decomposed in benzene, 5-nitro-3-phenylquinoline was obtained. Direct decomposition of the diazohydroxide compound in benzene with alkali, did not give any isolatable 5-nitro-3-phenylquinoline. Nitration of

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5-nitro-3-phenylquinoline gave a dinitro compound which did not depress the melting point of I.

EXPERIMENTAL[19]

3-Phenyl-2,4-quinolinedicarboxylic acid. Ethyl phenylethoxalylacetate[10] was hydrolyzed according to the method of Wislicenus.[11] The ester (0.4 mole) was heated under gentle refluxing with 1.25 l. of 10% sulfuric acid for 24 hr. The aqueous layer was separated from the oil and it was allowed to stand in a refrigerator for a day then the precipitated phenylpyruvic acid was removed by filtration. The oily layer, which had been separated, was subjected to further hydrolysis to yield an additional quantity of phenylpyruvic acid. The yield was 45–55%.

A stirred solution of 35.5 g. (0.216 mole) of phenylpyruvic acid and 32.1 g. (0.218 mole) of isatin in 190 ml. of 15% sodium hydroxide was heated gently for 3 hr. The hot solution was filtered and the cold filtrate was acidified with 2*N* hydrochloric acid. The brown colored granular solid was collected on a filter and was washed with water. The solid was shaken with 600 ml. of saturated sodium bicarbonate solution, filtered to remove the isatin, and the filtrate was acidified with hydrochloric acid. The yield of 3-phenyl-2,4-quinolinedicarboxylic acid was 43.7 g. (68%). The isatin recovered was 13.8 g.

3-Phenylquinoline. A stirred mixture of 1250 ml. of paraffin oil, 254 g. (0.86 mole) of 3-phenyl-2,4-quinolinedicarboxylic acid and 87 g. of copper bronze was heated to 280° at a rate (4 hr.) so as to prevent excessive frothing. When there was no further evolution of gas, the solution was cooled to room temperature, the oil was diluted with 800 ml. of dry ether, the solution was filtered to remove the copper, and the latter was washed with 300 ml. of dry ether. Dry hydrogen chloride was bubbled into the paraffin oil–ether solution until no further precipitate was formed. The white solid was collected by filtration and washed with two 150-ml. portions of dry ether. The hydrochloride was treated with 10% ammonia solution, the solution extracted twice with ether and the latter was dried with magnesium sulfate. After removal of the ether, the substance was distilled at 165–168° (1.5–2 mm.) yielding 207 g. (71%) of a pale yellow liquid which solidified when it cooled. The 3-phenylquinoline was recrystallized from hexane to yield fine white needles, m.p. 51–52°. This value has been reported by Adams.[9e]

7-Chloro-3-phenylcinchoninic acid. A solution of 2.8 g. (0.015 mole) of 6-chloroisatin[15] and 2.6 g. (0.016 mole) of phenylpyruvic acid in 40 ml. of 15% sodium hydroxide solution was heated for 2 hr. At the end of the time, the hot solution was filtered and the filtrate was acidified with hydrochloric acid. The solid was dissolved in sodium bicarbonate solution, then reprecipitated with dilute hydrochloric acid to yield 4.4 g. of 7-chloro-3-phenyl-2,4-quinolinedicarboxylic acid. The dicarboxylic acid was heated for 5–8 min. in boiling nitrobenzene. After the solution cooled, it was diluted with ether, the solid was collected on a filter and it was washed with two 25-ml. portions of ether. The yield was 3.7 g. (85%), m.p. 286–288°. After recrystallization from nitromethane, the substance melted at 287.5–288.5°.

Anal. Calcd. for $C_{16}H_{10}ClNO_2$: Cl, 12.52. Found: Cl, 12.72.

5-Chloro-3-phenyl-2,4-quinolinedicarboxylic acid. A solution of 1.84 g. (0.01 mole) of 4-chloroisatin[15] and 1.8 g. (0.011 mole) of phenylpyruvic acid in 39 ml. of 15% sodium hydroxide was refluxed for 2 hr. The hot solution was filtered, the filtrate was acidified with dilute hydrochloric acid and solid was collected on a filter. After solution in dilute sodium bicarbonate and reprecipitation with acid, the yield of the dicarboxylic acid was 2.45 g. (75%). It was recrystallized from benzene-ethanol (9:1), giving needles which melted at 189–190°.

Anal. Calcd. for $C_{17}H_{10}ClNO_4$: Cl, 10.84. Found: Cl, 10.87.

7-Chloro-3-phenylquinoline and 5-chloro-3-phenylquinoline were prepared by decarboxylation of the corresponding 2,4-quinolinedicarboxylic acid in paraffin oil in exactly the same procedure as used for the preparation of 3-phenylquinoline.

5-Chloro-3-phenylquinoline. Recrystallized from methanol as light yellow needles, m.p. 112–113°.

Anal. Calcd. for $C_{15}H_{10}ClN$: Cl, 14.82. Found: Cl, 15.20.

7-Chloro-3-phenylquinoline. Recrystallized from dilute ethyl alcohol as short needles, m.p. 111–112°.

Anal. Calcd. for $C_{15}H_{10}ClN$: Cl, 14.82. Found: Cl, 14.89.

Nitration of 3-phenylquinoline. Concentrated sulfuric acid (110 ml. was cooled to 0° and stirred while 20.5 g. (0.1 mole) of 3-phenylquinoline were added portion-wise. After the substance was dissolved the solution was cooled to −10° and a cold solution of 6.5 ml. of concentrated nitric acid in 25 ml. of concentrated sulfuric acid was added dropwise, with stirring, over a period of 3 hr. The nitration mixture was poured onto 750 ml. of ice and water, then it was neutralized with concentrated ammonia water (400 ml.). The solid was collected by filtration, washed, and dried. The yield was 23 g. The solid was refluxed with 700 ml. of benzene, filtered to remove insoluble material, and the solution was concentrated to about 400 ml. by distillation. After several recrystallizations and concentration of the mother liquors to about one-half the volume to obtain further solid for recrystallization, 16 g. (64%) of dark yellow needles were obtained which melted at 178–179°.

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: N, 11.20. Found: N, 11.15.

Three grams of the nitro compound was added to a solution of 200 ml. of 10% sulfuric acid and 10 g. of potassium permanganate. The solution was refluxed for 30 min. After cooling, the permanganate was destroyed with sodium bisulfite and the decolorized solution was filtered. The solid was washed with water and recrystallized from dilute (1:1) ethyl alcohol. The substance melted at 236–237°; a mixed melting point determination with authentic *p*-nitrobenzoic acid gave no depression. The benzanilide was prepared and it showed no melting point depression with authentic *p*-nitrobenzanilide, m.p. 211–212°.

3-(p-Nitrophenyl)quinolinium methiodide. Five grams of 3-(*p*-nitrophenyl)quinoline was heated under reflux for several hours with 10 g. of methyl iodide. The crude methiodide was recrystallized twice from ethyl alcohol, m.p. 247–249°.

Anal. Calcd. for $C_{16}H_{13}IN_2O_3$: N, 7.14. Found: N, 7.29.

1-Benzyl-3-(p-nitrophenyl)quinolinium chloride. 3-(*p*-Nitrophenyl)quinoline (0.5 g.) in 15 ml. of benzyl chloride was heated for 3 hr., then cooled, filtered, and washed with ether. Two recrystallizations from 50 ml. of a 1:1 solution of methyl alcohol–ethyl acetate gave a substance melting at 242–243°.

Anal. Calcd. for $C_{22}H_{17}ClN_2O_2$: N, 7.43. Found: N, 7.53.

1-Benzyl-3-phenylquinolinium chloride. This was prepared exactly as described for the *p*-nitrophenyl compound except that 5 ml. of benzyl chloride were used. It was recrystallized from absolute ethanol–ethyl acetate solution, m.p. 235–236°.

Anal. Calcd. for $C_{22}H_{18}ClN$: Cl, 10.70. Found: Cl, 10.85.

3-(p-Nitrophenyl)quinolinium picrate. The picrate was prepared by standard procedure; recrystallized from ethyl alcohol, the substance melted at 230.5–231.5°.

Anal. Calcd. for $C_{21}H_{13}N_5O_9$: N, 14.61. Found: N, 14.62.

1-Methyl-3-(p-nitrophenyl)-2-quinolone. To a stirred suspension of 5 g. (0.013 mole) of 3-(*p*-nitrophenyl)quinolinium methiodide in 300 ml. of water at 0° was added simultaneously over a 20-min. period, a solution of 13.2 g. (0.04 mole) of potassium ferricyanide in 75 ml. of water and 3.2 g. (0.08 mole) of sodium hydroxide in 50 ml. of water. The cold solution was stirred for 3 hr. The solid was collected, dried, and

(19) Microanalyses performed by Miss Joanna Dickey of this department.

recrystallized twice from ethyl alcohol to yield 1.5 g. (42%) of yellow needles which melted at 225–226°.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: N, 10.00. Found: N, 10.28.

1-Methyl-3-phenyl-2-quinolone. This substance was prepared from 10 g. (0.029 mole) of 3-phenylquinolinium methiodide[9c] as described for the *p*-nitrophenyl compound. Recrystallized from dilute ethyl alcohol and twice from ligroin (63–90°) gave a 28% yield of white prisms, m.p. 140–141°.

Anal. Calcd. for $C_{16}H_{13}NO$: N, 5.96. Found: N, 6.13.

3-(p-Nitrophenyl)quinoline-1-oxide. A solution of 9.8 g. (0.04 mole) of 3-(*p*-nitrophenyl)quinoline in 60 ml. of glacial acetic acid and 12 ml. (0.15 mole) of 30% hydrogen peroxide was warmed at 65–70° for 3 hr. The solution was concentrated in vacuum, then treated with 200 ml. of saturated sodium carbonate solution and the warm aqueous suspension was extracted with three 200-ml. portions of chloroform. After drying, the chloroform solution was concentrated to 150 ml., then cooled, and the solid was collected. Further concentration gave a second portion of solid. The crude substance (3.5 g.) was recrystallized five times from benzene to yield 2.6 g. (25%) of white needles which melted at 258.5–259.5°.

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: N, 10.53. Found: N, 10.44.

3-Phenylquinoline-1-oxide. This was prepared exactly as described above for 3-(*p*-nitrophenyl)quinoline-1-oxide, using 12.5 g. (0.06 mole) of 3-phenylquinoline. After extraction with two 200-ml. portions of chloroform, drying and concentration of the chloroform in vacuum to 50 ml., the solution was diluted with 100 ml. of ligroin (63–90°) then the solid collected on a filter. The solution was concentrated in vacuum again, then hot ligroin added to the hot solution until cloudiness developed. The yield of white granular material was 6 g. (38%); m.p. 117–120°. Recrystallization from benzene hexane (1:1) gave white prisms which melted at 123–124°.

Anal. Calcd. for $C_{15}H_{11}NO$: N, 6.33. Found: N, 6.45.

3-(p-Nitrophenyl)carbostyril. A solution of 1.5 g. 3-(*p*-nitrophenyl)quinoline-1-oxide in 30 ml. of acetic anhydride was refluxed for 3 hr. After cooling, the solid was collected by filtration and recrystallized from 85% acetic acid. A yield of 1 g. of white granular material, m.p. 320–321°, was obtained.

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: N, 10.53; C, 67.67; H, 3.76. Found: N, 10.78; C, 67.68; H, 4.11.

3-Phenylcarbostyril. This was prepared from 2.1 g. of 3-phenylquinoline-1-oxide as described above for 3-(*p*-nitrophenyl)carbostyril. The yield was 1.1 g. (44%), m.p. 227–229°. Recrystallized from benzene, the substance melted at 231–232°.

Anal. Calcd. for $C_{15}H_{11}NO$: N, 6.33. Found: N, 6.27.

2-Chloro-3-(p-nitrophenyl)quinoline. 3-(*p*-Nitrophenyl)-carbostyril (0.8 g.) was refluxed for 30 min. with 7 ml. of phosphoryl trichloride, then the solution was poured onto excess ammonia water and ice. The white solid was collected and was recrystallized twice from ethyl alcohol to yield 0.6 g. of white needles, m.p. 152–153°.

Anal. Calcd. for $C_{15}H_9ClN_2O_2$: Cl, 12.28. Found: Cl, 12.79.

3-(p-Aminophenyl)quinoline. To a cold stirred solution of 5.9 g. of stannous chloride dihydrate in 15 ml. of concentrated hydrochloric acid was added 1.9 g. of 3-(*p*-nitrophenyl)quinoline. After remaining at room temperature for 1.5 hr., the solution was heated to 85–90° then it was cooled and neutralized with concentrated ammonia water. The solid was collected, then it was warmed with 10% sodium hydroxide solution and the solution was filtered. The dried solid weighed 1.1 g. and melted at 173–175°. After recrystallization from benzene, the melting point of the substance was raised to 175.5–177°.

Anal. Calcd. for $C_{15}H_{12}N_2$: N, 12.72. Found: N, 12.54.

The *acetyl* derivative was prepared and recrystallized from benzene, m.p. 188–189°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: N, 10.68. Found: N, 10.67.

The *benzoyl* derivative: recrystallized from benzene, m.p. 203–204°.

Anal. Calcd. for $C_{22}H_{16}N_2O$: N, 8.61. Found: N, 8.74.

3-(p-Hydroxyphenyl)quinoline. One gram of 3-(*p*-aminophenyl)quinoline was warmed with 8 ml. of 40% sulfuric acid, then the solution was cooled to 0° and 0.35 g. of sodium nitrite in 2 ml. of water was added dropwise. After five minutes, the diazonium salt solution was added slowly to 20 ml. of boiling 40% sulfuric acid. After boiling for 3–5 min. the solution was cooled, poured onto ice, and neutralized with ammonia water. After collecting the solid, it was dried and recrystallized, with decolorization, from benzene. The yield of fine yellow needles was 0.15 g., m.p. 224.5–226°.

Anal. Calcd. for $C_{15}H_{11}NO$: N, 6.33. Found: N, 6.40.

Nitration of 3-(p-nitrophenyl)quinoline. To a stirred solution of 9.5 g. (0.038 mole) of 3-(*p*-nitrophenyl)quinoline in 55 ml. of concentrated sulfuric acid at −10° was added dropwise a solution of 2.6 ml. (0.04 mole) of concentrated nitric acid in 13 ml. of concentrated sulfuric acid. The addition was carried out over a 2-hr. period. After the nitration mixture stood at room temperature for a short time, it was poured onto 300 ml. of ice and water and the solution was neutralized with concentrated ammonia water. The solid was collected, dried, and refluxed with 2 liters of benzene. After the insoluble material was removed by filtration the benzene solution was concentrated to 700 ml. and allowed to cool. The dark yellow granular solid was collected and recrystallized from benzene to yield 0.8 g. of a substance II, which melted at 288.5–289.5°.

Anal. Calcd. for $C_{15}H_9N_3O_4$: N, 14.24. Found: N, 14.05.

The mother liquor, from which the above high melting dinitro compound II had separated, was concentrated to a small volume and the solid which separated was collected and recrystallized from one liter of 3:2 absolute ethyl alcohol–benzene solution. After removal of the light yellow solid, the filtrate was concentrated to about 500 ml. and the solid was collected by filtration. The combined solids were recrystallized from 3:1 ethyl alcohol–benzene solution and from absolute ethyl alcohol to yield 6.8 g. (57% of yellow colored needles (I) which melted at 224.5–226.5°.

Anal. Calcd. for $C_{15}H_9N_3O_4$: N, 14.24. Found: N, 14.00.

Oxidation of 3 g. of the dinitro compound (I) by refluxing in 100 ml. of 30% sulfuric acid containing 6 g. of chromic anhydride for five hours resulted in the recovery of 1.65 g. of the dinitro compound and 0.25 g. of a carboxylic acid which did not depress the melting point of an authentic sample of *p*-nitrobenzoic acid.

5-Nitro-3-(p-nitrophenyl)quinolinium methiodide. 5-Nitro-3-(*p*-nitrophenyl)quinoline (0.25 g.) was heated on a steam bath for one hour with 10 g. of methyl sulfate. The cold solution was diluted with 50 ml. of ether and the white precipitate was collected on a filter. The solid was warmed with 50 ml. of saturated potassium iodide solution, cooled, and the red crystalline methiodide was recrystallized from absolute ethyl alcohol. The yield was 0.2 g. (54%), m.p. 234–235.5°.

Anal. Calcd. for $C_{16}H_{12}IN_3O_4$: N, 9.61. Found: N, 9.26.

5-Nitro-3-(p-nitrophenyl)quinoline-1-oxide. This was prepared from 3 g. of 5-nitro-3-(*p*-nitrophenyl)quinoline according to the method described for 3-(*p*-nitrophenyl)quinoline. The substance was recrystallized from 50% acetic acid and twice from absolute ethanol. The yield was 1.75 g. (50%), m.p. 263–265°.

Anal. Calcd. for $C_{15}H_9N_3O_5$: N, 13.50. Found: N, 13.70.

5-Nitro-3-(p-nitrophenyl)carbostyril. This substance was prepared from 1.25 g. of the above *N*-oxide according to the method for 3-(*p*-nitrophenyl)carbostyril. The yield of crude white solid was 0.9 g. (72%), m.p. 365–367°. The melting point was raised to 366–367° by recrystallization from glacial acetic acid.

Anal. Calcd. for $C_{15}H_9N_3O_5$: N, 13.50. Found: N, 13.90.

2-Chloro-5-nitro-3-(p-nitrophenyl)quinoline. Two-tenths gram of the above carbostyril was refluxed with 4 ml. of phosphoryl trichloride for one hour, then it was poured onto flaked ice and neutralized with ammonia water. The solid was collected and recrystallized twice from 95% ethyl alcohol to yield 0.12 g. of white short needles, m.p. 214–215°.

Anal. Calcd. for $C_{15}H_8ClN_3O_4$: Cl, 10.78. Found: Cl, 11.15.

5-Amino-3-(p-aminophenyl)quinoline. To a stirred solution of 18 g. (0.08 mole) of stannous chloride dihydrate in 20 ml. of concentrated hydrochloric acid at 5°, was added portionwise 3 g. of 5-nitro-3-(*p*-nitrophenyl)quinoline. After addition the solution was cooled, then it was made alkaline with sodium hydroxide. The solid was collected and recrystallized four times from dilute ethyl alcohol to yield 0.7 g. of tan needles, m.p. 127.5–129.5°.

Anal. Calcd. for $C_{15}H_{13}N_3$: N, 17.86. Found: N, 17.21.

3-Methylquinoline. α-Methylacrolein diacetate was prepared from purified α-methylacrolein[20] according to a procedure described in patent literature.[21] 3-Methylquinoline was prepared from methacrolein diacetate according to the general procedure of Untermohlen[17a] but using the specific procedure described in Organic Reactions[17b] for the preparation of 3-ethylquinoline. The yield was 52%.

Nitration of 3-methylquinoline. A solution of 17.5 ml. (0.272 mole) of concentrated nitric acid in sulfuric acid was added dropwise to a stirred solution of 39 g. (0.272 mole) of 3-methylquinoline dissolved in 207 ml. of concentrated sulfuric acid. The temperature was maintained at 10° and the addition was carried out over a period of seven hours. After the nitration mixture warmed to 0°, it was poured onto 500 ml. of ice and water and then it was neutralized with concentrated ammonia water. The precipitate was removed by filtration, washed thoroughly, and was dried in air. The yield was 40 g. (78%) and the material melted at 68–82°. The solid was dissolved in 800 ml. of hot 10% nitric acid and the solution was allowed to cool. The white crystalline nitrate salt was removed by filtration and the solid was washed with cold dilute nitric acid. The filtrate was concentrated to one-half the volume and the solution was cooled finally in a freezing mixture. The solid was collected as previously described. The combined fractions were dissolved in warm water and the solution was neutralized with concentrated ammonia water. The yellow solid was collected on a filter, washed, and dried in air. The yield was 26 g. (51%), m.p. 106–107°. The 5-nitro-3-methylquinoline was recrystallized from hexane, giving light yellow needles; the melting point was not changed.

Anal. Calcd. for $C_{10}H_8N_2O_2$: N, 14.90. Found: N, 14.75.

Nitrate salt. Recrystallized from water, m.p. 164.5–165.5°.

Anal. Calcd. for $C_{10}H_9N_3O_5$: N, 16.73. Found: N, 16.47.

The nitric acid mother liquor from the separation of 5-nitro-3-methylquinolinium nitrate was neutralized with concentrated alkali. The deep yellow solid was collected on a filter, washed, and dried. The yield was 13 g. (26%), m.p. 95–99°. After four recrystallizations from hexane, the substance melted at 109.5–111°. The reported[18] melting point for 8-nitro-3-methylquinoline is 110°.

5-Nitro-3-quinolinecarboxylic acid. To a stirred refluxing solution of 10 g. (0.053 mole) of 5-nitro-3-methylquinoline and 0.7 g. of manganese dioxide in 300 ml. of 30% sulfuric acid solution, was added dropwise a solution of 20 g. (0.2 mole) of chromium trioxide in 100 ml. of 39% sulfuric acid. After refluxing for 3 hr., the hot solution was filtered through a sintered glass funnel and the filtrate was poured into 2 liters of water. After the solution remained in a refrigerator for a day, the long colorless needles were collected on a filter, washed, and finally dried in a vacuum. The yield was 3.2 g., m.p. 274–278° (dec.). The substance was recrystallized from nitromethane and the solid was refluxed with diethyl ether to remove any of the recrystallization solvent. The substance melted at 279–281° (dec.). No further change in melting point could be obtained.

Anal. Calcd. for $C_{10}H_6N_2O_4$: N, 12.84. Found: N, 12.83.

The acidic filtrate was neutralized with concentrated ammonia water to a *p*H 4–5 and after standing for several hours, the precipitate was collected. The dried solid weighed 5.3 g. The substance was shaken with dilute sodium bicarbonate and the insoluble portion removed by filtration. The recovered 5-nitro-3-methylquinoline weighed 4.25 g. (42.5%) and melted at 103–104°. Neutralization of the sodium bicarbonate filtrate with hydrochloric acid gave an additional 0.7 g. of the carboxylic acid which brought the combined yield to 3.9 g. (34%).

Decarboxylation of 5-nitro-3-quinolinecarboxylic acid. To a solution 0.3 g. of silver nitrate in 25 ml. of water was added a solution of 0.35 g. of 5-nitro-3-quinolinecarboxylic acid in 100 ml. of ethyl alcohol then the solution was heated for 5 min. The alcohol removed by distillation, an equal volume of water was added and the silver salt removed by filtration. The dried solid was placed in a vacuum sublimation apparatus and heated at 0.5 mm. at 285° for several hours. The sublimate melted at 65–67°; after recrystallization from hexane, it melted at 68.5–70°. A mixed melting point determination with authentic 5-nitroquinoline (m.p. 70–71°) gave a m.p. 69.5–70.5°.

Ethyl 5-nitro-3-quinolinecarboxylate. A solution of 2.9 g. (0.013 mole) of 5-nitro-3-quinolinecarboxylic acid in 25 ml. of thionyl chloride was refluxed for 2 hr. The excess thionyl chloride was removed by distillation and the residue was refluxed for 15 min. with 40 ml. of absolute ethyl alcohol. After most of the alcohol had been removed by distillation, the solution was diluted somewhat with water and neutralized carefully with dilute alkali. The yield of the ester was 2.9 g. (90%), m.p. 101.5–102°. It was recrystallized from hexane, without change in the melting point, giving clear, pale yellow needles.

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: N, 11.38. Found: N, 11.35.

Methyl 5-nitro-3-quinolinecarboxylate was recrystallized from hexane and from ethyl alcohol, m.p. 135.5–136.5°.

Anal. Calcd. for $C_{11}H_8N_2O_4$: N, 12.07. Found: N, 11.92.

5-Nitro-3-quinolinecarboxamide. The acid chloride was prepared from 2 g. of the carboxylic acid as described above, and after removal of the excess thionyl chloride, the residue was treated with concentrated ammonia water containing ice. The precipitate was collected, dried, and recrystallized from ethyl alcohol. The substance melted at 258.5–259°.

Anal. Calcd. for $C_{10}H_7N_3O_3$: N, 19.35. Found: N, 19.20.

5-Nitro-3-quinolinecarbonyl azide. A solution of 3 g. (0.014 mole) of 5-nitro-3-quinolinecarboxylic acid in 20 ml. of thionyl chloride was refluxed for two hours, after which the thionyl chloride was removed, leaving a solid residue. The residue was refluxed with 70 ml. of dry acetone until the solid had disintegrated into a fine suspension. The cold acetone suspension was added portionwise at 5–10° to a solution of 3.6 g. (0.056 mole) of sodium azide in 15 ml. of water. After standing at 10° for 15 min., the solution was diluted with 200 ml. of water and ice and after 20 min. the solid was collected upon a filter, washed, and finally dried in a vacuum desiccator. The substance melted at 125–126°; the yield was 1.96 g. (58%). Attempts at recrystallization gave inconsistent results. In recrystallization, the azide was dissolved in a solvent such as benzene at room temperature, then hexane was added and the solution cooled to a low temperature. However, a sample was not obtained which gave an analysis close to the theoretical value. On the average, about 20% of the 5-nitro-3-quinolinecarboxylic acid could be recovered from the aqueous acetone filtrate.

Anal. Calcd. for $C_{10}H_5N_5O_3$: N, 28.81. Found: N, 26.63.

Ethyl 5-nitro-3-quinolylurethan. A solution of 1.2 g. (0.005 mole) of 5-nitro-3-quinolinecarbonyl azide in 50 ml. of absolute alcohol was refluxed for one hour, after which the volume was reduced to one-half by distillation, and 50 ml. of water was added. The solution was concentrated and diluted with water, and the precipitated solid was collected. The dried substance was recrystallized from a 2:1 hexane-

(20) We are grateful for a generous supply provided by the Shell Development Co., Emeryville, Calif.

(21) J. H. Brant and F. R. Conklin, U. S. Patent **2,393,740** [*Chem. Abstr.*, **40**, 3127 (1946)].

benzene solution. The yield of fine yellow needles was 1.1 g. (85%), m.p. 141–142°.

Anal. Calcd. for $C_{12}H_{11}N_3O_4$: N, 16.09. Found: N, 16.14.

5-Nitro-3-aminoquinoline. One gram (0.004 mole) of ethyl 5-nitro-3-quinolylurethan was refluxed with 50 ml. of 6*N* hydrochloric acid for 8 hr. and the volume reduced to one-half by distillation. The solution was allowed to cool on ice, after which the white solid was removed by filtration and the hydrochloride decomposed with sodium carbonate solution. The solid was collected, dried, and refluxed for 2 hr. with a solution of 9 ml. of acetic anhydride in 50 ml. of benzene. About one-half of the solvent was removed by distillation, the solution was cooled in ice water, and the solid was collected by filtration. The yield of crude 5-nitro-3-acetamidoquinoline was 1 g. (88%), m.p. 195–199°. The acetamido derivative was refluxed for one hour with 50 ml. of 20% hydrochloric acid and the solution was concentrated. When the solution cooled, the hydrochloride was collected by filtration. The substance was treated with sodium carbonate solution to liberate the amine which was recrystallized first from benzene, and then from water. The yield of bright red granular solid, m.p. 184.5–185° was 0.54 g. (70%).

Anal. Calcd. for $C_9H_7N_3O_2$: N, 22.22. Found: N, 22.22.

5-Nitro-3-acetamidoquinoline was purified by recrystallization from benzene. The substance melted at 202.5–203.5°.

Anal. Calcd. for $C_{11}H_9N_3O_3$: N, 18.18. Found: N, 18.14.

5-Nitro-3-phenylquinoline. 5-Nitro-3-aminoquinoline (1.1 g., 0.006 mole) was dissolved in 80 ml. of hot 28% hydrochloric acid. The solution was cooled rapidly to 0° and it was diazotized by the dropwise addition of 0.44 g. of sodium nitrite in 5 ml. of water. After the solution remained at 0° for a short time, 0.4 g. of urea was added. The cold diazonium salt solution was allowed to drip into a cold stirred solution of 10 ml. of 25% dimethylamine and 38 g. of sodium carbonate in 150 ml. of ice water. The temperature was held at 8–12°. After stirring for 30 min., the olive green solid was removed by filtration, washed, and dried in a vacuum. The yield of crude 1-(5-nitro-3-quinolyl)-3,3-dimethyltriazene, m.p. 103–105°, was 1.27 g. (80%).

A 200-ml. three-necked flask was fitted with a mechanical stirrer, dropping funnel, and a reflux condenser to which was attached a bubble counter. A solution of 1.27 g. of the dry crude triazene in 50 ml. of benzene was poured into the flask and the stirred solution was heated to boiling while 1.5 g. of toluenesulfonic acid in 30 ml. of benzene was added dropwise over a 20-min. period. The solution was refluxed until there seemed to be no further evolution of nitrogen. The benzene solution was washed with 100 ml. of 5% sodium hydroxide solution, then with water, and it was dried over sodium sulfate. After removal of the solvent, the residue was sublimed by heating it at 180° under 1–2 mm. pressure. A yield of 0.45 g. (35%) of pale yellow needles, m.p. 125–130°, was obtained. After a recrystallization from dilute ethyl alcohol and from hexane, the melting point was elevated to 156–156.5°.

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: N, 11.20. Found: N, 11.56.

The *methiodide* was prepared by refluxing 5-nitro-3-phenylquinoline with methyl iodide and recrystallizing the substance from ethyl alcohol, m.p. 237–238°.

Anal. Calcd. for $C_{16}H_{12}IN_2O_2$: N, 7.14. Found: N, 7.07.

Nitration of 5-nitro-3-phenylquinoline. Nitration of 0.1 g. of this substance and isolation was carried out exactly like the procedure used for 3-(*p*-nitrophenyl)quinoline, using proportional amounts of reagents. A yield of 0.07 g. (58%) of product, m.p. 198–212°, was obtained. The substance was recrystallized from ethyl alcohol and from benzene–hexane to give fine yellow needles, m.p. 224.5–226°. A mixed melting point determination with the dinitro compound I showed no depression.

5-Chloro-3-(p-nitrophenyl)quinoline. Two-tenths gram of 5-chloro-3-phenylquinoline was nitrated and the product isolated by exactly the same procedure as for the previous nitrations. The crude nitration product was recrystallized from methanol-hexane solution and from absolute ethanol, giving slightly yellow needles, m.p. 183–184°. Oxidation of a sample yielded *p*-nitrobenzoic acid.

Anal. Calcd. for $C_{15}H_9ClN_2O_2$: Cl, 12.44. Found: Cl, 12.21.

The *methiodide* was obtained as fine yellow needles by refluxing 5-chloro-3-(*p*-nitrophenyl)quinoline with methyl iodide and recrystallization of the product from absolute ethanol, m.p. 247–249°.

Anal. Calcd. for $C_{16}H_{12}ClIN_2O_2$: N, 6.56. Found: N, 6.49.

BLOOMINGTON, IND.

[CONTRIBUTION FROM THE AMERICAN OIL CO.]

Effect of Amines on Hydrogenolysis of Alkylphenols

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It has been demonstrated that the hydrogenolysis of alkyl phenols over nickel-on-kieselguhr catalyst can be inhibited by organic amines, although the latter do not prevent hydrogenation of the benzene ring. The data obtained support the hypothesis that both acidic sites and hydrogenation sites are present on the nickel catalyst.

In the hydrogenation of unsaturated alcohols with nickel catalysts both hydrogenation of the unsaturated double bonds and hydrogenolysis of the hydroxyl groups can occur. Recently Pines, *et al*[1] have proposed a carbonium ion mechanism for the hydrogenolysis reaction involving acidic sites on the catalyst. Pines reported that if the sites active for hydrogenation are poisoned with sulfur, only hydrogenolysis occurs. If both pyridine and a sulfur-containing compound are present in the charge, no reaction occurs. According to Pines' hypothesis, the pyridine poisons the acidic catalyst sites responsible for hydrogenolysis.

In order to obtain further evidence for acidic sites in addition to hydrogenation sites on nickel catalysts, the effect of organic bases on the hydrogenolysis of the hydroxyl group in alkylphenols was studied. The hydrogenation of phenol and cresols with a nickel catalyst yields the correspond-

(1) H. Pines, M. Shamaiengan, and W. S. Postl, *J. Am. Chem. Soc.*, **77**, 5099 (1955).

TABLE I

HYDROGENATION OF C_{15}-C_{18} ALKYLPHENOLS

Run No.	Alkyl-phenol, g.	*n*-Heptane, g.	Pyridine, g.	Catalyst[a]	Grams of Catalyst	Max. Temp., °C.	Max. H_2 Press., p.s.i.g.	Mole % Alcohol Yield Based on Alkylphenol Charged
83	200	200	0	Ni	140	218	1900	0
103	50	100	35	Ni	70	210	1500	49
24	46	70	0	Ni	70	249	1705	0
107	52	70	38	Ni	70	243	1500	92
95	100	100	0	Pt	45	256	1700	14
22	50	44	37	Pt	25	257	1440	35

[a] Ni is nickel-on-kieselguhr catalyst, Pt is 0.6% platinum on alumina.

ing cyclohexanols below 250°.[2,3] Secondary alcohols, however, undergo hydrogenolysis to hydrocarbons at 250° over a Raney nickel catalyst.[4] Thus, at and above 250°, the hydrogenation of phenol or the cresols gives hydrocarbons rather than alcohols as the main product.[2,3] In the present investigation the hydrogenations were carried out over nickel-on-kieselguhr catalysts using temperatures and catalyst concentrations at which hydrogenolysis occurred.

Several organic bases were found to be effective in preventing the hydrogenolysis of alkylphenols while not inhibiting the hydrogenation of the alkylphenol over nickel-on-kieselguhr catalyst. In the presence of pyridine, alkylphenols containing nine to twelve carbon atoms in the side chain can be readily hydrogenated to alkylcyclohexanol in high yields at 250°. In the absence of the organic base, such alkylphenols were completely reduced to hydrocarbons under the same conditions.

The yield of alkylcyclohexanol from various alkylphenols has been studied as a function of temperature and composition of the organic base. In almost all cases, the addition of an amine to the charge increased the yield over that obtained in the absence of the amine.

RESULTS AND DISCUSSION

In Table I are given the results for hydrogenation of a mixture of C_{15}–C_{18} alkylphenols both with and without pyridine added. Below 200°, even with large quantities of catalyst present, reaction of the alkylphenol with hydrogen was extremely slow. At 218° and above, complete reduction to alkylcyclohexanes took place in the absence of an organic base. That there were no hydroxyl groups in the product was verified by infrared spectroscopy.

The addition of pyridine to the charge, however, inhibited hydrogenolysis of the hydroxyl group, a 92 mole % yield of alkylcyclohexanol being obtained at 243°. This result is consistent with the hypothesis of Pines[1] that an organic base poisons the acidic catalyst sites active for hydrogenolysis. It can also be seen from the results that the organic base was effective with both nickel and platinum catalysts.

In order to study further the effect of amines on the hydrogenolysis of alkylphenols, several runs were made with *p-tert*-butylphenol at different temperatures. Conclusions as to the effect of pyridine or triethylamine on the hydrogenolysis of the phenol could not be made because of a side reaction between the amine and phenol or its hydrogenation products. In every run in which either pyridine or triethylamine was added to the charge, there was produced a complex mixture of high molecular weight amines, which formed insoluble hydrogen chloride salts. No such products were formed, however, in the hydrogenation of the C_{15}–C_{18} alkylphenols in the presence of pyridine. It is, thus, likely that the *p-tert*-butylphenol or one of its hydrogenation products takes part in the reaction producing the high molecular weight amines. On this basis it would be expected that the addition of sufficient pyridine to the reactants would lower the alcohol yield (based on pheno charged) below that obtained with no amine present. This conclusion is supported by the data in Table II.

The high molecular weight amines formed from *p-tert*-butylphenol and either pyridine or triethylamine were found to consist of a mixture of primary, secondary, and tertiary amines. The acetamides of the high molecular weight secondary amines from the reaction of either pyridine or triethylamine had infrared spectra identical to each other. These acetamides had molecular weights somewhat higher than the molecular weight of the corresponding derivative of bis(*tert*-butylcyclohexyl) amine.

Several reactions of amines under hydrogenating conditions have been reported in the literature. Dicyclohexylamine is produced in yields of 75% or higher by hydrogenation of mixtures of aniline

(2) S. Ando, *J. Soc. Chem. Ind. Japan*, **34**, Suppl. Binding, 320 (1931).

(3) P. Sabatiev and E. E. Reid, *Catalysis in Organic Chemistry*, D. Van Nostrand Co., New York, 1922, pp. 135, 166–7.

(4) B. Wojcik and H. Adkins, *J. Am. Chem. Soc.*, **55**, 1293 (1933).

TABLE II

HYDROGENATION OF *p-tert*-BUTYLPHENOL

Run No.	*p-tert*-Butylphenol, g.	*n*-Heptane, g.	Organic Base[a]	Organic Base, g.	Catalyst,[b] g.	Max. Temp., °C.	Max. H_2 Press., p.s.i.g.	Mole % Alcohol Yield Based on Alkylphenol Charged
27	80	36	—	0	70	182	1550	61
28	80	35	Pyd	17	70	177	1475	50
105	159	68	—	0	140	204	1700	36
10	80	35	TEA	16	70	204	1500	46
143	80	35	Pyd	17	70	207	1450	45
26	160	70	Pyd	81	140	207	1550	22
38	160	70	Pyd	80	140	212	1620	18
3	80	35	—	0	70	268	1500	2.1
137	80	34	Pyd	16	70	268	1500	5.7

[a] Pyd = Pyridine, TEA = Triethylamine. [b] Catalyst is nickel-on-kieselguhr.

TABLE III

EFFECT OF HIGH MOLECULAR WEIGHT AMINES ON THE HYDROGENATION OF *p-tert*-BUTYLPHENOL

Run No.	*p-tert*-Butylphenol, g.	*n*-Heptane, g.	Organic Base[a]	Organic Base, g.	Catalyst,[b] g.	Max. Temp., °C.	Max. H_2 Press., p.s.i.g.	Mole % Alcohol Yield Based on Alkylphenol Charged
10	80	35	TEA	16	70	204	1500	46
26	160	70	Pyd	81	140	207	1550	22
38	160	70	Pyd	80	140	212	1620	18
105	159	68	—	0	140	204	1700	36
14	80	95	a	90	70	204	1475	68
34	81	27	b	124	70	204	1500	68
37	80	13	b	62	70	207	1500	67
39	80	7	b	31	70	206	1570	66
27	80	36	—	0	70	182	1550	61
53	81	33	c	62	70	181	1500	82
63	80	35	—	0	70	157	1410	63
64	80	33	c	62	70	149	1500	90

[a] TEA = Triethylamine, Pyd = Pyridine, a = Product from Run 10, b = Product from Run 26, c = Product from Run 38. [b] Catalyst is nickel-on-kieselguhr.

and phenol over a Pd catalyst at 90–200°.[5] Sawa, *et al.*,[6] report that upon hydrogenating pyridine with nickel-on-kieselguhr catalyst in the presence of an alcohol, *N*-alkylpiperidine is formed. Thus, one probable tertiary amine from the reaction of *p-tert*-butylphenol with pyridine is *N*-(4-*tert*-butylcyclohexyl)piperidine.

In addition to the effect of pyridine on the hydrogenation of *p-tert*-butylphenol, the effect of temperature on the reaction may also be noted in Table II. As the temperature increases, the yield of alcohol, either in the presence or absence of organic base, decreases. This is to be expected since it is known that the extent of hydrogenolysis of alcohols increases with temperature.

In order to minimize condensation of *p-tert*-butylphenol with the amine, some experiments were made using samples of the mixture of amines that was produced in a previous reaction. This was done by adding to the charge an aliquot of the total product from the previous reaction. The amount of alcohol thus introduced into the reactants was subtracted from the total amount of alcohol found after the hydrogenation in order to obtain the yield. The results of these experiments are reported in Table III. It can be seen that in every run in which the high molecular weight amine was added, a substantial increase in yield was obtained over the corresponding run with no amine added. The alcohol yield was also greater than that in the run in which the high molecular weight amine was produced.

It can be seen from Runs 34, 37, and 39 in Table III that the yield is not affected by the concentration of the complex amine mixture in the charge. If it is assumed that the high molecular weight amines poison acidic catalyst sites active for hydrogenolysis, then the alcohol yield should be independent of the amine concentration provided enough amine is present to poison these acidic sites. It again can be seen from Table III that lowering the hydrogenation temperature increases

(5) L. J. Dankert and D. A. Permoda (to Dow Chemical Co.), U. S. Patent 2,571,016 (October 9, 1951).

(6) Y. Sawa, K. Inone, and S. Kitamava, *J. Pharm. Soc. Japan*, 63, 319 (1943).

TABLE IV
HYDROGENATION OF CRESYLIC ACIDS

Run No.	Cresylic Acid, g.	*n*-Heptane, g.	Organic Base[a]	Organic Base, g.	Catalyst	Catalyst,[a] g.	Max. Temp., °C.	Max. H_2 Press., p.s.i.g.	Mole % Alcohol Yield Based on Alkylphenol Charged
54	51[b]	35	—	0	Ni-WS	80	273	1780	0
113	51[b]	34	Pyd	35	Ni-WS	83	268	1900	20
99	129[c]	70	Pyd	80	Ni	140	180	1880	60
86	51[c]	35	—	0	Ni	70	177	1500	54
100	50[c]	23	a	56	Ni	70	184	1775	75

[a] Ni = Nickel-on-kieselguhr, Ni-WS = Tungsten-nickel-sulfide, Pyd = Pyridine, a = Product from Run 99. [b] Acid oils recovered from catalytic cracking. [c] "215/225 Cresylic Acid" supplied by Merichem Co.

the yield both with and without organic base present. The highest yield obtained was 90% at 149° in the presence of the complex amine mixture.

The effect of amines on the yield was also investigated in the hydrogenation of cresylic acids over nickel-on-kieselguhr and tungsten-nickel-sulfide catalysts. From Table IV it can be seen that with the latter catalyst some yield improvement was obtained in the presence of pyridine. In Run 99 high molecular weight amines were produced from pyridine and cresylic acid under hydrogenation conditions. When these amines were added to the charge in Run 100, a 50% improvement was obtained over the alcohol yield of Run 86, in which no amine was added.

CONCLUSION

It has been found that organic bases inhibit the hydrogenolysis of alkylphenols over nickel-on-kieselguhr catalyst but do not poison the hydrogenating activity of this catalyst. This result is consistent with the hypothesis that acidic sites on the catalyst surface bring about the hydrogenolysis of hydroxyl groups and that these sites may be poisoned with amines. One would predict from this mechanism that the yield of alkylcyclohexanol would be independent of the concentration of the base, as long as enough amine was present to poison all of the acidic sites on the catalyst. This prediction is also in agreement with the experimental results.

It can be concluded from the data presented that the beneficial effect of the amine on the yield is greater the higher the molecular weight of the alkylphenol. This trend is expected since hydrogenolysis, which the amine inhibits, is more extensive with the higher molecular weight phenols. It was also found that the lower the temperature, the higher the alcohol yields obtained from *p-tert*-butylphenol both with and without added amine.

