THE JOURNAL OF Organic Chemistry®

Volume 25, Number 9

September 7, 1960

[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS SCIENTIFIC LABORATORY]

The Conversion of Aldoximes to α-Oximinonitriles, α,α-Dinitronitriles, and 1,1-Dinitroparaffins[1]

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Received February 15, 1960

α-Oximinonitriles can be prepared conveniently by dehydrogenation of α-hydroxylaminonitriles which are accessible from aldoximes. The nitration of α-oximinonitriles with 100% nitric acid and ammonium nitrate leads to α,α-dinitronitriles. These in turn can be cleaved to 1,1-dinitroparaffins by action of ammonia.

Aldoximes react with hydrocyanic acid at room temperature to give α-hydroxylaminonitriles (I).[2] On reaction with nitrogen dioxide in chloroform or methylene chloride or with 100% nitric acid and ammonium nitrate these compounds are dehydrogenated and nitrated to α,α-dinitronitriles (II). It is established that the α-oximinonitriles (III)

$$\underset{\text{I}}{RCH(NHOH)C{\equiv}N} \longrightarrow \underset{\text{II}}{RC(NO_2)_2C{\equiv}N}$$

are intermediates in the reaction with nitrogen dioxide and that impurities with carbonyl absorption are introduced in this step. α-Hydroxylaminonitriles (I) can be dehydrogenated to III without undesirable by-products by heating with one molar equivalent of *p*-benzoquinone in benzene. This dehydrogenation of I is a general method of preparation for the previously difficultly accessible nitriles III.

The nitration of α-oximinonitriles (III) with nitrogen dioxide or with 100% nitric acid and ammonium nitrate yields the pure α,α-dinitronitriles II.[3] Their structures have been confirmed by infrared absorption spectra and the conversion of II to ammonium salts of 1,1-dinitroparaffins (IV)

$$\underset{\text{III}}{\begin{matrix}RCCN\\ \|\\ NOH\end{matrix}} \qquad \underset{\text{IV}}{\overset{-}{R}C(NO_2)_2\overset{+}{N}H_4}$$

by cleavage with ammonia. Previous attempts to prepared α,α-dinitropropionitrile by alkylation of dinitroacetonitrile have failed.[4]

The described reactions represent a new method for the conversion of aldoximes to 1,1-dinitroparaffins. Attempts to apply the reactions to fluorine-containing aldoximes have failed.

EXPERIMENTAL[5]

α-Hydroxylaminonitriles (I). The addition of hydrocyanic acid to aldoximes was carried out according to procedures A and C of Neelakantan and Hartung.[2] It was advantageous in the latter to reverse the order of addition—*i.e.*, adding a concd. aqueous cyanide solution to a stirred and cooled mixture of aldoxime and bisulfite solution. Procedure A gave better yields in all cases and the product was isolated in satisfactory purity when the reaction mixture was filtered

(1)(a) This work was performed under the auspices of the U. S. Atomic Energy Commission. (b) Presented at the Thirty-first meeting of the Colorado-Wyoming Academy of Science at Boulder, Colorado, May 13, 1960.

(2) L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **23**, 964 (1958) and cited references.

(3) The formation of carbonyl-containing impurities from α-hydroxylaminonitriles (I) and the failure to obtain them from α-oximinonitriles (III) under the same conditions is tentatively ascribed to the formation of intermediate nitrite esters, the elimination of nitrous acid, and hydrolysis of the resultant imines, as follows:

$$RCH(NHONO)CN \longrightarrow RC(=NH)CN \longrightarrow RCOCN.$$

(4) C-alkylation of dinitroacetonitrile and its salts has been successful only with allyl and *tert*-butyl compounds (C. O. Parker, W. D. Emmons, A. S. Pagano, H. A. Rolewicz, and K. S. McCallum, abstracts of the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 1959, p. 44P).

(5) All temperatures are corrected. Microanalyses by M. J. Naranjo.

after 24 hr. at 20–25°.[6] The reaction failed with trifluoroacetaldoxime, even under pressure and elevated temperature and in the presence of catalysts such as cuprous cyanide and pyridine.

INFRARED ABSORPTION BANDS IN POTASSIUM BROMIDE

α-Hydroxylaminonitriles	λ(OH, NH)	λ(NH)	λ(CN)	λ(NO) μ
Propio	3.04s 3.11s	6.17[a]	4.47m	9.92m
Butyro	3.09s 3.19s	—	4.47m	9.91m
Valero	3.10s 3.20s	—	4.47m	9.88m

[a] Absorption in the N—H deformation region was very weak and could be observed only after dilution of the sample and regrinding.

α-Oximinonitriles (III). α-Hydroxylaminonitriles (0.1 mole) suspended in benzene (500 ml.) were treated with *p*-benzoquinone (0.1 mole) in small portions with shaking. After completed addition, each reaction mixture was refluxed from a steam bath. Quinhydrone crystals deposited rapidly and were gradually replaced with hydroquinone during 3–5 hr. The mixture was cooled, filtered, and evaporated under reduced pressure. The residue was taken up in carbon tetrachloride or carbon tetrachloride–benzene mixtures, depending on solubilities, and filtered again, giving 99–100% yields of hydroquinone. The combined filtrates were evaporated under reduced pressure and distilled from molecular stills.[7] The pure α-oximinonitriles were obtained as colorless oils in yields of 41–64%.

α-Oximinopropionitrile boiled at 35° (0.9 mm.), n_D^{25} 1.4542.

Anal. Calcd. for $C_3H_4N_2O$: C, 42.86; H, 4.79; N, 33.33. Found: C, 42.44, 42.71; H, 4.93, 4.73; N, 33.20.

α-Oximinobutyronitrile[8] boiled at 42° (1 mm.), n_D^{25} 1.4528.

Anal. Calcd. for $C_4H_6N_2O$: C, 48.97; H, 6.16; N, 28.57. Found: C, 49.01, 48.55; H, 6.18, 5.85; N, 28.65, 28.74.

α-Oximinovaleronitrile boiled at 32° (0.03 mm.), n_D^{25} 1.4531.

Anal. Calcd. for $C_5H_8N_2O$: C, 53.51; H, 7.19; N, 24.99. Found: C, 53.59, 53.37; H, 7.40, 7.59; N, 25.07, 24.74.

INFRARED ABSORPTION BANDS—LIQUID FILMS

α-Oximinonitrile	$\lambda_{(OH)}$	$\lambda_{(C=N)}$	$\lambda_{(C=N)}$	$\lambda_{(N-O)}$, μ
Propio	3.03s	4.47m	6.16m	9.65s
Butyro	3.03s	4.47m	6.16m	9.95s
Valero	3.03s	4.47m	6.19m	10.02s

α,α-Dinitronitriles (II). (a) α-Hydroxylaminonitrile was added slowly with stirring to an equimolar mixture of 100% nitric acid and ammonium nitrate at 20°. The mixture was stirred for 1 hr. at 20° and poured on ice, extracted with methylene chloride, dried, and distilled.

(b) A 2% solution of α-hydroxylaminonitrile in methylene chloride was treated with a slow stream of nitrogen dioxide at 25° until the green solution turned yellow. Evaporation of this solution under reduced pressure gave a good yield of oil with the infrared spectrum of the α-oximinonitrile but containing also a carbonyl band at 5.80 μ. Continued reaction of this oil with nitrogen dioxide in methylene chloride gave oils with the characteristic spectra for the α,α-dinitro compound.

The α,α-dinitro nitriles obtained in these ways were colorless oils with characteristic absorption bands at 4.44 μ (C≡N), 6.26 μ (*asym*-NO_2) and 7.71 μ (*sym*-NO_2). They could be distilled from molecular stills but retained impurities with carbonyl absorption at 5.80 μ, which could not be separated by chromatographic adsorption on silica gel. The crude nitriles were therefore cleaved with ammonia and identified as ammonium salts of the 1,1-dinitroparaffins.

(c) α-Oximinonitrile was added with stirring at 10–20° to a ten-fold excess of an equimolar mixture of 100% nitric acid and ammonium nitrate. A transient blue color was noted immediately after each addition and is believed to be due to the intermediates $RC(NO)(NO_2)C{\equiv}N$. At 20° the blue color faded within a few seconds, while at 10° it was stable for several minutes. After completed addition, during which nitrogen dioxide was evolved, the mixtures were stirred at 20° for 1 hr., poured on ice, extracted with methylene chloride, dried, and distilled. The residue oils were distilled twice from molecular stills.[7]

α,α-Dinitropropionitrile, b.p. 45° (7 mm.), n_D^{25} 1.4390 was obtained in 8% yield. On cooling to 0° it solidified to a low-melting solid.

Anal. Calcd. for $C_3H_3N_3O_4$: C, 24.84; H, 2.08; N, 28.96. Found: C, 25.09, 25.17; H, 2.18, 2.38; N, 28.90.

α,α-Dinitrobutyronitrile boiled at 40° (2 mm.), n_D^{25} 1.4372, yield 12%, $\lambda_{max}^{CH_3OH}$ 277 mμ (log ε 2.01).

Anal. Calcd. for $C_4H_5N_3O_4$: C, 30.19; H, 3.17; N, 26.41. Found: C, 30.13, 30.44; H, 3.27, 3.30; N, 26.61, 26.30.

α,α-Dinitrovaleronitrile, b.p. 45° (2 mm.), had n_D^{25} 1.4377, yield 22%.

Anal. Calcd. for $C_5H_7N_3O_4$: C, 34.70; H, 4.07; N, 24.28. Found: C, 34.40, 35.10; H, 4.06, 4.23; N, 24.21.

INFRARED ABSORPTION BANDS—LIQUID FILMS

α,α-Dinitronitrile	$\lambda_{(C=N)}$	$\lambda_{(as-NO_2)}$	$\lambda_{(sym-NO_2)}$, μ
Propio	4.43m	6.25s	7.67m
Butyro	4.44m	6.26s	7.70m
Valero	4.44m	6.26s	7.70m

1,1-Dinitroparaffin ammonium salts. A 1–2% solution of α,α-dinitronitrile in dichloromethane or chloroform was cooled to 0° and saturated with anhydrous ammonia. The mixture was allowed to stand for 1 hr. and evaporated under reduced pressure. Crystallization of the crude residue from methanol containing anhydrous ammonia gave pure yellow ammonium salts in yields of around 10%. The mother liquors contained much unchanged starting material and the optimum conditions for the cleavage reaction were not determined.

INFRARED ABSORPTION BANDS OF AMMONIUM SALTS[a,b]

1,1-Dinitroparaffin	λ, μ	λ, μ	λ, μ
Ethane	6.75m	8.11s	8.90s
Propane	6.77m	8.25s	8.95s
Butane	6.81m	8.32s	8.88s
Pentane	6.78m	8.38s	8.99s

[a] 0.1–0.5% in potassium bromide.

[b] Three bands in the region recorded have been observed also in hydrazinium and potassium salts of 1,1-dinitroparaffins in this Laboratory and are attributed to absorption of the anion.

(6) Longer reaction times caused the product to be more difficult to purify by crystallization from ether-petroleum ether (b.p. 30–60°).

(7) H. E. Ungnade, *Anal. Chem.*, **31**, 1126 (1959).

(8) T. K. Walker [*J. Chem. Soc.*, **125**, 1625 (1925)] prepared a compound believed to be α-oximinobutyronitrile by nitrosation of ethyl α-cyanobutyrate with ethyl nitrite and potassium ethoxide in ether.

(a) *1,1-Dinitroethane ammonium salt*, m.p. 116° dec., lit., m.p. 90–93° dec.,[9] 127–128°.[10]

Anal. Calcd. for $C_2H_7N_3O_4$: C, 17.53; H, 5.14. Found: C, 17.53; H, 5.07.

(b) *1,1-Dinitropropane ammonium salt*, m.p. 117° dec.

Anal. Calcd. for $C_3H_9N_3O_4$: C, 23.84; H, 6.00; N, 27.81. Found: C, 23.38, 23.97; H, 5.25, 5.53; N, 27.68, 27.18.

(c) *1,1-Dinitrobutane ammonium salt*, m.p. 128° dec.

Anal. Calcd. for $C_4H_{11}N_3O_4$: C, 29.09; H, 6.71; N, 25.45. Found: C, 29.30, 29.47; H, 7.03, 6.71; N, 25.67.

(d) *1,1-Dinitropentane ammonium salt*,[11] m.p. 131–132° dec.

Anal. Calcd. for $C_5H_{13}N_3O_4$: C, 33.52; H, 7.31; N, 23.46. Found: C, 33.30; H, 7.51; N, 23.66.

Infrared absorption spectra were determined with a Perkin-Elmer Model 21 spectrophotometer.

Los Alamos, N. M.

(9) T. S. Belew, C. E. Grabiel, and L. B. Clapp, *J. Am. Chem. Soc.*, **77**, 1110 (1955).

(10) M. F. Hawthorne, *J. Am. Chem. Soc.*, **78**, 4980 (1956).

(11) This salt was prepared from the dinitroparaffin and ammonia in chloroform.

[Contribution from the Carothers Research Laboratory, Textile Fibers Department, E. I. du Pont de Nemours and Co., Inc.]

The Beckmann Rearrangement of Fenchone Oxime

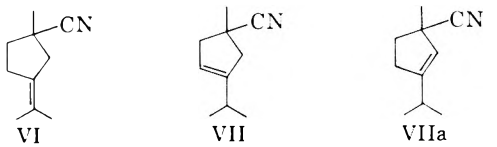
R. W. COTTINGHAM

Received January 7, 1960

The Beckmann rearrangement of fenchone oxime has been carried out under a variety of conditions to give apparently exclusive formation of products arising from scission of the bridgehead bond. It would appear that both the normal and anomalous products are derived from the concerted *anti*-migration process generally accepted as the initial step in the Beckmann rearrangement, and that the stability of the incipient carbonium ion adjacent to the oximino function is of importance only in determining the relative amounts of the two products.

The literature of the Beckmann rearrangement contains numerous examples of a competitive reaction in which an unsaturated nitrile rather than the usual amide is produced by treatment of a ketoxime with a strong acid.[1–3] Notable among compounds undergoing this anomalous reaction are the oximes of bicyclic ketones having bridgeheads adjacent to the oximino functions. The oximes of camphor,[4] verbanone,[5] and various norcamphane derivatives[6,7] give, under conditions commonly employed for the Beckmann rearrangement, mixed products to which the competitive reaction contributed appreciably. The rearrangement of fenchone oxime (I) is of particular interest in this connection, for despite the ditertiary structure of the oxime, both the normal and anomalous rearrangements proceeded exclusively *via* scission of the bridgehead bond.

Treatment of the sharp melting oxime with *p*-toluenesulfonyl chloride and pyridine, phosphorus pentachloride, or sulfuric acid lead in all cases to the formation of a single lactam which was isomeric with the oxime and a liquid which from its infrared spectrum was obviously an unsaturated nitrile (—C≡N stretching 4.50 μ, C=C stretching 6.03 μ, vinyl C—H stretching 3.32 μ).[8] The inference from infrared data of the presence of a single vinyl hydrogen in this nitrile was confirmed by the ratio of vinyl to total hydrogen as determined by proton magnetic resonance, thus eliminating the possibility that the product might be the isopropylidenecyclopentanonitrile, VI, or any of the three isomeric structures possessing two vinyl hydrogens.

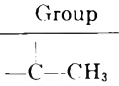
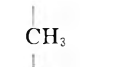
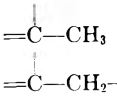
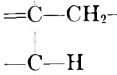
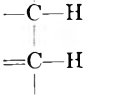


VI VII VIIa

From further consideration of the proton resonance data which are summarized in Table I, it appears that the unsaturated nitrile must have the

TABLE I

Proton Resonance Data

Group	Cps. from H_2O at 56.4 Mc.	Chemical Shift	
		Observed	Accepted[9]
	214	3.8	4.1 ± 0.6
	183	3.2	3.3 ± 0.5
	148	—	—
	127	—	—
	−23	−0.4	−0.6 ± 0.7

(1) A. H. Blatt, *Chem. Revs.*, **12**, 215 (1933).

(2) B. Jones, *Chem. Revs.*, **35**, 335 (1944).

(3) L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, (in press).

(4) J. Bredt and W. Holz, *J. prakt. Chem.*, **95**, 133 (1917).

(5) H. Wienhaus and P. Schumm, *Ann.*, **439**, 38 (1924).

(6) M. Gates and S. P. Malchick, *J. Am. Chem. Soc.*, **79**, 5546 (1957).

(7) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **82**, 1209 (1960).

(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1956.

(9) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959, p. 23.

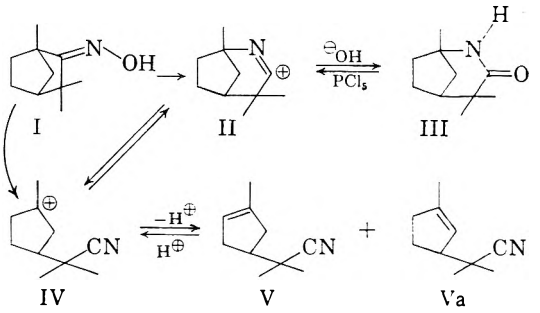
structure V or Va rather than the possible, albeit less likely, isomeric structures VII or VIIa, as the major peak attributed to the *gem* methyls was extremely sharp and devoid of any indication of the splitting expected of the isopropyl group common to the latter pair. Moreover, the band at 183 cps. appears to require the presence of the allylic methyl group of the structures V and Va.

As a mixture of α- and β-fencholenonitriles (V and VI) has been reported to arise from the treatment of fenchone oxime with boiling 5% sulfuric acid,[10] repetition of the work was undertaken for the purpose of comparing the mixed product with that obtained under dehydrating conditions. The nitrile obtained from the dilute acid treatment of the oxime was indistinguishable in infrared and proton resonance spectra from a sample of the product of the reaction with *p*-toluenesulfonyl chloride in pyridine. Vapor phase chromatography[11] showed no separation of the product isomers despite the fact that they are reported to differ in boiling point by 7°. Moreover, alkaline hydrolysis under conditions reported by Cockburn to give good conversion of V to α-fencholenamide of VI to β-fencholenic acid yielded largely amide and recovered nitrile with a total crude acidic product which accounted for only 10% of the theoretical amount. That this product was largely α-fencholenic acid was shown by a strong proton resonance band for vinyl hydrogen, vapor phase chromatography which gave one peak accounting for at least 80% of the crude mixture, and conversion of the crude acid to an amide identical with that obtained in the hydrolysis step by treatment with oxallyl chloride and ammonia.

The disparity between the results of the present and earlier studies may be attributable to a difference in isomeric purity of the starting materials. The assumption that the oxime employed in the earlier work contained an appreciable amount of the low melting isomer described by Delepine[12] would account for the formation of mixed rearrangement products. As the low melting oxime is unstable with respect to the high melting isomer in alcohol solution, it would appear that the alcohol-recrystallized starting material employed in the present work contained little if any of the unstable isomer. From the present data it may be concluded that the nitrile produced from the high melting isomer of fenchone oxime arises preponderantly if not exclusively from cleavage of the bridgehead bond even in dilute aqueous acid.

The identity of the lactam was established as 1,4,4-trimethyl-2-azabicyclo[3.2.1]octan-3-one (III) by interconversion with the nitrile. Treatment of the lactam with phosphorus pentachloride under the same conditions as were employed in the Beckmann rearrangement produced an unsaturated nitrile identical in infrared spectrum with that obtained from the rearrangement; moreover, a mixture of the two nitriles was inseparable by vapor phase chromatography.[11] Conversion of the original nitrile to the lactam was effected by the Ritter reaction[13] with sulfuric acid, and the lactam formed in this manner was shown to be identical with that produced directly from the oxime in melting point, mixed melting point, and infrared spectrum. While the yield of lactam derived from the Ritter reaction was poor, these interconversions determine unequivocally that both of the isolated products (accounting in one case for 96% of the theoretical total) arise from cleavage of the bridgehead bond.

This unidirectional rearrangement would appear to imply that the initial step in both the normal and anomalous reactions involves a concerted cleavage of the N—O bond and migration of either the bridgehead atom or the electrons involved in the bridgehead bond to form the intermediate ions II or IV respectively. That either of these



processes is compatible with the generally accepted *trans*-migration mechanism of the Beckmann rearrangement is apparent from a consideration of the steric relationships in the oxime. The coplanarity of the bridgehead methyl group with the oximino function should sterically favor the oxime isomer having the hydroxyl group *syn* to the *gem* methyls which are located symmetrically on opposite sides of the oximino plane; hence the high melting compound which was obtained should have the configuration depicted in I with the bridgehead bond *trans* to the hydroxyl function.

That the ion II rather than IV is the initial intermediate in the formation of the lactam may be inferred from the relative amounts of lactam obtained from the rearrangement and the Ritter reaction. As the ion IV must be the precursor of II in the latter reaction, which produces much less lactam than is derived directly from the oxime under the same conditions, IV must not be involved in the major reaction path leading to the lactam. The assumption that both of the rearrangement products arise *via* the initial formation of

(10) G. B. Cockburn, *J. Chem. Soc.*, 501 (1899).

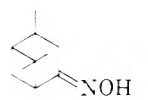
(11) Twelve-foot helical column packed with silicone grease on Chromasorb, elution with helium at *ca.* 10 p.s.i. 80 ml./min.

(12) (a) M. Delepine, *Compt. rend.*, 178, 1721 (1924). (b) J. L. Simonsen, *The Terpenes*, Cambridge University Press, London, 1932, vol. II, page 473.

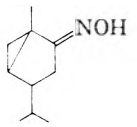
(13) J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, 70, 4048 (1948).

the bicyclic ion II followed by the product-forming steps which have been shown to be reversible is compatible with the generally accepted mechanism of the Beckmann rearrangement and is attractive but for the fact that a competitive path leading to the unsaturated nitrile through the direct formation of IV may exist.

Irrespective of which of these species is the initial intermediate in the formation of the nitrile, it may be concluded that the direction of the anomalous reaction like that of the normal process is determined by the configuration of the oxime and that the stability of the incipient carbonium ion *trans* to the hydroxyl group is of importance only in determining the relative amounts of nitrile and lactam in the products. This latter conclusion is in at least qualitative agreement with the results of the rearrangements of a number of closely related oximes. Camphor[4] and fenchone oximes yielded unsaturated nitriles as the major products of this reaction; verbanone oxime[5] (VIII) gave only a small amount of the corresponding product; and β-dihydroumbellulone oxime[14] (IX) produced only lactam in excellent yield in keeping with the diminishing stability of the substituted cyclopentyl,



VIII



IX

cyclobutyl, and cyclopropyl carbonium ions as evidenced by the relative rates of solvolysis of the cycloalkyl halides.[15]

EXPERIMENTAL[16]

Fenchone oxime. Commercial racemic fenchone was distilled at atmospheric pressure through a 90 cm. packed column and a fraction boiling at 195° was collected. Vapor phase chromatography of samples immediately preceding and following the product fraction showed them to be of at least 99% purity.

A mixture of 90 g. of fenchone purified in this manner, 78 g. of hydroxylamine hydrochloride, 70 ml. of 30% sodium hydroxide, 110 ml. of water, and 375 ml. of 95% ethanol was heated under reflux for 20 hr. and then cooled in an ice bath.[17] The crystalline product which precipitated was filtered, washed with water, recrystallized from ethanol, and air dried to give 93.0 g. (94%) of fenchone oxime, m.p. 162–163° (previously published value 158–160°).[12b]

The Beckmann rearrangement. (a) *With p-toluenesulfonyl chloride.* A modification of the method of Burrows and Eastman[11] gave excellent conversion of the oxime to rearranged products. Ice cold solutions of 14.4 g. (0.086 mole) of fenchone oxime in 30 ml. of dry pyridine and 25 g. of *p*-toluenesulfonyl chloride in 30 ml. of the same solvent were mixed and the resultant solution was allowed to warm to room temperature. After the vigorously exothermic reaction subsided, the bright yellow solution was allowed to stand overnight. It was then warmed on the steam bath for 30 min. and poured into a mixture of 30 ml. of 36*N* sulfuric acid and 125 g. of ice.

The acidic suspension was extracted with three 100-ml. portions of ether; the ethereal solution was washed with 5% aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent from the dried ether solution left a two-phase residue which was shown to contain three volatile components separable by vapor phase chromatography. Two of these were later identified as water and the unsaturated nitrile described below. The third component was not found in the crude product when phosphorus pentachloride was used to effect the rearrangement, and no attempt at its identification was made.

The crude product was triturated with 50 ml. of petroleum ether (b.p. 30–60°) and the hydrocarbon solution was distilled through a 45-cm. spinning band column to give, after removal of the solvent, 10.1 g. of a colorless liquid, b.p. 100–102°/19.5 mm. which was shown by infrared analysis to be an unsaturated nitrile. Elemental analysis and proton magnetic resonance data (Table I) indicated that this product was one of the cyclopentenylisobutyronitriles V or Va, or a mixture of the two.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.58; H, 10.13. Found: C, 80.70, 80.80; H, 10.13, 10.25.

The petroleum ether insoluble material from the above step was combined with the residue in the still pot, and this mixture was recrystallized from the minimal amount of 95% alcohol which would dissolve it at the boil (*ca.* 20 ml.) to give 4.7 g. of fine needles, m.p. 163–164°. An analytical specimen of this product was sublimed at reduced pressure (130°/10 mm.), and the product so obtained was shown by elemental analysis, infrared spectrum, and interconversion with the nitrile described above to be 1,4,4-trimethyl-2-azabicyclo[3.2.1]octan-3-one.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.84; H, 10.25. Found: C, 71.64, 71.72; H, 10.00, 10.19.

The total isolated products of this reaction accounted for 96% conversion of the oxime to what appeared to be a single nitrile and a single lactam.

(b) *With phosphorus pentachloride.*[18] Fenchone oxime (16.7 g., 0.1 mole) was added slowly with stirring to a suspension of 17 g. of phosphorus pentachloride in 175 ml. of petroleum ether (b.p. 30–60°) at a rate which maintained vigorous boiling of the solvent. When the reaction had subsided, the mixture was allowed to stand overnight and the solvent was removed by evaporation on the steam bath. Ice (200 g.) was added to the residue, the aqueous suspension was extracted with three 100-ml. portions of ether, and the products were isolated in the manner described above to give 10.5 g. of the unsaturated nitrile and 1.3 g. of the lactam (total yield 78%).

(c) *With concentrated sulfuric acid.*[3] Fenchone oxime (16.7 g., 0.1 mole) was added portionwise to 20 ml. of cold 36*N* sulfuric acid with stirring and ice cooling to maintain the reaction temperature below 25°. When the addition was completed, the mixture was allowed to stand in a water bath at 25° for *ca.* 5 min., whereupon the temperature rose spontaneously to 55° and the solution became dark red and then brown.

After neutralization with ice cold aqueous sodium hydroxide, the mixture was ether extracted and the products were isolated in the manner described above to give 5.6 g. of the nitrile and 1.2 g. of the lactam. The considerable amount of resinous material which remained after the isolation of these products was assumed to be a mixture of a low molecular weight polyamide[19] and hydrolysis products derived from the nitrile and lactam.

(14) W. D. Burrows and R. H. Eastman, *J. Am. Chem. Soc.*, **79**, 3756 (1957).

(15) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 667 (1956).

(16) Melting points were taken in a stirred oil bath with no correction for stem emergence. Microanalyses were conducted by Miss V. Jean Carrier.

(17) J. Cologne, *Bull. soc. chim. France*, **5**, 98 (1938).

(18) H. Rupe and I. Splittgerber, *Ber.*, **40**, 4313 (1907).

(19) C. J. Albisetti, U. S. Patent **2,620,327**.

(d) *With dilute sulfuric acid.*[10] The oxime (25 g.) was boiled for 1 hr. with a solution of 5 ml. of 36*N* sulfuric acid in 125 ml. of water and worked up in the manner of the reference cited to give a nitrile indistinguishable in its infrared and proton resonance spectra from that described above. No attempt at isolation of the lactam was made.

Hydrolysis of the nitrile. A mixture of 10 g. of the nitrile derived from the reaction of fenchone oxime with dilute sulfuric acid, 10 g. of potassium hydroxide, 25 ml. of methanol, and 10 ml. of water was heated under reflux for 60 hr. The methanol was removed by distillation at reduced pressure, water (50 ml.) was added, the mixture was cooled to 0°, and the oily solid which precipitated was filtered and recrystallized from benzene–petroleum ether (b.p. 30–60°) to give 4.8 g. (43%) of *dl*-α-fencholenamide as white platelets, m.p. 85–86.5°. An analytical specimen was prepared by sublimation at 100°/1 mm.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.84; H, 10.25; N, 8.38. Found: C, 71.71, 71.75; H, 10.22, 10.43; N, 8.42, 8.51.

Evaporation of the mother liquor from the recrystallization of the amide produced a liquid residue (3.2 g.) which was shown by its infrared spectrum to be largely unchanged starting material containing a small amount of the amide as evidenced by the amide carbonyl band.

The alkaline solution from the hydrolysis was cooled in ice and acidified with hydrochloric acid. The amber liquid which separated was removed and the aqueous phase was extracted with ether. The organic solutions were combined, dried with anhydrous magnesium sulfate, and the solvent was removed by distillation from a steam bath at 10 mm. The crude acidic product obtained in this manner was a viscous yellow-brown oil which was identified as containing largely α-fencholenic acid by the presence of a band for vinyl hydrogen in its proton resonance spectrum and vapor phase chromatography which indicated the crude acid was at least 80% one component.

The crude acid (0.8 g.) was heated under reflux for 2 hr. with 15 ml. of oxallyl chloride. The mixture was concentrated by distillation from the steam bath, and the brown oily residue was treated with 30 ml. of 30% aqueous ammonia to produce a brown solid. This product was twice recrystallized from benzene-petroleum ether (b.p. 30–60°) to give 0.3 g. of slightly yellow platelets identical in infrared spectrum, melting point and mixed melting point with the amide obtained directly from hydrolysis of the nitrile.

The Ritter reaction of the unsaturated nitrile.[13] The nitrile obtained from the above reactions (50 g., 0.33 mole) was added cautiously, with stirring, to 50 ml. of 36*N* sulfuric acid. The mixture was cooled in an ice bath throughout the addition to maintain the reaction temperature below 25°. When the addition of the nitrile was completed, the reaction mixture was allowed to stand in the ice bath for an additional 0.5 hr. and then warmed to room temperature, whereupon the temperature rose spontaneously to 60° and the mixture turned red and foamed slightly. The flask was then stoppered loosely and allowed to stand overnight.

The dark brown resinous mixture was poured into an ice cold solution of 80 g. of sodium hydroxide in 500 ml. of water and the aqueous suspension was extracted four times with a total of 1 l. of ether. The ethereal extract was dried over anhydrous magnesium sulfate and concentrated to dryness to give an oily brown residue which was triturated with petroleum ether (b.p. 30–60°) to remove the unsaturated nitrile.

The crude product was worked up in the usual manner to give 10 g. of unchanged nitrile and *ca.* 0.5 g. of lactam which was shown to be identical with the product obtained directly from the oxime in melting point, mixed melting point, and infrared spectrum. (As in the sulfuric acid catalyzed rearrangement, a large amount of resinous material was formed.)

Dehydration of the lactam.[20] A mixture of 3.24 g. of the lactam, 3.4 g. of phosphorus pentachloride and 35 ml. of petroleum ether (b.p. 30–60°) was allowed to stand for 48 hr. with periodic shaking and then heated for 1 hr. on a steam bath. The mixture was worked up in the manner described for the Beckman rearrangement with phosphorus pentachloride to give 1.9 g. of nitrile which was identical with that derived directly from the oxime in infrared spectrum and inseparable from the latter in vapor phase chromatography.

Acknowledgment. The author wishes to express his thanks to Mr. John A. Ray for assistance with the experimental work, Miss Ruth A. Staszesky for infrared spectra, and Dr. W. D. Phillips for assistance in the interpretation of the proton magnetic resonance data.

WILMINGTON, DEL.

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[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, KYOTO UNIVERSITY]

Synthesis of Two Isomeric *p*-Menthane-3,4-diols and Their Pinacolic Dehydration to a Menthone Mixture[1]

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Received January 13, 1960

Two isomeric *p*-menthane-3,4-diols, (+)-*cis*-4-hydroxymenthol (VIa) and (−)-*trans*-4-hydroxyneoisomenthol (VIb), were prepared by lithium aluminum hydride reduction of two isomeric *p*-menthane-4,8-epoxy-3-ols (Va) and (Vb) which were derived from (+)-pulegone. With 10% sulfuric acid, VIa and VIb were dehydrated to a menthone mixture (VII) which was composed of 65% (−)-menthone and 35% (+)-isomenthone.

The pinacolic dehydration of *p*-methane-3,4-diol (VI) to a menthone mixture[2–4] appears to be significant for the industrial production of synthetic menthol, because VI can be easily prepared from

(1) Presented at the meeting of the Kansai Branch of the Agricultural Chemical Society of Japan, Nara, Japan, October 17, 1959.

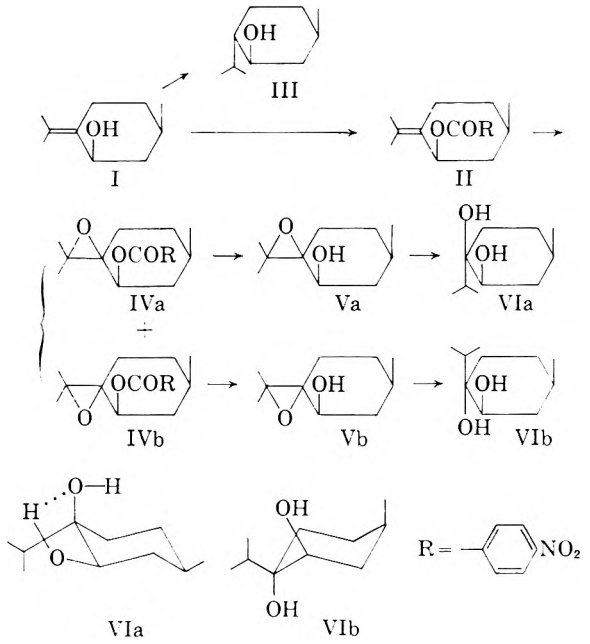
(2) S. Tanaka, *J. Chem. Soc. Japan*, **53**, 668 (1932); *Mem. Coll. Sci. Kyoto Univ.*, **22A**, 97 (1939).

(3) Y. Ogata, *J. Soc. Chem. Ind. Japan*, **45**, 1157 (1942).

(4) Y. R. Naves, *Helv. Chim. Acta*, **42**, 1174 (1959).

terpinene-1-ol-4,α-terpineol, limonene, or α-pinene via 3-*p*-menthene. According to Klyne,[5] the course of a pinacolic rearrangement depends on whether an axial or an equatorial hydroxyl group is eliminated. Therefore, the information regarding the predominant conformation of isomeric VI may contribute to the understanding of the stereochemistry of the above reaction. From this viewpoint the results hitherto obtained[2-4] are not considered to be satisfactory because of the uncertainty about the relationship between the C_1-methyl group and other substituents in VI.

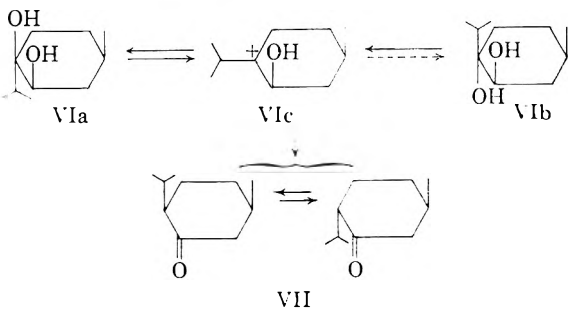
(+)-*cis*-4-*Hydroxymenthol* (VIa) *and* (−)-*trans*-4-*hydroxyneoisomenthol* (VIb). Usually VI is prepared by the oxidation of 3-*p*-menthene[2-4,6-8] but this oxidation yields theoretically four geometrical isomers. Consequently the assignment of configuration may be difficult. Another possible route starting from 4-bromomenthone was examined by Jefferies and Milligan[8] but the product was *p*-menthane-2,3-diol.



For the starting compound, we prepared pure (−)-*cis*-pulegol (I), which has a higher melting point and higher optical rotation than reported by Macbeth and Shannon[9] for an impure specimen. Because hydrogenation of I over palladium-charcoal yields quantitatively (−)-menthol (III), the *cis* relationship between the C_1-methyl and C_3-hydroxyl group in I is established. The infrared spectrum indicates that the double bond in I is of the isopropylidene type.[9] Epoxidation of (−)-*cis*-pulegyl-*p*-nitrobenzoate (II) with perbenzoic acid yields two isomeric epoxides (IVa) and (IVb) in the ratio 1:1.3 with traces of triol mono-*p*-nitrobenzoate. The epoxides (IVa)(m.p. 134–135°) and (IVb)(m.p. 128–129°) are hydrolyzed to the corresponding *p*-menthane - 4,8 - epoxy - 3 - ols (Va) (m.p. 73–75°) and (Vb)(an oil) without opening the oxide ring. In ether, IVa is reduced with lithium aluminum hydride to (+)-*cis*-4-hydroxymenthol (VIa)(m.p. 80–81°), whereas IVb resists the reduction giving only Vb. In tetrahydrofuran, however, all of the isomers of IV and V are reduced with lithium aluminum hydride to the corresponding diols, VIa and (−)-*trans*-4-hydroxyneoisomenthol (VIb)(m.p. 75–76°).

The *cis* and *trans* relationships between the two hydroxyl groups in VIa and VIb are determined by the fact that VIa is cleaved faster than VIb with lead tetraacetate. Such relationships are also deduced from the infrared spectra of VIa and VIb in dilute solution (carbon tetrachloride). In VIa an intramolecular hydrogen bonded O—H stretching absorption[10,11] is observed at 3584 cm.$^{-1}$ besides a free O—H stretching absorption at 3636 cm.$^{-1}$, whereas in VIb only the latter absorption is observed at 3623 cm^{-1}. From the absence of hydrogen bonding in VIb, the predominant conformation of VIb is considered as such that the comparatively large isopropyl group takes an equatorial position and this forces the hydroxyl groups to take a diaxial conformation. The isopropyl group in VIa may also take an equatorial conformation, because such conformation seems to be more energetically favored than an axial conformation.

Pinacolic dehydration of VIa and VIb. With 10% sulfuric acid, VIa and VIb are dehydrated to a menthone mixture (VII). The infrared spectrum of VII corresponds to that of a mixture of (−)-menthone and (+)-isomenthone. The composition of VII can be calculated[12,13] from the optical rotation of VII ($[\alpha]_D^{20}$ +15°) as composed of 65%



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(7) H. Hock and S. Lang, *Ber.*, **75**, 300 (1942).
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(13) The rotations, $[\alpha]_D^{20}$ −25° (*c*, 2 in methanol) for (−)-menthone and $[\alpha]_D^{20}$ +90° (c, 2 in methanol) for (+)-isomenthone, were used for this calculation.

(−)-menthone and 35% (+)-isomenthone. From VII, the semicarbazone and 2,4-dinitrophenylhydrazone of (−)-menthone are isolated. The corresponding derivatives of (+)-isomenthone are not obtained.

According to Klyne,[5] *trans* geometry between a departing and a migrating group determines the reaction course of the pinacolic dehydration of cyclohexane diols. But such *trans* geometry is not possible in the dehydration of VIb to VII. The present result can be explained well by assuming an intermediate carbonium ion,[14,15] which is logical as VIb is partly isomerized into VIa in aqueous acetic acid. Both VIa and VIb would form the same carbonium ion (VIc), which would rearrange to (−)-menthone or to (+)-isomenthone. In this case, the preponderance of (−)-menthone does not necessarily mean that the rearrangement of VIc is favored with the formation of (−)-menthone, because an equilibration will occur between two isomeric menthones in acid media and (−)-menthone will dominate in the equilibration mixture.[16]

EXPERIMENTAL[17]

(−)-cis-Pulegol (I) *and (−)-cis-pulegyl-p-nitrobenzoate* (II).[9] (+)-Pulegone [isolated from pennyroyal oil as a sodium sulfite addition compound, b.p. 80° (4 mm.), $[\alpha]_D^{19}$ +22.8° (homogeneous)] was reduced with lithium aluminum hydride in anhydrous ether to give a crude pulegol mixture which was then converted to the *p*-nitrobenzoate. The ester was repeatedly recrystallized from petroleum ether (b.p. 40–60°) to give II (yield 60%), m.p. 60–61°, $[\alpha]_D^{20}$ −110° (*c*, 2 in chloroform) (reported[9]: $[\alpha]_D^{20}$ −104°), and this was then hydrolyzed (by the potassium hydroxide–methanol-ether method[9]) to give I, b.p. 84–85° (3 mm.), m.p. 34–35°, $[\alpha]_D^{20}$ −104° (*c*, 2 in methanol) (reported[9]: $[\alpha]_D^{18}$ −85°). The yield of *trans* isomer separated as the 3,5-dinitrobenzoate (m.p. 102–103°) was lower than 10%.

Hydrogenation of I. Hydrogenation of I over 10% palladium-charcoal in methanol yielded crude (−)-menthol (III) (yield 93%), $[\alpha]_D^{20}$ −45° (*c*, 2 in methanol). The crude product gave (−)-menthyl-3,5-dinitrobenzoate (yield 90%), m.p. 154–155°, and no depression of the melting point was observed by admixture with the authentic sample.[18]

Epoxidation of II *with perbenzoic acid.* Into a cold solution of II 83 g. (0.274 mole) in chloroform (100 ml.) was added dropwise under stirring the chloroform solution of perbenzoic acid (590 ml., containing the peracid, 0.270 mole), and then the reaction mixture was left for 20 hr. at room temperature. This reaction mixture was washed with 10% sodium carbonate and water, dried over magnesium sulfate, and then the solvent was removed. The resulting crude crystals (m.p. 85–105°) were separated into three fractions by repeated recrystallization from *n*-hexane.

The first fraction (IVa) was the *p*-nitrobenzoate of *p*-menthane-4,8-epoxy-3-ol, hardly soluble in hot *n*-hexane and stout yellow rods, m.p. 134–135°, $[\alpha]_D^{20}$ −65° (*c*, 2 in chloroform), yield 30 g.

Anal. Calcd. for $C_{17}H_{21}O_5N$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.13; H, 6.67; N, 4.09.

The second fraction (IVb) was an isomer of IVa, soluble in hot *n*-hexane and pale yellow needles, m.p. 128–129°, $[\alpha]_D^{20}$ −16° (*c*, 2 in chloroform), yield 40 g.

Anal. Found: C, 63.78; H, 6.72; N, 4.69.

The third fraction was the mono-*p*-nitrobenzoate of *p*-methane-3,4,8-triol, insoluble in hot *n*-hexane, m.p. 151–153° (recrystallized from methanol), yield 3 g.

Anal. Calcd. for $C_{17}H_{23}O_6N$: C, 60.51; H, 6.87; N, 4.15. Found: C, 60.93; H, 6.88; N, 4.10.

p-Menthane-4,8-epoxy-3-ols (Va) *and* (Vb). The epoxides IVa and IVb were hydrolysed (by the potassium hydroxide–methanol-ether method[9]) to the corresponding *p*-menthane-4,8-epoxy-3-ols (Va) and (Vb), yield 90%.

Va, colorless needles, was recrystallized from petroleum ether (b.p. 40–60°), b.p. 103–105° (6 mm.), m.p. 73–75°, $[\alpha]_D^{20}$ +34° (*c*, 2 in methanol).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.42; H, 10.64.

Vb was an oil, b.p. 103–106° (6 mm.), $[\alpha]_D^{20}$ +1° (*c*, 2 in methanol).

Anal. Found: C, 69.90; H, 10.65.

Reduction of IVa, IVb, Va, *and* Vb *with lithium aluminum hydride.* a). *In anhydrous ether.* Because IVa is slightly soluble in ether, IVa (4 g.) was placed in a continuous extractor and transferred to a stirred suspension of lithium aluminum hydride (2 g.) in anhydrous ether (200 ml.). The reflux of ether was regulated to avoid a vigorous reaction. The reaction mixture was stirred 4 hr., then decomposed with water, and filtered. The red ethereal filtrate was dried over magnesium sulfate, the solvent was removed, and the residue was distilled to give pale red camphorous crystals (1.8 g.), b.p. 135–137° (16 mm.). This crude product was recrystallized from petroleum ether (b.p. 40–60°) to give colorless needles, (+)-*cis*-4-hydroxymenthol (VIa), m.p. 80–81°, $[\alpha]_D^{20}$ +13° (*c*, 2 in methanol).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.51; H, 11.76.

Mono-3,5-dinitrobenzoate, m.p. 124–125°, was recrystallized from *n*-hexane.

Anal. Calcd. for $C_{17}H_{22}O_7N_2$: C, 55.73; H, 6.05. Found: C, 55.62; H, 6.23.

VIa showed three infrared absorptions due to O—H stretching at 3636 cm.$^{-1}$, 3584 cm.$^{-1}$, and 3527 cm.$^{-1}$ in higher concentration, but in lower concentration (less than 0.015*M* in carbon tetrachloride) the latter absorption (3527 cm.$^{-1}$) disappeared.

Under the same reduction conditions, IVb yielded only Vb.

b). *In anhydrous tetrahydrofuran.* IVa, IVb, Va, and Vb were all reduced to the corresponding diols, VIa and (−)-*trans*-4-hydroxyneoisomenthol (VIb). As an example, the reduction of Vb is described.

A solution of Vb (7 g.) in anhydrous tetrahydrofuran (50 ml.) was dropped into the stirred suspension of lithium aluminum hydride (2 g.) in anhydrous tetrahydrofuran (50 ml.) and this was refluxed for 3 hr. After decomposition with water, the reaction mixture was filtered and concentrated under reduced pressure. The resulting oil was dissolved in ether and the ether solution was washed with water and dried over magnesium sulfate. From this ether solution, VIb (5.8 g.) was obtained, b.p. 106–108° (2 mm.), m.p. 75–76° (recrystallized from petroleum ether (b.p. 40–60°)), $[\alpha]_D^{20}$ −6° (*c*, 2 in methanol).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.61; H, 11.90.

Mono-3,5-dinitrobenzoate, m.p. 143–144°, was recrystallized from *n*-hexane.

Anal. Calcd. for $C_{17}H_{22}O_7N_2$: C, 55.73; H, 6.05. Found: C, 55.83; H, 5.92. VIb showed only one infrared absorption

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(15) R. F. Brown, J. B. Nordmann, and M. Madoff, *J. Amer. Chem. Soc.*, **74**, 432 (1952).

(16) J. Read and G. J. Robertson, *J. Chem. Soc.*, 2209 (1926).

(17) All melting and boiling points were uncorrected.

(18) H. Ueda and T. Mitsui, *J. Agr. Chem. Soc. Japan*, **28**, 945 (1954).

due to free O—H stretching at 3623 cm.$^{-1}$ in lower concentration (less than 0.015*M* in carbon tetrachloride).

Lead tetraacetate cleavage was carried out according to Criegee's method,[19] $K_{20} > 1000$ for VIa and $K_{20} = 9$ for VIb.

Dehydration of VIa *and* VIb. A heterogeneous mixture of VIa (1 g.) and 10% sulfuric acid (10 ml.) was refluxed for 2 hr. The resulting oil was extracted with ether, and the ether layer was washed with water and dried over magnesium sulfate. The ether was removed and the residue was distilled to give a menthone mixture (VII) (yield 800 mg.), b.p. 103–105° (27 mm.), $[\alpha]_D^{20}$ +15° (c, 2 in methanol), ketone % = 98.5 (hydroxylamine method). By the same procedure, VIb yielded the same VII (yield 700 mg.).

From VII, the semicarbazone (m.p. 186–187°; yield 45%) and 2,4-dinitrophenylhydrazone (m.p. 145–147°; yield 50%) of (−)-menthone were obtained and no depression of their melting points were observed by admixture with the authentic samples.[20] The infrared spectrum of VII coincided with that of the authentic mixture of (−)-menthone and (+)-isomenthone showing the following absorptions: 1249, 1203, 1094, 1043, 865, 837, 748 (cm.$^{-1}$) for (−)-menthone[21]; and 1227, 1076, 1024, 832, 797, 768 (cm.$^{-1}$) for (+)-isomenthone.[21]

Isomerization of VIb *to* VIa. A solution of VIb (500 mg.) in 50% aqueous acetic acid (5 ml.) containing 1 drop of sulfuric acid was heated under reflux for 1 hr. and extracted with ether. From this extract, an oil was obtained which was a mixture of diols and ketones. The diols were converted to the 3,5-dinitrobenzoates. The ketones were separated from the esters by steam distillation. The esters (250 mg.) were separated by repeated recrystallization from *n*-hexane into mono-3,5-dinitrobenzoate of VIa (50 mg., m.p. 124–125°) and mono-3,5-dinitrobenzoate of VIb (100 mg., m.p. 142–143°). The ketone fraction was identified by infrared spectrum as a menthone mixture.

Acknowledgment. The authors wish to express their sincere thanks to Dr. T. Hashizume, Messrs. Z. Kumazawa, and T. Fujita of Kyoto University, Kyoto, Japan, for their helpful suggestions.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Alkylation of Bimalonic Ester[1]

C. F. KOELSCH AND J. R. SJOLANDER

Received March 7, 1960

Methyl 1,1,2,2-ethanetetracarboxylate (bimalonic ester) can be alkylated only once, even though it contains two acidic hydrogen atoms. Failure to undergo a second alkylation is a result of steric hindrance. Replacement of both hydrogens when a difunctional alkylating agent is used results because the second step is intramolecular.

Bimalonic ester (I) contains two acidic hydrogen atoms, and replacements of both of these by use of dihalogen compounds have been used in synthesis of several cyclic substances. For example methyl 1,1,2,2-cyclopentanetetracarboxylate (II) has been obtained by alkylation with 1,3-dibromopropane.[2]

I II

Use of monohalogen compounds has often led to low yields of poorly characterized products.[3] But it has now been found that these substances actually react quite satisfactorily, and alkylation products have been obtained using methyl iodide, ethyl iodide, *n*-butyl bromide, allyl bromide, benzyl chloride, and acrylonitrile.

It is interesting that only one of the acidic hydrogens of bimalonic ester can be replaced using these reagents. Even when a large excess of alkylating agent is used or when the monoalkylated product is isolated and treated again, a monoalkylated product is obtained.

Resistance to dialkylation might be caused by low acidity of the monoalkylated bimalonic ester. Attempts to study this factor by the method of Pearson[4] were unsuccessful because of low solu-

(1) From the Ph.D. thesis of John R. Sjolander, August 1950.

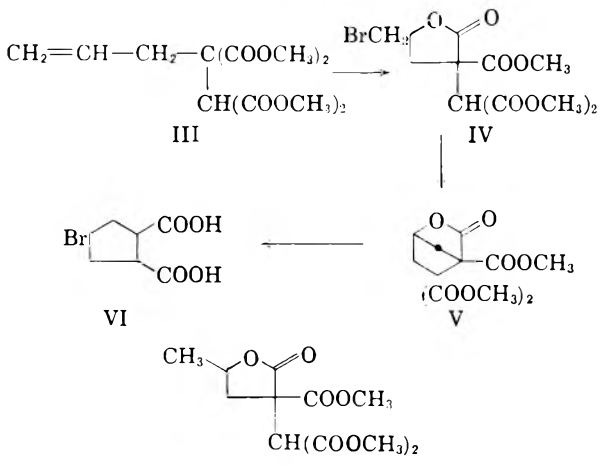
(2) A. Kötz and P. Spiess, *J. prakt. Chem.* **64**, 394 (1901). Other dihalogen compounds which yield the expected cyclic products are methylene iodide (Kötz and Spiess, *loc. cit.*), α,α'-dibromo-*o*-xylene [A. Baeyer and W. H. Perkin, *Ber.*, **17**, 448 (1884); *J. Chem. Soc.*, **53**, 1 (1888)], 2,2′-bisbromomethylbiphenyl [J. Kenner, *J. Chem. Soc.*, **103**, 613 (1913)], ethyl α,β-dibromopropionate [L. J. Goldsworthy and W. H. Perkin, *J. Chem. Soc.*, **105**, 2665 (1914)], ethyl α,β-dibromosuccinate [Y. Schibata, *Ber.*, **43**, 2619 (1910)], α,α'-dichlorodimethylsulfide [F. G. Mann and W. J. Pope, *J. Chem. Soc.*, **123**, 1172 (1923)], β,β'-dibromodiethylether [I. Ali-Zade and B. A. Arbuzov, *J. Gen. Chem., U.S.S.R.*, **13**, 113 (1943); *Chem. Abstr.*, **38**, 352 (1944)]. 1,3-Dibromobutane, once believed to yield ethyl methylcyclopentanetetracarboxylate [R. G. Fargher and W. H. Perkin, *J. Chem. Soc.*, **105**, 1353 (1914)] has been shown to yield only ethyl 2-hexene-5,5,6,6-tetracarboxylate [R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *J. Am. Chem. Soc.*, **80**, 3413 (1958)].

(3) C. A. Bischoff and C. Rach, *Ber.* **17**, 2788 (1884); *Ann.*, **234**, 54 (1884); A. Baeyer and W. H. Perkin, *J. Chem. Soc.*, 1 (1888); C. A. Bischoff, *Ber.*, **40**, 3150 (1907); F. Bachér, *J. prakt. Chem.*, **120**, 301 (1929); O. Silberad, *J. Chem. Soc.*, 611 (1904).

(4) R. G. Pearson, *J. Am. Chem. Soc.*, **71**, 2212 (1949).

bilities of the compounds involved. But C-ethylbimalonic ester was brominated readily in presence of sodium methoxide, indicating that the ester did form an anion.

It is likely that resistance to dialkylation is simply a result of steric hindrance, for it is well known[5] that even *sec*-alkylated malonic esters are difficult to alkylate, and a monoalkylated bimalonic ester is sterically comparable to a *tert*-alkylated malonic ester. Double alkylation (cyclization) using dihalogen compounds succeeds because the second step in the reaction is intramolecular. Here steric factors are of minor importance, for the reactive centers are in approximately proper position by virtue of the geometry of the molecule. It was possible that cyclizations occurred for another reason: Energy from the first alkylation was not dissipated rapidly but served to activate the molecule for the second step. This possibility has been eliminated by carrying out typical cyclizations in two separate stages. C-Allylbimalonic ester (III) was treated with hydrogen bromide in presence of peroxide,[6] and the resulting γ-bromopropylbimalonic ester was then converted to methyl 1,1,2,2-cyclopentanetetracarboxylate by action of sodium methoxide. C-Allylbimalonic ester was also treated with bromine, and the resulting bromolactone (IV) was similarly cyclized to V. Structure of the latter product was proved by using hydrobromic acid, giving VI, a compound which furnished known *trans*-1,2-cyclopentane dicarboxylic acid when it was dehalogenated with hydrogen in presence of palladium.



III IV V VI VII

EXPERIMENTAL

Bimalonic ester was obtained from methyl malonate, sodium methoxide, and bromine[7] in yields of 70–85%. Alkylations were generally carried out using an excess of both sodium methoxide and halogen compound. For example, 13.1 g. of bimalonic ester was mixed with a solution of 2.3 g. of sodium in 55 ml. of methanol, and then 19 g. of benzyl chloride was added dropwise. The mixture was boiled for 3 hr., then evaporated under reduced pressure, and steam distilled to remove excess benzyl chloride. Crystallization of the organic residue gave pure methyl 3-phenyl-1,1,2,2-propane tetracarboxylate. In all cases the alkylated products were hydrolyzed and decarboxylated by boiling for 12 hr. with excess constant-boiling hydrochloric acid, and the resulting substituted succinic acids (yields 80–90%) were identified by melting point and neutral equivalent. Results of the alkylations are given in Table I.

Acrylonitrile (5 ml.) and a few crystals of quinone were added to a solution of 2.6 g. of bimalonic ester in 15 ml. of *t*-butyl alcohol that had been saturated with potassium hydroxide. The mixture was boiled for 20 hr., then filtered, and diluted with water. Crystallization from methanol, then benzene-ligroin gave 1.2 g. (66%) of pure methyl 4-cyano-1,1,2,2-butane tetracarboxylate, m.p. 84–86°.

Anal. Calcd. for $C_{13}H_{17}NO_8$: C, 49.5; H, 5.44. Found: C, 49.8; H, 5.67.

Hydrolysis of the cyano compound gave β-carboxyadipic acid, crystals, from nitromethane, m.p. 116–118° in agreement with reported values.

Allylbimalonic ester and hydrogen bromide. A solution of 7 g. of allylbimalonic ester in 10 ml. of toluene was cooled to 0° for 45 min. while hydrogen bromide was passed in. The solution was kept at room temperature for a few hours, then warmed under reduced pressure to remove hydrogen bromide and toluene. Trituration with ether-ligroin and crystallization from methanol gave about 4 g. of the *lactone trimethyl ester of 4-hydroxy-1,1,2,2-pentanetetracarboxylic acid*, colorless rhombs m.p. 75–77°. The infrared spectrum showed sharp absorption bands at 1740 (ester) and 1770 cm.$^{-1}$ (five-membered lactone) allowing assignment of structure VII.

Anal. Calcd. for $C_{12}H_{16}O_8$: C, 50.0; H, 5.60. Found: C, 50.3; H, 5.86.

When 12 g. of allyl bimalonic ester in 20 ml. of toluene containing 0.5 g. of benzoyl peroxide was treated with hydrogen bromide in the same way, the product (10 g.) was an oil, b.p. 185–195° at 3–4 mm. A 6.5-g. portion of this γ-bromopropylbimalonic ester was dissolved in 25 ml. of methanol containing 0.4 g. of sodium and boiled for 4 hr. Fractionation of the product gave 1.7 g. of methyl 1,1,2,2-cyclopentanetetracarboxylate, b.p. 155–170° at 3–4 mm., which gave 0.3 g. of *trans*-1,2-cyclopentane dicarboxylic acid, m.p. 157–159° alone or mixed with an authentic sample.

Allylbimalonic ester and bromine. A solution of 8.25 g. of allylbimalonic ester in 50 ml. of chloroform was treated with 4.7 g. of bromine in 25 ml. of chloroform, and the solvent was then removed by distillation. Crystallization of the residue from dilute methanol gave 6.8 g. of the *lactone trimethyl ester of 5-bromo-4-hydroxy-1,1,2,2-pentanetetracarboxylic acid*, colorless rhombs m.p. 87–89°. The infrared spectrum contained absorption bands at 1740 and 1770 cm.$^{-1}$, indicating structure IV.

Anal. Calcd. for $C_{12}H_{15}BrO_8$: C, 39.3; H, 4.12. Found: C, 39.5; H, 4.34.

When 18.5 g. of this bromolactone was boiled with a solution of 1.15 g. of sodium in 25 ml. of methanol for 4 hr., the solution became neutral. There was obtained 3.1 g. of the *lactone trimethyl ester of 4-hydroxy-1,1,2,2-cyclopentane tetracarboxylic acid* (V), long flat needles from water, m.p. 110–112°.

Anal. Calcd. for $C_{12}H_{14}O_8$: C, 50.4; H, 4.93. Found: C, 50.7; H, 5.07.

A solution of 2 g. of V in 25 ml. of 48% hydrobromic acid was boiled for 1 hr., the spent acid was then removed by distillation and replaced with 25 ml. of concd. material. After another hour of boiling, the mixture was concentrated to about 5 ml. and cooled, giving 0.95 g. of *4-bromo-1,2-*

(5) A. C. Cope, W. H. Hartung, E. M. Hancock, and F. S. Crossley, *J. Am. Chem. Soc.*, **62**, 314 (1940).

(6) In absence of peroxide, hydrogen bromide simply causes interaction of the double bond with an ester group. Methyl bromide is eliminated, and VII is formed.

(7) J. Walker and J. R. Appleyard, *J. Chem. Soc.*, **67**, 768 (1895).

TABLE I

ALKYLATION PRODUCTS OF BIMALONIC ESTER, $RC(COOCH_3)_2$
$CH(COOCH_3)_2$

RX	Yield, %	M.P. (B.p.°/mm.)	Formula	Calcd. C	Calcd. H	Found C	Found H
CH_3I	74	(142–145/5)[a]	$C_{11}H_{16}O_8$	47.8	5.84	47.8	6.14
C_2H_5I	82	54–56 (150/3)	$C_{12}H_{18}O_8$	49.6	6.25	49.5	6.42
n-C_4H_9Br	30[c]	67–70	$C_{14}H_{22}O_8$	52.8	6.97	52.5	7.22
CH_2=$CHCH_2Br$	89[d]	(151/3)[b]	$C_{13}H_{18}O_8$	51.7	6.00	51.8	6.20
$C_6H_5CH_2Cl$	79	98–100	$C_{17}H_{20}O_8$	57.9	5.68	58.0	5.97

[a] n_D^{22} 1.4468. [b] n_D^{25} 1.4589. [c] 50% of bimalonic ester recovered, 11 hr. reaction time. [d] Hydrolysis and decarboxylation using hydrochloric acid gave the known lactone of 4-hydroxy-1,2-pentanedicarboxylic acid, m.p. 66–68°.

cyclopentanedicarboxylic acid (VI), crystals from ether-ligroin, m.p. 146–148°.

Anal. Calcd. for $C_7H_9BrO_4$: C, 35.5; H, 3.83; N.E., 118.5. Found: C, 35.8; H, 4.02; N.E., 120.

Hydrogenolysis of VI (0.6 g.) by shaking with palladium on barium sulfate in water for 3 hr. consumed 85% of the calculated amount of hydrogen and gave 0.18 g. of 1,2-cyclopentanedicarboxylic acid, m.p. 159–160° alone or mixed with an authentic sample.

Bromination of C-ethylbimalonic ester. A solution of 0.23 g. of sodium in 25 ml. of methanol was treated with 2.9 g. of C-ethylbimalonic ester, and then with 1.6 g. of bromine in 16 ml. of methanol, resulting in immediate reaction. Methanol was removed and replaced with ether, and the product was washed with water, and dried. There was obtained 2.88 g. of crude or 1.5 g. of pure methyl 1-bromo-1,1,2,2-butanetetracarboxylate, colorless crystals from dilute methanol, m.p. 106–107°.

Anal. Calcd. for $C_{12}H_{17}BrO_8$: C, 39.0; H, 4.64. Found: C, 39.3; H, 4.97.

Acknowledgment. The authors thank R. W. Amidon, J. S. Buckley, R. W. Cummings, and H. W. Turner for the analytical results.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Condensed Cyclobutane Aromatic Compounds. XIII. An Attempted Synthesis of 1,2-Diphenylbenzocyclobutene

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Received January 14, 1960

The synthesis of 1,3-diphenyl-1,3-dihydroisothianaphthene-2,2-dioxide (IV), starting from *o*-dibenzoylbenzene, is described. Pyrolysis of IV at 250° gives 9-phenyl-9,10-dihydroanthracene (XII), rather than the expected 1,2-diphenylbenzocyclobutene (V). The existence of the intermediary quinodimethane (XV) was demonstrated by a Diels-Alder trapping reaction.

Since the pyrolysis of 1,3-dihydroisothianaphthene-2,2-dioxide (I) yields either benzocyclobutene (II) or 1,2,5,6-dibenzocyclooctadiene (III), depending on the conditions used,[1] the pyrolysis of 1,3-diphenyl-1,3-dihydroisothianaphthene-2,2-dioxide (IV) was investigated as a possible route to 1,2-diphenylbenzocyclobutene (V).

Sulfone IV, m.p. 200–201°, was obtained by the peracetic acid oxidation of the known sulfide, VI.[2] Methods are described in the literature for each of the preceding synthetic steps, *viz.*, the reduction of *o*-dibenzoylbenzene (VII) to 1,3-diphenylisobenzofuran (VIII);[3] the conversion of VIII to 1,3-diphenylisothianaphthene (IX) by phosphorus pentasulfide;[4] and the reduction of IX to the sulfide, VI. However, since we experienced considerable difficulty in obtaining reproducible results in all three of these reactions, modified preparations of VI and IX were developed, and these are reported in the Experimental section In addition, a new method is reported for the conversion of *o*-dibenzoylbenzene (VII) into furan VIII by the partial reduction of VII with potassium borohydride, followed by treatment of the primary reduction product (X) with acid. The success of this procedure is probably due to the tendency of the intermediary ketoalcohol, X, to exist mostly as the phthalan (XI)[5] in the basic reduction medium. Even so, good yields of VIII could be ob-

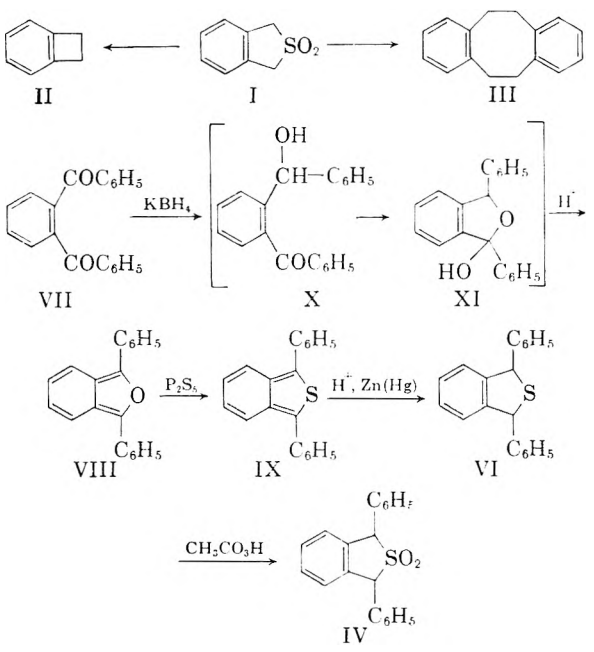
(1) M. P. Cava and A. A. Deana, *J. Am. Chem. Soc.*, **81**, 4266 (1959), paper VI of this series.

(2) A. Bistrzycki and B. Brenken, *Helv. Chim. Acta*, **5**, 20 (1922). The precursor of VI (compound IX) is described incorrectly in this paper as "*phenylmesothioanthracendihydrid.*" See ref. 4 for the clarification of this point.

(3) R. Adams and M. H. Gold, *J. Am. Chem. Soc.*, **62**, 56 (1940).

(4) C. Dufraisse and D. Daniel, *Bull. soc. chim.*, [5] **4**, 2063 (1937).

(5) A. Guyot and J. Catel, *Compt. rend.*, **140**, 1348 (1905).



tained only by treating VII alternately with borohydride and mineral acid, thereby avoiding the accumulation of large amounts of the intermediate in the reaction mixture. It may be noted that furan VIII was found to be completely stable under the conditions of the reduction.

When the pyrolysis of sulfone IV was carried out in diethyl phthalate at 250°, neither 1,2-diphenylbenzocyclobutene (V) nor a dimer of this substance was obtained. There was isolated instead, in 94% yield, 9-phenyl-9,10-dihydroanthracene (XII), the constitution of which was confirmed by dehydrogenation to 9-phenylanthracene with the mild reagent, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[6] The thermal decomposition of sulfone IV therefore follows a course analogous to that of 1,1,3-triphenyl-1,3-dihydroisothianaphthene-2,2-dioxide (XIV)[7,8] which similarly yields anthracene derivatives by intramolecular rearrangement of the primary pyrolysis product.[9] The great ease with which the expected pyrolysis intermediate XV rearranges to 9-phenyl-9,10-dihydroanthracene is demonstrated by an experiment in which sulfone IV was pyrolyzed at 250° in the presence of an excess of 1,4-naphthoquinone. Diels-Alder addition of the intermediary quinomethane XV to 1,4-naphthoquinone did indeed occur, as shown by the isolation in 42% yield of 6,11-diphenyl-5,12-naphthacenequinone (XVII).[10]

(6) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954). We are indebted to Dr. P. M. G. Bavin for a sample of this quinone.

(7) H. Staudinger and F. Pfenninger, *Ber.*, 49, 1941 (1916).

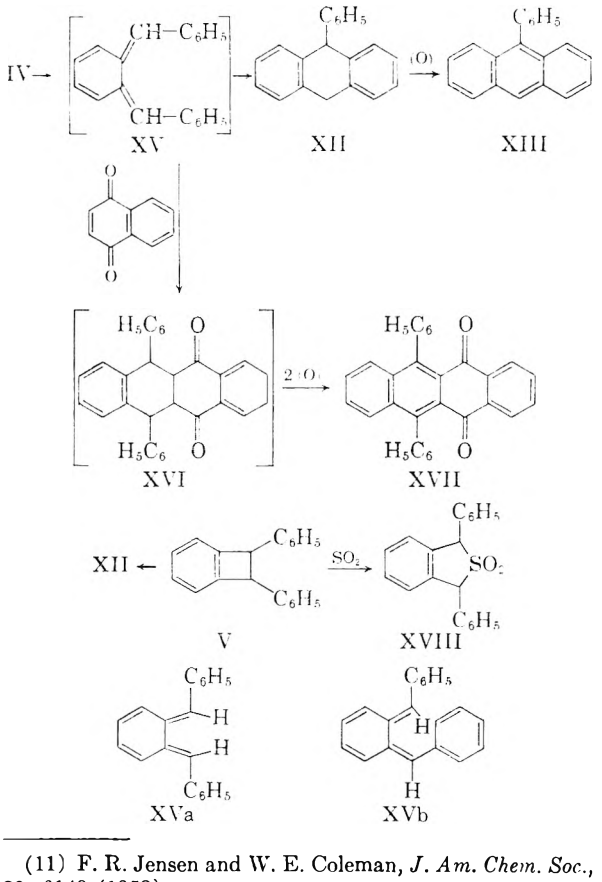
(8) H. Klosterziel and H. J. Backer, *Rec. trav. chim.*, 71, 1235 (1952).

(9) For a more complete discussion of this case, see ref. 1.

(10) C. Dufraisse and P. Compagnon, *Compt. rend.*, 207, 585 (1938)

However, a significant portion of intermediate XV failed to react with the naphthoquinone, as evidenced by the isolation in 20% yield of the aromatized rearrangement product, 9-phenylanthracene (XIII).

During the course of this work a successful synthesis of 1,2-diphenylbenzocyclobutene (V) was reported.[11] The diphenyl derivative was found to be remarkably reactive; on heating, it rearranged to 9-phenyl-9,10-dihydroanthracene (XII), probably *via* the transient intermediate XV. In addition, it reacted with sulfur dioxide under surprisingly mild conditions to yield a sulfone (XVIII), m.p. 232.5–234° dec.; this sulfone differs from our sulfone IV which has a melting point of 200–201° dec.,[12] yet it gives the same pyrolysis product, hydrocarbon XII. The two sulfones, IV and XVIII, are apparently related as *cis-trans* isomers. Sulfone IV and its precursor, sulfide VI, are probably *trans* isomers, since VI is derived from the isothianaphthene IX by a metal and acid reduction, a process which may favor the formation of the thermodynamically stable *trans* product. Furthermore, the sulfone derived from 1,2-diphenylbenzocyclobutene and sulfur dioxide, *i.e.*



(11) F. R. Jensen and W. E. Coleman, *J. Am. Chem. Soc.*, 80, 6149 (1958).

(12) In addition, the melting point of sulfone IV is depressed (185–193°) upon admixture with sulfone XVIII, and the infrared spectra of the two sulfones differ in the 8–15 μ range. We are indebted to Dr. F. R. Jensen for a comparison sample of authentic sulfone XVIII.

sulfone XVIII, might be expected to be the *cis* isomer, since sulfur dioxide probably adds in a concerted manner to quinodimethane XV, or at least takes part in a transition state approaching structure XV. It is to be noted that, of the various *cis* and *trans* isomers which can be drawn for XV, only isomer XVa, which would give a *cis*-sulfone when treated with sulfur dioxide, fulfills the steric requirements for full resonance stabilization as a coplanar structure. Indeed, mild thermal isomerization of XVa would lead to structure XVb which would have not only *less* orbital overlap stabilization, but a more favorable conformation for subsequent intramolecular ring closure to form XII.

EXPERIMENTAL[13]

1,3-Diphenylisobenzofuran (VIII). A solution of 2.86 g. (0.01 mole) of *o*-dibenzoylbenzene[3] in 60 ml. of refluxing ethanol was treated with 2 ml. of a 6% aqueous potassium borohydride solution. Reduction was allowed to proceed for exactly 1 min. and was then stopped by the addition of excess (1–2 ml.) of 5*N* sulfuric acid in ethanol. The reaction mixture was stirred rapidly under reflux for 10 min. and was then made basic by the addition of 5*N* alcoholic potassium hydroxide solution. (The product itself, which is canary-yellow in acid and orange-yellow in base, was used as an internal indicator.) After stirring and refluxing the basic solution for 10 min., a second 2-ml. portion of borohydride solution was added, reduction was again allowed for 1 min. and was then stopped, as before, with acid. The entire cycle was repeated five times *in toto*. After the final reduction step, the reaction mixture was treated with 60 ml. of aqueous 1.5*N* sulfuric acid, heated on the steam bath for 15 min., cooled, and filtered with suction. The crude product (bright yellow flakes) was dried and leached with 100 ml. of warm petroleum ether (b.p. 55–60°) to give 2.1 g. (78%) of the product, 1,3-diphenylisobenzofuran, m.p. 130–131° (reported[3] m.p. 126°), which was obtained in three crops.

1,3-Diphenylisothianaphthene (IX). In a 250-ml., one-neck, round-bottom flask provided with a 1-inch magnetic stirring bar and two dozen 6-mm. glass beads were placed 150 ml. of carbon disulfide and 2 g. of phosphorus pentasulfide. The phosphorus pentasulfide was finely dispersed in the carbon disulfide by 1 hr.'s rapid stirring with the glass beads. 1,3-Diphenylisobenzofuran (1.0 g., 3.7 mmoles) was then added, and stirring was continued for 12 hr. at room temperature, in the dark, and under dry nitrogen. Another 2-g. portion of phosphorus pentasulfide was added, and stirring was resumed for a second 12-hr. period. The product was isolated by Dufraisse's method[4]: thus, the reaction mixture was filtered with suction, the filtrate was evaporated to dryness *in vacuo;* the residue was extracted with two 100-ml. portions of benzene, and the extract was refluxed for 4 hr. with 100 ml. of 10% aqueous sodium hydroxide solution in order to remove inorganic sulfides. The resulting clear benzene layer was separated, dried over sodium sulfate, treated with a solution of 500 mg. of maleic anhydride in 5 ml. of benzene to remove unchanged starting material, allowed to stand for 30 sec., and finally was washed thoroughly with three 50-ml. portions of 5% aqueous sodium hydroxide solution. The organic layer was again dried over sodium sulfate and was then evaporated to dryness *in vacuo*. Recrystallization of the residue from ethanol gave 0.64 g. (60%) of the product, 1,3-diphenylisothianaphthene, bright yellow needles, m.p. 119–120° (reported[4] m.p. 118–119°).

1,3-Diphenyl-1,3-dihydroisothianaphthene (VI). To a rapidly stirred solution of 100 mg. (0.35 mmole) of 1,3-diphenylisothianaphthene in 20 ml. of warm glacial acetic acid was added 15 g. of amalgamated zinc dust.[14] The resulting suspension was stirred rapidly for 5 min. at 80–85°; 5 ml. of concd. hydrochloric acid was then added all at once, and reduction was allowed to proceed for 1 to 1.5 min. The almost colorless reaction mixture was quickly filtered with suction, and the filtrate was diluted with hot water until a persistent cloudiness was observed. The filtrate was cooled to 15° to give 65 mg. (64.5%) of 1,3-diphenyl-1,3-dihydroisothianaphthene. Recrystallization from ethanol-water gave long white needles, m.p. 107–108° (reported[2] m.p. 106.5–107.5°, 29% yield).

1,3-Diphenyl-1,3-dihydroisothianaphthene-2,2-dioxide (IV). A solution of 2.0 g. (7.0 mmoles) of 1,3-diphenyl-1,3-dihydroisothianaphthene in 50 ml. of glacial acetic acid was added dropwise over a period of 30 min. to 20 ml. of commercial (Becco) 40% peracetic acid kept at 25°. The reaction mixture was allowed to stand at room temperature for 2 days and was then treated with 50 ml. of water to give 1.86 g. of small white needles. Concentration of the mother liquor gave a second crop (260 mg.). Recrystallization of the product from methylene chloride–petroleum ether (b.p. 35–55°) gave a total yield of 2.01 g. (90%) of 1,3-diphenyl-1,3-dihydroisothianaphthene-2,2-dioxide, obtained as fine white needles, m.p. 200–201° dec.

Anal. Calcd. for $C_{20}H_{16}O_2S$: C, 74.97; H, 5.03; S, 10.01. Found: C, 74.70; H, 4.96; S, 9.91.

Pyrolysis of 1,3-diphenyl-1,3-dihydroisothianaphthene-2,2-dioxide. A solution of 160 mg. (0.5 mmole) of dioxide IV in 100 ml. of diethyl phthalate was heated in an oil bath at 250° under a slow stream of nitrogen. The nitrogen–sulfur dioxide gas mixture from the reaction vessel was bubbled through an aqueous solution containing an equivalent amount (0.5 mmole) of iodine (prepared from 5 ml. of 0.03*M* potassium iodate, 1 ml. of saturated potassium iodide solution, and 10 drops of 6*N* hydrochloric acid). When the iodine solution had been decolorized (heating time, 45 min.), the reaction mixture was poured into 200 ml. of 5% alcoholic potassium hydroxide. The resulting soap slurry was allowed to stand in a water bath at 50° for 12 hr. It was then evaporated almost to dryness *in vacuo*, dissolved in 200 ml. of water, and extracted with four 50-ml. portions of petroleum ether (b.p. 30–60°). The combined organic extracts were dried over sodium sulfate and evaporated to dryness *in vacuo* to give 150 mg. of crude product. Chromatography on Grade I neutral alumina (Woelm) with 1:4 ether-benzene, followed by recrystallization from ethanol, gave 120 mg. (94%) of pure 9-phenyl-9,10-dihydroanthracene (XII), m.p. 86–87° (reported[15] m.p. 87–88°). The dihydro compound was characterized further by conversion into 9-phenylanthracene (XIII): thus, a solution of 11.5 mg. (0.045 mmole) of 9-phenyl-9,10-dihydroanthracene in 2 ml. of benzene was mixed with a solution of approximately 35 mg. (0.15 mmole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[6] in 6 ml. of benzene and warmed in a water bath (75°) for 1.5 hr. The reaction mixture was evaporated to dryness under an air jet, and the residue was triturated with 1 ml. of petroleum ether (b.p. 30–60°) and then extracted twice with the same solvent. Chromatography of the extract

(13) Melting points are corrected. The analysis of IV was carried out by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(14) The amalgamated zinc dust was prepared by shaking 50 g. of zinc dust with 100 ml. of 1.5% aqueous ammonium chloride solution for 15 min., adding 150 ml. of saturated aqueous mercuric chloride solution, shaking for another 15-min. period, and then washing by decanting with four 100-ml. portions of distilled water. The amalgam was allowed to stand for 24 hr. under the last wash water and was filtered with suction just before use.

(15) W. Schlenk and E. Bergmann, *Ann.*, **463**, 161 (1928).

on Grade I neutral alumina (Woelm) with 1:4 ether-benzene gave 6.8 mg. (59%) of 9-phenylanthracene, m.p. 154–156° (reported[15] m.p. 152°), identical by mixed melting point and ultraviolet analysis ($\lambda_{max}^{C_2H_5OH}$ 255 mμ, log ε = 5.16)[16] with an authentic sample of XII prepared from anthrone and phenylmagnesium bromide.[17]

6,11-Diphenyl-5,12-naphthacenequinone (XVII) *and 9-phenylanthracene* (XIII). Sulfone IV (160 mg., 0.5 mmole) and 395 mg. (2.5 mmoles) of 1,4-naphthoquinone were mixed together in a test tube (0.8 × 5 cm.). The upper part of the test tube was then melted and drawn out into a fine capillary, which was left open. The tube was immersed up to its tip in a hot oil bath (250°) for 15 min., then cooled and wiped dry. Both the tube and its contents were ground to a fine powder in a mortar and extracted with two 20-ml. portions of 1:4 ether-benzene. The extracts were combined and evaporated to dryness *in vacuo*. The residue was taken up in 10 ml. of 1:4 ether-benzene and chromatographed with the same solvent on Grade I neutral alumina (Woelm). The first fraction (blue-fluorescent) to leave the column consisted of 26 mg. (20%) of 9-phenylanthracene, m.p. 150–153°, identical in mixed melting point with an authentic sample prepared from anthrone.[17] The second fraction (yellow) consisted of 86 mg. (42%) of 6,11-diphenyl-5,12-naphthacenequinone, m.p. 287–288°, identical in melting point and infrared spectrum with an authentic sample prepared from 1,3-diphenylisobenzofuran and 1,4-naphthoquinone.[10]

(16) E. Clar and D. G. Stewart, *J. Am. Chem. Soc.*, **74**, 6237 (1952).

(17) J. W. Cook, *J. Chem. Soc.*, 2170 (1926).

Acknowledgment. We wish to thank the Research Corporation for a grant supporting a part of this work.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, DIAMOND ALKALI COMPANY]

The Addition-Chlorination of Aniline

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Received January 26, 1960

The benzene ring of aniline has not undergone chlorination by addition in the past because the electron-releasing amine group enables substitution to take place too readily. The use of two electron-withdrawing acyl groups attached to the amine group in aniline did not enable addition-chlorination to take place. Instead, monodeacetylation took place, followed by substitution-chlorination of the acetanilide to 2,4-dichloroacetanilide. The use of non-cleavable electron-withdrawing groups permitted addition-chlorination to take place readily. Thus, phenyl isocyanate and *N*-phenylimidocarbonyl chloride were chlorinated by addition in good yields. Hydrolysis of the addition products suggests that the major stable product from any attempted addition-chlorination of aniline would be 2,4,6-trichloroaniline.

In our previous paper on the addition-chlorination of phenol,[1] we demonstrated that the combination of the phenolic oxygen atom with groups exerting a negative inductive effect permits addition-chlorination of the benzene ring to take place readily. Thus, phenyl trichloroacetate was addition-chlorinated in near quantitative yields.

Aniline, like phenol, contains a strong electron-releasing atom, and readily undergoes substitution chlorination, even in the absence of catalysts. It was the purpose of this work to add chlorine to the benzene ring of an aniline derivative, and to determine the nature of the product of the addition-chlorination of aniline. The direct addition-chlorination of aniline was not attempted because of its ease of substitution, and because the expected product is a *gem*-chloroamine, II, an unstable structure which would not be identifiable.

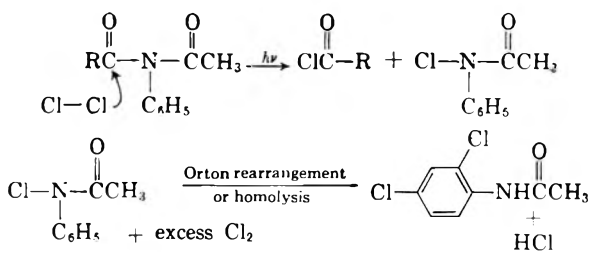
It is known that the single acetylation of aniline diminishes the *ortho-para*-orienting power of the acetylated group, but does not reduce it sufficiently for *meta* orientation of an incoming group to take place. In another instance, it is known that the single acylation of nitrogen, as in aceto-*p*-toluidide, is not sufficient to reduce the orienting power of the acylamine group below that of the methyl group. However, double acylation is sufficient to enable the methyl group to take control.[2]

In view of the above information, it seemed likely that a doubly acylated amine group would be less *ortho-para* directing than the singly acylated group. It was expected that the deactivation of the nucleus would reduce the rate of the substitution chlorination reaction and permit addition-chlorination to take place more readily. Attempts were made to addition-chlorinate diacetanilide and α,α,α-trifluorodiacetanilide. It was hoped that the presence of the halogens on the acetyl group would also tend to reduce the *ortho-para* orientation by virtue of their added inductive effect in this system. The diacetanilide, together with carbon tetrachloride and the theoretical amount of chlorine for addition, was sealed in a borosilicate glass tube and exposed to ultraviolet irradiation. Some activation is needed for the reaction to take place; there is no reaction in the dark. With both starting materials, the same product, 2,4-dichloroacetanilide, was isolated in fair yields. It was assumed that this product was formed predominantly *via* the reaction scheme shown below, involving cleavage of an acyl group

(1) I. Rosen and J. P. Stallings, *J. Org. Chem.*, **24**, 1523 (1959).

(2) O. L. Brady, W. G. E. Quick, and W. F. Welling, *J. Chem. Soc.*, **127**,2264 (1925).

and subsequent substitution of the benzene ring. The conversion of the *N*-chloroacetanilide to the ring chlorinated product can take place *via* the Orton rearrangement, or by a homolytic mechanism under the influence of light, or by both means.[3]



A diacylated aniline can be very readily cleaved to a monoacylated aniline.[4] Once hydrochloric acid is formed in the reaction, some of the diacetanilide will be cleaved to acetanilide, which can then undergo a substitution reaction with chlorine.

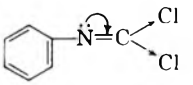
Although one of the two acyl groups is readily cleaved, the remaining one is fairly stable. In order to avoid this cleavage and still try to maintain the reduced *ortho-para* directing power of the nitrogen atom, one of the acyl groups was replaced by a methyl group. The use of the compound, *N*-methyl, α,α,α-trichloroacetanilide, under conditions suitable for addition-chlorination, however, resulted only in a substitution reaction. For the conditions used, this means of achieving control over the nitrogen atom's electron-releasing properties proved ineffective.

In order to overcome the deficiencies in the preceding systems, it was apparently necessary to use a non-cleavable electron-withdrawing group attached to the amine. Thus, phenyl isocyanate was chosen as the next material for chlorination. The nitrogen atom in this molecule has a reduced *ortho-para* orienting power compared with that in aniline. Because of the decreased tendency for substitution in the benzene ring, it was hoped that the addition-chlorination could compete with the substitution-chlorination.

The benzene ring of phenyl isocyanate was readily addition-chlorinated in good yield. The addition-chlorinated product still possessed the isocyanate group intact. The product was identified by its elemental analysis and by its hydrolyzable chlorine content. The structure was confirmed by infrared analysis. The infrared spectrum of this product contained a strong absorption band at 2260 cm.$^{-1}$ for the isocyanate group, and no absorption bands for the benzene ring. The product was thus identified as 1,2,3,4,5,6-hexachlorocyclohexyl isocyanate.

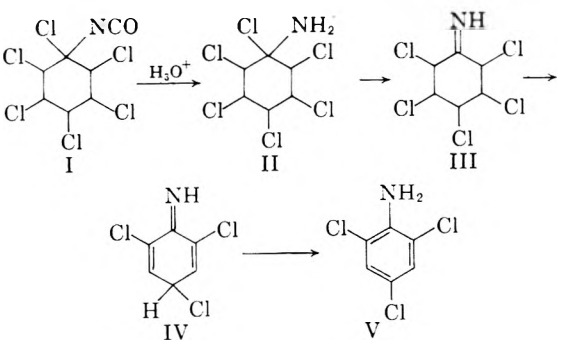
The by-product of this chlorination appeared to be *p*-chlorophenylcarbamoyl chloride. This material has been obtained previously by others by the reaction of chlorine with phenyl isocyanate in both carbon tetrachloride and chloroform, but no physical properties were reported.[5,6] The structure of the by-product was indicated by its elemental analysis and by its hydrolyzable chlorine content, and confirmed by infrared analysis. The infrared spectrum contained strong absorption bands at 1780 cm.$^{-1}$ and 1530 cm.$^{-1}$, assignable to a carbonyl adjacent to an electronegative group, and to N—H stretch, respectively.

An extension of the above work on addition-chlorination involved the substitution of another electron-withdrawing group (chlorine) for the oxygen in the isocyanate. This change was made to determine if the *ortho-para* orienting power would still be reduced sufficiently to enable addition-chlorination to take place. The inductive effect of the two chlorine atoms should decrease the availability of the nitrogen electrons toward participation in ring activation. The *N*-phenylimidocarbonyl



chloride was prepared by a published method.[7] It readily underwent the addition of chlorine to the benzene ring to yield 1,2,3,4,5,6-hexachlorocyclohexylimidocarbonyl chloride. This compound was identified by elemental and infrared analyses. The infrared spectrum contained a strong band at 1680 cm.$^{-1}$ for C=N stretch, and no absorption bands for the benzene ring.

In order to get some idea as to what the addition-chlorinated product of aniline might be, the 1,2,3,4,5,6-hexachlorocyclohexyl isocyanate was treated with dilute hydrochloric acid. Normally, the use of dilute acid converts an aromatic isocyanate into a mixture of aromatic amine and urea. The product which was obtained in our hydrolysis was 2,4,6-trichloroaniline (66% crude yield).



The proposed explanation for the formation of the 2,4,6-trichloroaniline rather than other isomers

(3) E. D. Hughes and C. K. Ingold, *Quart. Revs.*, 6, 34 (1952).

(4) E. J. Bourne, S. H. Henry, C. F. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952).

(5) F. Gumpert, *J. prakt. Chem.*, (2), **32**, 278 (1885).

(6) N. S. Dokuniklin, L. A. Gaeva, and I. D. Pletneva, *J. Gen. Chem. U.S.S.R.*, **24**, 177 (1954); *Zhur. Obshchei Khim.*, **24**, 174 (1954).

(7) R. S. Bly, W. L. Lewis, and G. A. Perkins, *J. Am. Chem. Soc.*, **44**, 289 (1922).

is represented by the above sequence of steps. In the first step, the isocyanate, I, should be hydrolyzed to the *gem*-chloroamine, II, which is the product of the addition-chlorination of aniline. The *gem*-chloroamine, II, then should undergo dehydrochlorination to the 2,3,4,5,6-pentachlorocyclohexylimine, III, and then probably to a dienimine such as IV. Finally, IV should rapidly undergo rearrangement to the product, V. An inference of the results is that if aniline were addition-chlorinated to II, II would probably undergo the same dehydrochlorination path and sequence of steps and yield V as the major stable product.

EXPERIMENTAL

Preparation of the N-substituted anilines. Diacetanilide. This compound was prepared in 65% yield by refluxing a mixture of acetanilide, acetic anhydride, and acetyl chloride for 12 hr. The compound was recrystallized from *n*-hexane, and had a m.p. of 39.0–40.5° (lit.[8] m.p. 37.5°).

α,α,α-Trifluorodiacetanilide. This compound was prepared in 71% yield by refluxing a mixture of acetanilide and trifluoroacetic anhydride. The compound was purified by distillation, b.p. 78–82°/0.6–0.7 mm. (lit.,[4] b.p. 121–125° (bath temperature)/12 mm.).

N-methyl,α,α,α-trichloromethyl acetanilide. This compound was prepared in 70% yield by refluxing a mixture of *N*-methylaniline and trichloroacetyl chloride in ether. The compound was purified by distillation, b.p. 120–122°/0.7 mm., m.p. 50–51° (lit.,[9] m.p. 55°).

N-phenyl imidocarbonyl chloride. This compound was prepared in 83% yield from the reaction of chlorine with phenyl isothiocyanate. The compound was purified by distillation, b.p. 110°/33 mm. (lit.,[7] b.p. 104–106°/30 mm.).

Eastman White Label grade phenyl isocyanate was used in this work. It was distilled prior to use.

Addition-chlorination of the substituted anilines. Preparation of 1,2,3,4,5,6-hexachlorocyclohexyl isocyanate (I). In a thick-walled borosilicate glass tube of 2.5 cm. i.d. were placed 11.0 g. (0.095 mole) of phenyl isocyanate and 30 ml. of carbon tetrachloride. Chlorine gas was bubbled into the solution until the slight exothermic reaction ceased. The tube was then cooled and 24.7 g. (0.348 mole) of chlorine added. The tube was sealed and placed adjacent to a black light fluorescent lamp (General Electric Co. catalog No. F15T8-BL) for 22 hr. When the tube was opened, no hydrogen chloride was detected. A solid which had formed inside the tube was filtered. The solid was recrystallized from benzene, yielding white needles, m.p. 127° dec. The yield was 2.0 g. (12%) of a by-product, *p*-chlorophenylcarbamoyl chloride.

Anal. Calcd. for $C_7H_5Cl_2NO$: C, 43.25; H, 2.67; hydrolyzable Cl, 18.7. Found: C, 43.92; H, 2.87; hydrolyzable Cl, 18.9.

The infrared spectrum of this compound was obtained using the potassium bromide pellet technique. The spectrum contains the following assignable bands: 3350 cm.$^{-1}$, N—H stretch; 1780 cm.$^{-1}$, carbonyl stretch in an acid chloride; 1530 cm.$^{-1}$, N—H deformation; 1600 cm.$^{-1}$, skeletal benzene ring; and 3050 cm.$^{-1}$, CH stretch in benzene. There was no band for the R—NCO stretch. This evidence indicates the compound is probably *p*-chlorophenylcarbamoyl chloride, previously reported prepared by the reaction of chlorine with phenyl isocyanate in chloroform.[5,6]

The filtrate of the original reaction mixture was evaporated under vacuum to remove the carbon tetrachloride. The amber oil which remained weighed 23.6 g. (84%), but decomposed on attempted distillation at 0.1 mm. The infrared spectrum of the oil contained a very strong absorption band at 2260 cm.$^{-1}$, assignable to the —NCO group. The spectrum also contained no evidence of aromatic character. A weak absorption at 1780 cm.$^{-1}$ indicated that a carbamoyl chloride impurity was present in the oil, probably as a hexa- or heptachlorocyclohexylcarbomoyl chloride.

Anal. Calcd. for $C_7H_5Cl_6NO$ (hexachlorocyclohexyl isocyanate): C, 25.30; H, 1.51; Cl, 64.0; hydrolyzable Cl, 32.0. Found: C, 25.25; H, 1.41; Cl, 61.8; hydrolyzable Cl, 31.4.

Preparation of 1,2,3,4,5,6-hexachlorocyclohexylimidocarbonyl chloride. In a thick-walled borosilicate glass tube of 2.5 cm. i.d. were placed 23.8 g. (0.137 mole) of phenyl imidocarbonyl chloride, 20 ml. of carbon tetrachloride, and 42.6 g (0.60 mole) of chlorine. The tube was sealed and placed adjacent to the black light fluorescent lamp for 18 hr. A solid formed in the tube during this time. The tube was cooled in Dry Ice and vented. The remaining chlorine was removed with the aid of a vacuum. The mixture was filtered. The crude solid weighed 23.9 g. The carbon tetrachloride was removed from the filtrate under the vacuum of a water aspirator. The amber oil which remained weighed 20.8 g. The total yield of solid and oil was 44.7 g. (84%). The crude solid was recrystallized twice from *n*-hexane, m.p. 138–143°.

Anal. Calcd. for $C_7H_5NCl_6$ (hexachlorocyclohexylimidocarbonyl chloride): C, 21.75; H, 1.30; Cl, 73.4. Calcd. for $C_7H_4NCl_9$: C, 19.94; H, 0.95; Cl, 75.8. Found, Crystals: C, 21.1; H, 1.5; Cl, 74.4. Found, Oil: C, 21.4; H, 1.3; Cl, 74.3.

The infrared spectra of the crystals and oil contain the following assignable bands: 1680 cm.$^{-1}$, C=N stretch; and 2960 cm.$^{-1}$, aliphatic C—H stretch. There was no evidence of aromaticity in the spectra.

Acid hydrolysis of 1,2,3,4,5,6-hexachlorocyclohexyl isocyanate (I). Into a 50-ml. one-necked round bottomed flask fitted with a magnetic stirrer and reflux condenser were placed 1.000 g. (0.0030 mole) of I, 18 ml. of 6*N* aqueous hydrochloric acid, and 18 ml. of 95% ethanol. Upon warming, a homogeneous solution was obtained. After refluxing for 3 hr. the solution had turned deep red and a small amount of sediment had accumulated. The mixture was cooled and filtered. The filtrate was made basic with 1*N* sodium hydroxide and extracted with three 50-ml. portions of ether. The ether extracts were combined, dried, and evaporated. The residue weighed 0.371 g. and was recrystallized from *n*-hexane. The crystals of 2,4,6-trichloroaniline weighed 0.257 g. (44%), m.p. 77.5–79.0°. Mixture with an authentic sample of 2,4,6-trichloroaniline did not depress the melting point.

Acknowledgment. The authors wish to thank J. J. Mannion and T. S. Wang of the Diamond Alkali Company Analytical Section for their aid in obtaining the infrared spectra.

PAINESVILLE, OHIO

(8) C. G. Derick and J. H. Bornman, *J. Am. Chem. Soc.*, **35**, 1269 (1913).

(9) L. Spiegel and P. Spiegel, *Ber.*, **40**, 1730 (1907).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

The Bromination of Ethyl *p*-*t*-Butyl-β-cyano-α-hydroxycinnamate Intermediates

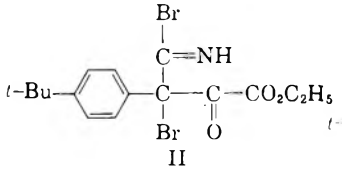
GLENN S. SKINNER AND GEORGE R. HARTRANFT

Received March 3, 1960

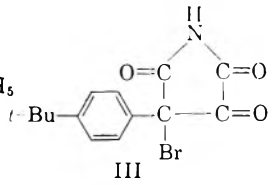
The bromination of ethyl *p*-*t*-butyl-β-cyano-α-hydroxycinnamate (I) in dry carbon tetrachloride gives an intermediate dibromide (II) and a monobromide (III) each of which is converted to *p*-*t*-butylphenylhydroxymaleimide by appropriate means. When the single reactive hydrogen in the enolic group of I is blocked by an ethyl group, the reaction with bromine does not take place and the ethyl ether of I is recovered unchanged. The experiments performed in the determination of the structure of the bromides are described and their significance is discussed.

Previous studies in this laboratory have indicated that bromine reacts with chloroform solutions of β-cyano-α-hydroxycinnamic esters in the presence of water to give *p*-bromoarylhydroxymaleimides. If the *para* position is blocked, cyclization occurs but bromine does not enter the ring.[1] If all *ortho* and *para* positions are substituted by methyl groups, an amide ester results in which the bromine is in the *alpha* position in the side chain. This is reminiscent of the similar behavior of ethyl cyanomethylpyruvate[2] and is a further indication that bromine first enters the side chain.

This work was undertaken for the purpose of the isolation and characterization of the intermediate reaction products in order to establish more definitely the course of the reaction. For this purpose we selected I, as it contains no easily displaceable hydrogen except that of the enolic group and this can be removed from the sphere of action by prior formation of the ether. Carefully purified carbon tetrachloride and dried reagents were used and the experiment was conducted under protection from outside moisture. The dibromide (II) precipitated relatively rapidly in a few hours and the monobromide (III) from the filtrate relatively slowly in a few weeks.



II



III

The dibromide was stable *in vacuo* over potassium hydroxide and phosphorus pentoxide for at least seven months and, therefore, does not seem to be a molecular complex. It was quite reactive toward either water or ethyl alcohol. Either reagent converted it to *p*-*t*-butylphenylhydroxymaleimide. It reacted with toluene to give benzyl bromide but upon standing with benzene free bromine was literated.

Hydrolysis of the dibromide in alcoholic potassium hydroxide gave *p*-*t*-butylphenylacetamide which was also formed by similar hydrolysis[1] of the hydroxymaleimide. Under these conditions it is probable that the hydrolysis proceeds through the intermediate formation of the hydroxymaleimide. On the other hand, if the dibromide were added to hot aqueous potassium hydroxide and the hydrolysis then completed, *p*-*t*-butylmandelic acid was the only identified product. This indicates the direct hydrolysis of the dibromide, that one of the bromine atoms is joined to the carbon *alpha* to the aromatic ring, and that both are capable of hydrolytic cleavage.

The dibromide is neither a molecular complex nor a simple addition product of bromine to the starting ester (I), as cyclohexene removed the bromine to give 1,2-dibromocyclohexane without regenerating the starting ester. It contains carbon-bromine bonds[3] as shown by infrared absorption bands at 17.5 and 18.2 μ with overtones at 8.8 and 9.2 μ.

The monobromide is considerably more stable than the dibromide, as it could be crystallized from carbon tetrachloride as well as chromatographed in chloroform solution. The bromine atom, however, is a reactive one which liberated iodine from a solution of sodium iodide in acetone and also gave an immediate precipitate with acidified alcoholic silver nitrate. The compound is not an enol, as it did not give the characteristic color with ferric chloride but when the solution was warmed a deep orange color developed. The almost white color of the monobromide is also in agreement with that of a series[4] of 1,4,4-trialkylpyrollidinetriones. The hydroxymaleimides are all colored yellow.

The monobromide by hydrolysis in aqueous potassium hydroxide gave *p*-*t*-butylmandelic acid as well as oxalic acid. This indicates that the bromine atom is at a position *alpha* to the aromatic nucleus. The products of this hydrolysis indicate especially that the monobromide is 4-bromo-4-

(1) Glenn S. Skinner, Jules A. Gladner, and Richard F. Heitmiller, *J. Am. Chem. Soc.*, **73**, 2230 (1951).

(2) W. Wislicenus and W. Silberstein, *Ber.*, **43**, 1834 (1910).

(3) L. A. Henderson, thesis, University of Delaware, 1951.

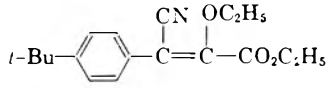
(4) G. S. Skinner and R. E. Ludwig, *J. Am. Chem. Soc.*, **78**, 4656 (1956).

p-t-butylphenylpyrrolidinetrione (III). In this connection, if the bromine atom were replaced with hydrogen, *p-t*-butylphenylhydroxymaleimide was formed. This reaction was carried out in excellent yield by heating the dibromide with toluene to form also benzyl bromide.

The assigned structure of the monobromide is further supported by the infrared[5] spectrum which shows a band at 3.16 μ that is attributed to the N–H bond. Bands arising from the carbonyl functions are also present at 5.52, 5.58, and 5.83 μ. This splitting to form a doublet at 5.52 and 5.84 μ probably results from the two carbonyl functions involved in the imide structure.

One of the bromine atoms in the dibromide also must be in the *alpha* position to the aromatic nucleus as the dibromide, in a separate experiment under identical conditions, was converted to this monobromide. This conclusion is further supported by the fact that aqueous alkaline hydrolysis of the dibromide gave the identical *p-t*-butylmandelic acid.

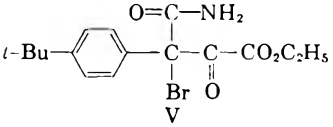
The above behavior of the dibromide and its relation to the monobromide indicate very strongly that the two bromine atoms are vicinal. The formation of a debromination product different from the original ester can be explained by the loss and readdition of hydrogen bromide to the nitrile function. As support for this interpretation of the reaction may be cited the fact that the ethyl ether



IV

(IV) of the starting ester did not react with bromine in anhydrous carbon tetrachloride although it was converted to *p-t*-butylphenylethoxymaleimide by hydrochloric acid in alcohol. The ether contains no reactive hydrogen to form hydrogen bromide. This explains why the ether did not react with bromine under these conditions.

Bromine did not react with *p-t*-butylphenylhydroxymaleimide to give the monobromide. Its formation most likely proceeds through the partially hydrolyzed dibromide (V), which has not been isolated in this case. The water necessary for this reaction may have become slowly available through the ground glass joints or, more likely, by oxidation, as the dibromide was converted to the hydroxymaleimide by ethanol as well as by water.



V

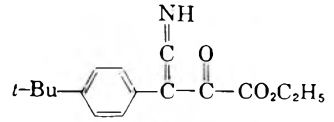
The debrominated product from the reaction of the dibromide with cyclohexene is not a simple dimerization product of a ketenimine but a compound which also requires water for its formation. Its analysis and molecular weight indicate that it is derived from two molecules of the starting ester and that the molecular formula is $C_{30}H_{36}O_7N_2$. This bimolecular compound on hydrolysis with aqueous potassium hydroxide ultimately yielded only *p-t*-butylphenylacetic acid. Reaction with hot 30% sulfuric acid gave one mole of *p-t*-butylphenylhydroxymaleimide and some *p-t*-butylphenylpyruvic acid also. The distillate contained ammonia and gave a positive iodoform test. The reaction of the bimolecular compound with alcoholic hydrochloric acid gave more than one mole of *p-t*-butylphenylhydroxymaleimide. In addition there was obtained a small amount of the ethyl ether of the hydroxymaleimide.

As the bimolecular compound was formed in spite of careful exclusion of water in the reaction of cyclohexene with the dibromide, the water needed for partial reaction must have arisen within the medium. This necessity for water is borne out by the fact that the addition of a very small amount of water to the filtrate, from the bimolecular compound, yielded more of it in considerable amount.

More than one mole of *p-t*-butylphenylacetic acid was obtained on alkaline hydrolysis, which indicates that both moieties of the bimolecular compound must be capable of hydrolysis to this acid. The reaction with 30% sulfuric acid gives a strong indication that one part of the molecule was furnished by *p-t*-butylphenylhydroxymaleimide. This must be joined to another part which is capable of acid hydrolysis to *p-t*-butylphenylpyruvic acid. The amount of this acid under identical conditions from the hydroxymaleimide was far less.

The reaction of the bimolecular compound with hydrogen chloride in ethanol to give more than one mole of the hydroxymaleimide shows that both parts of the molecule were converted to *p-t*-butylphenylhydroxymaleimide. The fact that *p-t*-butylphenylethoxymaleimide also was isolated while none was obtained from the hydroxymaleimide under identical conditions shows that only the other part of the molecule is capable of yielding this ether.

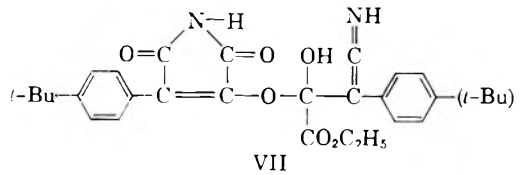
The starting ester is converted to the hydroxymaleimide by bromine with free access of water.[1] Although we apparently have failed in our efforts to keep all moisture from the reaction mixture during the debromination with cyclohexene, we have succeeded in preventing complete conversion of the intermediate to the hydroxymaleimide. The initial debrominated intermediate, we believe,



VI

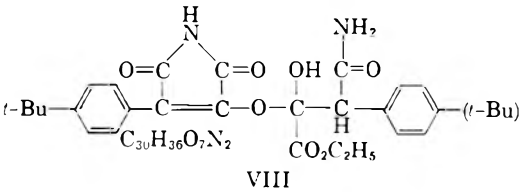
(5) Consultation with Dr. H. C. Beachell.

is the ketenimine VI. The formation of the bimolecular compound can be explained by its partial conversion in the presence of insufficient water to the hydroxymaleimide, which adds to more of the ketenimine to give VII. This then may react with water to precipitate the less soluble bimolecular



VII

compound VIII. Although it is unstable near its



VIII

melting point, the substance is quite stable in the lower temperature ranges and is easily purified by crystallization from ethanol.

EXPERIMENTAL

Bromination of ethyl p-t-butyl-β-cyano-α-hydroxycinnamate in dry carbon tetrachloride. The bromination was conducted in an Ace Glass Mini Lab set up to provide for addition of reagents, stirring, exclusion of atmospheric moisture and filtration. Dry bromine (4.5 cc.; 1.2 mole) was added in one portion to a stirred solution of 13.8 g. (0.066 mole) of the ester in 45 cc. of dried and distilled carbon tetrachloride. In 6–7 min. brick-red crystals began to separate. After 24 hr. the brick-red solid was filtered on the sintered glass plate and washed with three 40-cc. portions and one 60-cc. portion of carbon tetrachloride. As soon as the excess liquid had been removed, the flask containing the brick-red solid was placed *in vacuo* over potassium hydroxide and phosphorus pentoxide. If the transfer were not rapid, the brick-red solid became tinged with yellow. After standing *in vacuo* for 1–2 weeks, it assumed a permanent tan-orange color, m.p. 156.5–157.5° dec.

Anal. Calcd. for $C_{16}H_{19}O_3NBr_2$: C, 44.36; H, 4.42; N, 3.23; Br, 36.90. Found: C, 44.0; H, 4.0; N, 3.4; Br, 35.1.

Trituration of the dibromide with water gave *p-t*-butylphenylhydroxymaleimide,[1] m.p. 249–250°. Crystallization of the dibromide from ethanol also gave the identical hydroxymaleimide.

Reaction of the dibromide with alcoholic potassium hydroxide. The dibromide (2.5 g.; 0.0058 mole) was added to a refluxing mixture of 20 cc. of ethanol and 3 cc. of 40% potassium hydroxide solution. A yellow solid formed immediately. Heating was continued for 28 hr. during which 9 cc. of water and 4–5 pellets of potassium hydroxide were added. The solution was cooled and the white precipitate was filtered and washed with 2:1 ethanol-water to give 0.9 g. of potassium oxalate. The residue from the evaporation of the filtrate gave a white solid soluble in ether that after two recrystallizations from benzene-ligroin had a melting point of 125.5–127[c] which was not depressed by an authentic sample of *p-t*-butylphenylacetamide, m.p. 126–127°. The above basic solution upon acidification gave a viscous oil which could not be induced to crystallize.

Reaction of the dibromide with aqueous potassium hydroxide. To a stirred hot solution of 1.7 g. of potassium hydroxide in 20 cc. of water was added 1.5 g. (0.0035 mole) of the dibromide. Immediately there was formed a yellow solid which gradually changed to an oil that remained after refluxing 2 hr. Alcohol (6.5 cc.) was added and the heating was continued for 36 hr. The solution was extracted with ether to remove a drop or two of a dark oil. The acid from the aqueous layer amounted to 0.8 g. of a brown oil which after long standing deposited crystals that were filtered and washed with pentane. Two recrystallizations from benzene gave 0.025 g. of *p-t*-butylmandelic acid, m.p. 149–150°, lit.,[6] m.p. 149.5–150°. Ammonia and oxalic acid also were formed in the hydrolysis.

Reaction of the dibromide with toluene. The dibromide (0.50 g.) was allowed to stand 5 months in an all-glass container with 5 cc. of dry toluene. The products isolated were *p-t*-butylhydroxymaleimide (0.22 g.) and ammonium bromide (0.02 g.) from the precipitate and from the toluene free bromine and 0.1 g. of a lachrymator which was identified as benzyl bromide by conversion to benzyl *β*-naphthyl ether, m.p. 100–101°.

Reaction of the dibromide in benzene. The dibromide (0.9 g.) in an all glass container with 9 cc. of dry benzene dissociated bromine almost immediately. After 3 days the solid (0.23 g.) was filtered and identified as the hydroxymaleimide, m.p. 248–250°. The red liquid distillate of bromine and benzene required 4–5 drops of cyclohexene for decolorization. A reddish tar (0.25 g.) remained in the residue.

Reaction of cyclohexene with the dibromide. For this purpose the dibromide was prepared from 9.1 g. (0.033 mole) of the starting ester. When the precipitation appeared complete (6 hr.) the red dibromide was filtered and washed in the Mini Lab with three 9-cc. portions of dry carbon tetrachloride. Then 13 cc. of carbon tetrachloride was stirred into a smooth paste. Cyclohexene (5 cc.) freshly distilled from sodium in a nitrogen atmosphere was added at once with good stirring. The temperature rose to 30–35° and solution was complete in 1 min. except for a minute amount of solid dispersed in the light wine-colored liquid. The precipitation of a yellow solid began in 5 min. and was essentially complete in 15 min. After standing 45 min. longer, the product was filtered and washed with 8-cc. portions of carbon tetrachloride. It was crystallized from ethanol to yield 1.1 g. of yellow fibrous material which began to darken at 210° and melted at 220–222° dec.

The mother liquor, from which the yellow solid precipitated, was shaken with 1 cc. of water. Within 1 min. a yellow solid started to separate. The mixture was allowed to stand 3 hr. after which the yellow solid was filtered and washed well with carbon tetrachloride. Crystallization from ethanol gave 0.7 g. more of the identical compound, m.p. 220–222° dec.

Anal. Calcd. for $C_{30}H_{36}O_7N_2$: C, 67.16; H, 6.75; N, 5.22. Found: C, 67.22; H, 6.77; N, 5.24.

The above carbon tetrachloride mother liquor which had been treated with water was distilled under diminished pressure to give 2 g. of 1,2-dibromocyclohexane, n_D^{25} 1.5507,

Wt. of Compound	Wt. of Camphor	Molality	$-\Delta t$	M.W.
0.0162	0.0697	0.433	18.2	507
0.0303	0.1400	0.403	17.0	505
0.0106	0.0602	0.328	12.4	564
0.0100	0.0712	0.288	11.1	553
0.0104	0.0846	0.229	8.7	560
0.0132	0.1609	0.153	6.6	490
				Av. 530
Calcd. for $C_{30}H_{36}O_7N_2$				537

(6) J. L. Riebsomer, J. Irvine, and R. Andrews, *J. Am. Chem. Soc.*, **60**, 1015 (1938).

lit.,[7] n_D 1.5507, b.p. 50.5–52° (0.2 mm.). There remained 0.6 g. of a reddish oil.

Molecular weight of the compound $C_{30}H_{36}O_7N_2$. The following relatively low melting solvents were unsuited because of lack of solubility: borneol, camphene, naphthalene, phenanthrene, tribromophenol, and triphenylmethane. The initial melting with camphor had to be done as rapidly as possible, as in some cases the samples on recooling and remelting gave still lower melting points.

Basic hydrolysis of the compound $C_{30}H_{36}O_7N_2$. A mixture of 0.50 g. of the substance, 1.0 g. potassium hydroxide, 10 cc. of water and 5 cc. of ethanol was refluxed for 21 hr. Ammonia was evolved. The colorless solution was evaporated to half its volume and acidified to give 0.33 g. of solid which from petroleum ether (b.p. 00–00°) melted at 79–80°. Admixture with an authentic sample of *p-t*-butylphenylacetic acid showed no depression in the melting point. The aqueous filtrate gave a positive test for oxalate ion.

Hydrolysis of $C_{30}H_{36}O_7N_2$ *with 30% sulfuric acid.* A mixture of 1.0 g. of the substance and 25 cc. of 30% sulfuric acid was refluxed for 48 hr. The yellow solid (0.83 g.), filtered and washed at room temperature, was heated with 20 cc. of ligroin containing 1 cc. of benzene and filtered hot, then washed several times with hot ligroin to give 0.58 g. which from toluene gave 0.46 g. of *p-t*-butylphenylhydroxymaleimide, m.p. 248.5–250°.

From the ligroin filtrate there was obtained 0.08 g. of solid which from benzene gave 0.06 g. of white crystals, m.p. 164–165°. Likewise from the above toluene filtrate there was obtained 0.05 g., m.p. 164–165°. Mixed with an authentic sample of *p-t*-butylphenylpyruvic acid the melting point was unchanged. The infrared spectra were also identical. It was further identified by oxidation[8] with hydrogen peroxide to *p-t*-butylphenylacetic acid, m.p. 79–80°, yield 82%.

The original acid filtrate afforded a distillate which gave the iodoform reaction. The residue gave tests for ammonia and oxalate ion.

When 0.50 g. of *p-t*-butylphenylhydroxymaleimide was refluxed similarly with 30% sulfuric acid there was obtained 0.36 g. of the unchanged maleimide, m.p. 248–250°, and 0.046 g. of material, m.p. 156–161°. The melting point of the recrystallized product was 160–162°, mixed with the sample, m.p. 164–165°, the melting point was 160–162°.

Reaction of the substance $C_{30}H_{36}O_7N_2$ *with hydrogen chloride in ethanol.* Hydrogen chloride was passed into a mixture of 1.0 g. (0.19 mole) of the substance, 30 cc. of ethanol, and 0.05 cc. of hydrochloric acid (s.g. 1.18) for 1 hr. The resulting solution was heated on the steam bath for 3 hr. After standing overnight it was concentrated under diminished pressure to half its volume to give 0.42 g. of yellow crystals. Further concentration gave 0.25 g. The combined product was washed with a little benzene and crystallized from toluene, yield 0.50 g., m.p. 248–250°. Ammonium chloride (0.05 g.) was filtered from the hot toluene solution.

The above benzene washings were evaporated to an oil which crystallized when warmed with ligroin. Recrystallization from benzene gave 0.09 g., m.p. 128–131°, which then yielded 0.08 g., m.p. 130–132°. This melting point was not depressed by authentic *p-t*-butylphenylethoxymaleimide. The filtrate gave 0.23 g. of a light yellow oil which would not crystallize.

When *p-t*-butylphenylhydroxymaleimide was treated in the same way with ethanolic hydrochloric acid 89% of the starting material was recovered and there was no *p-t*-butylphenylethoxymaleimide. The only other products were 0.01 g. of ammonium chloride and 0.07 g. of an uncrystallizable oil.

Isolation of the monobromide (III). The carbon tetrachloride filtrate from the precipitate of dibromide (II) obtained from 19.0 g. of the ester (I) was quickly poured into a flask equipped with a tightly fitting glass stopper and allowed to stand in the closed flask. Red crystals slowly separated. At the end of 4 months the precipitate was filtered and washed with dry carbon tetrachloride until the washings from the yellow solid were colorless, weight 4.9 g., m.p. 145–150° dec.

This was chromatographed on a $1^1/_8$ in. column using 25 g. of silicic acid for 1.5 g. Elution was performed with chloroform. The upper narrow bright yellow band gave 1.8 g. of *p-t*-butylphenylhydroxymaleimide and the lower broad almost white band gave 2.8 g. of III, m.p. 163–165°. The ethanol solution of III made acid with nitric acid gave an immediate precipitate with silver nitrate. It also liberated iodine from an acetone solution of sodium iodide. Tribromophenol was used as the cryoscopic solvent.

Anal. Calcd. for $C_{14}H_{14}BrNO_3$: C, 51.9; H, 4.4; Br, 24.7; N, 4.3; Mol. Wt., 324. Found: C, 51.2; H, 4.5; Br, 25.3; N, 4.2; Mol. Wt., 320 ± 20.

The filtrate from the above 4.9 g., after removal of the solvent under diminished pressure, left 12.2 g. of reddish glassy material that could not be crystallized.

The monobromide also was obtained in poor yield by allowing the crystalline dibromide to stand 3 months in a closed system with carbon tetrachloride and a slight excess of bromine.

Hydrolysis of the monobromide. A solution of 0.70 g. of the monobromo compound in 10 cc. of water containing 1.0 g. of potassium hydroxide was obtained by heating 15–20 min. After refluxing 6.5 hr. the cooled solution was filtered. The reddish filtrate was extracted with ether to remove a slight amount of tar. The basic solution gave an oily solid acid which was collected with ether and crystallized from benzene-ligroin to give 0.18 g., m.p. 144–147°. This on crystallization from benzene gave 0.16 g. of *p-t*-butylmandelic acid, m.p. 149–150° identical with that obtained from the dibromide.

Reaction of the monobromide with toluene. The monobromide (0.52 g.) was covered with 4 cc. of dry toluene and heated 13 hr. at 95–100° protected from moisture. The yellow crystalline material was recrystallized from toluene to give 0.38 g. (97%) of *p-t*-butylphenylhydroxymaleimide, m.p. 249–250°.

Removal of the toluene under diminished pressure gave 0.25 g. of residual lachrymatory oil which reacted with β-naphthol in hot alcoholic sodium hydroxide to give, after crystallization from alcohol, 0.15 g. of benzyl β-naphthyl ether, m.p. 100–101°, identical with an authentic sample.

Ethyl p-t-butyl-β-cyano-α-ethoxycinnamate. A cold dry solution of 3.28 g. of diazoethane[9] in 150 cc. of ether was slowly poured into a well-swirled ice-cold solution of 16.0 g. of ethyl *p-t*-butyl-β-cyano-α-hydroxycinnamate in 50 cc. of ether. After standing overnight the ether was removed from the reddish solution and the residue was distilled, yield of light yellow product, 14.3 g., b.p. 153–153.5° (0.10 mm.); m.p. 41–43°; d_4^{24} 1.0389; n_D^{25} 1.5315.

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.72; H, 7.55; N, 4.79.

p-t-Butylphenylethoxymaleimide. Hydrogen chloride was passed into a mixture of 10 cc. of ethanol and 0.26 cc. of water for 35 min. Then 4.3 g. of ethyl *p-t*-butyl-β-cyano-α-ethoxycinnamate in 8 cc. of ethanol was added and the passage of hydrogen chloride was continued for 1 hr. Next day the mass of crystals was filtered and washed with dilute alcohol, yield, 3.2 g. Recrystallization from ligroin gave 2.8 g. of yellow crystals, m.p. 133–134°.

Anal. Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.28; H, 7.06; N, 5.12.

(7) S. Winstein, *J. Am. Chem. Soc.*, 64, 2792 (1942).

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Nonformation of a dibromide from ethyl p-t-butyl-β-cyano-α-ethoxycinnamate. Dry bromine (1.0 cc.) was added dropwise with stirring to a solution of 5.1 g. of the ester in 20 cc. cc. of carbon tetrachloride protected from moisture in the Mini Lab. After standing 7 days there was no evidence of reaction. The mixture was distilled under diminished pressure to give 4.3 g. of starting material, b.p. 156–159° (0.26 mm.); n_D^{25} 1.5320. No bromide could be isolated.

NEWARK, DEL.

[CONTRIBUTION FROM LABORATORY OF CHEMISTRY, RAMNARAIN RUIA COLLEGE, UNIVERSITY OF BOMBAY]

β-Arylglutaconic Acids. IV.[1] Synthesis of Crotono- and Valerolactones of β-Arylglutaconic and Glutaric Acids

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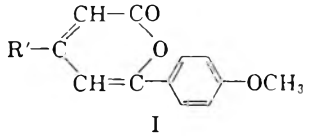
Received January 27, 1960

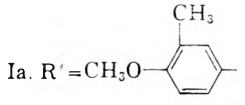
Through the condensation of β-arylglutaconic anhydrides with phenolic ethers in the presence of anhydrous aluminum chloride, a series of β-aryl-γ-benzoylcrotonic acids and their lactones were prepared. In addition, a general method for the synthesis of β,γ-substituted benzoylbutyric acids has been developed. These acids after reduction and lactonization gave the corresponding β,δ-substituted valerolactones. The crotono- and valerolactones are being tested for their anthelmintic activity and for their perfumery properties.

Though the relationship between chemical constitution and anthelmintic effect has not been fully elucidated, a number of the anthelmintics have been found which possess a lactonic group.[3] A detailed study by Rosenmund[4] and Nargund[5] has indicated that some arylbutyrolactones possess good anthelmintic effect. Moreover, unsaturation in the lactone ring has been shown to enhance the anthelmintic activity.[6]

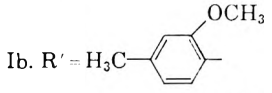
These findings have led us to prepare a number of unsaturated lactones with different aryl substituents (Type I) for testing their anthelmintic effects.



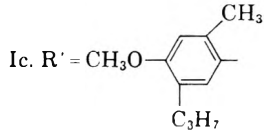
I



Ia. R′ = CH_3O



Ib. R′ = H_3C



Ic. R′ = CH_3O

Since 1926, the chemistry of lactones has assumed a great importance in the field of perfumery. Many naturally occurring lactones and their synthetic substitutes have been extensively studied in the light of their perfumery values.[7–9] The variation in odor of lactone has been studied as a function of the substituents attached to the lactone and, accordingly, a series of α and γ-substituted γ-butyrolactones were prepared.[10] Even the variation in intensity of odor with increase in the size of the lactonic ring was studied.[11] However, as yet, no definite relationship between the structure of a lactone and the intensity of its odor has been determined. It was therefore thought interesting to study the lactones (I) from the perfumery value point of view and attempt to gain some knowledge concerning the relationship between structure and odor intensity.

In the present work, condensation of (1) β-(4-methoxy-3-methylphenyl)-, (2) β-(2-methoxy-4-methylphenyl)- and (3) β-(4-methoxy-2-methyl-5-isopropylphenyl(glutaconic anhydrides in nitrobenzene with an equimolar quantity of anisole in the presence of anhydrous aluminum chloride was effected following the observation of Bhave.[12] From this reaction, two distinct products were isolated. The predominant product (80% yield) was a neutral compound and by analogy with

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(1) (a) Prior publications, *J. Org. Chem.*, 24, 520 (1959); (b) *J. Org. Chem.*, 24, 2055 (1959); (c) *J. Org. Chem*, in press.

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TABLE I

3-ARYL-4-AROYLBUTYRIC ACIDS

$HOOCCH_2CHCH_2COAr'$

Ar

IV

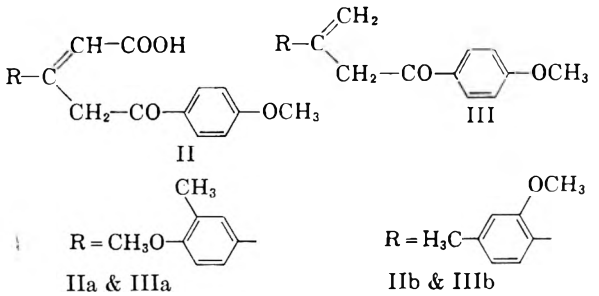
No.	Ar	Ar′	Yield, %	M.P. °	Formula	Analysis					
						Carbon		Hydrogen		Neut. Equiv.	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1	4-Methoxyphenyl[a,b]	Anisyl	55[c]	126	$C_{19}H_{20}O_5$	69.50	69.60	6.14	6.13	328.30	327.80
	Methyl ester[d]			65	$C_{20}H_{22}O_5$	70.16	69.95	6.48	6.45		
	Ethyl ester[e]			58	$C_{21}H_{24}O_5$	70.76	70.62	6.79	6.91		
	Phenylhydrazone[f]			176	$C_{25}H_{26}N_2O_4$					418.47	418.00
	Semicarbazone[g]			218	$C_{20}H_{23}N_3O_5$					385.41	384.60
	Oxime[h]			173	$C_{19}H_{21}NO_5$					343.37	344.80
2	4-Methoxy-3-methylphenyl[i]	Anisyl	53[j]	109	$C_{20}H_{22}O_5$	70.16	70.31	6.48	6.50	342.40	344.80
	Methyl ester[k]			66	$C_{21}H_{24}O_5$	70.76	71.06	6.79	6.45		
	Ethyl ester[l]			72	$C_{22}H_{26}O_5$	71.33	71.47	7.08	6.99		
	Phenylhydrazone[m]			184	$C_{26}H_{28}N_2O_4$					432.50	434.80
	Semicarbazone[n]			218	$C_{21}H_{25}N_3O_5$					399.40	400.00
	Oxime[o]			168	$C_{20}H_{23}NO_5$					357.40	360.40
3	2-Methoxy-5-methylphenyl[p]	Anisyl	61	112	$C_{20}H_{22}O_5$	70.16	68.98	6.48	6.76	342.40	343.90
	Phenylhydrazone[q]			182	$C_{26}H_{28}N_2O_4$					432.50	435.20
	Semicarbazone[r]			203 dec.	$C_{21}H_{25}N_3O_5$					399.43	398.20
	Oxime[s]			163	$C_{20}H_{23}NO_5$					357.39	358.40
4	4-Methoxyphenyl[t]	*o*-Cresylmethyl ether	64	124	$C_{20}H_{22}O_5$	70.16	70.38	6.48	6.58	342.4	344.2
	Methyl ester[u]			79	$C_{21}H_{24}O_5$	70.76	70.54	6.79	6.92		
	Phenylhydrazone[u]			171	$C_{26}H_{28}N_2O_4$					432.50	435.90
	Semicarbazone[u]			208	$C_{21}H_{25}N_3O_5$					399.43	397.42
	Oxime[u]			150	$C_{20}H_{23}NO_5$					357.39	354.30
5	2-Methoxy-5-methylphenyl[p]	*o*-Cresylmethyl ether	58	95	$C_{21}H_{24}O_5$	70.76	70.57	6.79	6.63		
	Methyl ester[u]			89	$C_{22}H_{26}O_5$	71.33	71.56	7.08	7.31		
	Phenylhydrazone[u]			158	$C_{27}H_{30}N_2O_4$					446.53	445.50
	Semicarbazone[u]			197 dec.	$C_{22}H_{27}N_3O_5$					413.46	415.30
	Oxime[u]			133	$C_{21}H_{25}NO_5$					371.42	369.60
6	4-Methoxyphenyl[t]	*m*-Cresylmethyl ether	64	101	$C_{20}H_{22}O_5$	70.16	70.41	6.48	6.36		
7	2-Methoxy-5-methylphenyl	*m*-Cresylmethyl ether	45	104	$C_{21}H_{24}O_5$	70.76	70.44	6.79	6.51	356.40	355.00
	Phenylhydrazone[q]			120	$C_{27}H_{30}N_2O_4$					446.53	443.80
8	4-Methoxyphenyl[t]	*p*-Cresylmethyl ether	59	122	$C_{20}H_{22}O_5$	70.16	70.43	6.48	6.42		
	Semicarbazone[v]			152	$C_{21}H_{25}N_3O_5$					405.40	399.43
9	2-Methoxy-5-methylphenyl[w]			108	$C_{21}H_{24}O_5$	70.76	70.94	6.79	6.37	356.40	355.00
	Semicarbazone			202 dec.	$C_{22}H_{27}N_3O_5$					413.46	416.38
10	4-Methoxyphenyl[t]	Thymolmethyl ether	67	117	$C_{23}H_{28}O_5$	71.85	71.78	7.34	7.37		
	Phenylhydrazone[u]			171	$C_{29}H_{34}N_2O_4$					474.58	471.30
11	2-Methoxy-5-methylphenyl[t]	Thymolmethyl ether	59	102	$C_{24}H_{30}O_5$	72.33	72.21	7.51	7.35		
12	4-Methoxyphenyl[t]	Resorcinyldimethyl ether	56	135	$C_{20}H_{22}O_6$	67.02	66.93	6.19	6.24	358.40	357.10
	Methyl ester[x]			78	$C_{21}H_{24}O_6$	67.73	67.40	6.50	6.49		
	Semicarbazone[v]			156	$C_{21}H_{25}N_3O_6$					417.40	415.43
	Oxime[o]			171	$C_{20}H_{23}NO_6$					375.60	373.39
13	2-Methoxy-5-methylphenyl[t]	Resorcinyldimethyl ether	60	89	$C_{21}H_{24}O_6$	67.73	67.90	6.50	6.47		
	Semicarbazone[v]			198 dec.	$C_{22}H_{27}N_3O_6$					429.46	431.58
	Oxime[x]			145	$C_{21}H_{25}NO_6$					387.42	391.45
14	4-Methoxyphenyl[y]	Hydroquinone dimethyl ether	68	130	$C_{20}H_{22}O_6$	67.02	66.74	6.19	6.23		
	Methyl ester[r]			45	$C_{21}H_{24}O_6$	67.73	68.01	6.50	6.36		
	Semicarbazone[q]			165	$C_{21}H_{25}N_3O_6$					419.70	415.43

TABLE I (*Continued*)

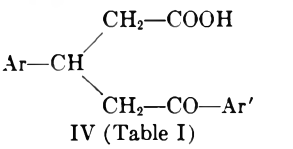
No.	Ar	Ar′	Yield, %	M.P. °	Formula	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Neut. Equiv. Calcd.	Neut. Equiv. Found
15	2-Methoxy-5-methylphenyl[z]	Hydroquinone dimethyl ether	63	117	$C_{21}H_{24}O_6$	67.73	67.32	6.50	6.20	372.40	368.90
	Semicarbazone[r]			196 dec.	$C_{22}H_{27}N_3O_6$					429.46	426.00
	Oxime[r]			201	$C_{21}H_{25}NO_6$					387.42	383.80
16	4-Methoxyphenyl[t]	Biphenyloxide	69	140	$C_{24}H_{22}O_5$	73.83	74.19	5.68	5.66		
	Methyl ester[z]			81	$C_{25}H_{24}O_5$	74.24	73.95	5.98	5.83		
	Semicarbazone[q]			221	$C_{25}H_{25}N_3O_5$					446.20	447.47
17	2-Methoxy-5-methylphenyl[z]	Biphenyloxide	71	104	$C_{25}H_{24}O_5$	74.24	73.92	5.98	5.79		
	Semicarbazone[u]			197 dec.	$C_{26}H_{27}N_3O_5$					461.50	461.00
18	4-Methoxy-2-methyl-5-isopropylphenyl[aa]	Anisyl	68	125	$C_{23}H_{28}O_5$	71.85	71.64	7.34	7.58		
	Oxime[u]			160	$C_{23}H_{29}NO_6$					399.47	402.04

[a] The intermediate, 4-methoxyphenylglutaric anhydride was prepared following the procedure of D. B. Limaye and R. G. Chitre, *J. Univ. Bombay*, **4**, 96 (1935). [b] White-needles from 50% acetic acid. [c] The yield was 61% when tetrachloroethane was used as solvent in place of nitrobenzene and 46% when carbon disulfide was used as solvent. [d] The ester was made using the Fischer Spier method, E. Fischer and A. Spier, *Ber.*, **28**, 3252 (1895); white crystals from methanol. [e] Prepared using Fischer Spier method, white crystals from ethanol. [f] White crystals from ethanol. [g] Colorless crystals from ethanol. [h] Shining needles from ethanol. [i] The intermediate glutaric anhydride was prepared following the procedure of Limaye and Chitre[a]; colorless needles from 50% acetic acid or a large quantity of water. [j] The yield was 65% using tetrachloroethane and 44% using carbon disulfide. [k] Dull white needles from methanol. [l] Shining white needles from ethanol. [m] White flakes from ethanol. [n] Colorless needles from ethanol. [o] Pale yellow needles from ethanol. [p] The intermediate glutaric anhydride was prepared following the procedure of Limaye and Chitre[a]; dull white crystals from 25% acetic acid. [q] White flakes from ethanol. [r] White needles from ethanol. [s] White shining flakes from ethanol. [t] White crystals from 50% acetic acid. [u] White crystals from ethanol. [v] White crystals from dilute ethanol. [w] Colorless needles from ethanol. [z] White needles from methanol. [y] White crystals from 50% methanol. [z] Dull white crystals from 10% acetic acid. [aa] See Experimental for the preparation of the intermediate β-(4-methoxy-2-methyl-5-isopropylphenyl)glutaric acid and its anhydride.

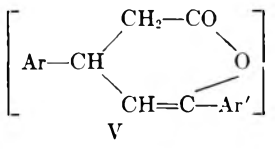
earlier work in our laboratory[12,13] was the β-aryl-γ-4-methoxybenzoylcrotonolactone (I). From the mother liquor of I, an acid product (10% yield) was isolated by treatment with dilute hydrochloric acid. It proved to be a monobasic acid by titration and it was shown to be ketonic in nature as evidenced through the formation of a semicarbazone and a phenylhydrazone. Its elementary analysis was also indicative of the structure II.



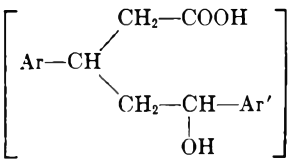
In an attempt to open the lactonic ring of I to produce II, I was treated with sodium ethoxide in ethanol. The resulting product was, however, a neutral ketone (III) which gave a crystalline phenylhydrazone. The same product (III) was obtained by decarboxylation of II, suggesting that probably under the conditions of the experiment, sodium ethoxide brought about hydrolysis and subsequent decarboxylation. Hydrolysis of I in alcoholic alkali, however, resulted predominantly in the formation of II (70–75% yield) and a small percentage (6–8%) of III. The keto acid (II) could be reconverted to the starting lactone I by treatment with mineral acid or acetic anhydride.



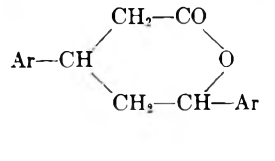
IV (Table I)



V



VI



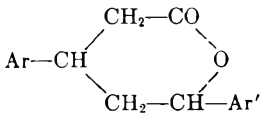
VII (Table II)

This reaction was extended by condensing several β-arylglutaric anhydrides with various phenolic ethers. Suprisingly, however, unlike the β-arylglutaconic anhydrides, β-aryl-γ-benzoylbutyric acids (IV, Table I) and not the lactones (V) were the only products isolated from the reaction. These acids were characterized through elementary analysis and through the formation of the usual ketonic derivatives. When IV was oxidized using alkaline potassium permanganate, free as well as substituted anisic acids were recovered as the products of reaction, supporting the assigned structure for

(13) V. M. Bhave and R. V. Bhagwat, *J. Indian Chem. Soc.*, 25, 425 (1948).

TABLE II

3-ARYL-5-ARYLVALEROLACTONES



VII

No.	Ar	Ar′	Yield, %	M.P. °	Formula	Analysis			
						Carbon		Hydrogen	
						Calcd.	Found	Calcd.	Found
1	4-Methoxyphenyl[a]	Anisyl	45	83	$C_{19}H_{20}O_4$	73.06	72.70	6.45	6.26
2	4-Methoxy-3-methylphenyl[a,b]	Anisyl	40	80	$C_{20}H_{22}O_4$	73.60	73.31	6.79	6.50
3	2-Methoxy-5-methylphenyl[c]	Anisyl	42	202	$C_{20}H_{22}O_4$	73.60	73.41	6.79	6.34
4	4-Methoxyphenyl[c]	*o*-Cresylmethyl ether	51	87	$C_{20}H_{22}O_4$	73.60	73.84	6.79	6.86
5	2-Methoxy-5-methylphenyl	*o*-Cresylmethyl ether	47	212	$C_{21}H_{24}O_4$	74.09	73.96	7.11	6.95
6	4-Methoxyphenyl[d]	Resorcinyldimethyl ether	39	106	$C_{20}H_{22}O_5$	70.16	70.41	6.48	6.76

[a] Plates from 50% ethanol, pleasant balsamic odor on melting but no odor in solid state. [b] No odor in solid state but faint aromatic odor on melting. [c] White crystals from ethanol, pleasant aromatic odor in liquid state. [d] Purified by vacuum distillation, balsamic odor.

IV. When IV was reduced in the presence of sodium amalgam in an attempt to obtain the corresponding hydroxy acid (VI), the latter proved to be very unstable, and it immediately lactonized to the corresponding β-aryl-δ-arylvalerolactone (VII, Table II) upon treatment with acetic anhydride.

EXPERIMENTAL[14]

3-(4-Methoxy-3-methylphenyl)-5-anisyl-5-oxo-2-pentenoic acid-eno-lactone (Ia). The general procedure of Bhave[13] was followed. To a well stirred solution of 2.3 g. (0.01 mole) of β-(4-methoxy-3-methylphenyl)glutaconic anhydride[15] and 1.1 g. (0.01 mole) of anisole in 10 ml. of freshly distilled nitrobenzene, in a dry flask equipped with an air condenser carrying a calcium chloride tube, 3 g. of freshly powdered anhydrous aluminum chloride was added in portions during a period of about 30 min. The reaction was exothermic and the temperature was controlled (15–20°) by immersing the reaction flask in a cold water bath. The mixture was stirred at room temperature for 4 hr., and then the resulting dark red mixture was poured slowly into 100 ml. of ice-cold water containing 10 ml. of concd. hydrochloric acid. The solvent nitrobenzene was removed by distillation and the residue collected, washed with water, and then treated with 10% sodium carbonate solution. From the alkaline filtrate 0.15 g. (5% yield) of the acid (IIa) was isolated. The neutral residue on the filter was well washed with water and upon drying, it was crystallized from alcohol to give 2.6 g. (80% yield) of Ia as yellow needles, m.p. 169–170.5°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.69; H, 5.79.

3-(4-Methoxy-3-methylphenyl)-5-anisyl-5-oxo-2-pentenoic acid (IIa). To a yellow solution of 1 g. of Ia in 100 ml. of boiling alcohol, a solution of 1.5 g. sodium hydroxide in 4 ml. of water was added. The resulting dark red solution was heated at reflux temperature for 15 min. After a portion of 25 ml. of water was added, the solvent alcohol was removed under water pressure vacuum. The alkaline solution was filtered, and the filtrate neutralized with dilute hydrochloric acid at ice bath temperature. The gummy solid which separated solidified upon standing. It was recrystallized from alcohol to afford 0.4 g. (43% yield) of IIa, m.p. 148–149.5° dec.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92; neut. equiv., 340.4. Found: C, 70.54; H, 5.76; neut. equiv., 341.9.

The residue collected after filtering the alkaline solution was washed thoroughly with water, dried, and recrystallized from alcohol to give 0.14 g. (15% yield) of IIIa, m.p. 87–88°.

2-(4-Methoxy-3-methylphenyl)-4-anisyl-4-oxo-butene-1 (IIIa). *Method A.* One gram of acid (IIa) was heated in a hard glass test tube at about 148–152° until no more carbon dioxide was evolved (tested by lime water). The brown gummy mass, which separated after chilling the contents of the tube, solidified upon trituration with alcohol. It was treated with dilute sodium bicarbonate solution and water. The dry solid was then recrystallized from alcohol giving 0.35 g. (38% yield) of IIIa, as faintly yellow crystals, m.p. 87–88°.

Method B. To a solution of 3.2 g. (0.01 mole) of Ia in 200 ml. of alcohol, a solution of sodium ethoxide, prepared from 0.46 g. of sodium and 25 ml. of alcohol, was added. The mixture was heated at reflux temperature for 15 min. Removal of the solvent left a residue, which after washing with water and drying, was recrystallized from alcohol to give 1.7 g. (60% yield) of IIIa, as faint yellow flakes, m.p. 87–88.5°. The melting point of a mixture of the samples prepared by methods *A* and *B* showed no depression.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.01; H, 6.80. Found: C, 76.74; H, 6.73.

3-(2-Methoxy-4-methylphenyl)-5-anisyl-5-oxo-2-pentenoic acid-eno-lactone (Ib). This lactone was prepared following the procedure for Ia. From 2.3 g. (0.01 mole) of β-(2-methoxy-4-methylphenyl)glutaconic anhydride,[16] 2.5 g. (78% yield) of Ib was obtained, m.p. 127.5–128°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.63; H, 5.67.

(14) All melting points are uncorrected.

(15) D. B. Limaye and V. M. Dixit, *Proc. Indian Sci. Congr.*, 167 (1930).

(16) D. B. Limaye and G. R. Gogte, *J. Univ. Bombay*, **3**, 135 (1934).

3-(2-Methoxy-4-methylphenyl)-5-anisyl-5-oxo-2-pentenoic acid (IIb). Following the procedure used in making IIa, this acid was obtained in 72% yield from Ib, m.p. 128–128.5° dec.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92; neut. equiv., 340.4. Found: C, 70.54; H, 5.76; neut. equiv., 343.7.

A phenylhydrazone of IIb was prepared by treating equimolar quantities of IIb and phenylhydrazine in acetic acid solvent. It was recrystallized from alcohol to give white crystals, m.p. 164–165.5° dec.

Anal. Calcd. for $C_{26}H_{26}N_4O_2$: Neut. equiv., 426.5. Found: Neut. equiv., 430.2.

A semicarbazone of IIb was also prepared, m.p. 178–179.5° dec.

Anal. Calcd. for $C_{21}H_{23}N_3O_5$: Neut. equiv., 397.4. Found: Neut. equiv., 399.4.

2-(2-Methoxy-4-methylphenyl)-4-anisyl-4-oxo-butene-1 (IIIb). This ketone was prepared from Ib in 46% yield and from IIb in 56% yield following the procedures used for IIIa. It was obtained as faint yellow crystals from alcohol, m.p. 83–84°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.18; H, 6.82.

3-(4-Methoxy-2-methyl-5-isopropylphenyl)-5-anisyl-5-oxo-pentenoic acid-eno-lactone (Ic). This lactone was obtained in about 53% yield from β-(4-methoxy-2-methyl-5-isopropylphenyl)glutaconic anhydride[17] following the general procedure outlined for making Ia; m.p. 158–159°.

Anal. Calcd. for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.82; H, 6.40.

3-Aryl-5-aryl-5-oxo-pentanoic acids (IV, *Table* I). *General procedure.* These substituted butyric acids were prepared from the corresponding β-arylglutaric anhydrides by adopting the general procedure used in making Ia, b, and c. The sticky solid left after removal of the solvent nitrobenzene was washed with water and then treated with 10% sodium bicarbonate solution. The clear solution was treated with active charcoal and then filtered. Upon neutralization of this filtrate, there was obtained a gum which solidified on standing. Two to three recrystallizations usually gave a pure sample of the acid.