EXPERIMENTAL

Materials. The C_{15}–C_{18} alkylphenols used were prepared by the BF_3-catalyzed addition to phenol of C_9–C_{12} polypropylene olefins with an average molecular weight of 139, and boiling range of 153–200°. These alkylphenols contained 4.5 meq. of hydroxyl groups per gram, while phenol itself contains 10.6 meq. of hydroxyl groups per gram. *p-tert*-Butylphenol was obtained from Eastman Kodak Co., and the purity was 98% as determined from the hydroxyl number. The Merichem Co. supplied the cresylic acid, which contained mainly xylenols and had a sulfur content of 0.04%. Phillip's pure grade *n*-heptane, c.p. pyridine, and Eastman triethylamine were also used.

The nickel-on-kieselguhr catalyst contained 65–70% nickel and was supplied by the Harshaw Chemical Co., while the tungsten-nickel-sulfide catalyst was obtained from the Shell Oil Co.

Hydrogenation procedure. All of the hydrogenation runs were conducted in a similar manner, and the procedure will be given for a typical example (Run 143). *p-tert*-Butylphenol (80.0 g.), *n*-heptane (35.3 g.), and pyridine (17.4 g.) were charged to an Aminco 1400-ml. stainless steel, high pressure bomb. Nickel-on-kieselguhr catalyst (70 g.) was reduced in a hydrogen stream for 1 hr. at 260–315° and then added to the charge. Hydrogen was pressured into the reactor up to 1000 p.s.i.g., heat supplied by electrical heaters, and the reactants agitated for 5 hr. after the reaction temperature of 204° had been reached. Hydrogen was added intermittently to keep the pressure between 1000 and 1450 p.s.i.g.

After cooling, the reactants were rinsed from the bomb with *n*-heptane and the catalyst filtered from the solution. In order to remove the complex mixture of amines formed during the reaction, 100 ml. of 1:1 HCl was added. The white solid which formed was filtered off and digested with *n*-heptane on a steam bath to dissolve the small amount of *tert*-butylcyclohexanol present. The *n*-heptane solutions so obtained were twice washed with 100 ml. of 5% NaOH. After drying over Na_2SO_4, the alcohol yield was determined by acetylation with acetic anhydride. In the case of the cresylic acids, the product was analyzed directly for hydroxyl groups without washing or prior removal of amines because of the partial solubility of the alkylcyclohexanols in water. The yield was determined by acetylating the products with acetic anhydride and correcting the results for the high molecular weight amines present. The products also were tested for unreacted alkylphenol with $FeCl_3$. In all runs reported in Table IV, the product contained less than 0.1% of the original phenolic compound.

Hydrogenation products. In order to characterize the compounds formed in a typical hydrogenation of *p-tert*-butylphenol, the product from Run 27 (Table II) was distilled and each of the fractions analyzed by infrared spectroscopy. The only products found were 4-*tert*-butylcyclohexanol (64 wt. %), *tert*-butylcyclohexane (14 wt. %), and an unknown compound or mixture boiling in the same range as the

alcohol (10 wt. %). This unknown compound was probably a condensation product from *p-tert*-butylphenol, but the infrared spectrum of this fraction showed no bands due to functional groups other than the hydroxyl group in *tert*-butylcyclohexanol. This alcohol was characterized by preparing its phenylurethan derivative (m.p. 161–163°). One conclusion that can be drawn from the data is that the tertiary butyl group was not cleaved from the ring during hydrogenation since neither cyclohexane nor cyclohexanol was found in the products.

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TEXAS CITY, TEX.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES OF THE ETHYL CORPORATION]

Convenient Syntheses of *p*-Bromo- and *p*-Aminophenol

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Convenient syntheses are described for preparing *p*-bromophenol in high yield and high purity and for *p*-aminophenol in high yield. Possible mechanisms for the copper sulfate-catalyzed ammonolysis of *p*-halophenols are discussed.

While investigating the synthesis of *p*-aminophenol from phenol *via* *p*-bromophenol, several interesting observations were made. It was found that the bromination of phenol by the *Organic Syntheses* procedure,[1] using equimolecular amounts of phenol and bromine in ethylene dichloride instead of carbon disulfide, gave an 83% yield of crude *p*-bromophenol containing as much as 12% 2,4-dibromophenol.[2] Variations in the rate of addition of the bromine solution, stirring, dilution, temperature (−5 to +5°), or dryness of the ethylene dichloride solvent gave little or no improvement in the conversion beyond 72% pure *p*-bromophenol. However, use of a 20% or greater excess of phenol resulted in a substantial decrease in the amount of 2,4-dibromophenol and a corresponding increase in the conversion and purity of *p*-bromophenol. The procedure developed here was found to be very convenient not only because of the high conversion to *p*-bromophenol but because of the ease of obtaining high purity *p*-bromophenol.

It is of interest to note that there was a direct correlation between the amount of 2,4-dibromophenol and the amount of unreacted phenol in the experiments where equimolecular amounts of phenol and bromine were used. Moreover, the ortho and meta isomers were in every case present to the extent of less than 1–2% and showed no variation with the amount of 2,4-dibromophenol formed. This indicates that the 2,4-dibromophenol was formed almost exclusively from *p*-bromophenol.

Although the aminolysis of *p*-bromophenol with methylamine has been reported,[3] the corresponding reaction with ammonia apparently has not been. References were found, however, to the ammonolysis of *p*-chlorophenol. In one reference[4] the conditions given involved reaction at 140° for 12 hr. in the presence of catalytic amounts of copper sulfate (no yield given), whereas in the other reference[5] the optimum conditions involved reaction of one volume *p*-chlorophenol with 4 volumes of 33% aqueous ammonia containing 16% copper sulfate at 185° for 3 hr. to produce an 82% yield of *p*-aminophenol. Since *p*-bromophenol reacts much more readily with methylamine than does *p*-chlorophenol, it appeared that considerably milder ammonolysis conditions could be used for the *p*-bromophenol than those reported for *p*-chlorophenol.

The initial ammonolysis experiments with *p*-bromophenol were therefore conducted in the presence of catalytic amounts of copper sulfate at 25° to 60°. It was found that no significant reaction occurred. Consequently, it appears that there is a considerable difference in the reactivity of ammonia and methylamine towards *p*-halophenols, possibly even more than would correspond to their relative basicities (which differ by a factor of about 30). Some experiments were then conducted in the presence of relatively large quantities of copper sulfate (0.34 mole per mole *p*-bromophenol) as specified in one of the references for the ammonolysis of *p*-chlorophenol. At 65 to 140° the conversion to *p*-aminophenol was at best only 39%, and at 140° appreciable tar formation also occurred. Use of milder conditions in the presence of catalytic amounts of copper sulfate was therefore indicated.

A reaction variable study gave the following results: (*1*) The yield of *p*-aminophenol from *p*-bromophenol increased appreciably from 25° to 120° and

(1) R. Adams and C. S. Marvel, *Org. Syntheses*, Coll. Vol. I, 128, (1941).

(2) 2,4-Dibromophenol and *p*-bromophenol boil within one degree at the distillation pressures used. The components were determined by infrared analyses.

(3) F. R. Bean (to Eastman Kodak) U. S. Patent 2,397,911, Apr. 9, 1946.

(4) German Patent 205,415, Dec. 31, 1907. Akt.-Ges. fur Anilin-Fabrikation, Berlin.

(5) A. I. Kipriyanov, G. I. Kipriyanov, and M. Dashevskii, *Ukrain. Khem. Zhur.*, 7 Wiss. Tech. Abt. 87–93 (1932).

decreased somewhat at temperatures above 140° due to side reactions; (*2*) the yield increased with an increase in the copper sulfate concentration up to a certain point and then decreased due to tar formation; (*3*) the yield increased with an increase in the ammonia concentration; and (*4*) the yield decreased somewhat in the presence of an equivalent of sodium hydroxide per equivalent of *p*-bromophenol. The best results were obtained by using 6–9 moles aqueous ammonia per mole *p*-bromophenol in the presence of 0.04 mole copper sulfate at 120° for 4 hr. or at 140° for 1.5–2.0 hr. These conditions resulted in a 62–66% yield of *p*-aminophenol isolated directly by filtration of the reaction mixture. It was estimated from solubility data that an additional 12–15% yield of *p*-aminophenol was present in the filtrate. The over-all yield of *p*-aminophenol (not allowing for recoverable *p*-bromophenol) was 74–81%.

Mechanism of the ammonolysis reaction. Although this study was not directed at determining the mechanism of the copper sulfate catalyzed ammonolysis of *p*-halophenol it is of interest to consider various mechanisms which are consistent with the observed facts. The ammonolysis of *p*-halophenols may be classified as an unactivated aromatic nucleophilic substitution reaction.[6] There are at least three types of mechanisms which have been advanced or in some cases pretty well established for reactions which may be so classified. (*1*) S_N1, such as the hydrolysis of diazonium salts[7] and the saponification of aryl halides at high temperatures,[8] (*2*) *cine* substitutions *via* a "benzyne" intermediate, such as the reaction of aryl halides with sodium amide in liquid ammonia,[9] and (*3*) S_N2, via a copper complex, such as the Ullmann and Sandmeyer reactions.[6] From the observed facts it would appear that the ammonolysis reaction in question bears the closest resemblance mechanistically to the latter type reactions. Although it resembles in certain respects the reactions of aryl halides with aqueous base at high temperatures, its apparent dependence upon the ammonia and catalyst concentrations, and the apparent lesser reactivity of the phenolate ion appears to rule out the S_N1 mechanism. The fact that only the normal substituted product is here obtained rules out the "benzyne" intermediate type of mechanism.[10]

There are at least three mechanisms which are consistent with the observed facts on the copper sulfate catalyzed ammonolysis of *p*-halophenols: (*1*) A termolecular mechanism involving "push" by ammonia and "pull" by cupric or copper ammino ions on bromine; (*2*) a two-step reaction involving formation of a loose complex between the bromo substituent and the cupric or copper ammino ions, followed by displacement of bromide by ammonia; and (*3*) a two-step reaction involving a fast reversible formation of a π complex between the halophenol and cupric or copper ammino ion followed by a rate determining displacement of bromide ion from the π complex by ammonia. At present there are insufficient data available to clearly distinguish between these mechanisms.

EXPERIMENTAL

For brevity, only the best procedures developed are described.

p-Bromophenol To a solution of 113 g. (1.2 moles) of phenol in 240 ml. of ethylene dichloride was added dropwise a solution of 160 g. (1.0 mole) of bromine and 105 ml. of ethylene dichloride at 0° over a period of 160 min. The mixture was stirred an additional 0.5 hr. at 0°, and then the ethylene dichloride was stripped at atmospheric pressure, b.p. 81–83°. The excess phenol and product were then rectified through an 18-in. heated Vigreux column at 15 mm. The *p*-bromophenol distilled at 120–122°/15 mm., 161 g. m.p. 63–65°[11] lit.[1] 63°, (93% yield, based on bromine) and is 98% pure (based on infrared analyses).

p-Aminophenol. *p*-Bromophenol (34.6 g., 0.2 mole) was dissolved in a solution of 2 g. of copper sulfate pentahydrate (0.008 mole) dissolved in 10 ml. of water and 120 ml. of concentrated ammonium hydroxide (28–30%, 1.8 moles) at 30–35°. Below this temperature there was a tendency for a precipitate to form. The mixture was then transferred to a 250-ml. Magne-Dash autoclave which was assembled and then heated rapidly to 140°. The temperature was maintained at 140° for 80–120 min. The bomb was then cooled with an air jet. The bomb was opened and the contents cooled to 0° and filtered (15.6 g. black solid). The product was slurried with 15–20 ml. of water, filtered, reslurried with 15–20 ml. of ether, and filtered again. The yield of dry *p*-aminophenol was 14.7 g., 63% (based on *p*-bromophenol) and 93% pure (based on nitrogen analysis), m.p. 180–183° dec. Recrystallization of 3 g. of this product from 80 ml. of boiling water and 1 g. of activated charcoal in the presence of 0.2 g. of sodium hydrosulfite gave 2.1 g. of light gray solid, m.p. 184–186° dec., lit.[12] 184–186° dec. (70% recovery, 98% pure or better, based on nitrogen analysis).

Alternate conditions giving about the same results involve reaction at 120° for 225 min. The pressure developed at 120° was about 90 p.s.i.g., whereas at 140° it was about 165 p.s.i.g., using the same amount of reactants.

BATON ROUGE, LA.

(6) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, 49, 273 (1951).

(7) M. L. Crossely, R. H. Kienle, and C. H. Benbrook, *J. Am. Chem. Soc.*, 62, 1400 (1940).

(8) W. J. Hale and E. C. Britton, *Ind. Eng. Chem.*, 20, 114 (1928).

(9) J. D. Roberts, *et. al.*, *J. Am. Chem. Soc.*, 75, 3290 (1953); 78, 601–614 (1956).

(10) The reaction of *p*-halophenols with amines in the presence of copper catalysts in anhydrous media or with liquid ammonia would be of interest in this connection.

(11) All melting points are uncorrected.

(12) Beilstein XIII-427, N. V. Sidgwick, and R. K. Callow, *J. Chem. Soc.*, 125, 522 (1924).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

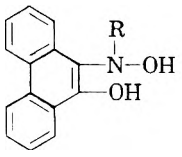
Studies of Quinoid Structures. II.[1] Action of Grignard Reagents on Phenanthrenequinone Monoxime, Chrysenequinone Monoxime and Chrysenequinonimine

WILLIAM IBRAHIM AWAD AND ABDEL REHIM ABDEL RAOUF

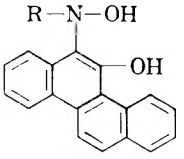
Received July 17, 1957

Alkyl- and arylmagnesium halides react with phenanthrenequinone monoxime and chrysenequinone monoxime by 1,2-addition to the carbonyl group and not by 1,4-addition as previously described.[2] The constitution of the products is discussed.

Mustafa and Kamel[2] claimed that when arylmagnesium halides are allowed to react with phenanthrenequinone monoxime and chrysenequinone monoxime, an addition occurs which they formulated as (I) and (II), 1,4-additions.

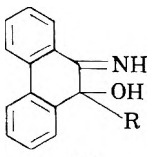


I
Ia, R = C_6H_4
Ib, R = $C_6H_4OCH_3$ (*p*)
Ic, R = $C_{10}H_7$(α)



II (or its isomer)
II, R = C_6H_5

The main line of evidence upon which these authors assigned the above structures is the reduction by lithium aluminum hydride of the compound thought to be 10-phenylhydroxylamino-9-hydroxyphenanthrene (Ia) to give the same product obtained by the action of phenylmagnesium bromide on phenanthrenequinonimine. Unfortunately, the previous workers thought the phenylmagnesium bromide–phenanthrenequinonimine reaction product was 10-phenylamino-9-hydroxyphenanthrene;[1] in reality, as we proved in our previous publication,[1] this reaction product is 9-phenyl-9,10-dihydro-10-imino-10-phenanthrol (IIIa). The correctness of this structure was established by conversion to 10-hydroxy-10-phenyl-9(10H)phenanthrone by acid hydrolysis; our phenanthrone had the same melting point as that recently reported by Shriner and Geipel.[3]

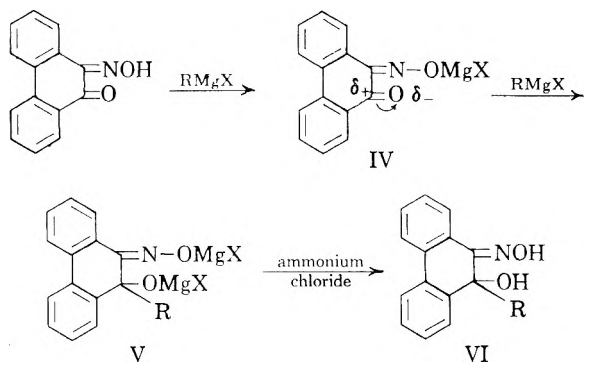


III

IIIa, R = C_6H_5
IIIb, R = $C_6H_4CH_3$(*o*)
IIIc, R = $C_6H_4CH_3$(*m*)
IIId, R = $C_{10}H_7$(α)

In addition, the preferential addition of Grignard reagents to the carbonyl group has been reported by Diels, *et al.*[4,5] to take place in the case of *N*-methyl biacetyl phenylhydrazone.

The present investigation deals with the action of alkyl and arylmagnesium halides on phenanthrenequinone monoxime. The reaction appears to proceed according to scheme A.



Scheme A

VIa, R = CH_3; VIb, R = C_2H_5; VIc, R = C_3H_7(*n*); VId, R = C_4H_9(*iso*)
VIe, R = C_6H_5; VIf, R = $C_6H_4OCH_3$(*p*); VIg, R = $C_6H_4CH_3$(*o*)
VIh, R = $C_6H_4CH_3$(*m*); VIi, R = $C_6H_4CH_3$(*p*); VIj, R = $C_{10}H_7$(α)

It should be noticed that oximes do not normally react readily with Grignard reagents except as "active hydrogen" compounds.[6] All other reactions reported have been carried out under more or less drastic conditions.[6,7]

Since, on steric grounds, chrysenequinone monoxime was assigned by Awad and Raouf[8] structure VII, the product of its interaction with alkyl and arylmagnesium halides is more likely represented by VIII.

(1) W. I. Awad and A. R. A. Raouf, *J. Org. Chem.*, **22**, 881 (1957).
(2) A. Mustafa and M. Kamel, *J. Am. Chem. Soc.*, **76**, 124 (1954).
(3) R. L. Shriner and L. Geipel, *J. Am. Chem. Soc.*, **79**, 227 (1957).
(4) O. Diels and F. ter Meer, *Ber.*, **42**, 1940 (1909).
(5) O. Diels and J. M. Johlin, *Ber.*, **44**, 403 (1911).
(6) Kharasch and Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 1217.
(7) M. Busch and R. Hobein, *Ber.*, **40**, 2096 (1907).
(8) W. I. Awad and A. R. A. Raouf, *J. Am. Chem. Soc.*, **77**, 3913 (1955).

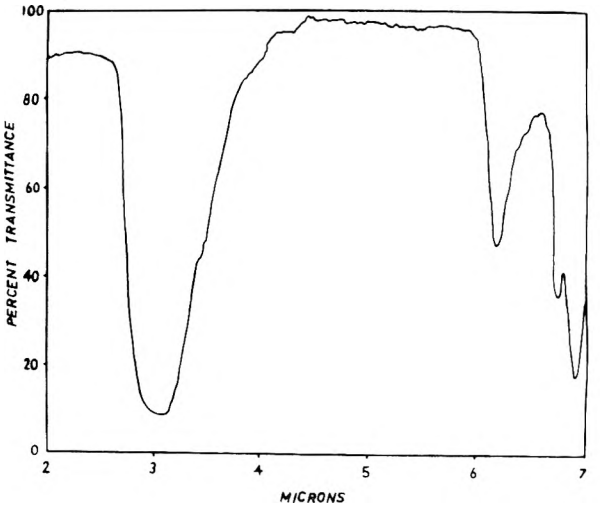


FIG. 1. 9-*o*-TOLYL-9,10-DIHYDRO-10-OXIMINO-9-PHENANTHROL (VIg) (potassium bromide wafer technique).

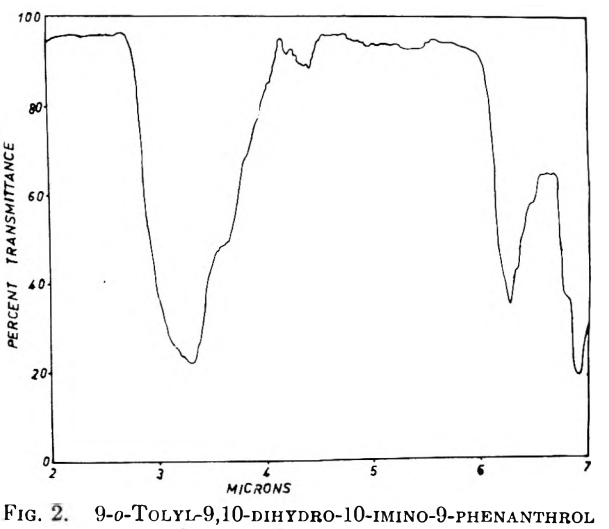
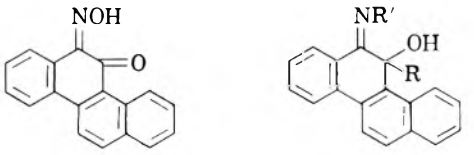


FIG. 2. 9-*o*-TOLYL-9,10-DIHYDRO-10-IMINO-9-PHENANTHROL (potassium bromide wafer technique).



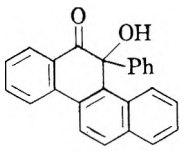
VII VIII

VIIIa, R′ = OH, R = CH_3; VIIIb, R′ = OH, R = C_2H_5; VIIIc, R′ = OH, R = C_4H_9(*iso*); VIIId, R′ = OH, R = C_6H_5; VIIIe, R′ = OH, R = $C_6H_4OCH_3$(*p*).

The constitution of the Grignard products is based upon the following: (*i*) the preferential addition of the Grignard reagent to the carbonyl group,[1,3,4] (*ii*) the reduction of (VIe) and (VIh) to the same products obtained by the action of phenyl- and *m*-tolylmagnesium halides on phenanthrenequinonimine, respectively.

Products (VI) are stable to hydrolysis in contrast to the corresponding imino compounds (III).[1]

However, we find that when chrysenequinonimine is allowed to react with phenylmagnesium bromide, a nitrogen free keto compound (IX) is obtained directly instead of the expected compound VIII, (R′=H).



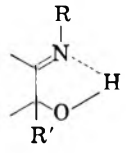
IX

It is suggested that this compound IX results from the direct hydrolysis of the imino compound on decomposition of the Grignard product. The constitution of IX is established by its identity with the ketone obtained by the hydrolysis of (VIIId). Similar keto compounds are obtained by the acid hydrolysis of III.[1]

This shows that the products in the chrysenequinonimine series are more readily hydrolyzed than those in the phenanthrenequinonimine series.

The ease of hydrolysis of the products of chrysenequinonimine (VIII, R′=H) is also manifested by the hydrolysis of VIIId and the failure of the corresponding phenanthrene derivatives (VIe) to do so.

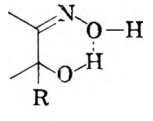
Comparison of the infrared curves of VIg and its corresponding imino compound (*cf.* Figs. 1 and 2 respectively) shows conjugated C=N stretching frequency[9] at 6.2–6.3 microns. This is in favor of the structure assigned to these compounds. The curves also show stretching frequencies in the intramolecular hydrogen bridge[10] (3.1–3.3 microns) which suggests the chelated structure (X).



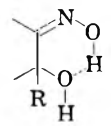
X

R = H or OH
R′ = $C_6H_4CH_3$(*o*)

Similarly the absence of a free OH stretching frequency at 2.7-2.8 microns[10] in the case of oximino products (VIg) (*cf.* Fig. 1) may be attributed to chelated structures (XI and XII).



XI



XII

The ultraviolet spectra of VIe (Fig. 3) and VIg (Fig. 4) and their imino analogs show a great similarity between the oximino- and imino-compounds.

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen; London, 1956, p. 223.

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen; London, 1956, p. 84.

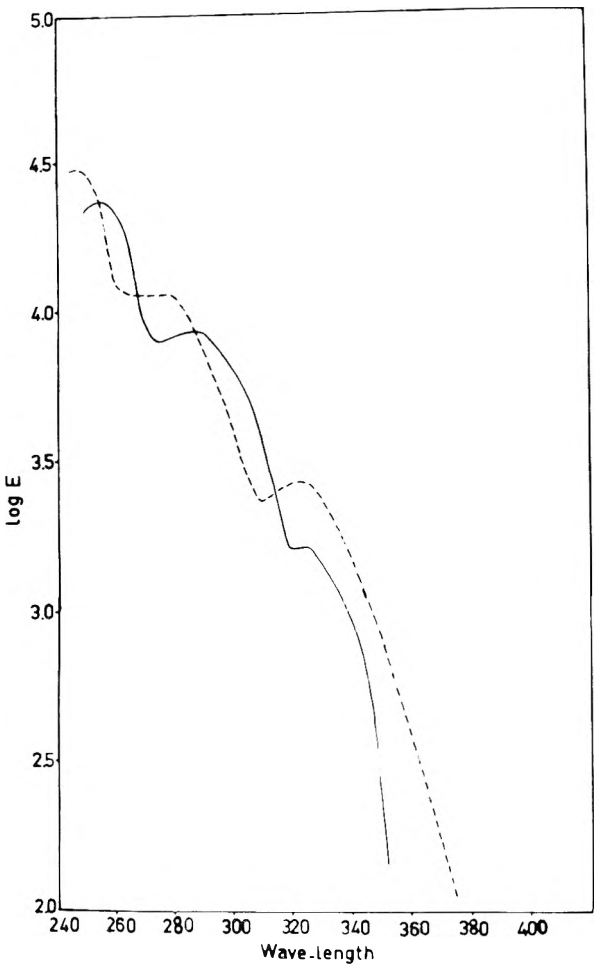


FIG. 3. ULTRAVIOLET SPECTRA. ——— VIe in chloroform; - - - - imino analog in chloroform.

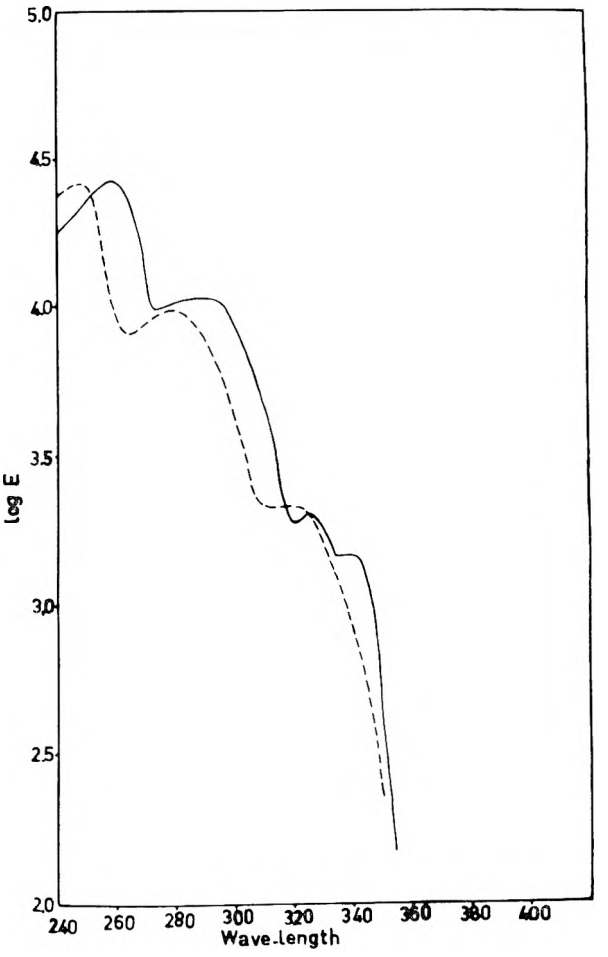


FIG. 4. ULTRAVIOLET SPECTRA. ——— VIg in chloroform; - - - - imino analog in chloroform.

EXPERIMENTAL[11]

Reaction of phenanthrenequinone monoxime with methylmagnesium iodide. A solution of phenanthrenequinone monoxime (2 g.) in hot dry benzene (100 ml.) was added to an ethereal solution of methylmagnesium iodide (from methyl iodide, 7.5 g. and magnesium, 1.2 g.) and the reaction mixture was heated under reflux for 2 hr. After cooling, it was poured slowly into 200 ml. of saturated aqueous ammonium chloride solution, and the ether-benzene layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The product was precipitated by the addition of petroleum ether (40–60°) and was recrystallized from benzene to give VIa as colorless crystals, m.p. 165°, yield 57%. It gave a brown color with concentrated sulfuric acid and the color then turned to yellowish green.

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.3; H, 5.5; N, 5.9. Found: C, 75.2; H, 5.8; N, 5.96.

Reaction of phenanthrenequinone monoxime with alkyl and arylmagnesium halides. The reaction was carried out as in the case of methylmagnesium iodide. The products are listed in Table I.

Reduction of VIe with lithium aluminum hydride. Dry ether (60 ml.) was added to pulverized lithium aluminum hydride (0.8 g.) and left for 15 min. A solution of VIe (1 g.) in dry benzene (100 ml.) was then added to the above mixture, refluxed for 3 hr., and then set aside overnight at room temperature. After treatment with cold aqueous ammonium chloride solution, the ethereal solution was dried over anhydrous sodium sulfate, and evaporated (blue violet fluorescence). The residue left was crystallized from benzene to give IIIa, identified by m.p. and mixed m.p. determinations, yield 66%. The substance gave an olive green color with concentrated sulfuric acid and changed to reddish brown and finally to brown on adding a crystal of potassium nitrate or a drop of nitric acid.

Hydrolysis of VIe. The compound was recovered unchanged on trying to hydrolyze it either with alcoholic hydrochloric acid or alcoholic potash.

Reduction of VIh with lithium aluminum hydride. Dry ether (60 ml.) was added to pulverized lithium aluminium hydride (0.8 g.) and left for 15 min. A solution of VIh (1 g.) in dry benzene (100 ml.) was added to the above mixture, refluxed for 3 hr. and then set aside overnight at room temperature. After treatment with cold aqueous ammonium chloride solution, the ethereal solution was dried over anhydrous sodium sulfate, and evaporated. The product came down during concentration, filtered, and crystallized from benzene to give IIIc identified by m.p. and mixed m.p. determinations, yield 55%.

Reaction of phenanthrenequinonimine with o-tolylmagnesium bromide. A solution of phenanthrenequinonimine (1 g.) in hot dry benzene (50 ml.) was added to an ethereal solution of *o*-tolylmagnesium bromide (from *o*-bromotoluene, 6 g. and magnesium, 0.6 g.) and the reaction mixture was refluxed for 3 hr., hydrolyzed with ammonium chloride solution, the ether-benzene layer separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The product was precipitated by the addition of petroleum ether (40–60°)

(11) Microanalyses were carried out by Alfred Bernhardt, Germany. Melting points are not corrected.

TABLE I

Compound	Solvent of Crystallization[a]	M.P., °C.	Yield,[b] %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Color with Concd. Sulfuric Acid
VIb	A	147	41	$C_{16}H_{15}O_2N$	75.9	75.3	5.97	5.5	5.5	5.8	Light green
VIc	A	141	30	$C_{17}H_{17}O_2N$	76.4	76.1	6.4	6.4	5.2	5.2	Light green
VId	B	194	56	$C_{18}H_{19}O_2N$	76.8	76.8	6.8	7.05	4.98	4.97	Lemon yellow
VIe	B	162	44	$C_{20}H_{15}O_2N$	79.7	79.8	5.0	5.4	4.7	4.3	Blue turned to purple
VIf	B	178	28	$C_{21}H_{17}O_3N$	76.1	75.6	5.2	5.1	4.2	4.1	Prussian blue
VIg	B	162	66	$C_{21}H_{17}O_2N$	80.0	80.3	5.4	5.4	4.4	4.4	Reddish brown[c]
VIh	B	188	57	$C_{21}H_{17}O_2N$	80.0	80.5	5.4	5.99	4.4	4.2	Green turned to blue
VIi	B	185	35	$C_{21}H_{17}O_2N$	80.0	79.9	5.4	5.8	4.4	4.2	Prussian blue turned to green blue
VIj	B	192[d]	20	$C_{24}H_{16}O_2N$	82.0	82.55	4.9	5.1	3.99	3.9	Dark green

[a] A, benzene-petroleum ether (40–60°); B, benzene. [b] Yield is calculated for pure material. [c] Turned to brown on adding a crystal of KNO_3. [d] Brown melt.

TABLE II

Compound	Solvent of Crystallization[a]	M.p., °C.	Yield,[b] %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Color with Concd. Sulfuric Acid
VIIIb	A	173	36	$C_{20}H_{17}O_2N$					4.6	4.5	Prussian blue turned to green[c]
VIIIe	A	178	42	$C_{22}H_{21}O_2N$	79.7	79.7	6.4	6.5	4.2	4.1	Prussian blue turned to green[d]
VIIId	B	202[e]	42	$C_{24}H_{17}O_2N$[f]							Violet blue turned to green blue
VIIIe	C	236[e]	62	$C_{25}H_{19}O_3N$	78.7	79.1	5.0	5.4	3.7	3.98	Olive green[g]

[a] A, benzene-petroleum ether (40–60°); B, benzene; C, ethyl alcohol. [b] Yield is calculated for pure material. [c] Turned to wine-red on adding one drop of concd. HNO_3. [d] Turned to pink on adding one drop of concd. HNO_3. [e] Brown melt. [f] Reported in Ref. 2. [g] Turned to blue on adding one drop of concd. HNO_3.

and was recrystallized from benzene to give IIIb as pale yellow crystals, m.p. 176°, yield 28%. It gave a green color with concentrated sulfuric acid and the color turned to blue on adding one crystal of potassium nitrate.

Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7; N, 4.7. Found: C, 84.0; H, 5.9; N, 4.6.

Reaction of chrysenequinone monoxime with methylmagnesium iodide. A solution of chrysenequinone monoxime (2.5 g.) in hot dry benzene (100 ml.) was added to an ethereal solution of methylmagnesium iodide (from methyl iodide, 7.5 g. and magnesium, 1.2 g.) and the reaction mixture was refluxed for 3 hr., hydrolyzed with ammonium chloride solution, the ether-benzene layer separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The product was precipitated by the addition of petroleum ether (40–60°) and was recrystallized from benzene to give VIIIa as pale yellow crystals, m.p. 176°, yield 50%. It gave a Prussian blue color with concentrated sulfuric acid, turned gradually to green.On adding one drop of concentrated nitric acid, the color changed to pink and finally to brown.

Anal. Calcd. for $C_{19}H_{15}O_2N$: C, 78.9; H, 5.2; N, 4.8. Found: C, 79.1; H, 5.4; N, 4.7.

Reaction of chrysenequinone monoxime with alkyl and arylmagnesium halides. The reaction was carried out as in the case of methylmagnesium iodide. The products are listed in Table II.

Hydrolysis of VIIId. A solution of 0.3 g. of VIIId in ethyl alcohol (100 ml.) and concentrated hydrochloric acid (3 ml.) was refluxed for 2 hr. on the steam bath. The compound dissolved gradually in the reaction mixture and the color of the solution changed from colorless to red brown with slight violet fluorescence. The product came down after concentration and cooling and was recrystallized from benzene-petroleum ether (40–60°) to give the nitrogen free keto-compound as colorless crystals, m.p. 172°, undepressed on admixture with IX; yield 30%. It gave a dark brown color with concentrated sulfuric acid.

Reaction of chrysenequinonimine with phenylmagnesium bromide. A solution of chrysenequinonimine (1 g.) in hot dry benzene (50 ml.) was added to an ethereal solution of phenylmagnesium bromide (from bromobenzene, 8 g. and magnesium, 1 g.) and the reaction mixture was refluxed for 3 hr., hydrolyzed with ammonium chloride solution, the ether-benzene layer separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The product was precipitated by the addition of petroleum ether (40–60°) and was recrystallized from benzene-petroleum ether (40–60°) (after allowing the solution to evaporate slowly by standing for several days) to give IX as colorless crystals, m.p. 172°, yield 31%. It gave a dark brown color with concentrated sulfuric acid.

Anal. Calcd. for $C_{24}H_{16}O_2$: C, 85.7; H, 4.8. Found: C, 85.2; H, 4.9.

Acknowledgment. The authors wish to express their thanks to Messrs. Samuel P. Sadtler and Son Inc., 1517 Vine Street, Philadelphia 2, Pa., for recording the infrared spectra.

ABBASSIA, CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE FACULTY OF SCIENCE, CAIRO UNIVERSITY]

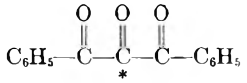
Diphenyltriketone-Benzoin Rearrangement in an Acidic Medium

A. SCHÖNBERG AND R. C. AZZAM

Received May 14, 1957

The formation of benzoin and benzil from diphenyltriketone and diphenyltetraketone is described and the reaction mechanism discussed.

The diphenyltriketone-benzoin rearrangement in an alkaline medium was discovered by de Neufville and Pechmann[1] who did not give the yield. Roberts *et al.*[2] who worked with C^{14}-labelled triketone I (using a 15% carbonate-free sodium hydroxide solution) reported a 5% yield.

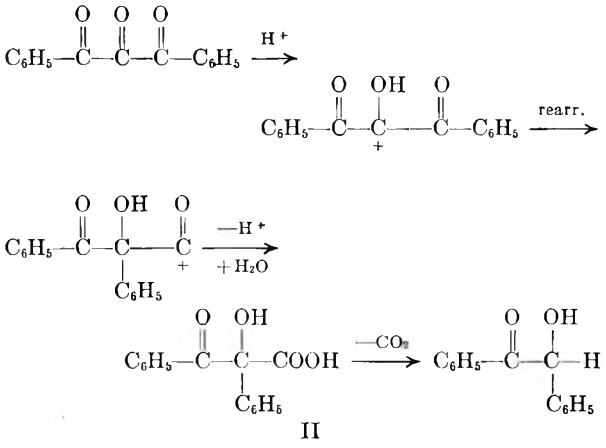


I

The diphenyltriketone-benzoin rearrangement in alkaline medium could have been expected and is to be considered as a type of benzilic acid rearrangement: the sodium salt of α-benzoylmandelic acid being an intermediate which, on acidification, is converted to benzoin with elimination of carbon dioxide.

The diphenyltriketone-benzoin rearrangement effected by the action of mineral acids[3] was discovered much later,[4] but has been described only very fragmentarily. This paper describes the best experimental conditions for the rearrangement, discusses the reaction mechanism and reports also on the formation of benzil from diphenyltriketone and diphenyltetraketone by the action of mineral acids.

Diphenyltriketone-benzoin rearrangement effected by dilute phosphoric and dilute sulfuric acids. By a careful study of the experimental conditions yields up to 55% have been obtained. The question whether the central carbonyl group is eliminated in the process can only be decided by working[5] with labelled triketone (*cf.* I). In case the terminal CO group is eliminated the following scheme (*inter alia*) may be considered:



II

The elimination of CO_2 has been proved in experiment II by absorption in lime water.

Formation of benzil by the action of mineral acids on diphenyltriketone or diphenyltetraketone. Besides benzoin, benzil is formed by the action of mineral acids on diphenyltriketone, *e.g.* when working with relatively strong sulfuric acids. As under these conditions benzoin is oxidized to benzil, it is most probable that at least a portion of the benzil so obtained from the triketone is formed *via* benzoin. The oxidation is not due to the action of air as benzil is also formed when the experiment is carried out in an atmosphere of carbon dioxide. Benzil was also obtained from diphenyltriketone when phosphoric acid was used and it seems possible that the formation of benzil does not proceed, in part, *via* the oxidation of benzoin. The formation of benzil may be explained by the loss of water and carbon monoxide from II.

When diphenyltriketone was treated with a mixture of acetic, sulfuric, and nitric acids benzil, but not benzoin, was isolated: benzoin is first formed but is ozidized to benzil by the action of nitric acid. Under the same conditions benzil was obtained from diphenyltetraketone. It is believed that the tetraketone is first transformed into IIIa or IIIb (compare with the formation of benzoin from the triketone), II is then oxidized by the action of nitric acid to diphenyltriketone which is finally changed into benzil as described above.

(1) R. de Neufville and H. v. Pechmann, *Ber.*, **23**, 3375 (1890).

(2) J. D. Roberts, D. R. Smith, and C. C. Lee, *J. Am. Chem. Soc.*, **73**, 618 (1951).

(3) J. D. Roberts *et al.* (*cf.* footnote 2) stated that the triketone is not changed by prolonged refluxing with glacial acetic acid.

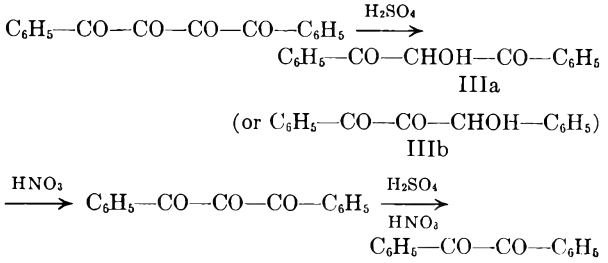
(4) A. Schönberg and R. C. Azzam, *J. Chem. Soc.*, 1428 (1939). J. D. Roberts *et al.* stated that they could not duplicate the decarboxylations of diphenyltriketone induced by sulfuric and phosphoric acids which had been reported by Schönberg and Azzam. For the decarboxylation with sulfuric acid *cf.* J. Wegmann and H. Dahn, *Helv. Chim. Acta*, **29**, 1248 (1946).

(5) This department is not equipped for investigations of this type.

TABLE I

Exp. No.[a]	Substance Used and Amount	Mineral Acid Used and Amount	Time of Boil, Min. With mineral acid	Time of Boil, Min. After addn. of AcOH[b]	Wt. of Crude Product	Pure Subst. Isolated
Ia	2 g. Diphenyltriketone	20 ml. H_2SO_4 (B)	30	30	1.11 g.	Benzil
II	1 g. Diphenyltriketone	10 ml. H_3PO_4 (D)	30	75	0.54 g.	Benzoin
III	1 g. Diphenyltriketone	10 ml. H_3PO_4 (C)	30	75	0.55 g. —	Benzoin Benzil
IVa	2 g. Benzoin	15 ml. H_2SO_4 (B)	30	60	1.52 g.	Benzil
Va	2 g. Benzoin	15 ml. H_3PO_4 (C)	30	60	1.93 g.	Benzoin
VIa	1 g. Benzil	10 ml. H_3PO_4 (D)	30	75	0.94 g.	Benzil

[a] The whole operation was carried out in an atmosphere of carbon dioxide. [b] The volume of acetic acid added was the same as that of the mineral acid used.



EXPERIMENTAL

The mineral acids used in these experiments were pure analytical reagents from Carlo Erba (Milan).

Sulfuric acid (sp. gr. 1.84) was diluted either (A) with 1.7 volume of distilled water or (B) with an equal volume of water. Phosphoric acid (sp. gr. 1.71) was either (C) used as such or (D) diluted with an equal volume of water.

The pure benzoin and benzil obtained in the various experiments always had the correct melting points which were not depressed by mixing with authentic samples of the substances.

Action of sulfuric acid on diphenyltriketone. Pure diphenyltriketone (1.00g.) was gently boiled under reflux with 10 ml. of sulfuric acid (diluted as in A) for 30 min. Ten milliliters of glacial acetic acid were then added and boiling continued for 30 min. more. The faintly yellow solution was cooled, poured into 150 ml. of cold water, and allowed to stand overnight. The solid which separated was filtered off, washed successively with water, sodium bicarbonate solution, and water, and dried in an exsiccator. The crude product (0.49 g.) was crystallized twice from 10 ml. of ethyl alcohol and pure benzoin (0.32 g.) was obtained.

The other experiments were carried out in a similar way and are summarized in Table I.