The use of tetrachloroethane as a solvent in place of nitrobenzene improved the yield but with carbon disulfide as a substitute for nitrobenzene, the yield was poorer.

Oxidation of 3-aryl-5-aryl-5-oxo-pentanoic acids (from Table I). To a solution of 1 g. of acid in 40 ml. of 2.5% sodium carbonate solution, 3 g. of finely powdered potassium permanganate was added in portions with vigorous stirring. After two hours' stirring at room temperature, the hydrated manganese dioxide was removed by filtration. The clear filtrate upon concentration to a small volume (about 10 ml.) was neutralized with concd. hydrochloric acid at ice bath temperature. Usually one of the substituted anisic acids was recovered as an insoluble precipitate, and the mother liquor contained water soluble oxidation products obtained from the other part of the molecule. The latter was subjected to continuous ether extraction and to the oily residue left after evaporation of the ether, 2 ml. of glacial acetic acid and 6 ml. of 0.3*N* hydrogen peroxide solution was added. Upon concentration of this solution at room temperature, there was left a solid which was characterized as the other substituted anisic acid by a melting point determination of a mixture with an authentic sample.

In some cases, both the oxidation products (anisic acids) were recovered as a mixture during potassium permanganate oxidation. They were separated by fractional crystallization and then identified by determining mixed melting points of a mixture with authentic samples. Two recrystallizations were usually necessary before a pure sample was obtained.

2-Oxo-4-aryl-6-aryl-tetrahydropyran (VII, *Table* II). *General procedure.* A solution of 2 g. of the butyric acid (Table I) in 1*N* sodium hydroxide solution sufficient for neutralization was shaken vigorously for about 45 min. in a stoppered bottle with 10 g. of 4% sodium-amalgam (prepared from 10 g. of mercury and 0.4 g. of sodium). After the evolution of hydrogen had ceased (about 2 hr.), the alkaline solution was filtered. Neutralization of the filtrate with hydrochloric acid at ice bath temperature gave a solid melting over a wide range (5–10°). All attempts to obtain a pure sample of the solid failed. To the crude dry solid in a flask, 3 ml. of acetic anhydride was added and the entire mixture was heated at 100° for 15 min. and then poured into 50 ml. of water. The solid which separated was washed with several portions of dilute sodium bicarbonate solution and then water. After drying, it was recrystallized several times to give a pure sample of the lactone.

β-(4-Methoxy-2-methyl-5-isopropylphenyl)glutaric acid. A solution of 5 g. of β-(4-methoxy-2-methyl-5-isopropylphenyl)glutaconic acid[17] in 1*N* sodium hydroxide solution sufficient for neutralization was taken in a stoppered bottle. A portion of 40 g. of 4% sodium amalgam (from 40 g. of mercury and 1.6 g. of sodium metal) was slowly added to this solution and the reaction mixture was vigorously shaken for 45 min. After the evolution of hydrogen had ceased (about 2 hr.), it was filtered and the filtrate was neutralized with concd. hydrochloric acid at ice bath temperature. A sticky and dull white mass which separated solidified after standing. It was collected on a filter and the dry solid was recrystallized twice from boiling water to give 4.1 g. (81% yield) of the reduced acid as white needles, m.p. 148–149°.

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53; neut. equiv., 147.17. Found: C, 65.40; H, 7.42; neut. equiv., 147.12.

β-(4-Methoxy-2-methyl-5-isopropylphenyl)glutaric anhydride. A mixture of 5 g. of the glutaric acid and 10 ml. of acetic anhydride was heated at reflux temperature for 5 min. The resulting gummy mass was washed with ether when it solidified. Recrystallization from benzene gave 4.1 g. (86% yield) of the anhydride as shining plates, m.p. 135–136.5°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.78; H, 7.22.

BOMBAY, INDIA

(17) V. M. Bhave, *J. Indian Chem. Soc.*, 29, 275 (1952).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

A Side Reaction in the Williamson Synthesis. II[1]

ROBERT H. BAKER AND WILLIAM B. MARTIN

Received March 8, 1960

The alkylation of sodium 2-phenylethoxide with benzyl chloride produces, in addition to the expected ether, 2-benzyl-2,3 diphenylpropanol. This abnormal reaction results from the presence of aldehydes or other phenylacetaldehyde precursors. Thus, the course of the reaction probably involves a sequence of oxidation-reduction steps and the successive alkylations of aldehyde enolates. In one experiment, with 3-phenylpropanol, the intermediate 2,2-dibenzyl-3-phenylpropanal was isolated. The abnormal alkylation has been accomplished also with 2-phenylethanol and allyl chloride and with 4-phenylbutanol and benzyl chloride. The products demonstrate that dialkylation is the rule and that only the β carbon atom is involved.

Some years ago it was shown that the reaction of sodium 2-phenylethoxide with benzyl chloride in toluene produced not only the ether but also a surprising quantity of the carbon-alkylation product, 2-benzyl-2,3-diphenylpropanol.[2] Subsequently, it was shown that this result could not be due to the presence of a carbanion which would be tautomeric with the phenylethoxide ion.[3] It was also demonstrated that freshly prepared alcohols such as 2,3-diphenylbutanol and 2,3-diphenylpropanol gave only the *O*-benzyl derivatives, and further that benzyl 2-phenylethyl ether, under the conditions of abnormal benzylation, gave none of the unusual alcohol.[4]

The fact that we were unable to perform the second stage of benzylation on the latter two alcohols, and indeed that we could not alkylate any but aged samples of 2-phenylethanol itself led to the investigation of aldehydes as possible promoters of the abnormal alkylation. With phenylacetaldehyde, up to 5 mole %, it was not possible to produce the C-alkylation product in high yield; but with benzaldehyde or ketones which cannot themselves be destroyed through aldol condensation, excellent yields were obtained as shown in Table I. For each of the promoters there was an optimum concentration at about 7.6 mole % (based on the alcohol) and best results were encountered when the aldehyde or ketone was added slowly as a solution in the alkylating agent.

It appears most reasonable that the reaction sequence involves the production of phenylacetaldehyde followed by the alkylation of its enolate ion; subsequent proton removal, a second alkylation, and finally, reduction completes the chain of events with regeneration of the promoter (or its equivalent). The minimum number of equations required to express the processes occurring prior to hydrolysis is six as represented in the reaction scheme.

TABLE I

EFFECTIVENESS OF VARIOUS CARBONYL COMPOUNDS ON YIELD OF 2-BENZYL-2,3-DIPHENYLPROPANOL

Aldehyde or Ketone	Equivalent, %[a]	Yield, %[b]
Phenylacetaldehyde	5.0	4.5
Benzaldehyde	3.8	11.6
Benzaldehyde	7.6	19.2
Benzaldehyde	7.6	12.3
Benzaldehyde	7.6	38.4[c]
Benzaldehyde	11.4	37.5
Benzaldehyde	15.2	34.6
Benzophenone	7.6	26.7
Fluorenone	7.6	23.6
Cyclohexanone	7.6	0.5

[a] Equivalent % is the moles per 100 moles of 2-phenylethanol. [b] The yield is based on the alcohol. [c] Twice the usual amount of benzyl chloride was used.

$$C_6H_5CH_2CH_2O^- + R_2CO \rightleftharpoons C_6H_5CH_2CHO + R_2CHO^- \quad (1)$$

$$C_6H_5CH_2CHO + C_6H_5CH_2CH_2O^- \rightleftharpoons C_6H_5{}^-CHCHO + C_6H_5CH_2CH_2OH \quad (2)$$

$$C_6H_5{}^-CHCHO + C_6H_5CH_2Cl \longrightarrow C_6H_5CH(CH_2C_6H_5)CHO + Cl^- \quad (3)$$

$$C_6H_5CH(CH_2C_6H_5)CHO + C_6H_5CH_2CH_2O^- \rightleftharpoons C_6H_5{}^-C(CH_2C_6H_5)CHO + C_6H_5CH_2CH_2OH \quad (4)$$

$$C_6H_5C^-(CH_2C_6H_5)CHO + C_6H_5CH_2Cl \longrightarrow C_6H_5C(CH_2C_6H_5)_2CHO + Cl^- \quad (5)$$

$$C_6H_5C(CH_2C_6H_5)_2CHO + C_6H_5CH_2CH_2O^- \rightleftharpoons C_6H_5C(CH_2C_6H_5)_2CH_2O^- + C_6H_5CH_2CHO \quad (6)$$

Such a lengthy path is not to be lightly accepted, particularly as in some of the experiments each molecule of aldehyde added must account for as many as five molecules of final product and that the enolate ions, though of necessity in low relative concentration, must compete with alkoxide ions for the alkylating agent. Further, this course of the reaction would account for a number of other by-products that have not been found. Among these would be the monoalkylated alcohol, its benzyl ether, and the intermediate aldehydes. The final products certainly do not consist wholly of ether and dialkylated alcohol, but characterization of the other products has not been possible except that when 3-phenylpropanol was used the dialkylated

(1) This work was supported by a grant from the Abbott Fund of Northwestern University.

(2) R. H. Baker, *J. Am. Chem. Soc.*, 70, 3857 (1948).

(3) R. H. Baker and S. H. Jenkins, Jr., *J. Am. Chem. Soc.*, 71, 3969 (1949).

(4) Maryann Compton, M. S. thesis, Northwestern University, 1949.

aldehyde was isolated. These difficulties in isolating other by-products calls attention to the fortunate circumstances attending the original isolation of 2-benzyl-2,3-diphenylpropanol which, because of its ease of crystallization, was readily separated from other reaction products.

Before accepting the oxidation-alkylation-reduction path, efforts were made to ensure that the reaction did not proceed by some simpler though possibly more obscure manner. That the source of the benzyl groups was wholly from the benzyl chloride and not from the solvent, toluene, was proved in two ways. First, benzene instead of toluene was used, and although the yield was reduced to 9% the result left little doubt that the explanation invoked merely the lower reflux temperature. Secondly, the benzyl chloride was replaced by allyl chloride whereupon a diallylphenethyl aldohol was obtained. With butyl bromide no C-alkylation product could be isolated and it is probable that only quite rapidly acting alkylating agents would be successful.

The phenyl group in the alcohol is without doubt of value in the success of the reaction sequence through its stabilizing effect on the enolate ions as seen in Equations 2 and 4. It did seem important, however, to determine not only if it were necessary but also, in homologues of phenethyl alcohol, if it rather than the potential aldehyde group might govern the position of alkylation. To this end 3-phenylpropanol and 4-phenylbutanol were subjected to the benzylation reaction and both were found to be alkylated in the 2-position. The yields in the latter two reactions were so low as to make isolation of the products difficult. This again points to the efficacy of the phenyl group, when properly placed, in promoting the side reaction.

EXPERIMENTAL[5]

2-Benzyl-2,3-diphenylpropanol. To 5.8 g. (0.25 mole) of powdered sodium under 150 ml. of toluene there was added dropwise with stirring 30.5 g. (0.25 mole) of 2-phenylethanol. Toward the end of the addition it was necessary to bring the suspension to reflux in order to continue stirring. When the evolution of hydrogen had ceased, there was added during 5 to 25 min. a solution of 31.5 g. (0.25 mole) of benzyl chloride containing 0.02 mole of benzaldehyde or other promoter as listed in Table I. After approximately 1 hr. of reflux and stirring, the mixture was cooled; water was added and the organic layer was separated and distilled. Toluene and then benzyl 2-phenylethyl ether were distilled up to 150° at 0.6 mm. The latter was not always isolated but generally occurred in about 40% yield. Treatment of the residue with petroleum ether (b p. 30–60°) gave the product, m.p., 101–103°.

Benzylation of 3-phenylpropanol. The reaction was carried out using the molar quantities and conditions described above, and using benzophenone as the promoter. Distillation of the hydrolyzed product gave three fractions, b.p. 200–217° at 2 mm. which partially solidified after several days. The material, 3.5 g., could not be purified by crystallization and was chromatographed over alumina. Benzene elution produced crystals of m.p. 118–120°, recrystallized from methanol-water, m.p. 122–124°, which proved to be an aldehyde. Methanol-benzene elution then produced the alcohol, m.p. 80°. The high melting substance showed the infrared absorption of an aldehyde and it yielded a 2,4-dinitrophenylhydrazone, crude m.p. 175–176°. The aldehyde, 0.4 g. was reduced by 0.1 g. of lithium aluminum hydride in ethyl ether to 2,2-dibenzyl-3-phenylpropanol, m.p. 80° (from methanol-benzene), which was identical with that synthesized below.

2,2-Dibenzyl-3-phenylpropanol. Tribenzylacetonitrile was prepared by the method of Bergstrom and Agostinho[6] except that three equivalents of benzyl chloride was used, and the solid product, after washing with alcohol, was crystallized from benzene; yield 59%, m.p. 223°. Hydrolysis of the nitrile was by Newman's method and like similar compounds, it gave the amide.[2] Diazotization of the amide[2] produced the crude tribenzylacetic acid, m.p. 111–113°; neut. equiv. 328, calcd., 330. The acid was reduced by lithium aluminum hydride in hot butyl ether.[2] After hydrolysis the product was washed with potassium hydroxide solution and was distilled, b.p. 200–205° at 0.05 mm. On standing the alcohol solidified, m.p. 80–81°. Its infrared spectrum was identical with that of the product described above.

Anal., Calcd. for $C_{23}H_{24}O$: C, 87.30; H, 7.65. Found: C, 87.9: H, 7.6.

Benzylation of 4-phenylbutanol. This alcohol as produced by hydrogenation of the ester[7] was difficult to purify and thus was treated with lithium aluminum hydride to produce the pure material, b.p. 92–93° at 0.3 mm., n_D^{25} 1.5170.

The alkylation was carried out as previously described, using benzophenone, and two equivalents of benzyl chloride. Distillation produced seven fractions; the first six, b.p. 124–138° at 0.3 mm., were fractionated in a 50-plate Podbielniak Heli-Grid column giving a 25% yield of *benzyl 4-phenylbutyl ether*, b.p. 133–134° at 1.1 mm.; n_D^{25} 1.5369.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.6, H, 8.6.

The last fraction from the preliminary distillation, b.p. 200–210° at 0.3 mm. weighed 6.7 g.; 8% crude yield. It could not be crystallized but was converted into *2,2-dibenzyl-4-phenylbutyl 3,5-dinitrobenzoate*, m.p. 174–175°, from methanol, which was identical with that from synthetic material.

Anal. Calcd. for $C_{31}H_{28}N_2O_6$: C, 70.99; H, 5.38; N, 5.34. Found: C, 71.1; H. 5.3; N, 5.5 (Dumas).

Synthesis of 2,2-dibenzyl-4-phenylbutanol. The benzylation of 4-phenylbutanonitrile, 0.5 mole, in liquid ammonia-sodamide followed the Bergstrom and Agostinho method[6] as modified above. The pasty mass obtained upon evaporation of ammonia was washed with methanol, then with water and was crystallized from methanol-benzene to give *2,2-dibenzyl-4-phenylbutanonitrile*, 50% yield, m.p. 131–133°. Two crystallizations from ethanol raised the melting point to 132–133°.

Anal. Calcd. for $C_{24}H_{23}N$: N, 4.30. Found: N, 4.5.

The nitrile, 30 g. (0.093 mole) was refluxed for 122 hr. in a solution containing 400 ml. of acetic acid, 50 ml. of sulfuric acid and 15 ml. of water.[2] Upon cooling to 5° there was added dropwise a solution of 6.4 g. of sodium nitrite in 30 ml. of water, then after 0.5 hr. the nitrosation was repeated and the solution deposited crystals. The solid was dissolved in aqueous potassium hydroxide and was filtered from a small amount of neutral material. Acidification produced 26 g., 82%, of *2,2-dibenzyl-4-phenylbutanoic acid;* m.p. 120–121°, after crystallization from methanol-water; neut. equiv., calcd. for $C_{24}H_{24}O_2$, 344, found, 340.

(5) Microanalyses were performed by Misses J. Sorensen, C. White and H. Beck. All melting points were observed on the hot stage of a polarizing microscope and are corrected.

(6) F. W. Bergstrom and R. Agostinho, *J. Am. Chem. Soc.*, **67**, 2152 (1945).

(7) H. Adkins, B. Wojcik, and L. W. Covert, *J. Am. Chem. Soc.*, **55**, 1669 (1933).

This acid, 8 g. (0.023 mole) was reduced by refluxing for 4 hr. with 1.5 g. (0.04 mole) of lithium aluminum hydride in ethyl ether. After hydrolysis the alcohol was distilled at 0.3 mm.; after some weeks it solidified: m.p. 76°. A small sample was converted into 2,2-dibenzyl-4-phenylbutyl 3,5-dinitrobenzoate, m.p. 174–175°, from methanol, whose infrared spectrum was identical with that of the analytical sample previously described.

Allylation of 2-phenylethanol. The alkoxide, 0.25 mole, was made and treated as previously described, but using benzaldehyde as promoter and allyl chloride, 0.028 mole, as alkylating agent. The product, after hydrolysis, was distilled at 5 mm. into eight fractions. Approximately 50% of the 2-phenylethanol was recovered. The last fraction, b.p. 135–137° at 5.5 mm., n_D^{25} 1.5416 was redistilled into three fractions, most of the material, *2,2-diallyl-2-phenylethanol* distilling at 98–99° at 0.6 mm., n_D^{25} 1.5406. With palladium-charcoal in acetic acid it absorbed 97% of the hydrogen required for two double bonds, and a Zerewitinoff determination showed 1.1 equivalents of active hydrogen.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.9; H, 8.9.

EVANSTON, ILL.

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

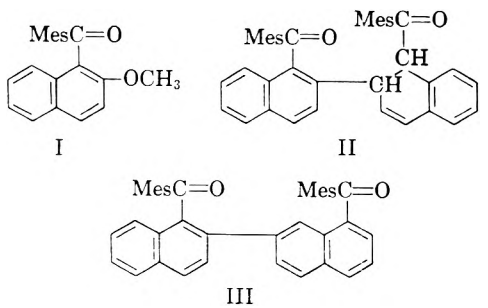
Conjugate Bimolecular Reduction of Hindered Ketones Involving Replacement of Methoxyl Groups. IV. Mesityl 2-Methoxy-1-naphthyl Ketone[1]

REYNOLD C. FUSON AND DAVID E. FRANKHOUSER[2]

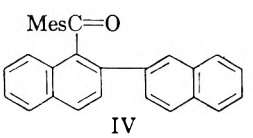
Received February 25, 1960

Reduction of mesityl 2-methoxy-1-naphthyl ketone with the binary mixture, magnesium–magnesium iodide, gave 1,2-dihydro-1,1′-dimesitoyl-2,2′-binaphthyl and 1,1′-dimesitoyl-2,2′-binaphthyl. The dihydro diketone underwent cleavage with chloranil to give a monoketone, 1-mesitoyl-2,2′-binaphthyl, and mesitoic acid. The monoketone, synthesized independently, was cyclized with polyphosphoric acid. Conversion of the dihydro diketone to the aromatic diketone was effected with palladium-on-charcoal.

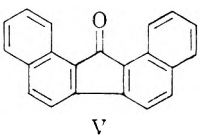
It has been shown that hindered *o*-methoxyphenyl ketones undergo reductive coupling and cyclization to yield the corresponding 9,10-diarylphenanthrenes.[3] The analogous behavior of mesityl 2-methoxy-1-naphthyl ketone (I) would afford a new entry into the picene family. A greater tendency for coupling might be expected in the naphthalene series as the methoxy ketone, because of the greater double bond quality of the 1,2-linkage, would be expected to behave more like an ester than does the benzene analog. Under reaction conditions very similar to those employed previously, the naphthyl ketone gave coupling products in comparatively high yields. The transformation stopped, however, at the diketone stage. The principal product II proved to be the dihydro derivative of the completely aromatized diketone III. The latter was obtained also but in much smaller amounts.



Of special interest was the transformation realized when the dihydroaromatic diketone II was treated with chloranil in anisole. The products were a monoketone, 1-mesitoyl-2,2′-binaphthyl (IV), and mesitoic acid. This result is unusual; the treatment with chloranil was expected to give the aromatized diketone. Aromatization was accomplished, however, by heating with palladium-on-charcoal.



IV



V

The monoketone IV was synthesized independently by displacement of the methoxyl group of the methoxy ketone I by the action of the 2-naphthyl Grignard reagent. Ring closure of the monoketone was effected with polyphosphoric acid, the product being the known 13H-dibenzo[a,i]fluoren-13-one (V).

The aromatic diketone presumably was produced by dimerization of the ketyl formed by the interaction of the methoxy ketone and the binary mixture, magnesium–magnesium iodide.[4] The dihydro diketone could conceivably be the intramolecular reduction product of the aromatic diketone, if ring closure were prevented by steric factors. Further reduction of the diketone pre-

(1) This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

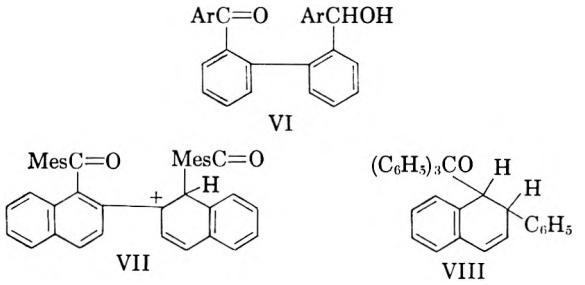
(2) American Cyanamid Company Fellow, 1958–1959.

(3) R. C. Fuson and R. O. Kerr, *J. Org. Chem.*, 19, 373 (1954).

(4) M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, 49, 236 (1927).

sumably would give a dienol, which, after ketonization, could then undergo an acid-catalyzed rearrangement to the dihydro product, the driving force being formation of the aromatic ring. The dihydro diketone is analogous to the keto alcohols VI, which have been isolated[5] by the reduction of hindered *o*-methoxyphenyl ketones, except that an aromatic ring underwent reduction rather than a carbonyl group.

The cleavage of the dihydro diketone is somewhat similar to the pyrolysis of 1,2-dihydro-2-phenyl-1-naphthyl triphenylmethyl ketone (VIII), which yields 2-phenylnaphthalene, triphenylmethane, and carbon monoxide.[6]



The cleavage of the dihydrodiketone II is not a pyrolysis, however, as evidence has been accumulated that chloranil is necessary; cleavage was not brought about by boiling in anisole without chloranil or by boiling with methoxide ion. An acid and not carbon monoxide is formed, so it seems that the two cleavage reactions are not related. According to the work of Braude, Jackman, and Linstead[7] on the mechanism of the dehydrogenation of dihydroaromatic hydrocarbons with quinones, the last step in the dehydrogenation of the dihydro diketone II would require the expulsion of a proton from the positively charged intermediate VII. Perhaps the mesityl carbonium ion, rather than a proton, is lost; the formation of the monoketone might be favored by steric factors.

EXPERIMENTAL[8]

Mesityl 2-methoxy-1-naphthyl ketone. The procedure used was that of Fuson and Fang[9] as modified by Mon.[10] A solution of 50.4 g. of mesitoyl chloride, prepared from 50 g. of mesitoic acid and 100 g. of thionyl chloride, and 39.6 g. of 2-methoxynaphthalene in 200 ml. of carbon disulfide were added, with stirring, over a period of 3 hr. to an ice-cold slurry of 33.6 g. of aluminum chloride and 200 ml. of carbon disulfide. The red mixture was stirred for 22 hr. while cooled in an ice bath and then poured into 1.5 l. of an ice water mixture to which 90 ml. of concd. hydrochloric acid had been added. The organic layer was washed with 200 ml. of 4% sodium hydroxide and with 200 ml. of water. Acidification of the sodium hydroxide wash gave 4.0 g. of mesitoic acid. The organic phase was dried over sodium sulfate, after which the solvent was evaporated to leave 60.4 g. of crude yellow solid. Three recrystallizations from petroleum ether (b.p. 90–110°) gave 51.5 g. (61.4%) of mesityl 2-methoxy-1-naphthyl ketone, m.p. 129.5–130.5°. A mixture of the sample with an authentic specimen showed no lowering of the melting point.

Reduction of mesityl 2-methoxy-1-naphthyl ketone. Ten grams of iodine was added slowly to a mixture of 9.57 g. of ground magnesium, 44 ml. of *n*-butyl ether, and 40 ml. of toluene. Heat was applied initially, and the reaction proceeded exothermically thereafter. The entire operation was carried out with stirring and in a nitrogen atmosphere. After the last portion of the iodine had been added, the mixture was heated under reflux for 15 min. to give a cloudy, greenish-gray suspension. To the heated mixture was added a solution of 6.00 g. of the ketone in 40 ml. of toluene. The addition took 5 min., after which time the bright red mixture was heated under reflux for 4 hr. and then poured into 200 ml. of 6*N* hydrochloric acid and cooled in an ice bath. The organic layer was washed with 5% sodium bicarbonate, with 5% sodium hydrogen sulfite, and finally with water. After the solution had been dried over sodium sulfate, the solvent was removed. Treatment of the reddish-brown residue with 25 ml. of acetone caused the separation of 1,2-dihydro-1,1′-dimesitoyl-2,2′-binaphthyl; m.p. 213–215°, yield 2.52 g. (46.6%). The analytical sample, crystallized from chloroform-ethanol, melted at 218–219°.

Anal.[11] Calcd. for $C_{40}H_{36}O_2$: C, 87.56; H, 6.61. Found: C, 87.41; H, 6.57.

The infrared spectrum[12] of the compound contains bands attributable to an unconjugated, hindered ketone (1698 cm.$^{-1}$), a conjugated, hindered ketone (1645 cm.$^{-1}$), a 1,2-disubstituted naphthalene ring (828 and 760 cm.$^{-1}$), and a mesityl group (850 cm.$^{-1}$). The ketone band at 1698 cm.$^{-1}$ is also present in the infrared spectrum of 1,2-dihydro-2-methyl-1-naphthyl mesityl ketone.

Evaporation of the acetone from the filtrate left 3.63 g. of dark brown solid, which was chromatographed on a 125-g. alumina column. Elution with 1:1 cyclohexane:ether gave, after combining fractions, 1.36 g. of crude 1,1′-dimesitoyl-2,2′-binaphthyl, m.p. 242–245°. Repeated recrystallization from chloroform-ethanol gave 0.19 g. (1.75%) of analytically pure diketone, m.p. 248–249°.

Anal. Calcd. for $C_{40}H_{34}O_2$: C, 87.77; H, 6.27. Found: C, 88.02; H, 6.39.

The infrared spectrum shows bands assignable to a hindered, conjugated ketone (1655 cm.$^{-1}$), a mesityl group (852 cm.$^{-1}$), and a 1,2-disubstituted naphthalene ring (830 and 740 cm.$^{-1}$). Elution with ether and with methanol gave 1.49 g. of intractable dark red oils, the infrared spectrum of which contains bands at 1687, 1645, and 855 cm.$^{-1}$

During one run the acetone filtrate was treated with copper acetate before removal of solvent. To the acetone solution, made up to a volume of 100 ml., was added 10 ml. of water and 1.50 g. of copper acetate. After the mixture had been shaken for 2 hr., the green complex was collected and hydrolyzed by shaking with 6*N* hydrochloric acid. Extraction with ether and evaporation of solvent gave 0.39 g. (6.8%) of a colorless solid. The infrared spectrum of this material contains a band at 1612 cm.$^{-1}$ attributable to a chelated aromatic ketone. The spectrum is identical with that of a compound which is currently under investigation in this laboratory.

(5) R. C. Fuson and C. Hornberger, Jr., *J. Org. Chem.*, **16**, 637 (1951).

(6) R. C. Fuson and K. D. Berlin, *J. Am. Chem. Soc.*, **81**, 2130 (1959).

(7) E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, 3548 (1954).

(8) All melting points are corrected.

(9) R. C. Fuson and F. T. Fang, *J. Am. Chem. Soc.*, **77**, 3781 (1955).

(10) Private communication.

(11) The microanalyses were carried out by Mr. Rollo Nesset, Mrs. Ruby Ju, Mrs. Alice Terra, and Miss Claire Higham.

(12) The infrared spectra were determined by Mr. James Brader, Mrs. Louise Griffing, and Mr. Sy Portnow.

On certain occasions it was possible to isolate a compound, m.p. 230–231°, which is presumably an isomer of the dihydroaromatic diketone. The infrared spectrum of this material is similar to that of the dihydroaromatic diketone. Conversion of the higher melting to the lower melting form was accomplished by passing the solid, dissolved in benzene, through an alumina column. Treatment with chloranil in *m*-xylene gave 1-mesitoyl-2,2′-binaphthyl in 31.6% yield.

Cleavage of 1,2-dihydro-1,1′-dimesitoyl-2,2′-binaphthyl. A solution of 0.67 g. of the dihydroaromatic diketone and 0.54 g. of chloranil in 12 ml. of anisole was heated under reflux under nitrogen for 36 hr. A test for evolved carbon monoxide was negative. After the reddish-brown solution had cooled, it was extracted twice with 5% sodium hydroxide, benzene and chloroform being added. The organic phase was washed with water and dried over sodium sulfate. Removal of solvent produced 0.59 g. of residue, which was chromatographed on a 25-g. alumina column. Elution with 5:1 cyclohexane:ether gave 0.23 g. (47.3%) of 1-mesitoyl-2,2′-binaphthyl, m.p. 180–181°. A mixture melting point with the monoketone synthesized independently was not depressed, and the infrared spectra of the two samples were superimposable.

When the combined sodium hydroxide extracts were acidified with dilute hydrochloric acid, a dark purple precipitate formed which dissolved readily in ether. The ether layer was washed repeatedly with water and dried over sodium sulfate. Solvent removal left a purple residue, which was then stirred with 5 ml. of concd. sulfuric acid. Ice and water were added, and the mixture was extracted with ether. The ether layer was washed with 5% sodium bicarbonate, the basic extract acidified, and the product taken up in ether, which was then evaporated. The residue was crystallized from methanol-water to give 0.32 g. (16%) of crude mesitoic acid, m.p. 147–150°, identified by reference to its infrared spectrum and by a mixture melting point determination.

1-Mesitoyl-2,2′-binaphthyl. A solution of 3.00 g. of mesityl 2-methoxy-1-naphthyl ketone in 15 ml. of benzene and 15 ml. of ether was added to a Grignard reagent prepared from 12.43 g. of 2-bromonaphthalene and 1.22 g. of ground magnesium in 30 ml. of ether and 30 ml. of benzene. The reaction mixture was heated under reflux for 4 hr. and poured into a saturated ammonium chloride solution. The organic layer was washed with water and dried over sodium sulfate. Evaporation of the solvent left a red residue, which, when treated with ether, gave 1.41 g. of colorless solid. Recrystallization from benzene produced 0.24 g. of 2,2′-binaphthyl, m.p. 183–185°. The benzene filtrate was taken to dryness; the residue crystallized from chloroform-ethanol to give 0.41 g. (10.4%) of 1-mesitoyl-2,2′-binaphthyl, m.p. 180–181°.

Anal. Calcd. for $C_{30}H_{24}O$: C, 89.96; H, 6.04. Found: C, 89.89; H, 5.92.

The infrared spectrum of this compound has bands attributable to a hindered, conjugated ketone at 1650 cm.$^{-1}$, to the mesityl group at 850 cm.$^{-1}$, and to a 1,2-disubstituted naphthalene ring at 740 and 825 cm.$^{-1}$.

Ring closure of 1-mesitoyl-2,2′-binaphthyl. Two milliliters of polyphosphoric acid and 0.11 g. of the monoketone were heated for 4 hr. at 100–110° and then for 1 hr. at 180°. The mixture was poured into ice and water, and the red solid which formed was removed by filtration. One recrystallization from benzene gave 0.023 g. (30.2%) of red plates, m.p. 264–266° (sealed tube). The infrared spectrum of the compound has a strong band at 1690 cm.$^{-1}$ which is also present in the spectrum of the known ketone.[13]

Dehydrogenation of 1,2-dihydro-1,1′-dimesitoyl-2,2′-binaphthyl. A mixture of 0.154 g. of the dihydroaromatic diketone and 0.021 g. of 10% palladium-on-charcoal was heated at 205° for 2 hr., during which time a stream of nitrogen was passed over the molten mixture. When cold the mixture was extracted with chloroform. Filtration gave a light yellow solution, which was boiled on a hot plate, ethanol being added to replace the chloroform removed by distillation. When the solution has cooled, 0.062 g. of the starting diketone crystallized. From the filtrate was obtained 0.019 g. (12.4%) of 1,1′-dimesitoyl-2,2′-binaphthyl, m.p. 248–249°. The infrared spectrum is superimposable on that of the 248–249° compound produced by the reduction of mesityl 2-methoxy-1-naphthyl ketone.

A solution of 0.204 g. of diketone in 4 ml. of anisole was heated under reflux for 36 hr. Evaporation of solvent yielded a residue which, after one recrystallization from chloroform-ethanol, gave 0.202 g. of the starting diketone.

A solution of 0.280 g. of diketone and 0.034 g. of sodium methoxide in 7 ml. of benzene and 3 ml. of methanol was heated under reflux for 12 hr. and then poured into water. The organic phase was washed twice with water and dried over sodium sulfate. Removal of solvent and crystallization of the residue from chloroform-ethanol gave 0.204 g. of the diketone taken as starting material.

URBANA, ILL.

(13) R. C. Fuson and F. W. Wassmundt, J. Am. Chem. Soc., **78**, 5409 (1956).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Action of Grignard Reagents. XX. Action of Organomagnesium Compounds and of Lithium Aluminum Hydride on 3-Substituted 3,4-Dihydro-4-keto-1,2,3-benzotriazines

AHMED MUSTAFA, WAFIA ASKER, ABDALLAH M. FLEIFEL, SAMIR KHATTAB, AND SAYED SHERIF

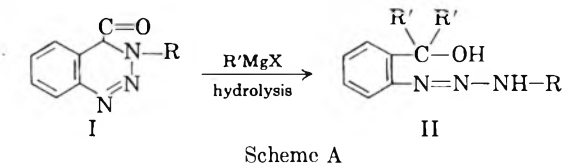
Received March 1, 1960

Treatment of Ib–h with Grignard reagents leads to opening of the heterocyclic ring with the formation of IIa–l. IIa–l now have also been obtained by the action of the same reagent on the corresponding methyl *o*-aryldiazoaminobenzoates (IIIa–g). Cleavage of the N—C bond of Ii and of Ij is effected by the action of phenylmagnesium bromide, and by the action of lithium aluminum hydride in the case of Ij. Treatment of Ij with aluminum chloride, similarly, effects elimination of the acyl group, with the formation of Ia. The stability of the —N=N— system in Ia toward the action of lithium aluminum hydride similates the behavior of methyl *o*-(*p*-tolyl)diazoaminobenzoate (IIIb) toward the same reagent, whereby, *o*-(*p*-tolyl)diazoaminobenzyl alcohol is produced.

The reactions of 3-substituted 3,4-dihydro-4-keto-1,2,3-benzotriazines have not been thoroughly studied. In their reactions, they behave as masked diazonium compounds and undergo ring opening; a number of these reactions have been described.[1] The recent literature[2,3] covers only the preparation and spectra of some new members of this class of compounds, the chemical properties of which are now further explored.

In continuation of the work of one of us on the ring-opening of heterocyclic compounds by the action of organomagnesium compounds, *e.g.*, in the case of benzoxazones,[4] of 2,3-diphenylquinazolone-4,[4] of benzo-, and of naphtho-2′,3′-oxazole-2-one, as well as their *N*-aroyl derivatives,[5] we now have investigated the behavior of 3-substituted 3,4-dihydro-4-keto-1,2,3-benzotriazines (Ib–h) toward the action of organomagnesium compounds and the action of lithium aluminum hydride. Thus, when 3-phenyl-3,4-dihydro-4-keto-1,2,3-benzotriazine (Ib) is treated with phenylmagnesium bromide, followed by hydrolysis, opening of the heterocyclic ring is effected with the formation of *o*-phenyldiazoaminotriphenyl carbinol (IIa). Similar treatment of Ic–h with the same reagent results in the formation of *o*-substituted phenyldiazoaminotriphenyl carbinols (IIb–g) respectively (*cf.* Scheme A). Action of methylmagnesium iodide on Ib–d, If, and Ig leads to the formation of *o*-substituted phenyldiazoaminodimethylphenyl carbinols (IIh–l).

The assigned structure for the Grignard products



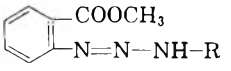
I II

Scheme A

Ia. R = H
b. R = C_6H_5
c. R = *p*-$CH_3C_6H_4$
d. R = *p*-$CH_3OC_6H_4$
e. R = *o*-$CH_3OC_6H_4$
f. R = *p*-BrC_6H_4
g. R = *p*-ClC_6H_4
h. R = *m*-ClC_6H_4
i. R = $COCH_3$
j. R = COC_6H_5

IIa. R = R′ = C_6H_5
b. R = *p*-$CH_3C_6H_4$; R′ = C_6H_5
c. R = *p*-$CH_3OC_6H_4$; R′ = C_6H_5
d. R = *o*-$CH_3OC_6H_4$; R′ = C_6H_5
e. R = *p*-BrC_6H_4; R′ = C_6H_5
f. R = *p*-ClC_6H_4; R′ = C_6H_5
g. R = *m*-ClC_6H_4; R′ = C_6H_5
h. R = C_6H_5; R′ = CH_3
i. R = *p*-$CH_3C_6H_4$; R′ = CH_3
j. R = *p*-$CH_3OC_6H_4$; R′ = CH_3
k. R = *p*-BrC_6H_4; R′ = CH_3
l. R = *p*-ClC_6H_4; R′ = CH_3

IIa–l, is inferred from the fact that they are identical with those obtained by the action of the Grignard reagents on the appropriate methyl *o*-aryldiazoaminobenzoate (IIIa–g).



IIIa. R = C_6H_5
b. R = *p*-$CH_3C_6H_4$
c. R = *p*-$CH_3OC_6H_4$
d. R = *o*-$CH_3OC_6H_4$
e. R = *p*-BrC_6H_4
f. R = *p*-ClC_6H_4
g. R = *m*-ClC_6H_4

For further study of the effect of the acyl group attached to heterocyclic nitrogen compounds with Grignard reagents, the action of phenylmagnesium bromide on 3-acetyl- (Ii) and on 3-benzoyl-3,4-dihydro-4-keto-1,2,3-benzotriazines (Ij) now has been investigated. Ii and Ij undergo elimination of the acyl group by the action of the same reagent forming 3,4-dihydro-4-keto-1,2,3-benzotriazine (Ia) together with diphenylmethyl- and triphenylcarbinol, respectively. The elimination of the acyl group by the action of Grignard reagent is analogous to the behavior of *N*-benzoylphthalimide and of *N*-benzoylbenzotriazole toward the action of phenylmagnesium bromide.[5]

The effect of substituents on the facile opening of the hetero-ring in Ib–h by the action of Grignard

(1) *The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines*, J. G. Erickson, P. F. Wiley, and V. P. Wystrach, Interscience Publishers, New York, 1956, p. 21–22.

(2) E. V. Heyningen, *J. Am. Chem. Soc.*, **77**, 6562 (1955).

(3) P. Grammatickis, *Compt. rend.*, **243**, 2094 (1956); Chem. Abst., **50**, 6189 (1956).

(4) A. Mustafa, W. Asker, M. Kamel, A. F. A. Shalaby, and A. E. A. E. Hassan, *J. Am. Chem. Soc.*, **77**, 1612 (1955).

(5) A. Mustafa, W. Asker and O. H. Hishmat, *J. Am. Chem. Soc.*, **77**, 5127 (1955).

TABLE I

o-SUBSTITUTED PHENYLDIAZOAMINOTRIPHENYL- AND DIMETHYLPHENYLCARBINOLS (IIa–g) AND (IIh–l)

Starting[a] Material	Product	Solvent[b]	M.P. °	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ib				60								
IIIa	IIa	A	179–180	80	Red	$C_{25}H_{21}N_3O$	79.15	79.16	5.59	5.64	11.08	10.83
Ic				85								
IIIb	IIb	A	154	87	Red	$C_{26}H_{23}N_3O$	79.38	79.12	5.80	5.91	10.68	10.76
Id				87								
IIIc	IIc	B	132–133	90	Red	$C_{26}H_{23}N_3O_2$	76.28	76.97	5.62	5.82	10.27	10.34
Ie				70								
IIId	IId	C	166 dec.	75	Dark brown	$C_{26}H_{23}N_3O_2$	76.28	76.16	5.62	5.64	10.27	10.26
If				85								
IIIe	IIe	B	130	90	Red	$C_{25}H_{20}N_3OBr$	65.50	65.76	4.36	4.25	9.16	9.21
Ig				75								
IIIf	IIf	C	147 dec.	80	Yellowish brown	$C_{25}H_{20}N_3OCl$	72.55	72.98	4.83	5.11	10.15	10.15
Ih				65								
IIIg	IIg	C	181 dec.	70	Dark red	$C_{25}H_{20}N_3OCl$	72.55	72.66	4.83	4.79	10.15	10.23
Ib				72								
IIIa	IIh	A	140	80	Red	$C_{15}H_{17}N_3O$	70.58	70.95	6.66	6.52	16.47	16.62
Ic				75								
IIIb	IIi	C	144–145	80	Red	$C_{16}H_{19}N_3O$	71.30	71.75	7.24	7.32	15.61	15.72
Id				65								
IIIc	IIj	B	125–126	70	Red	$C_{16}H_{19}N_3O_2$	67.36	67.71	6.66	6.58	14.73	14.62
If				80								
IIIe	IIk	B	135	90	Red	$C_{15}H_{16}N_3OBr$	53.89	54.30	4.79	5.0	12.57	12.42
Ig				65								
IIIf	IIl	C	126	70	Yellow	$C_{15}H_{16}N_3OCl$	62.17	62.57	5.52	5.21	14.50	14.21

[a] For the methods of their preparation *cf.* ref. 3; If and IIIe were prepared after F. D. Chattaway and A. G. Walker, *J. Chem. Soc.*, 323 (1927). [b] A = Alcohol; B = benzene-benzine; C = petroleum ether (b.p. 90–120°).

reagents is illustrated by the stability of 3,4-dihydro-4-keto-1,2,3-benzotriazine (Ia) toward the same reagent.

Lithium aluminum hydride. The action of lithium aluminum hydride on organic compounds[6] has shown a far-reaching analogy with that of Grignard reagents. We have found that hydrogenolysis with the hydride, like treatment with phenylmagnesium bromide followed by hydrolysis, brings about cleavage of N—C bond of Ij with the isolation of benzyl alcohol. Hydrogenolysis, under the influence of the hydride, of the acyl group attached to a nitrogen compound has been reported in the reduction of *N*-acetylcarbazole,[7] of acylated 2-benzoylaminothiazole,[8] of 1-benzoylbenztriazole,[9] and of dibenzoyl-L-histidine.[10]

Treatment of Ij with anhydrous aluminum chloride at 120–125° effects elimination of the benzoyl group with the formation of Ia.

The stability of Ia toward the action of lithium aluminum hydride parallels its behavior toward phenylmagnesium bromide (see above). *o*-(*p*-Tolyl)-diazoaminotriphenyl carbinol (IIb) has now been found to be stable toward the action of the same reagent under the given experimental conditions.[11]

The stability of the —N=N— system[12] in IIb toward the action of lithium aluminum hydride has also been observed when methyl *o*-(*p*-tolyl)diazoaminobenzoate (IIIb) is subjected to similar treatment whereby *o*-(*p*-tolyl)diazoaminobenzyl alcohol is produced, identified as the corresponding urethane.

EXPERIMENTAL

Action of Grignard reagents on 3-substituted 3,4-dihydro-4-keto-1,2,3-benzotriazines (Ib–h) *and methyl o-aryldiazoaminobenzoates* (IIIa–g). The following exemplifies the procedure. To a Grignard solution prepared from 0.9 g. of magnesium and 9 g. of bromobenzene in 50 ml. of dry ether (in the case of phenylmagnesium bromide) was added a solution of 1 g. of Ib or IIIa in dry benzene (50 ml.). The mixture was heated for 3 hr. on a steam bath. After standing overnight at 25°, it was poured slowly into 100 ml. of saturated aqueous ammonium chloride solution, extracted with ether, dried, and evaporated. The oily residue was washed several times with hot petroleum ether (b.p. 60–80°) and the resulting solid was crystallized from the proper solvent.

The products IIb–l listed in Table I were prepared similarly. In general they are soluble in hot benzene and chloroform, but are sparingly soluble in petroleum ether.

Action of phenylmagnesium bromide on 3-benzoyl-3,4-dihydro-4-keto-1,2,3-benzotriazine (Ij). A solution of 1 g. of Ij in 40 ml. of dry benzene was treated with phenylmagnesium bromide as described in the case of Ib. The ether-benzene solution was evaporated, and the solid residue that was obtained was extracted with cold benzene (*ca.* 25 ml.) and the insoluble part was recrystallized from hot alcohol as colorless crystals (*ca.* 0.42 g.), m.p. 212–213°; identified as Ia.[13] The benzene extract gave, on concentration and cooling, colorless crystals (*ca.* 0.39 g.) which were shown to be triphenylcarbinol (melting point and mixed melting point).

Action of phenylmagnesium bromide on 3-acetyl-3,4-dihydro-4-keto-1,2,3-benzotriazine (Ii). Similarly, the action of phenylmagnesium bromide on a solution of 1 g. of Ii[14] in 40 ml. of benzene was worked up as described above. Ia (*ca.* 0.72 g.) and diphenylmethylcarbinol (*ca.* 0.23 g.) were obtained. The carbinol melted, after washing with petroleum ether (b.p. 80–100°), at 82–83°[15] (melting point and mixed melting point). It gives a red color with sulfuric acid.

Action of lithium aluminum hydride on Ij *and* IIIb. Solvents dried over sodium were used. To 0.5 g. of lithium aluminum hydride was added 50 ml. of ether. After 15 min., a benzene solution (30 ml.) containing 1 g. each of Ij[14] and IIIb was added in portions. The reaction mixture was refluxed for 3 hr. and then left overnight at room temperature. After treatment with cold dilute hydrochloric acid, the ethereal solution was dried and evaporated. The solid residue, after washing with petroleum ether (b.p. 60–80°) was crystallized to yield *ca.* 0.42 g. of Ia. The petroleum ether washings on evaporation gave benzyl alcohol which was identified as phenylurethane (melting point and mixed melting point).[16]

In the case of IIIb, the colorless product was treated directly with phenylisocyanate, and the corresponding urethane was crystallized from alcohol in colorless crystals (*ca.* 0.24 g.), m.p. 119–120°.

Anal. Calcd. for $C_{21}H_{19}N_4O$: N, 16.32. Found: N, 15.97.

Action of aluminum chloride on Ij. A mixture of 1 g. of Ij and 2 g. of aluminum chloride was heated in an oil bath and the temperature was maintained at 120–125° for 1 hr. The reaction mixture was cooled, then decomposed with 100 ml. of ice water containing 5 ml. of concd. hydrochloric acid. The solid, so obtained, was collected and crystallized from alcohol as colorless crystals (*ca.* 0.62 g.), m.p. 212–213°, identified as Ia by melting point and mixed melting point.[13]

GIZA, CAIRO
EGYPT, U.A.R.

(6) A. Mustafa, W. Asker, O. H. Hishmat, A. F. A. Shalaby, and M. Kamel, *J. Am. Chem. Soc.*, **76**, 5447 (1954).

(7) K. Banholzer, T. W. Campbell, and H. Schmid, *Helv. Chim. Acta*, **35**, 1577 (1952).

(8) I. A. Kaye and C. L. Parris, *J. Org. Chem.*, **17**, 737 (1954).

(9) N. G. Gaylord, *J. Am. Chem. Soc.*, **76**, 285 (1954).

(10) P. Karrer, M. Suter, and P. Wasser, *Helv. Chim. Acta*, **32**, 1936 (1949).

(11) Triphenylcarbinol is recovered unchanged when treated with the same reagent under similar conditions.

(12) Azo compounds are resistant to attack by lithium aluminum hydride [R. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948), W. Reid and F. Müller, *Chem. Ber.*, **85**, 470 (1952), D. H. Smith, J. R. Schwartz and G. W. Wheland, *J. Am. Chem. Soc.*, **74**, 2282 (1952)]. Reduction of Ia with zinc dust and ammonium hydroxide is followed by heterocyclic ring contraction to give 3-ketodihydroindiazole [G. Heller, *J. prakt. Chem.*, **111**, 1 (1925)]. Moreover, sodium amalgam does not appear to be effective in opening the heterocyclic ring in 3-substituted 3,4-dihydro-4-keto-1,2,3-benzotriazines [H. Mehner, *J. prakt. Chem.* **63**, 241 (1901)].

(13) H. Finger, *J. prakt. Chem.*, **37**, 432 (1888).

(14) G. Heller, *J. prakt. Chem.*, **111**, 1 (1925).

(15) A. Klages, *Ber.*, **35**, 2646 (1902).

(16) A. I. Vogel, *A Text Book of Practical Organic Chemistry*, Longmans, Green and Co. London (1951) p. 264.

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

Ortho-Substitution of Benzyl-Type Grignard Reagents by Cyanogen and Thiocyanogen

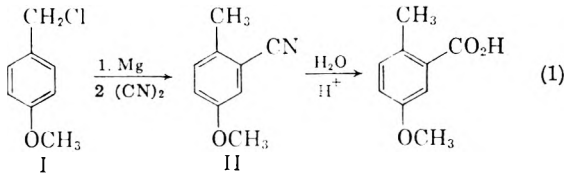
JEROME F. EASTHAM AND DICKSON Y. CANNON

Received February 29, 1960

Reactions of the Grignard reagents from 4-methoxybenzyl chloride, 2-chlorobenzyl chloride, and β-chloromethylnaphthalene with cyanogen proceed with *ortho*-substitution, which yields, respectively, 2-methyl-5-methoxybenzonitrile, 2-methyl-3-chlorobenzonitrile, and 2-methyl-1-naphthonitrile. Reaction of benzylmagnesium chloride with thiocyanogen proceeds with both direct and *ortho*-substitution which yields, respectively, benzyl mercaptan and *o*-tolyl thiocyanate. Possible mechanisms for the two thiocyanogen reactions are briefly discussed.

Recently it was found that benzylmagnesium chloride and cyanogen react to give *o*-tolunitrile and that this new *ortho*-substitution reaction occurs also with cyanogen and certain other benzyl-type Grignard reagents.[1] Reported in this paper is a further study of the scope of this reaction. Additional benzyl-type Grignard reagents and benzyllithium have been treated with cyanogen, and benzylmagnesium chloride itself has been treated with cyanogen bromide and with thiocyanogen.

When cyanogen was treated with the Grignard reagents from 4-methoxybenzyl chloride (I), 2-chlorobenzyl chloride, and β-chloromethylnaphthalene, there were produced, respectively, 2-methyl-5-methoxybenzonitrile (II), 2-methyl-3-chlorobenzonitrile, and 2-methyl-1-naphthonitrile. Each nitrile was hydrolyzed to the corresponding carboxylic acid for the purpose of identification. The reactions are illustrated (1) for 2-methoxybenzyl chloride.



The Grignard reagent in each of the above cases was prepared in the usual way and added to ethereal cyanogen. A more careful preparation of the Grignard reagents, to avoid coupling, would almost certainly improve the yield of nitrile, which was about 40% in this work. For example, from the reaction which gave 39% of nitrile from 4-methoxybenzyl chloride, there was also isolated a 42% yield of the coupled product, 1,2-bis(4-methoxyphenyl)ethane. When β-bromomethylnaphthalene (instead of the corresponding chloromethyl compound) was used, the yield of naphthonitrile was very low, probably as a consequence of the greater extent of coupling of the bromo compound.

Benzyllithium (III) was prepared from benzyl methyl ether and treated with cyanogen. In this case no *ortho*-substitution product was obtained but phenylacetonitrile was. The over-all yield of

$$C_6H_5CH_2OCH_3 \xrightarrow{Li} \underset{III}{C_6H_5CH_2Li} \xrightarrow{(CN)_2} C_6H_5CH_2CN \quad (2)$$

nitrile was poor, but this can be accounted for primarily as a consequence of the poor yield of benzyllithium. In our hands the cleavage of benzyl methyl ether by lithium could not be accomplished nearly so well (see Experimental) as has been reported.[2]

There are a number of compounds related to cyanogen, "pseudohalogens," whose reactions with the benzyl-type Grignard reagent might be of interest. The first two of these we have studied are thiocyanogen (NCSSCN) and cyanogen bromide (BrCN). The latter compound with benzylmagnesium chloride gives benzyl bromide in good yield. Cyanogen bromide is known to react with other Grignard reagents in a similar manner.[3]

Reactions between organometallics and the thiocyano group have received very little attention, and the specific reaction of thiocyanogen with a Grignard reagent does not appear to have been studied at all. Reactions of thiocyanogen with certain other organometallics yield organothiocyanates, *e.g.*, IV in Equation 3.[4] Reactions of organothiocyanates with Grignard reagents yield thiols and thioethers, *e.g.*, Equation 4.[5] For the latter reaction an attractive hypothesis for the intermediate yielding the thioether is structure V. Rearrangement of this complex could proceed as indicated (Equation 5) for the five-membered quasi-ring. Such an intramolecular rearrangement (rather than bimolecular attack involving a second molecule of Grignard reagent) should be favored by addition of the organometallic to the thiocyanate, and it was found that the formation of thioether is enhanced by this inverse addition.[5]

(1) J. F. Eastham and V. F. Raaen, *Proc. Chem. Soc.*, 149 (1958); V. F. Raaen and J. F. Eastham, *J. Am. Chem. Soc.*, **82**, 1349 (1960).

(2) H. Gilman, H. A. McNinch, and D. W. Henberg, *J. Org. Chem.*, **23**, 2044 (1958).

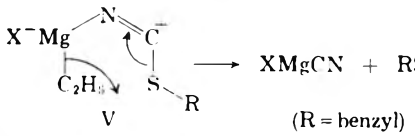
(3) V. Grignard and O. Kaschichi, *Bull. soc. chim.*, (4) **39**, 1589 (1926).

(4) E. Soderback, *Ann.*, **419**, 217 (1919).

(5) R. Adams, H. B. Bramlet, and F. H. Tendick, *J. Am. Chem. Soc.*, **42**, 2369 (1920).

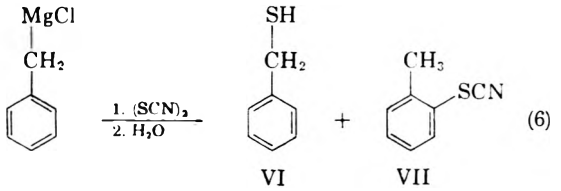
$$(C_6H_5)_2Hg \xrightarrow{(SCN)_2} \underset{IV}{C_6H_5SCN} + C_6H_5HgSCN \quad (3)$$

$$C_6H_5CH_2SCN \xrightarrow[2)\ H_2O]{1)\ C_2H_5MgCl} C_6H_5CH_2SH + C_6H_5CH_2SC_2H_5 \quad (4)$$



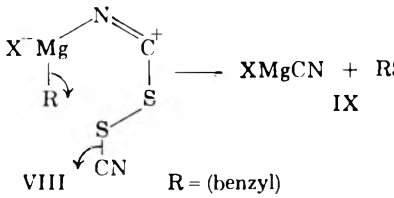
$$\longrightarrow XMgCN + RSC_2H_5 \quad (5)$$

After treatment of thiocyanogen with benzylmagnesium chloride, hydrolysis yields two products of interest: benzyl mercaptan (VI, 30% yield) and *o*-tolyl thiocyanate (VII, 10% yield). The Grignard reagent was added to the thiocyanogen, which was freshly prepared by the action of bromine on lead thiocyanate. Each product was characterized by its physical properties and by conversion to known derivatives.



(6)

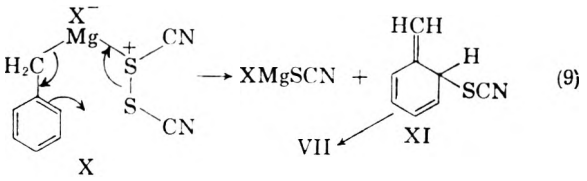
Formation of the major product, benzyl mercaptan (VI), may be rationalized with the intermediate VIII, whose rearrangement in the indicated manner (Equation 7) would yield benzyl thiothiocyanate (IX). Subsequent hydrolysis would convert the thiothiocyanate to a thiol (Equation 8).[6] Hypothesis of the rearrangement of V is comparable to that of VIII, except that the quasi-ring involved in this latter example is six-membered; in the former it is five-membered.



$$\longrightarrow \underset{IX}{XMgCN + RSSCN} \quad (7)$$

$$IX + H_2O \rightarrow VI + HOSCN \quad (8)$$

Formation of *o*-tolyl thiocyanate (VII) from benzyl magnesium chloride and thiocyanogen is a new *ortho*-substitution reaction, the first to involve reaction (rupture) of the sulfur-sulfur bond. Possibly the key intermediate for this reaction involves complexing of the Grignard reagent with sulfur, as in X. Rearrangement (Equation 9) of such a complex through a six-membered quasi-ring would produce an intermediate triene (XI), whose subsequent tautomerization would yield the isolable *o*-tolyl thiocyanate. This proposed mechanism is comparable to that substantiated for the reaction of cyanogen with benzyl-type Grignard reagents.[1]



(9)

The suggestion that thiocyanogen reacts by two different paths, Equations 9 and 10, requires additional evidence, which is being sought. It would in fact be of interest to learn more about the reactions between thiocyanogen and Grignard reagents in general, and between other sulfur-containing compounds and the benzyl-type Grignard reagent specifically. Apparently not even the reaction between sulfur itself and benzylmagnesium chloride has been studied.

EXPERIMENTAL[7]

Cyanogen. Cyanogen was prepared by treating a warm aqueous solution of copper sulfate with an aqueous solution of potassium cyanide. The gas liberated from the aqueous solution was passed through a calcium chloride drying tube and delivered into dry ether at 0° in a three-necked flask equipped with a stirrer and a Dry Ice reflux condenser. The cyanogen thus obtained, which was measured by the increase in weight of the ether solution, could be stored in the ether at 0° for several hours without appreciable loss.

2-Methyl-5-methoxybenzonitrile from 4-methoxybenzylmagnesium chloride. The Grignard reagent was prepared by the slow addition (2 hr.) of 29.2 g. of *p*-chloromethylanisole in 100 ml. of ether to 24 g. of magnesium turnings in 400 ml. of ether under a nitrogen atmosphere. The resultant solution was slowly added at 0° to 19.1 g. of cyanogen in 250 ml. of ether. The reaction mixture was refluxed for 1 hr. and allowed to stand overnight before hydrolysis with aqueous ammonium chloride. The ether layer was separated, washed with water, and dried over magnesium sulfate, and the ether was distilled at reduced pressure. The residue was distilled *in vacuo* to yield 10.5 g. (39% yield) of 2-methyl-5-methoxybenzonitrile, b.p. 104–108°/10 mm., n_D^{28} 1.5345 (lit. value[8] n_D^{20} 1.5368), λ_{max} 234 and 302 mμ (log ε 4.09 and 3.59, respectively). A brown crystalline material which was recovered from the distillation residue was recrystallized from methanol to yield 9.4 g. of cream-colored 1,2-bis(4-methoxyphenyl)ethane, m.p. 124–126° (lit.,[9] m.p. 125°).

A sample of the 2-methyl-5-methoxybenzonitrile was hydrolyzed with 60% sulfuric acid. The acid which precipitated was recrystallized from methanol-water to give 5-methoxy-2-methylbenzoic acid, m.p. 145–146° (lit.,[10] m.p. 146°).

2-Methyl-3-chlorobenzonitrile from 2-chlorobenzylmagnesium chloride. The Grignard reagent was prepared from 24.5 g. of 2-chlorobenzyl chloride and added in 500 ml. of ether to 12.2 g. of cyanogen in 250 ml. of dry ether at 0°; a yellow precipitate formed during addition. This mixture was re-

(6) Such thiothiocyanates as IX have been previously reported and are known to be about as easily hydrolyzed as an acid chloride, *cf.* H. Lecher and M. Wittmer, *Ber.*, **55**, 1474 (1922).

(7) Melting points are reported uncorrected. Ultraviolet absorption measurements were made using 95% alcohol solutions in a Beckman Model DU spectrophotometer.

(8) M. S. Carpenter and W. M. Easter, *J. Org. Chem.*, **20**, 401 (1955).

(9) M. Freund and H. H. Reitz, *Ber.*, **39**, 2235 (1906).

(10) O. Jacobsen, *Ber.*, **16**, 1964 (1883).

fluxed for 1 hr. and then hydrolyzed with cold aqueous ammonium chloride. The ether layer was separated, washed with water, dried, and evaporated. Distillation of the residue yielded two fractions. The first was 7.6 g. of 2-methyl-3-chlorobenzonitrile, b.p. 105–109°/25 mm. (lit.,[11] b.p. 107°/28 mm.), n_D^{28} 1.5480, λ_{max} 230 and 292 mμ (log ε 3.98 and 3.21, respectively). The second fraction, 4.2 g., was a pungent brownish oil, b.p. 115–120°/25 mm., which decomposed upon standing at room temperature to form a thick reddish liquid and which has not been identified.

Hydrolysis of a sample of the 2-methyl-3-chlorobenzonitrile with 60% sulfuric acid yielded 2-methyl-3-chlorobenzoic acid, m.p. 155–157° (lit.,[12] m.p. 156°).

2-Methyl-1-naphthonitrile from β-chloromethylnaphthalene. The Grignard reagent was prepared in 300 ml. of ether from 10.5 g. of β-chloromethylnaphthalene and added to 8.4 g. of cyanogen in 150 ml. of ether at 0°; a yellow precipitate formed. This mixture was refluxed for 30 min. and then was allowed to stand at room temperature overnight before it was hydrolyzed, first with aqueous ammonium chloride solution and then with dilute hydrochloric acid. The ether layer was treated in the usual manner and the product was distilled at reduced pressure to yield a clear liquid, b.p. 128–131°/1.25 mm., which crystallized. Recrystallization from ethanol yielded 8 g. of 2-methyl-1-naphthonitrile as white rhombic crystals, m.p. 85–87° (lit.,[13] m.p. 87–88°), λ_{max} 226 and 297 mμ (log ε 4.69 and 3.89, respectively).

Hydrolysis of a sample of the 2-methyl-1-naphthonitrile by refluxing it 1 hr. with 75% sulfuric acid yielded 2-methyl-1-naphthoamide, m.p. 141–142° (lit.,[13] m.p. 143°).

Benzyllithium from benzyl methyl ether. Benzyllithium was prepared by adding dropwise, over a 2-hr. period with vigorous stirring, 24.4 g. (0.2 mole) of benzyl methyl ether (in enough tetrahydrofuran to make up 100 ml. of solution) to 3.47 g. (0.5 mole) of powdered lithium metal in 400 ml. of tetrahydrofuran at −5 to −15° under a nitrogen atmosphere.[2] At the end of the addition and at 1-hr. intervals, 20-ml. aliquots were removed and shaken with 1.5 g. (0.008 mole) of benzophenone. Each sample was then hydrolyzed with aqueous ammonium chloride and extracted with ether. Evaporation of the ether and recrystallization of any solid material from ligroin (b.p. 60–90°) yielded colorless 1,1,2-triphenylethanol, m.p. 87–88° (lit.,[14] m.p. 89°). The yield of triphenylethanol from the aliquots increased slowly up to about 10 hr. after the benzyl methyl ether and lithium were mixed. The yield was then about 11% and did not exceed that after 13 hr.

Phenylacetonitrile from benzyllithium. Benzyllithium was prepared as in the previous section from 12.2 g. of benzyl methyl ether and 1.74 g. of powdered lithium metal in 500 ml. tetrahydrofuran. The benzyllithium solution was added at 0° to 14.8 g. of cyanogen in 250 ml. of dry ether; a brown precipitate formed immediately. The reaction mixture was hydrolyzed using aqueous ammonium chloride and the ether layer was separated. The aqueous layer was further extracted with three 50-ml. portions of ether and the ethereal solutions were combined, dried, and evaporated. Vacuum distillation of the residue yielded two main fractions. The first was 7.6 g. (62% unchanged) of benzyl methyl ether. The second fraction, 1.6 g. (36% yield based on unrecovered starting benzyl methyl ether) was phenylacetonitrile, b.p. 108–112°/14 mm. and 231–232°/745 mm. (lit.,[15] b.p. 107°/12 mm. and 223–234°/760 mm.). Hydrolysis of this nitrile with 65% sulfuric acid in the usual manner yielded an acid giving no melting point depression with authentic phenylacetic acid.

Benzyl bromide from benzylmagnesium chloride and cyanogen bromide. To the Grignard reagent prepared from 63 g. of benzyl chloride in 500 ml. of ether there was added dropwise at 0° with vigorous stirring 53 g. of cyanogen bromide in 100 ml. of ether. The reaction mixture was hydrolyzed with aqueous ammonium chloride and the ether layer separated, dried, and evaporated, and the residue distilled at reduced pressure. The first fraction, 3.0 g., b.p. 40–45°/17 mm., was identified as toluene. The second fraction was 26 g. of benzyl bromide, b.p. 107–112°/17 mm., n_D^{20} 1.5224. The third fraction, isolated from the distillation residue and recrystallized from 95% ethanol, was 18 g. of bibenzyl, m.p. 50–51°.

Preparation of anhydrous thiocyanogen in benzene solution.[16] Lead thiocyanate was precipitated from a lead nitrate solution with sodium thiocyanate at 0°. The product was collected by filtration, washed with ice water, and allowed to dry over phosphorus pentoxide at reduced pressure in the dark. If the product did not remain perfectly white it was not used. One part by weight in grams of lead thiocyanate was suspended in 5 to 10 parts in milliliters of dry benzene in a glass-stoppered flask and cooled to ice bath temperature. A solution of 10% bromine in the same solvent was then added in small portions with vigorous shaking until lead thiocyanate remained in about 10% excess. The solids were allowed to settle and the colorless thiocyanogen solution was decanted. Any pink coloration indicated the presence of moisture, which must be avoided.

Reaction of benzylmagnesium chloride with thiocyanogen. The Grignard reagent prepared from 25.3 g. of benzyl chloride in 500 ml. of ether was added slowly to 31.4 g. of thiocyanogen in 500 ml. of benzene at 0°; a bright yellow precipitate immediately formed. The resulting mixture was allowed to stand at 5° overnight before hydrolysis with aqueous ammonium chloride. The organic layer was separated, washed with water, dried, and evaporated. The residue was distilled under reduced pressure to obtain three fractions. The first was 7.3 g. of benzyl mercaptan, b.p. 85–90°/15 mm., 193°/748 mm. (lit.,[17] b.p. 194°/760 mm.). With 2,4-dinitrochlorobenzene, the mercaptan yielded a sulfide, m.p. 128–129° (lit.,[17] m.p. 130°) and the sulfide formed a sulfone, m.p. 179–180° (lit.,[17] m.p. 182°) on oxidation with permanganate. The second fraction was 3.6 g. of *o*-tolylthiocyanate, b.p. 120–125°/15 mm. (lit.,[18] b.p. 122.5°/15 mm.). With alkaline lead tartrate, this fraction gave a positive test for an organothiocyanate.[16] Treatment of the *o*-tolylthiocyanate with 95% sulfuric acid at 0–5° for 20 hr. yielded *o*-tolyl thiocarbamate, m.p. 136–138° (lit.,[18] m.p. 139°), which gave a precipitate with alcoholic silver nitrate.[18] *o*-Tolyl thiocarbamate also formed when the *o*-tolyl thiocyanate was allowed to stand in air at room temperature for several days. The third fraction was recovered from the distillation residue and recrystallized from 95% ethanol to yield 3.4 g. of bibenzyl, m.p. 49–50°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF SOUTH CAROLINA]

Metallation of 2,4-Lutidine and 2,4,6-Collidine with Phenyllithium

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Received November 12, 1959

2,4-Lutidine and 2,4,6-collidine reacted with phenyllithium to give lithium derivatives at the 2 position. These were identified by reaction with benzaldehyde to form the corresponding phenylcarbinols. No evidence of reaction at the 4 position could be detected.

Since its discovery by Ziegler and Zeiser[1] α-picolyllithium has become a very widely used reagent. It is conveniently prepared by the hydrogen-metal exchange reaction of α-picoline with phenyllithium at room temperature. Initial attempts to prepare γ-picolyllithium by a similar process were unsuccessful.[2] Gilman and Broadbent[3] added γ-picoline to a solution of *n*-butyllithium and found that at $-80°$ no reaction took place. However, at $-10°$ they found that addition across the C=N bond occurred producing, after heating, 2-*n*-butyl-4-methylpyridine. Erlenmeyer and coworkers[4] found that when phenyllithium was treated with γ-picoline and subsequently carbonated and hydrolyzed, the product was 2-phenylhomoisonicotinic acid. This involved both addition across the C=N bond and metallation of the methyl group. Wibaut and Hey[5,6] reversed the procedure and added the phenyllithium solution to the γ-picoline on the assumption that if the metallation reaction is the more rapid of the two, the γ-picolyllithium should be formed in good yield. The γ-picolyllithium formed in this manner was treated with alkyl bromides and yields of up to 60% of the alkyl pyridine compounds were obtained. The reactions were carried out at room temperature.

2,4-Lutidine has been treated with phenyllithium.[7,8] The products obtained correspond to those expected if metallation occurs only on the α-methyl groups. The authors did not report any careful study to detect the formation of any of the γ-isomers.

Condensations with aldehydes also indicate that the α-methyl group is more reactive than that in the γ-position. Thus 2,4-lutidine condenses with benzaldehyde in the presence of acetic anhydride[9] or zinc chloride[10] to yield 2-styryl-4-methylpyridine as the only monostyryl derivative along with some 2,4-distyrylpyridine. 2,4,6-Collidine also reacts with aldehydes to give condensation at the 2-position. Dubke[11] reported the preparation of 4,6-dimethyl-2-picolylphenylcarbinol and 4,6-dimethyl-2-stilbazole by condensation of benzaldehyde with collidine but he did not prove the structure of his products. Koenigs and Bentheim[12] obtained 4,6-dimethyl-2-stilbazole by the same reaction and identified the product by oxidation to 4,6-dimethylpicolinic acid. Several other condensations with aldehydes at the 2-position have also been reported.[13–16]

This work was undertaken to determine the relative reactivities toward metallation on the 2- and 4- positions of 2,4-lutidine and of 2,4,6-collidine. This was done by treating the pyridine homologs with phenyllithium. The resulting pyridinelithium compounds were identified by reaction with benzaldehyde and isolation of the resulting phenylcarbinols. In order for the ratio of the final yields of the isomers to be equivalent to the ratio of the lithium derivatives it must be assumed that the rate of addition of each isomer to the benzaldehyde is equal. This assumption seems reasonable since addition of organolithium compounds to benzaldehyde is a very rapid reaction.

DISCUSSION

The phenyllithium solution was added to the 2,4-lutidine to minimize addition across the azomethylene linkage. In the case of 2,4,6-collidine the normal addition of the base to the phenyllithium was followed. After addition of the benzaldehyde, the phenylcarbinols were purified by crystallization of the hydrochloride–mercuric chlo-

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TABLE I

METALLATION OF 2,4-LUTIDINE AND 2,4,6-COLLIDINE

	Base Added, G.	Base Recovered, G.	Reaction Product, G.	Phenyl-2-carbinol, G.	Unident. Product, G.	Reaction Prod., % 2-Carbinol	Reaction Prod., % Unident. product	Yield of 2-Carbinol, %[a]
2,4-Lutidine	25.0	14.5	18.1	17.9	0.2	99	1	85.8
2,4,6-Collidine	25.8	4.54	27.7	>26.3	<1.4	>95	<5	>64

[a] Based on pyridine homolog consumed in the reaction.

ride double salts. The results are summarized in Table I.

The 4-methyl-2-picolylphenylcarbinol was identified by dehydration to 4-methyl-2-stilbazole. The structure of the stilbazole had been proved previously[9] by oxidation to 4-methyl-2-picolinic acid and decarboxylation of this acid to 4-picoline.