Procedure used for the isolation of the pure products in the above experiments:

(I) The pasty brownish crude product was extracted with three portions of petroleum ether (b.p. *ca.* 50°) and the combined extracts (45 ml.) were evaporated to dryness leaving an orange oil which solidified on cooling and scratching. By crystallizing from 5 ml. of ethyl alcohol pure benzil (0.26 g.) was obtained. The residue from extraction failed to give any crystalline substance.

(II) The crude product was crystallized twice from small volumes of ethyl alcohol and pure benzoin (0.12 g.) was obtained. This experiment was carried out in a slight current of air washed from carbon dioxide and the gases coming out of the flask were passed in lime water and made it turbid.

(III) The crude product was dissolved in 10 ml. of ethyl alcohol and after concentration by slow evaporation (avoiding direct sunlight) a crystalline mass was deposited consisting of clusters of colorless needles and long yellow prismatic needles which were separated mechanically and found to be respectively benzoin (0.11 g.) and benzil (0.15 g.). That benzil was a genuine product of the reaction was proved by allowing an alcoholic solution of benzoin to stand under the same conditions for several days whereby no benzil was detected.

(IV) The crude product was not separated by filtration but by extraction with ether. After evaporation of the solvent the yellow oil which was left was extracted with petrol as in (I). The petrol was then evaporated and the product crystallized from 5 ml. of ethyl alcohol. Pure benzil (0.24 g.) was obtained. The residue from the petrol extraction failed to give any crystalline substance.

(V) When the acid mixture was poured into water a yellow sticky substance collected at the bottom of the beaker but soon a voluminous crystalline solid filled the liquid and was separated by filtration and found to be benzoin (0.23 g.) after being crystallized twice from ethyl alcohol. The noncrystalline fraction (1.7 g.) was dissolved in 15 ml. of ethyl alcohol, 5 ml. of conc. hydrochloric acid added and the solution boiled for 15 min. It was then poured into water, extracted with ether, the extract washed, dried (Na_2SO_4), and evaporated. The residue was repeatedly crystallized from ethyl alcohol to give a mass of ill-defined crystals from which no pure product could be obtained.

(VI) The product (0.94 g.) proved to be unchanged benzil.

Action of sulfuric and nitric acids on diphenyltriketone. Pure diphenyl triketone (1.00 g.) was boiled for 30 min. with a mixture of 10 ml. of sulfuric acid (A) and 10 ml. of glacial acetic acid. One ml. of nitric acid (sp. gr. 1.4) was then added and the mixture boiled for 1 hr. more, cooled, and poured into 100 ml. of ice-cold water. The yellowish solid (0.3 g.) was crystallized from 5 ml. of ethyl alcohol and found to be benzil.

Action of sulfuric and nitric acids on diphenyltetraketone. Diphenyltetraketone monohydrate (m.p. 83–85°; 1.00 g.) was boiled for 1 hr. with a mixture of 10 ml. of sulfuric acid (A) and 3 ml. of nitric acid (sp. gr. 1.4). Ten milliliters of glacial acetic acid were then added and boiling continued for 2 more hr. The crude yellowish product (0.22 g.), separated as in the previous experiment, was extracted twice with hot petroleum ether, the extract (20 ml.) concentrated to a small volume and cooled. Yellow needles (0.11 g.) separated and upon crystallization from 3 ml. of ethyl alcohol pure benzil was obtained.

Acknowledgment. The authors wish to thank M. B. E. Fayez (National Research Centre, Cairo) for checking some of the experiments.

CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF KANSAS STATE COLLEGE]

Acyloxysilanes and Their Reaction with Grignard Reagents[1]

F. C. LANNING AND M. MOORE[2]

Received June 18, 1957

Tetrabutyroxysilane, tetra(trichloroacetoxy)silane, tetracrotonoxysilane, tetra(3-phenylpropionoxy)silane, tetra(β-napthoxy)silane, tetracinnamoxysilane, tetra(*o*-chlorobenzoxy)silane, tetrastearoxysilane, and tetra(*p*-hydroxybenzoxy)silane have been prepared by the reaction of tetrachlorosilane with the sodium salts of the organic acids. The infrared spectra of these acyloxysilanes have been determined between 3 and 15 μ.

The following alcohols and ketones have been prepared by the reaction of acyloxysilanes with ethylmagnesium bromide: 3-methyl-3-pentanol and 2-butanone from tetraacetoxysilane; 3-pentanone from tetrapropionoxysilane; 3-ethyl-3-hexanol and 3-hexanone from tetrabutyroxysilane; and 3-ethyl-4-hexenol-3 and 2-hexenone-4 from tetracrotonoxysilane. 3-Ethyl-4-hexenol-3 is a new compound and its infrared spectrum has been determined between 3 and 15 μ. Ethyl siloxanes were produced along with the alcohols and ketones.

The reaction of tetrapropionoxysilane with ethylmagnesium bromide and phenylmagnesium bromide produced diphenylethylcarbinol, 3-ethyl-3-pentanol, 3-phenyl-3-pentanol, 3-pentanone, propiophenone, and a siloxane.

The method for preparing acyloxysilanes from tetrachlorosilane and sodium salts of organic acids has been used by Schuyten, Weaver, and Reid[3] to prepare tetraacetoxysilane and by Lanning[4,5] to prepare tetrapropionoxysilane and tetrabenzoxysilane. This method has been applied to the preparation of tetrabutyroxysilane, tetra(trichloroacetoxy)silane, tetracrotonoxysilane, tetrastearoxysilane, tetra(3-phenylpropionoxy)silane, tetra(β-napthoxy)silane, tetracinnamoxysilane, tetra(*o*-chlorobenzoxy)silane, and tetra(*p*-hydroxybenzoxy)silane in yields of 62.4 to 83.8% (Table I). Tetrasalicyloxysilane could not be prepared.

The infrared spectra of these compounds were determined between 3 and 15 μ. The spectra for tetrabutyroxysilane, tetracrotonoxysilane, and tetra(trichloroacetoxy)silane are shown in Figs. 1, 2 and 3.

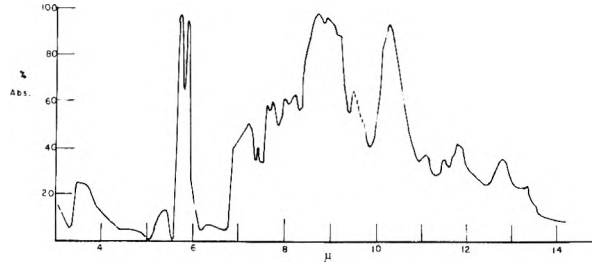


FIG. 1. INFRARED SPECTRUM OF TETRABUTYROXYSILANE.

Tetrabutyroxysilane is a liquid while the others are white solids. Like other acyloxysilanes[4-6] these compounds react with alcohols and water. They are also unstable to heat.

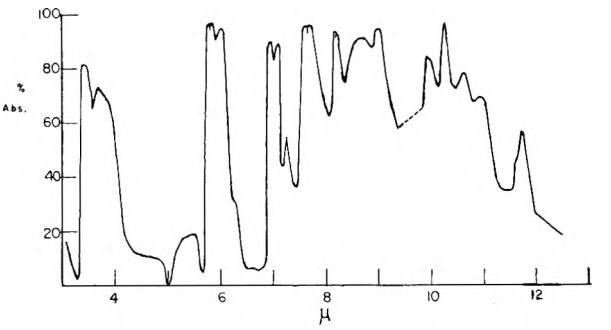


FIG. 2. INFRARED SPECTRUM OF TETRACROTONOXYSILANE.

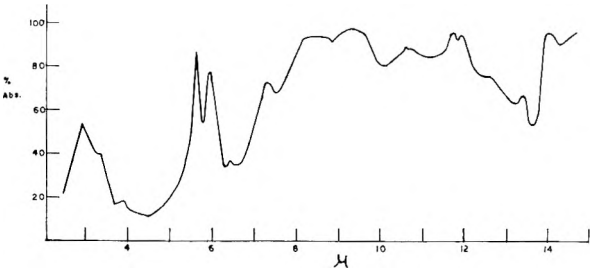


FIG. 3. INFRARED SPECTRUM OF TETRA(TRICHLOROACETOXY)-SILANE.

Petrov and Itkina[7] have reported the preparation of tetrabutyroxysilane in a 78.6% yield by the reaction of butyric acid and tetrachlorosilane. The white solid they obtained may have been a polymer rather than the simple compound, tetrabutyroxysilane, as they removed the HCl by heating the products over a water bath.

Ether solutions of tetrabutyroxysilane, tetraacetoxysilane, and tetracrotonoxysilane react with Grignard reagents in the same manner that tetrapropionoxysilane[4] and tetrabenzoxysilane[5] do. 3-Ethyl-3-hexanol has been prepared by the reaction of ether solutions of tetrabutyroxysilane with excess ethyl magnesium bromide and subsequent hydrolysis. If only 0.8 of the calculated stoichio-

(1) This work was supported by a Frederick Gardner Cottrell Grant from Research Corporation.

(2) Most of this paper is from the M.S. thesis of M. Moore.

(3) H. A. Schuyten, J. W. Weaver, and J. D. Reid, *J. Am. Chem. Soc.*, 69, 2110 (1947).

(4) F. C. Lanning, *J. Am. Chem. Soc.*, **75**, 1596 (1953).

(5) F. C. Lanning, *J. Org. Chem.*, 19, 1171 (1954).

(6) C. Friedel and A. Ladenburg, *Ann.*, **145**, 174 (1868).

(7) K. D. Petrov and M. I. Itkina, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 220 (1947).

TABLE I

ANALYSIS OF ACYLOXYSILANES

Compound	Yield, %	RCO_2^-, % Calcd.	RCO_2^-, % Found[9]	Silicon, % Calcd.	Silicon, % Found[10]
$(CCl_3CO_2)_4Si$	62.4	95.85	95.76	4.15	4.12
$(C_3H_7CO_2)_4Si$	81.2	92.55	91.94	7.45	7.43
$(CH_3C{=}C(H){-}COO)_4Si$	74.4	92.4	92.27	7.60	7.53
$(C_{17}H_{35}{-}COO)_4Si$	76.7	97.59	97.63	2.41	2.35
$(C_6H_5CH_2CH_2COO)_4Si$	83.8	95.51	95.52	4.49	4.52
$(C_6H_5CH{=}CHCO_2)_4Si$	78.5	95.45	95.45	4.55	4.55
$(o\text{-}ClC_6H_4CO_2)_4Si$	75.7	95.69	95.62	4.31	4.27
$(p\text{-}HOC_6H_4CO_2)_4Si$	78.6	95.14	95.04	4.86	4.80
$(2\text{-}C_{10}H_7CO_2)_4Si$	73.4	96.07	95.94	3.93	3.88

metric amount of the Grignard reagent was used, less 3-ethyl-3-hexanol was formed and some 3-hexanone was formed.

Up to 67% of the silicon was converted to ethylsiloxanes with infrared spectra identical with those obtained for ethyl siloxanes by Young, Servais, Currie, and Hunter.[8]

Tetracrotonoxysilane reacts with ethyl magnesium bromide to form 2-hexenone-4, 3-ethyl-4-hexenol-3, and ethyl siloxanes. 3-Ethyl-4-hexenol-3 is a new compound and its infrared spectra, Fig. 4, was determined between 2.5 and 15 μ.

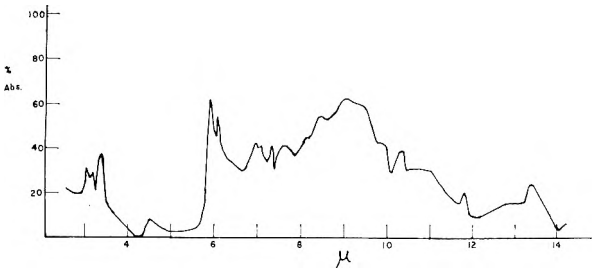


FIG. 4. INFRARED SPECTRUM OF 3-ETHYL-4-HEXENOL-3.

Tetraacetoxysilane reacts with an excess of ethyl magnesium bromide to form 3-methyl-3-pentanol and ethyl siloxanes. With 0.8 of the stoichiometric amount of ethyl magnesium bromide some methyl ethyl ketone was produced. Under these same conditions diethyl ketone was produced from tetrapropionoxysilane.

Numerous products have been prepared by treating tetrapropionoxysilane first with ethylmagnesium bromide and then with an equal amount of phenylmagnesium bromide. No excess of the Grignard reagents was used. The products identified were diphenylethylcarbinol, 3-ethyl-3-pentanol, 3-phenyl-3-pentanol, 3-pentanone, and propiophenone.

(8) C. W. Young, P. C. Servais, C. C. Currie, and M. J. Hunter, *J. Am. Chem. Soc.*, **70**, 3758 (1948).

(9) W. I. Patnode, quoted in Rochow, *An Introduction to the Chemistry of Silicones*, 2nd ed., John Wiley and Sons, New York, 1951, p. 165.

(10) J. F. Hyde and R. C. DeLong, *J. Am. Chem. Soc.*, **63**, 1194 (1941).

EXPERIMENTAL

The apparatus used in preparing the acyloxysilanes was very similar to that used by Schuyten, Weaver, and Reid.[3] The tetrachlorosilane used was purified by redistillation. The sodium salts were C.P. Reagents. Anhydrous diethyl ether was used as the diluent.

The preparations were carried out by adding 10.38 grams of tetrachlorosilane, dissolved in 50 ml. of ether, dropwise into a slurry of 1.25 times the calculated amount of anhydrous sodium salts dispersed in 300 ml. of ether. Tetrachlorosilane was added at such a rate that gentle refluxing was maintained. The mixture was stirred during the addition of the tetrachlorosilane and for 1 hr. afterwards while the mixture was kept at the boiling point. When the ether solution gave no test for chloride ion, the sodium chloride and excess sodium salts were removed. The ether was removed from the filtrate under reduced pressure at 0°, leaving the nearly pure acyloxysilanes. The analyses and yields of these compounds are given in Table I.

Tetracinnamoxysilane could be prepared only by keeping the temperature at 0° throughout the reaction time. Apparently the compound was so unstable at 36° that it decomposed into cinnamic anhydride and SiO_2 as fast as it formed.

Tetrasalicyloxysilane was apparently too unstable to be recovered even at 0°. The instability may be due to hydrogen bonding which could occur between the carbonyl group of the acid and the adjacent OH group. This could result in the formation of salicyl cations, salicylate ions, and SiO_2. The salicyl cations and the salicylate ions could unite to form salicylic anhydride. A white crystalline compound, melting at 158–158.5° and having a neutral equivalent corresponding to salicylic anhydride, was recovered.

The molecular weights of tetrabutyroxysilane and tetracrotonoxysilane were determined by the Beckmann[11] method, using benzene as a solvent. The molecular weights of the other acyloxysilanes could not be determined this way because of the high molecular weight and low solubility in benzene. Tetrabutyroxysilane. Calcd.: 376.22. Found: 381.96. Tetracrotonoxysilane. Calcd.: 368.38. Found: 363.6.

Reaction of acyloxysilanes with ethylmagnesium bromide. These reactions were carried out with tetraacetoxysilane, tetrapropionoxysilane, tetrabutyroxysilane, and tetracrotonoxysilane at several different concentrations and temperatures.

In each case a dilute diethyl ether solution of the acyloxysilane was added through a dropping-funnel drop by drop into the Grignard reagent prepared from ethyl bromide in the usual manner. The mixture was stirred for 1 hr. Then the Grignard complex was hydrolyzed in an ammonium chloride solution containing some ice. Some dilute sulfuric acid was added afterwards to dissolve the precipitate. The

(11) E. Beckmann, *Z. phys. Chem.*, **2**, 683 (1888).

TABLE II

ALCOHOLS OBTAINED FROM THE REACTION OF ACYLOXYSILANES WITH 0.8 AND 3.5 TIMES THE STOICHIOMETRIC AMOUNT OF ETHYLMAGNESIUM BROMIDE

Items	Alcohols			
	3-Ethyl-3-hexanol	3-Ethyl-3-pentanol	3-Methyl-3-pentanol	3-Ethyl-4-hexenol-3
Acyloxysilane from which alcohol was prepared	Tetrabutyroxysilane	Tetrapropionoxysilane	Tetraacetoxysilane	Tetracrotonoxysilane
Reaction temperature	36°	36°	36°	0°
Yield, %				
1 to −0.8	45	42	43	
1 to 3.5	56	59	56	
Boiling point				
Found	160.1	142–143	101–102	
Lit.	160.5	142	102	
Melting point				68–69°
Index of refraction				
Found	n_D^{13} 1.4322	$n_D^{28.5}$ 1.4246	n_D^{20} 1.4182	
Lit.	n_D^{13} 1.4322	$n_D^{22.3}$ 1.4266	n_D^{21} 1.4180	
Allophanate derivative				
Found	153–154	172–173	151–152	126–127.5°
Lit.		172–173	152	

TABLE III

KETONES OBTAINED FROM THE REACTION OF ACYLOXYSILANES WITH 0.8 AND 3.5 TIMES THE STOICHIOMETRIC AMOUNT OF ETHYLMAGNESIUM BROMIDE

Items	Ketones			
	3-Hexanone	3-Pentanone	2-Butanone	2-Hexenone-4
Acyloxysilane from which the ketone was prepared	Tetrabutyroxysilane	Tetrapropionoxysilane	Tetraacetoxysilane	Tetracrotonoxysilane
Reaction temperature	36°	36°	36°	0°
Yield, %				
1 to 0.8	26	27	29	Low
1 to 3.5	Much less	Much less	Much less	
B.p. of ketones				
Found	123–124°	102–103°	80–81°	
Lit.	123–123.5°	102°	80°	
Index of refraction				
Found	n_D^{25} 1.3998	n_D^{25} 1.3907	n_D^{25} 1.3782	
Lit.	n_D^{22} 1.3990	n_D^{25} 1.3905	n_D^{20} 1.3791	
2,4-Dinitrophenylhydrazone derivatives				
M.p. Found	129–130°	150–152°	113–114°	
Lit.	130°	156°	114°	
Semicarbazone derivative				
Found				156.5–157°
Lit.				157°

organic layer was separated and dried with $CaCl_2$. After evaporation of the ether, the colorless oily liquid residue was distilled.

The first set of reactions was carried out at 36° and 3.5 times the stoichiometric amount of ethylmagnesium bromide. A second set of reactions was carried out at the same temperature but with only 0.8 of the stoichiometric amount of ethyl magnesium bromide. A stoichiometric amount would be 4 molecules of the Grignard reagent to one of the acyloxysilane. Both alcohols and ketones were produced. These, along with their physical constants and derivatives, are shown in Tables 2 and 3, respectively.

The reaction of tetracrotonoxysilane with ethylmagnesium bromide was carried out at 0° to yield yellow flake-like crystals and an oil. The crystals, 3-ethyl-4-hexenol-3, were filtered out, washed with Skellysolve F, and recrystallized from ethyl alcohol by precipitating it out with water. The oil was distilled. With the same concentrations of Grignard reagents as in sets 1 and 2 at a temperature of 0°, the same reactions took place more slowly and yields were somewhat lower. The siloxanes were purified by treating hot benzene solutions with activated carbon. These solutions were then filtered and the benzene evaporated. The siloxanes were shown by chemical analysis and infrared spectroscopy, to be ethyl siloxanes.

Siloxanes 1 and 2 are typical of the siloxanes obtained. Siloxane 1, 75% yield, was the residue left from the fractional distillation of the oily liquid produced by the reaction of 0.8 of the stoichiometric amount of ethylmagnesium bromide with tetrabutyroxysilane. Siloxane 2, 69% yield, was obtained in the same manner by use of 3.5 times the stoichiometric amount of Grignard reagent. Siloxanes 1 and

2 were, by the following analysis, indicated to be ethyl siloxanes.

Anal. Calcd. for $(C_2H_5)_2SiO$: C, 47.06; Si, 27.45; H, 9.80; O, 15.70. Found in siloxane 1: C,[12] 40.35; Si,[10] 31.6; H, 8.90; O, 19.15. Found in siloxane 2: C, 46.08; Si, 27.49; H, 9.82; O, 16.61.

In order to get an accurate silicon analysis by the method of Hyde and Delong,[10] it was necessary to use 90% pure HNO_3 (fuming nitric acid).

The analysis of sample 1 corresponds to a C_2H_6/Si value of 1.55. Silicone 2 corresponds to a C_2H_6/Si value of 1.96.

Reaction of tetrapropionoxysilane with both ethylmagnesium bromide and phenylmagnesium bromide. A dilute diethyl ether solution containing 16.53 g. of tetrapropionoxysilane was added through a dropping funnel into an ether solution containing 0.5 of the stoichiometric amount of ethylmagnesium bromide. The mixture was stirred for 5 min. and then an ether solution containing 0.5 of the stoichiometric amount of phenylmagnesium bromide was added through the dropping funnel. Stirring was continued for 1 hr. at 36°. The mixture was hydrolyzed and the products isolated from the ether in the manner previously described.

The product consisted of nearly white crystals and an oily liquid. The crystals were filtered out and purified by recrystallization from Skellysolve F.

Distillation separated the oily liquid into diphenylethylcarbinol (m.p. found 93–94°; lit. 95°), 3-pentanone (b.p. found 100–101°; lit. 102°) n_D found 1.3935 [20°]; lit. 1.3905 [25°]), 3-ethyl-3-pentanol (b.p. found 140–142°; lit. 142°) (n_D found 1.4220 [20°]; lit. 1.4266 [22°]), propiophenone (n_D^{20} found 1.5230; lit. 1.5369), and 3-phenyl-3-pentanol (n_D^{20} found 1.515; lit. 1.5165).

The following derivatives were prepared: 3-pentanone 2–4 dinitrophenylhydrazone (m.p. found 153–155°, lit. 156°), propiophenone 2–4 dinitrophenylhydrazone (m.p. found 186–187.5°; lit. 187–189°), and the nitrosochloride of 3-phenyl-3-pentanol (m.p. found 114–115°; lit. 117°).

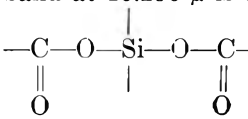
A siloxane which was probably an ethyl phenyl siloxane, was also produced.

Infrared absorption. The infrared spectra of the acyloxysilanes were determined from benzene solutions or potassium bromide pellets with a Perkin-Elmer, Model 112, infrared spectrometer using a rock salt prosm. The solutions or potassium bromide pellets, contained 5 to 10% by weight of the products. A background trace of pure solvent, or potassium bromide, was run so that it was superimposed, and a point by point measurement of per cent absorption was made at intervals.

Spectra of the ethyl siloxanes were made by using very thin layers of these materials. The spectrum of 3-ethyl 4-hexenol-3 was made from a pellet containing the compound and potassium bromide.

DISCUSSION

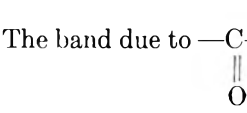
The more significant infrared absorption peaks in the spectrum of tetrabutyroxysilane, other than the Si—O band near 9.236 μ which is found in all acyloxysilanes, are at 5.74, 5.876, 8.762, and 10.296 μ. Peaks at 5.74 and 5.876 μ are due to —C=O bond. These peaks occur in organic esters[13] and are found in the spectra of all the acyloxysilanes studied. The peak at 8.76 μ is characteristic of esters of butyric acid.[13] A strong band at 10.296 μ is due to some vibration of the



—C—O—Si—O—C— structure. All of the acyloxysilanes show such a band between 10.296 and 10.915 μ. The position of the band shifts towards higher wavelengths as the molecular weight of the organic radical increases. The highest value was obtained for tetrabenzoxysilane.[5]

Bands in the spectrum of tetracrotonoxysilane are stronger than those for tetrabutyroxysilane due to the use of a more concentrated solution of the compound. The only major differences are the bands at 6.05 and 9.94 μ which are due to the double bonds in the molecule.

The spectrum of tetra(trichloroacetoxy)silane is somewhat different as there are no C—H bonds and the corresponding absorption bands are missing. The band due to



—C—O—Si—O—C— structure has shifted to 10.6 μ due to the heavy C—Cl_3 radical. The bands at 11.74 and 11.938 μ are more pronounced in esters of trichloroacetic acid. Bands at 2.958 and 14.0 μ are due to the C—Cl bond and the C—Cl_3 group respectively.

The spectrum of silicone 1 is identical with the ethyl silicone spectra reported by Young, Servais, Currie, and Hunter.[8] Silicone 2 has an extra band at 11.7 μ. This band often occurs in straight chain polysiloxanes.[14]

Significant absorption bands occur in the infrared spectrum of 3-ethyl-4-hexenol-3 at 3.05, 3.20, 3.40, 4.5 to 4.6, 5.86, 6.07, 6.95 to 7.10, 7.35, 7.60 to 7.70, 8.40 to 8.50, 9.00 to 9.50, 9.90, 10.35, 11.8, and 13.4 μ. Randall, Fowler, Fuson and Dangl[13] report absorption bands for ethyl alcohol at 3.00, 3.40, 4.69, 6.06, 7.23, 7.39, 7.76, 7.88, and 9.18 to 9.62 μ. Strong bands at 6.07 and 8.50 μ are due to the double bond and tertiary alcohol groups, respectively.

MANHATTAN, KAN.

(12) H. Roth, *Angew Chem.*, **50**, 593 (1937).

(13) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., New York, 1949.

(14) N. Wright and M. J. Hunter, *J. Am. Chem. Soc.*, 69, 803 (1947).

[CONTRIBUTION FROM THE INSTITUTE OF POLYTECHNICS, OSAKA CITY UNIVERSITY]

Synthesis and Intramolecular Rearrangements of Chloromethylpentamethyldisilane and 1-Chloromethyl-2-chlorotetramethyldisilane

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Chloromethylpentamethyldisilane (I) was prepared by two methods: (*1*) photochemical chlorination of the disilane fraction, followed by methylation with Grignard reagent and (*2*) peroxide-catalyzed chlorination of hexamethyldisilane. 1-Chloromethyl-2-chlorotetramethyldisilane (II) was prepared by demethylation of I with concentrated sulfuric acid, followed by treatment with ammonium chloride. Intramolecular rearrangements of I and II with anhydrous aluminum chloride led to the formation of the corresponding disilmethylene derivatives, indicating that the substituted silyl groups migrate in preference to a methyl group.

The literature of organosilicon compounds contains no example of a disilane with an aliphatic organo-functional substituent. In the present paper there is presented the synthesis of the first two compounds of this type having both a silicon-silicon linkage and a chloromethyl group in the molecule, and there is described an interesting observation on their intramolecular rearrangements with aluminum chloride.

The preparation of a chloromethyldisilane was first accomplished through peroxide-catalyzed chlorination with sulfuryl chloride of hexamethyldisilane. However, extensive cleavage of the silicon-silicon bond took place,[1] and the yield of the desired chloromethyldisilane (I) was only 42%.

$$Me_3SiSiMe_3 \xrightarrow[(PhCO_2)_2]{SO_2Cl_2} Me_3SiCl + Me_3SiSiMe_2CH_2Cl$$

I

A more satisfactory method for introducing a chloromethyl group into the disilane was the liquid phase photochemical chlorination of the disilane fraction of the methylchlorosilane residue,[2] followed by methylation with Grignard reagent, as indicated by the following sequence

$$Me_n\,Cl_{6-n}\,Si_2 \xrightarrow[U.V.]{Cl_2} ClCH_2Me_{n-1}Cl_{6-n}Si_2 \xrightarrow{MeMgBr}$$

disilane fraction

$$ClCH_2Me_2SiSiMe_3$$

I

In marked contrast to hexamethyldisilane and methylchlorodisilanes of lower chlorine content, the disilane fraction was found so stable to silicon-silicon cleavage that photochemical chlorination was carried out as successfully as that of methylchlorosilanes.[3] Fractional distillation at reduced pressure of the chlorination product gave no definite compound but a fraction consisting of a rather complex mixture of monochloromethyl derivatives of disilanes and probably of siloxanes as well. Exhaustive methylation of the fraction followed by treatment with concentrated sulfuric acid in the cold, for the purpose of removing siloxanes, rendered fractionation easy, yielding a pure sample of chloromethylpentamethyldisilane (I).

The second chloromethyl-containing disilane, 1-chloromethyl-2-chlorotetramethyldisilane (II) was prepared from compound I by applying to it an excellent technique of Sommer and his coworkers[4] which involves the reaction with concentrated sulfuric acid of trimethylsilyl containing compounds under proper conditions to give selective cleavage of one methyl group from a trimethylsilyl group. The demethylation of I took place very smoothly at about 40° to give nearly 90% of the theoretical yield of methane in a period of a few hours and to leave a homogeneous sulfuric acid solution. Addition of ammonium chloride to the solution yielded an organic layer, which on fractionation gave highly pure compound II in average yield of 70%.

$$I \xrightarrow[2.\ NH_4Cl]{1.\ H_2SO_4} ClCH_2Me_2SiSiMe_2Cl + CH_4$$

II

Structure proof for II was afforded by cleaving the ethylated product (III) with bromine in ethyl bromide.[5] Dimethylethylbromosilane was isolated as a cleavage fragment in almost theoretical yield, while another fragment of cleavage was recovered in part as bromomethyldimethylbromosilane. Not all of the chloromethyl-containing moiety was

(1) *Cf.* M. Kumada, K. Shiina, and M. Yamaguchi, *J. Chem. Soc., Japan, Ind. Chem. Sect.*, **57**, 230 (1954) [*Chem. Abstr.*, 49, 11542 (1955)].

(2) The disilane fraction refers to a fraction boiling over the range about 150–160°, which is obtained by fractionation of the higher-boiling fraction of methylchlorosilanes produced by the so-called "direct synthesis." It is composed mainly of $MeCl_2SiSiMeCl_2$ and $Me_2ClSiSiMeCl_2$, somewhat contaminated by siloxanes. See M. Kumada, M. Yamaguchi, Y. Yamamoto, J. Nakajima, and K. Shiina, *J. Org. Chem.*, **21**, 1264 (1956).

(3) J. L. Speier, *J. Am. Chem. Soc.*, **73**, 824 (1951).

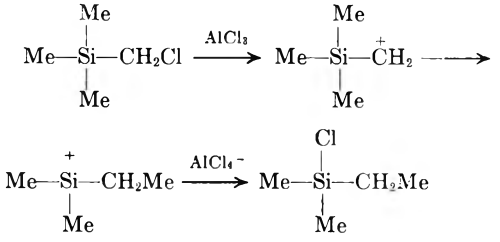
(4) L. H. Sommer, N. S. Marans, G. M. Goldberg, J. Rockett, and R. P. Pioch, *J. Am. Chem. Soc.*, **73**, 882 (1951) and subsequent papers.

(5) See ref. 1, and H. Gilman, R. K. Ingham, and A. G. Smith, *J. Org. Chem.*, **18**, 1743 (1953), for cleavage of alkyl-substituted disilanes by bromine.

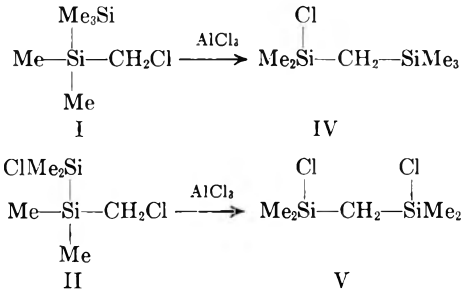
accounted for in the latter product, some having been lost in the intermediate fraction probably containing chloromethyldimethylbromosilane.

$$\text{II} \xrightarrow{\text{EtMgBr}} \underset{\text{III}}{\text{ClCH}_2\text{Me}_2\text{SiSiMe}_2\text{Et}} \xrightarrow{\text{Br}_2} \text{Me}_2\text{EtSiBr} + \text{BrCH}_2\text{Me}_2\text{SiBr}$$

Whitmore and his collaborators[6,7] have reported intramolecular rearrangements of chloromethyl and chloroethyl derivatives of silicon with anhydrous aluminum chloride. Thus, in case of chloromethyltrimethylsilane a methyl group migrates with its shared electron pair from silicon to the electron-deficient carbon, as formulated below:



It was of considerable interest to us to determine which group, methyl or the substituted silyl, should migrate more easily if the rearrangement be carried out with compounds I and II. A very clear-cut result was obtained in each case. Pentamethylchlorodisilmethylene (IV) was the only product isolated from I, while tetramethyl-1,3-dichlorodisilmethylene (V) was the only product from II, thus indicating that both silyl groups, Me_3Si and Me_2ClSi, have much greater migratory aptitudes than the methyl group. Regardless of the detailed mechanism,[8] the reactions are formulated as follows:



Evidence that the reaction represented by the former of the above two equations produced compound IV, not isomeric $Me_3SiSiClMeEt$, was afforded by the following facts. First, the product was quite indifferent to the action of bromine, indicating the absence of a Si—Si bond.[9] Second, the Raman spectrum[10] was practically identical with that of an authentic sample prepared by treating dimethyldichlorosilane with trimethylsilylmethylmagnesium chloride. Other physical properties of the two samples also conformed. The structure V was demonstrated by its insusceptibility to the attack of bromine,[9] by comparison of the physical properties with those reported for this compound in the literature,[11,12] and by its conversion, on hydrolysis, to the known dihydroxy derivative,[11,13] $HOMe_2SiCH_2SiMe_2OH$, and its cyclic dimeric dehydration product,[11,13] $(Me_2SiCH_2SiMe_2O\text{-})_2$. Further studies of the chemical properties of compounds I and II are in progress.

EXPERIMENTAL[14]

Starting materials. The higher-boiling residue of methylchlorosilanes was supplied by the Tokyo-Shibaura Elec. Co., Ltd. The disilane fraction, b.p. *ca.* 150–160°, was obtained by fractionation of the residue through a 1.3 × 100 cm. Fenske column.

Chloromethylpentamethyldisilane (I). The chlorination technique followed in detail that used by Speier[3] in the chlorination of methylchlorosilanes. For example, from the chlorination of 1061 g. of the disilane fraction (% Cl, 56.2) in the presence of light from an incandescent lamp at 50–60°, 1202 g. of a product boiling over the range 70–185° at 50 mm. was obtained upon flash distillation at reduced pressure. Redistillation through a 1.3 × 100 cm. Fenske column gave the following fractions: (*a*) recovered disilane fraction, b.p. 45–55° (13 mm.), 543 g.; (*b*) mainly, monochloromethyl disilanes, b.p. 80–100° (17 mm.), 409 g.; and (*c*) polychlorination products, b.p. 100–145° (17 mm.), 133 g.

To the Grignard reagent prepared from 74 g. (3.05 g.-atoms) of magnesium and 300 g. (3.17 moles) of methyl bromide in 1.5 l. of absolute ether was differentially added 170 g. of fraction (*b*) (titrable Cl, 51.6%) with stirring and external cooling. After completion of addition the reaction mixture was heated to reflux for 9 hr. A large part of the ether was distilled off and then the mixture was hydrolyzed with dilute hydrochloric acid. The organic layer was separated, washed until neutral, and dried over calcium chloride, and then solvent ether was distilled.

An additional run, identical to the above, was carried out.

(6) F. C. Whitmore, L. H. Sommer, and J. R. Gould, *J. Am. Chem. Soc.*, **69**, 1976 (1947).

(7) L. H. Sommer, D. L. Bailey, J. R. Gould, and F. C. Whitmore, *J. Am. Chem. Soc.*, **76**, 801 (1954).

(8) The sum of the bond energies of the linkages of Si—Si and C—C is 135.9 kcal./mole. The corresponding value for 2Si—C is 150.0 kcal./mole [*cf.* H. Gilman and G. E. Dunn, *Chem. Revs.*, **52**, 77 (1953)]. Thus, the thermodynamic stability of $ClMe_2SiCH_2SiMe_3$ and $ClMe_2SiCH_2SiMe_2Cl$ exceeds that of $Me_3SiSiClMeEt$ and $ClMe_2SiSiClMeEt$, respectively, by 14.1 kcal./mole.

(9) Unpublished results in this laboratory indicate that methylchlorodisilanes of lower chlorine content such as $Me_3SiSiMe_2Cl$ and $Me_2ClSiSiMe_2Cl$ react vigorously with bromine in the cold to give Si—Si fission products; hence, it would not be unreasonable to expect that the disilanes such as $Me_3SiSiClMeEt$ and $Me_2ClSiSiClMeEt$ will also react with bromine.

(10) The authors are indebted to Dr. H. Murata of Osaka Municipal Technical Research Institute for Raman data.

(11) B. A. Bluestein, *J. Am. Chem. Soc.*, **70**, 3068 (1948).

(12) R. O. Sauer and E. M. Hadsell, *J. Am. Chem. Soc.*, **70**, 3590 (1948).

(13) M. Kumada and A. Habuchi, *J. Inst. Polytech., Osaka City Univ., Ser. C*, **3**, 65 (1952) [*Chem. Abstr.*, **48**, 9907 (1954)].

(14) All temperatures reported here are uncorrected. Molar refractions were calculated by the method of Vogel *et al.* [A. I. Vogel, W. T. Cresswell, and J. Leicester, *J. Phys. Chem.*, **58**, 174 (1954)]. Silicon analyses were made by a method previously reported (ref. 2).

Crude products from the two runs were combined and treated with sulfuric acid in the cold leaving an acid-insoluble colorless layer, which was, after washing with dilute sodium bicarbonate, fractionally distilled under vacuum in a modified Stedman column rated at about 20 theoretical plates to give chloromethylpentamethyldisilane, b.p. 87.0–87.5° at 58 mm., m.p. 6–7°, n_D^{20} 1.4576, d_4^{20} 0.8837, MR 55.77 (calcd. 56.03), in addition to 17 g. of forerun and 56 g. of after-run, b.p. 107–110° (58 mm.).

Anal. Calcd. for $C_6H_{17}ClSi_2$: Si, 31.1. Found: Si, 30.9, 31.0.

Peroxide-catalyzed chlorination of hexamethyldisilane. In a 100-ml. three-necked flask equipped with an air-tight stirrer, a dropping funnel, and an efficient reflux condenser leading to a Dry Ice–acetone trap there was placed 40 g. (0.27 mole) of hexamethyldisilane. All exits were protected by calcium chloride drying tubes. Sulfuryl chloride (36.5 g., 0.27 mole) containing 0.2 g. of benzoyl peroxide was added dropwise with stirring over 3 hr. at a temperature of 80–90°. Then the mixture was heated to reflux. The reaction was assumed to be complete when further heating caused no increase in liquid (sulfur dioxide) in the trap. The content of the reaction flask was then fractionally distilled in a small Stedman column (initially, at atmospheric pressure; later, at reduced pressure) to give the following two fractions: (*a*) trimethylchlorosilane, b.p. 57.0–58.5°, n_D^{20} 1.3850 (literature,[15] b.p. 57.7°; literature,[16] b.p. 58° (734 mm.), n_D^{20} 1.3884), % Cl 31.9 (calcd. 32.7), 25 g., yield 43%; and (*b*) chloromethylpentamethyldisilane, b.p. 60° at 14 mm., n_D^{20} 1.4578, d_4^{20} 0.8835, 22 g., yield 42%.

1-Chloromethyl-2-chlorotetramethyldisilane (II). This compound was prepared from I in essentially the same manner as that previously reported for methyldisilanes with chlorine attached to silicon.[2] A 500-ml. three-necked flask was fitted with an air-tight stirrer, a thermometer, and a gas-outlet tube which was connected to an apparatus for collecting gas. In the flask were placed 50 g. (0.25 mole) of compound I and 200 g. of concd. sulfuric acid of sp. gr. 1.84. The mixture was stirred at 38 ± 2°. The reaction began at once as evidenced by the evolution of gas. After 2 hr. 6.0 l. (91%) of methane was collected and no more gas evolved on further stirring. At this point the mixture was cooled by means of an ice bath and 30 g. (0.56 mole) of dry pulverized ammonium chloride was added to the mixture with stirring. Stirring was continued for an additional 30 min. Separation followed by fractionation through a Stedman column of 20 theoretical plates gave practically a single substance, 1-chloromethyl-2-chlorotetramethyldisilane, b.p. 79.5° at 17 mm., m.p. *ca.* 9°, n_D^{20} 1.4735, d_4^{20} 1.0206, MR 55.45 (calcd. 55.59), 38 g., yield 70%.

Anal. Calcd. for $C_5H_{14}Cl_2Si_2$: Cl (titrable), 17.6. Found: Cl (titrable), 17.7.

1-Chloromethyl-2-ethyltetramethyldisilane (III). Compound II, 46 g. (0.22 mole), was added to a Grignard solution prepared from 6.5 g. (0.27 g.-atom) of magnesium and 30 g. (0.28 mole) of ethyl bromide in 100 ml. of ether. Heating to reflux for 8 hr. produced a white granular precipitate. The reaction mixture was then hydrolyzed with dilute hydrochloric acid. Separation, washing, and drying of the organic layer was followed by distillation of the solvent, which left 42 g. of a residue. It was then treated with concd. sulfuric acid in the cold, yielding 37 g. of an acid-insoluble layer. Rectification of this layer furnished 30 g. (68%) of 1-chloromethyl-2-ethyltetramethyldisilane, b.p. 79° at 26 mm., n_D^{20} 1.4662, d_4^{20} 0.8933, MR 60.85 (calcd. 60.68).

Anal. Calcd. for $C_7H_{19}ClSi_2$: Si, 28.8. Found: Si, 28.8.

Cleavage of compound III *with bromine.* To a stirred solution of 19 g. (0.098 mole) of III in 30 g. of ethyl bromide was gradually added a solution of 16 g. (0.1 mole) of bromine in 30 g. of ethyl bromide at room temperature. Initially, instantaneous decolorization took place with considerable evolution of heat, but later, it was necessary to heat the mixture to reflux. After complete addition of the bromine, the mixture was refluxed for an additional 3 hr. to insure completeness of reaction. Then it was submitted to fractional distillation to give the following fractions: (*a*) dimethylethylbromosilane, b.p. 110–110.5° (calcd. b.p.[17] 110.4°), 15.8 g. (99%), % Br 50.0 (calcd. 48.4); (*b*) intermediate fraction, b.p. 130–140° (mostly at 133°), 7.5 g.; and (c) bromomethyldimethylbromosilane, b.p. 154°, 7.3 g. (32%), % Br (titrable) 36.0 (calcd. 34.4).

Intermolecular rearrangement of compound I. To 40 g. (0.22 mole) of compound I stirred and protected from moisture was added a small amount of anhydrous aluminum chloride. A vigorous, exothermic reaction took place and it was necessary to cool the flask. When the reaction subsided gentle heat was applied to the flask for a short period of time and then an additional small amount of aluminum chloride was introduced with cooling. Addition of catalyst with cooling and application of heat to the flask was continued repeatedly until no more noticeable change occurred. During the period (*ca.* 10 hr.) required to complete the reaction it was necessary to add a total of *ca.* 1 g. of catalyst. The reaction mixture was heated on a steam bath for an additional 3 hr., and then was flash-distilled under vacuum to separate the product from aluminum catalyst. Fractionation of this catalyst-free distillate (37 g.) through a Stedman column gave 32 g. (82%) of pentamethylchlorodisilmethylene, b.p. 153°, n_D^{20} 1.4322, d_4^{20} 0.8846 (literature,[18] b.p. 154.5° (740 mm.), n_D^{25} 1.4277, d^{25} 0.8662; literature,[19] b.p. 154–5°, n_D^{20} 1.4320, d_4^{20} 0.8846), MR 53.03 (calcd. for $Me_3SiCH_2SiMe_2Cl$ 53.24; calcd. for $Me_3SiSiMeEtCl$ 55.39), % Cl 19.6 (calcd. 19.6). A sample of this compound did not react with bromine at all even on heating, indicating complete absence of silicon-silicon linkage in the molecule. This compound was further characterized by comparison of its Raman spectrum with that of an unequivocal sample (b.p. 153°, n_D^{20} 1.4310) prepared from trimethylsilylmethylmagnesium chloride and dimethyldichlorosilane (Table I).

TABLE I

COMPARISON OF RAMAN SPECTRA FOR SAMPLES OF PENTAMETHYLCHLORODISILMETHYLENE FROM TWO DIFFERENT SOURCES

Rearrangement Product		Grignard Product	
$\Delta\nu$[a]	I[b]	$\Delta\nu$[a]	I[b]
165	(3s)	165	(6s)
193	(4s)	190	(6s)
229	(4s)	230	(5s)
260	(2s)	257	(4s)
333	(2s)	332	(3s)
406	(4s)	409	(3s)
463	(4s)	465	(5s)
572	(7s)	570	(6s)
632	(3s)	635	(3s)
685	(5s)	685	(5s)
1258	(2s)	1255	(3s)
1322	(3s)	1325	(5s)
1408	(4b)	1405	(5b)
2824	(3b)	—	—
2900	(10s)	2897	(10s)
2972	(10s)	2970	(10s)

[a] $\Delta\nu$ = Raman displacement in cm.$^{-1}$ [b] I = relative intensity; s = sharp; b = broad.

(15) W. F. Giliam and R. O. Sauer, *J. Am. Chem. Soc.*, **66**, 1793 (1944).

(16) B. O. Pray, L. H. Sommer, G. M. Goldberg, G. T. Kerr, P. A. Digiorgio, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 433 (1948).

(17) R. N. Lewis and A. E. Newkirk, *J. Am. Chem. Soc.*, **69**, 701 (1947).

(18) J. T. Goodwin, U. S. Patent **2,507,518** [*Chem. Abstr.*, **45**, 3410 (1951)].

(19) I. Hizawa and E. Nojimoto, *J. Chem. Soc., Japan, Ind. Chem. Sect.*, **59**, 1359 (1956).

Intramolecular rearrangement of compound II. The procedure was the same as above except that 50 g. (0.25 mole) of compound II was allowed to react with a total of 1.8 g. of aluminum chloride. Fractionation of the catalyst-free distillate (41 g.) through a column similar to that used above gave 25 g. (50%) of tetramethyl-1,3-dichlorodisilmethylene, b.p. 58° at 10 mm., n_D^{20} 1.4483, d_4^{20} 1.013, MR 53.22 (calcd. for $Me_2ClSiCH_2SiMe_2Cl$ 52.78; calcd. for $Me_2ClSiSiMeEtCl$ 56.83), % Cl 35.6 (calcd. 35.6). This substance did not react with bromine even on heating, indicating no presence of silicon-silicon bond in the molecule. A boiling point of 95° at 50 mm., n_D^{20} 1.4480, d_4^{20} 1.016 has been reported[11] for tetramethyl-1,3-dichlorodisilmethylene.

Another fraction, a total of 9.0 g., b.p. 60–64° (10 mm.), n_D^{20} 1.4675–1.4711, was obtained. This fraction reacted vigorously both with bromine and with aluminum chloride in the cold; hence, it undoubtedly seemed to be a mixture containing the unchanged starting material.

Hydrolysis of tetramethyl-1,3-dichlorodisilmethylene. In accordance with the procedure (Method A) by George, Sommer, and Whitmore[20] for dialkylsilanediols from dialkyldichlorosilanes, to a vigorously stirred mixture of 100 ml. of aqueous solution of sodium hydroxide (5 g.) and 50 ml. of ether was added a solution of 10 g. (0.05 mole) of tetramethyl-1,3-dichloro-disilmethylene in 100 ml. of ether over a period of 4 min. at 0°. The ether solution combined with a single ether extract of the aqueous layer was worked up in essentially the same manner as that of the literature,[20] giving 4.4 g. of white needles melting at 86.5–87.0° (literature,[11] m.p. 84–86°; literature,[13] m.p. 86.5°) when petroleum ether (b.p. 45–60°) was added. Concentration of the mother liquor gave an additional 1.2 g. of white needles, m.p. 86.5°. The two crops constituted a 68% yield of tetramethyldisilmethylene-1,3-diol. Complete removal of the solvent from the mother liquor by evaporation left 2 g. of oily matter which mostly solidified at 0°. A week later, a large rhombic plate of 2,2,4,4,6,6,8,8-octamethyl-1,5-dioxa-2,4,6,8-tetrasilacyclooctane, m.p. 27° (literature[11–13] 28–29°), 0.21 g., crystallized from the oil.

(20) P. D. George, L. H. Sommer and F. C. Whitmore, *J. Am. Chem. Soc.*, **75**, 1585 (1953).

Acknowledgment. The authors wish to express their great appreciation to Prof. Minoru Imoto for his continued interest during the course of this investigation. They are also indebted to the Tokyo-Shibaura Elec. Co., Ltd. for a generous gift of the methylchlorosilane residue and for financial assistance.

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Notes

A department for short papers of immediate interest.

Tetracarbamyl Derivatives of 1,2-Bis(2-aminoethyl)ethylenediamine

ROY G. NEVILLE

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The reaction of phenyl isocyanate with 1,2-bis(aminoethyl)ethylenediamine, the "triethylenetetramine" of Hofmann,[1,2] to form 1,2-bis{3′-phenyl-1′-[2″-(3‴-phenylureido)ethyl]ureido}ethane was first reported by van Alphen.[3] Phenyl isothiocyanate reacts to produce the corresponding thioureido derivative. Although other derivatives of this tetrafunctional amine have been described,[4–6] the products of reaction of other monoisocyanates have not been reported.

During a study of the reaction of mono- and polyisocyanates with various polyamines the work of van Alphen was confirmed and a series of new derivatives of 1,2-bis(2-aminoethyl)ethylenediamine has been synthesized. Using a 1:4 molar ratio of tetramine:isocyanate in chloroform solution the following strongly exothermic reaction occurred in almost theoretical yield:

$$H_2N(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2 + 4\ RNCO \longrightarrow RNHCONH(CH_2)_2N(CONHR)(CH_2)_2N(CONHR)(CH_2)_2NHCONHR$$

As anticipated, attempts to react di- and tri-isocyanates, for example toluene-2,4-diisocyanate or toluene-2,4,6-triisocyanate, resulted in the formation of viscous polymers.[7] Using smaller amine:isocyanate ratios it was not found possible to isolate mono-, di-, or tri-substituted derivatives.

Products ranged from white crystalline solids, soluble with difficulty in isopropyl alcohol, in the case of short-chain compounds, to waxy solids, easily soluble in alcohol, in the case of long-chain derivatives.

TABLE I

TETRACARBAMYL DERIVATIVES OF 1,2-BIS(2-AMINOETHYL)ETHYLENEDIAMINE

$[CH_2N(CONHR)(CH_2)_2NHCONHR]_2$

R	Formula	Yield, %	M.P., °C.[9]	% N	
				Calcd.	Found
Allyl	$C_{22}H_{38}N_8O_4$	97	211	23.4	23.3
Isopropyl	$C_{22}H_{46}N_8O_4$	96	245–247 dec.	23.0	22.8
n-Butyl	$C_{26}H_{54}N_8O_4$	98	216–217	20.7	20.7
Cyclohexyl	$C_{34}H_{62}N_8O_4$	100	246–247 dec.	17.3	17.1
Phenyl	$C_{34}H_{38}N_8O_4$	100	237–238	18.0	18.1
n-Octyl	$C_{42}H_{86}N_8O_4$	98	97–98	14.6	14.5
n-Dodecyl	$C_{58}H_{118}N_8O_4$	96	170–171	11.3	11.1
n-Octadecyl	$C_{82}H_{166}N_8O_4$	95	162	8.4	8.3
1-Naphthyl	$C_{50}H_{46}N_8C_4$	98	182	13.6	13.7
2-Biphenylyl	$C_{58}H_{54}N_8C_4$	92	222	12.1	11.9

EXPERIMENTAL

Technical grade triethylenetetramine[8] and reagent grade isocyanates were obtained from Distillation Products Industries, Rochester, N. Y. Di- and tri-isocyanates were supplied by the Mobay Chemical Company, New Martinsville, W. Va.

The triethylenetetramine was fractionally distilled under reduced pressure, the liquid of b.p. 157°/20 mm. being collected and stored under nitrogen in dark bottles.

General preparative procedure. Four one-hundredths of a mole of isocyanate was added cautiously to a mechanically stirred mixture of 1.46 g. (0.01 mole) of triethylenetetramine dissolved in 10–20 ml. of ice cold chloroform. The reaction was strongly exothermic and care was taken not to allow the temperature to exceed about 30°. On cooling, the finely crystalline derivative was filtered, washed with chloroform followed by isopropyl alcohol, then dried *in vacuo*. Recrystallization was effected from isopropyl alcohol in which the lower members were very sparingly soluble. The products are listed in Table I.

(1) A. W. Hofmann, *Proc. Roy. Soc.*, **10**, 224, 619 (1860); **11**, 413, 424 (1862); *Ber.*, **3**, 762 (1870); **4**, 666 (1871); **23**, 3297, 3711 (1890).

(2) F. G. Mann, *J. Chem. Soc.*, 461 (1934); *Chem. Abstr.*, **28**, 4379 (1934).

(3) J. van Alphen, *Rec. trav. chim.*, **55**, 412 (1936).

(4) D. H. Peacock, *J. Chem. Soc.*, 1518 (1936).

(5) R. G. Fargher, *J. Chem. Soc.*, **117**, 1351 (1920).

(6) I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, volume 4, p. 571.

(7) British Patent, **706,717** (April 7, 1954).

(8) Contaminated with small amounts of diethylenetriamine, tetraethylenepentamine, and pentaethylenehexamine.

(9) Melting points are uncorrected.

When 1:2 or 3:4 molar ratios of triethylenetetramine and toluene-2,4-diisocyanate or toluene-2,4,6-triisocyanate were reacted the products were viscous polymers.

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Carbonyl Derivatives of γ-Cyano and γ-Carboxy-α,α-dimethylpentanal

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Although γ-cyano-α,α-dimethylpentanal, also called Ibanitrile, and γ-carboxy-α,α-dimethylpentanal, also called Iba-acid, have been known for some time,[1,2] several of the simple carbonyl derivatives of these compounds have not been previously described. The availability of Ibanitrile from the reaction of isobutyraldehyde with acrylonitrile suggests that the data for these compounds be made available. We have prepared several of these derivatives whose properties are recorded in the table. All were prepared by standard methods. The unusual formation of the hydrazone, rather than the azine, from equimolar quantities of Ibanitrile and hydrazine is noteworthy. Usually the azine is the exclusive product from the reaction of an aliphatic aldehyde with hydrazine. Only the azine was obtained from hydrazine and Iba-acid.

TABLE I

DERIVATIVES OF IBANITRILE AND IBA-ACID

	M.P. or B.P.[a]	Yield, %	Analysis[b] Calcd.	Found
Ibanitrile Derivatives				
Hydrazone	b103/1.5[c]	60	30.19N	29.92N
Azine	m76–78EW	75	68.25C	68.52C
			9.00H	9.07H
Methylhydrazone	b104/4[d]	87	27.43N	27.51N
Dimethylhydrazone	b90/3[e]	76	25.13N	25.13N
Semicarbazone	m154W	84	30.75N	30.53N
Thiosemicarbazone	m95MW	62	28.25N	28.36N
Aminoguanidine sulfate	m166M	43	29.81N	29.92N
Iba-acid Derivatives				
Azine	m165MW	95	9.99N	10.07N
			140.1NE	143.0NE
Dimethylhydrazone	m73PC	55	15.04N	15.01N
			186.2NE	185.4NE
Semicarbazone	m175W	98	20.88N	20.95N
			201.2NE	201.9NE
Thiosemicarbazone	m160W	99	19.33N	19.51N
			217.3NE	218.4NE
2,4-Dinitrophenylhydrazone	m147E	99	17.27N	17.22N

[a] Solvents for recrystallization: B, benzene; M, methanol; W, water; C, carbon tetrachloride; P, petroleum ether; E, ethanol. [b] C, carbon; H, hydrogen; N, nitrogen; NE, neut. equiv. [c] n_D^{25} 1.4805. [d] n_D^{24} 1.4770. [e] n_D^{24} 1.4660.

EXPERIMENTAL[3]

γ-Carboxy-α,α-dimethylpentanal. This acid was obtained in 75% yield by hydrolysis of the nitrile with 25% aqueous hydrochloric acid; b.p. 130–132°/3 mm.; n_D^{25}, 1.4450.

Derivatives of γ-cyano-α,α-dimethylpentanal. Hydrazone. The nitrile (12.5 g.) was added dropwise to a solution of 10 g. of hydrazine in 50 ml. of benzene. The mixture was refluxed for 1 hr. with azeotropic removal of the water formed in the reaction. The benzene solution was dried and evaporated to leave a residue which was fractionated to give 8.3 g. (60%) of the hydrazone, b.p. 101–103/1.5 mm.; n_D^{25}, 1.4805. Attempted refractionation partially converted this material to the azine. *Azine.* A solution of 4.0 g. of hydrazine and 2.5 g. of nitrile in 100 ml. of benzene was refluxed for 1 hr. with azeotropic removal of the water formed in the reaction. Evaporation of the solvent left a solid residue, 2.9 g. (75%), which was recrystallized from ethanol-water, m.p. 76–78°. The infrared absorption spectrum for this azine shows strong absorption bands at 2250 cm.$^{-1}$ (C≡N stretching frequency); 1630 cm.$^{-1}$ (C=H stretching frequency); 1450 cm.$^{-1}$ (C—H deformation frequency in CH_2); 1380 cm.$^{-1}$ and 1358 cm.$^{-1}$ [C—H deformation frequency in $(CH_3)_2C$]; and 1195 cm.$^{-1}$ and 770 cm.$^{-1}$ [$(CH_3)_2C$ skeletal vibration]. *Methylhydrazone and dimethylhydrazone.* These compounds were prepared by refluxing the aldehyde with methyl- and dimethylhydrazine. Properties are given in the table. *Dinitrophenylhydrazone.* This compound was prepared as previously described,[4] m.p. 139–140°. *Semicarbazone.* This compound precipitated from a solution of the aldehyde, semicarbazide hydrochloride, and sodium acetate in water. *Thiosemicarbazone.* A solution of 12.5 g. of the nitrile and 9.0 g. of thiosemicarbazide in 40 ml. of ethanol was refluxed for 2 hr. The precipitated solid left on evaporation of the ethanol was recrystallized from methanol-water to give 12.4 g. (62%) of the product, m.p. 95–96°. *Aminoguanidine sulfate.* A mixture of 26.5 g. of aminoguanidine sulfate, 25 g. of the aldehyde, and 2 drops of concd. sulfuric acid were agitated to homogeneity. After standing at room temperature for 24 hr., the solvent was evaporated under vacuum at room temperature. The viscous residue solidified on standing and was recrystallized by dissolving in methanol at 45° and cooling to −20°.

Derivatives of γ-carboxy-α,α-dimethylpentanal. Azine. The white solid product separated from a benzene solution of the aldehyde and an equivalent amount of hydrazine. *Dimethylhydrazone, semicarbazone, thiosemicarbazone.* These derivatives were prepared using the procedures given above for the derivatives of the nitrile. *2,4-Dinitrophenylhydrazone.* This compound precipitated from an acidic aqueous solution of the hydrazine and the aldehyde.

Both aldehydes react with phenylhydrazine to give products which could not be recrystallized.

(1) N. E. Thiele and W. Franke, Publication Board Reports **35**, 102; **35**, 103 (1944).

(2) W. Retter and W. Franke, Publication Board Report **35**, 112 (1944).

(3) Analyses by Micro Tech Laboratories, Skokie, Ill.

(4) G. Tschuči and S. Schinz, *Helv. Chim. Acta*, **33**, 1870 (1950).

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Synthesis and Properties of *N*-Acetoxytrimethylammonium Bromide[1]

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N-Acetoxytrimethylammonium bromide, which is the initial member of a homologous series of parasympathomimetic substances including acetyl-*nor*-choline[2] (acetoxymethyltrimethylammonium bromide), acetylcholine, and acetyl-*homo*-choline[3] (3-acetoxy-*n*-propyltrimethylammonium bromide), seems not to have been previously described. This substance may be considered to be an acetylated derivative of trimethylamine-*N*-oxide, or as a quaternary hydroxylammonium salt. It has been found possible to prepare the substance by the reaction of acetyl peroxide with trimethylamine:

$$Ac_2O_2 + Me_3N \longrightarrow (Me_3NOAc)^+ + OAc^-$$

Attempts to make the compound by other routes, such as the reaction of trimethylamine with lead tetraacetate, acetylation of trimethylamine-*N*-oxide with acetyl bromide, and methylation of the *O*-acetyl-*N*-dimethylhydroxylamine with methyl iodide seem to have led to poor yields of highly impure material, since biological assay of the crude products showed only low levels of parasympathomimetic activity.

The assigned structure is supported both by the analytical data, and by the properties of the substance. The presence of a trimethylamino group was indicated by the formation of trimethylamine on both acid and alkaline hydrolysis. Reaction with Hestrin's[4] reagent solutions (alkaline hydroxylamine followed by acidified ferric chloride), which indicates the presence of an ester-like linkage, proceeded somewhat more slowly than with acetylchlorine, 15 minutes being required at 25°. The product had the same molar extinction coefficient at 540 mμ as acetylcholine.

N-Acetoxytrimethylammonium bromide shows parasympathomimetic properties. The substance causes the contraction of guinea pig ileum at $1.7 \times 10^{-6}M$, an action which is prevented by atropine, $4.8 \times 10^{-5}M$. The substance also stimulates eserinized leech dorsal muscle at $1.7 \times 10^{-5}M$, and eserinized frog *rectus abdominis* muscle at $4.3 \times 10^{-6}M$.

N-Acetoxytrimethylammonium bromide is not hydrolyzed by the acetylcholinesterase of guinea pig brain, but is hydrolyzed by horse serum cholinesterase about one-tenth as rapidly as acetylcholine. *N*-Acetoxytrimethylammonium bromide, $1.8 \times 10^{-3}M$, does not inhibit the action of horse serum cholinesterase on acetylcholine.

EXPERIMENTAL

N-Acetoxytrimethylammonium bromide. To 118 g. of a 25% solution of acetyl peroxide (0.25 mole) in dimethyl phthalate,[5] cooled to −5°, was added over 2 hr. 7.4 g. of trimethylamine (0.125 mole) in 25 ml. of sodium-dried ether. (Insufficient cooling has led to explosions.) The reaction mixture was kept at −5° for 48 hr., and was then shaken with 100 ml. of water and 60 ml. of ether. The *p*H of the aqueous layer, originally about 4.6, was adjusted to 3.6 by adding about 12 ml. of concentrated hydrobromic acid, and was re-extracted with about ten 50-ml. portions of ether until a test for peroxides with starch-iodide paper was negative. The *p*H was continuously readjusted to 3.6 during this process. The aqueous solution was concentrated under reduced pressure to a crystalline mass, which was dried *in vacuo* over phosphorus pentoxide. The dried solid was refluxed with several 100-ml. portions of dry chloroform, and the extracts were chilled overnight at −5°. The crystals that appeared were filtered off, washed with cold chloroform, and dried *in vacuo* over phosphorus pentoxide. The yield was usually about 3.5 g. The substance (noticeably hygroscopic) melted at 148° with gas evolution.

Anal. Calcd. for $C_5H_{12}O_2NBr$: C, 30.32; H, 6.11; N, 7.07; Br, 40.35. Found:[6] C, 29.65; H, 6.78; N, 6.67; Br, 39.34.

The data indicate the presence of about 2% of water. The chloroplatinate melted at 242°, the chloroaurate at 145°, and the reineckate at 159°. All melting points have been corrected.

Hydrolysis of N-acetoxytrimethylammonium bromide. The substance (0.1 g.) was refluxed with 5.0 ml. of 0.1*M* hydrobromic acid for 1 hr. The hydrolyzate was evaporated to dryness *in vacuo*, and the residue crystallized from alcohol and ether. The product melted at 245°. A mixed melting point with an authentic sample of trimethylamine hydrobromide (melting point, 245°) showed no depression. Treatment of the substance with alkali, and aeration of the gaseous product into dilute hydrobromic acid, yielded the same product.

Anal. Calcd. for $C_3H_{10}NBr$: C, 25.79; H, 7.20; N, 10.00. Found:[6] C, 25.84; H, 7.33; N, 9.94.

Enzyme and pharmacological tests. The tests for susceptibility to acetylcholinesterase and cholinesterase were made manometrically, as described by Augustinsson.[7] The assays with guinea-pig ileum, leech dorsal muscle, and frog *rectus*

(1) Supported by grants from the National Heart Institute (H-2321), and the National Science Foundation (G-2500).

(2) R. R. Renshaw and J. C. Ware, *J. Am. Chem. Soc.*, **47**, 2990 (1925).

(3) D. Glick, *J. Biol. Chem.*, **125**, 729 (1938).

(4) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

(5) From Becco Chemical Division, Food Machinery and Chemical Corp., Buffalo 7, N. Y.

(6) By Joseph F. Alicino, Box 267, Metuchen, N. J.

(7) K. B. Augustinsson, *Acta Physiol. Scand.*, **15**, Suppl. 52, 37 (1948).

abdominis muscle were made as described by MacIntosh and Perry.[8]

SEMMES CHEMISTRY LABORATORY, TRINITY UNIVERSITY, AND SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION
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(8) F. C. MacIntosh and W. L. M. Perry in *Methods in Medical Research*, Vol. III, 78, Year Book Publishers, New York, 1950.

Cyclopropene. II. The Pyrolysis of *trans*-2-Acetoxycyclopropanecarboxylates[1]

KENNETH B. WIBERG AND ROBERT K. BARNES

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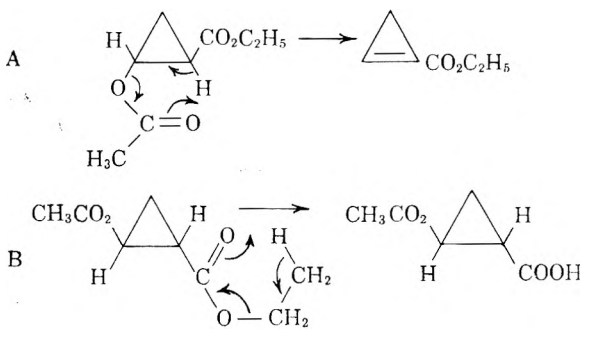
The results obtained in the attempted dehydrobromination of ethyl 2-bromocyclopropanecarboxylate[2] indicate that ethyl cyclopropenecarboxylate is particularly reactive towards Michael addition of nucleophilic agents. It would then be desirable to try to prepare this compound using a reaction which may be effected in the absence of any nucleophilic agents. A particularly attractive reaction is the thermal elimination of acetic acid from an acetate ester.

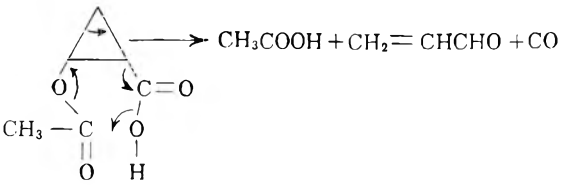
D'yakonov[3] found that the reaction of ethyl diazoacetate with vinyl acetate gave an ethyl 2-acetoxycyclopropanecarboxylate (I). This probably has the *trans*-configuration in analogy with other compounds prepared by this method.[4] The pyrolysis of acetates probably proceeds *via* a cyclic activated complex[5] giving *cis*-elimination. Ethyl 2-acetoxycyclopropanecarboxylate thus has the proper stereochemistry for this type of elimination, and



should give a cyclopropenecarboxylic ester as the product of the pyrolysis if the ease of introducing a double bond into the cyclopropane ring is greater than that of introducing a double bond into the ethyl group. It is known that the pyrolysis of 2° acetates proceeds much faster than that of 1° acetates and this one factor will favor the desired course.

The pyrolysis was first effected at 500°C.[6] using a short contact time, giving starting material, acrolein, acetic acid, ethylene and a small amount of acetic anhydride as the main products. There was also obtained a small amount of a solid acid with an empirical formula $C_6H_8O_4$, which had carbonyl bands in its infrared spectrum at 5.69 μ and 5.87 μ, and also had a broad absorption at 8.12–8.19 μ. The 5.69 μ and 8.12–8.19 μ bands probably correspond to an acetoxy group, and the 5.87 μ band probably corresponds to the carboxylic acid function. The small amount of material available precluded a more thorough investigation, but the available data, and the method of preparation suggest that it is 2-acetoxycyclopropanecarboxylic acid formed by path B.

The other products could arise from this acid as follows:



A *cis*-configuration would appear desirable for this reaction. It is possible that at the reaction temperature the *trans*-compound may be converted to *cis*, or under these conditions, a direct reaction of the *trans*-compound may be possible.

Since the difficulty with this reaction might have been a consequence of initial elimination of ethylene from the ester, followed by decomposition of the acid, the methyl ester which could not lead to the acid was prepared. The pyrolysis of the methyl ester led to the same mixture of products as did the ethyl ester, except that instead of ethylene and acetic acid, methyl acetate was obtained. Thus, this mode of ring cleavage is possible even with an ester.

In connection with other experiments, the methyl ester was subjected to acid catalyzed cleavage. The expected product, methyl β-formylpropionate was formed.

EXPERIMENTAL

Ethyl 2-acetoxycyclopropanecarboxylate. The procedure of D'yakonov[3] was used. A mixture of 290 ml. of freshly dis-

(1) Taken from part of a thesis submitted by R. K. Barnes to the University of Washington in partial fulfillment of the requirements for the Ph.D. degree, 1955. Shell Oil Co. fellow 1953–5.

(2) K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Am. Chem. Soc.*, **79**, 4994 (1957).

(3) I. A. D'yakonov, *Zhur. Obshchei Khim.*, **20**, 2289 (1950).

(4) Ethyl acrylate, vinyl bromide, and *t*-butyl vinyl ether all give predominantly the trans isomer on reaction with ethyl diazoacetate (*cf.* ref. 2).

(5) C. D. Hurd and F. H. Blunck, *J. Am. Chem. Soc.*, **60**, 2419 (1938).

(6) At lower temperatures, considerable starting material was recovered and the course of the reaction was unchanged. It should be noted that the observed products could not be formed by a route involving the formation of the cyclopropenecarboxylic ester followed by the decomposition of the latter.

tilled vinyl acetate (b.p. 72–73°) and 1.0 g. of powdered anhydrous cupric sulfate was stirred and heated to boiling. A cold mixture of 58 g. of ethyl diazoacetate (0.51 mole) and 58 g. of vinyl acetate was added to the boiling solution at such a rate as to maintain gentle refluxing. The addition required approximately 35 min. The solution was then heated for an additional 15 min., cooled, and filtered. The solvent was removed at atmospheric pressure, and the residue was distilled under reduced pressure giving 55.5 g. (67%) of ethyl 2-acetoxycyclopropanecarboxylate, b.p. 72–78° at 2 mm., n_D^{25} 1.4345.

The unsaturated impurities were removed as follows. The ester (20 g.) was stirred with 250 ml. of 0.15 *M* sodium bicarbonate solution and a stream of carbon dioxide was passed through the solution during the oxidation reaction. Solid potassium permanganate was added in small portions to the buffered solution until an excess had been added. The solution was stirred for 10 min. and then extracted with four 100 ml. portions of ether. The ether solution was dried over calcium sulfate and distilled giving an 80–95% recovery of the acetoxy ester. The pure ester had b.p. 105–106° at 13 mm., n_D^{25} 1.4330.[7]

The methyl ester was prepared by the same method, giving 32% of purified ester b.p. 90° at 10 mm., n_D^{25} 1.4358.

Anal. Calcd. for $C_6H_{10}O_4$: C, 53.2; H, 6.4. Found: C, 52.9; H, 6.6.

The infrared spectrum of the ethyl ester contained two peaks of equal intensity in the carbonyl region at 5.69 μ and 5.79 μ and a strong band at 8.09 μ presumably due to the acetate group.[8]

Pyrolysis of ethyl 2-acetoxycyclopropanecarboxylate. All pyrolysis experiments were carried out in a dry, oxygen free, nitrogen atmosphere. A 24 × 1 inch glass column, packed with glass helices and mounted in a vertical position, was used as the reaction chamber. Ethyl 2-acetoxycyclopropanecarboxylate (5 g.) was dropped into the column which was heated to 500°. The addition required 30 min. during which time a nitrogen flow of approximately 26 l. per hour was maintained. The effluent vapors were collected in a Dry Ice-acetone cooled trap, and in a liquid nitrogen cooled trap. There was obtained 2.2 ml. of a strongly acidic and lachrymatory liquid. Distillation, followed by infrared analysis of the lower boiling fractions indicated the presence of acetic acid, acrolein, and acetic anhydride. The higher boiling fraction was distilled under reduced pressure giving a small amount of starting material, and a small amount of a solid. The solid was recrystallized twice from carbon tetrachloride, m.p. 97.5–98.5°, a total of 10 mg. being obtained.

Anal. Calcd. for $C_6H_8O_4$: C, 50.0; H, 5.6. Found: C, 49.7; H, 5.7.

The solid was acidic to bicarbonate and contained two bands in the carbonyl region of the infrared spectrum, at 5.69 μ and 5.85–5.89 μ, as well as broad absorption at 8.12–8.19 μ. The small amount of this material precluded a more thorough investigation, but these data suggest that it was 2-acetoxycyclopropanecarboxylic acid.

Pyrolysis of the ester at 520° with a flow rate of 3.3 l. per hour was carried out, and the low boiling material was distilled and identified. Ethylene from the liquid nitrogen trap was identified by its characteristic infrared absorption spectrum. The approximate yield estimated from the pressure produced by the gas in a vessel of known volume was 61%. Acrolein, b.p. 50–53°, n_D^{21} 1.3987, was characterized by its infrared spectrum and by its 2,4-dinitrophenylhydrazone, m.p. 163–163.9°, mixed m.p. with an authentic sample, 164–165°.[9] The yield of acrolein was 18%, and a considerable amount of this material probably polymerized in the reaction tube. Acetic acid, obtained in 62% yield, was characterized by its infrared spectrum and by the melting point of the *p*-bromophenacyl ester, m.p. 84–85°.[10] Acetic anhydride was detected in the middle boiling fraction by its characteristic infrared spectrum. Only a trace of this compound was obtained.

In another pyrolysis experiment, a 4 l. gas fraction was collected over water. The ethylene and water vapor were trapped from the gas, and the infrared spectrum of the remaining gas showed the presence of carbon monoxide. The yield, estimated using the intensity of the spectrum, was 39%.

Pyrolysis of methyl 2-acetoxycyclopropanecarboxylate. The methyl ester was pyrolyzed at 520° with a flow rate of 3 l. per hour. The products were found to be methyl acetate, acrolein, acetic acid, and a small amount of acetic anhydride. No attempt was made to identify carbon monoxide in this case.

Hydrolysis of methyl 2-acetoxycyclopropanecarboxylate. A solution of 4.76 g. (30 mmoles) of the ester, 100 ml. of methylene chloride, 10 ml. of concentrated hydrochloric acid, and 30 ml. of methanol was heated under reflux for 26 hr. The solution was cooled, the organic layer was separated, washed with water, 5% sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the product was distilled giving 3.20 g. (92%) of methyl β-formylpropionate, b.p. 78–80° at 13 mm., n_D^{25} 1.4168–1.4153. The infrared spectrum of this material corresponded to that of an authentic sample, and the 2,4-dinitrophenylhydrazone, m.p. 130–131.5° gave no depression of the m.p. of an authentic sample[2] on admixture.

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(7) Ref. 3 reported b.p. 90–92.5° at 7 mm., n_D^{25} 1.433.

(8) A. W. Thompson and P. Torkington, *J. Chem. Soc.* 640 (1945).

(9) C. F. H. Allen, *J. Am. Chem. Soc.*, **52**, 2955 (1930) reported the 2,4-dinitrophenylhydrazone, m.p. 165°.

(10) C. G. Moses and E. E. Reid, *J. Am. Chem. Soc.*, **54**, 2101 (1932) reported the m.p. of the *p*-bromophenacyl ester as 86°.

Addition of Phenylacetic Acid to a Schiff Base with Formation of a β-Amino Acid

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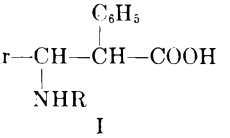
Beta amino acids of general formula I have, according to recent reports, been synthesized by the



I

following methods involving addition reactions to the carbon-nitrogen double bond of Schiff bases. (a) Addition of C_6H_5—CH(MgCl)—COONa[2] (sodium phenylacetate plus a Grignard reagent), of C_6H_5—CHNa—COONa[3] (sodium phenylacetate

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(2) B. I. Kurtev and St. Robev, *Doklady Bolgar. Akad. Nauk*, **4**, 37 (1951); *Chem. Abstr.*, **49**, 958g (1955).

(3) A. Spasov and St. Robev, *Doklady Akad. Nauk S.S.S.R.*, **95**, 817 (1954).

plus sodamide) or of C_6H_5—CHLi—COONa[4] to Schiff bases. (b) Addition of ethyl phenylacetate to Schiff bases in the presence of aluminum chloride, followed by alkaline hydrolysis.[5–7]

We wish to report that a simple mixture of phenylacetic acid and *N*-benzylidenemethylamine, after being heated at about 100°, affords I, Ar = C_6H_5, R = CH_3. No catalyst is necessary. A discussion of possible reaction mechanisms is postponed until we have determined the stereochemical nature (DL-erythro, DL-threo, or some mixture of these) of products formed by the various methods. Only malonic acid has previously been reported capable of adding without catalyst to a carbon-nitrogen double bond to give a beta amino acid.[8]

EXPERIMENTAL

2,3-Diphenyl-3-methylaminopropanoic acid. Equimolecular quantities of phenylacetic acid and *N*-benzylidenemethylamine[9,10] are heated at 100° for 2 hr. in a flask equipped with a calcium chloride drying tube. The reaction mixture, which is almost completely solid at the end of the heating period, is cooled and treated with a 0.1*M* NaOH solution. Any alkali-insoluble material is removed by filtration. A stream of carbon dioxide gas is then passed through the alkali solution until the β-aminoacid precipitates. After being filtered, washed with water, and dried it melts at 200°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.81; H, 6.85; N, 5.30.

Yields are variable but may reach approximately 75%. Polymerization reactions of the imine, which appear to reduce the yield, may possibly be minimized by the use of an inert diluent.

The β-aminoacid dissolves in very dilute hydrochloric acid. When concentrated hydrochloric acid is added to such a solution, then the hydrochloride of the β-aminoacid precipitates. This substance is easily water soluble but only slightly soluble in fairly concentrated (3*M* or higher) hydrochloric acid. It melts sharply, but with decomposition, anywhere between 194.5° and 198°, depending on the rate of heating.

Anal. Calcd. for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; Cl, 12.15; N, 4.80. Found: C, 65.89; H, 6.34; Cl, 11.99; N, 4.69.

A sample of β-aminoacid hydrochloride prepared by Mollov according to method (b) was reported to melt with decomposition at 190–191°.[7] The free β-aminoacid was not described by Mollov.

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(4) N. Marécoff, G. Vassileff, and D. Ivanoff, *XVIth International Congress of Pure and Applied Chemistry*, Paris, July 1957, Congress Handbook Vol. II, Division of Organic Chemistry, pp. 119–120.

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(6) N. M. Mollov and B. I. Kurtev, *Doklady Akad. Nauk S.S.S.R.*, **102**, 287 (1955).

(7) N. M. Mollov, *Doklady Akad. Nauk S.S.S.R.*, **106**, 482 (1956).

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(9) H. Zaunschirm, *Ann.*, **245**, 279 (1888).

(10) C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 1204 (1929).

Levulinic Acid. II.[1] Some Derivatives of 2-Aminoethyl Levulinate

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In connection with other studies a series of esters of levlulinic acid were required; most of these have been described previously. Attempts to prepare 2-aminoethyl levulinate by azeotropic esterification of a mixture of levulinic acid and ethanolamine only yielded a viscous gum which could not be distilled; hydrogenation of the same mixture gives 1-(ethan-2-ol)-5-methyl-2-pyrrolid-one.[2,3] Using the azeotropic method, levulinic acid was successfully esterified with 2-dimethylaminoethanol, 2-diethylaminoethanol, and *N*-2-hydroxyethylphthalimide.

EXPERIMENTAL[4]

2-Dimethylaminoethyl levulinate. Levulinic acid (116 g., 1.0 mole), 2-dimethylaminoethanol (89 g., 1.0 mole), and benzene (100 ml.) were refluxed in a flask fitted with a Dean and Stark adaptor; water (18 ml.) separated in 24 hrs. The reaction product was washed with water, sodium bicarbonate, and dried. After removal of the solvent the ester had b.p. 156–158°/30 mm ; n_D^{23} 1.4395; yield 61 g. (33%).

Anal. Calcd. for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.49. Found: C, 57.32; H, 9.08; N, 6.90%.

2-Diethylaminoethyl levulinate. This ester was prepared in a similar manner and had b.p. 172–176°/30 mm., n_D^{27} 1.4435; yield 46%.

Anal. Calcd. for $C_{11}H_{21}O_3N$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.54; H, 9.45; N, 6.32%.

2-Phthalimidoethyl levulinate. N-2-hydroxyethyl phthalimide[5] (95.5 g., 0.5 mole.) and levulinic acid (58 g., 0.5 mole.) in benzene (100 ml.) were refluxed for 48 hrs. in a flask fitted with a Dean and Stark adaptor; water (9.5 ml.) separated. After cooling the reaction mixture was washed twice with 2*N* sodium carbonate; at this stage the product crystallized and was collected by filtration. The dried product was recrystallized from ethanol m.p. 90–93°; yield 89 g. (62%).

Anal. Calcd. for $C_{15}H_{15}O_5N$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.58; H, 5.35; N, 4.91%.

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(2) R. B. Moffett, *J. Org. Chem.*, **14**, 862 (1949).

(3) Y. Hachihama and I. Hayashi, *Technol. Rep. Osaka Univ.*, **4**, No. 108, p. 177 (1954).

(4) Analyses by Drs. Weiler and Strauss, Oxford.

(5) H. Wenker, *J. Am. Chem. Soc.*, **59**, 422 (1937).

Monomeric and Polymeric Compositions from Carbethoxymethyl Isocyanate[1]

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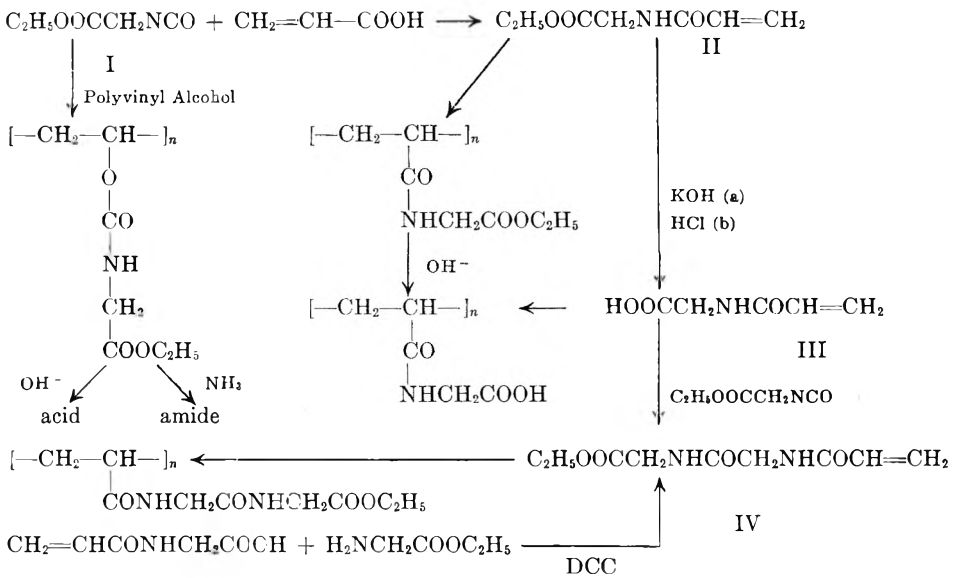
Recent work in the field of synthetic polypeptides has provided improved techniques for the

(1) Communication No. 1915 from the Kodak Research Laboratories.

preparation of these materials. We have been concerned in the present work with the synthesis of polymers which have peptide side chains attached to a carbon–carbon backbone. To this end we have prepared ethyl acrylamidoacetate (II) by the reaction of carbethoxymethyl isocyanate with acrylic acid. This compound can be polymerized by free radical initiation and the resultant product saponified to the acid. The conversion of II to acrylamidoacetic acid (III) is accomplished by saponification in alcoholic potassium hydroxide and acidification of the isolated potassium salt in alcohol suspension. The acid (III) undergoes polymerization unless handled at low temperatures; however, the monomeric material can be separated from the polymer by cold recrystallization from acetonitrile.



The appendage of a second glycine unit to the acid (III) is satisfactorily accomplished by reaction with a second equivalent of carbethoxymethyl isocyanate to give ethyl acrylamidoacetamidoacetate (IV). The identity of this compound was verified by preparing it from III and ethyl aminoacetate using dicyclohexylcarbodiimide, according to the method of Sheehan.[2] Attempts to saponify IV and continue the stepwise operation were unsuccessful, probably because of cyclization and/or polymerization.

As an alternative method, we attempted to build peptide side chains directly on a polymer chain. Carbethoxymethyl isocyanate (I) reacted smoothly with polyvinyl alcohol and other hydroxyl-containing polymers to give carbethoxymethyl urethans. These could be saponified readily, but the resulting polymeric acid on treatment with a second mole of the isocyanate (I) formed a cross-linked gel.

(2) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

EXPERIMENTAL

Ethyl acrylamidoacetate. To 100 g. (1.38 moles) of acrylic acid (stabilized with methylene blue) was added dropwise, with stirring, 140 g. (1.16 moles) of carbethoxymethyl isocyanate. During the addition, the temperature was kept at 38–42° by external cooling. When the addition was complete, the mixture was heated slowly to 60° and a few crystals of cupric acetate were added. This resulted in a brisk evolution of carbon dioxide and a rapid increase in temperature to 67°. The solution was allowed to stand 3 days, then heated briefly to 80°, and distilled under reduced pressure. The fraction boiling at 120–140° and 2–3.5 mm. was collected and redistilled from a few grams of Aranox No. 2. The yield of ethyl acrylamidoacetate, a colorless oil which crystallized on cooling, was 65 g. (36%), b.p. 111–114°/1 mm.

Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.5; H, 7.01; N, 8.92. Found: C, 52.9; H, 7.1; N, 8.7.

Acrylamidoacetic acid. To a solution of 5.6 g. (0.1 mole) of potassium hydroxide in 75 ml. of ethanol was added 15.7 g. (0.1 mole) of ethyl acrylamidoacetate. The crystalline potassium salt began to separate almost immediately. After vigorous stirring for 30 min., the mixture was filtered and the product washed with ethanol and dried *in vacuo*. Yield, 9.5 g. (57%).

Anal. Calcd. for $C_5H_6NO_3K$: C, 35.9; H, 3.6; N, 8.4. Found: C, 35.5; H, 4.1; N, 8.0.

A suspension of 35.0 g. (0.21 mole) of potassium acrylamidoacetate in 200 ml. of ethanol was chilled in a freezing mixture and treated with 22.5 ml. of 2.9*N* hydrochloric acid in ethanol so that the temperature did not exceed 0°. Potassium chloride was removed by filtration, the filtrate was concentrated to about 40 ml., and chilled overnight in the refrigerator. The crystalline acid was collected and dried, yield 10.5 g. (39%), m.p. 110–123°. On several occasions the product had partially polymerized at this point. The monomeric material could be separated by extraction with warm acetonitrile. Two recrystallizations from acetonitrile raised the melting point to 130–132°.

Anal. Calcd. for $C_5H_7NO_3$: C, 46.5; H, 5.43; N, 10.8. Found: C, 46.0; H, 5.4; N, 11.4.

Ethyl acrylamidoacetamidoacetate. (a). Four grams of acrylamidoacetic acid (0.03 mole) and 6 ml. of carbethoxymethyl isocyanate (0.04 mole) were combined and kept at 60°. After a few minutes, evolution of carbon dioxide was brisk and solution occurred. On further heating, the solution solidified and was then treated with ether and the solid

collected and dried, yield 2.6 g. (42%). Recrystallization from hot water gave pale yellow leaflets melting at 149–150°. A mixed melting point with *N,N'*-dicarbethoxymethylurea (m.p. 147–148°) was depressed to 125–131°.

Anal. Calcd. for $C_9H_{14}N_2O_4$: C, 50.5; H, 6.55; N, 13.1. Found: C, 50.8; H, 7.0; N, 12.9.

(*b*) A solution of 10.6 g. (0.01 mole) of ethyl glycinate (freshly distilled) and 21.0 g. (0.1 mole) of dicyclohexylcarbodiimide in 50 ml. of ethanol was treated with 13.0 g. (0.1 mole) of acrylamidoacetic acid dissolved in a little ethanol. After shaking 30 min., the mixture was filtered and the solid washed with ethanol. The filtrate was evaporated to dryness, yielding 1.5 g. of impure material which was not worked up. The solid was repeatedly extracted with hot acetonitrile, the combined extracts were concentrated and chilled, yielding 12.3 g. (58%) of colorless crystals, m.p. 148–150°. A mixed melting point with the product obtained in (*a*) was not depressed.

Poly(ethyl acrylamidoacetate). A solution of 10.0 g. (0.047 mole) of ethyl acrylamidoacetate in 30 ml. of water was treated with a trace of ammonium persulfate and kept at 60° for 2 hr. The soft white cake was separated and squeezed dry. It was soluble in alcohol and other organic solvents in the freshly prepared state but drying rendered it insoluble.

Ammonolysis of this product with aqueous ammonia at room temperature gave a polymer which showed thermally reversible gelation.

Saponification of the polymeric ester with dilute sodium hydroxide at room temperature yielded the acid which also showed gelation properties.

Poly(ethyl acrylamidoacetamidoacetate). Ethyl acrylamidoacetamidoacetate in aqueous solution gave a soft spongy polymer when heated with a trace of potassium persulfate. This material could be converted to the acid as in the previous example, but it did not show gelation properties.

Poly(vinyl carboxymethylcarbamate). A suspension of 50 g. of polyvinyl alcohol (Elvanol 71–30) in 500 ml. of pyridine was treated with 180 g. of carbethoxymethyl isocyanate and stirred on the steam-bath for 1 hr. The resulting solution was poured into a large volume of cold water and the rubbery precipitate washed. The ester was converted to the acid by stirring at 25° with a solution of 45 g. of sodium hydroxide in 800 ml. of water. This operation produced an almost clear solution from which the product was isolated by precipitation in dilute hydrochloric acid. The product was purified by solution in methanol and precipitation in acetone.

Treatment of this material with carbethoxymethyl isocyanate in dimethylformamide solution at 150° gave a crosslinked product.

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Decarbonylation of 3-Indoleglyoxalyl Chloride

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The observation that 3-indoleglyoxalyl chloride may be prepared in excellent yield by the reaction of indole with oxalyl chloride[1] and that *p*-dimethylaminobenzoyl chloride, the expected product from the decarbonylation of *p*-dimethylaminophenylglyoxalyl chloride, may be obtained by the reaction of dimethylaniline with oxalyl chloride[2] led us to investigate the possibility of using 3-indoleglyoxalyl chloride as an intermediate in the preparation of 3-indolecarbonyl chloride.

When a solution of 3-indoleglyoxalyl chloride in tetrachloroethane was heated to 115–120°, carbon monoxide was evolved and when hexane was added to the cooled reaction mixture a precipitate was obtained. Fractional recrystallization of this precipitate from a mixture of benzene and hexane gave 3-indolecarbonyl chloride in yields of 16–23% based upon indole. The acid chloride was identified by hydrolysis to the known 3-indolecarboxylic acid[3] and by alcoholysis to the known methyl and ethyl 3-indolecarboxylates.[3,4]

Because of the ease with which indole can be transformed into 3-indolecarbonyl chloride, the relatively low yield of *ca.* 20% is not too disturbing. However, in order to understand the reasons for the low yield, the crude reaction product was analyzed and it was observed that it contained but *ca.* 25% of the expected amount of chlorine. When an infrared spectrum of the crude reaction product disclosed the presence of two carbonyl peaks, *i.e.*, one at *ca.* 1750 cm.$^{-1}$ and the other at *ca.* 1690 cm.$^{-1}$, and when it was found that alkaline hydrolysis of the same material gave, after acidification, 3-indolecarboxylic acid in yields of *ca.* 95%, it became evident[5] that the crude reaction product was a mixture containing *ca.* 25% of the expected 3-indolecarbonyl chloride with the remainder being principally a polymeric amide arising from the reaction of the acid chloride with itself. All attempts to limit the formation of this latter substance, except by the impractical procedure of conducting the reaction under conditions of extreme dilution, were unsuccessful. The remaining alternative of hydrolyzing the polymeric amide to 3-indolecarboxylic acid and then attempting to convert this substance to the acid chlorine was also considered impractical because of the availability of both indole and oxalyl chloride and the ease of obtaining the desired acid chloride from the crude reaction product.

Since our interest in 3-indolecarbonyl chloride was generated by its anticipated use in the acylation of α-amino acid derivatives, it was gratifying to find that 3-indolecarboxanilide, 3-indolecarbox-*p*-toluide, 3-indolecarbonylglycine ethyl ester, and 3-indolecarbonyl-L-phenylalanine methyl ester could be prepared in 30–50% yields from the acid chloride and the amine using conventional procedures.

(1) M. E. Specter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(2) H. Staudinger and H. Stockmann, *Ber.*, **42**, 3485 (1909).

(3) R. Majima, *Ber.*, **55**, 3865 (1922).

(4) C. Zahi and A. Ferratini, *Ber.*, **23**, 2297 (1890).

(5) L. J. Bellamy, *Infra-red Spectra of Complex Molecules*, John Wiley and Sons, New York, N. Y. (1954).

EXPERIMENTAL[5,7]

3-Indolecarbonyl chloride. The 3-indoleglyoxalyl chloride obtained from the reaction of 10 g. of indole with 10 ml. of oxalyl chloride in 100 ml. of ether[1] was dissolved in 150 ml. of tetrachloroethane and the solution heated to 115–120°. After the rapid evolution of carbon monoxide had ceased, the deep brown solution was rapidly cooled to room temperature, 450 ml. of hexane added to precipitate the crude reaction product, the latter collected, washed with hexane, and dried in a stream of dry air to give *ca.* 10 g. of crude reaction product in the form of a brownish yellow powder. Analysis of a representative product gave Cl, 4.7%; calcd. for 3-indolecarbonyl chloride, 11.1%. An infrared spectrum, determined in solid KBr, exhibited two peaks of *ca.* equal intensity, one at *ca.* 1750 cm.$^{-1}$ and the other at *ca.* 1690 cm.$^{-1}$ The crude reaction product was dissolved in boiling benzene, the solution filtered, 25 ml. of hexane added to the hot solution, the dark brown precipitate which appeared on cooling discarded, an additional 5 ml. of hexane added to the filtrate, the brown precipitate again discarded, 75 ml. of hexane added to the now light yellow solution to give after collection by filtration and drying 2.5–3.5 g., (16–23% based upon indole) of 3-indolecarbonyl chloride in the form of yellow crystals.

Hydrolysis of the above acid chloride in the presence of 1*M* aqueous sodium bicarbonate gave, after acidification, 3-indolecarboxylic acid, m.p. 217–219° dec. (lit.[6] m.p. 218–220).

The crude reaction product, 10.61 g., was suspended in 60 ml. of aqueous 1*M* sodium bicarbonate, the insoluble residue collected and the solution acidified to give 1.17 g. (11%) of 3-indolecarboxylic acid, m.p. 217–219° with dec. The insoluble residue was dissolved in 60 ml. of 1*M* aqueous sodium hydroxide, the solution filtered and the filtrate acidified to give 6.17 g. (58%) of 3-indolecarboxylic acid, m.p. 214–217° dec. Hydrolysis of the crude reaction product with 1*M* aqueous sodium hydroxide under more drastic conditions gave, after acidification, *ca.* 95% of the above carboxylic acid.

To a filtered solution of 3 g. of the crude reaction product in 25 ml. of anhydrous methanol, was added 30 ml. of water. The solid product which formed was recrystallized from aqueous methanol to give *ca.* 1 g. of methyl 3-indolecarboxylate, m.p. 144–145.6° (lit.,[4] m.p. 147–148°).

The similar reaction of 3 g. of the crude reaction product with 25 ml. of absolute ethanol gave, after three recrystallizations from aqueous ethanol, *ca.* 1 g. of ethyl 3-indolecarboxylate, m.p. 119–123° (lit.,[3] m.p. 118–120°).

3-Indolecarboxanilide. Recrystallized 3-indolecarbonyl chloride was added to an excess of aniline in anhydrous ethyl acetate, the ethyl acetate solution washed with aqueous hydrochloric acid, aqueous sodium hydroxide and water and then dried. The addition of hexane to the dry ethyl acetate solution gave 3-indolecarboxanilide, m.p. 175.5–176.2° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{15}H_{12}ON_2$ (236): C, 76.3; H, 5.1; N, 11.9. Found: C, 76.4; H, 5.2; N, 11.8.

3-Indolecarbox-p-toluide. The reaction of the recrystallized acid chloride with *p*-toluidine as described above for the corresponding anilide gave 3-indolecarbox-*p*-toluide, m.p. 200.9–201.1°, after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{16}H_{14}ON_2$ (250): C, 76.8; H, 5.6; N, 11.2. Found: C, 76.9; H, 5.7; N, 10.8.

3-Indolecarbonylglycine ethyl ester. A solution of 1.55 g. of glycine ethyl ester hydrochloride in 5 ml. of water containing 3.18 g. of potassium carbonate was placed in a separatory funnel containing 60 ml. of ethyl acetate. Two grams of recrystallized 3-indolecarbonyl chloride in 30 ml. of ethyl acetate was added to the reaction mixture which was then shaken for 10 min. The ethyl acetate phase was separated, washed with water, dried, and the solvent removed to give 0.84 g. (30%) of 3-indolecarbonylglycine ethyl ester, m.p. 159–160°, after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$ (246): C, 63.4; H, 5.7; N, 11.4. Found: C, 63.5; H, 5.7; N, 11.6.

3-Indolecarbonyl-L-phenylalanine methyl ester. The reaction of 2 g. of 3-indolecarbonyl chloride, 3.2 g. of L-phenylalanine methyl ester hydrochloride and 4.18 g. of potassium carbonate was conducted as described for the glycine analog. The oily product recovered from the ethyl acetate phase was dissolved in methanol and this solution was brought to the cloud point by the addition of water. After standing for 20 hr. at 4°, the product was collected and recrystallized from aqueous methanol to give 1.08 g. (30%) of 3-indolecarbonyl-L-phenylalanine methyl ester, m.p. 133–134°.

Anal. Calcd. for $C_{19}H_{18}O_3N_2$ (322): C, 70.8; H, 5.6; N, 8.7. Found: C, 70.8; H, 5.6; N, 8.7.

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CONTRIBUTION NO. 2222 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY
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(6) All melting points are corrected.

(7) Microanalyses by Dr. A. Elek.

Glycolamide Esters of Acylated α-Amino Acids

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It is common knowledge that a number of acylated α-amino acid alkyl esters are hydrolyzed in the presence of the pancreatic proteases. However, their use as specific substrates in studies with the above enzymes frequently is limited by their relatively low solubility in water.

In the course of a search for a class of neutral water soluble acylated α-amino acid esters capable of functioning as specific substrates for α-chymotrypsin, it was observed that benzoylglycolamide, prepared by the condensation of sodium benzoate and chloracetamide, was sufficiently soluble in water to permit the preparation of 0.1 *M* solutions. While the very water soluble acetyl-DL-phenylalanine glycolamide ester could be prepared in an analogous manner, it was clear that a more satisfactory synthesis was required.

When acetyl-DL and L-phenylalanine were employed as representative examples, it was found that reaction of the corresponding cyanomethyl esters[1] with an excess of hydrogen chloride and one mole equivalent of methanol in benzene, followed by removal of the benzene by distillation at atmospheric pressure, gave the desired acetyl-DL- and L-phenylalanine glycolamide esters in good yields. McElvain and Nelson[2] have noted that imidoes-

(1) R. Schwyzer, M. Feurer, B. Iselin, and H. Kagi, *Helv. Chim. Acta*, 38, 80 (1955).

(2) S. M. McElvain and J. N. Nelson, *J. Am. Chem. Soc.*, 64, 1825 (1942).

ter hydrochlorides when heated to 60–80° give the corresponding amides and alkyl halides.

When examined in aqueous solutions at 25° and *p*H 7.9, acetyl-L-phenylalanine glycolamide ester was rapidly hydrolyzed, to acetyl-L-phenylalanine and glycolamide, by α-chymotrypsin.

EXPERIMENTAL[3,4]

Acetyl-DL-phenylalanine cyanomethyl ester. The reaction of 14.4 g. of acetyl-DL-phenylalanine with 9.08 g. of redistilled chloracetonitrile in the presence of triethylamine according to the procedure of Schwyzer *et al.*[1] gave 11.0 g. (64%) of crude cyanomethyl ester. The crude ester was recrystallized twice from a mixture of anhydrous ethanol and hexane to give acetyl-DL-phenylalanine cyanomethyl ester, colorless needles, m.p. 94–95°.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$ (246): C, 63.4; H, 5.7; N, 11.4. Found: C, 63.5; H, 5.7; N, 11.4.

Reaction of the cyanomethyl ester with benzylamine[1] gave acetyl-DL-phenylalaninebenzylamide, m.p. 161.5–162.9°.

Anal. Calcd. for $C_{17}H_{18}O_2N_2$ (282): N, 9.5. Found: N, 9.5.

Acetyl-DL-phenylalanine glycolamide ester. A solution of 2.46 g. of acetyl-DL-phenylanine cyanomethyl ester in 75 ml. of benzene and 3.3 ml. of 3 *M* methanol in benzene was saturated with dry hydrogen chloride. The solution was allowed to stand at room temperature for 15 min., the benzene removed by distillation at atmospheric pressure, and the colorless residue dissolved in 350 ml. of hot ethyl acetate. This solution was cooled to give 1.69 g. (64%) of the glycolamide ester which was recrystallized from ethyl acetate to give acetyl-DL-phenylalanine glycolamide ester, m.p. 160.5–161.5°.

Anal. Calcd. for $C_{13}H_{16}O_4N_2$ (264): C, 59.1; H, 6.1; N, 10.6. Found: C, 59.1; H, 6.1; N, 10.7.

Acetyl-L-phenylalanine cyanomethyl ester. Acetyl-L-phenylalanine, 7.2 g., when treated with 4.5 g. of redistilled chloracetonitrile, as described for the DL-compound, gave 4.4 g. (52%) of crude cyanomethyl ester. Recrystallization of the crude ester from a mixture of anhydrous ethanol and hexane gave acetyl-L-phenylalanine cyanomethyl ester, colorless needles, m.p. 124.5–125.5°, $[\alpha]_D^{25.3}$ −11.2 ± 0.4 (c, 3.0% in acetone).

Anal. Calcd. for $C_{13}H_{14}O_3N_2$ (246): C, 63.4; H, 5.7; N, 11.4. Found: C, 63.6; H, 5.8; N, 11.4.

Acetyl-L-phenylalanine glycolamide ester. The reaction of 2.46 g. of acetyl-L-phenylalanine cyanomethyl ester with methanol and hydrogen chloride, under the conditions employed for the DL-compound, gave 1.6 g. (61%) of crude glycolamide ester. Recrystallization of the crude ester from a mixture of anhydrous ethanol and hexane gave acetyl-L-phenylalanine glycolamide ester, colorless needles, m.p. alanine glycolamide ester, colorless needles, m.p. 120.5–121.5°, $[\alpha]_D^{25.3}$ +2.2 ± 0.2° (c, 2.3% in absolute ethanol).

Anal. Calcd. for $C_{13}H_{16}O_4N_2$ (264): C, 59.1; H, 6.1; N, 10.6. Found: C, 59.1; H, 6.1; N, 10.6.

A mixture of the above compound and the DL-compound, m.p. 160.5–161.5 melted at 132–162°.

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(3) Melting points are corrected.
(4) Microanalyses by Dr. A. Elek.

Improved Preparation of 1-Iodo-2,4-dinitrobenzene[1]

J. F. BUNNETT AND R. M. CONNER

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Bennett and Vernon[2] prepared 2,4-dinitroiodobenzene in 30% yield by heating 2,4-dinitrochlorobenzene with five mole proportions of sodium iodide at reflux in ethylene glycol for 30 minutes. We have found that the yield can be raised to 70% by conducting the reaction in dimethylformamide solution. The procedure is simple, and this is now to be regarded as the method of choice for preparing this compound. Experiments which led to the development of optimum conditions are summarized in Table I, and our best procedure is described in the Experimental section.

TABLE I

PREPARATION OF 2,4-DINITROIODOBENZENE FROM 2,4-DINITROCHLOROBENZENE

Solvent[a]	Mole Ratio, NaI:$C_6H_3(NO_2)_2Cl$	Reflux Time, min.	Yield, %
Ethylene Glycol	5:1	60	37
DMF[b]	5:1	*ca.* 90	0[c]
DMF	5:1	30	49[d]
DMF	5:1	15	70
DMF	3:1	15	66
DMF	5:1[e]	15	71

[a] DMF stands for dimethylformamide. [b] In this experiment, technical DMF was used without being redistilled. [c] A dark tar was obtained when the reaction mixture was poured into water and no effort was made to isolate a pure product from it. [d] The crude product was recrystallized from ethanol and then from petroleum ether (b.p. 90–100°). [e] One mole of 2,4-dinitrochlorobenzene (5 times the usual amount) was used in this run.

The reaction was tried once in dimethyl sulfoxide solution. From the dark sludge obtained by pouring the reaction mixture into water, only 2,4-dinitrophenyl methyl sulfide, in 5% yield, was isolated. Presumably this compound arose from the following sequence of reactions: reduction of dimethyl sulfoxide to dimethyl sulfide by iodide ion, condensation of dimethyl sulfide with 2,4-dinitrochlorobenzene to form a sulfonium salt, and demethylation of the sulfonium salt by S_N2 attack of iodide ion on one of its methyl groups. It is interesting to note that Finger and Kruse[3] obtained small amounts of nitrophenyl methyl sulfides as by-products in the preparation of *o*- and *p*-fluoronitrobenzenes by reactions of the corresponding chloro

(1) Work supported in part by the Office of Ordnance Research, U. S. Army.

(2) G. M. Bennett and I. H. Vernon, *J. Chem. Soc.*, 1783 (1938).

(3) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956).

compounds with potassium fluoride in dimethyl sulfoxide solution.

EXPERIMENTAL

2,4-Dinitroiodobenzene, optimum conditions. To 200 cc. of redistilled dimethylformamide, 150 g. (1.0 mole) of sodium iodide and 40.5 g. (0.2 mole) of 2,4-dinitrochlorobenzene (Eastman Kodak white label) were added. The mixture was heated at reflux by means of a free flame for 15 min.; during the period of heating to reflux temperature, the flame was played against the side of the flask so as to dissolve the sodium iodide from the top downward. The hot reaction mixture was poured into ice and water and the precipitated tan solid was collected on a suction filter. The damp product was recrystallized from a mixture of 375 cc. of petroleum ether (b.p. 90–100°) and 125 cc. of benzene with use of charcoal and with final chilling to −20° in a freezing cabinet. The resulting orange-yellow crystalline product, m.p. 87–89°, weighed 41.4 g. (70%). Recrystallization of this product from petroleum ether (b.p. 90–100°) furnished lemon-yellow crystals, m.p. 88.5–90°. Körner[4] reported m.p. 88.5°.

A run at five times the above scale gave comparable results.

Formation of 2,4-dinitrophenyl methyl sulfide in dimethyl sulfoxide solvent. The reaction was conducted as described above except that 200 cc. of commercial dimethyl sulfoxide (Stepan Chemical Co.) was used as solvent and the period of reflux was 1 hr. The reaction mixture was poured into water and allowed to stand 5 days. By suction filtration, a brick-red solid was collected. This solid was extracted with hot petroleum ether (b.p. 90–100°); orange crystals were obtained by cooling the extract. Recrystallization from ethanol with use of charcoal furnished 2.7 g. (5%) of yellow-orange flakes, m.p. 126–127°. A mixed melting point with an authentic sample of 2,4-dinitrophenyl methyl sulfide of m.p. 127–128.5° was not depressed.

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(4) W. Körner, *Gazz. chim. ital.*, 4, 323 (1874).

2-Diphenylmethylene-3-dimethylamino-oxazolidine-4,5-dione

GLENN S. SKINNER AND W. J. STOUT

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A series of 2-dialkylmethylene-3-alkyloxazolidine-4,5-diones[1] has been prepared by the action of oxalyl chloride on *N*-alkyldialkylacetamides. We have extended this reaction by using *N*-diphenylacetyl-*N'*,*N'*-dimethylhydrazine (I) in place of the amide. The resulting compound possesses typical oxazolidinedione properties and is formulated as 2-diphenylmethylene-3-dimethylaminooxazolidine-4,5-dione (II).

The infrared spectrum for this compound shows bands which can be attributed to a lactone and two carbonyl functions. The spectrum agrees with those of previously reported oxazolidinediones. Likewise, the behavior toward bromine in carbon tetrachloride and potassium permanganate in acetone is the same.

The behavior of the previously studied oxazolidine-4,5-diones in ethanol depends on the type and degree of substitution. 3-Alkyl-2-monoalkylmethyleneoxazolidine-4,5-diones rearrange to the corresponding hydroxymaleimides. Similar treatment of the 2-monoalkyl- or 2-dialkylmethyleneoxazolidine-4,5-diones results in cleavage to the corresponding amides. 3-Alkyl-2-dialkylmethyleneoxazolidine-4,5-diones rearrange to trialkylpyrrolidine-2,3,5-triones. It is, therefore, of interest to report from this study that II undergoes neither of the above reactions with alcohol. In this case, the ring opens at position 2 to give ethyl diphenylacetate.

In the course of this work previously unreported *N*-dialkylacetyl-*N'*,*N'*-dimethylhydrazines were prepared.

EXPERIMENTAL

Preparation of I. To a stirred solution of 19.5 g. (0.325 mole) of *N*,*N*-dimethylhydrazine in 100 ml. of ether was added dropwise an ether solution of 75.0 g. (0.325 mole) of diphenylacetyl chloride. Simultaneously at a somewhat slower rate, a solution of 13.0 g. (0.325 mole) of sodium hydroxide in 65 ml. of water was added. The white precipitate was filtered and crystallized from 95 percent ethanol, yield 72 g. (87%), m.p. 168°.

Anal. Calcd. for $C_{16}H_{18}ON_2$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.39; H, 7.16; N, 11.01.

N-Diethylacetyl-N',N'-dimethylhydrazine. Similarly, from 30.0 g. (0.50 mole) of *N*,*N*-dimethylhydrazine in 150 ml. of ether, 67.3 g. (0.50 mole) of diethylacetyl chloride, and 20.0 g. (0.50 mole) of sodium hydroxide in 100 ml. of water, there was obtained from the ether layer 75.5 g. of a yellow oil which did not crystallize after standing 48 hr. in an ice bath. Distillation yielded 10.5 g. of a yellow oil, b.p. 85–108° (1.6 mm.) which did not solidify and 56 g., b.p. 109–114° (1.6 mm.) which was obtained as a sticky white solid, m.p. 93–97°. Redistillation gave 52 g. (66%), b.p. 109–112° (1.6 mm.), m.p. 95–96°.

Anal. Calcd. for $C_8H_{18}ON_2$: C, 60.72; H, 11.46; N, 17.71. Found: C, 61.04; H, 11.43; N, 17.89.

Preparation of II. To a stirred solution of 60 g. (0.26 mole) of I in 500 ml. of dry benzene at 55° was added during one hour 23 ml. (0.27 mole) of oxalyl chloride. One half of the theoretical amount of hydrogen chloride had been evolved at the end of this time. The mixture was then stirred for two hours at 55°. After cooling, the yellow precipitate was filtered with suction. Upon washing with benzene and then with petroleum ether a white residue of starting material remained. Distillation of the yellow filtrate to dryness under diminished pressure left 45 g. of a yellow solid, m.p. 169–175°. Recrystallization from 1:1 toluene-ligroin gave 42.5 g. (53%) of a yellow crystalline substance, m.p. 175–176°.

Anal. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.88; H, 5.27; N, 9.26.

Reaction of II with ethanol. A solution of 1.0 g. of II in 30 ml. of 95% ethanol was refluxed for 24 hr. No crystalline product separated on cooling. After the solution was concentrated under diminished pressure to one-third of its volume 0.2 g. of a white compound, m.p. 59–60°, was obtained. Addition of water to the filtrate caused the precipitation of 0.4 g. more of the same substance. Saponification gave diphenylacetic acid, m.p. 148°. The substance when mixed

(1) Glenn S. Skinner and Richard E. Ludwig, *J. Am. Chem. Soc.*, **78**, 4656 (1956).

with an authentic sample of ethyl diphenylacetate gave no depression in the melting point. Identical results were obtained using both 90% and absolute ethanol and varying the time of reflux from 8 to 30 hr.

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2,2′,4- and 2,2′,6-Trihydroxybenzophenone

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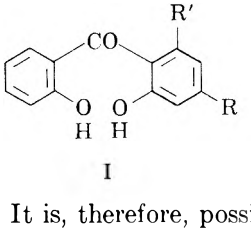
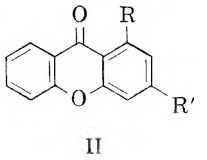
We have applied Grover, Shah, and Shah's[1] new synthesis of polyhydroxyxanthones to the preparation of 1-hydroxy-9-xanthenone[2] which is obtained in low yields by the usual methods.[3,4] Condensation of salicylic acid and resorcinol in the presence of anhydrous zinc chloride and phosphoryl chloride yielded a trihydroxybenzophenone. This substance has the same melting point as, and similar solubility properties to, 2,2′,6-trihydroxybenzophenone obtained by Michael[3] by fusing the same reactants in the absence of a condensing agent. Michael's compound was assigned the structure of 2,2′,6-trihydroxybenzophenone (I; R = H; R′ = OH) because it cyclized with zinc chloride to give 1-hydroxy-9-xanthenone (II; R = OH; R′ = H).[3,5] Our product, however, could not be made to cyclize with zinc chloride, but gave a quantitative yield of 3-hydroxy-9-xanthenone (II; R = H; R′ = OH), when heated with water in a sealed tube at 200–250°. This benzophenone is thus proved to be 2,2′,4-trihydroxybenzophenone (I; R = OH; R′ = H). Moreover the nonidentity of the two ketones was confirmed by a depression in their melting points and those of their triacetyl derivatives on admixture.



I



II

It is, therefore, possible by varying the reaction conditions to obtain either 2,2′,4- or 2,2′,6-trihydroxybenzophenone from the same reactants. The formation of 2,2′,4-trihydroxybenzophenone in the presence of phosphoryl chloride and zinc chloride is consistent with the findings of Grover, Shah, and Shah[1] who report that under these conditions hydroxybenzoic acids will substitute the resorcinol nucleus in the β-position only.

2,2′,4-Trihydroxybenzophenone has been previously mentioned by Atkinson and Heilbron[6] in connection with a by-product isolated from their preparation of 3-hydroxy-9-xanthenone (II; R = H; R′ = OH). No structural evidence was, however, given, except that, by drawing attention to its similarity to Michael's compound, the identity of the two substances was implied.

EXPERIMENTAL[7]

2,2′,4-Trihydroxybenzophenone. Salicylic acid (5 g.), resorcinol (6 g.), anhydrous zinc chloride (20 g.), and phosphoryl chloride (25 cc.) were heated on a water bath at 75–80° for 2 hr. The deep-red reaction mixture was poured onto crushed ice (400 cc.) containing concentrated hydrochloric acid (25 cc.). A red gum formed on standing and its mother liquor A was decanted off. On triturating the residue with aqueous sodium hydrogen carbonate an orange solid was obtained which yielded on recrystallization from water and from petroleum ether (b.p. 100–120°) 2,2′,4-trihydroxybenzophenone, m.p. 133° (0.37 g.) as colorless plates. More ketone (1.85 g.) was obtained from mother liquor A which deposited it as yellow needles on standing for 2 days and by acidification of the sodium hydrogen carbonate extract.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.8; H, 4.4. Found: C, 68.1; H, 4.4.

The ketone gives a deep red ferric color in water and dissolves in alkali to form a yellow solution. The triacetate was obtained in the usual way and crystallized from a mixture of ethyl acetate and petroleum ether (b.p. 40–60°) as blunt needles, m.p. 69–70°.

Anal. Calcd. for $C_{19}H_{16}O_7$: C, 64.0; H, 4.5. Found: C, 64.0; H, 4.7.

3-Hydroxy-9-xanthenone. 2,2′,4-Trihydroxybenzophenone (0.4 g.) and water (1.5 cc.) were heated in a sealed tube (50 cc.) for 2.5 hr. at 200–250°. Crude 3-hydroxy-9-xanthenone was obtained in theoretical yield as a yellow crystalline residue, m.p. 238–241°. Recrystallization from aqueous ethanol yielded the xanthone as white needles, m.p. 242° (Atkinson and Heilbron[6] give m.p. 246°).

Anal. Calcd. for $C_{13}H_8O_3$: C, 73.6; H, 3.8. Found: C, 73.8; H, 4.0.

The acetyl derivative had m.p. 156°. Kostanecki and Rutishauser[8] give m.p. 157–158°.

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 71.3; H, 4.0. Found: C, 71.1; H, 4.0.

Attempts to cyclize 2,2′,4-trihydroxybenzophenone with fused zinc chloride gave only starting material.

2,2′,6-Trihydroxybenzophenone was prepared as described by Michael.[3] The product crystallizes from petroleum ether (b.p. 100–120°) as white plates, m.p. 134–135° (Michael[3] gives m.p. 133–134°). Its mixed melting point with 2,2′,4-trihydroxybenzophenone was depressed.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.8; H, 4.4. Found: C, 67.7; H, 4.4.

The triacetate prepared by the acetic anhydride–pyridine method crystallized as blunt needles, m.p. 80–81° from a mixture of ethyl acetate and petroleum ether (b.p. 40–60°).

* Deceased.

(1) P. K. Grover, G. D. Shah, and R. C. Shah, *Chemistry & Industry*, 62 (1955); *J. Chem. Soc.*, 3982 (1955).

(2) 1-Hydroxy-9-xanthenone was needed for other work: see J. S. H. Davies, F. Scheinmann, and H. Suschitzky, *J. Chem. Soc.*, 2140 (1956).

(3) A. Michael, *Am. Chem. J.*, **5**, 81 (1883).

(4) K. S. Pankajamani and T. R. Seshadri, *J. Sci. Ind. Research (India)*, **13B**, 396 (1954).

(5) E. Dreher and St. v. Kostanecki, *Ber.*, **26**, 71 (1893).

(6) H. Atkinson and I. M. Heilbron, *J. Chem. Soc.*, 2688 (1926).

(7) All melting points are uncorrected. The analyses were done by Drs. Weiler and Strauss, Oxford.

(8) St. v. Kostanecki and R. Rutishauser, *Ber.*, **25**, 1651 (1892).

The mixed melting point with 2,2',4-triacetoxybenzophenone was depressed.

Anal. Calcd. for $C_{19}H_{16}O_7$: C, 64.0; H, 4.5. Found: C, 64.2; H, 4.3.

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The Stobbe Condensation on *p*-Methoxy-*m*-methylisobutyrophenone

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The substances described were prepared in preliminary experiments directed toward 7-hydroxy-1,6-dimethyl-4-isopropylnaphthalene whose unambiguous synthesis,[2] serving to confirm the structure of the sesquiterpene copaene,[3] was accomplished while this work was in progress. We therefore wish merely to record the results of these experiments which were discontinued at that time. The products obtained are intermediates in an adaptation of the general "tetralone" scheme developed by Johnson and coworkers.[4] Methyl *o*-cresyl ether readily entered into the Friedel-Crafts reaction with isobutyryl chloride to produce *p*-methoxy-*m*-methylisobutyrophenone. The use of carbon disulfide which gives inferior results with similar phenolic ethers in the reaction with succinic anhydride,[5] gave good yields in the present case. The crystalline acid ester, 3-carbomethoxy-4-(*p*-methoxy-*m*-tolyl)-5-methyl-3-hexenoic acid, was obtained in the Stobbe condensation with dimethyl succinate and sodium hydride. The assignment of the ethylenic linkage to the 3 position is in accord with the infrared absorption spectrum which exhibited in addition to the carboxyl band (5.79 μ) the maxima characteristic of the conjugated ester carbonyl and double bond (5.82, 6.11 μ).[6] The diacid was also prepared by saponification. Upon recrystallization from hot benzene–petroleum ether a small amount of a lower melting substance was isolated which is apparently the corresponding cyclic anhydride. A similar behavior has been noted for γ,γ-di-*p*-methoxyphenylitaconic acid,[7] which is a close electronic and steric analog.

EXPERIMENTAL[8]

p-Methoxy-m-methylisobutyrophenone.[9] To a well stirred ice-cooled mixture of 135.8 g. (1.04 moles) of anhydrous aluminum chloride and 160 ml. of dry carbon disulfide, 111 g. (1.04 moles) of carefully fractionated isobutyryl chloride[10] was added slowly, followed by 91.0 g. (0.745 mole) of *o*-methyl cresyl ether. The ether must be added cautiously to keep the copious evolution of gas under control. The mixture was stirred at 0° for 15 hr. and allowed to warm up to room temperature. Following cautious treatment with 400 ml. of ice and water, and 200 ml. of concentrated hydrochloric acid, most of the carbon disulfide was removed at reduced pressure. The product was extracted with ether, washed thoroughly with 5% sodium hydroxide, water, and dried over magnesium sulfate and freed from solvent. The residual oil from two such runs was distilled roughly under nitrogen and fractionated through a five-plate modified Widmer column to give 231 g. (81%) of the colorless ketone, b.p. 110–115° at 0.5 mm., m.p. 22–23°.

The *semicarbazone* was readily obtained in pyridine-methanol, melting at 143–145° after one recrystallization from aqueous methanol, and finally at 144–145°; λ_{max}^{Nujol} 5.92μ.[11]

Anal. Calcd. for $C_{13}H_{19}O_2N_3$: C, 62.62; H, 7.68. Found: C, 62.75, 62.70; H, 7.55, 7.55.

The *2,4-dinitrophenylhydrazone* crystallized from aqueous methanol in yellow blades, m.p. 151–152°.

3-Carbomethoxy-4-(p-methoxy-m-tolyl)-5-methyl-3-hexenoic acid. The Stobbe condensation[4] was run in dry benzene using 9.6 g. (0.05 mole) of the foregoing ketone, 26.1 (0.18 mole) of dimethyl succinate, and 2.9 g. (0.12 mole) of granular sodium hydride. The reactants were mixed all at once under dry nitrogen in an apparatus provided for entry and exit of gases and measurement of evolved hydrogen. It was necessary to add a few drops of methanol and to reflux the mixture for a few minutes to induce a steady evolution of hydrogen, which then continued at room temperature for approximately 26 hr.

Excess acetic acid was added cautiously, followed finally by water and ether, and the product was isolated by extraction with a 5% solution of sodium bicarbonate followed by acidification and re-extraction with ether. Drying over magnesium-sulfate and removal of solvent left a semi-crystalline solid, m.p. 95–105° from which one pure stereoisomer was obtained by successive recrystallization from benzene–petroleum ether (b.p. 30–60°), water, and hexane; 3.37 g. (22%); m.p. 120–121°; λ_{max}^{Nujol} 5.79, 5.82, 6.11μ.[11]

Anal. Calcd. for $C_{16}H_{21}O_3COOH$: C, 66.65, H, 7.24: neut. equiv., 306.4. Found: C, 66.88, 67.28; H, 7.44, 7.30; neut. equiv., 306.4, 309.0.

In separate experiments in which more methanol was used in priming, or glass marbles were added for pulverizing action,[12] the initial heating period was not required and the

(1) From the M.A. thesis of Ann Donaldson, 1949.

(2) L. H. Briggs, N. S. Gill, F. Lyons, and W. I. Taylor, *J. Chem. Soc.*, 1098 (1949).

(3) L. H. Briggs and W. I. Taylor, *J. Chem. Soc.*, 1338 (1947).

(4) W. S. Johnson and G. H. Daub, *Org. Reactions*, VI, 34 (1951); W. S. Johnson and A. R. Jones, *J. Am. Chem. Soc.*, 69, 792 (1947).

(5) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, 58, 2314 (1936).

(6) R. S. Rasmussen and R. R. Brattain, *J. Am. Chem. Soc*, 71, 1073 (1949).

(7) W. S. Johnson and M. W. Miller, *J. Am. Chem. Soc.*, 72, 511 (1950).

(8) Temperature readings are uncorrected.

(9) The orientation of the acyl function is assigned by analogy [*cf.* reference 5; G. Stadnikoff and A. Baryschewa, *Ber.*, 61, 1996 (1928); W. P. Campbell and M. D. Soffer, *J. Am. Chem. Soc.*, 64, 417 (1942)].

(10) R. E. Kent and S. M. McElvain, *Org. Syntheses*, 25, 58-60 (1941).

(11) We are indebted to Mr. Philip Sadtler of Samuel P. Sadtler and Son, Philadelphia, Pa., for the infrared determination.

(12) N. Green and F. B. LaForge, *J. Am. Chem. Soc.*, 70, 2287 (1948).

rate of gas evolution was markedly increased but the yield of pure product was somewhat decreased (13–16%).

3-Carboxy-4-(p-methoxy-m-tolyl)-5-methyl-3-hexenoic acid. The crude diacid (16.5 g., m.p. 114–116°) was refluxed for 6.5 hr. in 10% sodium hydroxide. The semicrystalline product isolated in the usual way (13 g., 83%) gave on recrystallization from benzene–petroleum ether (b.p. 90–100°) 9.5 g. of one relatively pure stereoisomer, m.p. 155–156°. Further recrystallization from the same solvent, aqueous methanol, and benzene-hexane gave the pure diacid, m.p. 162–163°. The same product was obtained in a preliminary experiment on the pure half ester.

Anal. Calcd. for $C_{14}H_{18}O(COOH)_2$: neut. equiv., 146.2. Found, neut. equiv., 146.6, 146.8.

From the preceding benzene petroleum ether mother liquors there was isolated 1.0 g. of crystalline material m.p. 119–120° which has the composition of *γ-(p-methoxy-m-tolyl)-γ-isopropylitaconic anhydride.* The melting point changes on exposure to air, apparently by absorption of moisture. A pure sample was prepared by repeated recrystallization from benzene–petroleum ether; m.p. 121–121.5°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C 70.33, 70.59; H, 6.53, 6.81.

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Glycol Esters of 3-Alkoxypropionic Acids

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The probability that glycol esters of 3-alkoxypropionic acids would be useful as plasticizers and lubricants prompted the synthesis of a number of these materials.

While the preparation of numerous monohydric esters of 3-alkoxypropionic acids by the base-catalyzed addition of an alcohol to an alkyl acrylate has been previously reported,[1,2] the synthesis of a glycol ester appears to be novel.

TABLE I

3-ALKOXYPROPIONIC ACIDS: R—O—$CH_2CH_2CO_2H$

R	B.P.,[3] °C.	Mm.	n_D^{30}
CH_2=$CHCH_2$—	110	5	1.4383
$(CH_3CH_2)_2CHCH_2$—	144	10	1.4301
$CH_3(CH_2)_3(CH_3CH_2)CHCH_2$—	142	5.5	1.4350

R	d_{20}^{20}	Purity, %[a]	Yield, %
CH_2=$CHCH_2$—	1.0562	98.1	73
$(CH_3CH_2)_2CHCH_2$—	0.9641	95.8	85
$CH_3(CH_2)_3(CH_3CH_2)CHCH_2$—	0.9248	99.7	82

[a] Based on titration with 0.1*N* sodium hydroxide.

(1) M. B. Dixon, C. E. Rehberg, and C. H. Fisher, *J. Am. Chem. Soc.*, **70**, 3733 (1948).

(2) C. E. Rehberg, M. B. Dixon, and C. H. Fisher, *J. Am. Chem. Soc.*, **69**, 2966 (1947).

(3) All temperatures are uncorrected.

TABLE II

GLYCOL ESTERS OF 3-ALKOXYPROPIONIC ACIDS: $(ROCH_2CH_2CO_2)_2R'$

R	R′	B.P., °C./mm.	n_D^{30}	d_{20}^{20}	Purity,[a] %	Yield, %	Calcd., % C	Calcd., % H	Found, % C	Found, % H
$CH_3(CH_2)_3(CH_3CH_2)CHCH_2$—	—CH_2CH_2—	154/0.2[b]	1.4439	0.9582	98.8	75	67.0	10.7	66.9	10.6
$CH_3(CH_2)_3(CH_3CH_2)CHCH_2$—	$O(CH_2CH_2-)_2$	180/0.2[b]	1.4464	0.9747	101	81	65.8	10.5	65.5	10.4
$CH_3(CH_2)_3(CH_3CH_2)CHCH_2$—	—$(CH_2)_6$—	181/0.25[b]	1.4472	0.9455	100	94	67.8	11.1	68.1	10.8
$(CH_3CH_2)_2CHCH_2$—	—$(CH_2CH(CH_3)O-)_2$	Residue	1.4431	0.9860	98.5	99	63.5	10.2	63.5	10.4
CH_2=$CHCH_2$—	—CH_2CH_2—	180/0.8	1.4533	1.0876	104.6	16	58.7	7.74	58.3	7.45

[a] Based on saponification and titration with 0.1*N* hydrochloric acid. [b] Falling film molecular still.