The reaction product from the 2,4,6-collidine, after treatment with hydrochloric acid and mercuric chloride, was separated into three fractions. The major fraction yielded pure 4,6-dimethyl-2-picolylphenylcarbinol and amounted to 92.25% of the total product recovered. The second fraction was an oily mercuric chloride double salt which could not be crystallized. The base from this salt amounted to 5.25% of the total product. Its infrared spectrum was essentially the same as that of the main fraction except for an extra peak appearing between 8.2 and 8.4 μ. Dehydration of this material produced 4,6-dimethyl-2-stilbazole, identified by mixed melting points of several derivatives. It was estimated that this fraction consisted of over 50% 4,6-dimethyl-2-picolylphenylcarbinol. The third fraction of mercuric chloride double salt yielded only 2.5% of the total basic products and was not identified.

The major reaction product, 4,6-dimethyl-2-picolylphenylcarbinol, had been prepared by Dubke in 1894 along with the corresponding stilbazole but no attempt had been made to prove the structure. Koenigs and Bentheim[12] prepared the stilbazole and proved its structure by oxidation to 4,6-dimethylpicolinic acid. The melting points of the derivatives of our carbinol agreed with those of Dubke but those of our stilbazole did not completely agree with either set of authors, ours being higher in all cases. Final proof of structure was made by oxidation of our compound to 4,6-dimethylpicolinic acid. This acid has been prepared[17] and its structure proved by decarboxylation to 2,4-lutidine.

These results show that metallation of 2,4-lutidine and 2,4,6-collidine occurs at the 2- position. No evidence could be obtained of metallation at the 4- position.

EXPERIMENTAL

Reaction of 2,4-lutidine. Phenyllithium was prepared from 135.6 g. (0.8 mole) of bromobenzene and 14 g. (2.02 g.-atoms) of lithium in 750 ml. of absolute ether. The concentration of phenyllithium was found by titration with standard acid to be 0.98*M*. This was subsequently checked by reaction with benzaldehyde to form benzhydrol and a value of 0.96*M* was obtained. Two hundred milliliters of this solution containing 0.196 mole of phenyllithium was added slowly to 25 g. of 2,4-lutidine (0.6 mole, a 30% excess) in 200 ml. of absolute ether under an atmosphere of nitrogen. The addition required 15 min. and the mixture was stirred an additional 15 min. An excess of benzaldehyde was then distilled directly into the reaction mixture. The product was decomposed and worked up in the usual manner. The basic constituents were obtained as a semisolid residue weighing 34.1 g. 2,4-Lutidine (14.5 g.) was separated by steam distillation and recovered, leaving 18.6 g. of nonvolatile material.

The residue was dissolved in dilute hydrochloric acid and precipitated with an excess of hot aqueous mercuric chloride. The mercuric chloride double salt separated initially as an oil. The liquid was decanted from this oil and the rest of the double salt separated as white crystals. By repeated extraction of the oily material the product was finally separated into a white solid as the major fraction and 1.2 g. of a dark brown residue. The mercury was precipitated from the mercuric chloride double salts with hydrogen sulfide and the free bases were recovered. The major fraction weighed 17.9 g. and melted at 92.1–92.3° and was shown to be 4-methyl-2-picolylphenylcarbinol.

Anal. Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09. Found: C, 78.92; H, 7.04.

The amorphous material was not identified. Since it amounted to only 1% of the product, this represents the upper limit of condensation which could have occurred in the gamma position.

Preparation of 2-styryl-4-methylpyridine. A sample of the 4-methyl-2-picolylphenylcarbinol was refluxed 1 hr. with acetic anhydride. The mixture was poured into dilute sodium hydroxide solution, the product was taken up in hexane and recrystallized several times from hexane: m.p., 71.8–72.3°; picrate, m.p., 259–260°. Mixed melting points with an authentic sample prepared by the method of Clemo and Gourlay[9] gave no depression.

Reaction of 2,4,6-collidine. The procedure was essentially the same as that used for the 2,4-lutidine except that the collidine was added to the phenyllithium since there was no likelihood of addition across the azomethylene linkage. 2,4,6-Collidine (25.8 g., 0.213 mole) in 100 ml. of absolute ether was added to 0.194 mole of phenyllithium in 200 ml. of ether. After decomposition of the reaction mixture with water and acid and after removal of the ether layer, the mixture was made alkaline and the basic constituents extracted with chloroform. Removal of the chloroform under vacuum in a rotary evaporator gave 37.7 g. of residue. This was dissolved in hydrochloric acid and treated with mercuric chloride. Working up the products as above gave 75 g. of a white crystalline product, 4.5 g. of a brown oil, and 2.8 g. of a brown amorphous solid, completely insoluble in water. The major fraction of the mercuric chloride double salt yielded 25.6 g. of 2-(4,6-dimethylpicolyl)phenylcarbinol. The brown oil, on precipitation of the mercury, gave 1.5 g. of an oil which was shown to be largely the same material, and the other fraction gave 0.7 g. of an unidentified base.

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Finally, 4.5 g. of 2,4,6-collidine was recovered from the aqueous mother liquor.

Anal. of the carbinol. Calcd. for $C_{15}H_{17}ON$: C, 79.26, H, 7.54. Found: C, 78.62; H, 7.63.

Mercuric chloride–hydrochloride salt, m.p. 98–99° (reported[11] m.p. 99–100°); platinum tetrachloride–hydrochloride salt, m.p. 126–129°(reported[11] m.p. 125–130°); hydrochloride, m.p., 208–209° (reported[11] m.p. 209–211°).

Preparation of 2-styryl-4,6-dimethylpyridine. The collidylphenylcarbinol was dehydrated to the corresponding stilbazole by refluxing with an excess of acetic anhydride for 1 hr. The product was not purified but several derivatives were made. Mercuric chloride–hydrochloride salt, m.p. 231–232° (reported, m.p. 218–219°,[11] 220–222°[17]); picrate, m.p. 256° (reported, m.p. 240–241°,[11] 240–242°[17]); auric chloride–hydrochloride salt, m.p. 188–189° (reported, m.p. 189–191°,[11] 192–193°[17]).

The crude stilbazole was oxidized with potassium permanganate in acetone to 4,6-dimethylpicolinic acid. The product was purified by precipitation of the copper salt from aqueous solution and removal of the copper with hydrogen sulfide. After recrystallization from alcohol the acid melted at 157–158° (reported,[17] m.p. 155–156°); hydrazide, m.p. 74–75° (reported,[17] m.p. 77°).

The second fraction from the mercuric chloride purification was dehydrated with acetic anhydride. Several derivatives were made and their melting points and mixed melting points with the corresponding derivative of the 2-stilbazole are as follows: mercuric chloride-hydrochloride salt, m.p. 220–222° and 224–225°; platinum tetrachloride-hydrochloride salt, m.p. 241–242° and 242–243°; picrate, m.p. 242–244° and 249–250°.

COLUMBIA, S. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Aromatic and Pseudoaromatic Nonbenzenoid Systems. II. Studies Directed toward the 1,2-Diaza-3,5,7-cyclooctatriene System[1,2]

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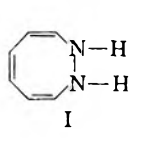
Received February 15, 1960

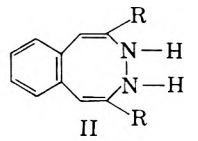
Molecular orbital calculations indicate a resonance energy of 2.99 β for 1,2-diaza-3,5,7-cyclooctatriene (I), and 4.76 β for the 5,6-benzo derivative (IIc). Compounds of structure IIIa and IIIb, which differ from derivatives of II only by the positions of double bonds, were synthesized. The failure of these derivatives of III to rearrange to the corresponding derivatives of II in the presence of a hydrogenation catalyst was noted. The calculated resonance energy of I, although large, is interpreted as being consistent with a lack of aromatic character in a ring system such as I.

According to the simple molecular orbital theory,[4,5] if cyclooctatetraene were planar it would have a significantly lower resonance energy than benzene (1.66 β *vs.* 2.00 β). In its simplest form the theory also predicts that a planar cyclooctatetraene would have a triplet ground state. Energy would be required to enlarge the interior natural angles of the tub form of cyclooctatetraene to force it into a planar configuration, and the resonance that could be gained is insufficient to bring this about. The molecule consequently exists in the tub form,[6,7] and has very little resonance energy.

From the molecular orbital point of view, 1,2-diaza-3,5,7-cyclooctatriene (I) is essentially a cyclooctatetraene containing 10 electrons. It therefore satisfies Hückel's rule ($4n+2$ π electrons)[8] and might be expected to be aromatic. It therefore



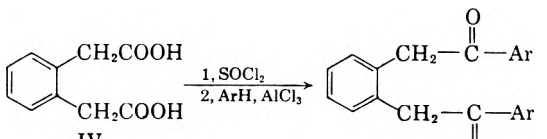
I



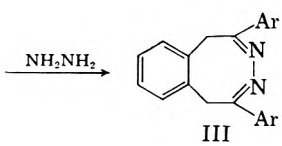
II

a. R = phenyl
b. R = 2,4-xylyl
c. R = H

seemed that the synthesis of such a system might be carried out, and more detailed molecular orbital calculations might be made and compared with experiment.



IV V



III

a. Ar = phenyl
b. Ar = 2,4-xylyl
c. Ar = H

The molecular orbital calculations were carried out for I with the usual assumptions[4,5]: (a) a planar system with exchange integrals all equal to β for adjacent atoms and zero otherwise, (b)

(1) Paper I, N. L. Allinger and G. A. Youngdale, *Tetrahedron* Letters, No. 9, 10 (1959).

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(8) Ref. 5, p. 145.

Coulomb integrals of α for carbon and $\alpha + 0.5\ \beta$ for nitrogen, and (c) neglecting overlap. The energy levels are given in Table I. The total π energy was found to be 10.99 β, and the resonance energy (relative to a single Kekule form) is 2.99 β.

For synthetic reasons, a study of the system II appeared to offer certain advantages. The calculations were therefore repeated for IIc. The total π energy found for this compound was 16.76 β, and this yields a resonance energy of 4.76 β. Since a benzene ring has a calculated resonance energy of 2.0 β, the additional resonance of the system (2.76 β) is a measure of the resonance of the heterocyclic ring, and differs little from the value calculated for the monocyclic compound. The energy levels are listed in Table I.

TABLE I

ENERGY LEVELS FOR THE 1,2-DIAZA-3,5,7-CYCLOOCTATRIENES

I	IIc
−1.917	−2.269
−1.384	−1.589
−1.193	−1.494
+0.104	−1.135
+0.150	−0.894
+1.460	0.000
+1.590	+0.244
+2.190	+0.949
	+1.316
	+1.544
	+2.000
	+2.329

A value for β of about 20 kcal./mole is generally accepted,[9] and would yield delocalization energies of 59.8 and 55.2 kcal./mole for the planar systems I and the heterocyclic ring of IIc respectively. From the appropriate bending frequency of ethylene[10] the energy required to distort the bond angles sufficiently to flatten out the tub can be calculated to be 31.5 kcal./mole. Clearly then, simple theory predicts planar systems will be more stable than the tub forms by 28.3 and 23.7 kcal./mole respectively for both I and II. It is possible to improve the values of the exchange and overlap integrals without too much labor,[4,5] but such improvements appear to have negligible effect on the total calculated energies and on the conclusions as to the presence or absence of aromaticity in other cases studied.[11] Electron correlation and configuration interaction are more difficult to treat,[12] and might be rather important here because of the relatively high electron density. No attempt has been made to pursue the theoretical calculations beyond this point, however, for reasons given below.

Compound IIIa, an isomer of IIa, was first prepared as outlined on the flow sheet. The known *o*-phenylenediacetic acid was converted *via* the acid chloride to diketone VIIa. This compound was allowed to react with hydrazine under high dilution conditions,[13] and gave IIIa in low yield. The structure of IIIa was established by analysis and molecular weight, and by the absence of any N—H stretching absorption in the infrared spectrum.

If the isomerization of an imine to a vinyl amine is endothermic by 3–6 kcal./mole, which are the values found for enolization of ketones,[14] the planar structure IIc would appear to be at least 11.7 kcal./mole more stable than the nonplanar IIIc, and it would appear that the reaction IIIc→IIc should proceed. However, prolonged treatment of IIIa with palladium-on-charcoal in refluxing xylene brought about no isomerization. There appeared therefore to be a conflict between the predicted and observed results. For simplification, the effect of the aromatic substituents had been ignored in the calculations. Since these substituents were conjugated with the azine system, the possibility existed that this conjugation tended to stabilize the azine arrangement and to prevent the isomerization. It is well known that the two rings in biphenyl can be forced from co-planarity by the presence of *ortho*-groups, and therefore the synthesis of IIIb was undertaken. This synthesis paralleled the earlier one, although the cyclization step had to be modified somewhat to obtain the desired product. It was found that IIIb was similarly reluctant to isomerize to the desired form (IIb).

It seems difficult to escape the conclusion that in this case the simple molecular orbital theory appears to fail to predict that which is experimentally found. Other apparent failures of the theory in predicting aromaticity have been reported in the past.[15] It may be noted, however, that although the predicted resonance energy of I (2.99 β) appears large relative to that of benzene (2.00 β), when other effects are taken into account, the predicted isomerization energy for IIIc→IIc amounts to only 12 kcal./mole, so that a lack of aromaticity in II cannot be considered alarming. Since the simple form of the molecular orbital theory appears to suffer from some basic difficulties

(9) Ref. 5, p. 669. The quantity referred to as β in the present work is called γ by Wheland.

(10) The value 0.8×10^{-11} ergs/radian^2 has been used for the force constant for reasons outlined by F. H. Westheimer in M. S. Newman's *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, 1956, p. 537.

(11) B. Pullman and A. Pullman in *Les Theories Electroniques de la Chimie Organique*, Masson et Cie, Editeurs, Libraires de l'Academie de Medecine 120, Boulevard Saint-Germain, Paris VI^e, 1952, p. 226.

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(14) G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, 30, 669 (1947).

(15) W. von E. Doering, Paper Presented at the Sixteenth National Organic Chemistry Symposium, Seattle, Wash., June, 1959.

which are at present the subject of considerable discussion,[16] it does not seem profitable to pursue this matter further at the present time.

EXPERIMENTAL

o-Phenylenediacetic acid (IV). A mixture of *o*-phenylenediacetonitrile,[17] 70 g., and 700 ml. of 6*N* hydrochloric acid was refluxed until a homogeneous solution was obtained. Five hundred milliliters of the solution was then distilled, and the remaining solution was cooled. The solid which separated was filtered and recrystallized from water to give 81 g. (93%) of product in the form of colorless needles, m.p. 149–150° (lit.,[18] m.p. 149–150°).

o-Phenylenediacetophenone (Va). Ten grams of diacid IV were converted to the corresponding acid chloride by heating at 70° with 15.3 g. of thionyl chloride for 6 hr. The excess thionyl chloride was then removed under reduced pressure and the acid chloride was dissolved in 30 ml. of benzene. The resulting solution was added over 30 min. to a stirred mixture of 16 g. of anhydrous aluminum chloride in 80 ml. of benzene. Stirring was continued for 2 hr. and the mixture was then poured onto a mixture of ice and hydrochloric acid. The aqueous layer was separated and extracted with benzene. The combined benzene layers were washed with dilute sodium carbonate solution, and then with water. The benzene solution was then concentrated to a volume of 100 ml., and deposited colorless crystals upon cooling. Two recrystallizations from benzene gave the diketone as needles, wt. 11.9 g. (74%), m.p. 181.5–182°.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.02; H, 5.77. Found: C, 84.30; H, 5.84.

2-Phenyl-3-benzoylindene. In another run, which was carried out in essentially an identical manner to that described, the isolation procedure gave a viscous black residue instead of the desired product. Distillation gave 40% yield of a material, b.p. 240–290° (4 mm.), which partially solidified. Upon recrystallization from dioxane the compound was obtained as colorless plates, m.p. 164–165°. The infrared spectrum showed absorption at 6.02 μ.

Anal. Calcd. for $C_{22}H_{16}O$; C, 89.14; H, 5.44. Found: C, 88.92; H, 5.46.

3,8-Diphenyl-1,2-diaza-5,6-benzo-2,5,8-cyclooctatriene (IIIa). The procedure used was adapted from that described by Overberger and Lapkin[13] for a similar cyclization. A warm solution of 6.28 g. of the diketone (V) in 110 ml. of dimethylformamide was mixed with a warm solution of 2.26 g. of hydrazine hydrobromide in 70 ml. of dimethylformamide. The resulting solution was allowed to stand for 2 days, and then was diluted with 400 ml. of absolute ethanol and added to 1500 ml. of absolute ethanol containing 60 ml. of pyridine under high dilution conditions over a period of 24 hr. The resulting mixture was then heated under reflux for 3 days, and concentrated under vacuum to a volume of 300 ml. This solution was poured into ice water. The yellow solid which separated was collected, wt. 6 g. A portion of this material was recrystallized twice from aqueous acetone and furnished large pale yellow needles, m.p. 157.5–158.5°, and a small amount of small golden plates, m.p. 244–244.5°, which were not further investigated. Recrystallization of the large needles from acetone gave colorless plates, m.p. 157.5–158.5°. The infrared spectrum showed absorption at 6.2, 6.3, 6.65, and 6.85 μ, quite like the absorption shown by benzalazine. No N—H absorption was evident. The ultraviolet spectrum showed a maximum at 267 mμ with ϵ 28,200 (95% ethanol).

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.10; H, 5.84; N, 9.03; mol. wt., 310. Found: C, 85.10; H, 5.92; N, 9.26; mol. wt., 307 (Rast).

Attempted isomerization of IIIa to IIa. A mixture of 0.1 g. of IIIa and 0.1 g. of 5% palladium-on-carbon in 25 ml. of xylene was heated under reflux for 48 hr. The solution was filtered and the xylene was evaporated. The residue was identified as IIIa by melting point, mixed melting point, and ultraviolet spectrum. No other compound was found.

o-Xylylene di(2,4-xylyl) ketone (Vb). The Friedel-Crafts reaction was carried out in a manner similar to that described for the synthesis of Va. The product, after two recrystallizations from petroleum ether, was obtained in 35% yield, m.p. 81–82°.

Anal. Calcd. for $C_{26}H_{26}O_2$: C, 84.29; H, 7.07. Found: C, 84.17; H, 6.87.

3,8-Di(2,4-xylyl)-1,2-diaza-5,6-benzo-2,5,8-cyclooctatriene (IIIb). The procedure was adopted from that described by van der Zanden and DeVries.[19] A solution of 18 g. of potassium acetate in 68 ml. of boiling alcohol was added to a hot solution of 9 g. of hydrazine dihydrochloride in 32 ml. of water and 45 ml. of alcohol. After cooling the reaction mixture, the solution was filtered and added to a suspension of 10 g. of Vb in 320 ml. of alcohol. The mixture was heated under reflux for 6 hr. One half of the alcohol was distilled, and the remaining solution was diluted with water and extracted with ether. The ether solution was washed and dried, and the ether was evaporated. The residue was a brown semisolid, wt. 10 g. Three grams of this material was dissolved in 10 ml. of benzene and adsorbed on 100 g. of neutral alumina. Elution of the column with 3:2 hexane-ether gave pale yellow crystals which were recrystallized from ether-hexane, m.p. 156–157.5°, wt. 0.43 g. (14%). For analysis a sample was recrystallized and gave colorless needles, m.p. 158–159°. The ultraviolet spectrum showed a maximum at 260 mμ, ϵ 19,200 (95% ethanol). The infrared spectrum showed no bands in the N—H or C=O regions.

Anal. Calcd. for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.65; mol. wt. 366. Found: C, 84.97; H, 6.89; N, 7.46; mol. wt., 384 (Rast).

Attempted isomerization of 3,8-di-(2,4-xylyl)-1,2-diaza-5,6-benzo-2,5,8-cyclooctatriene (IIIb). A mixture of 0.1 g. of V and 0.1 g. of 5% palladium-on-charcoal in 25 ml. of xylene was heated under reflux for 18 hr. Filtration and removal of the solvent gave good recovery of V, identified by melting point and mixed melting point. No other product was found.

Molecular orbital calculations. In each case the matrix was formulated from the integrals in the usual way[4] and diagonalized with the aid of an IBM 650 computer using a standard matrix diagonalization program. The total π energies and resonance energies were calculated from the eigen values in each case in the usual way. Since the physical systems of interest if they existed, would very likely be nonplanar, calculations of electron densities, bond orders, and free valence did not seem meaningful, and were not carried out.

DETROIT 2, MICH.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, INDIANA UNIVERSITY]

Ortho-Substituted 2-Phenylquinolines[1]

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Received October 9, 1959

A series of 2-(*o*-halophenyl)quinolines (X = F, Cl, or Br) was prepared for the purpose of a preliminary investigation of hindered rotation. *o*-Haloacetophenones and -propiophenones were subjected to the Pfitzinger reaction to give 2-(*o*-halophenyl)cinchoninic acids and the corresponding 3-methyl compounds. Using *o*-halophenacyl acetates in the Pfitzinger reaction, 2-(*o*-halophenyl)-3-hydroxycinchoninic acids were obtained. The cinchoninic acids were decarboxylated to the corresponding 2-(*o*-halophenyl)quinolines which were, in turn, converted to the methiodides. An attempt was made at resolution by conversion of some of the methiodides to diastereoisomeric camphor sulfonates but no separation could be demonstrated. A comparison of the ultraviolet spectra of the methiodides of the 2-(*o*-halophenyl)quinolines and the corresponding ones with a methyl group in the 3-position did not show any differences which could be used to indicate hindered rotation.

Hindered rotation in the properly substituted biaryls and in a variety of other molecules has been a well established fact for a long time. The first attempt at the resolution of a heterocyclic-containing biaryl, 3-(2′-nitrophenyl)indole-2-carboxylic acid by Kermack and Slater.[3] Adams and students[4,5] resolved compounds such as *N*-(2′-carboxyphenyl)-2,5-dimethylpyrrole-3-carboxylic acid and *N,N′*-(2,2′,5,5′-tetramethyl)bipyrrole-3,3′-dicarboxylic acid but a substance without the hindering *ortho* groups, such as *N*-(3-carboxyphenyl)-2,5-dimethylpyrrole-3-carboxylic acid[6] could not be resolved. More recently, Webb[7] isolated one of the optical antipodes of 2,2′-(*N,N′*,3,3′,5,5′-hexamethyl)bipyrrole-4,4′-dicarboxylic acid. Biaryls in the furan series, such as 3-(2′-nitrophenyl)-2,5-dimethylfuran-4-carboxylic acid, have been separated into its optical isomers by Khawam and Brown.[8] Owen and Nord[9] have resolved biaryls such as 2-(2′-methyl-6′-nitrophenyl)thiophene-3-carboxylic acid as well as tetra *ortho*-substituted bithienyls.

Many of the earlier attempts at isolation of optically active biaryls in the pyridine series were unsuccessful[10–12]; 6,6′-diphenyl-3,3′-bipyridyl-2,2′,-4,4′-tetracarboxylic acid[13] was resolved but it racemized rapidly. Breckenridge and co-workers[14] have reported more recently the successful resolution of compounds such as *N*-methyl-2-(2′-carbomethoxyphenyl)-3-carbomethoxypyridinium iodide and *N,N′*-dimethyl-3,3′-dicarbomethoxy-2,2′-bipyridinium diiodide.[15] There has been some investigation in the biquinolines. Bell and Morgan[16] tried the resolution of 8,8′-biquinoline and Crawford and Smyth[17] actually resolved 4,4′- and 5,5′-biquinoline. The hindrance to coplanarity in these examples with attributed to factors other than the size of the atoms. Similar resolutions have also been done in the biisoquinoline series.[18]

It was the purpose of this research to synthesize some arylquinolines having bulky groups in *ortho* positions and do a preliminary study of the resolution of some of these. The 2-arylquinolines were chosen because synthesis appeared to be simpler through either a Conrad-Limpach reaction or the Pfitzinger reaction or even by alkylation in the *alpha* position by a lithium aryl. After some preliminary work the Pfitzinger reaction seemed to offer the best method. The prerequisite *o*-haloaceto- and *o*-halopropiophenones were prepared essentially according to the procedure of Lutz.[19] The phenacyl acetates were obtained by the action of potassium acetate upon the phenacyl halides. The methyl phenacyl ethers were not used as the preparation of these was not highly successful. The Pfitzinger reaction proceeded smoothly with the phenacyl acetates and decarboxylation[20] of the cinchoninic

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acids offered no difficulty. However, the Pfitzinger reaction was unsuccessful with *o*-nitropropiophenone. The 3-methoxy-2-(*o*-halophenyl)quinolines were more conveniently prepared by methylation of the corresponding 3-hydroxy compounds. Except for the latter compounds, the methiodides were prepared by treatment of the quinoline compound with methyl sulfate and precipitation of the iodide by treatment of the aqueous methosulfate solution with potassium iodide.

On the basis of the accepted values for bond distances[21] used in the biphenyls, the *N*,3-dimethyl-2-(2′-chlorophenyl)quinolinium *d*-camphorsulfonate and the corresponding 3′-bromo- compound should have been resolvable. The overlap or hindrance value should be 0.22 Å for the 2′-chloro and 0.35 Å for the 2′-bromo compound. However, if interatomic distances are shorter as claimed by Hillemann,[22] or if one used the more generally accepted values, then the 2′-chloro compound would give no overlap while the 2′-bromo compound would give a 0.12 Å interference.

From the work on the hindered phenylfurans,[8] these substances seem to follow the biphenyls closely, but the ease of racemization and/or the isolation of only one optically active form of a pair in the case of the hindered thiophenes,[9] the pyrroles,[7] and phenylpyridines[15] would indicate that the interatomic distances must be different or the electron-releasing effect may allow coplanarity of the aryl rings.

It has been reported by Pickett, Walter, and France,[23] Rodebush,[24,25] and others that biphenyls exhibiting hindrance due to bulky groups in the *ortho* positions have ultraviolet spectra like that of the simple substituted benzene, while biphenyls in which free rotation occurs have different ultraviolet spectra. 2,2′,4,4′-6,6′-Hexamethylbiphenyl has an ultraviolet spectra like that of mesitylene while 4,4′-dimethylbiphenyl has a spectrum different from that of toluene. This is explained on the basis that in the latter biphenyl, the aromatic rings can become coplanar to allow reasonance between them while in the hindered biphenyl, the rings cannot become coplanar; therefore, the spectra are not altered because of resonance between the rings. Examples of this in the heterocyclic series have been reported. It has been shown that the ultraviolet spectra of 4,4′- and 5,5′-biquinoline[17] is like that of quinoline. Jean and Nord[26] found that the spectrum of 3-(2-methyl-6-nitrophenyl)-2,5-dimethylthiophene-4-carboxylic acid was similar to that of a composite of *m*-nitrotoluene and 2,5-dimethyl-3-thenoic acid while that of 3,3′,5,5′-tetranitro-2,2′-bithienyl was not like that of 3,5-dinitrothiophene.

With the above in mind, the ultraviolet spectra of a series of arylquinolines were studied. The spectra of the methiodides of 2-(2′-halophenyl)-quinolines, which should show no hindrance, were the same as for the methiodides of 3-methyl-2-(2′-halophenyl)quinolines. On the basis of this observation, even *N*,3-dimethyl-2-(2′-bromophenyl)quinolinium iodide did not show hindrance.

EXPERIMENTAL[27]

o-Fluorophenacyl bromide, o-chlorophenacyl bromide, and o-bromophenacyl bromide were prepared by the customary method[19] of bromination of the corresponding acetophenone. The 2,4-dinitrophenylhydrazone derivatives of these are summarized in Table I. The *phenacyl bromides* were converted to the *acetates* by the conventional procedure. These are summarized in Table II and the 2,4-dinitrophenylhydrazones in Table I.

TABLE I

2,4-DINITROPHENYLHYDRAZONE DERIVATIVES

$$o\text{-}XC_6H_4C(=NNHC_6H_3(NO_2)_2)CH_2Y$$

X	Y	M.P., °	Formula	Analysis, % Calcd.	Found
F	Br	178–179	$C_{14}H_{10}BrFN_4O_4$	14.11[a]	14.39
Cl	Br	178–179	$C_{14}H_{10}BrClN_4O_4$	27.89[b]	27.75
Br	Br	174–175	$C_{14}H_{10}Br_2N_4O_4$	34.89[b]	34.81
F	CH_3CO_2	179–180	$C_{16}H_{13}FN_4O_6$	14.89[a]	15.14
Cl	CH_3CO_2	167–168	$C_{16}H_{13}ClN_4O_6$	14.27[a]	14.34
Br	CH_3CO_2	164–165	$C_{16}H_{13}BrN_4O_6$	18.28[b]	18.50

[a] Nitrogen. [b] Halogen.

TABLE II

ACETATE DERIVATIVES

$$o\text{-}XC_6H_4COCH_2O_2CCH_3$$

X	Yield, %	B.P., ° Mm.	Formula	Analysis, % Calcd.	Found
F	48	100 (0.1 mm.)	$C_{10}H_9FO_3$	C, 61.22	61.51
				H, 4.62	5.29
Cl	62	88 (0.05 mm.)	$C_{10}H_9ClO_3$	Cl, 16.67	16.70
Br	45	135–136 (0.1 mm.)	$C_{10}H_9BrO_3$	Br, 31.09	31.12

2-(2′-Fluorophenyl)-3-hydroxycinchoninic acid. To a refluxing solution of 100 ml. of 6*N* potassium hydroxide, 60 ml. of ethyl alcohol, and 9 g. (0.061 mole) of isatin was added dropwise a solution of 11 g. (0.056 mole) of *o*-fluorophenacyl acetate in 100 ml. of ethyl alcohol. After refluxing the solution for 9 hr., 150 ml. of distillate was removed and the residue was poured into a slurry of 300 g. of ice and 70 ml. of

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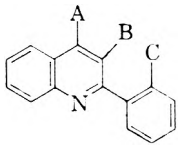
(27) Microanalyses performed by Miss Joanna Dickey of this department.

TABLE III

CINCHONINIC ACIDS AND QUINOLINES



A	B	C	Yield, %[a]	M.P., °	Formula	Halogen, % Calcd.	Halogen, % Found
CO_2H	H	F	63[b]	236 (dec.)	$C_{16}H_{10}FNO_2$	[c]	
$CO_2C_2H_5$	H	F	[b]	56.5–57	$C_{18}H_{14}FNO_2$	[d]	
H	H	F	40	[f]	$C_{15}H_{10}FN$	[e]	
CO_2H	CH_3	Cl	84[g]	310 (dec.)	$C_{17}H_{12}ClNO_2$	11.91	11.69
$CO_2C_2H_5$	CH_3	Cl	[h]	67–68	$C_{19}H_{16}ClNO_2$	10.88	10.81
H	CH_3	Cl	74[h]	89–90	$C_{16}H_{12}ClN$	13.97	13.66
CO_2H	CH_3	Br	78[g]	320 (dec.)	$C_{17}H_{12}BrNO_2$	23.36	22.96
$CO_2C_2H_5$	CH_3	Br	[h]	79–80	$C_{19}H_{16}BrNO_2$	21.59	21.60
H	CH_3	Br	33[i]	83.5–84.5	$C_{16}H_{12}BrN$	26.80	26.65
CO_2H	H	Cl	82[j]	266 (dec.)	$C_{16}H_{10}ClNO_2$	12.50	11.88
$CO_2C_2H_5$	H	Cl	[h]	81.5–82	$C_{12}H_{14}ClNO_2$	11.37	11.44
H	H	Cl	58[i]	79.5–80	$C_{16}H_{10}ClN$	14.79	14.72
CO_2H	H	Br	67[b]	240 (dec.)	$C_{16}H_{10}BrNO_2$	24.35	24.07
$CO_2C_2H_5$	H	Br	[b]	78.5–79	$C_{18}H_{14}BrNO_2$	22.43	22.57
H	H	Br	49[i]	72–73	$C_{15}H_{10}BrN$	28.13	28.25
CO_2H	OH	Cl	34[b,g]	204 (dec.)	$C_{16}H_{10}ClNO_2$	11.83	11.72
$CO_2C_2H_5$	OH	Cl	[b]	123–124	$C_{18}H_{14}ClNO_3$	10.79	11.05
H	OH	Cl	74[b]	232–233	$C_{13}H_{10}ClNO$	13.87	13.88
CO_2H	OH	Br	13[b]	205 (dec.)	$C_{16}H_{10}BrNO_3$	23.22	22.88
$CO_2C_2H_5$	OH	Br	[b,h]	135.5–136.5	$C_{18}H_{14}BrNO_3$	21.24	21.32
H	OH	Br	64[b]	244–245	$C_{15}H_{10}BrNO$	26.63	26.57
H	OCH_3	Cl	29[k]	125–125.5	$C_{16}H_{12}ClNO$	13.15	13.26
H	OCH_3	Br	40[b]	126–127	$C_{16}H_{12}BrNO$	25.44	25.21
Cl	Br	H	81[l]	134–135	$C_{15}H_9BrClN$	36.23	36.08
CH_3O	Br	H	45[m]	142–143	$C_{16}H_{12}BrNO$	25.44	25.82
HO	H	Br	20[b]	245–246	$C_{15}H_{10}BrNO$	26.62	26.67
Cl	H	Br	88[m]	140.5–141	$C_{15}H_9BrClN$	36.23	36.56
HO	Br	Br	53[m,n]	317–318	$C_{15}H_9Br_2NO$	42.32	42.57
Cl	Br	Br	75[m]	148–149	$C_{15}H_8Br_2ClN$	49.12	49.28

[a] Solvent for recrystallization. [b] Aqueous ethyl alcohol. [c] *Anal.* Calcd.: N, 5.24. Found: N, 5.36. [d] *Anal.* Calcd.: N, 4.74. Found: N, 4.82. [e] *Anal.* Calcd.: N, 6.38. Found: N, 6.48. [f] B.p., 127–129° at 0.02 mm.; n_D^{23} 1.6624. [g] Methyl cellosolve. [h] Aqueous acetone. [i] Petroleum ether (b.p. 30–60°). [j] Aqueous methyl cellosolve. [k] Aqueous methyl alcohol. [l] Acetone–ethyl alcohol. [m] Ethyl alcohol. [n] Nitromethane.

concd. hydrochloric acid. The yield of somewhat brown colored solid was 14.5 g. (91%) which melted with decomposition at 195°. Recrystallization from 70% ethyl alcohol gave a golden yellow colored solid which melted with decomposition at 197°.

Anal. Calcd. for $C_{16}H_{10}FNO_3$: N, 4.95. Found: N, 5.27.

The *ethyl ester*, prepared by direct esterification, was recrystallized from 50% ethyl alcohol; m.p. 109–109.5°.

Anal. Calcd. for $C_{18}H_{14}FNO_3$: N, 4.50. Found: N, 4.62.

2-(2'-Fluorophenyl)-3-hydroxyquinoline. To 50 ml. of boiling nitrobenzene was added 3 g. (0.011 mole) of 2-(2'-fluorophenyl)-3-hydroxycinchoninic acid; the solution was allowed to boil for about 5 min. After the solution cooled, it was extracted with three 50-ml. portions of 10% potassium hydroxide solution; the combined alkaline solution was extracted with two 75-ml. portions of ether. The alkaline solution was acidified with concd. hydrochloric acid to *p*H 6. The precipitated solid was collected by filtration and was recrystallized from 55% ethyl alcohol. The yield of tan colored needles was 2.25 g. (88%); m.p. 206–209°. Three recrystallizations from dilute ethyl alcohol raised the melting point to 209.5–210.5°.

Anal. Calcd. for $C_{15}H_{10}FNO$: N, 5.86. Found: N, 5.86.

N-Methyl-2-(2'-fluorophenyl)-3-methoxyquinolinium iodide. A solution of 0.86 g. (0.0036 mole) of 2-(2'-fluorophenyl)-3-hydroxyquinoline and 1 g. of sodium methoxide in 50 ml. of absolute methanol was refluxed for 22 hr. with 5 ml. of methyl iodide; then 25 ml. of distillate was removed. Absolute ether (200 ml.) was added to the residual liquid. The solid (0.51 g.) was recrystallized twice from absolute ethyl alcohol to give a yellow-orange substance which melted, with decomposition, at 187°.

Anal. Calcd. for $C_{17}H_{15}FINO$: I, 32.11. Found: I, 32.53.

2-(2'-Fluorophenyl)-3-methoxyquinoline. The ether-methanol filtrate from the isolation of the above methiodide was evaporated to 10 ml., then 100 ml. of water containing 2 g. of sodium thiosulfate was added to this residual solution. The solution was heated to boiling, then cooled, and the solid was collected by filtration. The substance was recrystallized from 70% ethyl alcohol, giving 0.46 g. of fine cream colored needles, m.p. 142–143°.

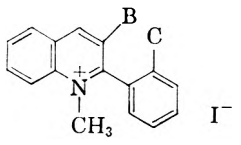
Anal. Calcd. for $C_{16}H_{12}FNO$: N, 5.53. Found: N, 5.65.

The other 2-(2'-halophenyl)-3-hydroxycinchoninic acids and 2-(2'-(halophenyl)-3-hydroxy- and -3-methoxyquinolines are summarized in Table III. The other 2-(2'-halophenyl)-3-methoxyquinoline methiodides are summarized in Table IV.

N,3-Dimethyl-2-(2'-fluorophenyl)quinolinium iodide. A solution of 1.5 g. of 2-(2'-fluorophenyl)-3-methylquinoline in 10 ml. of dimethyl sulfate was heated at 110° for 2 hr. After the solution cooled to room temperature, 40 ml. of absolute ether was stirred into it and the solid was removed

TABLE IV

METHIODIDE DERIVATIVES



B	C	Yield, %[a]	M.P., °	Formula	Halogen,[e] % Calcd.	Found
CH_3	Cl	81[b]	200–201	$C_{17}H_{15}ClIN$	41.04	40.91
CH_3	Br	92[b]	200–201	$C_{17}H_{15}BrIN$	46.99	46.56
OCH_3	Cl	56[c,d]	200 dec.	$C_{17}H_{15}ClINO$	39.44	39.02
OCH_3	Br	46[c,b]	194 dec.	$C_{17}H_{15}BrINO$	45.34	45.07
H	F	85[b]	198 dec.	$C_{16}H_{13}FIN$	34.75[f]	34.96[f]
H	Cl	70[d]	199 dec.	$C_{16}H_{13}ClIN$	42.55	42.33
H	Br	90[b]	213 dec.	$C_{16}H_{13}BrIN$	48.54	48.63

[a] Solvent for recrystallization. [b] Ethyl alcohol. [c] Prepared by the sodium methoxide–methyl iodide method. [d] Water. [e] Combined halogen content. [f] Iodine only.

by filtration. The crystalline methosulfate was washed with absolute ether. The solid was mixed with 25 ml. of water; then it was filtered and the filtrate was poured, with stirring, into a solution of 6 g. of potassium iodide in 10 ml. of water. The yellow colored solid was collected and after drying, it was recrystallized from absolute ethyl alcohol. The yield of deep yellow colored needles was 2.1 g. (85%), m.p. 240° (dec.).

Anal. Calcd. for $C_{17}H_{15}FIN$: I, 33.47. Found: I, 33.74.

The other methiodides are summarized in Table IV.

2-(2′-Chlorophenyl)-3-quinolinecarboxylic acid.[28] A solution of 38 g. (0.15 mole) of 2-(2′-chlorophenyl)-3-methylquinoline in 800 ml. of 30% sulfuric acid contained in a 3-l. three necked flask fitted with a stirrer, condenser, and a dropping funnel was heated to boiling. A 2-g. sample of manganese dioxide was added and a solution of 80 g. of chromic anhydride in 400 ml. of 30% sulfuric acid was added over a period of 2 hr. The refluxing was continued for 2 hr. The reaction mixture was poured into 18 l. of hot water. After it cooled somewhat, the solution was made alkaline with concd. ammonia water, then filtered through a sintered glass funnel, and finally evaporated to about 3 l. volume. The solution was acidified with acetic acid and the solid was collected. The yield was 24.5 g. (58%), m.p. 269° dec. The melting point could not be raised by recrystallization from 60% aqueous methyl cellosolve.

Anal. Calcd. for $C_{16}H_{10}ClNO_2$: Cl, 12.50. Found: Cl, 12.22.

The *ethyl ester* was prepared through the intermediate acid chloride and was recrystallized from aqueous acetone; m.p. 123–124°.

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: Cl, 11.37. Found: Cl, 11.45.

2-(2′-Chlorophenyl)-3-quinolinecarboxyhydrazide. A solution of 10.4 g. (0.033 mole) of ethyl 2-(2′-chlorophenyl)-3-quinolinecarboxylate and 3 g. (0.094 mole) of freshly dried hydrazine in 2 ml. of absolute ethyl alcohol was refluxed for 16 hr. The solution was poured into 150 ml. of 2*N* hydrochloric acid, and then filtered and the filtrate made alkaline with sodium carbonate. The solid was collected. The crude hydrazide (8.3 g., 87%) melted at 200–204°. It was recrystallized from toluene; m.p. 205.5–206.5°.

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: N, 14.12. Found: N, 14.29.

Ethyl N-[2-(2′-chlorophenyl)-3-quinolyl]urethan. A solution of 2.8 g. (0.0094 mole) of 2-(2′-chlorophenyl)-3-quinolinecarboxyhydrazide in 80 ml. of 1*N* hydrochloric acid was cooled to −4° and, while stirring, a solution of 2.1 g. of sodium nitrite in 30 ml. of water was added over a period of 20 min. After standing at room temperature for 10 min., the solid was collected and then was refluxed with 80 ml. of absolute ethyl alcohol until there was no further evolution of gas. Bright yellow crystals separated when the solution cooled. The crude substance (2 g., 65%), which melted at 150–152°, was recrystallized from ethyl alcohol yielding short needles which melted at 154.3–154.7°.

Anal. Calcd. for $C_{18}H_{16}ClN_2O_2$: N, 8.58. Found: N, 8.73.

The *methyl urethan* was obtained in 73% yield by an analogous procedure; it was recrystallized from methyl alcohol, m.p. 158–158.5°.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$: N, 8.96. Found: N, 9.18.

2-(2′-Chlorophenyl)-3-aminoquinoline. A solution of 26.5 g. (0.085 mole) of methyl *N*-[2-(2′-chlorophenyl)-3-quinolyl]urethan was refluxed for 24 hr. with 250 ml. of concd. hydrochloric acid. Then it was concentrated in a vacuum to a small residue. The residue was diluted with 250 ml. of boiling water then made alkaline with sodium carbonate. The solid was collected, dried, and refluxed with 2 l. of ligroin (b.p. 63–99°). The solution was filtered and concentrated to one-half its volume, yielding cream colored needles (15 g., 69%) which melted at 99–101°. Recrystallization from ligroin raised the melting point to 101–102°.

Anal. Calcd. for $C_{15}H_{11}ClN_2$: N, 11.00. Found: N, 11.13.

The *acetyl* derivative was recrystallized from dilute alcohol, m.p. 171.5–172.5°.

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: N, 9.44. Found: N, 9.58.

The *benzoyl* derivative was recrystallized from ethyl alcohol, m.p. 150.5–151.5°.

Anal. Calcd. for $C_{22}H_{15}ClN_2O$: N, 7.81. Found: N, 8.04.

The *picrate* was recrystallized from absolute ethyl alcohol, m.p. 188–189°.

Anal. Calcd. for $C_{21}H_{14}ClN_5O_7$: N, 14.48. Found: N, 14.44.

2,(2′-Chlorophenyl)-3-chloroquinoline.[28] A stirred solution of 15 g. (0.06 mole) of 2-(2′-chlorophenyl)-3-aminoquinoline in 300 ml. of concd. hydrochloric acid was cooled to −14° and was diazotized by the dropwise addition of 7.2 g. of potassium nitrite in 60 ml. of water. The solution was kept at −15° for 1.5 hr., then warmed to 25° for 30 min., heated quickly to 80°, and cooled rapidly to 25° again. This solution was poured into 420 g. of potassium carbonate in 500 ml. of water. The solid was collected by filtration, extracted with 10% potassium hydroxide, and recrystallized from absolute ethyl alcohol. The white solid (4.3 g., 26%), which melted at 143–145°, on further recrystallization melted at 147–147.5°.

Anal. Calcd. for $C_{15}H_9Cl_2N$: Cl, 25.87. Found: Cl, 25.76.

N,3-Dimethyl-2-(2′-chlorophenyl)quinolinium d-camphorsulfonate. A solution of 3.96 g. (0.01 mole) of *N*,3-dimethyl-

(28) H. John and H. Ottawa, *J. prakt. Chem.*, **131**, 266, 354 (1931).

2-(2′-chlorophenyl)quinolinium iodide in 50 ml. of hot 50% ethyl alcohol was added to a solution of 3.4 g. (0.01 mole) of silver *d*-camphorsulfonate dissolved in 20 ml. of 50% ethyl alcohol. The hot solution was filtered to remove the silver iodide and the filtrate was evaporated to dryness. The residue was dissolved in 50 ml. of chloroform, 200 ml. of absolute ether was added, and the solution was allowed to stand overnight in a refrigerator. The white solid (2.9 g.) melted at 188–190°. After recrystallization from absolute ether-chloroform and from acetone, the white granular solid melted at 190–191°.

Anal. Calcd. for $C_{27}H_{30}ClNO_4S$: C, 64.84; H, 6.05; S, 6.41; Cl, 7.09. Found: C, 64.39; H, 5.95; S, 6.37; Cl, 7.08.

All of the fractions in recrystallization of this substance gave the same optically inactive iodide when the aqueous solution of the *d*-camphorsulfonate salt was treated with potassium iodide. Also prepared by the same method were the *N*,3-dimethyl-2-(2′-chlorophenyl)quinolium *d*-α-bromo-π-camphorsulfonate, $[\alpha]_D^{28} = +47.3°$, and *N*,3-dimethyl-2-[2′-bromophenyl]quinolinium *d*-α-bromo-π-camphorsulfonate, $[\alpha]_D^{28} = +45.7°$, but it could not be demonstrated that either of these yielded diastereomers and no optical activity was demonstrated when they were reconverted to the iodides.

Ethyl o-bromobenzoylacetate (b.p. 116° at 0.4 mm.) was prepared from *o*-bromobenzoyl chloride and ethyl acetoacetate in a 41% yield using the method described for ethyl *p*-bromobenzoylacetate.[29] The 2-(*o*-bromophenyl)quinolines prepared from it are summarized at the bottom of Table III.

BLOOMINGTON, IND.

(29) C. E. Kaslow and S. J. Nix, *Proc. Indiana Acad. Science*, **61**, 121 (1952).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

9-Vinylacridine: Preparation and Some Reactions of It and Related Substances of Possible Application in the Synthesis of Acridine Amino Alcohols

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Received January 4, 1960

Dehydrobromination of 9-α-bromoethylacridine gives 9-vinylacridine (III). The structure is confirmed by reduction of 9-ethylacridane. 9-α-Bromoethylacridine and 9-β-bromoethylacridine as well as III react with piperidine to give 9-β-piperidinoethylacridine.

Some time ago we reported[1] the preparation of acridine amino alcohols of type I. We also wished to prepare II and IIa, but the effort failed because we were unable to prepare the 9-metalated acridine derivatives necessary to react with the appropriate amino aldehydes.[2] The reverse procedure (in which an amino organometallic compound reacts with acridine-9-aldehyde [V]) cannot be applied here as one- and two- carbon amino organometallic compounds cannot be prepared.[3]

There are other approaches to this synthetic problem, however, and it is the purpose of this paper to present a partial investigation of one of them, namely, the route employing 9-vinylacridine (III). The results presented here are incomplete. We have, however, discontinued this work some time ago, and, as there is no likelihood of its being resumed, we would like to present the results at this time.

In 1936, O. Eisleb reported[4] a number of acridine derivatives which might lead to the preparation of II. Acridine-9-carboxyaldehyde (V) was condensed with nitromethane to yield XIV. The latter could not be reduced to the desired amino alcohol. He also prepared 9-acetylacridine (XV), which was subsequently converted to both XVI and XVII. He was unable to convert either of these to the desired amino alcohol.

In 1940, Braz and Gortinskaya[5] reported the conversion of acridine-9-carboxylic acid to XVI *via* the diazo ketone. XVI was mentioned as an intermediate for the synthesis of possible antimalarial pharmaceuticals, but as none of its reactions were described, it is reasonable to assume that these workers encountered the same difficulty as did Eisleb. As Eisleb did not characterize XVI, it is not possible to compare his substance with that of the Russian scientists.

Subsequently, Braz and Kore[6] studied the reaction of XVI with piperidine and with diethyl-

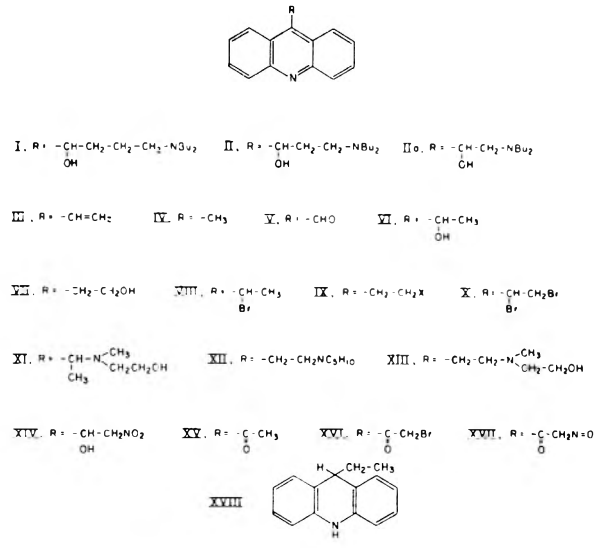
(1) T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 533 (1949).

(2) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953).

(3) Wittig and Wetterling (*Annalen*, **557**, 193–201 (1947)) report that ylides such as $(CH_3)_3N^+-CH_2^-$ behave like organometallic compounds and add to carbonyl compounds. We have not investigated the application of ylides to this problem. The writer has also been informed (personal communication from Dr. E. M. Fry of this laboratory) that diethylaminomethyl methyl ether reacts with lithium metal to yield 1,2-bisdiethylaminoethane. This is a coupling product of the expected diethylaminomethyllithium, reminiscent of that encountered in the reaction of lithium with benzyl halides. Thus the dialkylaminomethyl lithium compound probably may have a transitory existence and might be trapped.

(4) O. Eisleb, *Medizin und Chemie*, Band III, Bayer, Leverkusen a.Rh., 1936, p. 41.

(5) G. I. Braz and T. V. Gortinskaya, *J. Gen. Chem. (USSR)*, **10**, 1751 (1940); *Chem. Abstr.*, **35**, 4025[8].



amine. No amino ketone was isolated, but they were able to recover acridone and XV, along with a large amount of amine hydrobromide. Speculations upon possible mechanisms for these reactions leads one to the conclusion that the presence of the 9-α-keto group is perhaps the feature of XVI, which is responsible for these untoward results. Unfortunately, the facile reduction of acridine itself discourages one from attempting to transform XVI into the corresponding carbinol, as has been done[7] with other α-halo ketones.

One very attractive synthesis of amino alcohols consists of the addition of secondary amines to epoxides. As the latter compounds may be prepared by the epoxidation of vinyl compounds, we decided to investigate the preparation and reactions of 9-vinylacridine (III). Perhaps the most logical approaches to III involve the dehydration of 9-α- (and β)-ethanols (VI and VII), and dehydrohalogenation of the derived 9-α- and β-haloethylacridines (VIII and IX). The first and third of these materials appeared to be the most attractive. All four were prepared by the methods described by Eisleb.

When VIII was treated rather gently with *t*-butanolic potassium hydroxide, we obtained pale yellow parallelograms of 9-vinylacridine (III) which melted at 85–87°. Hydrogenation of III yielded a tetrahydroderivative identical with the 9-ethylacridane (XVIII) obtained by an entirely unrelated sequence of reactions. Moreover, an addition reaction with piperidine, which will be discussed later in this paper, lends strong confirmatory evidence for the proposed structure. A quinuclidine-like rather than a vinyl configuration seems unlikely.

9-Vinylacridine resists ozonization, adds bromine to give the dibromide (X), and appears to add the elements of hydrogen chloride when treated with hypochlorous and hydrochloric acid. As would be expected of a compound of this structure, III behaves as an active vinyl monomer, and polymerizes readily with the production of resinous material, either on standing or when the free base is regenerated from its salts. An acetone solution of the perchlorate similarly undergoes polymerization. While considerable purification may be effected by sublimation and crystallization from petroleum ether, it is difficult to obtain III in a state of analytical purity. However, a sample of the base which had been treated with *t*-butyl hypochlorite followed by dibutylamine (in an abortive attempt to prepare the chlorhydrin and the amino alcohol), yielded III analytically pure, melting at 82–85°. Of the salts, the perchlorate is a suitable derivative, melting at 221–222° dec., while with picric acid one obtains (presumably) the picrate, which decomposes at 188°.

Of the remaining three methods proposed above for the synthesis of III, the dehydration of VII was not investigated at all, and the dehydrohalogenation of IX (x = chlorine) only in one experiment. The dehydration of VI led to a material of undetermined composition which showed a different melting point from that of III, although its analyses and salts suggest a similar or identical composition.

As alluded to above, 9-vinylacridine with piperidine yielded an adduct which subsequently proved to be XII, identical with the Mannich product obtained by Monti[8] from 9-methylacridine (IV), formaldehyde and piperidine hydrochloride. XII was also obtained by treatment of *either* VIII or IX[3] with piperidine. The reaction no doubt proceeds *via* III as an intermediate. Eisleb prepared a product which he formulated as XI by treating methylethanolamine with VIII. In the light of the present work, the true formulation of this product probably corresponds to XIII.

EXPERIMENTAL[9]

9-Methylacridine (IV) *and acridine-9-aldehyde* (V) were prepared as described previously.[1]

9-α-Hydroxyethylacridine (VI) was prepared by the action of methyllithium on V; m.p. 178–180°. Eisleb[4] reports m.p. 178–180° for this compound.

9-β-Hydroxyethylacridine (VII) was obtained by the action of formaldehyde on IV according to Eisleb.[4] When crystallized from benzene, it crystallized as white warts at temperatures above 40° and as yellow needles below this temperature. Both forms melt at 154° and are interconvertible. Eisleb gives the m.p. 154°.

9-α- (and β-) Bromoethylacridines (VIII and IX) were prepared by the method of Eisleb.[4] As might be expected, these compounds could not be obtained in a state of analytical purity. The β-bromoethylacridine hydrobromide ap-

(6) G. I. Braz and S. A. Kore, *J. Gen. Chem. (USSR)*, **23**, 909–913 (1953); *Chem. Abstr.*, **48**, 3979[d].

(7) P. G. Stevens, O. C. W. Allenby, and A. S. Dubois, *J. Am. Chem. Soc.*, **62**, 1424 (1940).

(8) L. Monti, *Gazz. Chim. Ital.*, **63**, 724 (1933); *Chem. Abstr.*, **28**, 2357[3].

(9) All melting points are corrected.

parently list a little hydrogen bromide when recrystallized from water.

Anal. Calcd. for $C_{15}H_{13}NBr_2$, m.w. 367.09; C, 49.07; H, 3.57. Found: C, 49.35, 49.60; H, 3.97, 3.90.

9-Vinylacridine (III). Warming 1 g. of VIII hydrobromide for 0.5 hr. on the steam bath with 25 ml. of a saturated solution of potassium hydroxide in *t*-butyl alcohol, and partitioning the cooled reaction mixture between water and ether gave III in the ether layer. The product was purified by sublimation and crystallization from petroleum ether (b.p. 30–60°), m.p. 85–87°, yield, 0.5 g. This material was not directly analyzed. However, material which was recovered from an attempted reaction with *t*-butyl hypochlorite followed by dibutylamine melted at 82–85°.

Anal. Calcd. for $C_{15}H_{11}N$, m.w. 205.25: C, 87.77; H, 5.40. Found: C, 87.53; H, 5.48.

The III perchlorate, quite insoluble in water or alcohol, may be crystallized from acetone by adding petroleum ether (b.p. 30–60°), m.p. 221–222° (rapid heating, darkens at 215°).

Anal. Calcd. for $C_{15}H_{12}NClO_4$, m.w. 305.72: C, 59.20; H, 3.96. Found: C, 59.07; H, 3.71.

Acetone solutions of this salt decompose on standing with the deposition of polymer but the base may be obtained quite pure by liberation from fresh solutions of the perchlorate.

Treatment of III with twice the theoretical amount of 1*M* bromine in acetic acid, followed by passing in hydrogen chloride, results in the immediate formation of a yellow crystalline precipitate of 9-α,β-dibromoethylacridine (X), m.p. 187–189°, (gassing, heated rapidly) which may be recrystallized from 75% acetone: 25% water, or from hydrochloric acid. The compound was vacuum dried 4 hr. at 76° prior to analysis.

Anal. Calcd. for $C_{15}H_{12}NBr_2Cl$, m.w. 401.55: C, 44.86; H, 3.01. Found: C, 45.10; H, 2.74.

If the drying were omitted the *sesquihydrate* was obtained.

Anal. Calcd. for $C_{15}H_{12}NBr_2Cl.1.5H_2O$: C, 42.03; H, 3.53. Found: C, 42.01; H, 3.74.

III promptly decolorizes solutions of potassium permanganate and bromine. It appears to resist ozonization, as a large amount of starting material may be recovered and aldehyde tests on the reaction mixture are negative. With picric acid, a *substance* is obtained which decomposes at 188–190° without melting. III appears to polymerize slowly when it is allowed to stand. A sample, m.p. 82–83°, after standing 4.5 days exposed to air melted at 83–86° with sintering at 81°. Treatment of III with water in the presence of *t*-butyl alcohol and base yields a material, m.p. 153–162°, which gives a strong melting point depression when mixed with VII.

After treatment of 1 mmole of III with 15 ml. of 0.14*N* monoperphthalic acid in ether, and the addition of 30 ml. of chloroform, the mixture was allowed to stand for 2 days; it yielded reddish brown crystals (from ether), m.p. 173–174°.

Anal. Calcd. for $C_{15}H_{13}ON$, m.w. 223.26: C, 80.69; H, 5.87. Found: C, 80.42, 80.56; H, 5.46, 5.49.

Treatment of the III from 1.0 g. of VIII hydrobromide with 5.0 ml. of 0.543*N* hypochlorous acid plus 2.0 ml. of hydrochloric acid for 45 min., yielded a complex mixture from which we isolated a base which was extracted from water by ether, m.p. 125° (from ether). This is perhaps a *chloroethylacridine.*

Anal. Calcd. for $C_{15}H_{12}NCl$, m.w. 241.72: C, 74.53; H, 5.00. Found: C, 74.64; H, 4.68.

Dehydration of VI was effected by heating with "naturcupfer C" copper bronze in a sublimation apparatus until an oil refluxed, then applying vacuum to sublime the product, which was purified as the *sulfate,* which darkens but does not melt by 270° (from ethanol or ethanol-ether).

Anal. Calcd. for $C_{15}H_{13}NSO_4$, m.w. 303.32: C, 59.39; H, 4.32. Found: C, 59.64; H, 4.37.

The *base* was obtained from the sulfate along with a certain amount of polymer, and was purified by sublimation and crystallized from petroleum ether (b.p. 30–60°); m.p. 108.2–109.4°. It was perhaps not analytically pure.[10]

Anal. Calcd. for $C_{15}H_{11}N$, m.w. 205.25: C, 87.77; H, 5.40. Found: C, 87.34, 87.21; H, 5.37, 5.11.

The material turns brown on standing. Treatment of the base with picric acid yields a substance which may be a *picrate hemihydrate,* m.p. 185–187° (from aqueous ethanol).

Anal. Calcd. for $C_{21}H_{14}N_4O_7 + 0.5H_2O$, m.w. 443.36: C, 56.89; H, 3.41. Found: C, 57.06; H, 3.51.

This base (from VI) is unsaturated to potassium permanganate. Attempted ozonization yielded a black tar which got hot on exposure to air. Considerable starting material, m.p. 108.3–109.1 was recovered, and aldehyde tests were negative. Attempted oxidation with chromic anhydride in glacial acetic acid led only to an extremely insoluble chromate salt, from which starting material could be recovered, m.p. 108°.

Preparation of 9-ethylacridane (XVIII). (*a*) *By hydrogenation of* III. A hydrogenation reaction of 1.0 g. of III (m.p. 87.5–88.5°) in 25 ml. of ethanol with 115 mg. of platinum oxide catalyst absorbed 275 ml. of hydrogen in 50 min. This is approximately the theoretical amount for two double bonds. The product, XVIII, was crystallized from petroleum ether (b.p. 30–60°) as beautiful white prisms, m.p. 112°.

Anal. Calcd. for $C_{15}H_{15}N$, m.w. 209.28: C, 86.08; H, 7.23. Found: C, 85.86; H, 7.24.

(*b*) *From diphenylamine and propionic anhydride.* Refluxing 50 g. of diphenylamine, 36 g. of propionic anhydride, and 35 g. of fused zinc chloride for 4 hr. led to 9-ethylacridine, m.p. 106–109°. Hydrogenation of the latter with platinum oxide catalyst in ethanol produced XVIII, m.p. 110–111.5°, undepressed upon admixture of material from (*a*).

Hydrogenation of VII (0.4 g.) with 40 mg. of platinum oxide catalyst in ethanol solution yielded a mixture of yellow prisms, m.p. 160–164°, and white prisms, m.p. 132.5–134°. The latter had the correct analysis for *9-β-hydroxyethylacridane.*

Anal. Calcd. for $C_{15}H_{15}ON$, m.w. 225.28: C, 79.97; H, 6.71. Found: C, 79.80; H, 6.81.

9-β-Chloroethylacridine, m.p. 112° was obtained when 1.4 g. of VII was let stand with a mixture of 0.5 ml. of thionyl chloride and 20 ml. of chloroform, then refluxed 1 hr., and the base liberated. As the base is heated, it fuses, then resolidifies to a yellow solid which melts at 228°.

Anal. Calcd. for $C_{15}H_{12}NCl$, m.w. 241.72: C, 74.55; H, 5.00. Found: C, 75.22; H, 5.05.

The base decomposed on standing. Treatment of the base with *t*-butanolic potassium hydroxide, according to the directions given for the preparation of III, yielded a substance, m.p. 75–80°, which is probably crude III.

9-β-Piperidinoethylacridine (XII). (*a*) *By addition of piperidine to* III. Freshly prepared III was heated overnight on the steam bath with excess piperidine. The excess piperidine was removed, leaving a brown oil which crystallized very readily upon adding acetone to pale yellow crystals, m.p. 134–136°. Repeated crystallization from acetone raised the m.p. to 137–138°.

Anal. Calcd. for $C_{20}H_{22}N$, m.w. 290.40: C, 82.71; H, 7.64. Found: C, 82.37, 82.36; H, 7.66, 7.66.

(*b*) *From* IV, *formaldehyde and piperidine.* Piperidinemethylol was prepared from 9.9 ml. of piperidine and 8.4 ml. of 36% formaldehyde, and diluted to a volume of 30 ml. with methanol. Three milliliters of this solution (0.01 mole) was added dropwise to a refluxing solution of 1.9 g. of IV in methanol. After a further 15 min. of refluxing the mixture was concentrated to dryness, washed with water, and the yellow XI crystallized from acetone, m.p. 135–136°. Monti[8] did not report the melting point of this material, but Eisleb[4] gives the value 137.5°. The hydrochloride melted at 171–173°. Monti reported the value as 169°.

(10) Acridine melts at 110° and the calculated analytical values are C, 87.12; H, 5.06.

(c) *From 9-α-bromoethylacridine* (VIII). Warming VIII hydrobromide on the steam bath with excess piperidine and washing the reaction mixture yielded the insoluble XI, m.p. 134–135°.

(d) *From 9-β-chloroethylacridine.* Following the procedure used by Eisleb with IX, we obtained pale yellow crystals of XI from acetone, m.p. 133°.

(e) *From 9-β-bromoethylacridine* (IX). Eisleb's procedure was repeated. The resultant XI melted at 135–136°.

By repeated crystallization, all of these XI specimens can be brought to melting point 135–137° and upon admixture with material from (a) no melting point depression is observed. With picric acid we obtained a material which sintered at 180° and melted at 218–220°. Monti reported the dipicrate to melt at 138–140°.

Acknowledgment. Microanalyses were performed by Betty Mount and Charles Kinser.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, UNIVERSITY OF CAIRO]

Thermochromism of Dixanthylenes. Reactions with Substituted Xanthones. III[1a]

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Received January 8, 1960

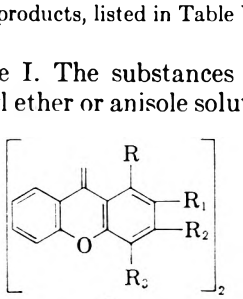
Substitution in dixanthylene (Ie) in position 1 and 1′, which hinders the planarity of the whole molecule, is detrimental to the development of thermochromic properties (Table I). Fission of the central ethylene linkage in dixanthylenes is brought about by the action of thionyl chloride followed by water to give the xanthone derivatives (Va–d) and by the action of sulfur at 270° to yield the corresponding xanthione derivatives (VI, Table III). The new xanthone derivative Ve, needed in this investigation has been synthesized. 1-Chloroxanthone (Va) condenses with aromatic thiols in the presence of potassium hydroxide to yield the corresponding arylmercapto derivatives (VIII, Table IV) which are oxidized readily to the corresponding sulfone derivatives (IX, Table IV). Photochemical dehydrogenation of 2-methylxanthene is effected by the action of Vb and/or Vg–h. 9-Phenyl-4-chloroxanthene (Xb) undergoes photochemical oxidation in sunlight in the presence of oxygen, yielding 4-chloro-9-phenylxanthyl peroxide (XIb). Reduction of substituted xanthones with lithium aluminum hydride and with metallic sodium and alcohol led to the formation of the reduction products, listed in Table V.

In continuation of the study of the constitutional changes in thermochromic substances,[1] we now have extended our previous investigations[1(a)] to show how substitution affects the thermochromic properties of dixanthylene (Ie) a strongly thermochromic substance. The crystals are colorless at liquid air temperature, turn blue-greenish on heating and the melt is deep blue-green. The results are shown in Table I. The substances were tested in boiling diphenyl ether or anisole solutions.

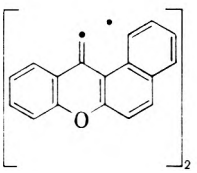
TABLE I

THERMOCHROMIC PROPERTIES

	R	R_1	R_2	R_3	
(a)	Cl	H	H	H	Very weakly thermochromic
(b)	CH_3	H	H	CH_3	Not thermochromic[1(a)]
(c)	CH_3	H	CH_3	H	Not thermochromic[1(a)]
(d)	Cl	H	H	CH_3	Not thermochromic[1(b)]
(e)	H	H	H	H	Strongly thermochromic[1(c)]
(f)	H	Br	H	H	Strongly thermochromic[1(a)]
(g)	H	Cl	H	H	Strongly thermochromic[1(b)]
(h)	H	CH_3	H	H	Strongly thermochromic
(i)	H	C_6H_5	H	H	Strongly thermochromic
(j)	H	H	H	Br	Strongly thermochromic[1(a)]
(k)	H	H	H	Cl	Strongly thermochromic[1(b)]
(l)	H	H	H	CH_3	Strongly thermochromic
(m)	H	CH_3	CH_3	H	Strongly thermochromic[1(a)]
(n)	H	CH_3	H	CH_3	Strongly thermochromic[1(a)]

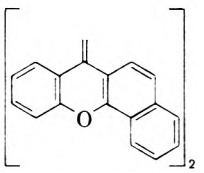


I



(Weakly thermochromic)

II



(Strongly thermochromic)

III

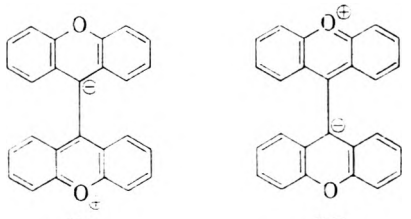
DISCUSSION

Recently, Schönberg, Mustafa, and Asker[1(d)] advanced a hypothesis that "in overcrowded molecules in which planarity is hindered, the degree of non-planarity changes with temperature. This is associated with the change of color, one reason being that resonance is related to planarity." Dixanthylenes, *e.g.*, Ie, a thermochromic compound, lose this property upon substitution at position 1 and 1′ (*cf.* Table I). The loss of the thermochromic properties is due to a constitutional change in I, overcrowding of the molecule to such a degree that planarity is hindered even at high

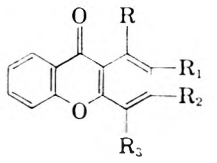
(1) (a) For part II *cf.* A. Mustafa, and M. E. D. Sobhy, *J. Am. Chem. Soc.*, **77**, 5124 (1955). (b) A. Schönberg, A. Mustafa, and M. E. D. Sobhy, *J. Am. Chem. Soc.*, **75**, 3377 (1953). (c) A. Schönberg and W. Asker, *J. Chem. Soc.*, 725 (1942). (d) A. Schönberg, A. Mustafa, and W. Asker, *J. Am. Chem. Soc.*, **76**, 4134 (1954).

temperatures.[2] In accordance with this conception is the lack of thermochromic properties of Ib–d and the weakly thermochromic properties of Ia and II since their molecules are much less overcrowded. From this, it has been concluded that the green forms of Ie and its analogs, "the colored molecules" have a greater degree of planarity; the experiments of thermochromic bianthrones have led Hirshberg, Loewenthal, Bergmann, and Pullman[3] to a similar conclusion.

Action of thionyl chloride on dixanthylenes. Dixanthylene shows remarkable behavior toward thionyl chloride, followed by the action of water.[1(c)] Fission of the central ethylene bond, which has single bond character (*cf.* IVa and IVb), occurs and xanthone is formed. We have now found that, analogously, the substituted xanthones (Va–d) are obtained by the action of thionyl chloride on the corresponding dixanthylenes followed by treatment with water.

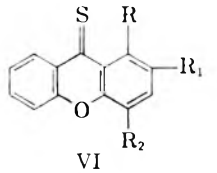


IVa IVb



Va. R = Cl; $R_1 = R_2 = R_3 = H$
b. R = H; $R_1 = CH_3$; $R_2 = R_3 = H$
c. R = H; $R_1 = C_6H_5$; $R_2 = R_3 = H$
d. $R = R_1 = R_2 = H$; $R_3 = CH_3$
e. $R = R_3 = CH_3$; $R_1 = R_2 = H$
f. $R = R_2 = CH_3$; $R_1 = R_3 = H$
g. $R = R_2 = H$; $R_1 = R_3 = CH_3$
h. $R = R_3 = H$; $R_1 = R_2 = CH_3$

Action of sulfur on dixanthylenes. Treatment of the corresponding dixanthylenes with sulfur at 270° for a few minutes effects fission of the central ethylene bond[1(a)] with the formation of the substituted xanthiones (VI; *cf.* Table III).

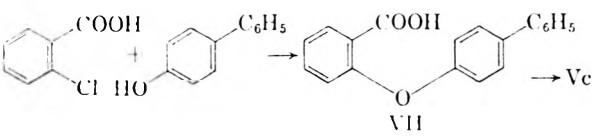


VI

Methods of preparation. (a). *Dixanthylenes.* The dixanthylene derivatives listed in Table II were prepared by treating the corresponding xanthone derivatives with thionyl chloride, followed by the action of copper bronze,[1(a)] and by the action of copper bronze on the corresponding xanthiones.[1(a)] They also have been obtained by treating the corresponding xanthones with zinc dust and acetic acid in the presence of concentrated hydrochloric acid.[1(a)]

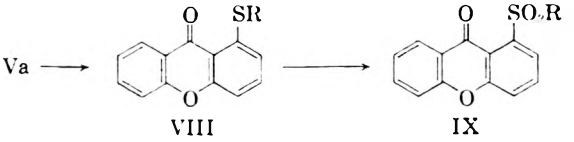
(b). *Xanthiones.* The xanthiones, listed in Table III, were prepared as mentioned above and by the action of phosphorus pentasulfide on the corresponding xanthones.[1(a)] They also have been obtained by the action of thiolacetic acid on the product obtained by the action of thionyl chloride on the corresponding xanthones.