3-Alkoxypropionic acids were readily prepared by the cyanoethylation of an alcohol[4] and hydrolysis of the 3-alkoxypropionitrile thus formed with mineral acid.[5] Esterification was accomplished by the usual azeotropic technique. Physical properties for the several 3-alkoxypropionic acids are given in Table I and the data concerning the glycol esters are shown in Table II.

Acknowledgment. The author is grateful to Messrs. H. C. Shue and J. Smith, Jr. for technical assistance.

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(4) H. A. Bruson, *Org. Syntheses*, V, 122 (1948).
(5) R. V. Christian and R. M. Hixon, *J. Am. Chem. Soc.*, 70, 1334 (1948).

Cyclic Peroxide By-product from the Alkaline Epoxidation of Mesityl Oxide

GEORGE B. PAYNE

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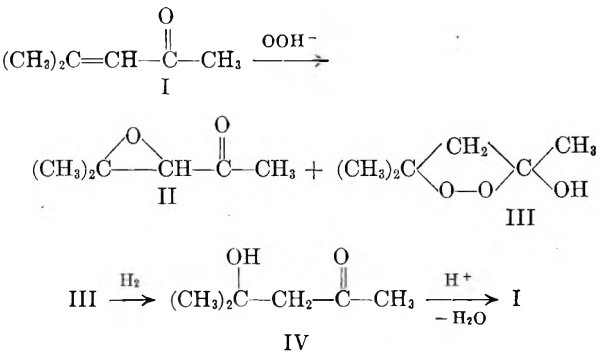
The alkaline epoxidation of mesityl oxide, 4-methyl-3-penten-2-one (I), to give 3,4-epoxy-4-methyl-2-pentanone (II), has been carried out several times in the past.[1] Nazarov and Akhrem,[1d] however, were the only ones to separate and purify a slightly higher boiling by-product. They established its formula as $C_6H_{11}O_2(OH)$ by carbon and hydrogen and hydroxyl analysis.

Using a modification of the procedure employed by Wilder and Dolnick[1b] we have carried out the epoxidation of mesityl oxide and obtained the high boiling impurity in 3% yield along with an 85% yield of II. Its structure has been established as 3-hydroxy-3,5,5-trimethyl-1,2-dioxacyclopentane (III) by ultimate analysis, peroxide titration, qualitative reaction with ferrous ion and by quantitative hydrogenation to 4-methyl-4-hydroxy-2-pentanone (IV). The latter, when allowed to react with 2,4-dinitrophenylhydrazine under acidic conditions, afforded the 2,4-dinitrophenylhydrazone of mesityl oxide (I). An authentic sample of IV exhibited this same behavior.

(1) (a) Weitz and Scheffer, *Ber.*, 54, 2327 (1921); (b) Wilder and Dolnick, U. S. Patent 2,431,718 (Dec. 2, 1947); (c) Bunton and Minkoff, *J. Chem. Soc.* 665 (1949); (d) Nazarov and Akhrem, *J. Gen. Chem.* (*U.S.S.R.*), 20, 2183 (1950); *Chem. Abstr.*, 45, 7062 (1950); (e) House and Wasson, *J. Am. Chem. Soc.*, 78, 4394 (1956).



The infrared spectrum of III, with the exception of the presence of a strong band for hydroxyl, was markedly similar to that recently given for 3,3,5,5-tetramethyl-1,2-dioxacyclopentane.[2]

EXPERIMENTAL

3-Hydroxy-3,5,5-trimethyl-1,2-dioxacyclopentane (III) *and 3,4-epoxy-4-methyl-2-pentanone* (II). To a 3-l. round-bottom flask equipped with stirrer, thermometer, and dropping funnel were charged 450 ml. of water and 392 g. (4.0 moles) of freshly distilled mesityl oxide. With stirring was added a solution of 8 g. of sodium hydroxide in 100 ml. of water followed by 5 g. of magnesium sulfate dissolved in 50 ml. of water. With vigorous stirring and ice bath–cooling to maintain a temperature of 25–30°, there was then added 555 g. (5.0 moles) of 30% hydrogen peroxide over a period of 40 min. After stirring an additional 2 hr., 200 g. of sodium sulfate was added followed, 0.5 hr. later, by 400 ml. of benzene. After another 0.5 hr. of stirring, excess salt was removed by filtration and washed with 50 ml. of benzene. Distillation of the benzene layer of the filtrate through a 10-tray Oldershaw column afforded 387 g. (85%) of *3,4-epoxy-4-methyl-2-pentanone*, b.p. 61–62° (20 mm.); n_D^{20} 1.4235 (reported[1b] values: b.p. 155.5–157.5°; n_D^{20} 1.4238).

The 28 g. residue from the above distillation was distilled through an 18-in. glass spiral packed column to give 16 g. (3%) of *3-hydroxy-3,5,5-trimethyl-1,2-dioxacyclopentane*, b.p. 69–70° (10 mm.); n_D^{20} 1.4320 (reported[1d] values: b.p. 79–81°/15 mm.; n_D^{20} 1.4328).

The infrared spectrum exhibits strong bands at 2.91μ (hydroxyl) and at 6.88, 7.32, 7.68, 10.31, 11.25, 11.52 (probably O—O stretching) and 12.6μ. 3,3,5,5-Trimethyl-1,2-dioxacyclopentane is reported[2] to exhibit strong bands at 6.86, 7.32, 7.67, 11.47, and 12.55μ along with weaker bands at 10.28 and 11.22μ.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.5; H, 9.2; active O, 12.1. Found: C, 54.5; H, 9.2; active O, 11.8.[3]

Reaction of III with hydrogen. Conversion to 4-methyl-4-hydroxy-2-pentanone (IV). Ten g. of cyclic peroxide III (0.076 mole) and 100 ml. of methanol were charged to a 450 ml. capacity glass hydrogenation bottle along with 1 g. of 5% palladium on barium sulfate catalyst. The mixture was shaken at room temperature with hydrogen at a starting pressure of 50 lb. Within 1 hr., 0.074 mole of hydrogen had been absorbed and the rate of uptake was then very slow. Distillation of the filtered solution afforded 7.2 g. of *4-methyl-4-hydroxy-2-pentanone*, b.p. 56–61° (10 mm.); n_D^{27} 1.4204. The refractive index of Eastman Kodak Co. White Label diacetone alcohol, taken at the same time, was n_D^{27} 1.4200.

(2) Criegee and Paulig, *Ber.*, 88, 712 (1955).
(3) Sample heated with 56% aqueous hydrogen iodide in glacial acetic acid at 60° for 45 minutes, liberated iodine titrated with standard thiosulfate; milder methods of analysis gave lower values.

The 2,4-dinitrophenylhydrazone[4] of the distillate melted initially at 175–180°, but after two recrystallizations from ethyl acetate it melted at 196–197°. The 2,4-DNP prepared from authentic diacetone alcohol exhibited the same melting point behavior. The mixed melting point between the two recrystallized samples was not depressed. A mixed melting point with the 2,4-DNP prepared from I (m.p. 196–197°) was also not depressed.

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(4) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York 1948, p. 143.

Bromination of Naphthalene with Dioxane Dibromide

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Yanovskaya[1,2] has reported the quantitative preparation of 1,4-dibromonaphthalene by the reaction of naphthalene with dioxane dibromide in a one to two mole ratio, at 40°. We have attempted this preparation and find that it is neither quantitative nor specific for the 1,4-dibromonaphthalene, 1,5-dibromonaphthalene and 2-bromonaphthalene also being formed.

EXPERIMENTAL

The bromination was studied varying the temperature and the time of the reaction. In two runs, solutions of the products were analyzed by means of infrared spectrophotometry. The absorption frequencies (in wave numbers) used for analysis are: naphthalene, 782, 955, 1010; 1-bromonaphthalene, 768, 794; 2-bromonaphthalene, 742, 812, 887; 1,4-dibromonaphthalene, 760, 823; 1,5-dibromonaphthalene, 704, 782.

Bromine, 17.0 g. was added to 9.5 g. of dioxane (0.106 moles of dioxane dibromide) in a 100 ml. round-bottom flask. To this solid complex, 6.4 g. (0.05 moles) of naphthalene was added. The reaction began immediately, the mixture turned a deep red, the temperature rose to 39° and HBr fumes were evolved. The mixture was stirred periodically for 3 hr. and some solid formed; it was left standing overnight. After being made basic to litmus with 10% NaOH, white crystals formed and were filtered, washed with water, and recrystallized from 95% ethanol. The yield was 9.9 g. of crude material, (70%) and had a melting point of 77–80°. It contained about 78% of the 1,4-isomer, the balance being the 1,5-isomer with a trace of 1-bromonaphthalene.

The above crude product was recrystallized twice from absolute methanol. The melting point was 83–83.5°. The infrared spectrum showed trace amounts of impurities.

Dioxane dibromide, 24.8 g. (0.1 moles) was added to 6.4 g. of naphthalene (0.05 moles) in a 300 ml., three neck round-bottom flask. Two of the necks were left open so that there was ample room for the HBr to escape. After standing an hour, the liquid mixture was stirred and maintained at 40° for 6 hr. by means of a water bath. It was then allowed to stand overnight. The reaction mixture was neutralized with 10% NaOH and filtered. A white crystalline residue (7.240 g.) was air dried. It contained about 95% 1,4-dibromonaphthalene, the remainder being the 1,5-isomer and 1-bromonaphthalene. The oil, (3.6068 g.) from the above filtration, was washed with water, and taken up in ether. A qualitative analysis showed it to be mainly 1-bromonaphthalene and 1,4-dibromonaphthalene. There was estimated to be about 10% 1,5-dibromonaphthalene and about 5% 2-bromonaphthalene in the oil.

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(1) L. A. Yanovskaya, *Doklady Akad. Nauk SSSR*, **17**, 693 (1950).

(2) A. P. Terent'ev, L. I. Belen'kii, and L. A. Yanovskaya, *Zhur. Obshchei Khim.*, **24**, 1265 (1954).

Nitration of Amines with Dinitrogen Pentoxide[1]

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In spite of the fact that dinitrogen pentoxide, N_2O_5, has been known for many years, its use as an alkaline nitration reagent for amines has not been investigated generally. A number of aromatic amines have been converted to the corresponding nitramines with dinitrogen pentoxide[4,5] but other than a report that triethylamine and dinitrogen pentoxide form an unstable explosive complex,[6] aliphatic amines do not appear to have been investigated.

It has been found that secondary aliphatic amines react smoothly with dinitrogen pentoxide to give secondary nitramines in excellent yields.

$$2R_2NH + N_2O_5 \longrightarrow R_2NNO_2 + R_2NH_2^+NO_3^-$$

The reactions were carried out by addition of dinitrogen pentoxide in carbon tetrachloride solution to excess amine also in carbon tetrachloride at −25°. Yields obtained with a number of amines are summarized in Table I. The yields of nitramines obtained in this way are excellent testimony to the effectiveness of dinitrogen pentoxide for the preparation of secondary nitramines. This is particularly true for the branched secondary amines which gave essentially quantitative conversions to the nitramines; it will be recalled that acetone cyanohydrin nitrate was virtually ineffective with those

(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

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(4) E. Bamberger, *Ber.*, **27**, 584 (1894); **28**, 397 (1895).

(5) E. Hoff, *Ann.*, **311**, 91 (1900).

(6) L. B. Haines and H. Adkins, *J. Am. Chem. Soc.*, **47**, 1419 (1925).

amines having high steric requirements such as diisopropylamine.[7]

TABLE I

NITRATION OF SECONDARY AMINES WITH DINITROGEN PENTOXIDE

Nitramine	Yield, %	B.P., °C.	n_D^{20}
Nitropiperidine[a]	64	120 (20 mm.)	1.4960
Diisopropyl[b]	91	M.p. 105–106°	
Di-*n*-propyl[c]	84	106–108 (9 mm.)	1.4540
Diisobutyl[d]	97	M.p. 80–82°	
Nitromorpholine[e]	91	M.p. 50–52°	
Diethyl[f]	81	38° (0.05 mm.)	1.4523
Nitropyrrolidine[g]	91	M.p. 58–59°	

[a] Lit. b.p. 62–64° (0.2 mm.), n_D^{20} 1.4968 (ref. 7). [b] G. F. Wright, *et al.*, *Can. J. Research*, *26B*, 114 (1948) report m.p. 108–108.5°. [c] Lit. b.p. 90–92° (8 mm.), n_D^{20} 1.4558 (ref. 7). [d] Lit. m.p. 79–80° (ref. 7). [e] Lit. m.p. 51–53° (ref. 7). [f] Lit. b.p. 50–52° (0.2 mm.), n_D^{20} 1.4525. [g] Lit. m.p. 55–57° (ref. 7).

The nitration of primary amines took a somewhat different course. *n*-Octylamine yielded octyl nitrate as the major product isolated. Only a trace of nitramine was formed. No appreciable nitramine was produced from cyclohexylamine or hexylamine and dinitrogen pentoxide. In order to investigate the possibility that primary nitramines are destroyed by dinitrogen pentoxide under these relatively mild reaction conditions (the acid-catalyzed decomposition of primary nitramines is well known),[8] *n*-octylnitramine was allowed to react with dinitrogen pentoxide in carbon tetrachloride at −25° both in the presence and absence of excess *n*-octylamine. In both cases about 55% of the *n*-octylnitramine was recovered. Octyl nitrate and smaller amounts of unidentified products, including a solid material, were obtained. These results suggest that N_2O_5 will cause the acid-catalyzed decomposition of primary nitramines; however, from the limited amount of experimental data available it cannot be ascertained whether or not the nitramine is a primary product of the reaction.

The reaction of dinitrogen pentoxide with tertiary amines was examined briefly. It was hoped that the reported insoluble complexes formed from a tertiary amine and dinitrogen pentoxide,[6] presumably the nitronium nitrate salt of the amine, would be good alkaline nitration reagents.

$$R_3N + N_2O_5 \longrightarrow R_3NNO_2^+, NO_3^-$$

It was found, however, that the complexes formed by pyridine, 2-chloropyridine or triethylamine and dinitrogen pentoxide would not nitrate secondary amines.

(7) W. D. Emmons and J. P. Freeman, *J. Am. Chem. Soc.*, **77**, 4387 (1955).

(8) J. Barrett, I. N. Denton, and A. H. Lamberton, *J. Chem. Soc.*, 1798 (1953).

EXPERIMENTAL

Dinitrogen pentoxide. For most of the experiments reported here dinitrogen pentoxide was prepared from trifluoroacetic anhydride and absolute nitric acid.[9] The material was recrystallized from carbon tetrachloride-methylene chloride at −50° and dried in a stream of dry nitrogen. The sample was then dissolved in carbon tetrachloride at −10° to 0°, and an aliquot hydrolyzed and titrated with standard base to determine the dinitrogen pentoxide concentration. A more satisfactory procedure for the preparation of larger quantities of dinitrogen pentoxide free of trifluoroacetic anhydride is that given in *Inorganic Syntheses*.[10,11] This method has been outlined elsewhere.[12]

Nitration of secondary amines. The yields of secondary nitramines obtained from dinitrogen pentoxide and a secondary amine by the procedure given below for diisopropylnitramine are shown in Table I. A solution of 0.069 mole of dinitrogen pentoxide in 200 ml. of carbon tetrachloride was added over 15 min. to 20 g. (0.2 mole) of diisopropylamine in 150 ml. of carbon tetrachloride cooled to −30°. The reaction was maintained between −30° and −20° throughout the addition by means of a Dry Ice-acetone bath. The solution was allowed to warm to 0°, and the organic layer was then washed with 10% hydrochloric acid solution and water. The organic layer was dried over magnesium sulfate and then evaporated to give 9.2 g. (91%) of diisopropylnitramine, m.p. 100–105°. After recrystallization from aqueous ethanol the sample melted at 105–106°.

Dinitrogen pentoxide and n-octylamine. A solution of 38 g. (0.3 mole) of *n*-octylamine in 150 ml. of carbon tetrachloride was cooled to −30°, and 0.070 mole of dinitrogen pentoxide in 200 ml. of carbon tetrachloride was added over 15 min. while the temperature of the reaction mixture was maintained between −20 and −30°. The reaction mixture was allowed to come to room temperature, and then 250 ml. of 10% potassium hydroxide was added and the mixture stirred for 30 min. The aqueous layer was separated, acidified at 0° with 10% sulfuric acid, and extracted with ether. The ether extract was washed with water and dried over magnesium sulfate. Evaporation of the ether left 0.9 g. of a red oil whose infrared spectrum indicated it was mainly *n*-octylnitramine. The carbon tetrachloride solution was washed with 10% hydrochloric acid and water and dried over magnesium sulfate. Evaporation of the carbon tetrachloride left a red oil containing some solid material. After addition of 30 ml. of petroleum ether, the solution was filtered to give 1.5 g. of a white solid, m.p. 89–91°. After recrystallization from ethanol the solid, whose identity has not been established, melted at 90–91°.

Anal. Found: C, 72.37, 72.48; H, 12.75, 13.24; N, 8.96, 8.87.

The petroleum ether was removed from the filtrate, and the red oil remaining was distilled through a Holzman column to give forerun, b.p. 82–95° (20 mm.), 1.5 g., and *n*-octyl nitrate, b.p. 96–106° (20 mm.), 4.5 g. (37%), n_D^{20} 1.4284.

Dinitrogen pentoxide and n-octylnitramine. A solution of 6.5 g. (0.037 mole) of *n*-octylnitramine in 100 ml. of carbon tetrachloride was treated with 0.040 mole of dinitrogen pentoxide in the manner described above for *n*-octylamine.

(9) J. H. Robson, *J. Am. Chem. Soc.*, **77**, 107 (1955).

(10) L. F. Audrieth, *Inorganic Syntheses*, Vol. III, McGraw-Hill Book Company, New York (1950), p. 78.

(11) Although many experiments were carried out using carbon tetrachloride as the solvent for dinitrogen pentoxide, methylene chloride appeared to be the solvent of choice.[12] The greater solubility of dinitrogen pentoxide in the latter solvent allowed one molar solutions to be handled readily.

(12) T. E. Stevens and W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 6008 (1957).

From the potassium hydroxide extract was recovered 3.5 g. (54%) of *n*-octylnitramine. From the carbon tetrachloride solution was obtained 1.7 g. of liquid whose infrared spectrum showed nitrate ester absorption.

When dinitrogen pentoxide (0.065 mole) was added to a mixture of *n*-octylamine (17.0 g., 0.13 mole) and *n*-octylnitramine (11.5 g., 0.066 mole) in the above manner, there was obtained 6.5 g. of *n*-octylnitramine, 2.2 g. of the unidentified solid, and 7.0 g. of residue whose infrared spectrum indicated it was mainly *n*-octyl nitrate.

Dinitrogen pentoxide, triethylamine and diisopropylamine. A solution of 0.070 mole of dinitrogen pentoxide in 200 ml. of carbon tetrachloride was added to 20.2 g. (0.20 mole) of triethylamine in 150 ml. of carbon tetrachloride at −30°. The solution turned red. After complete addition of the dinitrogen pentoxide, 20.2 g. (0.20 mole) of diisopropylamine was added dropwise. The solution was allowed to warm to room temperature and then washed with water, 10% hydrochloric acid, and again with water. After drying over magnesium sulfate, the carbon tetrachloride was removed to leave only 0.2 g. of residue. Similar results were obtained when the dinitrogen pentoxide-triethylamine solution was allowed to warm to 20° before addition of the diisopropylamine, and when the dinitrogen pentoxide was added to a triethylamine–diisopropylamine mixture.

Dinitrogen pentoxide, pyridine and diisopropylamine. A solution of 3.3 ml. (0.041 mole) of pyridine in 50 ml. of methylene chloride was cooled to −20° and 0.037 mole of dinitrogen pentoxide in 30 ml. of methylene chloride was added dropwise. A white solid precipitated. The mixture was stirred 5 min. at −20° after addition of the dinitrogen pentoxide, and then 11.2 ml. (0.08 mole) of diisopropylamine was added dropwise. The reaction mixture slowly turned a deep red. When the reaction mixture had warmed to 0°, 10% hydrochloric acid was added and the organic layer was then separated and washed with water. Evaporation of the methylene chloride left 1.5 g. of a dark residue, the infrared spectrum of which indicated no secondary nitramine was present.

Dinitrogen pentoxide, 2-chloropyridine and diisopropylamine. When dinitrogen pentoxide (0.045 mole) in methylene chloride (30 ml.) was added to 2-chloropyridine (0.10 mole) in 60 ml. of methylene chloride at −20° there was a yellowing of the solution but no solid precipitated. Diisopropylamine (0.10 mole) was then added, and the reaction worked up as in the case of pyridine. There was no evidence for the formation of diisopropylnitramine.

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Bromination in the Thianthrene System

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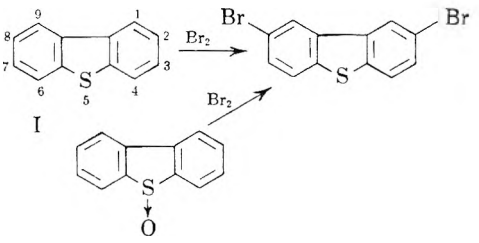
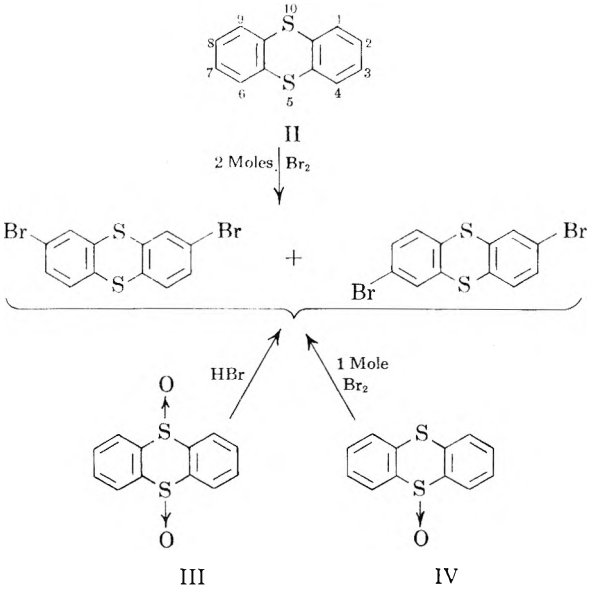
Successful bromination of heterocycles is of significance in synthetic organic chemistry since the bromo derivatives can be converted to the corresponding carboxylic acids, boronic acids, silanes, amines, and phenols through a halogen-metal interconversion reaction followed by treatment with carbon dioxide, tri-*n*-butyl borate, chlorotriphenylsilane, methoxylamine, and oxygen, respectively. Dibenzothiophene (I) brominates in the 2,8-positions.[1] The 2,8-dibromodibenzothiophene is also obtained by the action of bromine on dibenzothiophene-5-oxide,[2] a reaction in which the sulfoxide undergoes bromination accompanied by reduction.



Thianthrene (II) reacts[3] with a molar equivalent of bromine to give a fair yield of 2-bromothianthrene, and with two molar equivalents of bromine to give a high yield of a mixture of 2,7- and 2,8-dibromothianthrene. The isomeric mixture was also obtained in high yields by the action of hydrobromic acid on thianthrene-5,10-dioxide (III) and of bromine on thianthrene-5-oxide (IV).[3] The product could not be separated into the two isomers probably due to the very similar physical properties of the two dibromothianthrenes. Oxidation of the mixture with hydrogen peroxide yielded another product which also melted over a wide range after several recrystallizations but gave an analysis corresponding to a dibromothianthrene-5,5,10,10-tetroxide.[3]



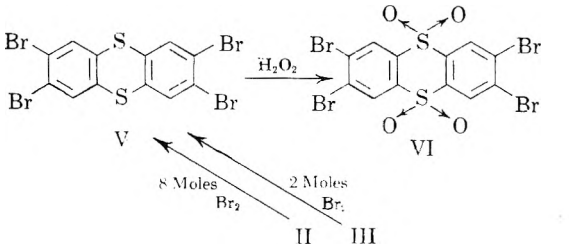
In the present investigation we found additional support for considering the dibromothianthrene as a mixture of 2,7- and 2,8-dibromothianthrene. The thianthrene molecule has the 2-, 3-, 7-, and 8-posi-

(1) C. R. Neumoyer and E. D. Amstutz, *J. Am. Chem. Soc.*, **69**, 1920 (1947).

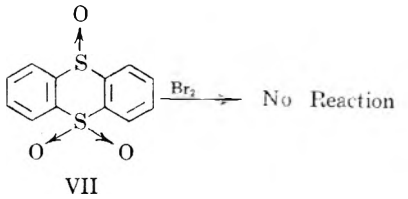
(2) H. Gilman and R. K. Ingham, *J. Am. Chem. Soc.*, **73**, 4982 (1951).

(3) H. Gilman and D. R. Swayampati, *J. Am. Chem. Soc.*, **77**, 5944 (1955).

tions *para* to one or the other of the two sulfur atoms. Considering that the bromination should occur at one or more of the *para* positions,[1,3,4] it is seen that the treatment of II with bromine should give one monobromo-, two dibromo-, one tribromo- and one tetrabromothianthrene. Hence, in the formation of a tri- or tetrabromothianthrene the difficulty of obtaining a sharp-melting product would not be encountered. We found that II and an excess of bromine gave a 41% yield of 2,3,7,8-tetrabromothianthrene (V), melting at 291–292°. The same product was also obtained in 28% yield by the action of two molar equivalents of bromine on III. Oxidation of V with hydrogen peroxide gave an excellent yield of 2,3,7,8-tetrabromothianthrene-5,5,10,10-tetroxide (VI), melting at 357–358° with decomposition.



Thianthrene-5-oxide,[3] like other sulfoxides such as dibenzothiophene-5-oxide[2] and 10-ethylphenothiazine-5-oxide,[4] is reduced during the process of bromination. Thianthrene-5,5-dioxide, a sulfone, does not react with bromine.[3] It was considered interesting to study the action of bromine on thianthrene-5,5,10-trioxide (VII), which has both the sulfoxide and the sulfone groups. Bromine was found to have no action on VII when a mixture of the two was refluxed for a period of 16 hours.



EXPERIMENTAL[5]

Thianthrene (II) *and bromine.* To 6.48 g. (0.03 mole) of II[6] was added 38.4 g. (0.24 mole) of bromine. The reaction commenced immediately with the evolution of hydrogen bromide. To the dark solid was added 20 ml. of glacial acetic acid and the resulting red suspension was refluxed for 16 hr. The mixture was treated with a dilute solution of sodium thiosulfate to remove the excess bromine. The white product was filtered, washed with water, and dried to give 15.32 g. of crude 2,3,7,8-tetrabromothianthrene (V) melting over the range 247–264°. Two recrystallizations from xylene (Norit-A) yielded 6.56 g. (41%) of nearly pure V melting at 288–290°. The analytical sample, obtained by an additional recrystallization from xylene, melted at 291–292°.

Anal. Calcd. for $C_{12}H_4Br_4S_2$: Br, 60.08; S, 12.03. Found: Br, 59.72, 59.53; S, 12.02.

Thianthrene-5,10-dioxide (III) *and bromine.* To 1.5 g. (0.006 mole) of the α-form[7] of III[8] was added 2 ml. of bromine. To the resulting dark solid was added 5 ml. of glacial acetic acid and the solution was refluxed for 5 hr. A crystalline product began to crystallize out soon after the solvent began to reflux. At the end of the reaction period the mixture was cooled and treated with a dilute solution of sodium thiosulfate to remove the unused bromine. The white product was filtered, washed with water, and dried to give 3.35 g. of the crude V. Successive recrystallizations from chloroform and xylene yielded 0.9 g. (28%) of pure V melting at 291–292°. A mixture of this product with that obtained from II and bromine melted undepressed.

2,3,7,8-Tetrabromothianthrene-5,5,10,10-tetroxide (VI). To a hot suspension of 2.13 g. (0.004 mole) of V in 50 ml. of glacial acetic acid was added a solution of 5 ml. of 30% hydrogen peroxide in 20 ml. of glacial acetic acid and the suspension was refluxed for 4 hr. The mixture was cooled and the white product was filtered and dried to give 2.25 g. (95%) of VI melting at 357–358° with decomposition.

Anal. Calcd. for $C_{12}H_4Br_4O_4S_2$: Br, 53.63; S, 10.73. Found: Br, 52.99, 52.91; S, 10.63, 10.61.

Thianthrene-5,5,10-trioxide (VII) *and bromine.* A mixture of 2.64 g. (0.01 mole) of VII,[3] 2 ml. of bromine, and 2 ml. of glacial acetic acid was refluxed for 16 hr. The excess bromine was destroyed with a dilute solution of sodium thiosulfate. The white product was filtered, washed with water, and dried to yield 2.52 g. (95%) of crude VII melting over the range 210–221°. Recrystallization from glacial acetic acid yielded 2.14 g. (81%) of pure VII melting at 221.5–222.5°. A mixture of the product with authentic VII[3] melted undepressed.

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(4) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, **77**, 3862 (1955).

(5) All melting points reported herein are uncorrected.

(6) K. Fleischer and J. Stemmer, *Ann.*, **422**, 265 (1921).

(7) E. Bergmann and M. Tschudnowsky, *Ber.*, **65**, 457 (1932).

(8) K. Fries and W. Vogt, *Ber.*, **44**, 756 (1911).

Tetrasubstituted Higher Aliphatic and Phenyl Silanes

R. H. Meen and Henry Gilman

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We wish to report the synthesis and physical properties of a number of new tetra-substituted silanes prepared in connection with a study in this laboratory of the higher aliphatic silanes. These compounds, Table I, were prepared by treatment of a slight excess of a chlorosilane with an organolithium compound according to the usual procedure.

$$(C_6H_5)_2SiCl_2 + 2RLi \longrightarrow (C_6H_5)_2SiR_2 + 2LiCl$$

The intermediate organolithium compounds were obtained directly by the action of lithium on *n*-octyl-, 2-octyl-, 2-ethylhexyl- and 2-cyclohexylethylbromides in yields of 87, 76, 64 and 88%, respectively.

TABLE I

TETRA-SUBSTITUTED SILANES

Reagent	Reaction Time (hr.) with RLi	Product	Yield, %	M.P., °C.	B.P. °C.	B.P. Mm.	n_D^{20}	d_4^{20}	MR_D Calcd.[d]	MR_D Found	Formula	Silicon, % Calcd.	Silicon, % Found
Triphenylchlorosilane	10	Triphenyl-*n*-octylsilane	76	73–75[a]	182	0.02					$C_{26}H_{32}Si$	7.54	7.51, 7.46
Triphenylchlorosilane	2	Triphenyl-2-octylsilane	44		153–155	.04	1.5748	1.009	122.2	122.0	$C_{26}H_{32}Si$	7.54	7.57, 7.65
Triphenylchlorosilane	18	Triphenyl-2-ethylhexylsilane	50		163–166	.03	1.5734	1.005	122.2	122.3	$C_{26}H_{32}Si$	7.54	7.67, 7.50
Triphenylchlorosilane	12	Triphenyl-2-cyclohexylethylsilane	63	58–59[a]	168	.03					$C_{26}H_{30}Si$	7.58	7.57, 7.64
Diphenyldichlorosilane	12	Diphenyldi-*n*-octylsilane	59		198	.12	1.5191	0.919	134.7	135.0	$C_{28}H_{44}Si$	6.87	6.87, 6.85
Diphenyldichlorosilane	2	Diphenylbis(2-octyl)silane	86		141–156[c]	.02	1.5305						
			13		186	.50	1.5266	.931	134.7	134.5	$C_{28}H_{44}Si$	6.87	6.88, 6.76
Diphenyldichlorosilane	6	Diphenylbis(2-ethylhexyl)silane	85		153–159[c]	.06	1.5220						
			31		158–159	.06	1.5226	.925	134.7	134.9	$C_{28}H_{44}Si$	6.87	6.95, 6.90
Diphenyldichlorosilane	12	Diphenylbis(2-cyclohexylethyl)silane	79		187	.03	1.5527	.993	130.5	130.3	$C_{28}H_{40}Si$	6.94	7.04, 7.03
Phenyltrichlorosilane	12	Phenyltri-*n*-octylsilane	80		181	.02	1.4841	.862	147.3	147.7	$C_{30}H_{56}Si$	6.31	6.45, 6.31
Phenyltrichlorosilane	18	Phenyltris(2-ethylhexyl)silane	70		150–157[c]	.01	1.4887						
			19		156–157	.01	1.4890	.875	147.3	146.8	$C_{30}H_{56}Si$	6.31	6.38, 6.40
Phenyltrichlorosilane	12	Phenyltris(2-cyclohexylethyl)silane	76		188	.02	1.5235	.954	140.9	140.7	$C_{30}H_{50}Si$	6.40	6.45, 6.62
Silicon tetrachloride	18	Tetra-*n*-octylsilane	63		192	.15	1.4589	.822	159.9	160.0	$C_{32}H_{68}Si$	5.84	5.86, 5.85
Silicon tetrachloride	24	Tetrakis(2-ethylhexyl)silane	50		135–155[c]	.05	1.4612						
			26		143	.05	1.4619	.842	159.9	157.0	$C_{32}H_{68}Si$	5.84	5.94, 5.92
Silicon tetrachloride	18	Tetrakis(2-cyclohexylethyl)silane	68	146–147[b]	206	.02					$C_{32}H_{60}Si$	5.94	5.87, 5.95
n-Dodecyltrichlorosilane	24	*n*-Dodecyltris(2-cyclohexylethyl)silane	57		211	.02	1.4885	.894	172.1	171.2	$C_{36}H_{70}Si$	5.29	5.17, 5.22

[a] Recrystallized from absolute ethanol. [b] Recrystallized from 1:1 benzene–absolute ethanol. [c] The crude product is possibly a mixture of stereoisomers. The purified sample was an arbitrarily selected distillation fraction. [d] Molar refractions were calculated from the values of E. L. Warrick, *J. Am. Chem. Soc.*, **68**, 2455 (1946).

EXPERIMENTAL[1]

n-Octyllithium.[2] A suspension of 13.7 g. (1.97 g.-atoms) of lithium wire, cut into 2–3 mm. lengths, in 320 ml. of ethyl ether was stirred at −15 to −30° while a solution of 155 g. (0.8 mole) of *n*-octyl bromide in 100 ml. of ethyl ether was added during 45 min. The temperature was maintained at −15 to −30° for 2 hr. and then at −5 to 0° for 1 hr. After filtration the yield was 87%, as determined by the double titration procedure.[3]

This method was also used for the preparation of 2-ethylhexyllithium and 2-cyclohexylethyllithium from 2-ethylhexylbromide and 2-cyclohexylethyl bromide, respectively.

2-Octyllithium.[4] A solution of 74.3 g. (0.5 mole) of 2-octyl chloride in 200 ml. of pure pentane was added during 3 hr. to a stirred refluxing suspension of 13.9 g. (2.0 g.-atoms) of lithium foil in 200 ml. of pentane. The refluxing was continued for a further 2 hr. After filtration the yield was 76% according to the double titration procedure.

General synthetic method. A. Preparation of triphenyl-n-octylsilane. A suspension of 56 g. (0.19 mole) of triphenylchlorosilane in 235 ml. of ethyl ether was maintained at −20 to −10° while an ether solution of 0.21 mole of *n*-octyllithium was added during 15 min. The mixture was allowed to come to room temperature and stirred for 10 hr., by which time Color Test I[5] was negative. After hydrolyzing the reaction mixture with cold dilute sulfuric acid, the ether layer was separated, dried over sodium sulfate, and distilled, giving a main fraction distilling at 182° (0.02 mm.) and melting at 72–74°. One recrystallization from absolute ethanol gave 54 g. (76%) melting at 73–75°.

Anal. Calcd. for $C_{26}H_{32}Si$: Si, 7.54. Found: Si, 7.51, 7.46.

This same procedure was used with all of the compounds, Table I, with the exception of those prepared from silicon tetrachloride.

B. Preparation of tetra-n-octylsilane. A solution of 14.1 g. (0.083 mole) of silicon tetrachloride in 170 ml. of ethyl ether was maintained at −20° while an ether solution of 0.39 mole of *n*-octyllithium was added rapidly. The mixture was kept at room temperature for 10 hr. and then was refluxed for 8 hr., by which time Color Test I was negative. Working up as in procedure A gave a main fraction of 25.3 g. (63%) distilling at 191–192° at 0.15 mm., n_D^{20} 1.4589, d_4^{20} 0.822.

Anal. Calcd. for $C_{32}H_{68}Si$: Si, 5.84. Found: Si, 5.86, 5.85.

Silicon analyses. The procedure usually used in this laboratory,[6] in which about a 0.2-g. sample is wetted with a few drops of nitric acid, digested with 1 ml. of concentrated sulfuric acid, and finally ignited gave erratically low results with some of these compounds. Successful analyses were obtained by digestion of the samples in covered Vycor crucibles with 3 ml. of a 2:1 mixture of sulfuric and nitric acids. Additional nitric acid was added as necessary to complete the oxidation.

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(1) All melting and boiling points are uncorrected. All operations involving organolithium compounds were carried out under an atmosphere of dry oxygen-free nitrogen in sodium-dried solvents.

(2) For a general reference to the preparation of aliphatic lithium compounds see, H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(3) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).

(4) D. S. Tarbell and M. Weiss, *J. Am. Chem. Soc.*, **61**, 1203 (1939), obtained a 56% yield from the chloride by a similar procedure in ethyl ether solution.

(5) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(6) H. Gilman, B. Hofferth, H. W. Melvin, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 5767 (1950).

A Synthesis of 5-Ketolilolidine[1]

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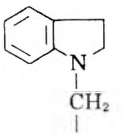
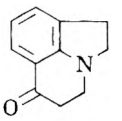
Our interest in the synthesis of 5-ketolilolidine (II) arose from the consideration that this compound would be a useful intermediate in syntheses directed toward apo-β-erythroidine and related compounds.[2] Braunholtz and Mann have reported the cyclization of aromatic cyanoethyl amines to give ketojulolidine derivatives,[3a,b] and it seemed likely that *N*-(β-cyanoethyl)indoline (I) would undergo cyclization in a similar manner to give 5-ketolilolidine (II).



I



II

Preparation of the starting material, *N*-(β-cyanoethyl)indoline, was readily accomplished by the addition of acrylonitrile to indoline. However, when *N*-(β-cyanoethyl)indoline was treated with aluminum chloride and hydrochloric acid in chlorobenzene, as described for the preparation of 1,6-diketojulolidine,[3] the only apparent reaction was one of dissociation to indoline and acylonitrile. The conditions for effecting cyclizations of this type seem to be quite critical and eventually it was found that, by the use of anhydrous aluminum chloride in *o*-dichlorobenzene, 5-ketolilolidine could be obtained consistently in yields varying from 8 to 13%. In the isolation procedure developed, 5-ketolilolidine was separated from the other reaction products by use of Girard's reagent and a product of high purity resulted. For purposes of characterization, the oxime and 2,4-dinitrophenylhydrazone derivatives were prepared. Also, to establish its identity, 5-ketolilolidine was reduced by the Wolff-Kishner procedure and the properties of the product were shown to be in agreement with those reported for lilolidine.[4]

Because of the low yields encountered in the cyclization step, alternate methods were investigated but without success. Hydrolysis of *N*-(β-cyanoethyl)indoline occurred smoothly to give the corresponding acid, *N*-(β-carboxyethyl)indoline. But,

(1) Aided by a grant from the United Cerebral Palsy Association, Inc.

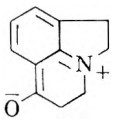
(2) M. F. Grundon, G. L. Sauvage, and V. Boekelheide, *J. Am. Chem. Soc.*, **75**, 2550 (1953).

(3) (a) J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1817 (1953); (b) J. A. C. Allison, J. T. Braunholtz, and F. G. Mann, *J. Chem. Soc.*, 403 (1954).

(4) G. Barger and E. Dyer, *J. Am. Chem. Soc.*, **60**, 2414 (1938).

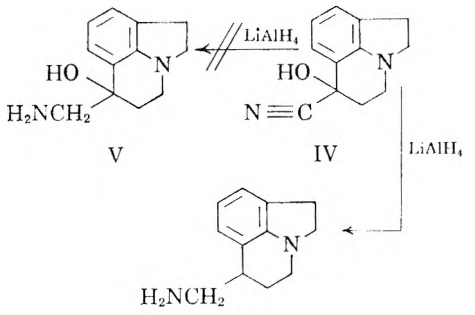
again, attempted cyclization with the usual Friedel-Crafts reagents was unsuccessful.

The infrared spectrum of 5-ketolilolidine shows strong absorption at 6.04 μ. Since the usual region for absorption by aromatic ketones is about 5.95–5.98 μ,[5] it would appear that there is appreciable interaction between the amine and carbonyl functions, probably due to contributions of the type shown by III. Support for this hypothesis comes from the fact that the molecule is only feebly basic and is readily extracted from aqueous acid. Under the usual conditions, 5-ketolilolidine did not form either a picrate or hydrochloride.



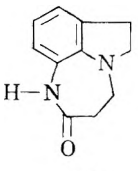
III

Attempts to effect a ring expansion of 5-ketolilolidine by reaction with diazomethane led to recovery of the unchanged ketone. Similarly, 5- ketolilolidine was unaffected by treatment with nitromethane under the usual conditions for condensation. Again, the lack of reactivity may be a reflection of the interaction of the carbonyl and amine functions. By the use of forcing conditions it was possible to obtain the corresponding cyanohydrin (IV). However, reduction of the cyanohydrin with lithium aluminum hydride did not lead to the expected amino carbinol (V) but, instead, gave an oxygen-free product for which we tentatively assign structure VI.

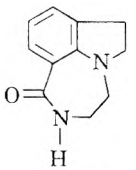


V IV VI

In view of our lack of success with the conventional methods for ring expansion of ketones, we tried ring expansion procedures involving introduction of nitrogen for purposes of comparison. Although various attempts to effect a Beckmann rearrangement of the oxime of 5-ketolilolidine were unsuccessful, the direct reaction of hydrazoic acid with the ketone by the Schmidt procedure did give a product having the composition expected of the desired amide. By analogy, it would be expected that this product should be VII. However, the spectra and properties of the product could be accommodated equally well by structure VIII; conclusive evidence is not available to decide between the two possibilities.



VII



VIII

EXPERIMENTAL[6]

N-(β-Cyanoethyl)indole, I. A mixture of 25.0 g. of indoline and 23.0 g. of freshly distilled acrylonitrile in 25 ml. of acetic acid was heated in a sealed tube at 145° for 12 hr. At the end of this time, the contents of the tube were removed and fractionally distilled. The portion boiling at 150–160° at 2 mm. was collected and then redistilled to give 31.5 g. (87%) of a pale yellow, viscous oil; b.p. 129–133° at 1 mm., n_D^{20} 1.5748. On standing, the oil crystallized and could be obtained from a hexane-benzene mixture as transparent plates, m.p. 104–105°.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.60; H, 7.16; N, 15.82.

The corresponding *methiodide* was prepared for characterization and was obtained after crystallization from a hexane-ethanol mixture as hexagonal plates, m.p. 142–144°.

Anal. Calcd. for $C_{12}H_{15}N_2I$: C, 45.91; H, 4.82. Found: C, 45.78; H, 4.92.

N-(β-Carboxyethyl)indoline. A mixture of 1.5 g. of *N-*(β-cyanoethyl)indoline and 15 ml. of a 10% aqueous sodium hydroxide solution was boiled under reflux until a clear solution resulted (2.5 hr.). When the cold solution was brought to *p*H 5.0 by addition of acid, an oil separated which slowly solidified. Crystallization of the resulting solid from ethanol gave 900 mg. (54%) of white crystals, m.p. 77–78.5°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.37; H, 6.94.

Attempts to convert this acid to 5-ketolilolidine under the usual conditions for Friedel-Crafts type cyclizations were unsuccessful.

5-Ketolilolidine, II. To a mixture of 50 g. of anhydrous aluminum chloride in 30 ml. of *o*-dichlorobenzene there was added 10.0 g. of freshly distilled *N-*(β-cyanoethyl) indoline. The mixture became warm and turned a deep red; it was then heated at 185° for 8 hr. with rapid stirring. At the end of this time the warm mixture was poured onto crushed ice and the *o*-dichlorobenzene was removed by steam distillation. The aqueous solution was then exhaustively extracted with chloroform (700 ml.). In this way the cyclization product was separated from indoline and other basic substances which remained in the aqueous layer. The combined, fluorescent, chloroform extracts were dried, concentrated, and the residual oil was distilled. From spectral analysis and from tests with 2,4-dinitrophenylhydrazine reagent, the main ketone-containing fraction was determined to be that boiling in the range of 120–140° at 0.7 mm. and this amounted to 4.1 g. To obtain the 5-ketolilolidine in a pure state it was dissolved in a solution containing 50 ml. of ethanol, 5 ml. of glacial acetic acid and 5 g. of Girard's P Reagent. After the solution had been boiled under reflux for 2 hr., it was poured into a solution of 4.0 g. of potassium hydroxide in 250 ml. of water. Unreacted mate-

(5) V. Boekelheide and J. Godfrey, *J. Am. Chem. Soc.*, **75**, 3679 (1953).

(6) All melting points are corrected. Analyses by Miss A. Smith.

rial was removed by extraction with ether, and the solution was made acidic by addition of 25 ml. of concentrated hydrochloric acid. After the solution had stood for 2 hr., it was again extracted with ether. Concentration of the ether solution gave 1.3 g. (13%) of a yellow solid which, after sublimation at 70–80° at 0.5 mm., melted at 54–57°. Recrystallization from hexane gave 1.13 g. of yellow needles, m.p. 58–59°, which showed a greenish fluorescence. The infrared spectrum of this ketone had a single strong band at 6.04 μ in the carbonyl region.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.05, 76.25; H, 6.81, 6.65; N, 8.00.

The *2,4-dinitrophenylhydrazone* of 5-ketolilolidine was obtained after crystallization from a hexane-dioxane mixture as scarlet-black crystals, m.p. above 270° w. decomp.

Anal. Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.78; H, 4.28. Found: C, 57.76; H, 4.39.

The *oxime* of 5-ketolilolidine was obtained after crystallization from hexane as yellow needles, m.p. 152–154°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43. Found: C, 69.79; H, 6.37.

Reduction of 5-ketolilolidine to lilolidine. To a solution of 510 mg. of 5-ketolilolidine in 20 ml. of trimethylene glycol there was added 4 ml. of hydrazine hydrate and 1.0 g. of potassium hydroxide, and the mixture was heated at 180° for 1.5 hr. The temperature was then raised to 215° and heating was continued for an additional 2 hr. After the solution had cooled, it was poured into water and extracted with chloroform. The chloroform extracts were dried, concentrated, and the residue was dissolved in ether. The ether solution was extracted with 6*N* hydrochloric acid. The aqueous layer was made basic and again extracted with ether. Concentration of the ether extract followed by distillation gave 90 mg. of a yellow oil, b.p. 90–100° at 0.5 mm. The *picrate* of this oil formed readily and was obtained, after crystallization from ethanol, as yellow plates, m.p. 167.5–168.5° (Barger and Dyer[4] report the m.p. of lilolidine picrate as 168–170°).

Anal. Calcd. for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15. Found: C, 52.75; H, 4.36.

5-Ketolilolidine cyanohydrin, IV. A solution of 600 mg. of 5-ketolilolidine and 10 mg. of potassium cyanide in 5 ml. of anhydrous hydrogen cyanide was allowed to stand at 5° for 3 hr. At the end of this time, the excess hydrogen cyanide was allowed to evaporate and the residue was extracted with boiling hexane. Concentration of the hexane solution followed by cooling gave 200 mg. (28%) of yellow needles, m.p. 110–112°. From the hexane-insoluble residue 360 mg. of 5-ketolilolidine was recovered.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04. Found: C, 72.26; H, 6.30.

Lithium aluminum hydride reduction of the cyanohydrin of 5-ketolilolidine. A solution of 170 mg. of 5-ketolilolidine cyanohydrin in ether was added to a solution 1.0 g. of lithium aluminum hydride in ether. The mixture was boiled under reflux for 24 hr. and then decomposed by addition of 20 ml. of 10% aqueous sodium hydroxide solution. The ether layer was separated, dried, and concentrated. Distillation of the residue gave 50 mg. of a yellow oil, b.p. 130° at 0.005 mm., to which structure VI is assigned.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57. Found: C, 76.98; H, 8.73.

Schmidt Reaction with 5-ketolilolidine. To a solution of 1.0 g. of 5-ketolilolidine in 20 ml. of chloroform, there was added a prepared solution obtained by treating 2.0 g. of sodium azide in 70 ml. of chloroform with 1.2 g. of concentrated sulfuric acid. The rapidly stirred mixture maintained at 30° was then treated dropwise with an additional 2.0 g. of sulfuric acid. After stirring an additional hour, the mixture was poured into 30 ml. of water. Separation of the chloroform layer followed by concentration gave 420 mg. of an amorphous powder. Repeated crystallization of this from hexane gave 195 mg. (18%) of yellow plates, m.p. 140–141°, softening at 138°. The infrared spectrum of the crystals (VII or VIII) showed NH absorption at 2.52 μ and carbonyl absorption at 6.11 μ. The ultraviolet absorption spectrum of the crystals showed maxima at 227 mμ (log ϵ, 4.19), 263 (3.71), 310 (3.49) and 353 (3.40).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.9. Found: C, 69.7; H, 6.7; N, 14.8.

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Preparation of 7-Nitro-1-naphthylamine and 7,7′-Dinitro-1,1′-azonaphthalene

H. J. Shine

Received August 29, 1957

Recent publications[1,2] on the chemistry of 7-nitro-1-naphthylamine prompt us to report some observations on the preparation of this amine, which was needed for diazo-coupling to 7,7′-dinitro-1,1′-azonaphthalene.

We have followed the method of Schroeter[3] in preparing the amine by a Semmler aromatization.[1] However, the directions given in the literature are rather scant,[1,3] and it was because of this that, in improvising on the directions, the following observations were made. These observations may be of interest and of help to others.

The oxime of 7-nitro-α-tetralone is best prepared by heating an aqueous ethanol solution of the ketone, hydroxylamine hydrochloride, and sodium acetate. Several attempts with the use of sodium hydroxide to neutralize hydroxylamine hydrochloride in preparing the oxime gave only starting material. The oxime acetate may be conveniently prepared by acetylating the oxime in pyridine with acetic anhydride.

The oxime acetate is very sensitive to light. Sunlight, both direct and indirect, and even electric light, cause the solid oxime acetate to turn pink. The discoloration occurs on the surface exposed to the light; under-surfaces remain white. The solid turns pink even when in suspension in the aqueous pyridine–acetic acid solution from which it is first precipitated. After observing this we carried out all subsequent preparations in subdued light and stored the oxime acetate in protected bottles. We do not know whether the use of pink material will affect subsequent reactions in which the oxime acetate is used. The color change is reversible if, after a few minutes of exposure, the solid is placed in the dark. However, exposures of longer than five minutes appear to be irreversible, and exposures of an hour or more turn the solid a tan color. From the directions

(1) A. Hardy, E. R. Ward, and L. A. Day, *J. Chem. Soc.*, 1979 (1956).

(2) A. Hardy and E. R. Ward, *J. Chem. Soc.*, 2634 (1957).

(3) G. Schroeter, *Ber.*, **63**, 1308 (1930).

given by Schroeter[3] it would appear advisable to use the oxime acetate for the Semmler aromatization. Further, it would appear that the aromatization is achieved by saturating a solution of the oxime acetate in acetic acid–acetic anhydride with hydrogen chloride and heating. It is not necessary to use the oxime acetate;[4] the oxime may be used itself. Also, it is necessary to keep the acetic acid–acetic anhydride solution saturated with hydrogen chloride while heating;[5] if this is not done the yield of amine is lowered considerably.

The 7-nitro-1-naphthylamine obtained from our work was diazotized and coupled by the general method of Cohen and Oesper.[6] The 7,7′-dinitro-1,1′-azonaphthalene, m.p. 311–312°, was obtained in 37.6% yield. This compound does not appear to have been reported hitherto.

EXPERIMENTAL

7-Nitro-α-tetralone oxime. Thirty grams of 7-nitro-α-tetralone was dissolved in 400 ml. of hot 95% ethanol. To this was added a solution of 75 g. of hydroxylamine hydrochloride and 75 g. of sodium acetate in 150 ml. of water. A further 350 ml. of ethanol was added and the mixture was heated until all solid dissolved. After standing overnight 1800 ml. of water was added. The finely crystalline precipitate was filtered, washed with water, and dried under vacuum. The yield was 31.9 g. (98.5%), m.p. 169–170.5°.

7-Nitro-α-tetralone oxime acetate. Two grams of the oxime was dissolved in 10 ml. of pyridine and 10 ml. of cold acetic anhydride was added. The solution was refrigerated for 3 hr. Chipped ice was added followed by water. The suspension thus formed turned pink. Filtration gave a pink solid. This was dissolved in ethanol and the solution was acidified with 5 ml. of 10% hydrochloric acid. Dilution with water gave a white flocculent precipitate. Filtration, washing with water, and drying under vacuum were carried out in subdued light, giving 2.29 g. (95%) of a fluffy white solid, sintering at 103°, melting sharply at 114.5–115.5°. The solidified melt remelted sharply at 114.5–115.5°.

7-Nitro-1-naphthylamine. In separate tubes containing 6 ml. of acetic acid and 0.2 ml. of acetic anhydride protected by calcium chloride were placed 0.5 g. of oxime acetate and 0.5 g. of oxime. The tubes were heated in boiling water for 30 min. while anhydrous hydrogen chloride was passed through the solution. After cooling and filtering the solid obtained in each case was triturated with sodium acetate solution, washed and dried to yield 0.15 g. (35.6%), and 0.18 g. (40%), respectively. The amine in each case was purified by dissolving in warm aqueous ethanol containing ammonia. Crystallization gave red needles, m.p. 130–131°.

7,7′-Dinitro-1,1′-azonaphthylamine. By using the general procedure[6] 3.66 g. amine gave 4 g. of tan solid. This was extracted in a Soxhlet apparatus with 95% ethanol for 7 hr.; the ethanol solution was discarded. The insoluble material was then similarly extracted with chloroform for 6 hr. On standing the chloroform solution deposited purple needles, 1.36 g. (37.6%). Recrystallization from 1200 ml. of boiling benzene gave 1.25 g. fine lustrous needles, m.p. 311–312°.

Anal.[7] Calcd. for $C_{20}H_{12}N_4O_4$: C, 64.51; H, 3.25; N, 15.04. Found: C, 64.47; H, 3.28; N, 14.63.

Acknowledgment. This work was part of a program of research generously supported by the Robert A. Welch Foundation.

DEPARTMENT OF CHEMISTRY AND
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(4) This was first brought to our notice by Dr. E. R. Ward.

(5) After making this observation we were notified by Dr. Ward that the same was found in his laboratory.

(6) S. Cohen and R. E. Oesper, *Ind. Eng. Chem., Anal. Ed.*, 8, 306 (1936).

(7) Analysis by Schwarzkopf Microanalytical Laboratories, Woodside 77, N. Y.

The Chemistry of Oxamidines. II. Reaction with Hydrogen Sulfide[1]

HENRY M. WOODBURN, WALTER PLATEK, AND
EDMOND L. GRAMINSKI

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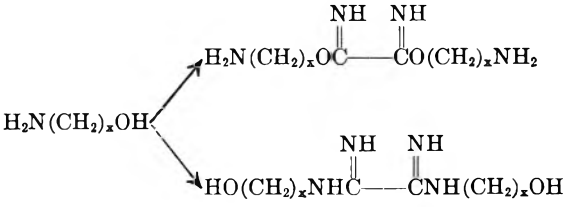
In a study of the reaction of cyanogen with alkanolamines, Graminski[2] had the problem of deciding under what conditions the product was an oxaldiimidate and when it was an oxamidine:



A possible method of differentiation resulted from the discovery that *N,N′*-bis(2-hydroxyethyl)dithiooxamide, a compound whose properties and structure were known,[3] could be made from one of the products originating in ethanolamine but not from the other.

Inspection of the reaction equations, whereby the dithiooxamide would be formed from either the oxaldiimidate or the oxamidine, argues for its formation from the oxamidine. Experimentally, this was confirmed by the treatment of oxamidines of known structure with hydrogen sulfide to yield dithiooxamides which were identified by independent synthesis using the Wallach method:[4]

(1) Mainly from the thesis submitted by Walter Platek in partial fulfillment of the requirements for the B.A. degree, University of Buffalo, June 1957. Paper I, *J. Org. Chem.*, 23, 263 (1958).

(2) E. L. Graminski, Doctoral Dissertation, University of Buffalo, June 1956.

(3) Private communication, James Venerable, Mallinckrodt Chemical Works.

(4) O. Wallach, *Ann.*, 262, 354 (1891).

sym - Bis(2 - methylaminoethyl)oxaldiimidate, $(CH_3NHC_2H_4OC(=NH)-)_2$ gave no such reaction with hydrogen sulfide.

The hydrogen sulfide reaction resembles the partial hydrolysis of oxamidines which can be accomplished by allowing a cold aqueous solution to stand in the presence of amine.[5]

$$(RNHC(=NH)-)_2 + 2HOH \xrightarrow{RNH_2} (RNHC(=O)-)_2 + 2NH_3$$

EXPERIMENTAL

Oxamidines were prepared by the reaction of cyanogen with amines.[6] Dithiooxamide was a gift from the Mallinckrodt Chemical Works.

N,N'-Di-n-butyldithiooxamide. (*a*) A cold solution of *sym*-di-*n*-butyloxamidine, prepared by dissolving 2 g. of the compound in the smallest possible amount of ethanol and adding water as long as the solution remained clear, was saturated with hydrogen sulfide. The solution gradually acquired a reddish-brown color and a few orange crystals appeared. After standing overnight the mixture was filtered and the orange solid recrystallized as follows: 2 ml. of water was added to remove any ammonium sulfide and the solid residue dissolved in ethanol at 40°. After filtration to remove sulfur, water was added until a cloudiness persisted, then a few drops of ethanol. The mixture was finally cooled in an ice bath. After three recrystallizations the melting point of the orange needles was 41.5–43.0°. The yield of crude material was 70%.

Anal. Calcd. for $C_{10}H_{20}N_2S_2$: N, 12.1; S, 27.6. Found: N, 12.1; S, 27.2.

(*b*) Di-*n*-butyldithiooxamide was also prepared by the method of Wallach.[4] To a suspension of 12.0 g. (0.1 mole) of dithiooxamide in 48 g. of ethanol was added 15.6 g. (2.1 moles) of *n*-butylamine. Hydrogen sulfide and ammonia were evolved and some of the dithiooxamide went into solution. The mixture was heated until clear, after which a few drops of dilute sulfuric acid were added. Orange crystals formed on standing overnight. These were recrystallized as above and melted at 41.5–42.5°.

A mixed melting point with the product from (*a*) showed no depression. Infrared curves (10% solution in $CHCl_3$) of the two products were identical.

N,N'-Diethyldithiooxamide. (*a*) Saturation with hydrogen sulfide of a concentrated ethanolic solution of diethyloxamidine produced orange needles melting at 57.5–59.0°. Recrystallization from ethanol-water was carried out below 55°. The yield of crude product was 45%.

This compound had previously been prepared by Wallach.[4] A sample prepared by his method mixed with the product from above showed no depression of melting point. Infrared curves of the two products were identical.

(*b*) Oxamidines are often best isolated as dihydrochlorides. Saturation with hydrogen sulfide of either an aqueous or ethanolic solution of diethyloxamidine dihydrochloride failed to yield the dithiooxamide. Consequently a solution of 0.5 g. of diethyloxamidine dihydrochloride in the minimum amount of water was made basic to litmus with dilute sodium hydroxide and then treated with hydrogen sulfide until it became pale yellow and a few crystals appeared. More crystals formed overnight. Recrystallization gave orange needles which showed no melting point depression when mixed with the product from (*a*). The yield was 50%.

N,N'-Bis(3-methoxypropyl)-dithiooxamide. (*a*) One gram of *sym*-bis(3-methoxypropyl)oxamidine[2] was dissolved in 95% ethanol and saturated with hydrogen sulfide. The solution turned orange-red and a few reddish crystals appeared on standing. These were filtered off and proved to be dithiooxamide. Water was added to the filtrate until it became cloudy and crystallization was completed by cooling in the ice chest. The product was obtained after one recrystallization from ethanol-water (below 40°) as orange-yellow needles melting at 44.0–45.5°. The yield of crude product was 60%.

Anal. Calcd. for $C_{10}H_{20}N_2O_2S_2$: N, 10.6; S, 24.2. Found: N, 10.5; S, 23.7.

(*b*) Following the method of Wallach,[4] dithiooxamide and 3-methoxypropylamine gave crystals which showed no melting point depression when mixed with the product from (*a*). Infrared curves (10% solution in $CHCl_3$) of the two products were identical.

N,N'-Bis(2-ethoxyethyl)dithiooxamide was prepared from *sym*-bis(2-ethoxyethyl)oxamidine[2] and hydrogen sulfide as described above. After recrystallization from ethanol-water, the yellow needles melted at 51–52°. Because of the small amount of starting material available, the yield of purified product was not sufficient for analysis.

N,N'-Bis(2-hydroxyethyl)dithiooxamide. (*a*) Hydrogen sulfide was passed into a solution of 1.0 g. of *sym*-bis(2-hydroxyethyl)oxamidine[2] in 20 ml. of water until an orange precipitate began to form. After standing for 4 hr. the mixture was filtered. The solid proved to be dithiooxamide.

The filtrate was extracted with 25-ml. portions of ether. Evaporation of the extracts produced 0.1 g. of yellow-orange crystals melting at 83–85°. The yield was 8.5%.

(*b*) To 12 g. (0.2 mole) of ethanolamine was added 6 g. (0.06 mole) of dithiooxamide. An immediate reaction produced much heat and hydrogen sulfide. After the initial reaction had subsided, the flask was heated gently with constant stirring for 0.5 hr.

After cooling, the mixture was diluted with 20 ml. of water and crystallization induced by scratching the inner surface of the flask. The yield of crude product was 29%. Recrystallization was accomplished from ethyl acetate–carbon tetrachloride. The yellow solid melted at 89–91° and gave no depression of melting point when mixed with the product from (*a*).

Anal. Calcd. for $C_6H_{12}N_2O_2S_2$: N, 13.4; S, 30.7. Found: N, 13.2; S, 30.3.

Attempted reaction of *sym*-bis(2-methylaminoethyl)-oxaldiimidate[2] with hydrogen sulfide: One gram of the hydrochloride of *sym*-bis(2-methylaminoethyl)oxaldiiminate was dissolved in the minimum amount of water. The solution was made basic with dilute sodium hydroxide. Hydrogen sulfide was passed in until the solution was pale green in color. No crystals formed. The aqueous solution was extracted with ether and the extracts evaporated to dryness. No residue was obtained.

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(5) H. M. Woodburn, B. Morehead, and M. C. Chen, *J. Org. Chem.*, 15, 535 (1950).

A New Synthesis of 3-Indolesuccinic Acid

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Maleyldiindole,[3] an addition product of indole and

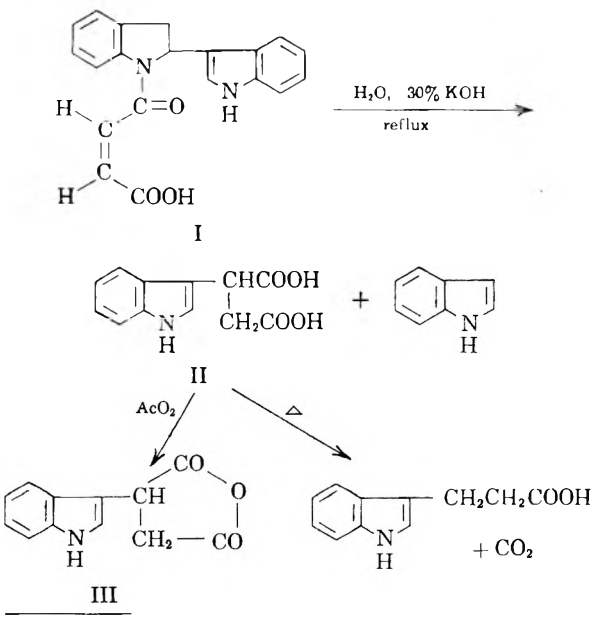
(1) We are indebted to the Graduate School of the University of Minnesota for a 1957 Faculty Summer Research Appointment held by W. E. N.

(2) Research Corporation Research Assistant, 1956–1957. We are indebted to the Research Corporation for a Frederick Gardner Cottrell grant in support of this research.

(3) O. Diels, F. Alder, and W. Lübbert, *Ann.*, 490, 277 (1931).

maleic anhydride, is formulated[4] as I, based on the now established[5] structure for diindole. It has been reported previously that malelydiindole is hydrolyzed by refluxing with 30% potassium hydroxide solution to indole (in 71% yield of one mole) and a *dibasic acid* (in 71–86% yield), m.p. 197°, having the composition of a molecule of indole plus a molecule of maleic acid. This dibasic acid yielded a dimethyl ester, m.p. 74°; neither the diacid nor the diester absorbed hydrogen in the presence of platinic oxide.[3]

We have found that the diacid has a molecular weight consistent with the formula $C_{12}H_{11}NO_4$. It has an intact indole nucleus, as shown by the ultraviolet spectrum. Alkylation on nitrogen has not occurred, as shown by the presence of NH stretching absorption in the infrared spectrum. An unsubstituted 2- or 3-position is indicated by a positive Ehrlich[6] test. Pyrolysis of the diacid gave carbon dioxide and 3-indolepropionic acid, as shown by comparison with an authentic sample. Anhydride exchange between the diacid and acetic anhydride gave an anhydride (III, in 84% yield), m.p. 102.5–103.5°. Finally, the diacid was found to be identical with a sample of 3-indolesuccinic acid[7] (II) prepared by coupling indole with diethyl diazosuccinate, as shown by no depression in mixed melting point and identity of the infrared spectra. The melting point of the diethyl ester of the diacid was also in agreement with that reported.[7] Thus, alkaline hydrolysis of maleyldiindole (I) appears to represent a most convenient synthesis of 3-indolesuccinic acid (II).



Indole and maleic or fumaric acids do not react under the same alkaline hydrolysis conditions as those under which II was formed. It appears, therefore, that II is formed from I prior to the formation of free indole and maleate dianion. The results of our study of the mechanism of this interesting rearrangement will be reported later.

EXPERIMENTAL

Melting points were determined on a calibrated hot stage.

Alkaline hydrolysis of maleyldiindole (I): preparation of 3-indolesuccinic acid (II). The procedure is that described previously,[3] except for modifications in the workup procedure.

Maleyldiindole[3,4] (10.0 g., 0.0301 mole) was refluxed for 3 hr. with 30% aqueous potassium hydroxide solution (100 cc.). The reaction mixture was cooled and extracted with ether, and the ether was evaporated, yielding crude indole (3.41 g., 0.0291 mole, 97%), m.p. 41–45°. The alkaline solution was acidified to Congo Red with dilute sulfuric acid and extracted with ether for 1–2 days in a liquid-liquid extractor. Evaporation of the ether left a pink solid (5.12 g., 0.0220 mole, 73%). Recrystallization, with charcoal, from ethanol-water yielded very pale pinkish white platelets (4.08 g.), m.p. 197–198° d. (with gas evolution). Mol. wt: Calcd. for $C_{12}H_{11}NO_4$: 233.22. Found (Rast): 274, 251, 272, average 266.[8] λ_{max} in 95% EtOH: 221 mμ (log ε 4.98), 273 (4.04), 280 (4.06), 290 (4.00).[8] ν_{NH} 3390, ν_{OH} ~2630, $\nu_{C=O}$ 1686 cm.$^{-1}$ in Nujol. Mixed m.p. with 3-indolesuccinic acid[7,9] of m.p. 195–197°, 195–197° d.; reported m.p. 199° d.[7] The infrared spectra of the two samples in Nujol were identical.

The diethyl ester of the diacid had m.p. 77–78.5°, in agreement with that reported for diethyl 3-indolesuccinate, m.p. 79–80°.[7] Heating of the diacid for 30 min. in an oil bath maintained at 201–204° caused evolution of a gas which formed a white precipitate when passed into barium hydroxide solution. Recrystallization of the pyrolysis residue, with charcoal, from ethanol-water gave white platelets in 44% yield, m.p. 131.5–132.5°, mixed m.p. with 3-indolepropionic acid,[10] 131.5–132.5°. The infrared spectra of the two samples in KBr disks were identical.

3-Indolesuccinic anhydride (III). 3-Indolesuccinic acid (2.00 g., 0.00858 mole), derived from the alkaline hydrolysis of maleyldiindole, was dissolved in freshly distilled acetic anhydride (50 cc.) and set aside at room temperature for 2 days. The acetic acid and acetic anhydride were removed at 0.3 mm. during 5 hr. while the temperature was kept below 70°. After standing for 2 days at room temperature the light brown residue crystallized in long needles (1.56 g., 0.00726 mole, 85%), m.p. 96.5–99.5°. Three recrystallizations from methylene chloride-light petroleum (b.p. 60–68°) and one recrystallization from methylene chloride at dry ice temperature yielded white crystals, m.p. 102.5–103.5°. ν_{NH} 3440 in Nujol, 3420 in KBr, 3510 in $CHCl_3$; $\nu_{C=O}$ 1861, 1781 in Nujol, 1863, 1776 in KBr, 1866, 1788 cm.$^{-1}$ in $CHCl_3$.

(4) W. E. Noland, R. K. Lange, F. B. Stocker, and G. L. Sauer, Paper 10 presented before the Organic Division at the 132nd National American Chemical Society Meeting, New York, N. Y., Sept. 9, 1957, Abstracts, p. 6P.

(5) (a) G. F. Smith, *Chemistry & Industry*, 1451 (1954). (b) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 3544 (1957).

(6) A. Treibs and E. Herrmann, *Hoppe-Seyler's Z. physiol. Chem.*, 299, 168 (1955).

(7) R. W. Jackson and R. H. Manske, *Can. J. Research*, 13B, 170 (1935).

(8) Gerald L. Sauer, M. S. thesis, University of Minnesota, 1955.

(9) We are grateful to Dr. Léo Marion, Director, Division of Pure Chemistry, National Research Council, Ottawa, Ont., and to Dr. R. H. Manske for sending us a sample of 3-indolesuccinic acid prepared by Dr. Manske.

(10) We are indebted to Mr. L. A. Crisorio, Carbide and Carbon Chemicals Company, Chicago, Ill., for a generous sample of 3-indolepropionic acid.

Anal. Calcd. for $C_{12}H_9NO_3$ (215.20): C, 66.97; H, 4.22; N, 6.51. Found: C, 66.92; H, 4.20; N, 6.28.

Attempted reaction of indole and maleic and fumaric acids under alkaline hydrolysis conditions. Indole (7.06 g., 0.0602 mole) and maleic acid (3.49 g., 0.0301 mole) were refluxed for 3 hr. with 30% aqueous potassium hydroxide solution (100 cc.). The reaction mixture was cooled, extracted with ether (3–50 cc. portions), and the ether evaporated, yielding crude indole (6.88 g., 97%), m.p. 39–42°.

In an identical experiment, with fumaric acid in place of maleic acid, the recovery of crude indole was 7.05 g., 100%, m.p. 39–43°.

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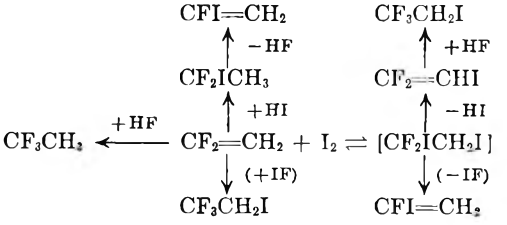
Thermal Reaction of 1,1-Difluoroethylene with Iodine[1]

MURRAY HAUPTSCHEIN, ARNOLD H. FAINBERG, AND MILTON BRAID

Received March 25, 1957

1,1-Difluoroethylene has been found to react thermally with iodine to form quite unexpectedly, 1,1,1-trifluoro-2-iodoethane as the major product. Another principal product of the reaction was an olefin boiling at *ca.* 40°, for which the structure 1-fluoro-1-iodoethylene is proposed. Two minor products were also identified in the reaction mixture, 1,1-difluoro-1-iodoethane and 1,1-difluoro-2-iodoethylene, as well as some polymeric material. In the presence of the very large excess of 1,1-difluoroethylene used in the present work, 1,1,1-trifluoroethane was a major by-product.[2]



It is obvious that the conditions employed in the single experiment reported herein were not designed to produce the iodine-containing products in optimum yields, which, of course, would be greatly improved by use of an excess of iodine.

EXPERIMENTAL

Thermal reaction of 1,1-difluoroethylene with iodine. Into a 170-ml. monel autoclave were placed 63.5 g. (0.25 mole) of crystalline iodine. The autoclave was cooled in liquid nitrogen, and 80 g. (1.25 moles) of 1,1-difluoroethylene were condensed in it by means of gaseous transfer *in vacuo*. After heating at 185° with shaking for 160 hr., during which the pressure dropped from 3200 to 1300 p.s.i., the autoclave was cooled to room temperature and vented at atmospheric pressure into a liquid nitrogen-cooled receiver.

The recovered product consisted of 53 g. of material, gaseous at room temperature, shown by infrared analysis to consist only of unreacted CH_2=CF_2 (mostly) and CF_3-CH_3,[3] 53 g. of liquid product, and 37 g. of solids, containing some polymeric material and unreacted iodine. Distillation of the liquid product gave 38 g. of liquid boiling below 55°, and 14 g. of polymer boiling above 145°.

Fractional distillation of a 25-g. portion[4] of the liquid product through a 2 ft. × 8 mm. Mini-Cal Podbielniak column gave several fractions totalling 8 g., b.p. 40–46°, n_D^{29} 1.39–1.41 and 16 g. of CF_3CH_2I, b.p. 54–55°, center cut: b.p. 55.0° (756 mm.), n_D^{29} 1.3962, reported[5] b.p. 55.0°, n_D^{25} 1.3981. Its infrared spectrum was identical with that of an authentic sample prepared by iodide displacement on 2,2,2-trifluoroethyl *p*-toluenesulfonate. Principal infrared bands for CF_3CH_2I: 3.36, 6.81, 7.01, 7.43, 7.78, 8.19, 8.90, 9.44, 11.9, 14.9μ.

The infrared spectrum of the fractions b.p. 40–46° showed that the mixture consisted principally of an olefin A, b.p. *ca.* 40°, with a double bond stretching band at 6.09, 6.14μ (doublet). Also indicated were minor amounts of a second olefin B, boiling virtually at the same temperature as A (perhaps slightly higher), having a double bond stretching band at 5.79μ, and a saturated compound boiling several degrees higher than the olefins, and exhibiting remarkably intense C—H stretching bands at 3.33 and 3.40μ.

The saturated compound was identified as CH_3CF_2I, reported[6] b.p. 45°, n_D^{19} 1.4183 on the basis that the infrared spectrum of the mixture contained the nine major peaks found[7] for an authentic sample. Olefin B was similarly identified spectroscopically as CF_2=CHI, reported[8] b.p. 35.5° at 622 mm.

Olefin A has principal peaks in the infrared at 6.09, 6.14, *ca.* 8.3, 8.68, 8.95, 9.55, 9.60, 10.20, 11.03, 11.82, and 12.26μ. Its double bond stretching frequency is consistent with a CH_2=CFX type of structure,[9] and the structure CH_2=CFI, is proposed.

PHILADELPHIA, PA.

(1) The work herein reported was carried out under contract between the Office of Naval Research and the Pennsalt Chemicals Corp. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) All of the products isolated can be related schematically through the iodine adduct of 1,1-difluoroethylene (not isolated) as shown below:

(3) A.P.I. Research Project 44, Catalog of Infrared Spectral Data, No. 979.

(4) This portion was not an entirely representative sample of the 38 g. of liquid boiling below 55°, but was richer in the least volatile component.

(5) G.V.D. Tiers, H. A. Brown, and T. S. Reid, *J. Am. Chem. Soc.*, 75, 5978 (1953).

(6) R. N. Haszeldine, *J. Chem. Soc.*, 61 (1956).

(7) R. N. Haszeldine, private communication: 3.34, 3.40, 7.20, 8.47, 9.03, 9.07, 10.40, 11.27, 11.35μ.

(8) Private communication of J. D. Park; M. Hein, Ph.D. Thesis, University of Colorado (1954): 5.80, 7.62, 7.68, 8.77, 8.85, 10.52, 10.63, 13.58μ.

(9) *E.g.*, the double-bond stretching frequency of CH_2=CClF is 6.08μ. See I. P. Torkington and H. W. Thompson, *Trans. Faraday Soc.*, 41, 236 (1945).

Dimerization of Perfluoro-2-azapropene, $CF_3N{=}CF_2$[1]

MURRAY HAUPTSCHEIN, MILTON BRAID, AND FRANCIS E. LAWLOR

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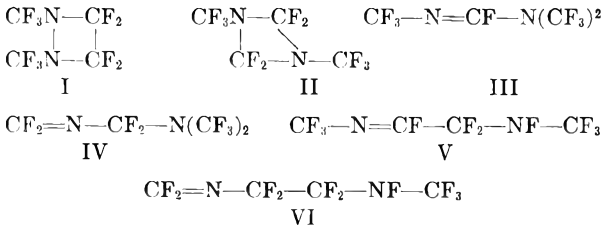
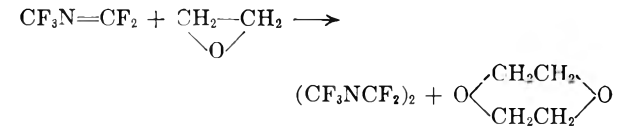
Perfluoro-2-azapropene, $CF_3N{=}CF_2$,[2,3] has been made to dimerize in 80% conversion and yield by ultraviolet irradiation in the presence of ethylene oxide.[4] The analytically pure dimer $C_4F_{10}N_2$, b.p. 39°, can have six possible structures.



The presence of —CF=N— unsaturation is revealed in the non-complex infrared spectrum (expected of a chemical individual) by a very strong absorption at 5.66 μ. Thus the saturated cyclic dimers[5] I and II are eliminated as possibilities or can at most be minor impurities. Furthermore, since $CF_3{-}N{=}CF_2$ has a strong band at 5.54 μ which is assigned to the N=C stretching vibration, structures IV and VI which also contain terminal $-N{=}CF_2$ groups and thus would be expected to have bands nearer 5.54 μ rather than at 5.66 μ, are very improbable. Structures III or V, therefore, remain as possibilities.

Is is also of considerable interest to note that the other principal product of this reaction was 1,4-dioxane, which is a dimer of ethylene oxide. Dimerization was not observed when either component was irradiated in the absence of the other under identical conditions. Thus the reaction is best represented by the equation:



EXPERIMENTAL

Pyrolysis of bis(trifluoromethyl)carbamyl fluoride. A modification of the procedure of Young *et al.*[3] was used. The pyrolysis was carried out in a platinum-lined 1″ O.D. nickel tube filled with CXA Columbia activated carbon (8 mesh). $(CF_3)_2NCOF$ was passed through this tube heated at 490° ± 10° over a 26″ length. The flow rate was 0.5–0.6 mole/hour. Conversions and yields of $CF_3N{=}CF_2$ and COF_2 were above 90%. At a temperature of 600° and a flow rate of 0.04 mole/hour only a very low yield of $CF_3N{=}CF_2$ was obtained; extensive decomposition of the azomethine must have taken place.

The dimerization of perfluoro-2-azapropene in the presence of ethylene oxide and ultraviolet light. Into a 90-ml. Pyrex glass ampoule 10.2 g. (0.767 mole) of $CF_3N{=}CF_2$ and 4.6 g. (0.104 mole) of ethylene oxide were introduced *in vacuo*. The sealed tube was exposed for 14 days to ultraviolet irradiation from a Hanovia SH burner. During this period the originally homogeneous solution separated into two layers. At the end of the reaction an amber colored upper layer represented about 40% of the total volume; the lower layer was colorless. The tube was opened at −78° and allowed to warm up to room temperature at atmospheric pressure. During this venting period no volatile products were collected in Dry Ice-cooled traps. Separation into two principal fractions was then accomplished by vacuum transfer at room temperature. The volatile, denser fraction on distillation in a small Vigreux unit gave 8 g. (78%) of a dimer, $(CF_3NCF_2)_2$, b.p. 39°, n_D^{22} 1.27.

Anal. Calcd. for $C_4F_{10}N_2$: C, 18.1; F, 71.4; N, 10.5. Found: C, 18.1; F, 71.3; N, 10.2.

The less volatile fraction (*ca.* 7 g.) had a wide boiling range, *ca.* 30° (90 mm.) to >90° (0.1 mm.). Three grams of this fraction, b.p. 40–44° (93 mm.), consisted of at least 80% pure dioxane, as shown by its infrared spectrum.

In another experiment, 7.0 g. (0.053 mole) of $CF_3N{=}CF_2$ and 12.1 g. (0.28 mole) of ethylene oxide, sealed in a Vycor No. 7910 tube, were exposed to ultraviolet irradiation for 9 days. There were obtained $(CF_3NCF_2)_2$, in about 80% conversion and yield, and 1,4-dioxane, b.p. 99–101°; middle cut, b.p. 101°, f.p. 12°, n_D^{30} 1.412, which was shown by its infrared spectrum to be at least 99% pure.

The principal infrared bands for $C_4F_{10}N_2$: 5.66, 7.18, 7.52, 7.89, 8.12, 8.38, 10.0, 12.05, 13.15, 13.37, 14.02, 15.23μ.

PHILADELPHIA, PA.

(1) The work herein reported was carried out under contract between the Office of Naval Research and the Pennsalt Chemicals Corp. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) D. A. Barr and R. N. Haszeldine, *J. Chem. Soc.*, 1881 (1955).

(3) J. A. Young, T. C. Simmons, and F. W. Hoffmann, *J. Am. Chem. Soc.*, **78**, 5637 (1956).

(4) Under these conditions, with $CF_3CF{=}CF_2$, where CF replaces N, copolymers with ethylene oxide are formed. See M. Hauptschein and J. M. Lesser, *J. Am. Chem. Soc.*, **78**, 676 (1956) for a description of the use of ethylene oxide in certain polymerizations of fluorinated olefins.

(5) These cyclic dimers may be considered the nitrogen analogs of the perfluoro(dimethylcyclobutanes) produced by the thermal dimerization of perfluoropropene. See M. Hauptschein, A. H. Fainberg, and M. Braid, *J. Am. Chem. Soc.*, in press.

Communications TO THE EDITOR

A Modification of Free Radical Reactions

Sir:

It has been observed that certain additives modify the course of free radical reactions. In the present communication we wish to describe the marked effect of trace amount of copper salts on both the rates and products of well known free radical reactions.

In the presence of 1 mole % of copper chloride benzoyl peroxide, *tert*-butyl peroxide, *tert*-butyl perbenzoate,[1] *tert*-butyl hydroperoxide, and α-cumyl hydroperoxide undergo a fast induced decomposition in solvents, whereas in the absence of copper chloride, these compounds normally undergo a slow first-order decomposition or no decomposition whatever. The products of the regular (R) and modified (M) reactions are quite different as illustrated in the following examples:

Decomposition of *tert*-butyl peroxide (1 mole) in benzaldehyde (7 moles) at 140°: (M) *tert*-butyl benzoate, 83%; benzpinacol dibenzoate, less than 5%. (R) only benzpinacol dibenzoate.[2]

Decomposition of benzoyl peroxide (1 mole) in cumene (10 moles) at 80°: (M) α-cumyl benzoate, 30% (b.p. 110°/0.1 mm., n_D^{20} 1.5560. *Anal.* Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.7. Found: C, 80.15; H, 6.9. The infrared spectrum and the hydrolysis products are in agreement with the structure proposed); isopropyl biphenyls, 20%; no dicumene. (R) dicumene, 35%; isopropyl biphenyls, 24%.[3]

Decomposition of *tert*-butyl perbenzoate (1 mole) in cumene (10 moles) at 90° (perbenzoate was added dropwise to the cumene containing 0.01 mole of copper chloride): (M) α-cumyl benzoate, 40%.

Decomposition of benzoyl peroxide (1 mole) in octene-1 (8 moles) at 90°: (M) high mol. wt. polymers, 7 g; benzoic acid 72%; phenyloctene, 8%; 1:1 adduct (one benzoyloxy to one octene), 35%; 1:2 adduct, 34%. The 1:1 adduct is mostly 1-benzoyloxy octene-2, mixed with benzoyloxyoctane and 3-benzoyloxy-1-octene. It is unsaturated to the extent of 77%. Its infrared spectrum has a strong band at 975 cm.$^{-1}$ (trans double bond) and a weaker band at 930 cm.$^{-1}$ (established to be characteristic of terminal double bonds in this type of compounds). (R) polymers, 340 g. (average mol. wt., 600); benzoic acid, less than 6%.

Decomposition of benzoyl peroxide (1 mole) in octene-2 (8 moles) at 90°: (M) 1:1 adduct, 80% (completely unsaturated); only traces of higher polymers. (R) 1:1 adduct, 85% (only 60% unsaturated); 1:2 adduct, 13%.

Decomposition of benzoyl peroxide (1 mole) in a solution of valeraldehyde (2 moles) in carbon tetrachloride: (M) benzoic acid, one mole, acid anhydrides, one mole; no attack on carbon tetrachloride. (R) chloroform, 1 mole; hydrochloric acid, 1 mole; acid anhydrides, 2 moles (due to the reaction between the initially formed acid chloride and benzoic acid).[4]

Pyrolysis of dicumene in bromobenzene at 250°: (M) 70% of dicumene is recovered unchanged after 20 hr. (R) all the dicumene disproportionates into cumene and α-methylstyrene.