(c). *Xanthones.* The new 2-phenylxanthone (Vc), needed in this work was prepared by the method of Dahr,[4] from *p*-hydroxydiphenyl and *o*-chlorobenzoic acid in the presence of sodium methoxide and copper powder, followed by ring closure of the intermediate phenoxybenzoic acid (VII) with sulfuric acid.



VII → Vc

Reactions of 1-chloroxanthone (Va) with aromatic thiols. In conjunction with a study of pharmacological action of sulfur-containing compounds against *Bilharziasis*,[5] the action of thiolate anion on Va now has been investigated. The lability of the halogen in halogenated xanthones was previously demonstrated.[6] When a solution of Va in amyl alcohol is heated with the appropriate thiol in the presence of solid potassium hydroxide, the corresponding arylmercapto derivatives (VIII; Table IV) are obtained which are readily oxidized to the corresponding sulfone derivatives (IX; Table IV).



Va → VIII → IX

Photochemical reactions. In continuation of some recent work,[7] we now have found that Vb effects a

(2) A. Schönberg and M. M. Sidky, *J. Am. Chem. Soc.*, **81**, 2259 (1959).

(3) Y. Hirshberg, E. Loewenthal, E. D. Bergmann, and B. Pullman, *Bull. soc. chim.*, (5) **18**, 88 (1951).

(4) S. N. Dahr, *J. Chem. Soc.*, **117**, 1053 (1920).

(5) (a) A. Mustafa, A. H. E. Harhash, and M. Kamel, *J. Am. Chem. Soc.*, **77**, 3860 (1955). (b) A. Mustafa, W. Asker, and M. E. D. Sobhy, *J. Am. Chem. Soc.*, 5121 **77**, (1955).

(6) *Cf.* the replacement reaction with thiolate anion (ref. 5(b)), with phenols [A. M. V. Dem Knesebeck and F. Ullmann, *Ber.*, **55**, 306 (1922)], anilines [H. Mauss, *Chem. Ber.*, **81**, 19 (1948)], aliphatic amines [S. Archer, L. B. Rochester, and M. Jackman, *J. Am. Chem. Soc.*, **76**, 588 (1954)], and alkylenediamines [S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4206 (1952)].

(7) A. Mustafa, A. H. E. Harhash, A. K. E. Mansour, and S. M. A. R. Omran, *J. Am. Chem. Soc.*, **78**, 306 (1956).

TABLE II

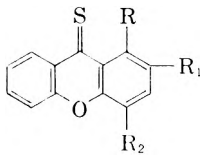
SUBSTITUTED DIXANTHYLENES

Dixanthylene[b,c]	M.P.[d]	Method of Preparation	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia	277	(B)	27	$C_{26}H_{14}O_2Cl_2$[e]	72.73	72.78	3.26	3.22
Ih	262[a]	(A)	73	$C_{25}H_{20}O_2$	86.60	86.61	5.15	5.13
		(B)	34					
		(C)	59					
Ii	Above 300	(A)	71	$C_{35}H_{24}O_2$	89.06	89.04	4.69	4.65
		(B)	32					
		(C)	55					
Il	246[a]	(A)	69	$C_{28}H_{20}O_2$	86.60	86.58	5.15	5.10
		(B)	29					
		(C)	57					

[a] Deep bluish green melt. [b] An orange-red color is developed when treated with sulfuric acid at 100°. [c] Xylene was used as a solvent for crystallization. The dixanthylenes are easily soluble in hot anisole, but difficultly soluble in alcohol. [d] Melting points are uncorrected. [e] *Anal.* Calcd.: Cl, 16.55. Found: Cl, 16.58.

TABLE III

SUBSTITUTED XANTHIONES OBTAINED USING METHOD (a)

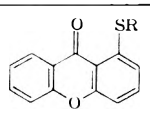
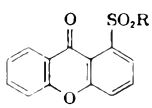


Xanthione Derivatives: R	R1	R2	M.P.[a]	Temp. of Reaction	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Cl	H	H	142	90	82	$C_{13}H_7OSCl$[b]	63.29	63.27	2.84	2.81	12.98	12.70
H	CH_3	H	129	115	76	$C_{14}H_{10}OS$	74.34	74.30	4.42	4.41	14.16	14.13
H	C_6H_5	H	152	140	73	$C_{19}H_{12}OS$	79.17	79.14	4.17	4.13	11.11	11.08
H	H	CH_3	124	110	80	$C_{14}H_{10}OS$	74.34	74.31	4.42	4.46	14.16	14.12

[a] Melting points are uncorrected. The melt is green. [b] *Anal.* Calcd.: Cl, 14.40. Found: 14.29.

TABLE IV

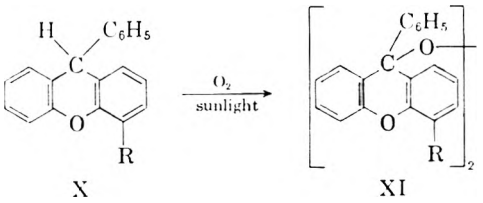
ARYLMERCAPTO DERIVATIVES

R	M.P.[a]	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
									
C_6H_5	113	73	$C_{19}H_{12}SO_2$	75.00	75.02	3.95	3.92	10.53	10.50
o-$CH_3C_6H_4$	170	69	$C_{20}H_{14}SO_2$	75.47	75.43	4.40	4.38	10.06	10.02
p-$CH_3C_6H_4$	129	77	$C_{20}H_{14}SO_2$	75.47	75.49	4.40	4.37	10.06	10.09
m-$CH_3C_6H_4$	164	62	$C_{20}H_{14}SO_2$	75.47	75.46	4.40	4.41	10.06	10.03
									
o-$CH_3C_6H_4$	202	71	$C_{20}H_{14}SO_4$	68.57	68.53	4.00	4.03	9.14	9.11
p-$CH_3C_6H_4$	207	73	$C_{20}H_{14}SO_4$	68.57	68.57	4.00	4.38	9.14	9.10
m-$CH_3C_6H_4$	196	66	$C_{20}H_{14}SO_4$	68.57	68.56	4.00	4.01	9.14	9.13

[a] Melting points are uncorrected.

photochemical dehydrogenation reaction,[8] yielding 2,2′-dimethyl-9,9′-bixanthene when its benzene solution is allowed to react with 2-methyl xanthene in sunlight and in the absence of oxygen. A similar photochemical dehydrogenation reaction has also been observed, yielding 2,2′-dimethyl-9,9′-bixanthene, when Vd, Vg, and/or Vh was used instead of Vb in the above reaction. The fate of the ketone has not yet been established.

9-Arylxanthenes, *e.g.*, 9-phenylxanthene (Xa), when their benzene solutions are exposed to sunlight in presence of air, form 9-arylxanthyl peroxides, *e.g.*, 9-phenylxanthyl peroxide (XIa).[5(b)] We now have found that Xb behaves, similarly, under the action of sunlight in the presence of oxygen, yielding 4-chloro-9-phenylxanthyl peroxide (XIb). Xb now has been obtained by the reduction of 4-chloro-9-phenylxanthhydrol with zinc and glacial acetic acid. The photoperoxide



X XI

a. R = H; b. R = Cl

formation of XI under the influence of sunlight possibly may be attributed to a direct attack by oxygen on an excited form of X. That XIb is a peroxide is established by the fact that it liberates iodine from potassium iodide solution in acetic acid; XIb gives 4-chloroxanthone on pyrolysis.

Reactions with lithium aluminum hydride. It been found that when certain aromatic ketones containing amino or methoxyl groups *ortho* or *para* to the carbonyl group are reduced under forcing conditions with excess lithium aluminum hydride at elevated temperature for long periods, reduction and hydrogenolysis occur to a methyl or methylene group.[9] Recently, similar behavior has been reported in the xanthone series. Thus, reduction of xanthone, 1,2-benzo-, and 3,4-benzoxanthones[10] and 10-thioxanthone with lithium aluminum hydride proceeds one step further to give the corresponding xanthenes.[11] Halogen substituted xanthones, *e.g.*, 2-chloro- and 4-chloroxanthones undergo reduction with the same reagent leading to the formation of xanthene in every case with the loss of halogen.[5(b)] The reduction of hydroxyxanthones, *e.g.*, 1-hydroxy- and 1-hydroxy-3-methylxanthone with the same reagent gives the corresponding xanthene derivatives, namely, 1-hydroxy- and 1-hydroxy-3-methylxanthene.[9] In none of the examples cited does fractional crystallization of the reaction products reveal the presence of the corresponding hydrols.[12] The reaction was carried out in all cases in boiling ether-benzene solution.

We now have investigated the reduction of a number of mono- and disubstituted xanthones with lithium aluminum hydride. Thus, when Vd–g are allowed to react with the same reagent in boiling ether-benzene solution for three hours and kept at room temperature overnight, followed by hydrolysis, the corresponding xanthhydrol derivatives, namely, 4-methyl-, 1,4-dimethyl-, 1,3-dimethyl- and 2,4-dimethylxanthhydrols (*cf.* Table V), are obtained, respectively, in an almost quantitative yield. Fractional crystallization of the reaction products does not reveal the presence of the corresponding xanthones. On the other hand, when Vb–c are treated with the same reagent under the same conditions, the corresponding xanthene derivatives, namely, 2-methyl- and 2-phenylxanthenes (*cf.* Table V) are obtained, respectively, in an almost quantitative yield.

The reduction of Vh with lithium aluminum hydride under the same conditions, led to the formation of a colorless product which upon fractional crystallization gave 2,3-dimethylxanthhydrol and 2,3-dimethylxanthene. We would like to report that, whereas, the 1- or 4-monosubstituted or the 1,4-disubstituted xanthones give the corresponding xanthhydrol derivatives on reduction with lithium aluminum hydride, the 2-substituted xanthones give the corresponding xanthene derivatives with the same reagent. Vh, on reduction with lithium aluminum hydride, gives a mixture of the corresponding xanthhydrol and xanthene derivatives. The study of the effet of substituent group[13] on the reduction of the xanthone derivatives with lithium aluminum hydride, under different experimental conditions, is under further investigation.

Treatment of Vc with metallic sodium and alcohol[14] gives the same reduction product, obtained by

(8) *Cf.* the photochemical dehydrogenation of diphenylmethane and anthrone by xanthone to give tetraphenylethane and 10,10′-bianthrone respectively (A. Schonberg and A. Mustafa, *J. Chem. Soc.*, **67** (1944); *Chem. Revs.*, **40**, 181 (1947)) and the photochemical dehydrogenation of xanthene by 4-chloroxanthone yielding 9,9′-bixanthene (ref. 5b).

(9) For references, *cf.* A. Mustafa and O. H. Hishmat, *J. Org. Chem.*, **22**, 1644 (1957).

(10) A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, 1343 (1952).

(11) *Cf.* the reduction of decussatin methyl ether (1,2,5,6-tetramethoxyxanthone) to the xanthene derivative when boiled with excess lithium aluminum hydride in ether for twelve hours (R. C. Shah, A. B. Kulkarni, and C. G. Joshi, *J. Sci. Ind. Research (India)*, **13B**, 186 (1954).

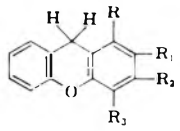
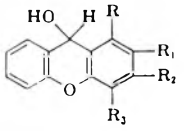
(12) *Cf.* the reduction of xanthone to xanthhydrol with the same reagent (P. Mirza and R. Robinson, *Nature*, **166**, 997 (1950) and the reduction of 1-chloro-4-methylxanthone to 1-chloro-4-methylxanthhydrol [ref. 6(b)].

(13) *Cf.* the effect of substituent in the 6-position on the ready reduction of 6-hydroxylbenzanthrone with lithium aluminum hydride, in contrast to the stability of the unsubstituted benzanthrone toward the same reagent [H. E. Zeiger and J. A. Dixon, Division of Organic Chemistry of the American Chemical Society, Abstracts of papers presented at Atlantic City, N. J., Sept. 13 to 18, 1959, (p. 19P).]

(14) J. Heller and St. Kostanecki, *Ber.*, **41**, 1325 (1908).

TABLE V

THE REDUCTION PRODUCTS OF SUBSTITUTED XANTHONES (Va–h)

Xanthone Derivative	Reduction Product R	R_1	R_2	R_3	Method of Reduction	Yield, %	M.P.[c]	Solvent for Cryst.[f]	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
													
Va	H	H	H	H	(b)	71	101	A	$C_{13}H_{10}O$	85.73	85.71	5.49	5.51
Vb	H	CH_3	H	H	(a)	62	98	A	$C_{14}H_{12}O$	85.71	85.63	6.12	6.10
Vc	H	C_6H_5	H	H	(a) and (b)	71, 79	130	A	$C_{19}H_{14}O$	88.37	88.33	5.43	5.37
Vh	H	CH_3	CH_3	H	(a) and (b)[3]	22, 78	124	A	$C_{15}H_{14}O$	85.71	85.73	6.67	6.62
													
Vd	H	H	H	CH_3	(a)	61	142	C	$C_{14}H_{12}O_2$[d]	79.25	79.17	5.66	5.69
Ve	CH_3	H	H	CH_3	(a) and (b)	73, 64	204	B	$C_{15}H_{14}O_2$	79.65	79.60	6.19	6.23
Vf	CH_3	H	CH_3	H	(a)	67	201	B	$C_{15}H_{14}O_2$	79.65	79.59	6.19	6.22
Vg	H	CH_3	H	CH_3	(a)	58	152	C	$C_{15}H_{14}O_2$	79.65	79.61	6.19	6.20
Vh	H	CH_3	CH_3	H	(a)[e]	42	208	B	$C_{15}H_{14}O_2$	79.65	79.61	6.19	6.24

[a] Reduction with lithium aluminum hydride. [b] Reduction with sodium and alcohol. [c] Melting points are uncorrected. [d] Mol. wt., calcd.: 212. Found: 220. [e] For the separation of 2,3-dimethylxanthene and 2,3-dimethylxanthhydrol, the reaction product was triturated with boiling alcohol, in which the xanthene derivative is soluble. [f] A is ethyl alcohol, B is benzene, and C is benzene-petroleum ether.

the action of lithium aluminum hydride on Vc. On the other hand, the reduction of Vh with metallic sodium and alcohol yields only 2,3-dimethylxanthene. Treatment of Va with metallic sodium and alcohol effects the formation of xanthene with the loss of halogen.[5(b)]

EXPERIMENTAL

Dixanthylene derivatives (I). *Method* (a). Two g. of the xanthone were refluxed (using a calcium chloride tube) with 15 ml. of thionyl chloride (or with 10 g. of oxalyl chloride) for 10 hr.; the excess thionyl chloride (or oxalyl chloride) was distilled, and the residual oil dissolved in 30 ml. of dry xylene and refluxed with 4 g. of copper bronze for 6 hr., with occasional shaking. The xylene solution was filtered while hot and concentrated; on cooling the dixanthylene derivative crystallized. (*cf.* Table II).

(b). One g. of the xanthone after 30 min. boiling with 0.5 g. of zinc dust and 15 ml. of glacial acetic acid in the presence of 2–3 drops of concd. hydrochloric acid gave the dixanthylene derivative.

(c). A solution of 1 g. of xanthione in 20 ml. of dry xylene was refluxed with 0.5 g. of copper bronze for 6 hr. The filtered xylene solution, on concentration, gave the dixanthylene derivative.

Dilute solutions of the dixanthylenes Ig,h,k in diphenyl ether or anisole are almost colorless at room temperature; the boiling solutions are bluish green; the color phenomenon is reversible.

Action of thionyl chloride. General procedure. A solution of 1 g. of the appropriate dixanthylene derivative in 30 ml. of thionyl chloride was refluxed for 6 hr.; the excess solvent was distilled completely (pump), and the residual oil was then dissolved in benzene and shaken with water at 30° for 30 min. The benzene layer was evaporated and the residual was crystallized from benzene-petroleum ether (b.p. 40–60°).

2-Chloroxanthone (Va) (melting point and mixed melting point and color reaction with sulfuric acid) was obtained in 73% yield.

Similar treatment of Ih with thionyl chloride gave 68% yield of 2-methylxanthone (Vb). 2-Phenylxanthone (Vc) was obtained in 66% yield from the corresponding dixanthylene derivative (Ii).

4-Methylxanthone (Vd) in 63% yield was, similarly, produced upon treatment of Il with thionyl chloride.

Action of sulfur. General procedure. One g. of the appropriate dixanthylene derivative was ground with 0.5 g. of sulfur and the mixture was heated at 270° (bath temperature) for 10 min., allowed to cool, powdered, and extracted repeatedly with hot petroleum ether (b.p. 60–80°). The extract was concentrated, cooled, filtered from precipitated sulfur, and the bluish green solution was further concentrated and cooled.

The xanthiones (VI, listed in Table III) were identified by melting point and mixed melting point determination with an authentic sample (see below) and by the formation of a reddish brown colored surface on the crystals of mercuric chloride added to their benzene solutions.[15]

Xanthiones. General procedure. (a). One g. of the xanthone was mixed thoroughly with 1.2 g. of phosphorus pentasulfide. The mixture was heated for 1 hr. and the solid mass, obtained on cooling, was powdered and extracted several times with hot benzene (*ca.* 50 ml.). The benzene solution was evaporated and the solid residue was dissolved in hot petroleum ether (b.p. 60–80°) and concentrated; on cooling, the xanthione derivative crystallized.

(15) For the formation of molecular compounds between xanthione and mercuric chloride, *cf.* A. Schonberg, *Ber.*, **58**, 1793 (1925).

(b). The orange oil, obtained by the action of 15 ml. of thionyl chloride on 1 g. of the xanthone, as described above, was dissolved in 40 ml. of dry benzene and refluxed for 6 hr. with 2 ml. of thiolacetic acid during which time a deep bluish green color developed. The excess benzene and acid were removed by distillation and on addition of light petroleum (b.p. 40–60°) to the residue, the xanthione derivative was deposited; it was recrystallized from petroleum ether (b.p. 60–80°).

The xanthiones (listed in Table III) were easily soluble in benzene, giving a bluish green solution, but sparingly soluble in petroleum ether and gave an orange-red color with sulfuric acid.

Method (b) was applied in the case of 4-methyl-, 2-methyl-,[16] and 2-phenylxanthiones; the yields were 73, 66, and 63% respectively.

Action of aromatic thiols. General proceaure. A solution of 2 g. of Va and 1.5 g. of the thiol in 25 ml. of amyl alcohol was treated with 0.1 g. of solid potassium hydroxide. The reaction mixture was refluxed for 3 hr. and kept overnight at room temperature. The yellow solid that separated was filtered, washed with cold ethyl alcohol, then with water and finally with cold acetone. It was extracted with hot petroleum ether (b.p. 60–80°, *ca.* 60 ml.) and the insoluble part was crystallized from glacial acetic acid.

The amylmercapto derivatives VIII (*cf.* Table IV) were oxidized to the corresponding sulfones (IX) as follows: A solution of 1 g. of the appropriate arylmercapto derivative in 25 ml. of glacial acetic acid was treated with 5 ml. of hydrogen peroxide (30%). The reaction mixture was heated (steam bath) for 1 hr. and kept overnight at room temperature. The resulting solid was crystallized from glacial acetic acid.

The sulfones IX (Table IV) are colorless, and easily soluble in hot xylene, but are sparingly soluble in cold ethyl alcohol and acetic acid. They give a pale yellow color with sulfuric acid.

Photochemical experiments. General remarks. The benzene was thiophene-free and dried over sodium. The reaction mixture was placed in a Schlenk tube[17] of pyrex glass, and the air then was displaced by dry carbon dioxide and the tube sealed by fusion.

The photoformation of peroxide was carried out as above, but in the presence of dry air. Control experiments in the dark, but otherwise under identical conditions, showed no reaction.

(a). *2-Methylxanthene*[18] *and* Vb. A solution of 1 g. of 2-methylxanthene and 1.3 g. of Vb in 30 ml. of benzene, after being exposed to sunlight for 10 days (July), acquired a green fluorescence, and the photoproduct separated during exposure as colorless crystals. These were collected, washed with cold benzene (*ca.* 10 ml.) and recrystallized from hot xylene. The yield of 2,2′-dimethyl-9,9′-bixanthene is 0.41 g. and melts at 250°.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 86.15; H, 5.64. Found: C, 86.21; H, 5.66.

It is almost insoluble in cold coned. sulfuric acid, but dissolves with difficulty at 100° giving an orange solution.

The above experiment was repeated using Vd, Vg, and/or Vh instead of Vb, and the above-mentioned compound was obtained in each case (*ca.* 4.0, 3.7, and 3.1 g., respectively) (identified by melting point and mixed melting point as 2,2′-dimethyl-9,9′-bixanthene).

(b). *9-Phenyl-4-chloroxanthene* (Xb) *and oxygen.* Xb was obtained in 65% yield upon reduction of 9-phenyl-4-chloroxanthhydrol[19] after the method of Ullmann and Engi.[20] It forms colorless crystals from petroleum ether (b.p. 40–60°), m.p. 114°. It is easily soluble in benzene and gives no color with sulfuric acid.

Anal. Calcd. for $C_{19}H_{13}ClO$: C, 77.98; H, 4.44; Cl, 12.13. Found: C, 77.80; H, 4.51; Cl, 12.10.

A solution of 1 g. of Xb in 30 ml. of benzene was exposed to sunlight for 15 days (May). The colorless crystals that separated during exposure were recrystallized from benzene (*ca.* 0.66 g.), m.p. 214° dec. (brown red melt).

Anal. Calcd. for $C_{38}H_{24}Cl_2O_4$: C, 74.15; H, 3.90; Cl, 11.54. Found: C, 74.31; H, 3.70; Cl, 11.35.

XIb is soluble in hot benzene and xylene, but difficultly soluble in ethyl alcohol and gives a yellowish green fluorescence with sulfuric acid.

Thermal decomposition of 0.5 g. of XIb for half an hour at 270° (bath-temp.) afforded 4-chloroxanthone (*ca.* 0.16 g.) (melting point and mixed melting point and color reaction with sulfuric acid) as a colorless sublimate.

Reduction of substituted xanthones: (a). *Lithium aluminum hydride. General procedure.* Solvents dried over sodium were used. To 0.7 g. of lithium aluminum hydride (New Metals and Chemicals, Ltd., London) was added 50 ml. of ether. After 15 min., a benzene solution (30 ml.) containing 1 g. of each of the appropriate xanthone (*cf.* Table V) was added in portions. The reaction mixture was refluxed for 3 hr. and then kept overnight at room temperature. After treatment with dilute hydrochloric acid the ethereal solutions were evaporated and the oily residues were solidified upon washing with light petroleum (b.p. below 40°) and crystallized from the proper solvent (*cf.* Table V).

(b). *Metallic sodium and alcohol.* A solution of 3 g. of each of the corresponding xanthone derivatives (*cf.* Table V) in 60 ml. of hot absolute ethyl alcohol was added dropwise to 7 g. of molten metallic sodium after the method described by Heller and Kostanecki.[14] The reaction mixture was steam distilled. The solid obtained from the distillate was crystallized from the appropriate solvent.

Xanthhydrol derivatives listed in Table V are sparingly soluble in petroleum ether (b.p. 50–70°) and difficultly soluble in ethyl alcohol. They give an orange-red color with sulfuric acid. The xanthene derivatives (*cf.* Table V) are easily soluble in benzene, sparingly soluble in cold ethyl alcohol, and give no color with sulfuric acid.

Preparation of 2-phenylxanthone (Vc). (a). A procedure similar to that described by Dahr[4] for the preparation of 2-chloroxanthone was used.

A mixture of 4.1 g. of *p*-hydroxydiphenyl, 3.2 g. of *o*-chlorobenzoic acid, 0.8 g. of metallic sodium, 20 ml. of methyl alcohol, and a trace of copper powder was heated gradually (oil bath) until all the alcohol evaporated. The reaction mixture was kept at 150° for half an hour and the temperature then was raised to 220°. It was cooled, powdered, and the solid was digested with dilute aqueous sodium hydroxide solution (8%, *ca.* 60 ml.). The filtered alkaline extract was acidified with cold dilute hydrochloric acid and the solid obtained was washed thoroughly with cold water, crystallized from ethyl alcohol, and finally from benzene. 2-(4-Phenylphenoxy)benzoic acid (VII), m.p. 147°, was obtained in 77% yield. It is easily soluble in hot benzene and alcohol and gives a yellow color with sulfuric acid.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.62; H, 4.83. Found: C, 78.60; H, 4.85.

VII (3 g.) was heated with 30 ml. of sulfuric acid (70%, stream bath) for 15 min. The cold reaction mixture was poured onto water and the solid substance that separated, was filtered, washed thoroughly with water, and crystallized from ethyl alcohol as colorless crystals (*ca.* 1.6 g.), m.p. 154°.

Anal. Calcd. for $C_{19}H_{12}O_2$: C, 83.82; H, 4.41. Found: C, 83.84; H, 4.40.

Vc is difficultly soluble in benzene and petroleum ether,

(16) While this paper was in progress A. Schönberg and M. M. Sidky (ref. 2) described the preparation of 2-methyl- and 4-methylxanthiones by a similar procedure; the results are concordant.

(17) W. Schlenk and A. Thal, *Ber.*, **46**, 2655 (1913).

(18) R. G. McConnel, V. Petrow, and B. Sturgeon, *J. Chem. Soc.*, 812 (1956).

(19) M. Gomberg and S. H. Cone, *Ann.*, **370**, 183 (1909).

(20) F. Ullmann and E. Engi, *Ber.*, **37**, 2341 (1904).

soluble in boiling ethyl alcohol, and gives a yellow color with a green fluorescence when treated with sulfuric acid.

(b). Vb and Vd were prepared from the condensation of *p*-cresol and *o*-cresol with *o*-chlorobenzoic acid, respectively, as described above without the isolation of the intermediate substituted phenoxy-*o*-benzoic acid, and proved to be identical with samples, prepared after Ullmann and Zlokasoff[21]; the yield was 69% and 73%, respectively.

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(21) F. Ullmann and M. Zlokasoff, *Ber.*, **38**, 2111 (1905).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Mixed Indole Dimers, Trimers, and Their Acyl Derivatives[1]

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Received January 25, 1960

The synthesis of the first mixed indole and indole:pyrrole dimers is described. They are derived from an A component (an indole having an open 2-position) and a B component (an indole or pyrrole more nucleophilic than the A component). Included are the dimers from indole with 2-methylindole (Ib), 1,2-dimethylindole (Ic), 2-phenylindole (Id), or 2,5-dimethylpyrrole (XIIa), and the dimer from skatole with 2-methylindole (IIIa). Structures are assigned on the basis of spectral data and by analogy with the proven structure of diindole (Ia). The competitive dimerization reaction of indole and 1-methylindole permitted isolation, after acylation with maleic anhydride, of only maleyldiindole (XVa). The competitive reaction of indole and skatole proceeded in rather clean-cut stepwise fashion with formation first of diindole hydrochloride and then of diskatole hydrochloride. A new homodimer, 1,3-dimethylindole dimer (VIb), has been prepared. Evidence is presented concerning the structure of diskatole (VIa). As byproducts in the preparation of the mixed dimers, the first mixed trimers have been prepared. Included are diindole:2-methylindole trimer (IIc); diindole:1,2-dimethylindole trimer (IId); and indole:di-2,5-dimethylpyrrole trimer (XIII). Diindole: 1,2-dimethylindole trimer (IId) is different from the dimethyltriindole obtained by methylation of triindole (IIa). Evidence is presented that, contrary to a previous report, the latter dimethyltriindole is in reality an *N,N*-dimethylaniline derivative (IIb) resulting from dimethylation of the primary amino group of triindole. Acyl derivatives of the mixed dimers and trimers have been prepared from maleic, succinic, itaconic, and citraconic anhydrides. Whereas acylation of diindole, indole:2-phenylindole dimer, and indole:2,5-dimethylpyrrole dimer with maleic anhydride gave only the maleyl derivatives, the corresponding reactions with indole:2-methylindole dimer and indole:1,2-dimethylindole dimer gave not only the maleyl derivatives (XVb–c) but also lesser amounts of the fumaryl derivatives (XVI b–c). In the two cases where both maleyl and fumaryl derivatives were obtained, hydrogenation of these stereoisomers gave the succinyl derivatives (XVIIb–c), which were also prepared independently by acylation of the dimers with succinic anhydride. Skatole:2-methylindole dimer with maleic anhydride gave the maleyl derivative (IIIb), but in more polar solvents an isomer was obtained to which the spiro indolenine structure XXI is assigned.

Mixed indole dimers and trimers. Although homodimers of indole,[4–7] skatole,[8,9] 1-methylindole,[10] and 7-methylindole[10] are known, and 2-methylindole dimer has been prepared by a method other than dimerization,[11] there appear to be no published reports of the synthesis of mixed indole dimers or their derivatives.[12] The mechanism proposed[6] for the formation of diindole (Ia) offered hope for the synthesis of mixed indole dimers. Requirements for indole dimerization appear to include a protonated indole with an open 2-position (which we shall designate as the A component) and an indole with a nucleophilic position, usually an open 3-position (B component). Consequently, although its dimer has been prepared by another synthetic route,[11] 2-methylindole does not undergo

(1) Presented in part as Paper 26 before the Organic Division at the 134th National Meeting of the Am. Chem. Soc., Chicago, Ill., Sept. 8, 1958, Abstracts, p. 14P.

(2) We are indebted to the Graduate School of the University of Minnesota for a 1957 Faculty Summer Research Appointment.

(3) From the Ph.D. thesis of Charles F. Hammer, May 1959. Research Corporation Research Assistant 1956–1959, Upjohn Company Summer Fellow 1958. We are indebted to the Research Corporation for a Frederick Gardner Cottrell Grant in support of this research, and to the Upjohn Company for a summer fellowship.

(4) O. Schmitz-Dumont and B. Nicolojannis, *Ber.*, **63**, 323 (1930).

(5) O. Schmitz-Dumont, K. Hamann, and K. H. Geller, *Ann.*, **504**, 1 (1933).

(6) G. F. Smith, *Chem. and Ind.* (London), 1451 (1954).

(7) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 3544 (1957).

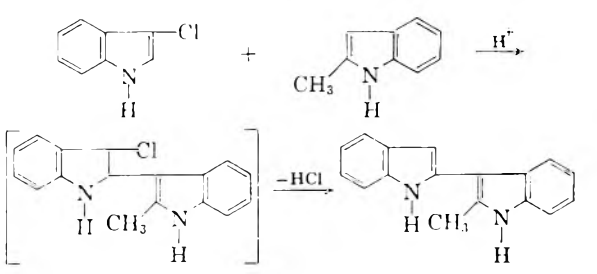
(8) B. Oddo and G. B. Crippa, *Gazz. chim. ital.*, **54**, 339 (1924).

(9) O. Schmitz-Dumont, *Ann.*, **514**, 267 (1934).

(10) O. Schmitz-Dumont and K. H. Geller, *Ber.*, **66**, 766 (1933).

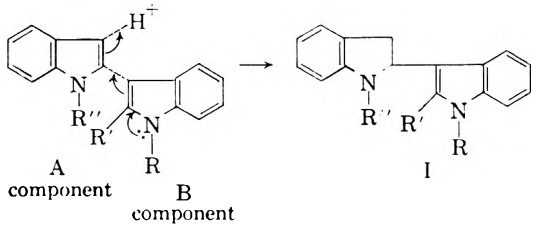
(11) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 713 (1951).

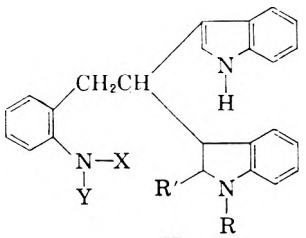
(12) Dr. G. F. Smith of the University of Manchester, England, has kindly informed us in a private communication (Nov. 22, 1957) that he has prepared a mixed diindolyl (corresponding to indole:2-methylindole dimer), the formation of which almost certainly involves an unstable mixed indole dimer as an intermediate:



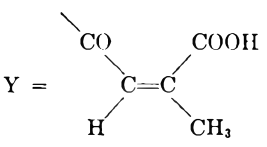
acid-catalyzed dimerization[9,13a] (an observation we have confirmed under our conditions), presumably because of the blocking methyl group in the 2-position of the A component. 2-Methylindole, however, is more nucleophilic at the 3-position than indole for the same reason that the *o*-positions of toluene are more reactive than any position of benzene. It was hoped, therefore, that 2-methylindole would be sufficiently better as a B component than indole so that isolation of a mixed dimer would be possible.

When dry hydrogen chloride was passed slowly into an equimolar solution of indole and 2-methylindole in dry ether, the mixed dimer hydrochloride precipitated in quantitative yield. The free indole:2-methylindole dimer (Ib), an oil, was characterized by acylation, which yielded crystalline amide derivatives in up to 57% yield. On some occasions, usually when hydrogen chloride was passed *rapidly* into an ether solution of the reactants, or else when moisture was present (possibly causing some of the dimer hydrochloride to dissolve and permit further reaction) during the passing in of hydrogen chloride, there was also isolated, in up to 15% yield as the succinyl derivative, and 62% yield as the citraconyl derivative, a mixed trimer, diindole:2-methylindole trimer (IIc). The structure of this mixed trimer is assigned from analogy with the structure of triindole (IIa)[6,13b] and on the basis of the elemental analyses of the succinyl and citraconyl derivatives and the neutralization equivalent of the succinyl derivative.

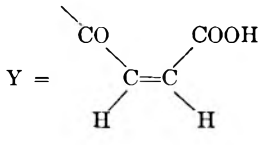




Ia. R = R′ = R″ = H
Ib. R = R″ = H, R′ = CH_3
Ic. R = R′ = CH_3, R″ = H
Id. R = R″ = H, R′ = C_6H_5
Ie. R = CH_3, R′ = R″ = H
If. R = R′ = H, R″ = CH_3
Ig. R = R″ = CH_3, R′ = H
IIa. R = R′ = X = Y = H
IIb. R = R′ = H, X = Y = CH_3
IIc. R = X = Y = H, R′ = CH_3
IId. R = R′ = CH_3, X = Y = H
IIe. R = X = H, R′ = CH_3
Y = $COCH_2CH_2COOH$
IIf. R = X = H, R′ = CH_3



IIg. R = R′ = CH_3, X = H



Similarly prepared were indole:1,2-dimethylindole dimer (Ic), m.p. 134–135°, also obtained in good yield, and the corresponding mixed trimer, diindole:1,2-dimethylindole trimer (IId), in 11% yield as the maleyl derivative, and in up to 14% yield as the free base along with 26% of unchanged 1,2-dimethylindole. The trimer has a melting point of 165–166°. A dimethyltriindole, m.p. 165–166°, from reaction of triindole with methyl iodide in the presence of potassium carbonate, has been described previously.[14] We have repeated the preparation of this dimethyltriindole. It depresses the melting points of diindole:1,2-dimethylindole trimer (IId), mixed m.p. 142–145°, and of triindole (m.p. 170–171°) mixed m.p. 146–149°.

On the basis of the incorrect assumption that no more than one methyl group would become attached to any single nitrogen atom of triindole, and the fact that reaction with cyanogen bromide replaced only one methyl group of the dimethyl derivative, it was claimed[14] that dimethyltriindole contains one C-methyl as well as one *N*-methyl group. The discovery that triindole contains a primary amino group,[6] however, permits the likely assumption that during methylation both methyl groups have become attached to the primary amino nitrogen, the most nucleophilic site in the triindole molecule. All of the reported[14] reactions of dimethyltriindole are consistent with this hypothesis.

We have examined the visible absorption maxima of solutions resulting from reaction of *p*-dimethylaminobenzaldehyde (Ehrlich reagent) with aniline derivatives in 95% ethanol containing perchloric acid. The Ehrlich reagent has its longest wave-length maximum in the ultraviolet region, at 340 mμ. With aniline there results an intense Schiff base maximum at 435 mμ. With *N*-methylaniline there is a less intense maximum at 406 mμ, and with *N*,*N*-dimethylaniline, which is incapable of forming a Schiff base-type product, there is no absorption maximum in the visible region.

Triindole (IIa) gives an intense Schiff base maximun at 421 mμ (the Schiff base maximum for the

(13) (a) B. Oddo, *Gazz. chim. ital.*, **43**, I, 385 (1913). (b) The structures of triindole (IIa) and of indole: di-2,5-dimethylpyrrole trimer (XIII) have recently been proved by an independent synthesis: W. E. Noland and W. C. Kuryla, *J. Org. Chem.*, **25**, 486 (1960).

(14) O. Schmitz-Dumont, J. ter Horst, and H. Müller, *Ann.*, **538**, 261 (1939).

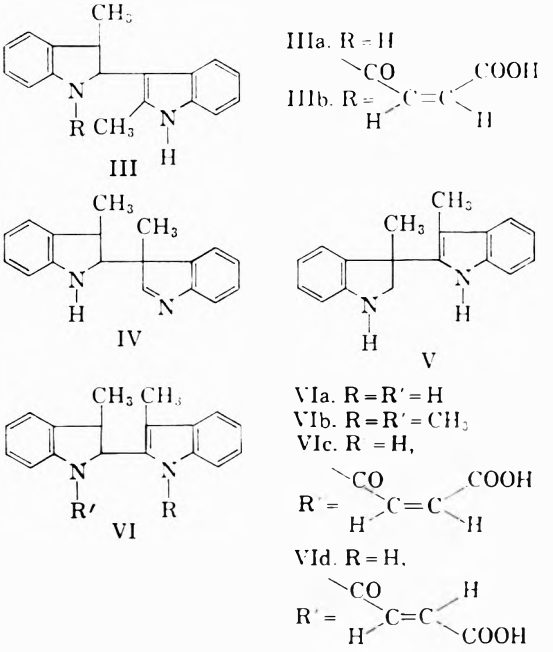
simple benzylidene derivative of triindole is at 324 mμ[6]), and less intense Ehrlich dye[15] absorption at 540 (inflection) and 566 mμ (maximum), attributed to condensation at the open 2-positions of the intact indole nuclei of triindole. Similarly, diindole:-1,2-dimethylindole trimer (IId) gives an intense Schiff base maximum at 417 mμ and less intense Ehrlich dye absorption at 545 mμ. Dimethyltriindole, on the other hand, gives no Schiff base maximum but only Ehrlich dye absorption at the corresponding positions (540, inflection, and 564 mμ, maximum). We conclude, therefore, that dimethyltriindole is an *N,N*-dimethylaniline derivative and we assign to it structure IIb.

Indole and 2-phenylindole also give a mixed dimer (Id), which was isolated in 23% yield as the maleyl derivative. There was no evidence for a mixed trimer analogous to those from the reactions of indole with 2-methylindole or 1,2-dimethylindole.

Our results suggest the generalization that indole will form mixed dimers with 2-substituted indoles more nucleophilic than indole itself. Presumably, however, at some point the steric hindrance of increasingly large substituents in the 2-position will so inhibit the formation of mixed dimers that diindole, which is also formed rapidly, will become the favored product. A comparable situation exists between indole and 1-methylindole, which is believed to be less nucleophilic than indole. In a competitive reaction between equimolar amounts of indole and 1-methylindole, a hydrochloride precipitated in a quantity which accounted for 84% of the mixed indoles used (calculated as the mixed dimer hydrochloride). From this hydrochloride, only diindole was isolated, as the maleyl derivative, in 52% yield of the indole used. The failure to isolate any other dimer as the maleyl derivative shows the absence of indole:1-methylindole dimer (Ie), which would have an acylable basic N—H group, but does not exclude the possible presence of 1-methylindole:indole dimer (If) or of 1-methylindole dimer,[10] to which the structure Ig is assigned by analogy with the structure of diindole.

A similar situation exists between indole and skatole. The competitive reaction of equimolar amounts of indole and skatole proceeded in rather clean-cut stepwise fashion. After dry hydrogen chloride gas had been passed into the ether solution for seven minutes, a quantitative precipitate of diindole hydrochloride was filtered off. Passing in hydrogen chloride was resumed and after thirty-eight more minutes an 85% yield of diskatole hydrochloride was filtered off. This stepwise formation of the homodimers shows that indole is more reactive than skatole, both as an A component and as a B component.

As skatole has an open 2-position, it should be capable of forming a mixed dimer with 2-methylindole. Furthermore, as 2-methylindole is much more nucleophilic (thus making it a better B component) than skatole, the mixed dimer might form in preference to diskatole. In accordance with this prediction skatole:2-methylindole dimer (IIIa) was obtained, in up to 37% yield as the maleyl derivative, but diskatole was also obtained, in up to 10% yield as the maleyl derivative, along with unchanged 2-methylindole, which was isolated



in up to 30% yield in the form of its reaction products with maleic anhydride.[16] These results show that the rates of reaction of skatole with 2-methylindole and with itself are of comparable magnitude.

A proof of structure for diskatole has not yet been published.[17] If the mechanism of skatole dimerization parallels that of indole,[6] then diskatole would have the dibasic indolenine structure IV, no longer containing an indole chromophore. The ultraviolet spectra of diskatole and several of its derivatives (Table I), however, contain the indole chromophore. Furthermore, diskatole,[18,19] like diindole,[4,13,20-22] forms a monohydrochloride. The infrared spectrum (in Nujol) of maleyldiskatole[16] (VIc) contains an NH band at 3320 cm^{-1}. Consequently, the indolenine structure IV is not valid

(15) A. Treibs and E. Herrman, *Z. physiol. Chem., Hoppe-Seyler's*, **299**, 168 (1955).

(16) O. Diels, K. Alder, and W. Lübbert, *Ann.*, **490**, 277 (1931).

(17) Structure VIa has been proved for diskatole by degradation, G. F. Smith and A. E. Walters, unpublished work, University of Manchester, England (private communication, Oct. 16, 1958).

(18) M. Wenzing, *Ann.*, **239**, 239 (1887).

(19) R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 976 (1952).

(20) K. Keller, *Ber.*, **46**, 726 (1913).

(21) O. Schmitz-Dumont, B. Nicolojannis, E. Schnorrenberg, and H. H. Saenger, *J. prakt. Chem.*, **131**, 146 (1931).

(22) O. Schmitz-Dumont and H. H. Saenger, *J. prakt. Chem.*, **132**, 39 (1931).

TABLE I

SPECTRAL DATA ON INDOLE DIMERS AND TRIMERS, AND RELATED COMPOUNDS

Compound	Ultraviolet: Wave lengths of maxima in mμ with intensities (log ε). Solvent: 95% ethanol			Infrared: Frequencies in cm.$^{-1}$ NH	Medium
Indoline[a]	[b]	240 (3.83)	— 292 (3.35)	3400	liquid
2-Methylindoline[a]	[b]	241 (3.84)	— 293 (3.34)	3390	liquid
Ia[c]	221 (4.61)	283 (3.92)	290 (3.91)	3410	KBr
Ia·HCl[d]	221 (4.56)	283 (3.94)	290 (3.94)	3330,[e] 2590, 2490, 3460[e], 2600, 2520	KBr Nujol
Di-2-methylindole[f]	226 (4.54)	284 (3.92)	291 (3.92)	3420,[e] 3330	$CHCl_3$
Ib·HCl[g]	225 (4.55)	281 (3.99)	288 (3.95)	3340, 3220,[e] 2770, 2540, 2480	Nujol
Ic	228 (4.57)	288 (3.97)	294 (3.98)	3420	$CHCl_3$
				3400	Nujol
Ic·HCl	219 (4.78)	281 (4.09)	287 (4.04)	3380, 2490[e]	Nujol
VIa	228 (4.60)	285 (4.09)	293 (4.06)	3470,[e] 3400	$CHCl_3$
				3420,[e] 3380	KBr
				3450, 3400[e]	Nujol
VIa·HCl[h]	228 (4.59)	285 (4.08)	293 (4.06)	3320	KBr
				3270	Nujol
Bisdiskatole oxalate	228 (4.60)[i]	285 (4.08)[i]	293 (4.06)[i]		
VIb	229 (4.63)	249[j] (4.16)	289 (4.07)	none	Nujol
VIb·HCl	229 (4.65)	249[j] (4.16)	289 (4.07)	2280	Nujol
XIIa·HCl	[b]	280 (3.82)	288 (3.81)	3250,[e] 3180, 2670, 2580, 2500	Nujol
IIb	225 (4.85)	283 (4.10)	291 (4.05)	3540,[e] 3480	$CHCl_3$
				3450	Nujol
IId	225 (4.82)	284 (4.14)	290 (4.12)	3420, 3350, 3260[e]	Nujol
XIII	[b]	283 (3.36)	—	3370,[e] 3300, 3220	Nujol

[a] Prepared as described in ref. 32. [b] Rising end absorption. [c] Ref. 33. [d] Obtained in 82% yield, m.p. 172–173°, by the method of ref. 13. Reported m.p. 180°,[13] >150°.[4] [e] Strongest NH band. [f] Sample kindly provided by Dr. Bernhard Witkop. See ref. 11 for preparation and source of infrared data. [g] Prepared and determined by George J. Meisters. [h] The m.p. 183–184° of our sample[8] was higher than that reported: 167–168°,[18] 173°,[3] 180°.[19] [i] Log ε/2. [j] Inflection.

for diskatole. If, in the formation of diskatole, protonation of skatole occurs at the 2-position, which appears to be the most nucleophilic center,[23] followed by attack at the 3-position by the B component from its 2-position, then diskatole would have structure V, requiring the formation of a quaternary carbon atom. If, however, skatole is protonated at the 3-position, followed by attack at the 2-position by the B component from its 2-position, then the least possible sterically hindered structure (VIa) for diskatole would result. Consistent with the formulation of diskatole as V or VIa is the fact that in the Ehrlich test diskatole gives Schiff base-type absorption at 442 (inflection) and 457 mμ (maximum) but no Ehrlich dye maximum, indicating the absence of an open 2- or 3-position in an indole nucleus. Diindole, in contrast, gives both the intense Schiff base-type absorption at 442 (inflection) and 453 mμ (maximum) and the Ehrlich dye maximum at 568 mμ, in agreement with the open 2-position in the indole nucleus of diindole. Indole itself gives only Ehrlich dye absorption at 540 (inflection) and 567 mμ (maximum), and skatole similarly gives maxima at 545 and 578 mμ, the latter maxmum being the more intense of the two.

Diskatole sublimes unchanged at 125–126° (0.2 mm.), and diskatole hydrochloride could even be sublimed without decomposition. Nevertheless, the reversion of diskatole hydrochloride into skatole upon warming with alkali[8,18] appears to rule out the possibility of carbon skeletal rearrangements occurring during its formation. It is interesting to note that 3-ethylindole, in contrast to skatole, has been reported not to dimerize,[10] but this report appears to be in error.[24]

The bisdiskatole oxalate, m.p. 180°, of Oddo and Crippa[8] was reinvestigated since the nitrogen analysis, which constituted the sole characterization, was in better agreement with $C_{38}H_{34}N_4O_2$, bisdiskatole oxamide, than with the formula $C_{38}H_{38}N_4O_4$ proposed. Our carbon, hydrogen, and nitrogen analyses, however, are in agreement with the bisdiskatole oxalate formula originally proposed.

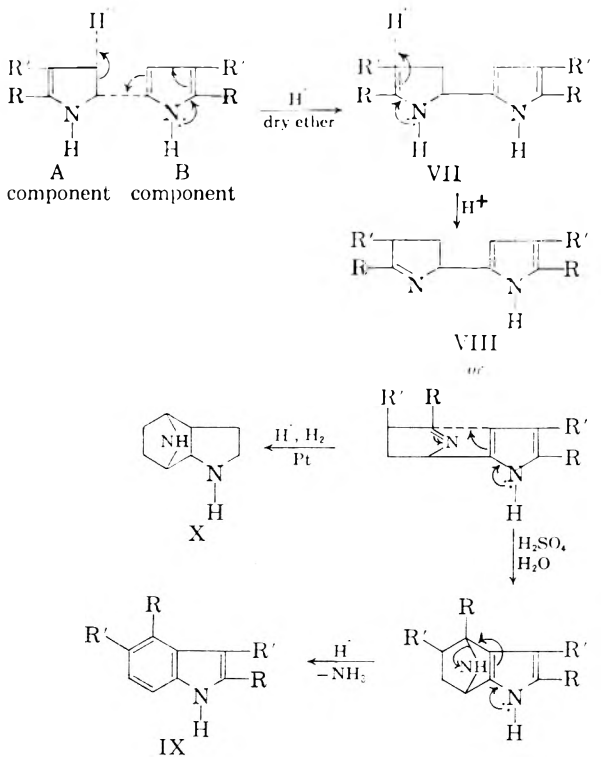
1,3-Dimethylindole forms a homodimer (VIb), m.p. 124–125.5°, analogous to diskatole, but the

(23) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

(24) Dr. G. F. Smith of the University of Manchester, England, has kindly informed us in a private communication (April 28, 1957) that he has found 3-*n*-propylindole to form a beautifully crystalline dimer hydrochloride at about the same rate as skatole dimerizes. On the other hand, he has prepared pure crystalline 3-t-butylindole and shown that it is completely unaffected by hydrochloric acid under conditions which lead to the rapid dimerization of skatole and 3-*n*-propylindole.

dimerization proceeds less rapidly. Even after hydrogen chloride had been passed into a stirred ether solution of 1,3-dimethylindole for three hours, the dimer hydrochloride was isolated in only 57% yield, and 26% of unchanged 1,3-dimethylindole was recovered after distillation.

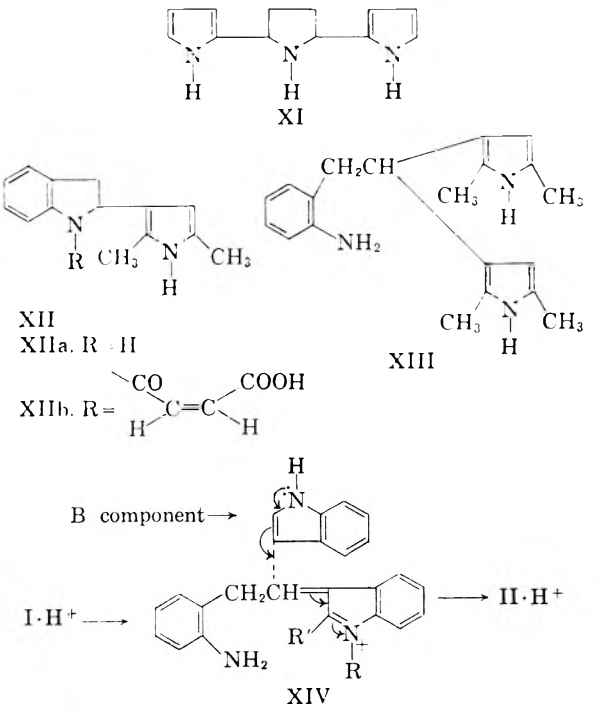
Substituted pyrroles have long been known to form monobasic dimer salts under the action of mineral acids in dry ether solutions.[25,26] The structure of 2-phenylpyrrole dimer has been proved to be VIIIa.[25] Unilaterally alkyl-substituted pyrrole dimers are inferred to have analogous structures (such as VIIIb–e), because under the action of



VIIIa. R = C_6H_5, R′ = H
VIIIb, IXb. R = CH_3, R′ = H
VIIIc, IXc. R = *i*-C_3H_7, R′ = H
VIIId, IXd. R = R′ = CH_3
VIIIe, IXe. R = H, R′ = CH_3
VIIIf, IXf. R = R′ = H

dilute sulfuric acid they lose ammonia and form substituted indoles (IX).[26] The indole from 2-methylpyrrole dimer has been proved to be 2,4-dimethylindole (IXb), in agreement with structure VIIIb for 2-methylpyrrole dimer.[26] The action of acid on pyrrole itself yields tripyrrole, which has been proved to have the linear structure XI,[27] as the stable product. The intermediate dipyrrole (VIIIe) has not been isolated, although a salt of the composition $(C_4H_5N)_2SnCl_4$ is known,[28] and dipyrrole has been trapped as the tetrahydro derivative (X) through catalytic hydrogenation of pyrrole in acetic acid or ethanolic hydrochloric acid solutions.[29] The structures VIII for pyrrole dimers are analogous to structure VIa for diskatole, except that the remaining vinylamine double bond of the A component (as in VII) has shifted into the more stable imine position. Such a shift does not occur in diskatole because the vinylamine double bond is already in its most stable position, as part of a benzenoid system.

The structures of pyrrole dimers and of tripyrrole show that the 2-position is the point of greatest reactivity in pyrroles, both when they are acting as A components and as B components. It was hoped that blocking both 2-positions of the pyrrole nucleus, as in 2,5-dimethylpyrrole, would inhibit homodimerization of the pyrrole, but leave (or produce) sufficient reactivity as a B component at the 3-position to permit the synthesis of mixed indole:pyrrole dimers. This objective was realized with indole and 2,5-dimethylpyrrole, which gave an almost quantitative precipitate of hydrochlorides, from which indole:2,5-dimethylpyrrole dimer (XIIa) was obtained in up to 67% yield as the maleyl derivative, and indole:di-2,5-dimethylpyrrole trimer (XIII), m.p. 197–199°, was isolated in up to 41% yield.



Like indole dimers, indole:2,5-dimethylpyrrole dimer forms a monohydrochloride. The infrared spectrum (in Nujol) of the maleyl derivative contains an NH band at 3300 cm.$^{-1}$. Consequently, structures analogous to VIII, in which 2,5-di-

(25) C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, **2**, 227 (1937).
(26) C. F. H. Allen, D. M. Young, and M. R. Gilbert, *J. Org. Chem.*, **2**, 235, 400 (1937).
(27) H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957).
(28) O. Schmitz-Dumont, *Ber.*, **62**, 226 (1929).
(29) C. D. Nenitzescu and V. Ioan, *Revue de chimie*, **1**, 55 (1956).

TABLE II

SPECTRAL DATA ON ACYL DERIVATIVES OF MIXED INDOLE DIMERS AND TRIMERS, AND RELATED COMPOUNDS

Compound	Ultraviolet: Wave lengths of maxima in mμ with intensities (log ε). Solvent: 95% ethanol					Infrared: Frequencies, cm.$^{-1}$ NH	C=O COOH	C=O CON	Medium
Acetyl-*N*-methyl-*o*-toluidine	[a]	263 (2.57)	270 (2.50)	—	—	none	none	1640	$CHCl_3$
								1642	KBr
1-Maleylindoline[b]	[c]	255 (4.05)	283 (3.87)	292[d] (3.84)	—	none	1710	1625	$CHCl_3$
							1701	1611[e]	KBr
1-Succinylindoline[b]	[c]	252 (4.19)	281 (3.65)	290 (3.58)	—	none	1705	1653	Nujol
1-Maleyl-2-methylindoline[b]	[c]	250 (4.04)	282 (3.75)	289 (3.74)	—	none	1704	1623	Nujol
XVa[f]	218 (4.67)	264 (4.17)	282 (4.13)	290 (4.07)	—	3480	1710	1623	$CHCl_3$
						3280	1703	1620	KBr
XVIIa[g]	219[d] (4.66)	254 (4.21)	281 (4.03)	290 (3.96)	—	3350	1705	1650	Nujol
XVIIIa	[c]	255 (4.21)	280 (4.05)	289 (3.98)	—	3380	1699	1652	Nujol
XXa	218 (4.69)	271 (4.03)		288 (3.92)	—	3400	1347[h]	1164[h]	KBr
XVb	219 (4.64)	262 (4.19)	282 (4.14)	289 (4.09)	—	3480	1709	1623	$CHCl_3$
						3390	1707	1622	KBr
XVIb	224 (4.68)	—	282 (4.07)	289 (4.05)	323[i] (3.88)	3350	1691	1630	KBr
						3360	1694	1635	Nujol
XVIIb	223 (4.60)	256 (4.19)	282 (4.06)	290 (3.98)	—	3340	1708	1633	Nujol
XVIIIb	222[d] (4.60)	257 (4.22)	282 (4.09)	290 (4.02)	—	3390	1687	1615[t]	Nujol
XIXb	221 (4.66)	269 (4.22)	281 (4.21)	288[d] (4.16)	—	3330	1693	1618	Nujol
XVc	225 (4.61)	259 (4.16)	284 (4.14)	292 (4.10)	—	none	1709	1621	$CHCl_3$
						none	1714[j]	1615[j]	KBr
						none	1714[k]	1613[k]	Nujol
XVIc	226 (4.68)	—	285 (4.05)	291[d] (4.04)	318 (3.83)	none	1683	1619[l]	KBr
						none	1685	1621[m]	Nujol
XVIIc	226 (4.60)	255 (4.18)	283 (4.07)	291 (4.02)	—	none	1693	1648	Nujol
XVd	235[d] (4.48)	—	294 (4.34)	302[d] (4.31)	—	3440	1703	1618	$CHCl_3$
						3260	1697	1621	KBr
						3260	1698	1620	Nujol
IIIb	[c]	261 (4.22)	280[d] (4.15)	288[d] (4.09)	—	3500	1715	1629	$CHCl_3$
						3290	1716	1624	Nujol
						3370[d]			
VIc	225 (4.63)	263 (4.20)	283 (4.21)	291[d] (4.09)	—	3310	1689	1622[n]	KBr
						3320	1689	1620[n]	Nujol
XIIb	[c]	252 (4.37)	283 (4.15)	291[d] (4.12)	—	3300	1688	1620	Nujol
IIe	225 (4.84)	—	283 (4.09)	291 (4.04)	—	3350	1715	1657	Nujol
						3410[o]			
IIf	225 (4.90)	274 (4.25)	278[d] (4.25)	290[d] (4.17)	—	3290	1688	1625	Nujol
						3360[o]			
IIg	225 (4.85)	—	284 (4.19)	291 (4.17)	—	3320	1704	1602[p]	KBr
						3320	1703	1600[p]	Nujol
IIg K salt	226 (4.81)	—	285 (4.15)	291[d] (4.12)	—	[a]	[a]	[a]	
XXI	222[d,q] (4.36)	253 (4.19)	280[d] (3.86)	291[d] (3.79)	—	none	—1688[r]—		Nujol
2,3,3-Trimethylindolenine[s]	216[t] (4.27)	255 (3.78)	—	—	—	none	none	1579[u]	liquid

[a] Not determined. [b] Preparation described in ref. 32. [c] Rising end absorption. [d] Inflection. [e] Also weaker band at 1651 cm.$^{-1}$. [f] The m.p., 162–163.5° dec. with carbon dioxide evolution, of our sample recrystallized from acetonitrile was higher than that reported, 157°.[16] [g] The m.p., 162–163° dec. with carbon dioxide evolution, of our sample recrystallized from acetonitrile was lower than that reported, 169–170°.[16] [h] Sulfur dioxide bands. [i] Also weaker band at 1634 and very strong band at 1586 cm.$^{-1}$. [j] Also weaker bands at 1682 and 1647 cm.$^{-1}$. [k] Also weaker bands at 1680 and 1647 cm.$^{-1}$. [l] Also strong band at 1644 cm.$^{-1}$. [m] Also strong band at 1650 cm.$^{-1}$. [n] Also strong band at 1590 cm.$^{-1}$. [o] Weaker band. [p] Also strong band at 1580 cm.$^{-1}$. [q] Also inflection at 228 mμ (log ε 4.25). [r] Single very strong carbonyl band; weaker bands at 1602 and 1583 cm.$^{-1}$. [s] Prepared by the method of G. Plancher, *Ber.*, **31**, 1496 (1898). Very unstable; it was redistilled just prior to analysis: colorless, n_D^{25} 1.5406, b.p. 105.5–106° (9 mm.); reported b.p. 227–229°. The picrate, prepared in ether, yellow needles from benzene, melted at 161–163°; reported m.p. 158°. *Anal.* Calcd. for $C_{17}H_{16}N_4O_7$ (388.33): C, 52.78; H, 4.15; N, 14.43. Found: C, 53.00; H, 4.08; N, 14.65. [t] Also inflection at 222 mμ (log ε 4.08). [u] Strong C=N band.

methylpyrrole has acted as an A component, either at its 2- or 3-positions, as well as structures in which it has acted as a B component at its 2-position, are invalid. Structure XIIa is left as the probable structure for indole:2,5-dimethylpyrrole dimer. It is completely analogous to other dimers in which indole has acted as an A component.

Indole:di-2,5-dimethylpyrrole trimer is assumed to have the analogous structure XIII.[13a] The ultraviolet spectrum (see Table I) has a single maximum

at 283 mμ (log ε 3.36), characteristic of the *o*-toluidine system resulting from opening of the single indole nucleus. *o*-Toluidine has maxima in alcohol at 284 mμ (log ε 3.23) and 234 (3.88).[30] In indole:di-2,5-dimethylpyrrole trimer (XIII), the lower wave-length *o*-toluidine band is overshadowed by rising end absorption, because of the two intact pyrrole nuclei, which, by analogy with those in tripyrrole (XI, 219, log ε 4.24[27]), should have their maximum below 220 mμ. The strong and dominant ultraviolet absorption maxima at about 225, 283, and 290 mμ, characteristic of intact indole nuclei, such as those in indole trimers (II), are absent.

The ultraviolet spectra of indole dimers (Table I) represent a composite of the spectra of the indole and indoline nuclei which they contain, but the indole absorption maxima, being more intense, dominate the spectra. The maximum at 240 or 241 mμ, present in the spectra of indoline and 2-methylindoline (see Table I), does appear, however, as a weak inflection at 244–248 mμ in the spectra of many indole dimers (Ia, di-2-methylindole, Ic, VIa) and their salts (Ia, Ib, VIa). With the dimer of 1,3-dimethylindole (VIb), and its hydrochloride, the indoline inflection at 249 mμ is of sufficient intensity to become an important part of the spectrum. The infrared spectra of acyl derivatives of all indole dimers (Ia, Ib, Id, IIIa, VIa) not derived from 1-methylindoles, as well as the maleyl derivative of indole:2,5-dimethylpyrrole dimer (XIIa), contain an NH band (see Table II). Thus, in agreement with the structures assigned, the original dimers must have contained *two* NH groups and could not have contained an indole nucleus in the indolenine form.

Indole:di-2,5-dimethylpyrrole trimer (XIII) differs from the mixed indole trimers in that only one indole molecule has gone into its formation. Here arises an interesting question as to the mechanism of formation of mixed indole trimers. The formation of trindole is assumed to proceed through nucleophilic attack at the 2-position of the indoline portion of protonated diindole by a third indole molecule acting as a B component.[6] That the corresponding reaction does not go at an unactivated (though much less sterically hindered) 2-position of an indoline nucleus is illustrated by the failure of indoline to undergo ring opening with 2-methylindole or 1,2-dimethylindole. After eighteen hours in homogeneous ethanolic hydrochloric acid solution at room temperature, no evidence was found for ring opening products; indoline was recovered (as 1-succinylindoline) in 97% and 74% yields, respectively, along with 72% 1,2-dimethylindole in the latter case. With indole dimers, the ease of the displacement reaction must depend upon the presence of the highly reactive gramine-type system; the reaction probably involves a prior ring opening to a 3H-pseudoindole intermediate[31] (XIV), which then undergoes Michael-type addition by the B-component. Either a mixed indole dimer (Ib or Ic) or diindole (Ia) might serve as the intermediate dimer, but the relative ease of formation of mixed dimers relative to diindole makes it most probable that the mixed dimers are the intermediates. If this is true, then the final B component must be indole and not the more nucleophilic 2-methylindole or 1,2-dimethylindole. This can only be because indole would offer the minimum steric hindrance to attack at a sterically hindered reaction site. 2,5-Dimethylpyrrole, however, is little more sterically hindered at the 3-position than indole. Being more nucleophilic than indole, it becomes the successful B component in the attack on indole:2,5-dimethylpyrrole dimer (XIIa), thus accounting for the two 2,5-dimethylpyrrole nuclei in indole:di-2,5-dimethylpyrrole trimer (XIII).

The physical properties and elemental analyses of the mixed indole dimers and trimers and their salts are reported in Table III.

Acyl derivatives. Two of the free dimers were oils (Ib, XIIa) and four others were difficult to isolate in pure crystalline form (Ia, Ic, Id, IIIa), probably because of a tendency to dissociate into the monomers. These dimers were commonly isolated as their amide derivatives, which had the dual advantage of being highly crystalline derivatives and of being stable with respect to dissociation into the monomers, because acylation ties up the electrons on the indoline nitrogen. A convenient derivatization procedure, commonly employed throughout this work, involved neutralization of the dimer and trimer hydrochlorides with aqueous ammonia in the presence of a water-immiscible organic solvent such as methylene chloride or benzene. The solution of the dimer and trimer in the organic solvent was then separated, dried over magnesium carbonate, and acylated, without necessity for isolation of the free dimer. Maleic anhydride, or one of its derivatives, was usually chosen as the acylating agent because the α,β-unsaturated derivatives of the dimers were desired for study in the novel rearrangement described in the following paper.[32]

Maleyldiindole[16] (XVa) was prepared in 90% yield from diindole hydrochloride by the acylation procedure described above. Succinyldiindole[16] (XVIIa) was obtained in 93% yield by succinylation of diindole. Itaconyldiindole was obtained in 93% yield from diindole hydrochloride by acylation of the neutralized base with itaconic anhydride. Itaconyldiindole underwent alkaline hydrolysis to diindole (isolated in 67% yield as succinyldiindole) and mesaconic acid (in 81% yield), an isomeriza-

(30) P. Grammaticakis, *Bull. soc. chim.*, 139 (1949).

(31) J. D. Albright and H. R. Snyder, *J. Am. Chem. Soc.*, 81, 2239 (1959).

(32) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, 25, 1536 (1960).

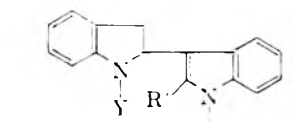
TABLE III

MIXED INDOLE DIMERS AND TRIMERS, AND THEIR SALTS

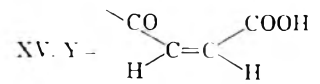
Compound Number	Compound Name	Best Yield, %	M.P.,° Color	Recrystallization Solvent	Molecular Formula and Weight	Analyses, % Found Calcd. C	H	N
Ib·HCl	2-Methyl-3-(2-indolinyl)indole hydrochloride	100[a]	133–135 light yellow	none	$C_{17}H_{17}NCl$ 284.78	72.00 71.70	6.14 6.02	9.94 9.84
Ic	1,2-Dimethyl-3-(2-indolinyl)-indole	98[b]	134–135 white platelets	methanol	$C_{18}H_{18}N_2$ 262.34	82.13 82.40	6.87 6.92	10.78 10.68
Ic·HCl	Hydrochloride of the above	82[c]	149–151 white	none	$C_{18}H_{19}N_2Cl$ 298.81	71.96 72.35	6.63 6.41	8.98 9.38
	Bisdiskatole oxalate	98[d]	184–185[e] white fine needles	ethanol	$C_{38}H_{38}N_4O_4$ 614.72	74.22 74.24	6.19 6.23	9.32[e] 9.12
VIb	1,3-Dimethyl-2-(1,3-dimethyl-2-indolinyl)indole	94	124–125.5 white	90% ethanol	$C_{20}H_{22}N_2$ 290.39	82.98 82.72	7.65 7.64	9.68 9.65
VIb·HCl	Hydrochloride of the above	98[c]	113–117 white	none	$C_{20}H_{23}N_2Cl$ 326.86	73.19 73.49	7.23 7.09	8.55 8.57
XIIa·HCl	2,5-Dimethyl-3-(2-indolinyl)-pyrrole hydrochloride	90[c]	134–136 white[g]	none	$C_{14}H_{17}N_2Cl$ 248.75	68.00 67.59	6.86 6.89	10.89 11.26
IId	Diindole:1,2-dimethylindole trimer	14	165–166 white	methanol	$C_{26}H_{25}N_3$ 379.48	82.50 82.29	6.77 6.64	11.00 11.07
XIII	Indole:di-2,5-dimethylpyrrole trimer	41[f]	197–199 white platelets	ethanol	$C_{20}H_{25}N_3$ 307.43	78.41 78.13	8.51 8.20	13.76 13.67

[a] Prepared from the monomers by George J. Meisters. [b] From alkaline hydrolysis of the maleyl derivative. [c] Prepared in ether solution from the free base. [d] Prepared essentially by the method of ref. 8. [e] Reported m.p. 180°, % N, 9.58.[8] [f] From neutralization of the crude hydrochloride in warm ethanol with aqueous 2N sodium hydroxide solution. [g] Unstable; turns orange and then brown at room temperature after a few days.

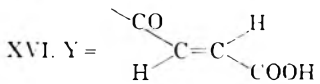
tion product of itaconic acid. The fact that itaconyldiindole does not undergo the rearrangement described in the following paper[32] leads in part to the assumption that the double bond is not conjugated with the carboxamide group and that acylation has occurred, as would be expected, at the less sterically hindered and less resonance-stabilized, saturated carbonyl group. Consequently, itaconyldiindole is tentatively assigned structure XVIIIa. Benzenesulfonyldiindole (XXa) was obtained in quantitative yield from the Hinsberg reaction of diindole and benzenesulfonyl chloride. When indole was substituted for diindole in the Hinsberg procedure, benzenesulfonyldiindole was again obtained. The diindole may have been formed by action of hydrochloric acid (from prior hydrolysis of benzenesulfonyl chloride in the organic layer) on indole– or benzenesulfonyldiindole may be formed by the direct action of benzenesulfonyl chloride on indole (in a manner similar to the direct action of maleic anhydride on indole, forming maleyldiindole[16,34]).



XV–XX



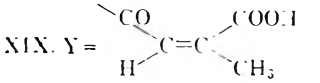
XV. Y =



XVI. Y =

XVII. Y = $COCH_2CH_2COOH$

XVIII. Y = $COCH_2C(CH_2)COOH$



XIX. Y =

XX. Y = $SO_2C_6H_5$

XVa, XVIIa, XVIIIa, XXa. R = R′ = H
XVb–XIXb. R = H, R′ = CH_3
XVc–XVIIc. R = R′ = CH_3
XVd. R = H, R′ = C_6H_5

(33) Fred B. Stocker, M.S. thesis, University of Minnesota, August 1955.

(34) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **23**, 320 (1958).

From indole:2-methylindole dimer hydrochloride, after neutralization and acylation with maleic anhydride, a stereoisomeric pair of maleyl (XVb) and fumaryl (XVIb) derivatives was obtained in yields of up to 54% and 19%, respectively. A novel rearrangement involving these derivatives is described in the following paper.[32] Both stereoisomers were hydrogenated over Raney nickel in yields of 95% and 88% to the succinyl derivative (XVIIb), which was prepared independently by substituting succinic anhydride for maleic anhydride in the acylation procedure. Similarly obtained were the itaconyl derivative (XVIIIb), in 33% yield by acylation with itaconic anhydride, and the citraconyl derivative (XIXb), in 25% yield by acylation with citraconic anhydride. The structures of these derivatives (XVIIIb, XIXb) are tentatively assigned on the basis of their behavior in the novel rearrangement and the considerations described in the following paper.[32]

From indole:1,2-dimethylindole dimer hydrochloride another stereoisomeric pair of maleyl (XVc) and furmaryl (XVIc) derivatives was obtained in yields of 47% and 7%, respectively, by acylation with maleic anhydride. Both stereoisomers were hydrogenated over Raney nickel to the succinyl derivative (XVIIc), which was prepared independently in 93% yield by succinylation of the pure dimer. The dimer (Ic) was obtained in yields of 98% and 39%, along with fumaric acid, from alkaline hydrolysis of the maleyl and fumaryl derivatives, respectively.

From indole:2-phenylindole dimer hydrochloride only a maleyl derivative (XVd) was obtained, in 23% yield. A novel rearrangement involving this derivative is described in the following paper.[32] From indole:2,5-dimethylpyrrole dimer hydrochloride again only a maleyl derivative (XIIb) was obtained, in 67% yield. Alkaline hydrolysis of this derivative gave, along with a quantitative yield of fumaric acid, the free dimer as an oil in 85% yield. This oil was reconverted into the maleyl derivative in 64% yield.