We wish to propose the formation of unstable copper organic complexes as intermediates in these reactions.

Acknowledgment. The authors are indebted to Otto B. May, Inc. for the financial support which made this work possible. They also wish to thank Drs. T. P. Rudy and N. C. Yang for much help in the laboratory and many fruitful discussions.

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(1) A separate investigation of the copper-catalyzed decomposition of *tert*-butyl perbenzoate by M. S. Kharasch and G. Sosnowsky is in press.

(2) F. F. Rust, F. H. Seubold, and W. E. Vaughn, *J. Am. Chem. Soc.*, 70, 3258 (1948).

(3) D. H. Hey, B. W. Pengilly, and G. H. Williams, *J. Chem. Soc.*, 1463 (1956).

(4) S. Winstein and F. H. Seubold, *J. Am. Chem. Soc.* 69, 2916 (1947).

(5) Deceased.

(6) Prepared the manuscript.

A New Method of Introducing Peroxy Groups into Organic Molecules

Sir:

We wish to report the discovery of a new reaction. We find that in the presence of trace amounts of copper, cobaltous or manganous salts, alkyl and aralkyl hydroperoxides react readily with organic molecules containing a slightly activated hydrogen, replacing it with a peroxy group.[1] For example, *tert*-butyl hydroperoxide reacts with cumene in the presence of a metal salt to give *tert*-butyl-α-cumyl peroxide. This method appears as effective in introducing a peroxy group as *N*-bromosuccinimide is in

(1) W. Pritzkow and K. A. Muller [*Ann.*, 597, 167 (1956) and *Ber.*, 89, 2321 (1956)] are the most recent to report that Cu, Co, and Mn salts catalyze the decomposition of hydroperoxides. But neither they, nor any previous author, reported any peroxides among the products.

introducing a bromine atom. The similarity does not hold where the bromination proceeds by an ionic mechanism, *e.g.*, the bromination of dimethyl aniline with *N*-bromosuccinimide. In such cases, a different hydrogen atom, the one most activated for free radical attacks, will be replaced by the peroxy group. The peroxydation of olefins, with cobaltous naphthenate as a catalyst, was already observed by Kharasch, Pauson, and Nudenberg.[2] These authors used a much larger amount of the catalyst, thus failed to obtain a reaction with cumene, and concluded that the reaction was only applicable to olefins. Using 0.2 mole % cobaltous 2-ethylhexoate or small amounts of cuprous or manganous salts (the reaction is less sensitive to excess of these catalysts) and warming to 60–70° the solution of the hydroperoxide and the substrate in a solvent, we observe that the reaction proceeds smoothly and rapidly. The reaction is 70% completed in less than 12 hr. Benzene, chloroform, heptane, *tert*-butyl alcohol, pyridine, acetic acid, nitrobenzene, and ethyl acetate are found to be suitable solvents. The use of excess substrate also favors the reaction. (Attention is drawn to the fact that nitrobenzene, an unsuitable solvent for regular free radical reactions, does not inhibit a modified radical reaction.)

The following peroxides have been prepared by this method (reaction temperature 70°, reaction time 24 hr.): α-cumyl-tert-butyl peroxide; yield 90%; physical constants and infrared spectrum identical with those of the known compound.[3] 2-methyl-2-*tert*-butylperoxycyclohexanone; yield 90%; b.p. 66°/2 mm.; n_D^{20} 1.4431. *Anal.* Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07; mol. wt. 200. Found: C, 65.9; H, 9.9; mol. wt., 189. The infrared spectrum indicates that the peroxy group is α to the carbonyl.

2-*tert*-Butylperoxycyclohexanone; yield, 20%; b.p. 52°/0.15 mm.; n_D^{20} 1.4500. *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.5; H, 9.74; mol. wt., 186. Found: C, 64.0; H, 9.5; mol. wt., 176. The infrared spectrum indicates that the peroxy group is α to the carbonyl. Decomposes on standing to yield large amounts of adipic acid.

α-Cumylperoxycyclohexene; yield, 90% b.p. 98°/0.1 mm.; n_D^{20} 1.5238. *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; mol. wt., 232. Found: C, 77.8; H, 8.8; mol. wt., 220.

The preparation of *tert*-butylperoxycyclohexene and 1-*tert*-butylperoxy-2-octene have been previously described.[1] A more careful investigation shows that the reaction of 1-octene with *tert*-butyl hydroperoxide yields equal amounts of 1-*tert*-butylperoxyoctene-2 and 3-*tert*-butylperoxyoctene-1. (B.p. 57°/2.5 mm.; n_D^{20} 1.4243.) *Anal.* Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.0; H, 12.2. Infrared spectrum, bands at 920 cm.$^{-1}$ and 990 cm.$^{-1}$

The general applicability of this new method is readily demonstrated by the preparation of *N*-methyl-*N*-*tert*-butylperoxymethylaniline, in 95% yield, from dimethyl aniline at room temperature in benzene as solvent. This peroxide can be titrated iodometrically in acetic acid, but is not decomposed after 24 hr. refluxing in benzene. (B.p. 75°/0.1 mm.; n_D^{20} 1.5160. *Anal.* Calcd. for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15; N, 6.70; mol. wt., 209. Found: C, 69.1; H, 8.9; N, 7.0; mol. wt., 212. The infrared spectrum indicated no nuclear substitution whatever.)

Investigation of the use of other possible metal salts as catalysts, other type of substrates[4] and other hydroperoxides and hydrogen peroxide for the synthesis of peroxides is in progress.

Acknowledgment. The authors are indebted to Otto B. May, Inc., for the financial support which made this work possible. They also wish to thank Drs. T. P. Rudy and N. C. Yang for much help in the laboratory and many fruitful discussions.

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(2) M. S. Kharasch, P. Pauson, W. Nudenberg, *J. Org. Chem.*, 18, 322 (1953).

(3) M. S. Kharasch, A. Fono, W. Nudenberg, *J. Org. Chem.*, 15, 753 (1950).

(4) Interesting examples of replacement of labile hydrogen atom by a *tert*-butylperoxy group have been observed by M. S. Kharasch and G. Sosnowsky in the course of the investigation of autoxidation of nitriles, and by the present authors in the peroxidation of xylenes, dioxane, etc. Results of these studies will be the subject of forthcoming publications.

(5) Deceased.

(6) Prepared the manuscript.

Radical Substitution Reactions

Sir:

We wish to describe free radical reactions in which a hydrogen atom is replaced by a benzoyloxy or a phthalimido group.

If *tert*-butyl hydroperoxide (one mole) and benzoic acid (one mole) are added to cyclohexene (10 moles) and the reaction mixture is warmed to 80° in the presence of 0.2 mol % cuprous chloride, there is obtained cyclohexenyl benzoate in over 90% yield. (B.p. 103°/0.15 mm., n_D^{20} 1.5380. *Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.29; H, 6.89; mol. wt., 202. Found: C, 77.50; H, 7.1; mol. wt., 203. Unsaturation, 100% by ozonolysis.) Using only a slight excess of cyclohexene, benzene, *tert*-butyl alcohol, and nitrobenzene were found suitable solvents for this reaction.

With octene-1 as the substrate and solvent, 3-benzoyloxyoctene-1 is isolated in 50% yield. (B.p. 105°/0.2 mm., n_D^{20} 1.4920. *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; mol. wt., 230. Found: C, 77.23; H, 8.81; mol. wt., 235.) The infrared spectrum indicates the presence of terminal double bonds only. The product is thus different from the one obtained by the action of benzoyl peroxide on

octene-1 (described in a previous communication). Both 1-*tert*-butylperoxyoctene-2 and 3-*tert*-butylperoxyoctene-1 are formed as by-products.

The formation of α-cumyl benzoate from cumene, equimolar amounts of *tert*-butyl hydroperoxide and benzoic acid in the presence of trace amounts of copper salts proceeds less readily and shows a remarkable solvent effect. The highest yield, 20%, is obtained in excess cumene, in the presence of less than 0.2 mol % catalyst. Increased amounts of catalyst decrease the yield in favor of the α-cumyl *tert*-butyl peroxide, which is always the major product. When benzene or *tert*-butyl alcohol is used as a solvent, in the presence of 1.5 mole of cumene and 0.002 moles copper chloride, α-cumyl benzoate is formed in yields of only 11% and 6%, respectively. With nitrobenzene pyridine, acetic acid, or heptane as the solvent, no benzoate could be detected.

When *tert*-butyl hydroperoxide (one mole) was added over a period of 3 hours at 80° to a suspension of phthalimide (one mole) in a benzene (10 moles) solution of cyclohexene (1.5 moles) containing 0.002 mole cuprous chloride, *N*-cyclohexenyl phthalimide (0.14 mole) was isolated. (M.p., 114.5°, from alcohol. *Anal.* Calcd. for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77; N, 6.16; mol. wt., 227. Found: C, 73.96; H, 6.0; N, 6.16; mol. wt. 240. Unsaturation 100% by ozonolysis.) Its infrared spectrum is in agreement with the assigned structure. A solvent effect similar to the one observed with α-cumyl benzoate is found. Best solvents are benzene, xylene, acetonitrile, and ethyl acetate. Work in progress indicates that with *tert*-butyl peroxide as oxidizing agent this reaction is almost quantitative. It also indicates that saccharin and pyrimidine are also able to give *N*-substituted products.

Substitution is observed also in radical reactions of the conventional type. Decomposition of di-*tert*-butyl peroxide in cumene, in the presence of benzoic acid yields about equal amounts of dicumene and α-cumyl benzoate. However, addition of one mole per cent cuprous chloride inhibits completely the formation of dicumene but increases the yield of α-cumyl benzoate.

The solvent effect observed in these reactions indicates that the radicals form a loose complex with the solvent. The most suitable solvents are those which are known to give stable complexes with triphenyl methyl radicals.[1]

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(1) M. Gomberg and L. H. Cone, *Ber.*, **38**, 1333 (1905).
(2) Deceased.
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Disproportionation Reaction of Diphenylsilane in the Absence of Any Added Catalyst

Sir:

Disproportionation reactions of organosilicon compounds have been known for a long time, one of the early reactions[1] of this type being that in which triethylphenylsilane (itself formed in a sealed tube reaction at 175° from diethylzinc and trichlorophenylsilane) disproportionated into diethyldiphenylsilane and tetraphenylsilane. This disproportionation reaction occurred during either the sealed tube reaction or subsequent manipulations including distillation. It seems likely that the zinc chloride by-product from the original reaction acted as a Lewis acid type catalyst. What may be the first example of the disproportionation of a silicon hydride compound can be found in the silane experiments of Stock and Somieski.[2] During the course of their work, silane and dichlorosilane were allowed to react in a sealed tube with aluminum chloride at 100° for 7 days. Subsequent work-up yielded a significant amount of chlorosilane. No reaction was noted in the cold without added catalyst.

While such disproportionation reactions had been known, it remained for Calingaert, Beatty *et al.*[3] to establish the identity of the "redistribution reaction," in which random distribution of all possible products is noted. There is ample proof that many such reactions do occur,[3,4,5] but in some cases, such as the methylchlorosilanes[6,7] and the ethoxychlorosilanes,[8] the distribution is nonrandom. As noted previously a disproportionation reaction of a silicon hydride compound has been reported.[2] Other similar reactions are known. For instance, Benkeser, Landesman and Foster[9] in several articles have reported the "apparent redistribution" reactions of phenylsilane and diphenylsilane in the

(1) A. Ladenburg, *Ber.*, **7**, 387 (1874). See also, C. Friedel and A. Ladenburg, *Ann.*, **143**, 124 (1867), and C. Friedel and J. M. Crafts, *Ann. chim. phys.*, (4) **9**, 5 (1866).
(2) A. Stock and C. Somieski, *Ber.*, **52**, 719 (1919).
(3) See G. Calingaert and H. A. Beatty in H. Gilman's *Organic Chemistry, An Advanced Treatise*, John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1943, pp. 1806–20 for a survey of work, including their own, on the redistribution reaction.
(4) H. H. Anderson, *J. Am. Chem. Soc.*, **66**, 934 (1944); **72**, 2091 (1950); **73**, 5800 (1951); G. S. Forbes and H. H. Anderson, *J. Am. Chem. Soc.*, **66**, 931 (1944); **67**, 1911 (1945).
(5) M. Kumada, *J. Inst. Polytech. Osaka City Univ., Ser. C*, **2**, 131 (1952); [*Chem. Abstr.*, **48**, 11303 (1954)].
(6) R. O. Sauer and E. M. Hadsell, *J. Am. Chem. Soc.*, **70**, 3590 (1948).
(7) P. D. Zemany and F. P. Price, *J. Am. Chem. Soc.*, **70**, 4222 (1948).
(8) M. Kumada, *J. Inst. Polytech. Osaka City Univ., Ser. C*, **2**, 139 (1952); [*Chem. Abstr.*, **48**, 11303 (1954)].
(9) R. A. Benkeser, H. Landesman, and D. J. Foster, *J. Am. Chem. Soc.*, **74**, 648 (1952); R. A. Benkeser and D. J. Foster, *J. Am. Chem. Soc.*, **74**, 4200, 5314 (1952).

TABLE I

DISPROPORTIONATION REACTION OF DIPHENYLSILANE, R_2SiH_2

Run	Reactants[a]	Time, hr.	t, °C.	Products, %[a]
1	R_2SiH_2, $H_2PtCl_6 \cdot 6H_2O$, furan	24[b]	100	Furan, 52; $RSiH_3$, 55.5; R_2SiH_2, 8.2; R_3SiH, 19.3; R_4Si, 0.1
2	R_2SiH_2	24.8[c]	100, 160[c]	R_2SiH_2, 61.3; a mixture[d] (*ca.* 20%) of R_3SiH and R_2SiH_2 also was obtained
3	R_2SiH_2, $H_2PtCl_6 \cdot 6H_2O$	24.8[c]	100, 160[c]	$RSiH_3$, 73; R_4Si, 15.7
4	R_2SiH_2[e]	13	230[f]	$RSiH_3$, 28.2; R_3SiH, 15.2; R_4Si, 8.1
5	R_2SiH_2, PtO_2[e]	13	230[f]	SiH_4, ?; $RSiH_3$, 26.2; R_2SiH_2, 21; R_3SiH, 10; R_4Si, 7.3
6	R_2SiH_2, Pt[e,g]	13	230[f]	SiH_4, ?; $RSiH_3$, ?
7	R_2SiH_2	3	300[h]	SiH_4, ?; $RSiH_3$, 11.2; R_2SiH_2, 45; R_3SiH, 11.8; R_4Si, 0.1

[a] R stands for C_6H_5. [b] Sealed tube reaction (all others under N_2 gas). [c] Heated first at 100° (24 hr.) then at 160° (8 hr.). [d] The mixture was identified by infrared spectra and n_D^{20}. [e] Reactions 4, 5, and 6 were run simultaneously and a common nitrogen train was used with a single mineral oil bubbler at the outlet. Silane was evolved at this bubbler as evidenced by burning and smoke (smoke identified as SiO_2). Heating 4, 5, and 6 separately indicated that silane was evolved from 5 and 6, but not from 4 (see, however, Reaction 7). [f] Bath temperature. [g] The platinum employed was sheet metal. Dr. Riley Schaeffer identified the silane evolved in this reaction. The gas was collected in a closed flask and later transferred to his vacuum system. When the collecting vessel was removed, a rather violent explosion of some silane remaining in the reaction vessel (ice-cooled) was observed, and the residue was not worked up. The silane sample which was collected melted soon after the liquid nitrogen bath (−196°) was removed and had a vapor pressure of 775 mm. of mercury at −111.9°; silane is reported [A. Stock and C. Somieski, *Ber.*, 49, 111 (1916)] to melt at −186° and to boil at −111.8°. The sample collected also had a trace of liquid which was apparently diphenylsilane (based on an infrared spectrum in carbon disulfide solution). [h] Bath temperature; diphenylsilane would probably boil at *ca.* 230° at atm. pressure [based on extrapolation of the recorded boiling point (ref. 8) at 0.06 mm. by use of a Pressure-Temperature Alignment Chart].

presence of potassium metal at room temperature or the presence of sodium metal in refluxing decalin. The authors[9] term the reaction "apparent redistribution" because of their theorized mechanism involving cleavage of phenyl groups by the metal, the formation of intermediate phenylsilylmetallic compounds and their subsequent hydrolysis. Such a mechanism is probably quite different from that involved in the use of the usual aluminum chloride type catalyst. However, phenylsilane and phenylmethylsilane have undergone disproportionation reactions in the presence of aluminum chloride.[10] The reactions were carried out at relatively low temperatures (20–50°) and tended to explode in the presence of atmospheric oxygen. Ether completely retards this reaction. The same authors[10] also report the disproportionation of phenylmethylsilane and of chlorophenylsilane using an aluminum chloride catalyst.

Most of the disproportionation or redistribution reactions of organosilicon compounds have been catalyzed by aluminum chloride[2,3,10–12] or related compounds (*e.g.*, zinc chloride in the sealed tube reaction mentioned previously[1]), or have had halosilanes present which may act as the catalyst. A recent series of patents[13] describes the catalysis of such reactions with alkali metal alkoxides. Some silicon hydride compounds are among those so disproportionated. In other recent work it has been shown[14] that alkylaluminum hydride compounds and silicon tetrahalides redistribute the hydrogen and halogen to give silicon hydride compounds rather than silicon alkyl compounds.

We now wish to report that diphenylsilane undergoes a disproportionation reaction in the presence of a platinum catalyst or *in the absence of any added catalyst*. The initial discovery was made during an attempt to add diphenylsilane to furan using chloroplatinic acid as the catalyst. The use of this catalyst for similar addition reactions has been recommended by Speier, Webster, and Barnes.[15] The original reaction was carried out in a sealed tube heated at 100° for 24 hr. Work-up of the reaction mixture, which originally contained 0.1 mole each of furan and diphenylsilane with a small amount of catalyst, yielded 52% of the furan, 8.2% of the diphenylsilane, 55.5% of phenylsilane, 19.3% of triphenylsilane, and 0.1% of tetraphenylsilane. A series of experiments, summarized in Table I, was carried out to establish whether chloroplatinic acid or another platinum catalyst, furan, or simply

(10) J. L. Speier and R. E. Zimmerman, *J. Am. Chem. Soc.*, **77**, 6395 (1955).

(11) P. D. George, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **77**, 1677 (1955).

(12) R. O. Sauer (to General Electric Co., Inc.) U. S. Patent **2,730,983**, Jan. 10, 1956; [*Chem. Abstr.*, **50**, 12108 (1956)].

(13) D. L. Bailey (to Union Carbide and Carbon Co., Inc.) U. S. Patent **2,723,983**; **2,723,984**; **2,723,985**; Nov. 15, 1955; [*Chem. Abstr.*, **50**, 10125 (1956)].

(14) R. Köster, *Angew. Chem.*, **68**, 383 (1956).

(15) J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Am. Chem. Soc.*, **79**, 974 (1957).

heat would cause the reaction. Comparison of Runs 4 and 5 indicates that there is no substantial difference in reactions containing catalyst and those not containing catalyst at this temperature (230°), although no silane gas was noted in the noncatalyzed reaction. At the lower temperature of Runs 2 and 3, the platinum definitely seems to act as a catalyst. Comparison of Runs 2, 4, and 7 shows that *increased temperature will cause disproportionation of diphenylsilane in the absence of any added catalyst.*

The fact that such disproportionations occur should be of interest in view of current research with regard to the addition reactions of silicon hydride compounds; these important side reactions may be caused by certain catalysts or take place in the absence of any added catalyst.

It would be interesting to consider whether many other substances may redistribute in the absence of added catalyst, provided that their decomposition temperatures are not too low.

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Stereoselectivity in the Carbanion-Catalyzed Isomerization of 1-Butene[1]

Sir:

The double bond isomerization of alkenes and cyclenes in the presence of a sodium catalyst has been reported recently,[2-4] and it was observed[3a,b] that this is a reversible reaction leading to an equilibrium mixture.

It was suggested that the double bond migration occurs through a chain mechanism involving a carbanion attack on an allylic hydrogen. In order to elucidate further the mechanism of double bond migration a kinetic study of the carbanion-catalyzed isomerization of alkenes was undertaken.

The present communication deals with the isomerization of 1-butene to 2-butenes in the temperature range of 37–195° using as catalysts sodium-anthracene, sodium-alumina, and lithium-alumina.

It was found that the initial products obtained from the isomerization of 1-butene over a sodium-anthracene catalyst are kinetically controlled and that the less stable *cis*-2-butene is produced at a higher rate than the *trans* isomer. The initial ratio of the *cis/trans* isomers decreases with increasing temperature, as indicated in Table I.

TABLE I

RESULTS OBTAINED FROM THE ISOMERIZATION OF 1-BUTENE[a]

Time, Min.	Butene % 1-	2-*trans*	2-*cis*	*cis/trans*[a]
	Temperature 145°			
10	95.9	1.4	2.7	2.0
40	86.6	4.5	8.9	2.0
70	71.5	9.6	18.9	2.0
160	20.0	30.9	49.1	1.6
	Temperature 195°			
10	87.4	5.7	6.9	1.20
25	74.5	11.8	13.7	1.16
45	55.5	21.4	23.1	1.1
65	39.9	31.0	29.1	0.94
105	22.3	46.5	31.2	0.67
145	18.1	50.4	31.5	0.63
245	14.7	54.4	30.9	0.57
Calcd.[b]	12.6	58.3	29.1	0.50

[a] The reaction was carried out in a 450-ml. capacity rotating autoclave charged with 5 g. of 1-butene, about 1 g. of sodium and 0.4 g. of anthracene. [b] Calculated from the thermodynamic data.[6]

When the sodium is dispersed on powdered alumina[5] it is possible to carry out the isomeriza-

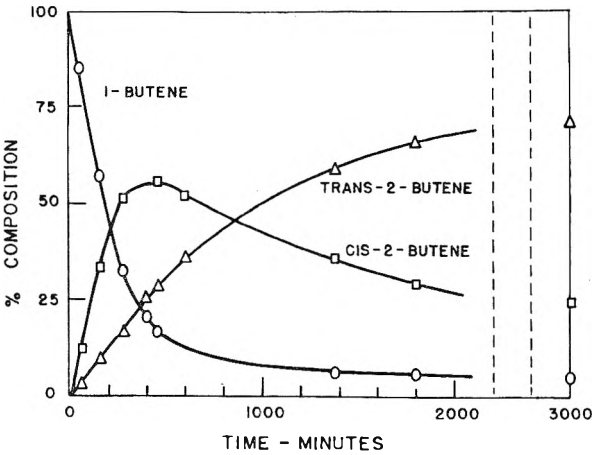


Fig. 1. Isomerization of 1-Butene. The reaction was made in a 450 ml. autoclave at 37° using 20 g. of 8% sodium on alumina and 16 g. of 1-butene

(1) Paper XII of the series "Base Catalyzed Reactions of Hydrocarbons." For paper XI see M. Kolobielski and H. Pines, *J. Am. Chem. Soc.*, 79, 5820 (1957).

(2) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Am. Chem. Soc.*, 77, 347 (1955).

(3) H. Pines and H. E. Eschinazi, *J. Am. Chem. Soc.*, (a) 77, 6314 (1955); (b) 78, 1178 (1956); (c) 78, 5950 (1956).

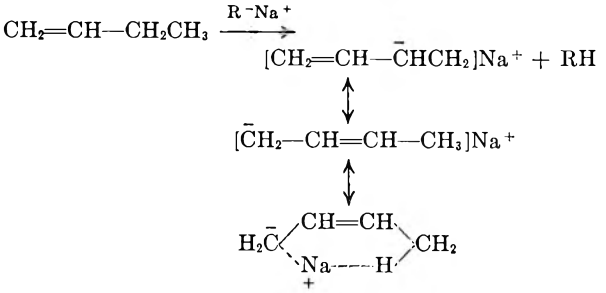
(4) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, 20, 839 (1955).

(5) S. E. Voltz, *J. Phys. Chem.*, 61, 756 (1957).

tion at much lower temperatures. It appears from the results which are presented in Fig. 1 that initially both *cis*- and *trans*-2-butene are produced at nearly constant rates, the ratio of the *cis/trans* isomers being about 15 times greater than that of the thermodynamic equilibrium mixture.[6] This fast double bond migration is accompanied by a much slower *cis-trans* isomerization. After 50 hr. of contact the composition of the 2-butene corresponded to the calculated equilibrium mixture.

A similar but less pronounced selectivity was noticed when lithium-alumina was used as a catalyst.

This stereoselective isomerization of 1-butene has not been reported previously. The preferred formation of the less stable *cis*-2-butene in the carbanion-catalyzed reactions can be explained by postulating the participation in the transition state of a cyclic structure:



An independent study in this laboratory demonstrated that aluminas showing only weak or no acidic properties can stereoselectively isomerize at 350° 1-butene to form preferentially the less stable *cis*-2-butene. Stereoselective reactions were also observed in the catalytic dehydration of 1- and 2-butanol and 2- and 3-pentanol.

The analysis of the butenes was performed by vapor phase chromatography using a 16-ft. column of tricresyl phosphate on firebrick as the stationary phase and helium as the carrier gas. The absence of isobutylene was established by using a 12-ft. column of silver nitrate–glycol on firebrick.

In the kinetic experiments, 0.5 ml. samples were withdrawn from the reaction vessel with a syringe and charged directly into the chromatograph.

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(6) J. E. Kilpatrick, E. J. Prosen, K. S. Pitzer, and F. D. Rossini, *J. Research Natl. Bur. Stand.*, **36**, 559 (1946).

Scyllitol Diborate

Sir:

The borate esters of the inositol isomers have been reported to exist as tridentate complexes.[1] Scyllitol, the all *trans* isomer of inositol, in its all equatorial conformation cannot form a tridentate complex and hence forms no borate derivative under mild conditions.[1] Theoretically, however, the all-axial conformation of scyllitol could form a double tridentate complex with borate (Fig. 1). In support of

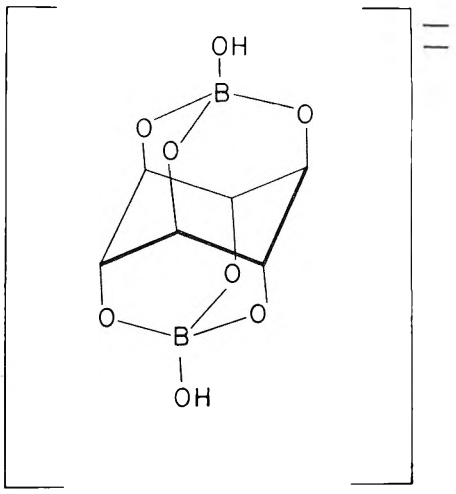

FIGURE 1

this hypothesis, scyllitol diborate has now been isolated.

The reduction of scyllo-myo-inosose with sodium borohydride has been reported to yield a mixture of 32% scyllitol and 45% myo-inositol.[2] During the course of this reduction, we observed that a white solid began to precipitate from the reaction mixture after a few hours. Precipitation ceased after 24–36 hours and this precipitate was collected, washed twice with small quantities of water and dried *in vacuo*. Starting with 1 gram of inosose, a yield of 0.9 gram of precipitate was obtained.

The material (I) isolated in this manner was distinguished from scyllitol, myo-inositol, and scyllo-myo inosose by paper chromatography using phenol saturated with water or acetone-water (85/15) as solvents and visualizing the spots with silver nitrate.[3] Upon paper ionophoresis in 0.125*M* sodium borate, compound I was observed to migrate twice as fast as myo-inositol which has been postulated to form a monoborate of the tridentate type under these conditions. Scyllitol, in this borate ionophoresis shows no migration.[1]

I is nonreducing in the Fehling or Park-Johnson

(1) S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 1433 (1957).

(2) D. Raymond, *Helv. Chim. Acta*, **40**, 492 (1957).

(3) E. F. L. J. Anet, and T. M. Reynolds, *Nature*, **174**, 930 (1954).

Test.[4] Treatment of I with acetic anhydride and sulfuric acid[2] yields scyllitol hexaacetate, m.p. 286°,[5] in 60–70% yield (based on the cyclitol content of I). *Anal.* Calcd. for $C_{18}H_{24}O_{12}$: C 49.95, H 5.60. Found C 49.93, H 5.67. Myo-inositol hexaacetate was not detected as a product. After acidification of I with sulfuric acid, the resultant solution was subjected to repeated evaporation to dryness *in vacuo* at 50° with methanol. The final residue was taken up in water, deionized with Amberlite MB-3, and the eluate again taken to dryness *in vacuo*. The deionized residue, obtained in 90% yield from I (based on cyclitol content of I), was shown to give only one spot with the same R_f as scyllitol in paper chromatography with phenol-water or acetone water.

From microanalysis[6] data, and with the assumption that it is monomolecular, compound I appears to be a monahydrate of scyllitol diborate. Calcd. for $C_6H_8O_8B_2Na_2 \cdot 9H_2O$; C 16.45, H 5.99, B 4.94, water content 37.02. Found C 16.52, H 6.07, B 4.87. Weight loss on drying at 100° for 18 hr., 37.27.

If scyllitol is heated at 100° with 0.125*M* borate, a compound migrating at the same rate as I in borate ionophoresis is obtained. Presumably this is also scyllitol diborate. The stereochemistry of the borate complex is still unproved and is being further investigated.

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(4) J. T. Park and M. J. Johnson, *J. Biol Chem.*, 181, 149 (1949).

(5) Melting point determined on a Fisher-Johns melting point block.

(6) I am indebted to Dr. W. C. Alford of the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health for the microanalyses.

An Improved Method for Preparing Sulfinyl Chlorides

Sir:

The new method for the preparation of sulfinyl chlorides recently reported[1] represented a great improvement over previously available methods. The procedure has certain disadvantages, however, in that one has difficulty in determining when the stoichiometric quantity of chlorine has been added, a relatively large volume of inert solvent must be used to impart fluidity to the two-phase system, and the reaction must be carried out at low temperatures to avoid the premature decomposition of the organosulfur trichloride.

We have recently found that if one mole of alkyl disulfide is mixed with exactly two moles of glacial acetic acid in the absence of solvent and chlorinated at 0° the reaction proceeds smoothly in a one-phase system and produces the desired sulfinyl chloride in high yield. On the first addition of chlorine the disulfide is transformed to the reddish orange sulfenyl chloride, RSCl. Additional chlorine apparently changes the sulfenyl chloride to the organosulfur trichloride, $RSCl_3$, which rapidly reacts with acetic acid to form acetyl chloride and the desired sulfinyl chloride. Since acetyl chloride is colorless and the sulfinyl chlorides are only faintly yellow, the disappearance of the reddish orange sulfenyl chloride color constitutes a good endpoint to indicate completion of the reaction. The products may be separated by fractionation of the reaction mixture without further treatment.

$$RSSR + 2CH_3COOH + 3Cl_2 \longrightarrow 2RSOCl + 2CH_3COCl + 2HCl$$

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(1) I. B. Douglass and D. R. Poole, *J. Org. Chem.*, 22, 536 (1957).

Base-Catalyzed Rearrangement of α-Haloacetanilide into α-Anilinoacid Derivatives

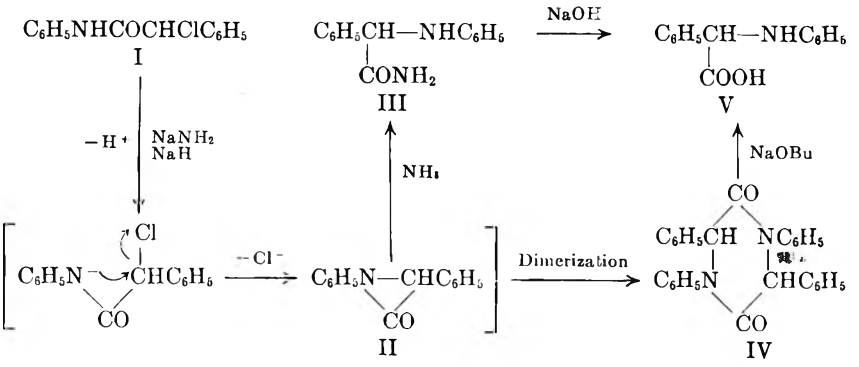
Sir:

It has already been demonstrated that the action of sodamide in liquid ammonia upon β-chloropropionanilide and acrylanilide produces *N*-phenyl-β-lactam in fair yields.[1] In this communication we wish to report our results obtained in a study of the reaction of sodamide in liquid ammonia, and of a suspension of sodium hydride in dry benzene, upon α-chloro-α-phenylacetanilide (I). We have found that (I) gives by the action of sodamide in liquid ammonia a mixture of three compounds of which two have been identified as α-anilinophenylacetamide (III) and 2,5-diketo-1,3,4,6-tetraphenylpiperazine (IV). Reaction of (I) with sodium hydride yielded IV as a major product.

To a solution of 5.1 g. (0.13 mole) of freshly prepared sodamide in 250 ml. of liquid ammonia was added 30 g. (0.12 mole) of solid (I)[2] with stirring during 1 hr. Within about 5 min. an orange-red solution was obtained which became brown-red at the end of the addition. The ammonia

(1) S. Sarel and R. Ben-Shoshan, *Bull. Res. Council of Israel*, 6A, 298 (1957).

(2) C. A. Bischoff and P. Walden, *Ann.*, 279, 124 (1894).



was allowed to evaporate overnight. The residue was extracted with dry ether leaving behind one gram (1%) of an insoluble yellow product, m.p. 260°. Repeated recrystallizations from glacial acetic acid yielded (IV), m.p. 277.5–278°, as a white crystalline product. *Anal.* Calcd. for $C_{28}H_{22}O_2N_2$: C, 80.36; H, 5.30; N, 6.70. Found: C, 80.70; H, 5.5; N, 6.80. It gave a single band at 1667 cm.$^{-1}$ in the carbonyl region of the infrared spectrum. The ethereal extract was chromatographed over silica-gel whereupon (III) was obtained (37% yield) as colorless prisms (from benzene), m.p. 129.5–130.5°. *Anal.* Calcd. for $C_{14}H_{14}ON_2$: C, 74.3; H, 6.2; N, 12.39. Found: C, 74.5; H, 6.4; N, 12.33. In the carbonyl region of the infrared spectrum (III) shows two absorption bands at 1680 cm.$^{-1}$ and 1700 cm.$^{-1}$

A suspension of (III) (1 g.) in 20 ml. of 1*N* sodium hydroxide was stirred and refluxed for 24 hr., at which time the solution became completely clear. An evolution of ammonia could be detected during the reflux period. From the cooled acidified solution crystalline α-anilinophenylacetic acid (V) (0.7 g., m.p. 174–175°) was recovered by ether extraction and crystallization from benzene. No depression in melting point was observed for a mixture with an authentic α-anilinophenylacetic acid (m.p. 174–175°) prepared from aniline and α-chlorophenylacetic acid, by the method of McKenzie and Bate.[4] A mixture of (IV) (0.5 g.) and a solution of sodium (0.5 g.) in 10 ml. 1-butanol was refluxed for 8 hr. After addition of 1 ml. water the reflux was continued for another 30 min. From the acidified solution crystalline (V) (0.3 g., m.p. 174°[4]) was obtained after recrystallization from benzene. It was identical with an authentic specimen, as described above.

To a suspension of 0.3 g. sodium hydride in boiling benzene was added dropwise with shaking a solution of (I) (2.5 g., 0.01 mole) in 50 ml. dry benzene, during 30 min. in an atmosphere of nitrogen. A vigorous evolution of hydrogen was observed during addition. The mixture was stirred for 18 hr. After filtration and removal of solvent at reduced pressure, the residue was extracted with dry ether, leaving behind 1.4 g. of insoluble white product, m.p. 277–278° (from glacial acetic acid), which was identified as (IV). From the ether extract 0.3 g. of a light yellow solid product was isolated, m.p. 79–81° (VI). *Anal.* Calcd. for $C_{14}H_{11}CN$: N, 6.70; mol. wt. 209. Found: N, 6.78; mol. wt. 220 (Rast). The structure of (VI) is currently under investigation.

The formation of (III) from (I) by the action of sodamide in liquid ammonia seems to be parallel to that of α-haloketones with strong bases.[5] In a like fashion it is plausible to assume that (I) is converted by the action of bases first to a three-membered ring intermediate (II)[6] (azacyclopropanone or α-lactam), which has so far not been isolated. This intermediate (II), presumably highly reactive, could be transformed to stable compounds either by dimerization into a six-membered ring product (IV)[7] or by reacting with the solvent[8] (ammonia) yielding an open-chain rearranged product (III). In an inert solvent only the first mechanism could operate, thus leading to a six-membered ring compound as the major product. This has been actually found in case of reaction of (I) with sodium hydride in benzene as solvent. Full account of this study will be published soon.

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(3) M. Henze, *Ber.*, **32**, 3058 (1899) record m.p. 263° for this compound.

(4) A. McKenzie and S. C. Bate, *J. Chem. Soc.*, **107**, 1682 (1915).

(5) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

(6) Similar intermediates have been proposed in the formation of olefins by the action of bases with α-halosulfones and in the formation of formaldehyde and ammonia from chloromethanesulfonamide. F. G. Bordwell and G. D. Coper, *J. Am. Chem. Soc.*, **73**, 5184, 5187 (1951); T. B. Johnson and I. B. Douglass, *J. Am. Chem. Soc.*, **63**, 1571 (1941).

(7) L. I. Smith, *Record Chem. Progress*, 11, 69 (1950); P. W. Abenius, *J. prakt. chem.*, (2) **40**, 426 (1899); D. Buckley and H. B. Henbest, *J. Chem. Soc.*, 1888 (1956).

(8) R. M. Dodson, E. F. Morello, and W. G. Dauben, *J. Am. Chem. Soc.*, **76**, 606 (1954); Ref. (5).

(9) Formerly Shalom Israelashvili.

A Total Synthesis of Alstonilinol

Sir:

In 1942 a minor alkaloidal constituent, alstoniline, was isolated from the tree bark of *Alstonia constricta F. Muell.*[1] On the basis of its degradation to 2-methylisophthalic acid and norharmine taken together with spectrographic data for a synthetic analog in which Ring C was open, a structure (VII) was proposed for alstoniline.[2,3]

We now wish to announce a total synthesis of alstonilinol which confirms the structure previously assigned to alstoniline. This is a direct result of investigations of the action of metal hydrides on β-(3-indolyl)ethyl-1-pyridinium and -2-isoquinolinium salts.[4]

6-Methoxyindole with oxalyl chloride yields 6-methoxy-3-indolylglyoxalyl chloride (I) in 86% yield.[5] On reduction with lithium aluminum hydride in tetrahydrofuran I gave 6-methoxytryptophol (II), white plates, m.p. 96–97°, in 79% yield (*Anal.* Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.91; N, 7.16). Condensation of the unstable β-(6-methoxy-3-indolyl)ethyl bromide (III) with 5-carbomethoxyisoquinoline[6] gave β-(6-methoxy-3-indolyl)ethyl-5-carbomethoxyisoquinolinium bromide (IV) as orange clumps, m.p. 270° (dec.), in 68% yield from 6-methoxytryptophol (*Anal.* Calcd. for $C_{22}H_{21}BrN_2O_3$: C, 59.85; H, 4.77; N, 6.35. Found: C, 59.97; H, 4.78; N, 6.35). Reductive ring closure of IV with lithium aluminum hydride in ether[7] gave tetrahydroalstonilinol (V), fine white needles from chloroform–petroleum ether, m.p. 220–224°, in 64% yield (*Anal.* Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.28; H, 6.77; N, 8.09). The hydrochloride formed white needles, m.p. 278° (dec.), from absolute alcohol (*Anal.* Calcd. for $C_{21}H_{22}N_2O_2 \cdot HCl$: C, 68.03; H, 6.29; N, 7.51. Found: C, 67.97; H, 6.01; N, 7.29). Tetrahydroalstonilinol and its hydrochloride as thus prepared furnished infrared spectra identical in all respects with the compounds prepared from alstoniline.[2]

(1) W. L. Hawkins and R. C. Elderfield, *J. Org. Chem.*, **7**, 573 (1942).

(2) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 683, 693 (1954).

(3) R. C. Elderfield and O. L. McCurdy, *J. Org. Chem.*, **21**, 295 (1956).

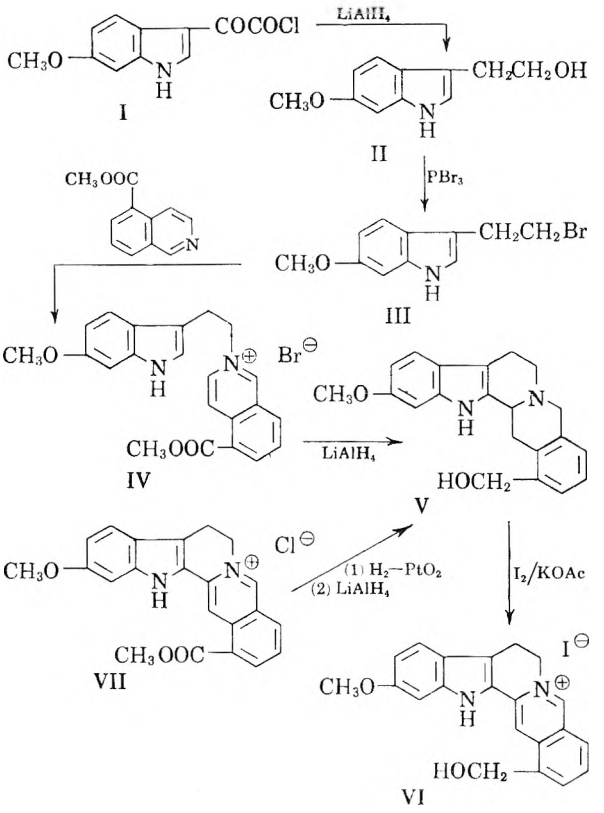
(4) R. C. Elderfield, B. A. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(5) F. A. Hochstein and A. M. Paradies, *J. Am. Chem. Soc.*, **79**, 5735 (1957).

(6) F. T. Tyson, *J. Am. Chem. Soc.*, 61, 183 (1939).

(7) Sir Robert Robinson and K. T. Potts, *J. Chem. Soc.*, 2675 (1955).

Dehydrogenation of V with iodine and potassium acetate in methanol gave alstonilinol iodide (VI) as orange clumps of needles, m.p. 320° (dec.), from methanol in 90% yield (*Anal.* Calcd. for $C_{21}H_{19}INO_2$: C, 54.90; H, 4.17; N, 6.10; I, 27.86. Found: C, 55.02; H, 4.20; N, 6.07; I, 27.52).



The structure previously assigned to alstoniline is thus confirmed. Further, it appears that reductive ring closure of β-(3-indolyl)ethyl-2-isoquinolinium bromides is capable of wide application in the synthesis of pentacyclic β-carbolines. Ring closure apparently occurs exclusively between the 2 position of the indole and the 3 position of the isoquinoline ring systems.

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