The reason for the concurrent formation of fumaryl as well as maleyl derivatives from maleic anhydride and dimers containing an indole with a 2-methyl group, but not from diindole, is unknown. An analogous pair of maleyl (VIc) and fumaryl (VId) derivatives of diskatole has been described[16]: the maleyl (white, m.p. 194°) being obtained from diskatole and maleic anhydride, and the fumaryl (yellow, m.p. 246°) from acid-catalyzed dimerization of skatole in the presence of maleic anhydride. On catalytic hydrogenation both stereoisomers gave succinyldiskatole, which was also prepared independently from succinic anhydride and diskatole. In our hands, all attempts to prepare fumaryldiskatole, according to the limited experimental details of the procedure[16] for the reaction of skatole with maleic anhydride catalyzed by sulfuric acid, were unsuccessful. Likewise, attempts to isomerize maleyldiskatole to fumaryldiskatole in ethanolic solutions containing sulfuric acid or iodine resulted in recovery of unchanged maleyldiskatole.

The assignment of configuration to the maleyl and fumaryl derivatives of indole dimers is based on the greater conjugation shown in the ultraviolet spectra (Table II) of the fumaryl derivatives (XVIb–c). Also, in the two cases where stereoisomeric pairs were obtained, the member to which we have assigned the fumaryl configuration has the higher melting point (Table IV). The two fumaryl derivatives have an absorption band at 318–323 mμ, not present in the maleyl derivatives or any of the other acyl derivatives. In contrast, except for the 2-phenyl-substituted case (XVd), the maleyl (IIIb, VIc, XIIb, XVa–c), as well as the succinyl (XVIIa–c), itaconyl (XVIIIa–b), and citraconyl (XIXb) derivatives, but not the fumaryl derivatives, have an absorption maximum in the 252–269 mμ region, which is also characteristic of the maleyl and succinyl indolines (250–255 mμ). The corresponding maximum in benzenesulfonyldiindole (XXa) occurs at 271 mμ. These maxima are completely lacking in the corresponding derivatives (IIe–g) of indole trimers (IIc–d). The trimers and their derivatives lack the indoline structure and, except for a band at 274 mμ in the citraconyl derivative (IIf), have only normal indole absorption. Besides the absorption bands mentioned above, all of the indole dimers, trimers, and their derivatives have the absorption bands associated with the indole nucleus, which occur at about 218–229 and 280–294 mμ. In the 2-phenylindole-substituted case (XVd) these bands have undergone the usual bathochromic shifts of about 10 mμ characteristic of 2-phenylindole and its derivatives.

All of the acyl derivatives containing unsaturation conjugated with the carboxamide group (maleyl, fumaryl, and citraconyl), except maleyldiskatole, are yellow in color (Table IV) because of a broad tailing out of ultraviolet absorption maxima into the visible region. The yellow color is instantly discharged when the free carboxyl group of the derivatives is neutralized by conversion to a salt. This fact is illustrated by conversion of yellow maleyldiindole:1,2-dimethylindole trimer (IIg) to its colorless potassium salt (Table IV). In contrast to the yellow unsaturated acid derivatives, all of the unconjugated acyl derivatives (such as the succinyl and itaconyl) are colorless.

Maleic anhydride acylation of the neutralization products of the viscous, oily mixture of hydrochlorides from the skatole:2-methylindole reaction gave a variety of products. Included among these were maleyldiskatole (VIc) and the 1:1 and 2:1 adducts of 2-methylindole with maleic anhydride.[16] When benzene was used as a solvent for acylation, the maleyl derivative (IIIb) of skatole:2-methylindole dimer began to precipitate after two minutes

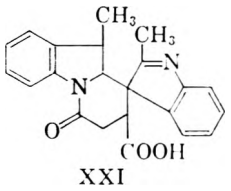
TABLE IV

ACYL DERIVATIVES OF MIXED INDOLE DIMERS AND TRIMERS, AND RELATED COMPOUNDS

Compound		Best Yield, %	M.P.,[c] Color	Recrystallization Solvent[j]	Molecular Formula and Weight	Analyses, % Found / Calcd.		
Number	Name					C	H	N
XVIIIa	3-(1-Itaconyl-2-indolinyl)-indole	93	164–165 dec.[a] White	E[j]	$C_{21}H_{18}N_2O_3$ 346.37	72.71 / 72.82	5.39 / 5.24	8.23 / 8.09
XXa	3-(1-Benzenesulfonyl-2-indolinyl)-indole	100	170–172 White	E-60[j]	$C_{22}H_{18}N_2O_2S$ 374.45	70.42 / 70.56	4.84 / 4.85	7.29 / 7.48
XVb	2-Methyl-3-(1-maleyl-2-indolinyl)-indole	54	156–157 dec.[a] Yellow	A[j]	$C_{21}H_{18}N_2O_3$ 346.37	72.69 / 72.82	5.38 / 5.24	8.09 / 8.09
XVIb	2-Methyl-3-(1-fumaryl-2-indolinyl)-indole	19	215–217 dec.[a] Yellow	A or C[j]	$C_{21}H_{18}N_2O_3$ 346.37	73.10 / 72.82	5.43 / 5.24	7.91 / 8.09
XVIIb	2-Methyl-3-(1-succinyl-2-indolinyl)-indole	39	135–137[b] White	A	$C_{21}H_{20}N_2O_3$ 348.39	72.35 / 72.39	5.67 / 5.79	8.27 / 8.04
XVIIIb	2-Methyl-3-(1-itaconyl-2-indolinyl)-indole	33	171–172 dec.[a] White	A	$C_{22}H_{20}N_2O_3$[k1] 360.40	73.14 / 73.31	5.86 / 5.59	7.88 / 7.77
XIXb	2-Methyl-3-(1-citraconyl-2-indolinyl)-indole	25	146–147 dec.[a] Yellow	A	$C_{22}H_{20}N_2O_3$ 360.40	73.07 / 73.31	5.82 / 5.59	7.90 / 7.77
XVc	1,2-Dimethyl-3-(1-maleyl-2-indolinyl)-indole	47[c]	164–165 dec.[a] Yellow fine needles	A	$C_{22}H_{20}N_2O_3$ 360.40	73.07 / 73.31	5.66 / 5.59	7.82 / 7.77
XVIc	1,2-Dimethyl-3-(1-fumaryl-2-indolinyl)-indole	7	211–212.5 dec.[a] Yellow platelets	A	$C_{22}H_{20}N_2O_3$ 360.40	73.37 / 73.31	5.72 / 5.59	7.85 / 7.77
XVIIc	1,2-Dimethyl-3-(1-succinyl-2-indolinyl)indole	93[d]	181–182 dec.[a] White	A	$C_{22}H_{22}N_2O_3$ 362.42	73.04 / 72.91	6.30 / 6.12	7.84 / 7.73
XVd	2-Phenyl-3-(1-maleyl-2-indolinyl)-indole	23	189.5–191 dec.[a] Yellow	A	$C_{25}H_{20}N_2O_3$ 408.44	76.64 / 76.45	5.17 / 4.94	6.97 / 6.86
IIIb	2-Methyl-3-(1-maleyl-3-methyl-2-indolinyl)-indole	37[e]	154–155 dec.[a] Yellow, hygroscopic	A	$C_{22}H_{20}N_2O_3$ 360.40	73.27 / 73.31	5.94 / 5.59	8.09 / 7.77
XIIb	2,5-Dimethyl-3-(1-maleyl-2-indolinyl)-pyrrole	67	156–157.5 dec.[a] Yellow[f] needles	A	$C_{18}H_{18}N_2O_3$ 310.34	69.89 / 69.66	5.93 / 5.85	9.24 / 9.03
IIe	Succinyldiindole: 2-methylindole trimer	15	224–225[g] White	A or E-W[j] A	$C_{29}H_{27}N_3O_3$[k2] 465.53	74.71 / 74.82	6.00 / 5.85	9.06 / 9.03
IIf	Citraconyldiindole: 2-methylindole trimer	62	196–197 dec.[a] Yellow	A	$C_{30}H_{27}N_3O_3$ 477.54	75.36 / 75.45	5.83 / 5.70	9.04 / 8.80
IIg	Maleyldiindole: 1,2-dimethylindole trimer	11[l]	183–183.5 dec.[a] Yellow fine needles	A	$C_{30}H_{27}N_3O_3$[k3] 477.54	75.53 / 75.45	5.89 / 5.70	8.85 / 8.80
IIg K salt	Monopotassium salt of the above	87	283–285 dec.[a] White	M[j]	$C_{30}H_{26}N_3O_3K$ 515.63	68.47 / 68.71[i]	5.17 / 5.08	8.21 / 8.15
XXI	Spiro[(8-carboxy-10-methyl-6,7,8,-9,9a,10-hexahydrobenzo[b]-pyrrocol-6-one)-9,3′-(2′-methyl[3]pseudoindole)]	10[h]	257–258 dec.[a] White	A	$C_{22}H_{20}N_2O_3$[k4] 360.40	73.17 / 73.31	5.54 / 5.59	7.93 / 7.77

[a] With carbon dioxide evolution. [b] After being dried at 90° *in vacuo* for 3 hr., the crystals softened at 118°, with partial melting, followed by solidification and remelting at 169–170°. The Nujol infrared spectra were sensitive to the length of the drying time at 90°. A sample prepared in methylene chloride melted at 133–134°. [c] Also regenerated from the pure dimer obtained by its alkaline hydrolysis. [d] From the pure dimer. [e] Prepared in benzene solution. [f] The impure compound is particularly unstable, and it must be recrystallized quickly. [g] A mixed melting point with succinyltriindole,[35] m.p. 213–214°, was depressed and the Nujol infrared spectra were different. [h] Prepared in 1:1 (by volume) methylene chloride-acetonitrile. [i] Allowing for 0.5 C-atom left as a residue of potassium carbonate. [j] E, ethanol; E-60, 60% ethanol; A, acetonitrile; C, acetone; E-W, ethanol-water; M, methanol. [k] Neutralization equivalent: k_1, 361; k_2, 458; k_3, 461; k_4, 346. [l] Also prepared in 97% yield by acylation of the free mixed trimer in acetonitrile solution.

and was obtained in 37% yield after three hours. When acylation was carried out in a more polar solvent (methylene chloride, or methylene chloride to which an equal volume of acetonitrile has been added), from which the maleyl derivative did not precipitate, the residue from overnight evaporation of the solvent contained 2–10% yields of a colorless (or grayish white) isomer, m.p. 257–258° dec. This isomer has been assigned the spiro indolenine structure XXI on the basis of the following evidence: (1) The elemental analyses and neutralization equivalent are consistent with a monobasic



XXI

acid of the formula $C_{21}H_{19}N_2O{\cdot}COOH$. The compound is soluble in acid as well as base; (2) The infrared spectrum in Nujol contains no NH band, but does contain a single very strong carbonyl band at 1688 cm.$^{-1}$. The intensity of the carbonyl band is consistent with its being the resultant of superposition of bands due to a six-membered ring lactam carbonyl and a carboxyl carbonyl. The infrared spectrum contains a double bond band at 1583 cm.$^{-1}$, similar to that at 1579 cm.$^{-1}$ in liquid 2,3,3-trimethylindolenine (see Table II); (3) The ultraviolet absorption maximum at 253 (4.19) is very similar to that in 1-succinylindoline at 252 (4.19) and is also similar in location to that at 255 mμ (log ϵ 3.78) in 2,3,3-trimethylindolenine; (4) The compound undergoes the alkaline hydrolysis rearrangement and yields the same products as does the maleyl derivative IIIb.[32]

Compound XXI is of great interest because it appears to have the structure proposed for the intermediate of the alkaline hydrolysis rearrangement.[32] It is assumed to arise from the maleyl derivative (IIIb) by addition of the nucleophilic 3-position of the 2-methylindole nucleus to the electrophilic double bond of the maleyl group at a position β- to the carboxamide group, followed by a proton transfer to the anionic α-carbon. If addition at the β-carbon were reversible, then configurational instability of the intermediate anion, or loss from the α-carbon of a different proton from the one which had added, could result in isomerization of the double bond to the fumaryl configuration. If the addition compounds formed in the indole:2-methylindole and indole:1,2-dimethylindole series, analogous to XXI in the skatole:2-methylindole series, formed but were relatively unstable, then they could serve as intermediates in formation of the fumaryl derivatives XVIb–c. As no clearcut evidence has as yet been obtained for isomerization of maleyl to fumaryl derivatives during purification by recrystallization, this possibility may not be admissible. A plausible alternative, which would account for isomerization *during* acylation, would be amine catalysis by reversible addition to the double bond by not yet acylated dimer.

EXPERIMENTAL

Melting points were determined on a calibrated Fisher-Johns hot stage.

The general procedure for the preparation of mixed indole dimer hydrochlorides and acyl derivatives is illustrated by the example given below. Usually the acylations were carried out in methylene chloride solution, except that mixtures of methylene chloride:acetonitrile (1:1 by volume) were used for the preparation of IIg, XVa, XVc, XVIc, and XXI; acetonitrile was used for the preparation of XVd; and benzene was used for the preparation of IIIb, VIc, XIIb, XVIIa, XVIIc, and XVIIIa. Details of the experimental procedures may be obtained from the thesis on which this paper is based.[3] Microfilm copies may be purchased from University Microfilms, Ann Arbor, Michigan.

2-Methyl-3-(2-indolinyl)indole hydrochloride (indole:2-methylindole dimer hydrochloride; Ib·*HCl*).[35] Dry hydrogen chloride was passed slowly into a stirred and ice-cooled solution of indole (8.93 g., 0.0762 mole) and 2-methylindole (10.00 g., 0.0762 mole) in dry ether (150 cc.). The hydrogen chloride was introduced very slowly for the first 10 min. and the rate was increased until saturation was achieved after about 1 hr. The light yellow precipitate was filtered and dried in a vacuum desiccator (21.92 g., 0.0770 mole, 101%), m.p. 133–135°. The sample was analyzed without attempted recrystallization. The spectral data are reported in Table I and the elemental analyses in Table III.

2-Methyl-3-(1-maleyl-2-indolinyl)indole (XVb) *and 2-methyl-3-(1-fumaryl-2-indolinyl)indole* (XVIb). Undried 2-methyl-3-(2-indolinyl)indole hydrochloride (20.0 g., 0.0702 mole) was overlaid with methylene chloride (250 cc.) and water (50 cc.) and then neutralized with aqueous concd. ammonium hydroxide (10.6 cc.). The methylene chloride layer was separated and dried over anhydrous magnesium carbonate. Maleic anhydride (7.10 g., 0.0723 mole) was added to the dried solution, with stirring to facilitate evaporation. After 1 hr. the yellow crystals (6.14 g.), m.p. 156–157° dec., were filtered. After 2 additional hr. of stirring and evaporation more yellow crystals (3.04 g.), m.p. 154–156° dec., were obtained, making the total 9.18 g., 0.0265 mole, 38%. One recrystallization from acetonitrile yielded 2-methyl-3-(1-maleyl-2-indolinyl)indole as yellow crystals, m.p. 156–157° dec. with carbon dioxide evolution.

After the methylene chloride mother liquor had been set aside for a longer time (3 days) another yellow crystalline compound (4.62 g., 0.0133 mole, 19%), m.p. 212–216° dec., was obtained. Three recrystallizations from acetone (or acetonitrile) yielded 2-methyl-3-(1-fumaryl-2-indolinyl)-indole as yellow microcrystals, m.p. 215–217° dec. with carbon dioxide evolution.

The spectral data for these maleyl and fumaryl derivatives are reported in Table II and the elemental analyses are given in Table IV.

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(35) Experiment performed by George J. Meisters.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

A Novel Rearrangement Involving Indole Dimers[1]

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Received January 25, 1960

The maleyl and fumaryl derivatives of indole:2-methylindole dimer (Ib) and the maleyl derivatives of skatole:2-methylindole dimer (*cis*-Id) and of indole:2-phenylindole dimer (*cis*-Ic) rearrange under alkaline hydrolysis conditions to the corresponding (2-methyl-3-indole)succinic acid (IIb) in the first three cases, or (2-phenyl-3-indole)succinic acid (IIc) in the latter case. The 2-substituent labels the indole nucleus to which migration of the maleyl or fumaryl group has occurred. Besides by means of the rearrangement, (2-phenyl-3-indole)succinic acid (IIc) has been prepared from the reaction of 2-phenylindole with maleic acid. The corresponding anhydride, (2-phenyl-3-indole)succinic anhydride, has been prepared from the diacid by anhydride exchange with acetic anhydride. For rearrangement to occur, the necessity of a hydrogen on nitrogen of the indole nucleus has been demonstrated. This is shown by the fact that the maleyl and fumaryl derivatives of indole:1,2-dimethylindole dimer (Ie) undergo simple alkaline hydrolysis, without rearrangement, to the dimer and fumaric acid. A mechanism for the rearrangement is proposed in which the maleyl or fumaryl group is transferred intramolecularly through a six-membered spiro ring intermediate from the 1-position of the indoline nucleus to the 3-position of the indole nucleus in the dimer with subsequent depolymerization. The isolation of an isomer of maleyl skatole:2-methylindole dimer, for which the spiro ring structure of the intermediate has been proposed, lends further support to the proposed intermediate in the mechanism. This isomer rearranges under alkaline hydrolysis conditions to the same product (IIb) as maleyl skatole:2-methylindole dimer. Some of the limits of the rearrangement are delineated by the facts that, like maleyl and fumaryldiskatole (VII), maleyl indole:2,5-dimethylpyrrole dimer (VIII) and itaconyldiindole undergo simple amide hydrolysis without rearrangement. Some of the value of the rearrangement, besides in the synthesis of (3-indole)succinic acid (IIa),[4] is illustrated by the fact that both the itaconyl (IX) and citraconyl (*cis*-X) derivatives of indole:2-methylindole dimer rearrange to the same new diacid, for which the 2-methyl-2-(2-methyl-3-indole)succinic acid structure (XI) is proposed. This diacid is different from another new diacid (XII) derived from hydrolysis of the anhydride adduct of 2-methylindole and itaconic anhydride. Likewise, the anhydrides of the two diacids are different.

We have previously shown that rearrangement of maleyldiindole (*cis*-Ia) under alkaline hydrolysis conditions yields (3-indole)succinic acid (IIa).[4] It was established that (3-indole)succinic acid does not form by addition of indole to maleate or fumarate anions, which might have resulted from prior alkaline hydrolysis of maleyldiindole. It follows then that during the rearrangement the 3-position of either the indoline or the indole nucleus of diindole must add to the α,β-unsaturation of the maleyl group.

Two possible reaction mechanisms, both involving six-membered ring intermediates, were considered as most plausible. One mechanism would require that a benzyl hydrogen at the 3-position of the indoline portion of maleyldiindole (*cis*-Ia) be sufficiently acidic so that a benzyl anion is formed, which could undergo intramolecular Michael addition to the maleyl or fumaryl group, forming the bicyclic six-membered ring intermediate (or transition state) III. Cleavage of the acyl-nitrogen bond in III could be concerted with the formation of III (resulting in a transient ketene intermediate) or cleavage could be the result of subsequent amide hydrolysis. In either case, the anion on nitrogen would have to depolymerize by eliminating an indole molecule, thus forming the indolenine IV, which would rapidly tautomerize to (3-indole)succinate IIa anion.

If maleyldiindole rearranges according to this mechanism, then 1-maleylindoline and 1-maleyl-2-methylindoline might undergo a similar cyclization step, perhaps more easily because of the absence of a large hindering substituent at the 2-position. In these cases, however, the (3-indoline)succinic acids should represent stable end products, since the hydrogen or methyl substituents in the 2-position should eliminate less readily as anions than indole. 1-Maleylindoline and 1-maleyl-2-methylindoline were prepared and subjected to the alkaline hydrolysis conditions of the rearrangement. They did not rearrange, but underwent simple amide hydrolysis instead. Indoline and 2-methylindoline were recovered as the picrates in 87 and 89% yields, respectively, along with 74 and 79% yields of fumaric acid, the alkaline isomerization product of maleic acid. Consequently, the validity of the mechanism proposed for the rearrangement of maleyldiindole, in which the maleyl group is transferred intramolecularly from the 1- to the 3- position of the indoline nucleus through intermediates like III, has not been demonstrated in these cases.

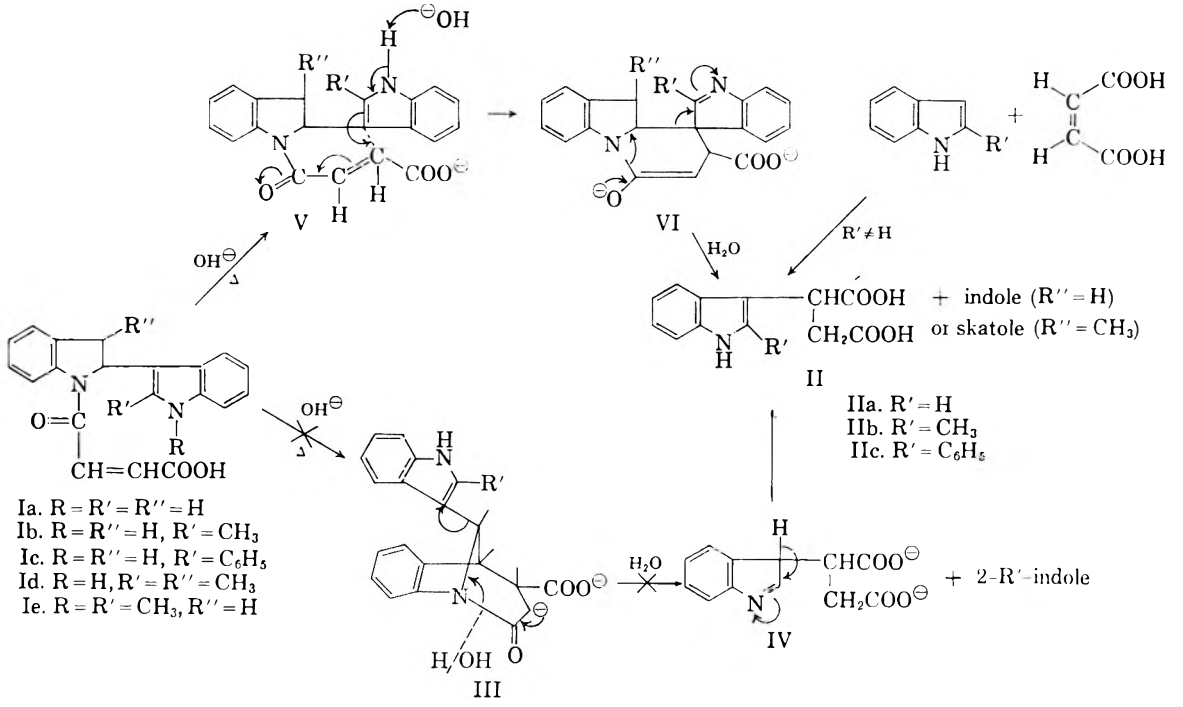
1-Maleylindoline crystallized from benzene as a yellow solvent complex containing one molecule

(1) Presented in part as Paper 26 before the Organic Division at the 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 8, 1958, Abstracts p. 14P.

(2) We are indebted to the Graduate School of the University of Minnesota for a 1957 Faculty Summer Research Appointment.

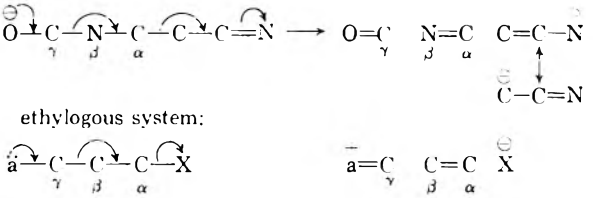
(3) From the Ph.D. thesis of Charles F. Hammer, May 1959, Research Corporation Research Assistant, 1956–59, Upjohn Company Summer Fellow 1958. We are indebted to the Research Corp. for a Frederick Gardner Cottrell Grant in support of this research, and to the Upjohn Co. for a summer fellowship.

(4) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **23**, 320 (1958).



of benzene for each two molecules of 1-maleylindoline. When dropped on a hot block, the yellow crystals melt at 128–130°, with the evolution of benzene, and then solidify to the white, benzene-free compound, m.p. 155–156.5° dec. When heated slowly, the yellow crystals turn white and evolve their benzene quantitatively within ten minutes at 100°. The white compound is reconverted to the yellow benzene complex upon recrystallization from benzene. 1-Succinylindoline was also prepared for the purpose of comparison of its physical properties.

The other most plausible mechanism for the rearrangement of maleyldiindole (*cis*-Ia) involves initiation (V) by removal of the acidic proton from nitrogen of the indole nucleus, giving a resonance-stabilized anion, quite probable under the alkaline conditions employed. Although neutral 3-alkylindoles normally undergo electrophilic substitution at the 2- position,[5] and indole anions add preferentially at the 1-position in *inter*molecular Michael additions,[6] steric factors in this *intra*molecular case would favor Michael addition (V) of the indole anion at its 3- position, yielding the six-membered spiro ring intermediate (or transition state) VI. Rapid alkaline hydrolysis of this intermediate (or of the ketene derivable from it by a concerted elimination) and elimination of an indole molecule would then yield (3-indole)succinate(IIa) anion. This elimination reaction is seen to be an example of Grob's "Principle of Ethylogy,"[7] in which a nitrogen atom has replaced a β-carbon atom of the usual ethylogous system.



To test the validity of this mechanism for the rearrangement, it is necessary to label one indole nucleus so that it can be distinguished from the other in the dimer. Conceivably this objective can be accomplished by labeling one of the indole nuclei with isotopic carbon or nitrogen. The presently available method of synthesis of diindole, by acid-catalyzed dimerization of indole, offers no hope, however, of specificity in this regard. Consequently, we turned to the synthesis of mixed indole dimers, which would contain the desired distinguishing label in the form of a substituent on one of the indole nuclei, the location of which must be established unambiguously. This is the subject of our preceding paper.[8]

Both the maleyl and fumaryl derivatives of indole:2-methylindole dimer (Ib) rearranged under alkaline hydrolysis conditions to (2-methyl-3-indole)succinic acid (IIb) in yields of 96% and 87%, respectively. No (3-indole)succinic acid (IIa) was formed, but indole was obtained in yields of 87% and 72%. The fact that both the maleyl and fumaryl derivatives rearrange shows that the steric requirements of the reaction at the double bond are

(5) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).
(6) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957).
(7) C. A. Grob, *Experientia*, **13**, 126 (1957).
(8) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960).

not a dominant factor. Likewise, a 3-methyl substituent on the indoline nucleus does not inhibit the reaction; the maleyl derivative of skatole:2-methylindole dimer (Id) rearranged to (2-methyl-3-indole)succinic acid (IIb, 100%) and skatole (95%). Similarly, the maleyl derivative of indole:-2-phenylindole dimer (Ic) rearranged to (2 phenyl-3-indole)succinic acid (IIc, 86%) and indole (79%). Since (2-phenyl-3-indole)succinic acid was previously unknown, it was prepared independently in 70% yield by warming 2-phenylindole with maleic acid according to a modification of the method of Noland and Lange[9] for (2-methyl-3-indole)succinic acid. (2-Phenyl-3-indole)succinic acid (IIc), which appeared to be unstable and did not crystallize well from other solvents, was best isolated from acetonitrile as a stable, crystalline solvent complex containing one molecule of acetonitrile for each two molecules of the acid. The acid was converted to the corresponding anhydride by anhydride exchange with acetic anhydride.

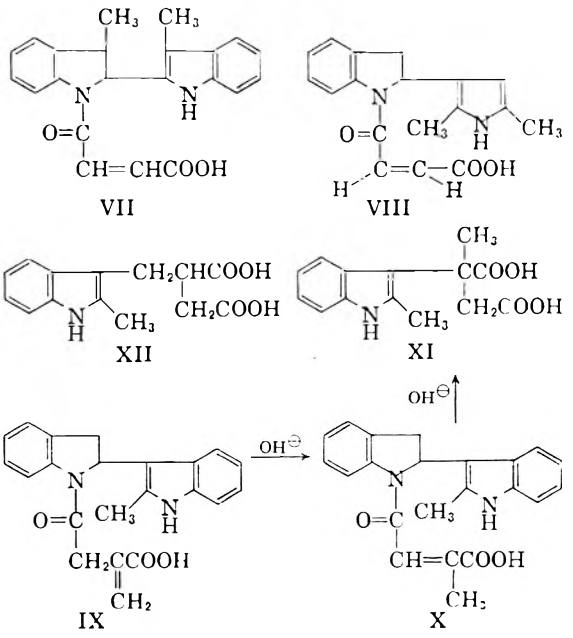
The results of the hydrolysis experiments involving derivatives of mixed indole dimers support the mechanism proposed for the rearrangement in which a maleyl (or fumaryl) group is transferred through intermediates like V and VI from the indoline to the indole nucleus of the dimer. The necessity in the rearrangement for an initiating step in which a proton is removed from nitrogen of the indole nucleus is suggested by experiments in which the N—H group of the indole nucleus is replaced by an N—CH_3 group. Alkaline hydrolysis of both the maleyl and fumaryl derivatives of indole:1,2-dimethylindole dimer (Ie) gave only the regenerated dimer in yields of 98% and 39%, respectively, along with fumaric acid, but no (1,2-dimethyl-3-indole)succinic acid.[8] These results indicate that the rearrangement does not proceed with maleyl and fumaryl derivatives of mixed indole dimers containing substituents other than hydrogen on nitrogen of the indole nucleus.

Of great interest in connection with proposal of VI as an intermediate in the rearrangement is the isolation from acylation of skatole:2-methylindole dimer with maleic anhydride in more polar solvents of a product for which a structure analogous to the keto form of VI has been proposed.[8] This rearrangement product (XXI in the preceding paper[8]) further rearranged under alkaline hydrolysis conditions in the same manner as its isomer, the maleyl derivative of skatole:2-methylindole dimer (Id), to give (2-methyl-3-indole)succinic acid (IIb) in 94% yield, and skatole in 94% yield.

Maleyldiskatole and fumaryldiskatole are reported to undergo alkaline hydrolysis without rearrangement, yielding diskatole and fumaric acid.[10] Since the structure of diskatole has been proved by degradation,[11] its maleyl and fumaryl derivatives will have the corresponding structures (VII). In these cases failure to rearrange is not due to lack of an N—H group on the indole nucleus.

If rearrangement were to occur at the 2- position, a common site for electrophilic substitution in skatole,[5] then structures VII would lead to a six-membered ring intermediate which would possess a driving force for elimination of a skatole molecule. That such rearrangement does not occur may be attributed to the lower nucleophilicity in indoles of a 2- position relative to a correspondingly substituted 3- position. For these diskatole derivatives to cyclize at the 3- position to intermediates analogous to VI would require the sterically less probable formation of a seven-membered ring. Even if such cyclization were to occur, however, a driving force for the elimination phase of the rearrangement would be lacking. Consequently, it is logical that the rearrangement does not occur with diskatole derivatives.

The maleyl derivative of indole:2,5-dimethylpyrrole dimer (VIII) also underwent alkaline hydrolysis without rearrangement, giving the dimer in 85% yield, along with a quantitative yield of fumaric acid.[8] The failure of this derivative to rearrange must be attributed to low nucleophilicity of the 3- position of the 2,5-dimethylpyrrole nucleus, which permits the rate of simple amide hydrolysis to exceed substantially the rate of rearrangement. Perhaps low acidity of the pyrrole N—H, which, unlike the indoles, lacks an *N*-phenyl



(9) (a) W. E. Noland, R. F. Lange, F. B. Stocker, and G. L. Sauer, Paper 10 presented before the Organic Division at the 132nd National Meeting of the American Chemical Society, Sept. 9, 1957, Abstracts, p. 6P; (b) Ronald F. Lange, Ph.D. Thesis, University of Minnesota, June 1958.

(10) O. Diels, K. Alder, and W. Lübbert, *Ann.*, **490**, 277 (1931).

(11) G. F. Smith and A. E. Walters, unpublished work, University of Manchester, England (private communication, Oct. 16, 1958).

substituent, makes anion formation relatively difficult.

The rearrangement described in this paper may have little practical value for the synthesis of (2-substituted-3-indole)succinic acids since they are conveniently prepared directly by addition of 2-substituted indoles to maleic acid.[9] The rearrangement does have value, however, in the synthesis of (3-indole)succinic itself,[4] and may have value in the preparation of (3-indole)propionic acids and their derivatives substituted in any position but the 1- position of the indole nucleus, starting from the appropriate acrylic derivatives of indole dimers. This phase of our research is currently under investigation.

In hope of using the rearrangement to synthesize (3-indole)succinic acids containing additional substituents in the succinic acid sidechain, we have prepared the itaconyl (IX) and citraconyl (*cis*-X) derivatives of indole:2-methylindole dimer and shown that they are different compounds.[8] Both derivatives rearranged under alkaline hydrolysis conditions to the same new diacid, m.p. 223–224.5° dec., in yields of 72% and 37%, along with indole in yields of 53 and 81%, respectively. This diacid is assigned the structure 2-methyl-2-(2-methyl-3-indole)succinic acid (XI), although the alternative structure, 2-methyl-3-(2-methyl-3-indole)succinic acid, has not been rigorously excluded. Assignment of structure XI to the diacid is based on the following plausible assumptions with respect to the structure of its acylated dimer precursors: (1) that, with itaconic anhydride, acylation has occurred at the less sterically hindered and less resonance stabilized, saturated carbonyl group; and (2) that, with citraconic anhydride, acylation has occurred at the less sterically hindered carbonyl group, the one β- to the methyl group.

It is evident that, under the alkaline conditions employed, the double bond of either the itaconyl or the citraconyl derivative has rearranged to the alternative position. That it is the double bond of the itaconyl derivative which has rearranged (into conjugation with both carbonyl groups) is established by the fact that the diacid product, m.p. 223–224.5° dec., is different from another new diacid, m.p. 149–151° dec., obtained by hydrolysis of the anhydride adduct of 2-methylindole and itaconic anhydride. Since the latter was formed under mild, nonalkaline conditions, the double bond of itaconic anhydride is assumed not to have rearranged prior to addition of 2-methylindole; consequently, structure XII appears to be established for the diacid, m.p. 149–151° dec., derived from this anhydride adduct. The anhydride, m.p. 144°, prepared from XI by anhydride exchange with acetic anhydride, like the parent diacids, was different from the anhydride adduct, m.p. 134–135°, from 2-methylindole and itaconic anhydride. The reactions of 2-methylindole with citraconic acid or citraconic anhydride failed to give either the diacids XI or XII or the corresponding anhydrides. Consequently, the rearrangement has synthetic value for the preparation of the diacid XI.

In contrast to the itaconyl derivative of indole:2-methylindole dimer (IX), which underwent double bond isomerization and then rearrangement, itaconyldiindole underwent alkaline hydrolysis without rearrangement, giving diindole in 67% yield, along with mesaconic acid, an isomerization product of itaconic acid, in 81% yield. The failure of itaconyldiindole to rearrange must be attributed to the lower nucleophilicity of the indole nucleus (relative to that of 2-methylindole), combined with a possibly greater rate of hydrolysis of the less hindered amide linkage, a rate which must substantially exceed the combined rates of double bond isomerization and subsequent rearrangement involving nucleophilic attack at a relatively hindered tertiary carbon atom.

Our work on the rearrangement has so far been carried out with hydrolysis under heterogeneous conditions, by refluxing with aqueous 30% hydroxide solution, and the yields have been good. It may be more convenient and desirable from a synthetic standpoint, however, to carry out the rearrangement under homogeneous conditions, in alcoholic alkali. Our experience indicates that (3-indole)succinic acid can be prepared in this way (see Experimental) in as good yield, and in a purer initial state, than by the method previously described.[4] A new and convenient synthesis of (3-indole)succinic acid has recently been reported.[12]

EXPERIMENTAL

Melting points were determined on a calibrated Fisher-Johns hot stage. In this paper, with reference to the melting points of carboxylic acids, "dec." indicates that melting occurred with gas evolution, in the form of steam or carbon dioxide.

Indoline. The procedure of King, Barltrop, and Walley[13] was used. Indole (100.0 g., 0.854 mole) in absolute ethanol (750 cc.) solution was hydrogenated at 100 atm. over Raney nickel at 95–101° for 4 hr. After filtration of the catalyst and removal of the solvent, vacuum distillation yielded a colorless oil (93.6 g., 0.785 mole, 92%), b.p. 65–67° (0.5–1.5 mm.). Fractional vacuum distillation yielded the ultraviolet sample, $n_D^{24.3}$ 1.5866, reported:[14] n_D^{20} 1.5923. $\lambda_{max}^{95\%\ C_2H_5OH}$: 240 m$\mu$ (log ϵ 3.83), 292 (3.35). ν_{NH} 3400 cm.$^{-1}$ on the liquid.

The picrate, after recrystallization from benzene, melted at 174–176° dec., reported:[13,15] 174°.

2-Methylindoline. The procedure of King, Barltrop, and Walley[13] for indoline was used. 2-Methylindole (25.0 g., 0.0190 mole) in absolute ethanol (150 cc.) solution was hydrogenated at 100 atm. over Raney nickel at a maximum temperature of 118° for 4 hr. After filtration of the catalyst and

(12) Y. G. Perron and W. F. Minor, *J. Org. Chem.*, **24**, 1165 (1959).

(13) F. E. King, J. H. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945).

(14) J. v. Braun, *Ber.*, **45**, 1285 (1912).

(15) G. Plancher and C. Ravenna, *Atti reale accad. Lincei*, [5]**14**, I, 632 (1905) [*Chem. Zentr.*, II, 335 (1905)].

removal of the solvent, fractional distillation yielded two principal fractions: (1) 2-methyloctahydroindole (10.03 g., 0.0721 mole, 38%), b.p. 79–84° (19 mm.), $n_D^{28.8}$ 1.4786, reported for *cis*-2-methyloctahydroindole:[16] n_D^{25} 1.4743, and (2) 2-methylindoline (8.51 g., 0.0639 mole, 34%), b.p. 112–114° (19 mm.), $n_D^{28.7}$ 1.5652, reported[17,18]: n_D^{15} 1.5719, $n_D^{23.4}$ 1.5687.

To obtain the ultraviolet sample, the picrate (described in the following section) was made alkaline with 20% sodium hydroxide solution, extracted with ether, and the ether solution washed with 20% sodium hydroxide. Evaporation of the ether and fractional distillation gave the ultraviolet sample, b.p. 108° (17 mm.), n_D^{24} 1.5653. $\lambda_{max}^{95\%\ C_2H_5OH}$: 241 mμ (log ε 3.84), 293 (3.34). ν_{NH} 3390 cm.$^{-1}$ on the liquid.

2-Methylindoline picrate. 2-Methylindoline was added to a solution of picric acid in ether. The crystalline precipitate was recrystallized from benzene, yielding yellow needles, m.p. 159–160°. Our melting point is higher than that reported,[19,20] 150–151°, 151°.

Anal. Calcd. for $C_{15}H_{14}N_4O_7$ (362.29): C, 49.73; H, 3.90; N, 15.47. Found: C, 50.03; H, 3.82; N, 15.31.

1-Maleylindoline. Indoline (10.0 g., 0.0839 mole) was added dropwise to a cold solution of maleic anhydride (8.30 g., 0.0847 mole) in benzene (65 cc.), causing immediate separation of bright yellow crystals (7.75 g., containing 0.0302 mole of 1-maleylindoline, 36%). When dropped on a hot block, the yellow crystals melt at 128–130°, with the evolution of benzene, and then solidify to a white compound, m.p. 155–156.5° dec. The white compound is conveniently obtained from the yellow crystals by heating below the melting point, at 100–110°, to drive off the benzene. Recrystallization from acetonitrile gives white crystals, m.p. 158–159° dec. Recrystallization of the white compound from benzene regenerates the yellow crystals.

(a) 1-Maleylindoline benzene complex, yellow crystals from benzene, m.p. 128–130°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 253 mμ (log ε/2 4.06), 282 (log ε/2 3.84), 290 inflection (log ε/2 3.82). ν_{OH} ~2430 in Nujol; $\nu_{C=O}$ 1716, 1629 in $CHCl_3$, 1706, 1656 (weaker band), 1615 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $(C_{12}H_{11}NO_3)_2 \cdot C_3H_6$ (512.54): benzene, 15.24; C, 70.30; H, 5.51; N, 5.47. Found: wt. loss after 10 min. at 100°, 15.81; C, 70.22; H, 5.65; N, 5.64.

(b) 1-Maleylindoline, white, m.p. 155–156.5° dec. $\lambda_{max}^{95\%\ C_2H_5OH}$: 255 mμ (log ε 4.05), 283 (3.87), 292 inflection (3.84). ν_{OH} ~2440 in $CHCl_3$, ~2490 in KBr; $\nu_{C=O}$ 1710, 1625 in $CHCl_3$, 1701, 1651 (weaker band), 1611 cm.$^{-1}$ in KBr.

Anal. Calcd. for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.34; H, 5.23; N, 6.44.

1-Succinylindoline. Indoline (2.38 g., 0.0200 mole) was added to a warm solution of succinic anhydride (2.00 g., 0.0200 mole) in benzene (35 cc.). The solution was cooled for 15 min., causing separation of white crystals (3.86 g., 0.0176 mole, 88%), m.p. 165–166.5°. Three recrystallizations from acetonitrile gave beautiful white needles, m.p. 167–168°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 252 mμ (log ε 4.19), 281 (3.65), 290 (3.58). ν_{OH} ~2670; $\nu_{C=O}$ 1705, 1653 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{12}H_{13}NO_2$ (219.23): C, 65.74; H, 5.98; N, 6.29. Found: C, 65.85; H, 5.93; N, 6.50.

1-Maleyl-2-methylindoline. 2-Methylindoline (6.46 g., 0.0485 mole) was added slowly to a cold solution of maleic anhydride (4.47 g., 0.0456 mole) in benzene. The solution was stirred and cooled in ice for 5 min. and then the bright yellow crystals of 1-maleyl-2-methylindoline (8.57 g., 0.0371 mole, 81%), m.p. 112–113.5° dec. were filtered. One recrystallization from benzene yielded the analytical sample, m.p. 114–114.5° dec. $\lambda_{max}^{95\%\ C_2H_5OH}$: 250 mμ (log ε 4.04), 282 (3.75), 289 (3.74). ν_{OH} ~2240; $\nu_{C=O}$ 1704, 1623 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{13}H_{13}NO_3$ (231.24): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.73; H, 5.65; N, 5.96.

Hydrolysis of 1-maleylindoline. 1-Maleylindoline (m.p. 155–156.5° dec., 5.61 g., 0.0258 mole) was added to aqueous 30% potassium hydroxide (43 cc.), causing the formation of a white gel, which dissolved upon heating, with the liberation of an oily layer of indoline. The mixture was refluxed for 3 hr., then cooled and extracted with ether. Evaporation of the ether left a residue of crude indoline (3.03 g., 0.0254 mole, 98%), which was converted in ether solution to the picrate (7.82 g., 0.0224 mole, 87%), m.p. 170–174° dec. One recrystallization from benzene gave yellow needles, m.p. 174–176° dec., mixed melting point with indoline picrate, 174–176° dec. The alkaline solution was neutralized slowly with hydrochloric acid. At a *p*H of about 8 a light violet powder precipitated, possibly monopotassium fumarate (0.44 g., 0.00285 mole, 11%), m.p. >300°, which did not contain nitrogen or halogen. The solution was then acidified to a *p*H of about 2 and extracted with ether in a liquid-liquid extractor for 2 days. Evaporation of the ether left a light brownish residue of fumaric acid (2.22 g., 0.0191 mole, 74%), which had an infrared spectrum in Nujol identical with that of an authentic sample.

Hydrolysis of 1-maleyl-2-methylindoline. 1-Maleyl-2-methyl-2-methylindoline (3.05 g., 0.0132 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 3 hr. The reaction mixture was cooled, extracted with ether, and the picrate (4.29 g., 0.0118 mole, 89%), m.p. 157–159°, prepared directly from the ether solution. One recrystallization from benzene gave yellow needles, m.p. 159–160°, mixed m.p. 159–160° with 2-methylindoline picrate. The colorless alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 36 hr. Evaporation of the ether gave fumaric acid (1.21 g., 0.0104 mole, 79%), sublimes above 210°.

(2-Methyl-3-indole)succinic acid (IIb). (a) *From rearrangement of 2-methyl-3-(1-maleyl-2-indolinyl)indole* (*cis*-Ib, *maleyl indole:2-methylindole dimer*). 2-Methyl-3-(1-maleyl-2-indolinyl)indole[8] (9.35 g., 0.0270 mole) was refluxed with aqueous 30% potassium hydroxide (90 cc.) for 3 hr. The reaction mixture was cooled and extracted with ether to remove indole (2.75 g., 0.0235 mole, 87%), m.p. 50–51° after sublimation, mixed m.p. 50–52° with an authentic sample. The infrared spectra in Nujol of the two samples were identical. The alkaline solution was acidified to Congo Red with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 2 days. Evaporation of the ether left a light yellowish solid (6.4 g., 0.0259 mole, 96%), m.p. 203–206° dec. Three recrystallizations from acetonitrile, with charcoal, yielded (2-methyl-3-indole)succinic acid as white crystals, m.p. 209–211° dec., mixed m.p. 209–212° dec. with an authentic sample[9,10] of m.p. 210–212° dec. The infrared spectra in Nujol of the two samples were identical.

(b) *From rearrangement of 2-methyl-3-(1-fumaryl-2-indolinyl)indole* (*trans*-Ib, *fumaryl indole:2-methylindole dimer*). 2-Methyl-3-(1-fumaryl-2-indolinyl)indole[8] (2.10 g., 0.00606 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 18 hr. The reaction mixture was cooled and extracted with ether to remove indole (0.51 g., 0.00435 mole, 72%), m.p. 51–52° after sublimation. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 4 days. Evaporation of the ether left a nearly violet residue, which was recrystallized once, with charcoal, from acetonitrile, yielding (2-methyl-3-indole)succinic acid as white crystals (1.31 g., 0.00530 mole, 87%), m.p. 205–208° dec., mixed m.p. 205–209° dec., with an authentic sample[9,10] of m.p. 208–210° dec.

(c) *From rearrangement of 2-methyl-3-(1-maleyl-3-methyl-2-indoliny')indole* (*cis*-Id, *maleyl skatole:2-methylindole dimer*). 2-Methyl-3-(1-maleyl-3-methyl-2-indolinyl)indole[8] (5.00 g.,

(16) S. Fujise, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **9**, 96 (1928).

(17) W. Leithe, *Monatsh. Chem.*, **52**, 161 (1929).

(18) J. W. Brühl, *Z. phys. Chem.*, **16**, 219 (1895).

(19) M. Wenzing, *Ann.*, **239**, 245 (1887).

(20) O. Carrasco, *Gazz. chim. ital.*, **38**, II, 306 (1908).

0.0139 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 3 hr. The yellow color of the solid disappeared immediately. After about an hour, an oil was observed on top of the solution and steam distilling up into the condenser. At the end of the reflux period, the reaction mixture was cooled, causing the oil to solidify. Extraction with ether (3 × 50 cc.) removed skatole (1.73 g., 0.0132 mole, 95%), m.p. 89–92°. Sublimation gave a sample, m.p. 95–96°, mixed melting point with an authentic sample, 95–96°. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 4 days. Evaporation of the ether gave a light tan solid (3.44 g., 0.0139 mole, 100%), m.p. 203–206° dec. Recrystallization from acetonitrile gave (2-methyl-3-indole)succinic acid as a white powder (3.12 g., 0.0126 mole, 91%), m.p. 207.5–209° dec., mixed m.p. 208–210° dec. with an authentic sample[9,10] of m.p. 208–210° dec. The infrared spectra in Nujol of the two samples, after drying at 90°, were identical.

(d) *From rearrangement of spiro[(8-carboxy-10-methyl-6,7,8,9,9a,10-hexahydrobenzo[b]pyrrocol-6-one)-9,3′-(2′-methyl[3]pseudoindole)] (rearrangement product of maleyl skatole:2-methylindole dimer).* The rearrangement product of maleyl skatole:2-methylindole dimer[8] (1.85 g., 0.00513 mole) was refluxed with aqueous 30% potassium hydroxide (25 cc.) for 13 hr. A white substance was observed steam distilling up into the condenser during the reflux period. The reaction mixture was cooled and extracted with ether (3 × 25 cc.), to remove skatole, m.p. 94–95°, which was purified by sublimation at 75° (12 mm.) (0.63 g., 0.0048 mole, 94%), m.p. 96°, and identified by mixed melting point and Nujol infrared comparison with an authentic sample. The aqueous solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 24 hr. Evaporation of the ether gave a white solid (1.35 g.), m.p. 198–205° dec. One recrystallization from acetonitrile gave (2-methyl-3-indole)succinic acid as a white powder (1.19 g., 0.00482 mole, 94%), m.p. 209–210.5° dec., mixed m.p. 208–210° dec. with an authentic sample[9,10] of m.p. 208–210° dec. The infrared spectra in Nujol of the two samples were identical.

(2-Phenyl-3-indole)succinic acid (IIc). (a) *From rearrangement of 2-phenyl-3-(1-maleyl-2-indolinyl)indole (cis-*Ic, *maleyl indole:2-phenylindole dimer).* 2-Phenyl-3-(1-maleyl-2-indolinyl)indole[8] (3.97 g., 0.00972 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 3 hr. Indole sublimed into the condenser during the reflux period. The reaction mixture was cooled and extracted with ether to remove indole. Considerable material (3.08 g.) was insoluble in both the ether and aqueous alkaline layers. This was assumed to be largely the potassium salt of unchanged starting material. It was refluxed with fresh aqueous 30% potassium hydroxide (50 cc.) for an additional 4 hr. and then worked up in the same manner as the original reaction mixture. This time no water- and ether-insoluble material remained. The original aqueous layer was acidified to Congo Red with 46% sulfuric acid, the solution evaporated to dryness on a steam bath, and the residue extracted with ether in a Soxhlet extractor for a day. Evaporation of the ether left a light pink residue of (2-phenyl-3-indole) succinic acid, m.p. 255–258° dec.

The total yields of products were: indole (0.35 + 0.55 g., 0.00767 mole) 79%, m.p. 50–51° after sublimation, and (2-phenyl-3-indole)succinic acid (1.33 + 1.26 g., 0.00838 mole) 86%. Three recrystallizations from acetonitrile, with charcoal, yielded (2-phenyl-3-indole)succinic acid-acetonitrile complex as white crystals, m.p. 183.5–184.5°, mixed m.p. 183–184° with a sample of m.p. 183–184° prepared from 2-phenylindole and maleic acid. The infrared spectra in Nujol of the two samples were identical.

(b) *From 2-phenylindole and maleic acid.* By a modification of the method of Noland and Lange[9] for the preparation of (2-methyl-3-indole)succinic acid, a mixture of 2-phenylindole (1.47 g., 0.00761 mole) and maleic acid (0.88 g., 0.00757 mole) was heated at 140° in an oil bath for 15 min. The dark blue-green melt solidified upon cooling. The acid appeared to be unstable and did not crystallize well from ethanol-water, chloroform, or methylene chloride. From acetonitrile, however, two recrystallizations, with charcoal, gave white crystals (1.74 g., 0.00528 mole of the acid, 70%), m.p. 185–186°. Three additional recrystallizations from acetonitrile, followed by drying *in vacuo* at 90°, yielded (2-phenyl-3-indole)succinic acid as an acetonitrile complex in the form of white crystals, m.p. 189–190°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 224 mμ (log ε/2 4.41), 234 inflection (log ε/2 4.35), 301 (log ε/2 4.22). ν_{NH} 3280 in KBr, 3310 in Nujol; ν_{OH} ~2600 in KBr and Nujol; $\nu_{C=O}$ 1682 in KBr, 1694 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $(C_{18}H_{15}NO_4)_2{\cdot}CH_3CN$ (659.67): neut. equiv. 164.92; C, 69.18; H, 5.04; N, 6.37. Found: neut. equiv. 172; C, 68.93; H, 5.08; N, 6.40.

(2-Phenyl-3-indole)succinic anhydride (anhydride of IIc). A solution of (2-phenyl-3-indole)succinic acid acetonitrile complex (2.50 g., 0.00758 mole of the acid) in acetic anhydride (50 cc.) was set aside for 2.5 days. The solvent was removed below 70° by vacuum distillation and the black residue was dissolved in methylene chloride–petroleum ether (b.p. 60–68°). After being set aside in a refrigerator for a month, the solution contained dark brownish crystals (0.78 g., 0.00268 mole, 35%), m.p. 190–193°. Five recrystallizations from methylene chloride–petroleum ether (b.p. 60–68°) yielded (2-phenyl-3-indole)succinic anhydride as slightly pinkish white crystals, m.p. 194°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 225 mμ (log ε 4.40), 232 inflection (4.37), 301 (4.25). ν_{NH} 3390; $\nu_{C=O}$ 1860, 1782 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{18}H_{13}NO_3$ (291.29): C, 74.21; H, 4.50; N, 4.81. Found: C, 73.96; H, 4.51; N, 4.61.

An attempt[21] to prepare (2-phenyl-3-indole)succinic anhydride directly by the reaction of 2-phenylindole and maleic anhydride in a manner comparable to that used successfully with 2-methylindole and 1,2-dimethylindole[10] gave less promising results. A mixture of 2-phenylindole (8.42 g.) and maleic anhydride (4.28 g.) was fused at 120–130° in an oil bath for 10 min. The vigorous reaction yielded as the only crystalline product about 20 mg. of (2-phenyl-3-indole)succinic anhydride, m.p. 192–194°, mixed melting point with the sample previously described, 192–194°. The rest of the product was a sticky blue-black tar.

2-Methyl-2-(2-methyl-3-indole)succinic acid (XI). (a) *From rearrangement of 2-methyl-3-(1-itaconyl-2-indolinyl)indole* (IX, *itaconyl indole:2-methylindole dimer).* 2-Methyl-3-(1-itaconyl-2-indolinyl)indole[8] (4.20 g., 0.0116 mole) was refluxed with aqueous 30% potassium hydroxide (100 cc.) for 25 hr. The reaction mixture was cooled and extracted with ether. Evaporation of the ether left a tan viscous oil (1.07 g.), which upon sublimation gave indole (0.72 g., 0.0061 mole, 53%), m.p. and mixed m.p. 51–52° with an authentic sample. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 24 hr. Evaporation of the ether gave a light orange solid (2.19 g., 0.00838 mole, 72%), m.p. 210–214° dec. Three recrystallizations from acetonitrile gave 2-methyl-2-(2-methyl-3-indole)succinic acid as white crystals, m.p. 223–224.5° dec., mixed melting point with the sample prepared as described in the following section, 222–224° dec. The infrared spectra in Nujol were identical. $\lambda_{max}^{95\%\ C_2H_5OH}$: 225 mμ (log ε 4.51), 282(3.85), 289 (3.80). ν_{NH} 3430; ν_{OH} 2650; $\nu_{C=O}$ 1691 cm.$^{-1}$ in Nujol.

(b) *From rearrangement of 2-methyl-3-(1-citraconyl-2-indolinyl)indole (cis-*X, *citraconyl indole:2-methylindole dimer).* 2-Methyl-3-(1-citraconyl-2-indolinyl)indole[8] (3.75 g., 0.0104 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 50 hr. The reaction mixture was cooled and extracted with ether. Evaporation of the ether left a tan oil (1.76 g.), part of which sublimed during 72 hr. at 70° (0.2 mm.), yielding indole (0.99 g., 0.0084 mole, 81%), m.p. 50–51° and mixed melting point with an authentic sample,

(21) Experiment performed by Larry L. Schaleger.

51–52°. The tan residual oil (0.77 g.) did not yield a crystalline succinyl derivative. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 3.5 days. The product is only slightly soluble in ether and precipitates from refluxing ether as white crystals of high purity. Evaporation of the ether gave 2-methyl-2-(2-methyl-3-indole)succinic acid (1.00 g., 0.00383 mole, 37%), m.p. 219–220° dec. Two recrystallizations from acetonitrile gave white microcrystals, m.p. 223–224° dec., mixed melting point with the sample prepared as described in the preceding section, 222–224° dec. The infrared spectra in Nujol and the ultraviolet spectra were identical.

Anal. Found: neut. equiv. 141; C, 64.53; H, 6.17; N, 5.64.

2-Methyl-2-(2-methyl-3-indole)succinic anhydride (anhydride of XI). 2-Methyl-2-(2-methyl-3-indole)succinic acid (0.66 g., 0.00252 mole) and acetic anhydride (25 cc.) were mixed and set aside at room temperature under a nitrogen atmosphere for 3 days. Since part of the acid remained undissolved, the mixture was warmed on a steam bath for 1 hr. and then set aside for 2 days. Evaporation of the solvent at 73° in a rotary vacuum evaporator left a brown residue, which was dissolved in methylene chloride–petroleum ether (b.p. 60–68°) and set aside in the refrigerator for 3 days. The resulting brownish precipitate (0.31 g., 0.00127 mole, 50%), m.p. 139–141°, was recrystallized four times from methylene chloride-petroleum ether (b.p. 60–68°), yielding 2-methyl-2-(2-methyl-3-indole)succinic anhydride as whitish crystals, m.p. 144°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 223 mμ (log ε 4.49), 282-(3.86), 289(3.80). ν_{NH} 3430, 3400 (doublet); $\nu_{C=O}$ 1846, 1821 (weak), 1770 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.25): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.12; H, 5.34; N, 5.70.

(2-Methyl-3-skatyl)succinic anhydride (anhydride of XII) (with William C. Kuryla). 2-Methylindole (12.1 g., 0.0921 mole) and itaconic anhydride (11.2 g., 0.100 mole) were fused on a steam bath for 15 min. The resulting brownish red oil had solidified to a hard glassy mass after 4 days. Crystallization from benzene gave a pinkish white solid (19.42 g., 0.0800 mole, 87%), m.p. 130–134°. Treatment with charcoal and three recrystallizations from benzene yielded (2-methyl-3-skatyl)succinic anhydride as a white solid, m.p. 134–135°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 227 mμ (log ε 4.52), 284(3.85), 291-(3.79). ν_{NH} 3450 in $CHCl_3$, 3390 in Nujol; $\nu_{C=O}$ 1854, 1773 in $CHCl_3$, 1848, 1765 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.25): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.00; H, 5.58; N, 5.56.

(2-Methyl-3-skatyl)succinic acid (XIX) (with T. R. Rajagopalan[22]). (2-Methyl-3-skatyl)succinic anhydride (1.50 g., 0.00575 mole) was dissolved in a solution of potassium hydroxide (10.7 g.) in water (37 cc.), and the resulting solution was refluxed for 3.5 hr. The cooled solution was acidified to Congo Red with concd. hydrochloric acid, causing the solution to become turbid. Extraction with ether and evaporation of the ether gave a light brown oil, which solidified after 2 or 3 days at room temperature. The resulting white solid was dissolved in aqueous sodium bicarbonate, the solution was washed with ether, and the aqueous phase was acidified and extracted with ether as previously described. The solidified residue from evaporation of the ether was filtered with the aid of benzene and dried, yielding (2-methyl-3-skatyl)succinic acid as a white solid (1.10 g., 0.00421 mole, 73%), m.p. 149–151° dec. $\lambda_{max}^{95\%\ C_2H_5OH}$: 226 mμ (log ε 4.52), 282 (3.84), 290 (3.79). ν_{NH} 3380, 3340 (stronger band); ν_{OH} 2650; $\nu_{C=O}$ 1698 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{15}NO_4$ (261.27): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.19; H, 5.81; N, 5.34.

The acid was recovered unchanged after attempted decarboxylation at 200–210°. A gas, assumed to be steam resulting from anhydride formation, was evolved at temperatures between the melting point and 210°, but, after alkaline hydrolysis of the cooled melt, the acid was recovered uncharged in 95% yield, as shown by mixed melting point and Nujol infrared comparisons.

(3-Indole)succinic acid (IIa) *from rearrangement under homogeneous conditions of 3-(1-maleyl-2-indolinyl)indole* (*cis*-Ia, *maleyldiindole*). A solution of maleyldiindole[4,9,10] (10.0 g., 0.0301 mole) in ethanolic 30% potassium hydroxide (30 g. potassium hydroxide in 86 cc. 95% ethanol) was refluxed for 3 hr. The solution was green at first but turned to orange when heating was begun, then back to green after cooling at the end of the reflux period. The ethanol was removed by vacuum distillation, and some indole also codistilled. The residue was washed with ether to remove remaining indole, then acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 5 days. Evaporation of the ether gave (3-indole)succinic acid as a light yellowish solid (4.97 g., 0.0213 mole, 71%), m.p. 197–198.5° dec. The product is obtained in a purer initial state than that resulting from hydrolysis under heterogeneous conditions with aqueous potassium hydroxide.

MINNEAPOLIS 14, MINN.

(22) Postdoctoral fellow, 1959. This part of the investigation was supported by Research Grant CY-4073 from the National Cancer Institute, U. S. Public Health Service.

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL]

Synthesis of Some 5- and 6-Chloro, 5-Methyl, and 5,6,7-Trimethyl Derivatives of Tryptamine

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Received February 26, 1960

The preparation of 5-chloro-*N*,*N*-dimethyl-, 6-chloro-*N*,*N*-dimethyl-, and 6-chlorotryptamine from the corresponding ring-chlorinated indoles has been carried out. A nine-step synthesis of 5,6,7,*N*,*N*-pentamethyltryptamine from 3,4,5-trimethylacetophenone and the preparation of 5,*N*,*N*-trimethyltryptamine from 5-methylindole are discussed. These compounds were prepared for psychopharmacological evaluation.

In a previous communication,[3] we reported that 4-chloro-, 4-methyl-, 3-methyl-, and 3,4,5-trimethyl-β-phenethylamine, at a dose level of 25 mg./kg. (intramuscular), evoked a strong rage response in

(1) Battelle Memorial Institute.

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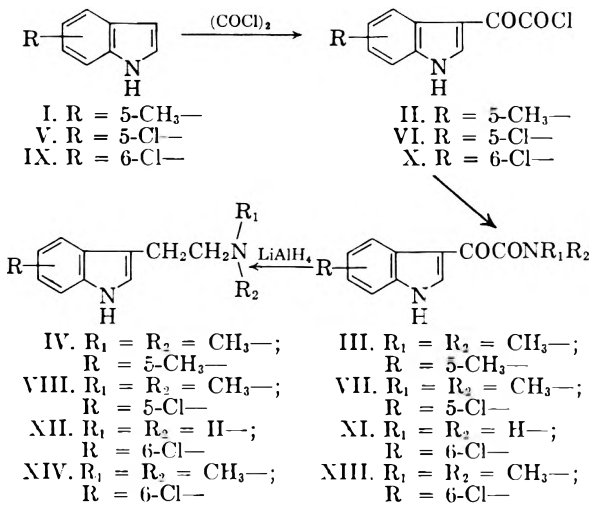
(3) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **23**, 1979 (1958).

cats. Recent unpublished studies in our laboratories have shown that 5-methoxy-*N*,*N*-dimethyltryptamine (*o*-methylbufotenine) is a more potent rage-producing substance than any of the substituted β-phenethylamines thus far studied. The work reported in this communication was undertaken with the idea of determining whether chloro or methyl groups introduced into the benzenoid ring of *N*,*N*-dimethyltryptamine would yield compounds having psychopharmacological activities comparable with the corresponding substituted β-phenethylamines.

The desired tryptamines were synthesized by application of the general method of Speeter and Anthony[4] to the appropriately substituted indoles as shown in Chart I. None of these reactions requires specific comment beyond the fact that the glyoxalyl chlorides II, VI, and X were isolated without characterization and immediately treated with either ammonia or dimethylamine to give the

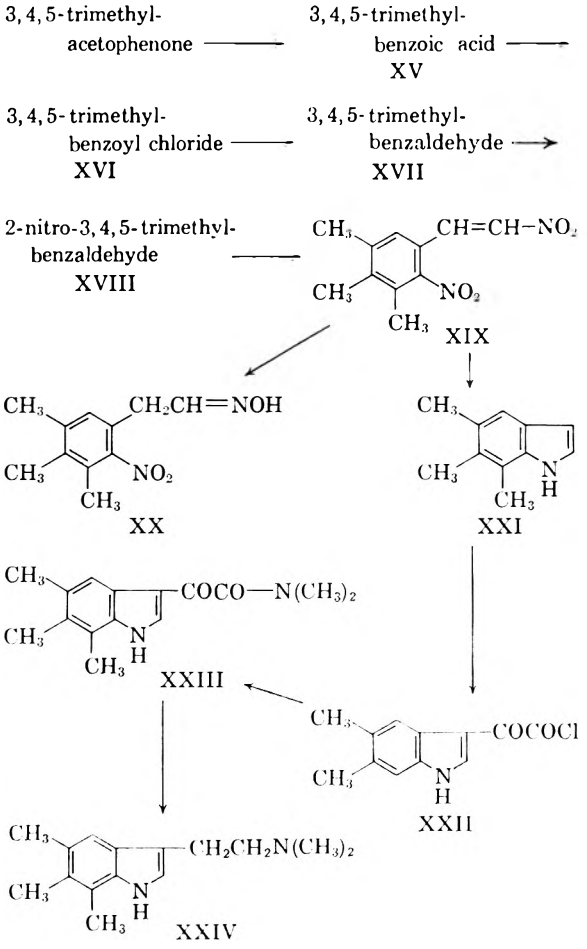
CHART I



more stable glyoxalamides III, VII, XI, and XIII. 5,*N*,*N*-Trimethyltryptamine (IV), which could not be converted to a crystalline hydrochloride, was finally isolated as the hydrogen maleate. The remaining tryptamines, VIII, XII, and XIV, formed stable and well defined crystalline hydrochlorides.

The synthesis of 5,6,7,*N*,*N*-pentamethyltryptamine (XXIV) and 5,6,7-trimethylindole (XXI) was accomplished *via* the route given in Chart II. When 3,4,5-trimethylacetophenone was subjected to a haloform reaction with potassium hypochlorite solution, degradation of the side chain to the expected carboxyl group occurred with simultaneous nuclear halogenation; the resulting compound was identified as 2-chloro-3,4,5-trimethylbenzoic acid. Nuclear halogenation during the Hoffman reaction between certain aromatic amides and sodium hypobromite is well known,[5] and sodium hypochlorite is usually the reagent of choice when this occurs. However, when 3,4,5-trimethylacetophenone[6] was treated with cold sodium hypobromite solution and allowed to react for eighteen hours, the halogen-free 3,4,5-trimethylbenzoic acid (XV) was obtained in 56% yield. After XV had been converted to the acid chloride XVI, the latter compound was changed to the aldehyde XVII by the action of hydrogen in the presence of the usual Rosenmund catalyst. Although the yield of 3,4,5-trimethylbenzaldehyde (XVII) was somewhat variable, depending upon reaction conditions, it was found that, by carrying out this reduction step in refluxing toluene for twenty-five hours, there resulted a 66% yield of the purified aldehyde XVII; a shorter reaction period in refluxing xylene gave lower yields.

CHART II



The nitration of 3,4,5-trimethylbenzaldehyde (XVII) was examined under several reaction conditions in an attempt to obtain 2-nitro-3,4,5-trimethylbenzaldehyde (XVIII). Apparently no reaction occurred between XVII and nitric-acetic

(4) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(5) E. S. Wallis and J. F. Lane, *Org. Reactions*, Coll. Vol. III, 267 (1946).

(6) G. Baddely, *J. Chem. Soc.*, 232 (1944).

acid mixture, since only unchanged XVII could be isolated from the final mixture. Nitration with mixed acid at 15°–20° afforded only the dinitration product 2,6-dinitro-3,4,5-trimethylbenzaldehyde. Howefer, by carrying out the nitration of XVII in sulfuric acid by the addition of solid potassium nitrate in accordance with a modification of the procedure given by Eichengrun and Einhorn,[7] the desired 2-nitro-3,4,5-trimethylbenzaldehyde (XVIII) was obtained in 89% yield, based on unrecovered XVII.

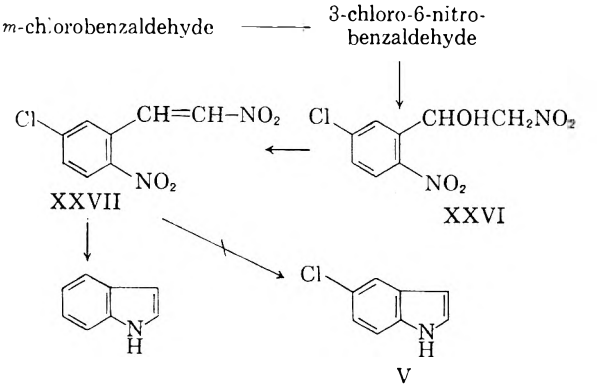
The base-catalyzed condensation of the nitroaldehyde XVIII with nitromethane using the procedure of Huebner *et al.*[8] gave a mixture of the 2,β-dinitrostyrene XIX and the corresponding nitroalcohol. Dehydration of the mixed product with sodium acetate–acetic anhydride gave pure 3,4,5-trimethyl-2,β-dinitrostyrene (XIX) in 76% yield.

Initially, the cyclization of XIX to 5,6,7-trimethylindole (XXI) was attempted using the iron powder–acetic acid procedure of Ek and Witkop,[9] since we had successfully prepared 5,6,7-trimethoxyindole from 3,4,5-trimethoxy-2,β-dinitrostyrene[10] using these reagents. However, none of the desired indole XXI could be isolated from the final reaction mixture. In an alternative approach to this cyclization, XIX in methanol–acetic acid–ethyl acetate solution was subjected to a low-pressure hydrogenation in the presence of a 10% palladium-on-charcoal catalyst.[8] The hydrogen uptake ceased at approximately 60% of the volume calculated to convert XIX completely to XXI. Although the crude reaction product gave a positive Ehrlich reaction, none of the indole XXI could be isolated by conventional methods. There was obtained from this reduction mixture a small amount of 2-nitro-3,4,5-trimethylphenylacetaldoxime(XX). The partial catalytic reduction of β-nitrostyrene in neutral solution to phenylacetaldoxime and polymolecular reduction products has been described by Kohler and Drake,[11] whereas in strongly acid media, complete reduction to β-phenethylamine[12] occurs.

Walker[13] has shown that the course of the reduction of certain *o*-nitrophenylacetonitriles to indoles is drastically influenced by the acidity of the medium. Thus, the intermediate *o*-aminophenylacetonitrile can undergo internal amidine formation and this, in turn, forms a protonated amidinium ion which is resonance stabilized against further reduction to the indole. Since the formation of similar stable protonated ions might be a possibility during the reductive cyclization of XIX in the presence of acetic acid, the hydrogenation was repeated using ethyl acetate–methanol as a reaction medium. The hydrogen uptake was rapid, exothermic, and quantitative. Under these conditions 5,6,7-trimethylindole (XXI) was obtained in 50% yield.

5,6,7,*N*,*N*-Pentamethyltryptamine (XXIV) was obtained *via* the indole glyoxalyl chloride (XXII) and the amide (XXIII), which was reduced by means of lithium aluminum hydride.[4] The free base XXIV was finally converted to the hydrochloride.

3-Chlorobenzaldehyde was selected as the starting material for the synthesis of the intermediate 5-chloroindole (V) required for the preparation of VIII. By following the reaction scheme



the chloroaldehyde was first converted to 2-nitro-5-chlorobenzaldehyde (XXV) in 66% yield by the method[7] already described for the preparation of XVIII. A base-catalyzed condensation of XXV with nitromethane in which tri-*n*-butylamine was used failed to give the nitroolefin XXVII. When the condensation was then repeated following the alcoholic alkali procedure of Worral,[14] α-(2-nitro-5-chlorophenyl)-β-nitroethanol was obtained rather than the expected XXVII. Dehydration of XXVI with anhydrous sodium acetate and acetic anhydride afforded a satisfactory yield of 5-chloro-2,β-dinitrostyrene (XXVII).

When the reductive cyclization of XXVII was attempted in accordance with the method described by Huebner,[8] indole was obtained instead of 5-chloroindole. This result is not surprising in light of the findings of Strel'tsova and Zelinskii,[15] who have demonstrated that hydrogenolysis of the halo group occurs simultaneously with reduction of the nitro group when either 2- or 4-chloronitrobenzene is treated with hydrogen in the presence of a noble-metal catalyst (palladium or platinum).

(7) A. Eichengrun and A. Einhorn, *Ann.*, **262**, 137 (1891).
(8) C. F. Huebner, H. A. Troxell, and D. C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).
(9) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).
(10) R. D. Morin, F. Benington, and L. C. Clark, Jr., *J. Org. Chem.*, **22**, 331 (1957).
(11) E. P. Kohler and N. L. Drake, *J. Am. Chem. Soc.*, **45**, 1281 (1923).
(12) K. Kindler, E. Brandt, and E. Gehlhaar, *Ann.*, **511**, 209 (1934).
(13) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).
(14) D. E. Worrall, *Org. Syntheses*, Coll. Vol. I. 413 (1941).
(15) A. A. Strel'tsova and N. D. Zelinskii, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 401 (1941); *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 56 (1943).

Since 5-chloroindole became commercially available during this study, this was used in the synthesis of the tryptamine VIII.

The 6-chloroindole (IX) required for the synthesis of XII and XIV was prepared from 2-nitro-4-chlorotoluene following the route of Rydon and Tweedle[16] in which this starting compound is first condensed with ethyl oxalate to give 4-chloro-2-nitrophenylpyruvic acid, which is next cyclized to 6-chloroindole-2-carboxylic acid by treatment with ferrous hydroxide; the acid is finally subjected to thermal decarboxylation in the presence of a copper chromite catalyst to give 6-chloroindole (IX).

EXPERIMENTAL[17]

5,N,N-Trimethyl-3-indoleglyoxalamide (III). A cold stirred solution of 10 g. of I in 200 ml. of dry ether was treated with 12 ml. of oxalyl chloride in 15 ml. of dry ether. The resulting insoluble glyoxalyl chloride (II) was collected, rapidly washed with additional dry ether, and resuspended in the same solvent. To the cold stirred slurry of II there was added dropwise 10.6 g. of anhydrous dimethylamine in dry ether. Stirring was continued for 1 hr. and then the reaction mixture was filtered and washed with additional ether. The crude cake was slurried in water to remove the soluble dimethylamine hydrochloride and finally collected. Recrystallization from hot benzene-ethanol gave 14.4 g. (82.2%) of pure III as colorless needles; m.p. 184–185°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.9; H, 6.10; N, 12.2. Found: C, 68.3; H, 5.9; N, 11.9.

5,N,N-Trimethyltryptamine (IV). To a stirred suspension of 9.9 g. of lithium aluminum hydride in 300 ml. of dry ether was added portionwise and cautiously a slurry of 14.4 g. of III in about 100 ml. of hot, dry benzene using additional dry ether to transfer the last of the solid. The mixture was refluxed for an additional hour, cooled in an ice bath, and cautiously treated with water to decompose excess hydride and the reaction complex. The ether-benzene solution of the product was filtered from the insoluble inorganic salts, dried over anhydrous magnesium sulfate, filtered, and the filtrate treated with hydrogen chloride gas. The precipitated oily salt could not be induced to crystallize and therefore the free base was regenerated with alkali. Vacuum distillation of the crude amine, b.p. 140–142°/0.3 mm., gave a colorless oil which crystallized to give 7.6 g. (59%) of base IV; m.p. 99–100°. To a solution of 6.0 g. of IV in boiling isopropyl acetate there was added a hot solution of 3.0 g. maleic acid in the same solvent. The precipitated salt amounted to 9.0 g. (quant.); m.p. 94–95°.

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.2; H, 6.9; N, 8.9. Found: C, 63.9; H, 6.8; N, 8.6.

α-(2-Nitro-5-chlorophenyl)-β-nitroethanol (XXVI). 2-Nitro-5-chlorobenzaldehyde (XXV) was obtained in 66.5% yield by adding dropwise 120.4 g. of 3-chlorobenzaldehyde to a stirred solution of 88 g. of potassium nitrate in 1200 ml. of concd. sulfuric acid, while maintaining the reaction temperature between 5–9°. The mixture was stirred for an additional 15 min. at 0–5°, and then poured onto cracked ice. The colorless solid was collected, washed with water, and finally recrystallized from ether–petroleum ether (b.p. 30–60°) as nearly colorless needles; m.p. 78.5–79.5° (reported,[7] m.p. 77.5°).

The nitroaldehyde XXV (122.9 g.) dissolved in a mixture of 40.4 g. of redistilled nitromethane and 132 ml. of methanol was cooled in an ice bath to 10–15°. To this mixture was added a solution of 27.8 g. of sodium hydroxide in 67 ml. of water at such a rate that the internal temperature did not exceed 15°. Following the addition, the entire mixture was kept at about 0–5° for 2 hr. and then the resulting semi-solid mass was dissolved in 700 ml. of an ice water mixture. The resulting clear yellow solution was poured slowly into a solution of 132 ml. of concd. hydrochloric acid in 198 ml. of water. The crude nitroalcohol (XXVI) was collected and washed with water; yield, 72 g. (51%), pure enough for the next reaction step. Poor recovery was experienced in recrystallizing this product from chloroform–petroleum ether. A recrystallized analytical specimen was obtained as light yellow prisms; m.p. 89–90°.

Anal. Calcd. for $C_8H_7ClN_2O_5$: C, 38.9; H, 2.84; Cl, 14.4; N, 11.35. Found: C, 38.95; H, 2.61; Cl, 14.57; N, 11.05.

2-Nitro-5-chloro-β-nitrostyrene (XXVII). Forty-six g. of sodium acetate trihydrate was converted to the anhydrous salt by fusion, ground to a fine powder, and suspended in 90 ml. of acetic anhydride. The nitroalcohol (XXVI) (20 g.) was then added and the mixture refluxed for 5 min. Upon cooling, the resulting solution was poured into 600 ml. of cold water. The precipitated light yellow oil solidified on standing at room temperature for 1 hr. The crude nitrostyrene (XXVII) after collection and air drying amounted to 17.6 g. (95.4%); m.p. 118.5–120°. Recrystallization from ethanol gave light yellow needles; m.p. 124–125°.

Anal. Calcd. for $C_8H_5ClN_2O_4$: Cl, 15.52; N, 12.25. Found: Cl, 15.7; N, 11.8.

Attempted reductive cyclization of XXVII to 5-chloroindole. A solution of 22.9 g of nitrostyrene XXVII in 185 ml. of ethyl acetate, 20 ml. of ethanol, and 23 ml. of glacial acetic acid containing 2 g. of 10% palladium-on-charcoal catalyst was hydrogenated in a Parr apparatus at room temperature. From an initial pressure of 60 p.s.i., the theoretical value of hydrogen was absorbed within about 2.25 hr. When the hydrogenation mixture was filtered free of ammonium acetate and spent catalyst, the deep blue filtrate was washed three times with 5% sodium bicarbonate solution, dried, and evaporated *in vacuo*. Distillation of the residue gave a main fraction, b.p. 95–98° (0.1 mm.), of a colorless product which was recrystallized from petroleum ether (b.p. 30–60°); 6.1 g.; m.p. 52.5–53°. The product gave a negative Beilstein test for halogen and did not give any depression in a mixed melting point with pure indole (yield 52.1%).

5-Chloro-3-indole-N,N-dimethylglyoxalamide (VII). A solution of 5.0 g. of 5-chloroindole (Aldrich Chemical Co.) in 70 ml. of dry ether was treated with 5.5 ml. of oxalyl chloride in 10 ml. of dry ether, and the glyoxalyl chloride (VI) was isolated and treated with 5 g. of dimethylamine (anhydrous) as described for the preparation of III. The precipitated amide was washed with ether and then water, and the product was air dried. There was obtained 5.5 g. (67%) of VII as colorless needles; m.p. 193–194°. An analytical sample recrystallized from hot benzene-ethanol had the same melting point.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.5; H, 4.4; N, 11.2. Found: C, 57.4; H, 4.6; N, 11.1.

5-Chloro-N,N-dimethyltryptamine (VIII). To a slurry of 3.6 g. of lithium aluminum hydride in 100 ml. of absolute ether was added 5.4 g. of VII as a slurry in 75 ml. of dry benzene. After refluxing and stirring for 1 hr., the product was worked up by the careful addition of enough water to hydrolyze the reaction complex and the excess reagent. After filtration, the ether-benzene layer was dried (magnesium sulfate) and treated with dry hydrogen chloride gas. The crude amine hydrochloride amounted to 5.1 g. (91%) of a nearly colorless powder. Recrystallization twice from hot ethanol-ether afforded 3.0 g. of pure VIII hydrochloride as colorless plates; m.p. 197–198°.

Anal. Calcd. for $C_{12}H_{16}N_2Cl_2$: C, 55.6; H, 6.2; Cl, 27.4. Found: C, 55.8; H, 6.4; Cl, 27.3.

(16) H. N. Rydon and J. C. Tweedle, *J. Chem. Soc.*, 1949 (1955).

(17) All melting points uncorrected.

6-Chloroindole (IX). Following the procedure of Rydon and Tweedle,[16] 2-nitro-4-chlorotoluene was condensed with ethyl oxalate to give 4-chloro-2-nitrophenylpyruvic acid (42%); (m.p. 140–141°; reported 136°). Reductive cyclization of this acid to 2-carboxy-5-chloroindole [m.p. 248–249° dec.; reported m.p. 244° dec.] with ferrous hydroxide afforded this compound in 65% yield (reported 85%). Decarboxylation of this intermediate in hot quinoline containing copper chromite as a catalyst gave the desired 6-chloroindole (66%); m.p. 86–87°; (reported, m.p. 86–87°).

6-Chloro-3-indoleglyoxalamide (XI). To a stirred solution of 22.7 g. of 6-chloroindole (IX) in 400 ml. of dry ether (ice bath) was slowly added 29.6 g. (20 ml.) of oxalyl chloride in 20 ml. of dry ether. The reaction mixture was allowed to stand at room temperature for 2 hr., during which time the glyoxalyl chloride (X) deposited as a yellow solid which, after collecting and washing with ether, amounted to 32 g. (88%). To 500 ml. of 28% ammonium hydroxide was added 32 g. of X under stirring and cooling. After the addition was complete, stirring was continued for half an hour at 40°. After cooling, the resulting mixture was filtered and the cake washed free of ammonium chloride with water. The air-dried amide (XI) weighed 27.8 g. (94.5%). An analytical sample was recrystallized from ethanol as colorless prisms, m.p. 269–270° dec.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 54.0; H, 3.15; N, 12.6. Found: C, 53.9; H, 3.15; N, 12.5.

6-Chlorotryptamine (XII). To a stirred solution of 13.6 g. of lithium aluminum hydride in 250 ml. of dry ether was added a slurry of 14 g. of XI in hot dry benzene. The hydrolysis was carried out as described for IV and the dry ether-benzene solution of the free base was treated with anhydrous hydrogen chloride gas to precipitate XII as the hydrochloride. The crude salt (4.5 g.; 41%) was recrystallized twice from ethanol-ether to give 4 g. of pure product as colorless crystals; m.p. 224–225°.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2$: C, 52.0; H, 5.2; N, 12.1. Found: C, 51.8; H, 5.4; N, 11.9.

6-Chloro-3-indole-N,N-dimethylglyoxalamide (XIII). To a stirred suspension of the glyoxalyl chloride (X), obtained from 15.2 g. of 6-chloroindole and oxalyl chloride, in 250 ml. of dry ether was added a solution of 13.5 g. of anhydrous dimethylamine in 25 ml. of dry ether. After stirring for 1 hr., the crude solid product was collected by suction filtration, washed with water and ether, and recrystallized from benzene-ethanol; yield, 21 g. (84%); m.p. 267–268°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.5; H, 4.4; N, 11.2. Found: C, 57.5; H, 4.4; N, 11.2.

6-Chloro-N,N-dimethyltryptamine (XIV). To a stirred solution of 11.7 g. of lithium aluminum hydride in 300 ml. of dry ether was added portionwise a slurry of 18 g. of XIII in 160 ml. of hot dry benzene. The mixture was stirred at reflux for 3 hr. and hydrolyzed and the product isolated as described for IV. The crude hydrochloride of the product (18 g.) was recrystallized from alcohol-ether; yield, 14.9 g. (80%) of colorless small needles; m.p. 196–197°.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2$: C, 55.6; H, 6.2; N, 10.8. Found: C, 55.6; H, 6.2; N, 10.8.

Action of potassium hypochlorite on 3,4,5-trimethylacetophenone. A solution of 176 g. of calcium hypochlorite in 880 ml. of water was cooled and treated with a second solution containing 123 g. of anhydrous potassium carbonate, 35 g. of potassium hydroxide, and 350 ml. of water. After standing 0.5 hr., the precipitated calcium carbonate was collected and washed with 40 ml. of cold water. The combined filtrates were heated to 55° (stirring), and 50 g. of 3,4,5-trimethylacetophenone was added in one portion. The resulting exothermic reaction was controlled by occasionally immersing the flask in an ice bath so that the internal temperature remained at 60–70°. When no further temperature rise was noted, the mixture was cooled and stirred for 40 min. at room temperature. The cold solution was first treated with 3 g. of sodium metabisulfite in 120 ml. of water to decompose the excess hypochlorite and then made strongly acid with concd. hydrochloric acid to precipitate the resulting substituted benzoic acid. The crude product was collected, washed with water, and air dried; yield, 59 g.; m.p. 170–200°. After recrystallization from hot benzene, the melting point of the product was 192–193° (reported[18] m.p. for XV, 215–216°). A strong positive Beilstein test indicated the presence of a nuclear chlorine group, since the acid did not give a silver chloride precipitate with warm alcoholic silver nitrate solution. Neut. equiv.: calcd. for 2-chloro-3,4,5-trimethylbenzoic acid: 200. Found: 199.5.

3,4,5-Trimethylbenzoic acid (XV). An aqueous solution of sodium hypobromite was prepared by adding dropwise 79.2 g. of bromine to a mechanically stirred solution of 1200 ml. of 5% sodium hydroxide so that the temperature did not rise above 15°. 3,4,5-Trimethylacetophenone (26.8 g.) was then added, and the mixture stirred for 18 hr.; after this time, no excess reagent was present. The heavy bromoform layer (40.2 g.) was removed, and the aqueous phase was extracted with 200 ml. of ether. The clear alkaline solution was then made strongly acid and the resulting precipitate collected and washed free of salts. After air drying, the crude acid XV weighed 22.0 g. (80%). Since this crude product contained some halogen and melted at 170–185°, it was recrystallized from hot ethanol. The pure XV (halogen-free) amounted to 17.4 g. (64%) and melted at 218–220°. Neut. equiv.: calcd. for $(CH_3)_3C_6H_2CO_2H$: 164. Found: 162.

3,4,5-Trimethylbenzaldehyde (XVII). 3,4,5-Trimethylbenzoyl chloride (XVI) was obtained in 99% yield by refluxing a mixture of 54.6 g. of XV, 100 ml. of purified thionyl chloride, and 50 ml. of dry reagent benzene for 3 hr. After removal of the solvent and excess thionyl chloride under reduced pressure, the residue was vacuum distilled to give 60.2 g. of pure XVIII, b.p. 100–105°/0.1 mm.; m.p. 46–47°.

Rosenmund reduction of XVI was most satisfactory when carried out as described[19] for preparation of 2-ethoxy-3,4-dimethoxybenzaldehyde. To a solution of 120 g. of XVI in 350 ml. of dry toluene was added 10 g. of palladium–on–barium sulfate catalyst. The suspension was mechanically stirred and refluxed while dry hydrogen gas (passed through sulfuric acid) was bubbled through the mixture for a 24-hr. period. After filtering (Norite) free of spent catalyst, the filtrate was stripped at diminished pressure and the residue subjected to a vacuum distillation. Following a small forecut, the aldehyde XVII (72.2 g.; 74%) was collected as a colorless oil (b.p. 80–85°/0.15 mm.) which rapidly crystallized in the receiver. Recrystallization from petroleum ether (b.p. 30–60°) gave 65.2 g. (67%) of colorless needles; m.p. 60–61° (reported[20] m.p. 52°).

2,6-Dinitro-3,4,5-trimethylbenzaldehyde. To a stirred mixture of 15 ml. each of concd. nitric and sulfuric acids, cooled to 15–20°, was added 3.1 g. of XVII. The nitration mixture stood at room temperature for 1 hr. and was poured onto ice and water, and the solid product collected on a filter. After drying, the crude nitration product weighed 4 g.; m.p. 125–135°. Two recrystallizations from hot ethanol afforded 1.7 g. of 2,6-dinitro-3,4,5-trimethylbenzaldehyde as granular yellow crystals, m.p. 154–155°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.4; H, 4.2; N, 11.8. Found: C, 50.7; H, 4.5; N, 11.4.

2-Nitro-3,4,5-trimethylbenzaldehyde (XVIII). To 150 ml. of concd. sulfuric acid was added 22.2 g. of finely powdered XVII with stirring and ice bath cooling (internal temperature <8°). When solution was complete (15–30 min.), the flask was placed in a Dry Ice–acetone bath in order to lower the internal temperature to −10° (bath at −25° to −30°). Powdered potassium nitrate was gradually added at a rate to keep the temperature below −5°. The Dry Ice bath was

(18) P. Jannasch and M. Weiler, *Ber.*, **27**, 3444 (1894).

(19) R. H. F. Manske, A. E. Ledingham, and H. L. Holmes, *Can. J. Research*, **23B**, 100 (1945).

(20) H. Kromer, *Ber.*, **24**, 2407 (1891).

then replaced with an ice bath and the temperature kept below 3° for an additional 1.5 hr. The cold nitration mixture was then added to about 1 l. of ice and water to precipitate the crude mononitration product. The solid was collected on a suction filter and washed thoroughly with water. Air drying gave 28.0 g. of crude XVIII which was further purified by vacuum distillation. After removing a forecut of 2.8 g. of unchanged XVII (b.p. 85–120°/0.1 mm.), 23.4 g. of the pure nitroaldehyde XVIII (b.p. 127–130°/0.15 mm.) was collected (89% based on XVII not recovered). The distilled XVIII after recrystallization from ethyl acetate–petroleum ether melted at 87–88°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.2; H, 5.7. Found: C, 62.3; H, 5.9.

3,4,5-Trimethyl-2,β-dinitrostyrene (XIX). To a stirred solution of 51.3 g. of XVI in 530 ml. of methanol and 20 ml. of redistilled nitromethane which had been precooled to 13° was added 37 ml. of 45% aqueous potassium hydroxide at a rate to maintain the mixture at 15° (ice bath). The resulting mixture was stirred for an additional 20 min. at 11–13° and then poured into a mixture of 175 ml. of concd. hydrochloric acid and ice. The solid which separated was collected, washed with water, and air dried. This product was a mixture of XIX and the corresponding nitroalcohol (m.p. 128–170°), which was dissolved in 50 ml. of acetic anhydride containing 5 g. of fused sodium acetate. The mixture was heated for 10–15 min., poured into cold water, and allowed to stand until the product solidified (1–1.5 hr.). The dried nitrostyrene weighed 47.4 g. (76%); m.p. 176–180°. A sample was purified for analysis by recrystallization from ethanol–ethyl acetate; m.p. 185–186°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 56.0; H, 5.1. Found: C, 56.2; H, 5.0.

5,6,7-Trimethylindole (XXI). To a solution of 5.9 g. of XIX in 250 ml. of hot ethyl acetate was added 2 g. of 10% palladium-on-charcoal catalyst. The hot mixture was placed in a Parr hydrogenation apparatus. From an initial gas pressure of 50 p.s.i. the theoretical amount of hydrogen was absorbed over a period of 13 min.; the effluent gas from the hydrogenation contained ammonia. The resulting hot ethyl acetate solution of the product was treated with Norite, filtered, and evaporated to a small volume of brown oil. This was taken up in 90 ml. of 1:1 benzene–petroleum ether (b.p. 30–60°) and passed through a column of chromatographic alumina (45 g.), which was, in turn, washed with 100 ml. of the same solvent mixture followed by 50 ml. of benzene. The effluent from the column was evaporated *in vacuo* to give a light yellow oil which crystallized when triturated with petroleum ether. Recrystallization from hot petroleum ether (b.p. 30–60°) gave 1.7 g. (42.8%) of colorless prisms, m.p. 66–67°.

Anal. Calcd. for $C_{11}H_{13}N$: C, 83.0; H, 8.2; N, 8.8. Found: C, 82.8; H, 8.2; N, 9.0.

Hydrogenation of XIX in acetic acid–ethyl acetate solution. To a hot solution of 16.5 g. of XIX in 200 ml. of ethyl acetate, 25 ml. of ethanol, and 25 ml. of glacial acetic acid was added 2 g. of 10% palladium-on-charcoal catalyst. The mixture was placed in a Parr hydrogenation apparatus at an initial hydrogen pressure of 60 p.s.i. Over a period of 1.2 hr., 24.4 p.s.i. of hydrogen was taken up (theory 35 p.s.i.) by the sample. The reaction mixture was filtered free of the spent catalyst, and the resulting dark filtrate was washed with 5% sodium bicarbonate. After drying the organic layer over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the dark residue distilled. A fraction amounting to 4.2 g. of a semisolid product boiling at 160–165°/0.7 mm. was collected and triturated with benzene–petroleum ether (b.p. 30–60°) to give 1.1 g. of a tan solid; m.p. 153–154°, with preliminary softening. Several recrystallizations from hot benzene afforded 500 mg. of colorless prismatic needles, m.p. 183–184°. This product gave a positive red spot test for an aliphatic oxime group when heated on a steam bath with benzoyl peroxide and the vapors were allowed to impinge on a filter paper which had been treated previously with equal parts of 1% solution of α-naphthylamine and sulfanilic acid in 30% acetic acid.[21] The partial reduction product XIX which was obtained was therefore *2-nitro-3,4,5-trimethylphenylacetaldoxime* (XX).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.3; N, 12.6. Found: C, 59.8; H, 6.5; N, 12.3.

5,6,7,N,N-Pentamethyl-3-indoleglyoxalamide (XXIII). A solution of 7.5 g. of XXI in 100 ml. of absolute ether was treated with 7.5 g. of oxalyl chloride in 10 ml. of the same solvent under stirring. The mixture was stirred for half an hour and the solid orange glyoxalyl chloride collected on a filter and washed with dry ether. The resulting dry powder was resuspended in about 100 ml. of dry ether and then treated with a solution of 6.8 g. of anhydrous dimethylamine in 10 ml. of dry ether (ice bath cooling and stirring). After remaining at room temperature for 1 hr., the crude precipitated amide (XXIII) was collected and washed thoroughly with ether and then with water. After air drying, the dark XXIII weighed 8.2 g. (68%). Recrystallization from hot benzene containing a little ethanol afforded 6 g. (50%) of the pure amide as nearly colorless needles, m.p. 192–193°.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.7; H, 7.0; N, 10.85. Found: C, 70.0; H, 7.1; N, 11.0.

5,6,7,N,N-Pentamethyltryptamine (XXIV). The amide (XXIII) (5.8 g.) in 50 ml. of hot dry benzene was added to a slurry of 3.7 g. of lithium aluminum hydride in 100 ml. of absolute ether and the product worked up in the manner described for the preparation of IV. The resulting dry benzene-ether solution of the base was treated with dry hydrogen chloride gas to precipitate 5.6 g. (93%) of XXIV as an oily compound which was taken up in ethanol; cooling and adding ether induced crystallization of the hydrochloride as nearly colorless prisms weighing 5.1 g. (85%); m.p. 124–125°, with some previous softening.

Anal. Calcd. for $C_{15}H_{23}ClN_2$: C, 67.5; H, 8.6; Cl, 13.3. Found: C, 67.8; H, 8.7; Cl, 13.2.

Acknowledgment. This research was supported by Battelle Memorial Institute funds and by Public Health Service Grant M-1588.

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(21) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Amsterdam, 5th ed., 1956, p. 228.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Synthesis of α-Methyltryptophans and α-Alkyltryptamines

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Received April 8, 1960

This paper reports the synthesis of a series of α-alkyltryptophans and tryptamines in which the indole nucleus may be substituted in the 5-position. The tryptophans were prepared by condensation of the appropriate gramine with ethyl α-nitropropionate followed by reduction and saponification. The tryptamines were prepared by four procedures: a) decarboxylation of the above nitroester followed by reduction of the nitro groups; b) alkylation of a nitroparaffin with a gramine or c) with an indole-3-carboxaldehyde, followed by reduction; d) treatment of tryptophan with an appropriate alkanoic anhydride followed by Wolff-Kishner reduction of the resulting acylaminoketone.

During the past few years many reports have been published concerning the formation[1] and metabolism[1,2] of serotonin as well as its possible role in such conditions as mental disease,[3] hypertension,[4] inflammatory processes[5] and gastrointestinal function.[6] Woolley[3b] has suggested that mental aberration might be due to lack of serotonin in the brain, and has reported[7a] that increasing brain serotonin by the administration of its precursor, 5-hydroxytryptophan, resulted in clinical improvement in cases of schizophrenia. Shore[7b] has demonstrated that iproniazide, a monaminoxidase inhibitor, *increases* serotonin brain levels by preventing its metabolism and Udenfriend[8] suggested that aminoxidase inhibitors, active *in vivo*, should be potentially useful in treating mental disease. Numerous reports on the use of iproniazide and other monaminoxidase inhibitors in depressive states have since appeared.[9]

On the other hand, three Rauwolfia alkaloids—reserpine, deserpidine and rescinnamine—also used in mental disease, *decrease* serotonin in the brain[10] and at least the first of these produces a decrease in both brain and peripheral norepinephrine and epinephrine.[11] Attempts to rationalize these facts have been made,[12] but from the conflicting data available it is impossible to predict the ultimate effect of an increased serotonin brain level. Indeed it is possible that both stimulation and depression could result depending on the dose of aminoxidase inhibitor administered or the brain serotonin level achieved.[12c]

In the course of a continuing study of the biological effects of various types of indole-containing compounds we undertook the preparation of a series of α-alkyltryptamines and tryptophans. Such tryptamines could conceivably act as serotonin-like compounds or as true serotonin antagonists in a manner similar to Woolley's BAS.[13] On the other hand they could act as competitive inhibitors of monamine oxidase and hence increase levels of serotonin and perhaps other physiologically active amines. The corresponding α-alkyltryptophans might represent potential sources of these tryptamines in the brain by acting as precursors capable of crossing the blood-brain barrier. This situation would resemble the case of 5-hydroxytryptophan,[1a] which enters the brain and is converted to serotonin which itself does not cross into the brain. On the other hand the tryptophans could act as 5-hydroxytryptophan decarboxylase inhibitors and thus decrease brain serotonin levels. In any event a study of the effects of these two classes of compounds would appear fruitful.

The tryptophans and tryptamines which we prepared are of the general types I and II.

(1) (a) S. Udenfriend, H. Weissbach, and D. F. Bogdanski, *Ann. N.Y. Acad. Sci.*, 66, 602 (1957); (b) *J. Biol. Chem.* 224, 803 (1957).

(2) (a) H. Blashko, *Biochem. J.*, 52 (Proceedings), page x (1952); (b) A. Sjoerdsma, T. E. Smith, T. D. Stevenson, and S. Udenfriend, *Proc. Soc. Exp. Biol. Med.*, 89, 36 (1955); (c) W. M. McIsaac and I. Page, *J. Biol. Chem.*, 234, 858 (1959).

(3) (a) J. H. Gaddum, Ciba Foundation Symposium on Hypertension, Humoral and Neurogenic Factors, Little, Brown and Company (Boston) 1954, page 75; (b) D. W. Woolley and E. Shaw, *Proc. Nat. Acad. Sci.*, 40, 228 (1954); (c) B. B. Brodie and P. A. Shore, *Ann. N.Y. Acad. Sci.*, 66, 631 (1957).

(4) (a) I. Page and J. W. McCubbin, *Circulation Res.*, 1 354 (1953); (b) D. W. Woolley and E. Shaw, *Science*, 124, 34 (1956).

(5) (a) M. A. Fink, *Proc. Soc. Exp. Biol. Med.*, 92, 673 (1956); (b) S. Udenfriend, P. A. Shore, D. F. Bogdanski, H. Weissbach, and B. B. Brodie, *Recent Progress in Hormone Research*, Vol. 13, page 4; (c) W. C. Spector and D. A. Willoughby, *Nature*, 179, 318 (1957).

(6) (a) E. Bülbring and R. C. Y. Lin, *J. Physiol. (London)*, 140, 381 (1958); (b) R. R. P. Warner, *J. Mt. Sinai Hosp., N.Y.*, 26, 450 (1959).

(7) (a) D. W. Woolley, *Science*, 125, 752 (1957); (b) P. A. Shore, J. A. R. Mead, R. G. Kuntzman, S. Spector, and B. B. Brodie, *Science*, 126, 1063 (1957).

(8) S. Udenfriend, paper presented at the Medicinal Chemistry Symposium, East Lansing, Michigan, June 1956.

(9) For example, *Ann. N.Y. Acad. Sci.*, 80, 551–1045 (1959).

(10) B. B. Brodie, P. A. Shore, and A. Pletscher, *Science*, 123, 992 (1956).

(11) B. B. Brodie, J. S. Olin, R. G. Kuntzman, and P. A. Shore, *Science*, 125, 1293 (1957).

(12) (a) B. B. Brodie, E. G. Tomich, R. G. Kuntzman, and P. A. Shore, *J. Pharmacol. Exp. Therap.*, 119, 461 (1957); (b) M. Chessin, E. R. Kramer, C. C. Scott, *J. Pharmacol. Exp. Therap.*, 119, 453 (1957); (c) P. A. Shore and B. B. Brodie, *Proc. Soc. Exp. Biol. Med.*, 94, 453 (1957).

(13) D. W. Woolley and E. Shaw, *Ann. N.Y. Acad. Sci.*, 66, 649 (1957).

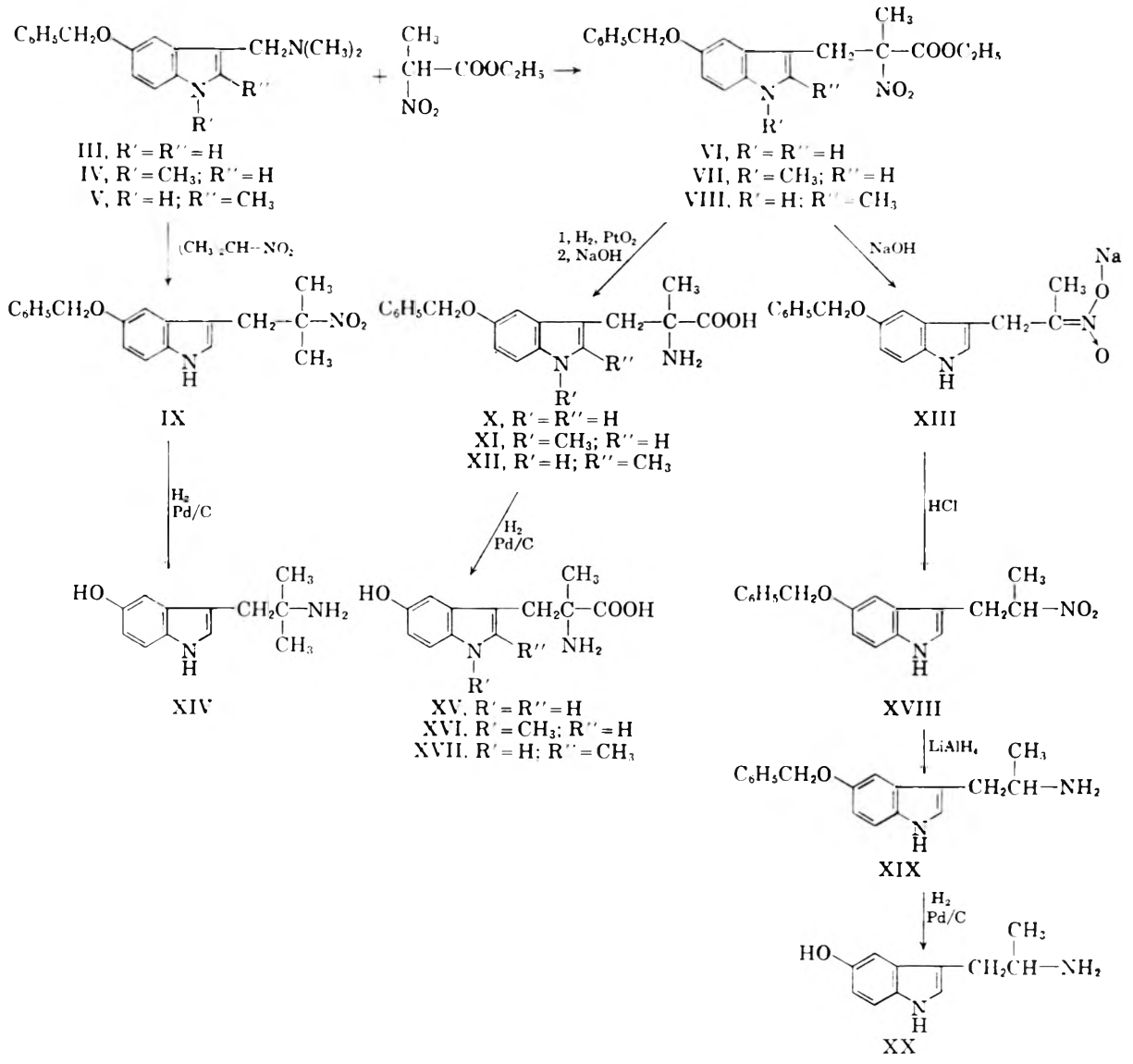
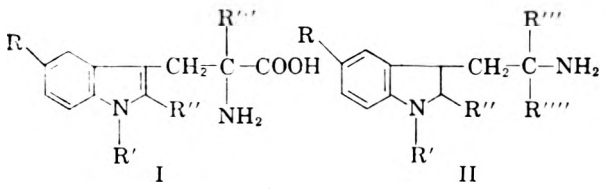


Fig. 1. Preparation of α-methyltryptophans



For the preparation of α-methyltryptophans (I R‴ = CH_3) we chose the general method, outlined in Fig. 1, involving interaction of the appropriately substituted gramine with ethyl α-nitropropionate following the published method used for tryptophan itself.[14] In the present case, however, the problem of dialkylation is eliminated by the presence of only one *alpha* hydrogen atom in the nitroester. Compound VII could also be prepared by methylation of VI using methyl iodide in the presence of sodium hydride.

α-Methyltryptophan, prepared previously[15] from 3-indoleacetone *via* the hydantoin, was produced in good yield through the nitropropionate. 5-Hydroxytryptophan itself[16] was obtained using the ethyl nitromalonate method of Weisblat and Lyttle.[17]

The tryptamines were prepared by four procedures, depending on the substituents present. The first method involved decarboxylation of the appropriate α-nitroester followed by reduction of the resulting nitroalkane by means of lithium

(14) D. A. Lyttle and D. I. Weisblat, *J. Am. Chem. Soc.*, **69**, 2118 (1947).

(15) K. Pfister and W. J. Leanza, U. S. Patent **2,766,255** (1956).

(16) Previously prepared by B. Witkop, *J. Am. Chem. Soc.*, **75**, 500 (1953); **76**, 5579 (1954), using the diethylformamidomalonate method.

(17) D. I. Weisblat and D. A. Lyttle, *J. Am. Chem. Soc.*, **71**, 3079 (1949).

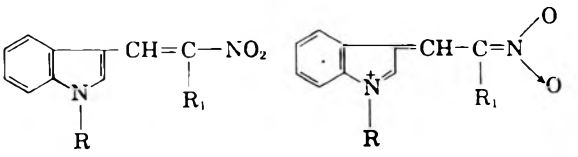
aluminum hydride (Fig. 1). According to the second method alkylation of 2-nitropropane with 5-benzyloxygramine to give IX occurred readily. In those cases in which the nitroparaffin contained two *alpha* hydrogen atoms dialkylation resulted, in agreement with the experience of Snyder and Katz[18] with gramine itself. The third procedure involved alkylation of the nitroparaffin with the appropriate indole 3-carboxaldehyde as outlined in Figure 2.[19] Compound XXIX was also prepared from tryptophan using the Dakin-West reaction[22] followed by Wolff-Kishner reduction of the resulting 1-(3′-indolyl)-2-acetamido-butanone-3. The same method was also used to prepare α-*n*-propyltryptamine.

The preparation of two of the substituted gramine intermediates required somewhat lengthy procedures. 5-Benzyloxy-1-methylgramine (IV) was prepared *via* 5-benzyloxyindole-3-carboxaldehyde, which, by virtue of the blocking group in the 3-position, could be methylated on the indole nitrogen using potassium carbonate as the base to yield XXIII. The blocking group was then eliminated by oxidation to the corresponding indole-3-carboxylic acid, followed by decarboxylation to 5-benzyloxy-1-methylindole, which was converted to the gramine in the usual way. In the synthesis of 5-benzyloxy-2-methylgramine, V, benzoquinone was condensed with ethyl β-aminocrotonate according to the method of Nenitzescu[23] to yield ethyl 5-hydroxy-2-methylindole-3-carboxylate. The latter was then converted to the corresponding 5-benzyloxy derivative, decarboxylated, and treated with formaldehyde and dimethylamine to yield V.

Two methods for the preparation of nitroalkenes XXIV to XXVII were available from the literature. The first method was reported by Majima and Kotake[24] in which 1-acetylindole-3-carboxaldehyde, nitromethane, and sodium hydroxide were used. The second method was reported by Seka[25] in which 2-methylindole-3-aldehyde, methylamine hydrochloride and sodium carbonate were employed. Neither of these methods was satisfactory, as the former did not afford a route to the 1-substituted indole-3-nitroalkenes and the latter was time-consuming and resulted in low yields.

Investigation of this problem disclosed that a satisfactory method for the preparation of these nitroalkenes was the reaction between the nitroalkane and indole-3-carboxaldehyde in the presence of acetic acid, ammonium acetate, and sodium acetate. This method was applicable to the preparation of both the 1-substituted and 1-unsubstituted indole nitroalkenes.

During the course of this work it became apparent that the structure of the reaction products was not represented by XXXIII. The absence of absorption bands corresponding to the nitro group in the infrared and the appearance of a new band at 1270 and 1223 cm.$^{-1}$, correlated with ultraviolet absorption in the 400 mμ region, strongly suggested that the compounds were actually inner nitronium salts as shown by formula XXIV. These compounds could be converted to the corresponding amines catalytically but were preferably reduced with lithium aluminum hydride in tetrahydrofuran.



XXXIII XXXIV

R = H, $-CH_3$
R_1 = H, $-CH_3$, $-C_2H_5$

Pharmacology. Some of the pharmacological testing carried out with certain of our compounds has already been published. Govier, Howes, and Gibbons[26] studied the action of monamine oxidase on α-ethyltryptamine (XXIX) *in vitro* and concluded that deamination did not occur. Barlow and Khan[27] have described the effects of 5-benzyloxy-α-methyltryptamine (XIX), 5-hydroxy-α-methyltryptamine (XX), and α-methyltryptamine (XXX) on the isolated rat uterus and isolated rat fundus strip preparation. Greig, Walk, and Gibbons[28a] have published the *in vitro* and *in vivo* effects of 5-hydroxy-α-methyltryptamine (XX), α-methyltryptamine (XXVIII), and α-ethyltryptamine (XXIX)[28b] in blocking the enzymes, monamine oxidase, and 5-hydroxytryptophan decarboxylase. The first two compounds are potent inhibitors of both enzymes *in vitro* while the third compound is much more selective in favor of monamine oxidase. *In vivo* studies indicate that XX is effective in inhibiting 5-hydroxytryptophan decarboxylase,

(18) H. R. Snyder and L. Katz, *J. Am. Chem. Soc.*, **69**, 3140 (1947).

(19) After the completion of our work Young[20] and Ash and Wragg[21] reported the preparation of XX by reaction of the indolealdehyde and nitroethane, followed by reduction. Our overall yield *via* the nitroester was approximately twice that reported[21] by the latter authors. These authors also describe the synthesis of XXVIII and XXIX by the procedure used in this paper, but few experimental details are given.

(20) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).

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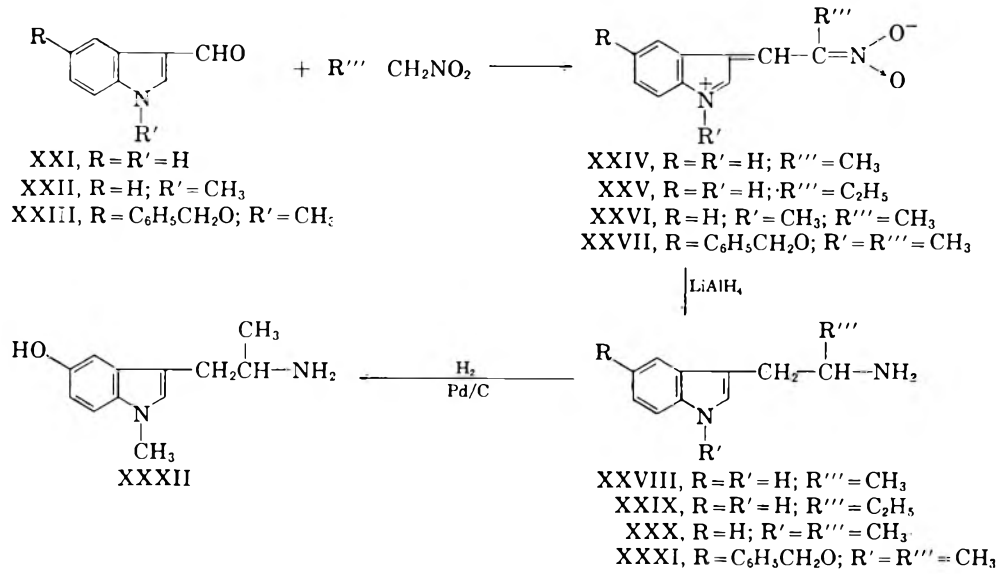

Fig. 2. Alkylation of the nitroparaffin with the appropriate indole

XXIX inhibits only monamine oxidase while XXVIII blocks both enzyme systems. Substitution of methyl groups in the 1- or 2-position of the indole ring decreases inhibitory activity somewhat. This effect of substitution in the indole ring is similarly apparent in the ability of 5-hydroxy-α-methyltryptophan (XV), 5-hydroxy-1-α-dimethyltryptophan (XVI), and 5-hydroxy-2,α-dimethyltryptophan (XVII) to block 5-hydroxytryptophan decarboxylase. Compound XV is a potent selective inhibitor of this enzyme, both *in vitro* and *in vivo* but, in rats at least, does not appear to be orally absorbed. This is somewhat surprising in view of its amino acid structure and the fact that that 5-hydroxytryptophan itself has been found by Dr. Greig to be orally active. Many factors, such as relative effects on various enzyme systems, relative effects on each enzyme system in brain *vs.* liver, relative toxicities, and other pharmacological effects, play a major role in the overall biological profile of even such a closely knit group of compounds as those reported in this paper.

EXPERIMENTAL[29]

A. *5-Hydroxy-α-methyltryptamine* (XX). *a. Preparation of ethyl α-methyl, α-nitro-β-[3-(5-benzyloxyindolyl)]propionate* (VI). (1) A mixture of 9.76 g. (0.0348 mole) of 5-benzyloxygramine[30] (III), ethyl α-nitropropionate[31] (5.13 g., 0.0348 mole), and 58 ml. of anhydrous toluene was stirred and refluxed for 3.5 hr. while a rapid stream of nitrogen was passed through the solution.

The reaction mixture was cooled to room temperature and 100 ml. of chloroform was added. The ice cold mixture was then washed with two portions of 10% hydrochloric acid (30 ml. each), once with 30 ml. of water, and then with two portions of 5% potassium hydroxide (30 ml. each). The organic layer was washed once with water (30 ml.), once with saturated salt solution, then dried over sodium sulfate and evaporated to dryness. A brown oil (II) was obtained, 12.8 g. (97% yield). The infrared spectrum was very similar to that of the sample which was purified by chromatography as described below.

(2) Sixty-six grams (0.236 mole) of 5-benzyloxygramine, 34.7 g. (0.236 mole) of ethyl-α-nitropropionate, and 235 ml. of dry xylene were placed in a 500 ml., three necked flask fitted with a stirrer, an efficient condenser, and a nitrogen inlet tube. The mixture was heated with stirring under reflux with a vigorous stream of nitrogen passing through to remove dimethylamine as it was formed. After 10 hr. dimethylamine evolution had practically stopped. The solution was cooled and washed with 2*N* hydrochloric acid, 2*N* sodium hydroxide, then water. It was dried over magnesium sulfate, decolorized with 10 g. of Magnesol, filtered, and the filtrate was concentrated *in vacuo*. The reddish-orange oil weighed 78.3 g. (90.0%). Fifteen grams was chromatographed over 1 kg. of Florisil. The oil was put on the column in benzene solution and the column was developed with 2 l. of 5% acetone in petroleum ether (b.p. 60–71°), 2 l. of 7.5% acetone in petroleum ether (b.p. 60–71°), and finally with five 3-l. portions of 10% acetone in petroleum ether (b.p 60–71°). The first 12 l. of 10% eluate gave, on concentration, 12.5 g. of clear, light yellow oil. Infrared: NH: 3425; C=O: 1740; C=C: 1623, 1587; NO_2: 1552; C—O: 1255, 1218, 1200; phenyl: 795, 733, 693.

Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.80; N, 7.33. Found: C, 66.02; H, 5.61; N, 7.54.

The remainder of the crude material was purified and decolorized by dissolving it in methylene chloride and treating it with 40 g. of Florisil, filtering and treating again with 30 g. After the solvent was evaporated, 36.4 g. of clear, light yellow oil (VI) remained. Florisil is a very specific adsorbent for impurities in this material.

b. *Preparation of α-methyl-β[3-(5-benzyloxyindolyl)]nitroethane* (XVIII). A solution of sodium hydroxide (3.6 g.) in 10 ml. of water was added to a solution of 12.8 g. of crude VI [prepared as described in (1) above] in 53 ml. of absolute

(29) Melting points were taken in a capillary tube and are uncorrected. Ultraviolet spectra (recorded in mμ) were determined in 95% ethanol using a Cary spectrophotometer Model 14. Infrared spectra (recorded in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer Model 21.

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ethanol. The mixture was allowed to stand at room temperature for 24 hr. The resulting suspension was then diluted with 10 ml. of absolute ethanol, filtered, and the precipitate washed with two portions of ethanol (10 ml. each), then with a total of 40 ml. of ether. The resulting solid sodium salt (III) (12.28 g.) contained sodium carbonate (as evidenced by titration).

The infrared clearly indicates that it is the *sodium salt of the corresponding nitronic acid* (XIII): No NO_2; NH: 3380, 3240, 3130, 3020; C=C: 1616, 1600, 1580; Na—O: 1450 cm.$^{-1}$.

The sodium salt (XIII) could be purified for analysis in the following way: *Ca.* 1.5 g. of the crude sodium salt was slurried in about 10 ml. of cold water. The resulting suspension was filtered and washed very slowly with 3.0 ml. of water. The slightly wet solid was transferred to a flask and mixed with acetone. The mixture was warmed on the steam bath and warm water added until the solution became clear. Warm acetone was then added dropwise until precipitation occurred (volume ratio *ca.* 10:1 acetone-water). The mixture was cooled in an ice bath and filtered. The white lustrous plates weighed 1.1 g. and melted to a glassy liquid at 112–115°. Neut. equiv. Calcd.: 332.33. Found: 345.4.

Anal. Calcd. for $C_{18}H_{17}N_2O_3Na \cdot 1.5H_2O$: C, 60.16; H, 5.61; N, 7.80. Found: C, 60.05; H, 6.13; N, 7.86.

The crude sodium salt was dissolved in 1 l. of water by warming to 40°. The solution was cooled to about 7° and acidified with 25 ml. of 10% hydrochloric acid while cooling. The resulting precipitate was filtered and washed with 100 ml. of water, sucked dry, and transferred to a beaker. This filtration and drying *should not* take more than 20 min., as the solid starts turning oily after standing for a short time. The solid was allowed to stand at room temperature for 56 hr. The resulting product was dissolved in 150 ml. of ether, dried over magnesium sulfate, and evaporated. The oily product (XVIII) weighed 7.5 g. and showed a small amount of carbonyl impurity at 1696 cm.$^{-1}$ (probably resulting from a side Nef-reaction).

A sample was recrystallized from ether–petroleum ether (b.p. 30–60°); m.p. 83–85°. Ultraviolet: f 224 (30,275); 276 (6,925); f 296 (5,350); f 308 (3,700). Infrared: NH: 3360; C=C: 1624, 1581, 1605; NO_2: 1550; C—O: 1211, 1182; aromatic: 796, 726, 689 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 70.15; H, 6.11; N, 9.27.

c. *Lithium aluminum hydride reduction of* XVIII *to α-methyl-β-[3-(5-benzyloxyindolyl)ethylamine]*(XIX): The crude XVIII (7.5 g.) in 50 ml. of anhydrous ether was added to a solution of lithium aluminum hydride (10 g.) in 600 ml. of ether with stirring and ice bath cooling. The resulting suspension was refluxed 2.5 hr. and then allowed to stand overnight at room temperature. It was then cooled in ice and decomposed first with 50 ml. of water, then with a large excess of 15% potassium hydroxide solution. The ethereal extracts were washed with water, dried over sodium sulfate, and concentrated to about 100 ml. Eight milliliters of saturated ethereal hydrogen chloride was then added while swirling in the cold. The resulting precipitate was filtered and washed with ether; 5.34 g., m.p. 244.5–246.5°. The hydrochloride was recrystallized by dissolving in 110 ml. of warm methanol and adding 420 ml. of ether. The mixture was allowed to stand overnight in the cold, filtered and washed with ether, 4.58 g., m.p. 253–254°. Ultraviolet: 220 (30,575); 277 (6,675); 296 (5,150); 308 (3,425). Infrared: NH: 3270; HCl: 2680, 2570, 2480, 2360; C=C: 1617, 1601, 1590, 1501, 1482; C_6H_5: 796, 755, 744, 710, 690.

Anal. Calcd. for $C_{18}H_{21}ClN_2O$: C, 68.23; H, 6.68; Cl, 11.19; N, 8.84. Found: C, 68.39; H, 6.65; Cl, 10.95; N, 8.66.

d. *Hydrogenolysis of* V *to 5-Hydroxy-α-methyltryptamine* (XX)[32]: Sixty grams (0.19 mole) of XVIII hydrochloride was suspended in 3 l. of water and 600 ml. of 10% aqueous potassium hydroxide was added. The resulting oil was extracted with three 3-l. portions of ether. The combined ether extract was washed with water, then with saturated salt solution, and dried over sodium sulfate. The solution was evaporated *in vacuo* at <50° to give 53 g. of product.

In order to ensure a minimum of coloration in the final product all subsequent operations should be run on the same day and all equipment should be rinsed with acetic acid and then with ethanol immediately before use.

The product was dissolved in 900 ml. of absolute ethanol, a slurry of 10% palladium on charcoal (30 g.) in ethanol was added, and the mixture was hydrogenated at 50 p.s.i. with good agitation until the theoretical amount of hydrogen had been taken up (5–6 hr.). The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo* at <50°. The crude product (36.4 g., 0.19 mole) was very hygroscopic and no satisfactory analytical data could be obtained. It was dissolved in 191 ml. of 1.0*N* sulfuric acid (0.095 mole) and water (492 ml.) was added. Creatinine sulfate (31.4 g. containing 2% of water; 0.095 mole) was then added and the mixture was stirred to achieve solution (filtered if necessary) and then it was freeze-dried. The resulting amorphous solid was ground and dried at 0.1 mm. to constant weight to give 70.6 g. of α-methyl serotonin (XX) creatinine sulfate complex. Ultraviolet (in 0.01*N* alcoholic sulfuric acid): 217.5 (24,725); 276 (5,175); 296 (4,250).

Anal. Calcd. for $C_{15}H_{25}N_5O_6S$: N, 17.45. Found: N, 17.18.

B. *Preparation of α,α-dimethylserotonin* (XIV). a. *5-Benzyloxy-3-(α,α-dimethyl-α-nitroethyl)indole* (IX). A suspension of 20.0 g. (0.07 mole) of 5-benzyloxygramine, 100 ml. of 2-nitropropane, and 5.2 g. (0.13 mole) of solid sodium hydroxide was agitated by a slow stream of nitrogen and refluxed for approximately 8 hr. until the evolution of dimethylamine ceased. The mixture was cooled and 50 ml. of 10% acetic acid was added. Ether (200 ml.) was added to the resulting solution and the layers were separated. The ether layer was washed four times with water and dried over magnesium sulfate. A mixture of Darco G-60 and Celite was added, the suspension was filtered, and the solution was concentrated. The residue was crystallized by trituration with ether, then recrystallized from benzene to yield 16.4 g. (70%) of product which melted at 114–115°. An analytical sample was prepared by recrystallization from alcohol, m.p. 114.5–116.5°.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.46; H, 5.98; N, 8.80.

b. *5-Hydroxy-3-(β,β-dimethyl-α-aminoethyl)indole* (XIV). A solution of 5.0 g. (0.015 mole) of IX in 200 ml. of absolute methanol and 1.0 g. of 10% palladium on charcoal were shaken for 20 hr. under 50 p.s.i. initial hydrogen pressure. After 4 mole equivalents of hydrogen were absorbed the mixture was filtered through Celite. The filtrate was concentrated to dryness under reduced pressure to yield 2.2 g. (71.8%) of a white solid. The solid melted at 74–84°, resolidified, and resinified. Ultraviolet: 216 (19,950); 276 (4,900); 300 (3,700).

Anal. Calcd. for $C_{12}H_{16}N_2O \cdot 1/2\ CH_3OH$: C, 68.15; H, 8.23; N, 12.71. Found: C, 68.47; H, 7.95; N, 12.79.

Creatinine sulfate (250 mg.) was added to a solution of 304.8 mg. of the above amine in 4.8 ml. of water and 1.5 ml. of 1*N* sulfuric acid. The solution was warmed to about 60° and 35 ml. of boiling acetone was added. After cooling at −5–0°, 600 mg. of the creatinine sulfate complex was collected by filtration. The complex softened at 91°, melted at 161°, and decomposed at 212°. The complex was 98–100% pure by ultraviolet analysis as compared with serotonin creatinine sulfate. Ultraviolet [pH 4.4 (sulfuric acid)]: 220 (17,425); 276 (4,800); 292 (4,025).

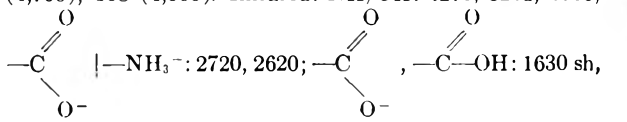
C. *5-Hydroxy-α-methyltryptophan* (XV). a. *5-Benzyloxy-α-methyltryptophan* (X). Ethyl α-nitro-α-methyl-β[3-(5-benzyloxyindole)]propionate (VI) (purified as described in the second experiment of the Experimental by successive treatments with Florisil; 60.3 g., 0.1628 mole) and 12.0 g. of fresh, brown platinum oxide (Adams catalyst, Baker) in 500

(32) We would like to acknowledge the assistance of Mr. P. E. Marlatt in carrying out this reaction.

ml. of 3-A alcohol were treated with hydrogen at 40 p.s.i. in a stirring autoclave. The calculated amount of hydrogen was taken up in 2.5 hr., at which time uptake had ceased. The autoclave was purged thoroughly with nitrogen, opened, and 81 g. of 20% sodium hydroxide was added. The autoclave was closed, a hydrogen atmosphere was re-established, and hydrolysis of the ester was allowed to proceed overnight at 35°. When the autoclave was opened, a few crystals of sodium hydrosulfite were added to retard air oxidation which is otherwise very rapid. Glacial acetic acid (25 ml.) was added, the catalyst was removed by filtration, and washed with 3-A alcohol. The filtrate was concentrated under vacuum, and when about 400 ml. had been removed, crystallization occurred. Four hundred milliliters of water was added and the mixture was cooled at 4° for 12 hr. The tan crystalline solid was collected and washed with water; 35.1 g. A second crop was obtained by concentrating the filtrate, 5.14 g.; total wt., 40.2 g. (75.7%). A sample from another run was recrystallized from alcohol-water (1:1); m.p. 273–275° dec. Ultraviolet: 275 (6,350); ⁻ 294 (4,950); f 306 (3,350). Infrared: NH: 3250; NH_3^+: s 2740, 2600, 2500; COO^-/C=C: s 1645, s 1630, 1610, 1586, 1487; aromatic substitution: 806, 796, 735, 692.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.64. Found: C, 70.74; H, 6.50; N, 8.76.

b. *5-Hydroxy-α-methyltryptophan* (XV). 5-Benzyloxy-α-methyltryptophan (X) (43.8 g., 0.135 mole) suspended in 200 ml. of 3-A alcohol and 400 ml. of water was reductively debenzylated in a Parr hydrogenator in the presence of 25 g. of 10% palladium-on-charcoal catalyst. The calculated amount of hydrogen was taken up in 1.5 hr. Most of the catalyst was removed by filtration, but some appeared to be colloidal, giving the solution a dark appearance which did not lighten on addition of a little sodium hydrosulfite. The alcohol was removed by concentration under vacuum. An equal volume of hot water was added and the dark solution was forced through a Seitz sterilizing filter under nitrogen pressure. Some black material was removed, but the solution was still dark. It was concentrated under slight vacuum until crystallization began. The mixture was chilled at 4° overnight, then the greyish-tan crystals were collected and washed with a little cold water; 17.8 g. The filtrate, to which a little sodium hydrosulfite had been added, was concentrated and a second crop was obtained; 6.39 g.; total wt., 23.9 g. (75.5%). A sample from another batch was recrystallized several times from water; the colorless product gradually darkens from 250°, does not melt below 296°.

The infrared spectrum of this compound contains all the expected absorptions and is quite similar to that of 5-hydroxytryptophan. Ultraviolet: 208 (27,500); 274 (6,400); 299 (4,700); 308 (4,000). Infrared: NH/OH: 3270, 3238, 3110, 
3040; 1615, 1561; C—O: 1255, 1210; C—N: 1107; ar. sub.: 874, 811.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.29; H, 5.68; N, 11.75.

D. *1,α-Dimethyl-5-hydroxytryptophan dihydrate* (XVI). a. *1-Methyl-5-benzyloxyindole-3-carboxaldehyde* (XXIII). A mixture of 37.5 g. (0.15 mole) of 5-benzyloxyindole-3-carboxaldehyde,[20,21] 300 ml. of Carbitol, 25 g. of methyl iodide and 22 g. of potassium carbonate was heated overnight on the steam bath, cooled, and diluted with water. The solid was collected, washed well with water, and recrystallized from alcohol to yield 30.4 g. of product (76%) which melted at 128–129°. Infrared: NH: absent; C=O: 1645; C=C: 1621, 1582, 1537.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.69; N, 5.27. Found: C, 76.97; H, 5.51; N, 5.24.

b. *1-Methyl-5-benzyloxy-3-indole carboxylic acid.* A solution of 20.0 g. (0.075 mole) of 1-methyl-5-benzyloxyindole-3-carboxaldehyde (XXIII) and 380 ml. of acetone was stirred and a solution of 24.0 g. (0.15 mole) of potassium permanganate and 300 ml. of water was added at such a rate as to keep the temperature below 40°. The mixture was stirred for 1 hr. and filtered. The solid was washed with 50% acetone and the combined filtrates were acidified with dilute hydrochloric acid. The solid was filtered, washed well with water, and air dried to yield 14.8 g. (70.0%) of product. After recrystallization from a large volume of alcohol, 12.0 g. (57% yield) of product was obtained which melted at 219–220.5°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.54; H, 5.37; N, 4.98. Found: C, 72.75; H, 5.32; N, 5.16.

c. *Decarboxylation to 1-methyl-5-benzyloxyindole.* 1-Methyl-5-benzyloxyindole-3-carboxylic acid (10 g., 0.035 mole) was placed in a flat-bottomed flask and immersed in an oil bath preheated to 245°. After 15 min. the flask was removed and allowed to cool. The dark solid was dissolved in hot acetone and diluted with 3-A alcohol to yield 7.0 g. (78.6%) of light tan product which melted at 130–131°. Infrared: C=C: 1616, 1600, 1573, 1555, 1494; C—O: 1235; ar. sub.: 846, 835, 797, 749, 745, 720, 693.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.03; H, 6.14; N, 5.61.

d. *5-Benzyloxy-1-methylgramine* (IV): A solution of 15 ml. of dioxane and 15 ml. of acetic acid was cooled to 10° and 1.2 ml. of 37% aqueous formaldehyde was added. A total of 3.3 ml. of 25% aqueous dimethylamine was then added over 5 min. The solution was stirred at 10° and a solution of 3.35 g. (0.014 mole) of 5-benzyloxy-1-methylindole in 15 ml. of dioxane was added over 30 min. The solution was allowed to stand overnight, 187 ml. of water was added and the mixture was filtered through Celite. An ice-cold solution of 14.0 g. of potassium hydroxide and 150 ml. of water was added to the filtrate. The resulting mixture was cooled in an ice bath and filtered. The product was washed well with water and dried in air to yield 3.3 g. (80%) of crude solid. After treatment with Nuchar 190-N and recrystallization from dilute alcohol the solid melted at 48–50°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51. Found: C, 78.08; H, 7.86; N, 9.69.

e. *Ethly α-methyl-α-nitro-β-[3-(1-methyl-5-benzyloxyindole)]propionate* (VII). (1) A mixture of 32.0 g. (0.108 mole) of 5-benzyloxy-1-methylgramine (IV), 15.8 g. (0.108 mole) of ethyl-α-nitropropionate, 1.0 g. (0.025 mole) of sodium hydroxide, and 120 ml. of xylene was refluxed for 24 hr. under a slow stream of nitrogen. The mixture was cooled and filtered. The filtrate was washed with water, dilute hydrochloric acid, and then with water until acid free. The solution was dried over potassium carbonate, then passed through Florisil in order to remove the dark color. Concentration of the solution yielded 5.5 g. (14%) of an impure amber-colored oil. Infrared: NH/OH absent; Ester C=O: 1745 $cm.^{-1}$; C=C: 1623, 1580, 1495; NO_2: 1555, 1355; C—N/C—O: 1305, 1262, 1225, 1210, 1125, 1020; ar. sub.: 854, 792, 730, 690 cm^{-1}.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 68.53; H, 7.20; N, 7.20.

(2) A solution of 45 g. (0.118 mole) of ethyl 1,α-dimethyl-α-nitro-β-[3-(5-benzyloxyindole)]propionate (VI) and 100 ml. of anhydrous dimethylformamide was added to a mixture of 5.0 g. (0.21 mole) of sodium hydride and 100 ml. of dimethylformamide which had been previously cooled to approximately −50°. When the liberation of hydrogen ceased, 29.8 g. (0.21 mole) of methyl iodide was added over 1 hr. The mixture was stirred at room temperature overnight and carefully diluted with 9.0 ml. of alcohol. The mixture was poured into water, refrigerated for several hours, and filtered. After four recrystallizations from methanol, the solid weighed 14.0 g. (30%) and melted at 75–76.5°. Infrared: NH: absent; Ester C=O: 1740; C=C: 1625, 1583, 1498; NO_2: 1557, 1365 sh, 1350 sh; CN/CO: 1311, 1268, 1260, 1240, 1222, 1205, 1135, 1123 sh, 1075, 1025; ar. sub.: 742, 722, 695, 653.

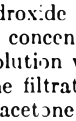
Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 66.41; H, 6.10; N, 7.04.

f. *1,α-Dimethyl-5-benzyloxytryptophan* (XI). A mixture of 5.4 g. (0.013 mole) of the above nitroester (VII), 1.0 g. of platinum oxide, 60 ml. of alcohol, and 30 ml. of ethyl acetate was hydrogenated at 50 p.s.i. for 1.5 hr. The vessel was opened and 6.6 ml. of 20% sodium hydroxide was added. The mixture was then shaken for 24 hr. under nitrogen. A few crystals of sodium hydrosulfite and 2.1 ml. of acetic acid were added and the mixture was filtered. The solid was washed with alcohol. The filtrates were combined and concentrated to dryness to yield 8.0 g. of crude solid. The solid was recrystallized from an alcohol-ether mixture to yield sodium acetate. The filtrate was concentrated and the solid was washed with water and recrystallized from an alcohol-ether mixture to yield 0.9 g. of product which melted at 234–238°.

Infrared data indicate the presence of an unexplained NH/OH component which may account for the low carbon value. Ultraviolet: 224 sh (28,125); 282 (7,650); f 288 (7,525); f 254 (7,272); f 305 (4,550). Infrared: NH/OH: 3400, 3080 sh, 2660, 2550, 2380, 2100; COOH: 1650 sh, 1622, 1592, 1515, 1488, 1400; C—O: 1285, 1220, 1205; ar. sub.: 802, 733, 695.

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 70.98; H, 6.55; N, 8.28. Found: C, 69.75; H, 6.57; N, 8.47.

g. *1,α-Dimethyl-5-hydroxytryptophan dihydrate* (XVI). A mixture of 1.4 g. (0.0041 mole) of 1,α-dimethyl-5-benzyloxytryptophan, 4.1 ml. of 0.1*N* hydrochloric acid, 25 ml. of water, 25 ml. of 3-A alcohol, and 1.0 g. of 10% palladium-on-carbon was shaken at 40° for 4 hr. at 50 p.s.i. hydrogen pressure. The mixture was neutralized with 4.1 ml. of 0.1*N* sodium hydroxide and filtered through a Seitz filter. The filtrate was concentrated to 10 ml. at a temperature below 25°. The solution was diluted with 100 ml. of acetone and filtered. The filtrate was again diluted with an additional 100 ml. of acetone and refrigerated at 0°. The filtrate was decanted from a colored oil and further diluted with 100 ml. of acetone. After 1 week at 0° a solid precipitated. After recrystallization from 6 ml. of water the product weighed 300 mg. (26%) and melted at 270–271°. Ultraviolet: 214 (25,875); 280 (6,425); 307 (5,175); f 317.5 (4,150). Infrared:



, NH_3^+, (H_2O), 1650 sh, 1630, 1610, 1430 sh, 1418; C=C: 1585, 1515, 1505; C—O/C—N: 1293, 1260, 1155, 1128; OH deformation (acid): 920 ar. sub.: 855, 815, 800, 776, 725.

Anal. Calcd. for $C_{13}H_{15}N_2O_3 \cdot 2H_2O$: C, 55.11; H, 6.75; N, 9.88. Found: C, 55.00; H, 7.21; N, 9.83.

The anhydrous material was obtained after drying at 55° (0.1 mm.) for 24 hr.

Anal. Calcd. for $C_{13}H_{15}N_2O_3$: C, 63.14; H, 6.11; N, 11.33. Found: C, 63.31; H, 6.62; H, 11.05.

E. *2-α-Dimethyl-5-hydroxytryptophan* (XVII). a. *5-Benzyloxy-3-carbethoxy-2-methylindole.* A solution of sodium ethoxide was prepared from 2.9 g. (0.126 mole) of sodium and 175 ml. of absolute ethanol. 2-Methyl-3-carbethoxy-5-hydroxyindole (27 g., 0.123 mole) and 16.5 g. (0.13 mole) of benzyl chloride were added and the mixture was refluxed under nitrogen for 2 hr. The resulting mixture was poured into water and the sticky solid filtered. The solid was boiled with 500 ml. of dry ether, the suspension was cooled, and the solid filtered and washed with ether; 9.5 g., m.p. 148.5–151°. The material was washed with alkali and this process raised the melting point to 152–152.5°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.78; H, 6.19. Found: C, 73.78; H, 6.12.

b. *5-Benzyloxy-2-methylindole and 5-benzyloxy-2-methylindole-3-carboxylic acid.* Five grams (0.016 mole) of 5-benzyloxy-3-carbethoxy-2-methylindole was added to a solution of 10 g. (0.18 mole) of potassium hydroxide in 10 ml. of water and 50 ml. of 95% ethanol. The mixture was refluxed for 18 hr. and the resulting solution was poured into 400 ml. of water. A gummy mass separated which was extracted into ether. The aqueous alkaline solution was light brown in color. On acidification a light brown solid separated which was filtered and dried. The material melted at 184–187° efferv. After recrystallization from ethyl acetate-methylcyclohexane crystals of 5-benzyloxy-2-methylindole-3-carboxylic acid were obtained which melted at 186–187°. Ultraviolet: 216 (37,875); 241.5 (20,500); 285 (9,675); 292 (9,625); f 304 (5,125). Infrared: NH: 3310; carboxyl OH: 3020, 2540, 2320; Conj. C=C: 1624, 1585, 1577, 1535; C—O: 1207, 1166; C_6H_5: 799, 731, 690.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.88, 72.83; H, 5.38, 5.48; N, 4.76, 4.85.

The ether solution of the alkali insoluble gum was dried and concentrated. A crystalline solid remained which was purified by crystallization from benzene-methylcyclohexane and finally from methylcyclohexane to give 2-methyl-5-benzyloxyindole; 4 g., m.p. 81–82°. Infrared: NH: 3365; Conj. C=C: 1650, 1618, 1599, 1585, 1545, 1481; C—O: 1180, 1174; ar. sub.: 976, 746, 695.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.97; H, 6.37; N, 5.90. Found: C, 81.11, 81.11; H, 6.42, 6.47; N, 5.63, 5.85.

c. *5-Benzyloxy-2-methylgramine* (V). A solution of 92 ml. of dioxane, 92 ml. of acetic acid, and 7.4 ml. of 37% aqueous formaldehyde was cooled to 10° and 20 ml. of 25% aqueous dimethylamine was slowly added. The solution was stirred for about 15 min. and a solution of 20 g. (0.08 mole) of 5-benzyloxy-2-methylindole and 92 ml. of dioxane was added over 30 min. The solution was allowed to stand overnight and then 1150 ml. of water and Nuchar 190-N were added. The mixture was filtered through Celite and the filtrate was made basic with 100 g. of potassium hydroxide and 900 ml. of water. The mixture was filtered and the solid was washed well with water and dried in air to yield 19.1 g. of crude product. After treatment with Nuchar 190-N and recrystallization from benzene the product weighed 16.1 g. (71%) and melted at 150–153°. Ultraviolet: 278 (8,525); 292 (7,750); 304 (4,600). Infrared: NH: 3110, 3000; tert. amine: 2780; C=C: 1625, 1588, 1495; C—O: 1237, 1220, 1195; ar. sub.: 840, 785, 727, 690.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 78.17; H, 7.27; N, 9.67.

d. *Ethyl α-methyl-α-nitro-β-[3-(2-methyl-5-benzyloxyindole)]propionate* (VIII). A mixture of 32.0 g. (0.108 mole) of the above gramine V, 15.8 g. (0.108 mole) of ethyl nitropropionate, 1.0 g. (0.025 mole) of sodium hydroxide, and 120 ml. of xylene was refluxed under a stream of nitrogen for 5 hr. when the evolution of dimethylamine ceased. The mixture was cooled and filtered. The filtrate was washed three times with water, dilute hydrochloric acid, then with water and dried over potassium carbonate. The filtrate was heated twice with Nuchar 190-N and filtered. The solution was concentrated to yield 32.5 g. (82%) of crude product.

A 5.0-g. aliquot was dissolved in 50 ml. of benzene and chromatographed on 300 g. of Florisil. The column was then eluted with 660 ml. of 7.5% acetone–petroleum ether (b.p. 60–71°) (discarded) followed by 4000 ml. of 10% acetone–petroleum ether (b.p. 60–71°). The separation was discontinued when a green band appeared at the bottom of the column. The filtrate from the second elution was concentrated to yield 4.8 g. of an amber-colored oil. Ultraviolet: 278 (8,250); f 293 (7,350); f 305 (4,200). Infrared: NH: 3400; Ester C=O: 1738; C=C: 1625, 1588, 1488; NO_2: 1550, 1350; Ester C—O: 1257, (1217, 1205); C—N/C—O: 1125, 1080, 1015; ar., 850, 798, 735, 695.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 66.68; H, 6.00; N, 7.03.

e. *2,α-Dimethyl-5-benzyloxytryptophan* (XII). A mixture of 4.5 g. (0.0134 mole) of the above nitro compound VIII, 0.9 g. (0.004 mole) of platinum oxide and 37.5 ml. of 95% alcohol was subjected to hydrogenation for 2 hr. (reduction took place in 20 min. and stopped). After reduction was complete, 6.0 ml. of 20% sodium hydroxide was added and

the mixture was shaken under hydrogen for 18 hr. A small quantity of sodium hydrosulfite and 1.9 ml. of acetic acid were then added and the mixture was filtered. The solid was washed with alcohol. The filtrates were combined and concentrated under reduced pressure to yield a white solid. The solid was recrystallized twice from an alcohol-water mixture and then from alcohol to yield 3.3 g. of product. The solid became dark at 218° and decomposed at 222–224°. Infrared: OH/NH: 3340, 3220, 2660; COO^-, NH_3^+: 1645, 1638, 1625, 1587, 1560, 1485; C—O/C—N: 1290, 1200, 1135, 1023; ar. sub.: 795, 732, 695.

Anal. Calcd. for $C_{20}H_{22}N_2O_3.H_2O$: C, 67.39; H, 6.79. Found: C, 67.33; H, 6.85.

The sample was dried at 100° for twelve hours to give a hygroscopic solid.

Wt. loss. Calcd.: 4.83%. Found: 4.85%.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28; Eq. wt., 354. Found: C, 71.81; H, 6.60; N, 8.02; Eq. wt., 358.

f. *2,α-Dimethyl-5-hydroxytryptophan* (XVII). A mixture of 3.0 g. (0.0084 mole) of 2,α-dimethyl-5-benzyloxytryptophan (XII), 20 ml. of 95% alcohol, 40 ml. of water, and 3.0 g. of 10% palladium-on-charcoal was hydrogenated at 50 p.s.i. initial pressure for approximately 30 min. The mixture was filtered and the solid was refluxed with water and filtered under nitrogen. The filtrates were combined and concentrated to dryness. The resulting semisolid was dissolved in hot water and diluted with acetone. A small amount of dark solid was removed and the filtrate was further diluted with acetone. A small amount of amorphous material was removed and the solution was concentrated to dryness. The residue was again recrystallized from a water-acetone mixture to yield 100 mg. of product. The melting point was indefinite. Ultraviolet: 220 (20,634); 279 (6,542); f 296 (6,621); 308 (3,811). Infrared: NH/OH: 3380, 3180; NH_3^+: 2730 sh, 2630 sh, 2550 sh, 2440 sh; COO^-: 1620 sh, 1584, 1398, 1392; C=C: 1510; C—N/C—O: 1265, 1233, 1207, 1093; ar. sub.: 880, 840, 790.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.49; N, 11.28. Found: C, 62.35; H, 6.82; N, 10.72.

F. *α-Methyltryptamine* (XXVIII). *Method A.* a. *α-Methyl-β-indolenideniumethyl Nitronate* (XXIV). (1) *With ammonium acetate.* A mixture of 22.0 g. (0.28 mole) of crystalline ammonium acetate, 6 ml. of acetic anhydride, and 20 ml. of glacial acetic acid was stirred and warmed for approximately 20 min. A mixture of 28.8 g. (0.2 mole) of indole-3-aldehyde (XXI), 100 ml. of nitroethane, and 120 ml. of acetic acid was added to the solution. When the mixture was brought to near reflux, 14.0 g. of anhydrous sodium acetate was added. At reflux, 20 ml. of acetic anhydride was added to the dark solution during 2 hr. After 2 hr., the solution was allowed to cool while 45 ml. of water was slowly added. The solid was collected, and washed with a solution of 100 ml. of acetic acid and 45 ml. of water. After crystallization from dilute alcohol, the product weighed 20.2 g. (50%) and melted at 190–192°. The analytical sample melted at 192–193°. Ultraviolet: 218 (28,400); 277 (7,450); 282.5 sh (7,100); 400 (14,950). Infrared: OH/NH: 3400; C=C: 1634, 1624, 1585, 1530; N—O: 1270, 1223; ar.: 747.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.85. Found: C, 65.23; H, 5.01; N, 14.03.

(2) *With ammonium phosphate.* A mixture of 7.2 g. (0.05 mole) of indole-3-aldehyde, 7.2 g. (0.054 mole) of dibasic ammonium phosphate, 25 ml. of nitroethane, and 28 ml. of acetic acid was refluxed for 3 hr., allowed to cool and filtered. After two crystallizations from alcohol, 6.0 g. (60%) of a product was obtained. It was identical with that obtained from the experiment with ammonium acetate.

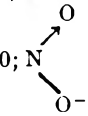
b. *α-Methyltryptamine* (XXVIII). Five grams (0.024 mole) of α-methyl-β-indolenideniumethyl nitronate was placed in a drip extractor. A mixture of 5.7 g. (0.15 mole) of lithium aluminum hydride and 2000 ml. of ether was stirred and refluxed for 4 hr. until all the compound was extracted into the reaction mixture. The mixture was decomposed with wet ether, followed by the addition of water and then potassium hydroxide. The suspension was filtered and the filtrate dried over potassium carbonate and concentrated. The residue was crystallized from ethyl acetate–petroleum ether (b.p. 60–71°) to give 2.0 g. (71%); m.p. 97–100°. Infrared: NH/OH: 3370, 3110, 3100; C=C: 1621, 1581, 1549, 1505; ar. sub.: 736.

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.09; N, 16.08. Found: C, 75.78; H, 8.07; N, 16.31.

An 0.85-g. sample of α-methyltryptamine was dissolved in 10 ml. of methanol and 0.5 ml. of acetic acid was added. The mixture was concentrated to dryness. The residue was dissolved by warming in 10 ml. of ethyl acetate and 2 ml. of alcohol. After refrigeration for 4 hr. 1.0 g. of α-methyltryptamine acetate was obtained; m.p. 143–146°. Ultraviolet: 219 (36,700); f 274 (5,700); 281 (6,150); 289 (5,300). Infrared: NH: 3300; Salt: 2700, 2660, 2590, 2500, 2140; NH_3, COO^-, C=C: 1630, 1565, 1555, 1510, 1490, 1412; ar. sub.: 745.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.63; H, 7.74; N, 11.95. Found: C, 66.43, 66.62; H, 7.56, 7.38; N, 11.62.

Method B. A solution of 10.0 g. (0.049 mole) of 3-indolyl-β-nitro-β-methylethylene[18] in 100 ml. of tetrahydrofuran was added dropwise (over 2.5 hr.) to a mixture of 10.7 g. (0.28 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was gradually heated to reflux during the addition. After the addition was complete the mixture was refluxed for 2 hr. and allowed to stand overnight. A solution of 20 ml. of water and 60 ml. of tetrahydrofuran was slowly added until the excess lithium aluminum hydride was destroyed, followed by 10 ml. of concd. sodium hydroxide. Ether (150 ml.) was then added and the mixture was rapidly stirred until no solid remained on the sides of the flask. The mixture was filtered and the solid was washed with 150 ml. of ether. The ether solutions were combined, dried over potassium carbonate, and concentrated to yield 9.2 g. of crude amine. The amine was dissolved in 110 ml. of methanol and 5.5 ml. of acetic acid was added. The solution was concentrated to dryness under reduced pressure and the residue was dissolved in 110 ml. of hot ethyl acetate. Upon cooling 8.2 g. (73.2%) of α-methyltryptamine acetate precipitated. After drying the salt melted at 143–144°.

G. *α-Ethyltryptamine* (XXIX) *acetic acid salt. Method A.* a. *α-Ethyl-β-indolenidenium ethyl nitronate* (XXV). A solution of 66.0 g. of crystalline ammonium acetate, 18 ml. of acetic anhydride, and 60 ml. of acetic acid was stirred for 20 min. at 50°. A mixture of 87.0 g. (0.6 mole) of indole-3-carboxaldehyde, 300 ml. of 1-nitropropane, and 360 ml. of acetic acid was added. The mixture was refluxed for 3 hr., cooled, diluted with 360 ml. of water, cooled for 6 hr. at 10°, and filtered. The solid was recrystallized from 600 ml. of 40% alcohol to yield 44.5 g. (34%) of product which melted at 128–131°. This solid contained traces of a nitrile but was satisfactory for the next step. Ultraviolet: 218 (31,250); 278 (7,950); f 283 (7,550); 402 (14,700). Infrared: NH: 3280; C≡N (weak): 2230; C=C/C=N: 1630, 1590, 1523, 1500;  : 1265, 1220; ar. sub.: 742.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.59; N, 12.95. Found: C, 67.54; H, 5.57; N, 12.77.

b. *α-Ethyltryptamine* (XXIX). Lithium aluminum hydride (1.7 g.) was added to 300 ml. of tetrahydrofuran. When the reaction ceased, 30.0 g. of lithium aluminum hydride was added and the mixture was stirred for 1.5 hrs. A solution of 36.0 g. (0.17 mole) of XXIV in 285 ml. of tetrahydrofuran was added dropwise over 3 hr. while the mixture was being gradually brought to reflux temperature. The suspension was refluxed an additional 2 hr. and allowed to stand overnight at room temperature. Wet ether (500 ml.) was cautiously added followed by a solution of 70 ml. of water and 100 ml. of tetrahydrofuran. When the reaction

ceased, 20 ml. of concd. sodium hydroxide was added. The mixture was stirred for 1 hr. and filtered. The solid was washed with 1500 ml. of ether and the filtrates were combined, dried over 50 g. of potassium carbonate, and concentrated. The residual oil (78.0 g.) was dissolved in 100 ml. of methanol and 12 ml. of acetic acid was added. The mixture was concentrated to dryness and the residue was dissolved in 250 ml. of ethyl acetate and 30 ml. of methanol. The product did not precipitate upon cooling. The solution was then concentrated to one third volume and 2 ml. of acetic acid was added. Upon cooling 17.0 g. (40%) of product precipitated; m.p. 164–165.5°. Ultraviolet: 220.5 (37,050); f 274 (5,750); 281 (6,150); 289.5 (5,350). Infrared: NH: 3280; acid salt: 2710, 2650, 2540, 2120 (1625), 1565, 1518; C=C: 1625, 1493.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.11; N, 11.28. Found: C, 67.63; H, 7.60; N, 10.90.

Method B. a. *1-(3′-Indolyl)-2-acetamido-butanone-3.*[22] A solution of acetic anhydride (1800 ml.) and pyridine (1280 ml.) was added to *dl*-tryptophan (480 g.; 2.35 moles) and the mixture was heated on the steam bath with stirring for 5.5 hr. Water (4 l.) was added to the resulting solution and it was then steam-distilled until about 8 l. were collected. The mixture was allowed to stand overnight and the resulting oily product was filtered and washed with water. It was crystallized from methanol to give 227.1 g. of a solid, m.p. 134–135.5°. The second crop amounted to 64.2 g., m.p. 133–135°.

The original filtrate was extracted five times with ethyl acetate (total 3250 ml.). The extracts were washed with water, 5% sodium bicarbonate solution, then with water, dried through sodium sulfate, and evaporated. The resulting brown oil was crystallized from methanol to give 58.9 g., of crystals, m.p. 134–136°. The total product amounted to 350.1 g. (61% yield).

A sample was recrystallized from methanol-water, needles, m.p. 136.5–137.5°. (Ghosh and Dutta[22] obtained this compound as an oil, which gave a well defined 2,4-dinitrophenylhydrazone derivative.) Ultraviolet: 221 (35,675); 275 (5,800); 281.5 (6,175); 290 (5,375). Infrared: NH: 3320, 3240; C=O: 1708; amide: 1660, 1548.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.50; H, 6.67; N, 11.40.

b. *α-Ethyltryptamine* (XXIX). A mixture of 56.1 g. (0.23 mole) of 1-(3′-indolyl)-2-acetamido-butanone-3, 43.8 g. (0.78 mole) of 85% potassium hydroxide, 31.2 ml. (0.825 mole) of 85% hydrazine hydrate, and 325 ml. of diethylene glycol was heated to 110° for 1–2 hr. The solvent was distilled until the temperature reached 195–205°. The solution was held at this temperature for 2.5 hr. The solution was cooled and water was added until precipitation occurred. The mixture was extracted with ether. The ether was washed with water, dried, and concentrated. The residue was dissolved in ethyl acetate and diluted with Petroleum ether (b.p. 60–71°) until precipitation occurred. The crystallization was repeated three times using Nuchar 190-N to yield 8.1 g. (19%) of α-ethyltryptamine; m.p. 97–99°. Ultraviolet: 220.5 (20,500), f 275 (1,100); 281 (6,000); 289.5 (5,200). Infrared: NH: 3320, 3270, 3100, 3060, 2740 sh, 2700 sh, 2590, 2550 sh; C=C: 1620, (1577), 1545, 1505; NH_2: 1577; C—N: 1380, 1336, 1345, 1230, 1110, 1093; ar. sub.: 800, 758, 733.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.54; H, 8.56; N, 14.82. Found: C, 76.51; H, 8.54; N, 15.13.

The hydrochloride salt melted at 215.5–218° and showed no depression when mixed with an authentic sample prepared by the condensation of gramine with 1-nitropropane followed by lithium aluminum hydride reduction.

A mixture of 5.0 g. of the base, 3.0 ml. of acetic acid and 25 ml. of methanol was concentrated to dryness. The residue was crystallized from ethyl acetate–methanol to yield 6.5 g. of the acetic acid salt which melted at 165–166°.

The filtrates from the base recrystallizations were combined and concentrated. The residue was distilled to yield 3.0 g. of a yellow oil, b.p. 80°/0.6 mm., which was not investigated further.

Anal. Found: C, 81.70, 82.20; H, 7.48, 7.89; N, 8.78.

The picrate melted at 165–166°.

Anal. Found: C, 49.58; H, 3.58; N, 14.85.

H. *α-n-Propyltryptamine.* a. *1-(3′-Indolyl)-2-propionamidopentanone-3.* A mixture of *dl*-tryptophan (107 g., 0.525 mole), propionic anhydride (400 ml.), and pyridine (285 ml.) was stirred and heated on the steam bath for 5.5 hr. It was then allowed to stand at room temperature for 2 days. Water (890 ml.) was added with cooling, maintaining the inside temperature at 30–40°.

The mixture was then steam distilled until 2 l. of distillate was collected. The resulting mixture containing a brown oil was extracted with ethyl acetate (500 ml., 2 × 250 ml.). The ethyl acetate extracts were washed with water (3 × 250 ml.), then with sodium bicarbonate solution, saturated salt solution, and dried over sodium sulfate. Evaporation *in vacuo* afforded 150 g. of a brown oil. The oil (146 g.) was dissolved in 100 ml. of benzene and 20 ml. of acetone and was chromatographed on 4380 g. of Florisil.

Elution with 5% acetone-benzene (38 l.), 10% acetone-benzene (6 l.), and 20% acetone-benzene (4 l.) gave 52.138 g. of material which was crystallized from 50 ml. of ether to give 22.9 g. (16% yield) of clusters of needles melting at 102–104°.

Two crystallizations from ether (with Nuchar 190-N) gave colorless needles, m.p. 104.5–106°. Ultraviolet: 220 (33,500); 274 (5,950); 281 (6,300); 288.5 (5,500). Infrared: NH: 3410, 3290, 3200 sh; C—O: 1715, 1645; amide II: 1500; C=C: 1620 sh, 1580 sh, 1512 sh; ring: 763, 752.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.53; H, 7.36; N, 10.00.

b. *α-n-Propyltryptamine.* A mixture of 27.0 g. (0.1 mole) of the crude (not chromatographed) 1-(3′-indolyl)-2-propionamidopentanone-3, 15 ml. of 85% hydrazine hydrate, 21.9 g. of 85% potassium hydroxide, and 160 ml. of diethylene glycol was heated to 110° over approximately 2 hr. The solvent was distilled until the temperature reached 195–205° (1 hr.). The temperature of the mixture was held at 195° for 2.5 hr. The mixture was cooled and water was added until precipitation occurred. The mixture was extracted with ether. The ether solution was washed with water (discarded); the ether solution was then extracted with 8% hydrochloric acid. The acid solution was made basic and extracted with ether. The resulting ether extract was dried over potassium carbonate and concentrated to yield a red viscous oil. The oil was dissolved in methanol and 4 ml. of acetic acid was added. The resulting deep green solution was concentrated to dryness on a Rinco. The residue was triturated with ethyl acetate and filtered. The solid was washed with ethyl acetate until all color was removed, then recrystallized from ethyl acetate containing a small amount of methanol; 1.3 g. (5%), m.p. 158–158.5°. Ultraviolet: 220 (35,700); 274 sh (5,750); 281 (6,150); 289.5 (5,350).

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.45; H, 8.61; N, 10.77.

I. *1,α-Dimethyltryptamine* (XXX). a. *1,α-Dimethyl-3-indolenylenium ethyl nitronate* (XXVI). A mixture of 2.2 g. (0.028 mole) of crystalline ammonium acetate, 0.6 ml. of acetic anhydride, and 2.0 ml. of acetic acid was warmed and stirred until the ammonium acetate became anhydrous. Then a mixture of 4.2 g. (0.026 mole) of 1-methyl-3-indolealdehyde (XXII),[33] 10 ml. of nitroethane, and 12 ml. of acetic acid was added. The mixture was heated to gentle reflux and 1.4 g. of anhydrous sodium acetate was added. The solution was heated to reflux and 20 ml. of acetic anhydride was added over 2 hr. The stirred solution was allowed to cool and 4.5 ml. of water was slowly added. The precipitated oil was neutralized with sodium bicarbonate and taken into ether. The ether solution was concentrated and the residue

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was recrystallized from alcohol to yield 1.9 g. (34%) of the desired product which melted at 132–134°. Ultraviolet (0.01*N* H_2SO_4): 224 (28,600); 281 (4,329); 405 (10,030).

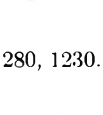
Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.59; N, 12.95. Found: C, 66.91; H, 5.05; N, 12.94.

b. *1,α-Dimethyltryptamine* (XXX). The nitronate XXVI (10.8 g., 0.05 mole) was extracted (with drip type extractor) into a stirred mixture of 10.2 g. (0.27 mole) of lithium aluminum hydride and 2500 ml. of ether over 6 hr. The mixture was cooled and treated with wet ether. When the excess lithium aluminum hydride was destroyed, water followed by potassium hydroxide solution was carefully added until a gelatinous mass precipitated. The mixture was filtered and the ether was dried over potassium carbonate and concentrated to yield a clear oil. The oil was dissolved in anhydrous ether and treated with anhydrous hydrogen chloride to yield 10.5 g. (93.7%) of 1,α-dimethyl-3-aminoethyl indole hydrochloride which melted at 223–227°.

Anal. Calcd. for $C_{12}H_{17}N_2Cl$: C, 64.13; H, 7.63; N, 12.47; Cl, 15.78. Found: C, 64.36; H, 7.65; N, 12.07; Cl, 15.66.

The picrate melted at 198–200°.

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.79; H, 4.59; N, 16.78. Found: C, 52.08; H, 5.47; N, 16.07.

J. *1,α-Dimethylserotonin* (XXXII). a. *5-Benzyloxy-1-α-dimethyl-β-indolenidenium ethyl nitronate* (XXVII). This compound was prepared in the same manner as XXVa from 1-methyl-5-benzyloxy-indole-3-aldehyde (XXIII) and nitroethane to yield 40% of product which melted at 163–164°. Ultraviolet (qualitative): 224, 283, sh 304, 415; in 0.01*N* KOH: 206, 278, 304, 405. Infrared  : 1280, 1230.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.78; H, 5.62; N, 8.68. Found: C, 70.96; H, 5.48; N, 8.96.

b. *5-Benzyloxy-1-α-dimethyltryptamine* (XXXI). This compound was prepared in the same manner as XXVIII to yield 84% of crude product. After crystallization from methylcyclohexane the yield dropped to 55%; m.p. 62–64°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.87; H, 7.29; N, 9.67.

The *hydrochloride* was crystallized from methanol-ether and melted at 193–195°.

c. *5-Hydroxy-1,α-dimethyltryptamine* (XXXII) *creatinine sulfate.* A mixture of 1.0 g. (0.0034 mole) of 5-benzyloxy-1,α-dimethyltryptamine, 150 ml. of absolute methanol and approximately 300 mg. of 10% Pd/C was hydrogenated at 50 p.s.i. (initial pressure) for 8 hr.

The mixture was treated with 3.5 ml. of 1*N* sulfuric acid and filtered. The filtrate was concentrated to dryness at 40–50° under reduced pressure. The dark residue was dissolved in 16.4 ml. of water, treated with a trace of Darco-60 and filtered. The flask and solid were washed with 5 ml. of water. A 500-mg. sample of creatinine sulfate was added to the combined filtrates. The filtrate was heated to about 50° and 105 ml. of boiling acetone was added. After refrigeration, 100 mg. of creatinine sulfate precipitated. The mixture was filtered and the filtrate was further diluted with acetone. After 2 days at 5°, 500 mg. (35%) of product was collected which was 91% pure by ultraviolet assay (compared with a standard sample of serotonin creatinine sulfate). Ultraviolet (*p*H 4.5 sulfuric acid): 304 (4,800); 281 (5,675); 222 (6,800).

K. *Synthesis of α-methyltryptophan.* a. *Ethyl α-nitro-α-methyl-β-(3-indole)propionate.* Gramine (34.85 g., 0.2 mole), ethyl-α-nitropropionate (29.42 g., 0.2 mole), and 200 ml. of dry toluene were placed in a 500 ml., three necked flask fitted with stirrer, nitrogen inlet tube, and an efficient condenser. The mixture was heated for 10 hr. under reflux with stirring and vigorous nitrogen flow to sweep out dimethylamine. The amber solution was cooled and washed with two 50-ml. portions of 2*N* hydrochloric acid, 100 ml. of water, two 50-ml. portions of 1*N* sodium hydroxide, then with two 50-ml. portions of water. The toluene solution was dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. An oil (51.0 g., 91.8%) remained. It was used directly for the reduction-hydrolysis steps.

b. *α-Methyltryptophan.* Ethyl α-nitro-α-methyl-β-(3-indole)propionate (48.0 g., 0.1735 mole) was placed in a stirring autoclave with 400 ml. of 3-A alcohol and 12.0 g. of fresh, brown platinum oxide. Reduction was carried out at 30° under 40–50 p.s.i. hydrogen pressure. Reduction went smoothly and the calculated amount of hydrogen was absorbed. The autoclave was purged with nitrogen, opened, and 80 g. of 20% sodium hydroxide was added. Hydrolysis was accomplished by heating at 40° under hydrogen for 16 hr. The catalyst was removed by filtration and was washed with water. Glacial acetic acid (25 ml.) was added to the combined filtrate and washes. The solution was concentrated *in vacuo* leaving a mixture of gum and some crystals. This was heated with about 300 ml. of absolute alcohol and then allowed to stand at room temperature overnight. Crystals were collected and washed with alcohol (8.47 g.). These were identified by infrared as sodium acetate. A second crop of sodium acetate was obtained after concentrating the mother liquor (8.1 g.). The solvent was removed from the filtrate *in vacuo* leaving a gum which resisted all attempts to induce crystallization. After it had stood for about 9 months, it had largely crystallized. A small amount was removed for seed, then the remainder was dissolved in 450 ml. of hot water. The hot solution was treated with charcoal, and an equal volume of acetone was added to the filtrate. After seeding, crystals slowly formed and after 4 days at 4° the crystals were collected and washed with water-acetone (1:1) to give 28.3 g. of the monohydrate; m.p. 178–194°. This material was recrystallized from a minimum of hot water to give 17.57 g. of needles, m.p. 198–203° (lit.,[15] m.p. 203–205°). This was recrystallized from water to give 12.73 g. of the monohydrate; m.p. 204–9°. Ultraviolet (in 0.01*N* alcoholic sulfuric acid): 218 (33,975); 273 (5,575); 280 (5,800); 289 (6,000). Infrared: NH: 3580, 3465, 3440, 3380, 3280, 2660, 2560; NH_3^+: 3100, 1635, 1530; COO^-: 1590, 1395; aromatic substitution: 740, 730.

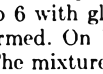
L. *Synthesis of 5-hydroxytryptophan.* a. *Ethyl α-nitro-α-carbethoxy-β[3-(5-benzyloxyindole)]propionate.* 5-Benzyloxygramine[29] (28.0 g., 0.1 mole), ethyl nitromalonate (20.52 g., 0.1 mole), and 225 ml. of dry toluene were placed in a 300 ml., three necked flask fitted with stirrer, nitrogen inlet tube and an efficient spiral tube condenser. The mixture was heated under reflux with stirring and with a vigorous stream of nitrogen passing through. When the materials were first mixed, a solution was obtained, but after heating was started a solid formed which made stirring difficult. As stirring and heating were continued, the solid disappeared. The solid is undoubtedly the salt of 5-benzyloxygramine and ethyl nitromalonate which decomposes to dimethylamine and the alkylated nitroester. The solution was heated until no more dimethylamine was evolved (about 4 hr.). The cool solution was washed twice with 100 ml. of 2*N* hydrochloric acid, twice with 100 ml. of 1*N* sodium hydroxide and twice with water. It was then dried with magnesium sulfate and partially decolorized with Magnesol. The clear solution obtained by filtration contained the ethyl α-nitro-α-carbethoxy-β[3-(5-benzyloxyindole)]propionate and was used directly for decarbethoxylation to the compound described below.

b. *Ethyl α-nitro-β[3-(5-benzyloxyindole)]propionate.* A solution of 2.3 g. (0.1 g.-atom) of sodium in 100 ml. of absolute alcohol was slowly added to the toluene solution above, while cooling in ice and stirring. When about 25 ml. of the alcohol solution had been added, a very thick precipitate formed which made stirring difficult. It was necessary to add 100 ml. of anhydrous ether in order to obtain a fluid slurry. The remainder of the alcohol solution was then added over 1.5 hr. and the slurry was stirred at room temperature overnight. The solid was collected and washed with ether, then placed in a separatory funnel with 200 ml. of ether and 75 ml. of 2*N* hydrochloric acid. The mixture was shaken until all of the solid disappeared. The ether layer

was washed twice with 50-ml. portions of 2*N* hydrochloric acid and then with water. It was dried over magnesium sulfate, treated with some Magnesol to remove color and, concentrated *in vacuo* to give the 5-benzyloxy nitroester as a red oil. The infrared spectrum of this material contained the expected absorptions.

c. *5-Benzyloxytryptophan.* Ethyl α-nitro-β[3-(5-benzyloxyindole)]propionate (3.7 g., 0.01 mole) in 50 ml. of absolute alcohol was hydrogenated at 40 p.s.i. of hydrogen using 1.0 g. of platinum oxide catalyst. Uptake of hydrogen ceased after 1.75 hr. After carefully purging with nitrogen, the bottle was opened and 4.0 g. of a 20% (by weight) solution of sodium hydroxide was added. A hydrogen atmosphere was re-established in the bottle and hydrolysis was allowed to proceed at room temperature overnight. It is very important to exclude air; otherwise, the solution darkens rapidly and purification of the product is difficult. Twenty milliliters of water was added and the catalyst was removed by filtration. The *p*H of the filtrate was adjusted to 6 with glacial acetic acid whereupon a gelatinous solid formed. On heating it gradually changed to solid material. The mixture was cooled and the solid was collected and washed with water to give 2.64 g. of 5-benzyloxytryptophan. The compound is amphoteric and can be partially purified by dissolving in either acid or base, treating with charcoal and then adjusting the *p*H to 6. A small amount was purified in this manner and then crystallized from water containing a little alcohol; m.p. (introduced at 270°) 280° dec. (lit.,[15] m.p. 280° dec.).

d. *5-Hydroxytryptophan.* 5-Benzyloxytryptophan (3.42 g.) was suspended in 50 ml. of alcohol and 50 ml. of water with 1.0 g. of 10% palladium-on-charcoal and hydrogenated at 10 p.s.i. Reduction was rapid and complete. The catalyst was removed by filtration, but the filtrate was dark because of the presence of colloidal catalyst. The filtrate was concentrated to a small volume under vacuum and the resulting dark crystals were dissolved in water. The hot solution was filtered and allowed to crystallize. The crystalline material was still dark; therefore it was recrystallized from water, using a Seitz filter to remove the colloidal catalyst; white crystals were obtained (1.23 g.). A second crop was obtained by concentrating the mother liquor (0.29 g.). Total weight, 1.52 g. (62.5%). A small sample was recrystallized for analysis; m.p. 285° dec.[16] Ultraviolet: 220 sh (23,850); 275 (6,050); 300 (5,750); 312 (3,725). Infrared: OH/NH: 3380, 3240; NH_3^+: 3120, 3060, 2720, 2630, 2510, 2420;



NH_3^+ deformation: 1632, 1596, 1403; C=C: 1612, 1495; C—O: 1233, 1221, ar. sub.: 855, 843, 813, 791, 765.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.50; N, 12.73. Found: C, 59.94; H, 5.50; N, 12.47.

Acknowledgment. The authors are indebted to Mr. W. A. Struck and associates of our Microanalytical Laboratory for analyses, to Mr. M. Grostic and Mr. J. Stafford for infrared and ultraviolet spectral data, and to Mr. L. G. Laurian for laboratory assistance. We also wish to thank Dr. M. E. Greig of our department of pharmacology for permission to discuss some of the enzymological data obtained in her laboratory.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE MEDICAL CENTER, UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND THE DEPARTMENT OF CHEMISTRY, FRESNO STATE COLLEGE]

Syntheses and Resolutions Involving Papain-Catalyzed Reactions between (Hydroxyalkyl)anilines and *N*-Acylamino Acids[1]

JOHN LEO ABERNETHY[2] AND BROTHER MYRON COLLINS[3]

Received June 4, 1959

Papain catalysis provides a means for acylating the amino group of substituted anilines containing an alcoholic hydroxyl without concurrent acylation of the alcoholic hydroxyl. These substituted anilines can be employed for resolution of certain *N*-acylamino acids like carbobenzoxy-DL-alanine, with papain as the catalyst and resolving agent. When the asymmetric center is shifted to the substituted aniline, as with *m*-(1-hydroxyethyl)aniline in its reaction with non-asymmetric hippuric acid, papain does not cause a resolution to take place, but a racemic product is formed in good yield instead. Reduction of *m*-aminoacetophenone to racemic *m*-(1-hydroxyethyl)aniline has been found to occur in good yield by means of lithium aluminum hydride. The optimum *p*H for the papain-catalyzed reaction between *m*-(1-hydroxyethyl)aniline and hippuric acid is about 4.7 for the experimental conditions employed.

Numerous papain-catalyzed syntheses of anilides[4-6] and phenylhydrazides[4,7,8] of *N*-acylamino acids have been studied, especially with reference to resolutions of *dl*-*N*-acylamino acids. Also, rates of precipitation of substituted hippuric anilides[9] have been investigated in relation to the effect of position of a given substituent on the aniline nucleus. However, nothing has been reported on the

(1) Taken mainly from a thesis of Brother Myron Collins to be submitted to the Graduate School of Fresno State College in partial fulfillment of the requirements for the degree of Master of Arts.

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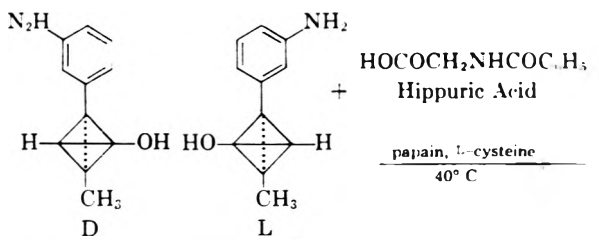
(9) J. L. Abernethy, J. Nakamura, and Bro. M. Collins, *J. Org. Chem.*, 22, 586 (1958).

behavior of *N*-acylamino acids toward substituted anilines containing a hydroxyalkyl substituent.

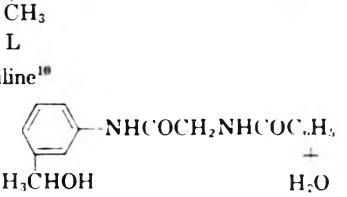
There are at least three significant reasons for such an investigation. First, this provides a procedure for acylating an amino group, without subjecting an alcoholic hydroxyl radical to concurrent acylation. Second, it is of interest to ascertain the ability of (hydroxyalkyl)anilines to bring about resolutions of racemic *N*-acylamino acids under the asymmetric influence of papain. Resolutions do not always occur[5] in reactions between racemic *N*-acylamino acids and aniline when papain is employed as the catalyst and resolving agent. Third, it is of particular value to shift the asymmetric center from the amino acid moiety to the substituted aniline moiety during the formation of the substituted anilide.

The substituted anilines ultimately chosen for investigation were *o*-aminobenzyl alcohol, *m*-aminobenzyl alcohol, *p*-(2-hydroxyethyl)aniline, and *m*-(1-hydroxylethyl)aniline. *N*-Acylamino acids selected were these relatively soluble ones: hippuric acid, benzoyl-DL-alanine, benzoyl-L-alanine, carbobenzoxy-DL-alanine, and carbobenzoxy-L-alanine.

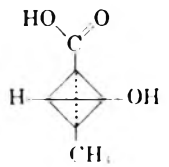
m-(1-Hydroxyethyl)aniline contains an asymmetric center at the carbon bonded to the hydroxyl. Its behavior toward hippuric acid is significant because no asymmetric center exists in hippuric acid.



m-(1-Hydroxyethyl aniline[10]



Hippuric *m*-(1-hydroxyethyl)anilide



The dependence of yield on *p*H for this reaction was determined, as shown in Fig. 1. As a consequence, all subsequent reactions were conveniently carried out at a *p*H of about 4.7, reasonably close to this optimum.

EXPERIMENTAL

Activation of papain. The procedure described previously for activation[9] of the papain was employed in the activation of separate 50-g. samples of Schwarz and Wallerstein papain.[11] The lightly crushed, dry, activated papain was stored in small, stoppered vials kept in a large brown bottle with a screw cap and refrigerated at about 5°.

(10) Appropriate degradation of the benzene ring would give direct configurational relationship to D-lactic acid.

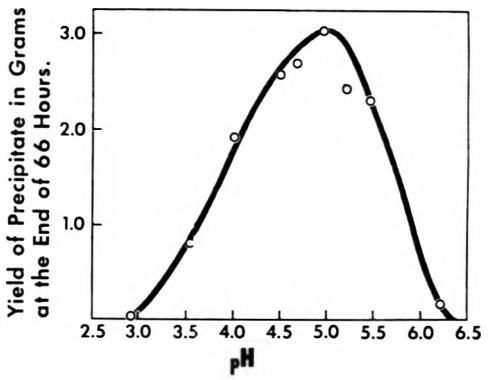


Fig. 1. Dependence of yield on *p*H for the papain-catalyzed synthesis of hippuric *m*-(1-hydroxyethyl)anilide from hippuric acid and *m*-(1-hydroxyethyl)aniline at 40°. Solutions involved: 0.0500 mol. hippuric acid; 0.0500 mol. *m*-(1-hydroxyethyl)aniline; 0.500 g. L-cysteine hydrochloride; 0.250 g. activated Schwarz papain; 250 ml. total solution.

Synthesis of m-(1-hydroxyethyl)aniline. m-Aminoacetophenone, practical grade from Eastman Organic Chemicals, was dissolved in a minimum amount of boiling water, treated with carbon black, filtered hot, and the solution was separated from a small amount of insoluble oily substance. Then the solution was evaporated to about one third of its original volume and cooled overnight in a refrigerator. The light yellow solid was removed by filtration and dried first in the atmosphere and subsequently over phosphorus pentoxide. This dried *m*-aminoacetophenone was used for reduction with lithium aluminum hydride.

Lithium aluminum hydride (10 g.) was weighed rapidly on glazed paper and added to a three-neck flask swept free of atmospheric gases by means of a continuous flow of dry nitrogen. Then 13.52 g. of powdered *m*-aminoacetophenone was partly dissolved in 500 ml. of absolute ether and the slurry was added dropwise over a period of 2 hr., with vigorous stirring, to the lithium aluminum hydride. The mixture was stirred for two more hours and allowed to stand overnight. Cautious addition of about 100 ml. of water was followed by addition of 250 ml. of 15% sodium hydroxide solution. The mixture was stirred for 2 hr. and the ether solution was separated. The aqueous layer was extracted with two 300-ml. portions of ether and the combined ether solutions were filtered and dried over anhydrous sodium sulfate. Then the ether solution was stirred with decolorizing carbon, filtered three times, and evaporated to dryness. The residue consisted of 11.0 g. (81% yield) of *m*-(1-hydroxyethyl)aniline, a cream colored product, m.p. 70–71°.

Anal. Calcd. for $C_8H_{11}ON$: N, 10.21. Found: N, 10.41.

Dependence of yield on pH for the formation of hippuric m-(1-hydroxyethyl)anilide from hippuric acid and m-(1-hydroxyethyl)aniline. Hippuric acid (0.050 mol.), *m*-(1-hydroxyethyl)aniline (0.050 mol.) and 0.500 g. of L-cysteine hydrochloride were dissolved in about 230 ml. of hot buffer solution. The solution was cooled to 35° and 0.250 g. of papain was ground with a small amount of the solution and added to it, with rinsing. More buffer was added to make the total volume 250 ml. The *p*H was adjusted to the value desired with the aid of a *p*H meter, then filtered, and incubated at 40° for 66 hr. Hippuric *m*-(1-hydroxyethyl)-anilide was removed by filtration, dried, and weighed. Re-

(11) This papain was generously supplied by the Schwarz Laboratories of Mount Vernon, N. Y., and the Wallerstein Laboratory of New York City.

TABLE I

PAPAIN-CATALYZED REACTIONS BETWEEN *N*-ACYLAMINO ACIDS AND NONASYMMETRIC (HYDROXYALKYL)ANILINES

(Hydroxyalkyl)aniline Reactant[a]	N-Acylamino Acid Reactant[b]			
m-Aminobenzyl Alcohol	Hippuric acid (HA)	Carbobenzoxy-DL-alanine (C-DL-A)	Carbobenzoxy-L-alanine (C-L-A)	Benzoyl-DL-alanine (B-DL-A)
Name of Product	*m*-Hippuramidobenzyl alcohol	2-(Benzyloxycarbonylamino)propionic *m*-(hydroxymethyl)anilide	L-2-(Benzyloxycarbonylamino)propionic *m*-(hydroxymethyl)anilide	2-(Benzoylamino)propionic *m*-(hydroxymethyl)anilide
Wt. of Product				
0–18 hr.	0.33 g.	1.78 g.	1.52 g.	0.00 g.
18–42 hr.	0.85 g.	0.53 g.	0.14 g.	0.00 g.
42–210 hr.	1.52 g.	0.32 g.	0.00 g.	0.00 g.
M.p.	185–186°	133.5–134.0°	133.5–134.0°	
$[\alpha]_D^{25°}$ 2% in pyridine		−31.30°	−33.00°	
% *N* calcd.	9.853	8.506	8.506	
% *N* found	9.73		8.28	
p-(2-Hydroxyethyl)aniline	(HA)	(C-DL-A)	(C-L-A)	(B-DL-A)
Name of Product	Hippuric *p*-(2-hydroxyethyl)anilide	2-(Benzyloxycarbonylamino)propionic *p*-(2-hydroxyethyl)anilide	L-2-(Benzyloxycarbonylamino)-propionic *p*-(2-Hydroxyethyl)anilide	2-(Benzoylamino)-propionic *p*-(2-Hydroxyethyl)anilide
Wt. of Product				
0–18 hr.	1.43 g.	2.45 g.	3.26 g.	1.28 g.
18–42 hr.	1.25 g.	0.185 g.	0.03 g.	0.62 g.
42–210 hr.	0.790 g.	0.280 g.	0.132 g.	0.21 g.
M.p.	173–174°	152–153°	155–155.5°	189–190°
$[\alpha]_D^{25°}$ 2% in pyridine		−43.8°	−44.9°	−76.0°
N calcd.	9.39	8.179	8.179	8.969
% *N* found	9.26		8.41	8.90

[a] 0.020 mol. [b] 0.020 mol. HA; 0.020 mol. C-DL-A; 0.010 mol. C-L-A; 0.020 mol. B-DL-A; 0.500 g. L-cysteine hydrochloride; 0.500 g. activated Wallerstein papain; 125 ml. total solution; pH ≃ 4.6.

sults are shown graphically in Fig. 1. The hippuric *m*-(1-hydroxyethyl)anilide was dissolved in hot ethanol, treated with decolorizing carbon, filtered hot three times, and poured into cold water. The precipitate was washed with hot water and dried over phosphorus pentoxide and then had a melting point of 154–155°.

Anal. Calcd. for $C_{17}H_{18}O_3N_2$: N, 9.39. Found: N, 9.36.

Attempted resolution of m-(1-hydroxyethyl)aniline by means of its papain-catalyzed reaction with hippuric acid. A mixture of 0.05 mol. (8.96 g.) of hippuric acid, 0.05 mol. (6.85 g.) of *m*-(1-hydroxyethyl)aniline, 1.000 g. of L-cysteine hydrochloride, and 200 ml. of buffer solution (*p*H 4.75) was heated to bring about rapid solution and then cooled. Then 0.500 g. of activated Wallerstein papain was added, and the resultant solution was filtered. After making up to a total volume of 250 ml. with more buffer, the solution was incubated at 40°. These weights of hippuric *m*-(1-hydroxyethyl)anilide were obtained: 0–16 hr., 0.00 g.; 16–24 hr., 1.40 g.; 24–48 hr., 2.80 g.; 48–72 hr., 1.56 g.; 72–96 hr. 0.80 g.; 96–120 hr., 0.44 g.; 120–144 hr., 0.21 g.; 144–168 hr., 0.09 g.; 168–336 hr., 0.37 g. After recrystallization the rotation was tested for each precipitate in a 2% solution in pyridine and found to be 0.000° in a Rudolph high-precision polarimeter. No detectable resolution had occurred.

Experiments with o-aminobenzyl alcohol. A series of reaction mixtures was set up using *o*-aminobenzyl alcohol with acylated amino acids in the usual way. No evidence was given that any papain-catalyzed reactions had occurred. The considerable insolubility of the *o*-aminobenzyl alcohol appeared to be a major factor in the failure of the reactions to take place.

Preparation of starting materials. Carbobenzoxy-DL-alanine and carbobenzoxy-L-alanine were synthesized by the method of Carter, Frank, and Johnston.[12] *o*-Aminobenzyl alcohol was prepared by reduction of anthranilic acid[13] and *m*-nitrobenzyl alcohol was reduced to *m*-aminobenzyl alcohol.[14] It was necessary to purify crude *p*-(2-hydroxyethyl)aniline as obtained from Eastman Organic Chemicals. This alcohol was treated with carbon in ethanol and warmed and filtered, and the process repeated five times. Evaporation of the solvent and subsequent cooling yielded white, flaky crystals of the alcohol, m.p. 110–110.5°.

Papain-catalyzed reactions between m-aminobenzyl alcohol and N-acylamino Acids. m-Aminobenzyl alcohol (0.020 mol.) was placed in separate flasks with these acylated amino acids: 0.020 mol. of hippuric acid; 0.020 mol. of carbobenzoxy-DL-alanine; 0.010 mol. of carbobenzoxy-L-alanine; 0.020 mol. of benzoyl-DL-alanine; 0.010 mol. of benzoyl-L-alanine. A total buffered solution of 125 ml. was made up in each case and each contained 0.500 g. of L-cysteine hydrochloride and 0.50 g. of activated Wallerstein papain. Incubation was carried out at 40°. Results of these experiments are tabulated in Table I. No reaction was given with either benzoyl-DL-alanine or benzoyl-L-alanine.

Papain-catalyzed reactions between p-(2-hydroxyethyl)-aniline and N-acylamino acids. The same procedure was followed as in the experiments with *m*-aminobenzyl alcohol except that 0.020 mol. of *p*-(2-hydroxyethyl)aniline was used with: 0.020 mol. of hippuric acid; 0.020 mol. of carbobenzoxy-DL-alanine; 0.010 mol. of carbobenzoxy-L-alanine;

(12) H. E. Carter, R. L. Frank, and H. W. Johnston, *Org. Syntheses*, **Coll. Vol III**, 168 (1955).

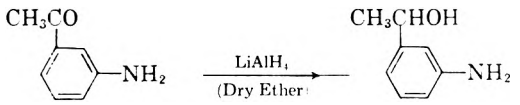
(13) W. G. Brown in "Organic Reactions," Vol. VI, R. Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, 1951, p. 491.

(14) A. P. Phillips and A. Maggiolo, *J. Org. Chem.*, **15**, 659 (1950).

0.020 mol. of benzoyl-DL-alanine; 0.020 mol. of benzoyl-L-alanine. No reaction was given with benzoyl-L-alanine. Results are tabulated in Table I.

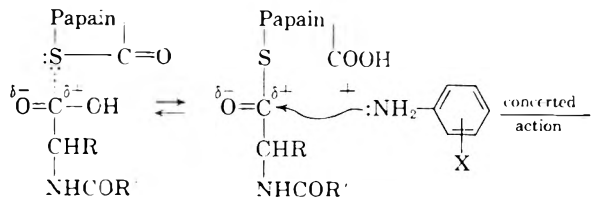
Discussion of results. The original plan of investigation called for a comparison of the rates of precipitation of substituted hippuric anilides formed from *o*-, *m*-, and *p*-aminobenzyl alcohols, as well as possible differences in abilities of these aminobenzyl alcohols to cause resolutions of *N*-acylamino acids. This plan was abandoned because *p*-aminobenzyl alcohol underwent polymerization[14] in an acid medium and *o*-aminobenzyl alcohol proved to be too insoluble. Satisfactory results were obtained in the use of *m*-aminobenzyl alcohol and *p*-(2-hydroxyethyl)aniline, which could be employed under the resolving influence of papain to bring about the resolution of carbobenzoxy-DL-alanine. Only *p*-(2-hydroxyethyl)aniline was able to resolve benzoyl-DL-alanine. Carbobenzoxy-L-alanine reacts with both of these amino alcohols but benzoyl-L-alanine reacts with neither. This is in accord with previous work.[15]

m-(1-Hydroxyethyl)aniline was prepared with ease in a yield of greater than 80% by reduction of *m*-aminoacetophenone with lithium aluminum hydride in dry ether. This substituted aniline was not

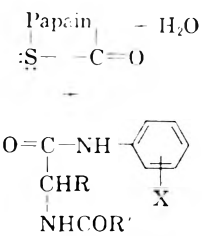


resolved in its papain-catalyzed reaction with hippuric acid, but the reaction did produce racemic hippuric *m*-(1-hydroxyethyl)anilide in good yield.

The mechanism of these papain-catalyzed reactions is considered to be essentially a reversal of the mechanism suggested for the hydrolysis of amide linkages.[16] For amide synthesis, this mechanism should be approximately the same as the one proposed for the papain-catalyzed synthesis of N^{α},N^{β}-diacylhydrazines.[15]



Active Complex



(R = —H or —CH_3; R' = —C_6H_5 or —$OCH_2C_6H_5$; X = —CH_2OH, —$CHOHCH_3$ or —CH_2CH_2OH)

(15) J. L. Abernethy, M. Kientz, R. Johnson, and R. Johnson, *J. Am. Chem. Soc.*, **81**, 3944 (1959).

(16) E. L. Smith, *J. Biol. Chem.*, **223**, 1392 (1958).

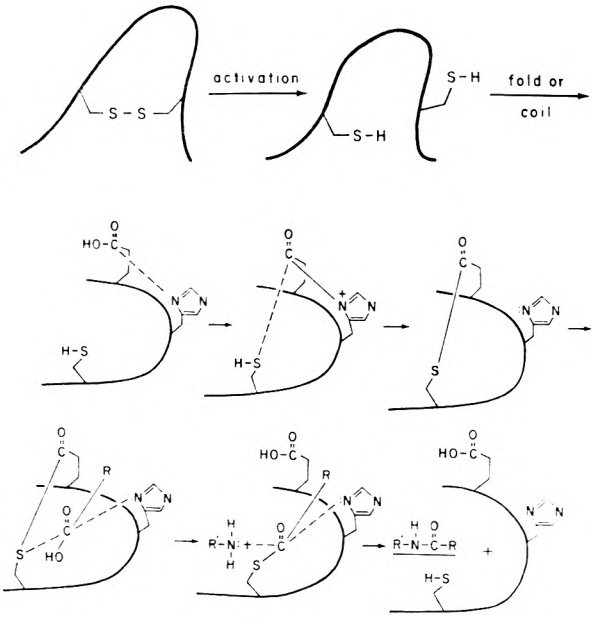


Fig. 2. Mechanism at Papain's active site

It has been suggested[17] that there is insufficient driving force between just a thiolactone and the carboxyl of an *N*-acylamino acid for a reaction to occur with the rapidity of this enzyme action. In view of the recent discovery that one histidine residue is within the active fragment of the papain molecule[18] and that *n*-propyl γ-(4-imidazolyl)thiobutyrate[19] is hydrolyzed exceedingly rapidly due to activation by the anchored imidazole group, it is possible that the imidazole ring performs an activating function here. Some such peptide sequence of amino acid residues, like L-cysteine, L-histidine (with its imidazole ring) and L-glutamic acid might be able to cause thiolactone formation, give a subsequent reaction with an *N*-acylamino acid substrate in producing an external thioester and be activated to undergo a rapid reaction with an amine substrate to form an amide. Also, the configuration of this active center of the enzyme ought to be stereospecific in displaying preference largely toward an L-*N*-acylamino acid substrate. Fig. 2 shows this.

It is possible that the *m*-(1-hydroxyethyl) radical is too far removed from the amino group on the benzene ring to create any stereospecificity at the moment reaction occurs with the active complex formed between the enzyme and the *N*-acylamino acid. It should be recalled, nevertheless, that the asymmetric center of acetyl-DL-phenylalanylglycine is considerably removed from the free carboxyl group, which contacts sulfur at the active center of

(17) Professor Saul Winstein of the UCLA Chemistry Department suggested this in a private conversation with the senior author, J. L. A. The subsequent mechanism was devised by J. L. A. to incorporate this suggestion.

(18) Information given to the senior author, J. L. A., by Professor Emil L. Smith of the College of Medicine, University of Utah, through correspondence.

(19) T. C. Bruice, *J. Am. Chem. Soc.*, **81**, 5444 (1959).

the enzyme. This racemic acid does undergo resolution[20] when subjected to anilide formation in the presence of papain to give acetyl-L-phenylalanylglycine anilide. Evidently some stereospecific contact of the enzyme with the asymmetric region of benzoyl-DL-alanylglycine gives preference to the L-antipode. Such a differentiating contact with racemic *m*-(1-hydroxyethyl)aniline must be absent.

Acknowledgments. This research was supported by grants-in-aid from the Society of Sigma Xi and RESA. The Research Corp. provided funds for the Rudoph high-precision polarimeter. Generous grants from the Fresno County Heart Association and California Heart Association permitted the purchase of chemicals and apparatus. Dr. Robert D. Beech, Dr. Kendall B. Holmes, and Mrs. Joyce Richardson of the Fresno County Heart Association and Dr. John J. Sampson, Dr. Robert H. Maybury, and Miss Phyllis Hecker of the California Heart Association were instrumental in securing these grants. Donations of papain were generously made by the Schwarz Laboratories of Mount Vernon, N. Y., and the Wallerstein Laboratories of New York City.

LOS ANGELES 24, CALIF.

(20) M. Bergmann, O. K. Behrens, and D. G. Doherty, *J. Biol. Chem.*, 124, 7 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF BRITISH COLUMBIA]

The Reaction of 2-Acetonaphthoxime with Carbon Monoxide and Hydrogen. A New Benzoquinoline Synthesis[1]

A. ROSENTHAL AND A. HUBSCHER

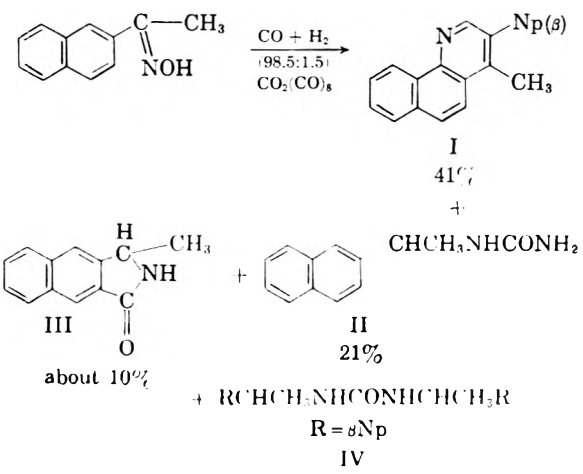
Received August 10, 1959

2-Acetonaphthoxime reacted with carbon monoxide and hydrogen at a pressure of about 4000 p.s.i. and at a temperature of about 220° in the presence of preformed dicobalt octacarbonyl as catalyst to yield 2-(β-naphthyl)-4-methylbenzo[h]quinoline, racemic 1-(β-naphthyl)ethylurea, and 3-methylbenzo[f]phthalimidine. Crystalline hydrochloride, methiodide, picrate and aldehyde derivatives of 2-(β-naphthyl)-4-methylbenzo[h]quinoline were obtained. The infrared and ultraviolet spectra of the aforementioned compounds are described.

This paper is concerned with an extension of our previous study[1,2] of the reaction of carbon monoxide with aromatic ketoximes. In particular, it deals with the reaction of 2-acetonaphthoxime with a mixture of carbon monoxide and hydrogen (98.5:1.5) at a pressure of about 4000 p.s.i. and at a temperature of about 220° in the presence of preformed dicobalt octacarbonyl as catalyst.

Whereas the expected cyclization reaction took place only to the extent of about 10% yielding product III, the main reaction was a condensation one resulting in the formation of 2-(β-naphthyl)-4-methylbenzo[h]quinoline(I) and racemic 1-(β-naphthyl)ethylurea(II).

Products I and II were easily isolated from the reaction mixture by fractional crystallization. 1-(β-naphthyl)ethylurea was slightly soluble in benzene or chloroform, whereas 2-(β-naphthyl)-4-methylbenzo[h]quinoline came down as the second product using ethanol as solvent. Direct chromatographic fractionation of the reaction mixture on alumina using benzene–petroleum ether as developer proved to be the best way to isolate product I (highly fluorescent) in pure form.



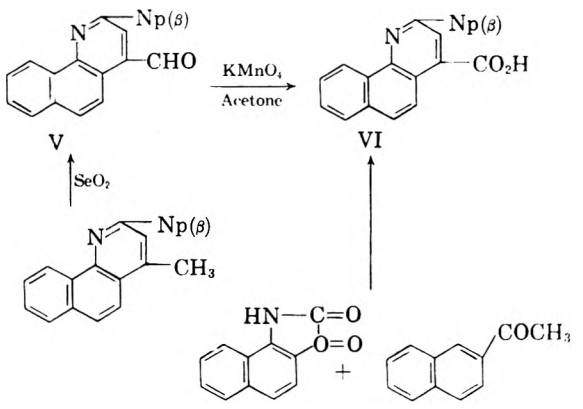
The empirical formula of compound I was $C_{24}H_{21}N$. Infrared analyses showed no NH stretching band. As compound I could not be reduced with magnesium in methanol it was assumed that the C=N— group must be part of an aromatic system. On the basis that compound I failed to react with maleic anhydride the linear benzoquinoline structure was eliminated.[3] A peak at 362 mμ in the ultraviolet spectrum of I suggested that the nucleus of

(1) Financial assistance by the National Research Council, Canada, and by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. Presented at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

(2) A. Rosenthal, R. F. Astbury, and A. Hubscher, *J. Org. Chem.*, 22, 1037 (1958).

(3) W. S. Johnson and F. J. Mathews, *J. Am. Chem. Soc.*, 66, 210 (1944).

the compound contained the angular benzoquinoline structure.[3] Further support for the tentative assignment of a benzoquinoline nucleus was provided by the inertness of compound I towards prolonged heating with molten sodium hydroxide or with boiling concentrated hydrochloric acid. Selenium dioxide oxidation of I gave an aldehyde (V) indicating the presence of an active methyl group. Further controlled oxidation of the aldehyde with potassium permanganate in acetone at room temperature or with silver oxide in ethanol gave a carboxylic acid (VI) having a melting point of 248–250°. The reported[4] melting point of 2-(β-naphthyl)benzo[h]quinoline-4-carboxylic acid is 227–228°. As the melting point of compound VI was in question, although its solubility characteristics were similar to that of the reported carboxylic acid,[4] 2-(β-naphthyl)-benzo[h]quinoline-4-carboxylic acid, the latter compound was synthesized by the condensation of α-naphthisatin with 2-acetonaphthone.[4] Purification of the acid was achieved by the method of Robinson and Bogert.[5] This purified carboxylic acid had an identical melting point with that of compound VI. Furthermore, a mixed melting point of compound VI and the authentic sample showed no depression. Thus, compound I was proven to be 2-(β-naphthyl)-4-methylbenzo[h]quinoline and the aldehyde (V) must be 2-(β-naphthyl)-benzo[h]quinoline-4-carboxaldehyde.



It is possible that the discrepancy in the melting point exhibited by compound VI and that reported in the literature of 2-(β-naphthyl)-benzo[h]quinoline-4-carboxylic acid might have been due to the use of a different method of purification.

Reaction of 2-(β-naphthyl)-4-methylbenzo[h]quinoline with gaseous hydrogen chloride in ether gave a yellow salt having a green fluorescence. Conversion of the base into the salt caused a bathochromic shift of about 30 mμ in the ultraviolet spectrum. On being heated, the salt decomposed slowly at 90–100° reforming the parent base. Titration of the salt in alcohol with standard potassium hydroxide gave a molecular weight of 314.

A crystalline methiodide salt was formed by prolonged heating of the base (I) with methyl iodide at 100°. Addition of picric acid in ethanol to the base immediately yielded the picrate.

Compound II was proven to be racemic 1-(β-naphthyl)ethylurea by direct comparison with an authentic sample[6] prepared by the condensation of 1-(β-naphthyl)ethylamine with urea. It is interesting to note that four of the bands (3435, 3350, 3230, and 1648 cm.$^{-1}$) in the infrared spectrum of compound II are similar to those of a monosubstituted urea.[7,8]

After compounds I and II were separated from the reaction mixture, the remaining residue when chromatographed on alumina using benzene-*t*-butyl alcohol as developer yielded impure compounds III and IV. Subsequent rechromatographic purification of III and IV on alumina using benzene–ethyl acetate as developer essentially freed compound III of impurities but failed to give an analytically pure sample of IV. Fractional crystallization of IV was unsuccessful, giving very low yields of a compound having a wide melting range.

On the bases of chemical and infrared analyses[2,9] (NH stretching at 3310 and lactam at 1690 cm.$^{-1}$), fraction III was assumed to be 3-methylbenzo[f]phthalimidine. Elemental analyses gave an empirical formula consistent with structure III. Support for the formation of the linear rather than an angular benzo[h]phthalimidine was deduced from the work of Murahashi[10] who found that 2-naphthaldehyde anil cyclized under similar conditions to yield the linear isomer.

On the bases of chemical and infrared analyses bands [at 3300, 1625, 1596 (sh), 1578 (sh), and 1562 cm.$^{-1}$], we suggest that compound IV is probably *sym*-di-1-(β-naphthyl)ethylurea formed by the condensation of 1-(β-naphthyl)ethylurea. Such condensations which are readily brought about by heating monosubstituted ureas are well known in the literature.[11] The similarity of the infrared spectra of IV with that of *sym*-dibenzylurea (3337, 1625, 1591, and 1575 cm.$^{-1}$) supports our assignment of structure IV.

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(5) E. A. Robinson and M. T. Bogert, *J. Org. Chem.*, **1**, 65 (1936).
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EXPERIMENTAL[12]

The equipment used was previously described.[2]

Reaction of 2-acetonaphthoxime (cis-methyl) with carbon monoxide and hydrogen. Into the glass liner contained in the high pressure bomb was introduced 100 ml. of thiophene-free anhydrous benzene, 2-acetonaphthoxime (15 g., 0.08 mole), and dicobalt octacarbonyl (10 g., 0.03 mole). The reactor was then closed and connected to a high pressure source (2140 p.s.i.) of mixed gas consisting of 98.5% carbon monoxide and 1.5% hydrogen. The bomb was rocked and heated at 210–235° for 50 min. After the vessel was cooled the pressure was 1950 p.s.i. Subsequent decomposition of the dicobalt octacarbonyl at 70–80° was followed by removal of the benzene under reduced pressure. Extraction of the residual wax with hot chloroform (Norit) gave a green solution which, upon evaporation, gave a brown wax; yield, 13.8 g. Crystallization of the wax from 100 ml. of chloroform at −15° for 1 day yielded product II (1.1 g., 8%) of white crystalline material having a melting point range of 170–205°. Essentially the same material could be obtained by partial crystallization of the product from benzene. Evaporation of the solvent left a residue which could be crystallized from ethanol yielding I.

A portion of the above residue (7.8 g.) was dissolved in 15 ml. of benzene and added to the top of a glass column containing a 150 × 70 mm. (diam.) adsorbent column of alumina. The following mixtures of developer were then added consecutively with the results as indicated. (1) 80 ml. of benzene–petroleum ether (b.p. 30–60°) (1:1/V:V) gave 0.16 g. of a sirup (showed no carbonyl in the infrared and did not fluoresce). (2) 700 ml. of the above developer yielded 3.15 g. (41%) of fluorescent I. (3) 500 ml. of same developer eluted a second fluorescent zone (0.23 g.). (4) 1000 ml. of benzene eluted 0.14 g. of nonfluorescent material. (5) 1750 ml. of benzene-*t*-butyl alcohol (98:2) eluted 2.30 g. of a mixture of III and IV. (6) 350 ml. of benzene-*t*-butyl alcohol (98:2) yielded 0.23 g. of III (compounds III and IV were difficult to separate with benzene-alcohol) (7) 450 ml. of benzene-ethanol (1:1) eluted 1.02 g. (13%) of material which was proved to be identical to compound II.

Compounds III and IV were rechromatographed on alumina using benzene–ethyl acetate (1:1) as developer. Compound IV had a faster rate of elution than compound III.

Characterization of fractions. Fraction I: 2-(β-naphthyl)-4-methylbenzo[h]quinoline. Two recrystallizations of compound I from ethanol gave white needles, m.p. 123–124°.

Anal. Calcd. for $C_{24}H_{17}N$: C, 90.26; H, 5.33; N, 4.39; mol. wt., 319. Found: C, 90.07; H, 5.37; N, 4.48; mol. wt. (Rast), 288.

Infrared spectrum of I (potassium bromide): 3070(W), 2940(W), 2860(W), 1621(W), 1595(S), 1556(W), 1520(W), 1460(M), 1388(W), 1245(W), 1198(W), 829(S), 801(S), 763(S).

Ultraviolet spectrum of I in 95% ethanol showed maxima at 362, 345, 322, 315, 287, 276, 243, 312 mμ (log ε = 4.14, 4.16, 4.36, 4.31, 4.30, 4.50, 4.60, and 4.44, respectively).

Sodium hydroxide fusion for 6 hr. or prolonged hydrolysis of compound I with boiling concd. hydrochloric acid gave unchanged material. An attempted reduction of I with magnesium in methanol according to the procedure of Zechmeister and Truka[13] gave unchanged starting material.

Compound I did not react with maleic anhydride when heated according to the method of Johnson and Mathews.[3]

Oxidation of compound I with acidic permanganate completely degraded it. Oxidation with potassium dichromate in glacial acetic acid,[3] or with chromic acid–acetic acid–sulfuric acid,[14] gave a quinone in low yield which polymerized in the presence of air. Further oxidation of the isolated quinone with chromic acid or permanganate[3] completely degraded it.

2-(β-Naphthyl)-4-methylbenzo[h]quinoline hydrochloride. Hydrogen chloride was bubbled through a solution of 2-(β-naphthyl)-4-methylbenzo[h]quinoline in ether and the greenish yellow precipitated hydrochloride was recovered by filtration, followed by drying over potassium hydroxide pellets under vacuum; m.p. 90–100° with decomposition to yield the original compound.

Anal. Calcd. for $C_{24}H_{17}N{\cdot}HCl$: mol. wt., 340. Found: 341 (by titration with standard potassium hydroxide in ethanol using phenolphthalein as indicator.

Ultraviolet spectrum of the hydrochloride in 95% ethanol showed maxima at 392, 366, 346, 316, and 287 mμ (log ε = 4.23, 4.14, 4.04, 4.47, and 4.49, respectively).

Reaction of 2-(β-naphthyl)-4-methylbenzo[h]quinoline with methyl iodide to yield the methiodide salt. An amount of 0.083 g. of 2-(β-naphthyl)-4-methylbenzo[h]quinoline in 3 ml. of methyl iodide was heated in a sealed tube at 100° for 170 hr. The product was washed with diethyl ether; m.p. 182–186°.

Anal. Calcd. for $C_{25}H_{20}NI$: I, 27.6%. Found: I, 30.3%.

Reaction of 2-(β-naphthyl)-4-methylbenzo[h]quinoline with picric acid to yield the picrate. The picrate was prepared according to a usual procedure[15] and recrystallized from ethanol, m.p. 233–236°.

Anal. Calcd. for $C_{30}H_{20}N_4O_7$: N, 10.22. Found: N, 9.99.

2-(β-Naphthyl)-benzo[h] quinoline-4-carboxaldehyde (V). Oxidation of 2-(β-naphthyl)-4-methylbenzo[h]quinoline (0.25 g.) with selenium dioxide (0.09 g.) at 180–200° for 15 min.; according to the method of Burger and co-workers[16] gave the crude aldehyde. Pure crystalline 2-(β-naphthyl)-benzo[h]quinoline-4-carboxaldehyde was obtained by chromatographic fractionation of the ether extract (residue) of the product on alumina (150 × 35 mm. diam.) using benzene–petroleum ether (b.p. 30–60°) (1:3/V) as developer. The first 300 ml. of developer eluted the original unoxidized compound, whereas the next 1200 ml. gave a trace of unidentified material. A further 2000 ml. of the same developer yielded 0.05 g. of bright yellow crystals which were recrystallized from ligroin; m.p. 140–142°.

Anal. Calcd. for $C_{24}H_{15}NO$: C, 86.46; H, 4.54; N, 4.20; O, 4.80. Found: C, 86.26; H, 4.68; N, 4.18; O, 4.70.

Infrared spectrum (potassium bromide): 2940(S), 2870(M), 1700(S), 1685(W), 1655(W), 1647(W), 1585(W), 1560(W), 1547(W), 1525(W), 1510(W), 1460(W), 1365(W), 1325(W), 1212(W), 1197(W), 1157(W), 1135(W), 1122(W), 1090(W), 1025(W), 928(W), 883(M), 852(M), 827(W), 815(M), 798(W), 745(S), 712(W), 707(W).

The aldehyde gave a positive Tollen's and negative Fehling's test. Treatment of the aldehyde with hydroxylamine hydrochloride gave a crystalline oxime, m.p. 170–185°, without recrystallization.

2-(β-Naphthyl)-benzo[h]quinoline-4-carboxylic acid (VI). A solution of 2-(β-naphthyl)benzo[h]quinoline-4-carboxaldehyde in acetone was oxidized with potassium permanganate in acetone at 30° for 15 min. After the mixture was filtered, the acetone was removed by evaporation. Extraction of the residue with hot aqueous 2*N* potassium hydroxide was followed by acidification of the filtrate (Norit) with glacial acetic acid. The product was further purified by the method of Robinson and Bogert[5]; m.p. 248–250°. Oxidation of the aldehyde (V) with silver oxide according to the procedure of Burger and Modlin[16] also gave the carboxylic acid (VI). An

(12) All melting points were obtained on a Leitz heating stage and are corrected. The infrared analyses were done on a Perkin-Elmer spectrophotometer, Model 21, using a sodium chloride crystal. Microanalyses were done by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, im Max-Planck Institut fur Kohlenforschung, Mülheim (Ruhr), Germany.

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(16) A. Burger and L. R. Modlin, Jr., *J. Am. Chem. Soc.*, **62**, 1079 (1940).

authentic sample of 2-(β-naphthyl)-benzo[h]quinoline-4-carboxylic acid was prepared by the condensation of α-naphthisatin with 2-acetonaphthone[4] and purified by the aforementioned method[5]; m.p. 248–250°; mixed m.p. of the authentic sample with compound VI 248–250°.

Fraction II: *racemic 1-(β-naphthyl)ethylurea.* Fraction II was thrice recrystallized from 3-pentanone, m.p. 198–200°; mixed m.p. with an authentic sample of racemic 1-(β-naphthyl)ethylurea, 198–200° (lit.,[6] m.p. 196–198°).

Infrared spectrum of II (potassium bromide): 3435(S), 3350(S), 3230(M), 3070(W), 2990(W), 2930(W), 1681(W), 1648(S), 1618(W), 1460(W), 1384(M), 1341(W), 1330(W), 1301(W), 1276(W), 1252(W), 1182(M), 1145(M), 1128(M), 1055(W), 1019(W), 968(W), 954(W), 909(W), 896(W), 878(W), 860(W), 825(S), 775(W), 750(S), 662(M).

The infrared spectrum of authentic 1-(β-naphthyl)ethylurea was identical with that of compound II.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.59; N, 13.08; O, 7.47. Found: C, 72.56; H, 6.62; N, 13.12; O, 7.81.

Fraction III: *3-methylbenzo[f]phthalimidine.* Fraction III was recrystallized from benzene-ethanol and from chloroform; m.p. 236–240°.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 78.80; H, 5.65; N, 7.10. Found: C, 78.90; H, 6.23; N, 6.97.

Infrared spectrum of III(potassium bromide): 3310(W), 3050(W), 3005(W), 2960(W), 2905(W), 1708(M), 1690(S), 1598(W), 1550(W), 1535(W), 1505(W), 1455(W), 1378(W), 1345(W), 1273(W), 1216(S), 1127(W), 1016(W), 950(W), 887(W), 855(W), 817(M), 752(S), 663(W).

Fraction IV: *sym-di-1-(β-naphthyl)ethylurea.* Fraction IV was recrystallized from ethanol; m.p. 226–230°. Further purification by chromatography on alumina using benzene–ethyl acetate (1:1) as developer gave a pure compound, m.p. 229–231°.

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.51; H, 6.57; N, 7.61; mol. wt., 368. Found: C, 81.61; H, 6.89; N, 7.52; mol. wt. (Rast) 394.

Infrared spectrum of IV (potassium bromide); 3300(S), 3035(W), 2955(M), 1625(S), 1596(sh), 1578(sh), 1562(S), 1504(W), 1450(W), 1373(S), 1325(M), 1291(W), 1272(W), 1236(S).

VANCOUVER 8, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Psoralenes. III. Cyclization Studies of Certain Substituted Coumarins and Coumarans[1]

ROBERT C. ESSE AND BERT E. CHRISTENSEN

Received December 14, 1959

The synthesis of a series of new 5,6-dialkyl-2,3-dihydropsoralenes is described along with the dehydrogenation of these derivatives to the corresponding psoralenes. A compound which may be the 6-coumaranyl ester of 2,3-dihydro-5-carboxypsoralene was prepared. This compound was dehydrogenated and also converted to the free acid. The free acid was also synthesized directly by a Pechmann type reaction. This acid was simultaneously decarboxylated and dehydrogenated to psoralene. An isomer of xanthotoxin, 5-methoxypsoralene, was prepared from the corresponding 2,3-dihydro derivative. 5-Acetoxypsoralene was prepared; this compound was stable toward dehydrogenation in contrast to 5-hydroxypsoralene which has been reported to decompose under dehydrogenation operations. The synthesis of a number of coumarin derivatives which might serve as intermediates for the preparation of psoralenes was accomplished. Extensive attempts to cyclize two of these intermediates, 7-(2-oxoethoxy)-4-methylcoumarin and 7-(2-bromoethoxy)-4-methylcoumarin, were unsuccessful. In several of the cyclization experiments where a pure product was isolated it was found that ether cleavage to 4-methylumbelliferone rather than ring closure had taken place.

In recent years the furocoumarin xanthotoxin has received considerable attention, both in the scientific literature[2] and the popular press. As xanthotoxin (9-methoxypsoralene) is obtained from natural sources and the number of known psoralenes are limited, it was worthwhile to investigate the procedures for the synthesis of these potential drugs as well as to prepare a number of new psoralenes for research purposes.

The starting material for the synthesis of psoralene compounds is resorcinol or its 2- or 5-substituted derivative. Two routes are available either (1) *via* conversion to 6-hydroxycoumaran, I (2,3-dihydro-6-hydroxybenzofuran) or (2) by way of 7-hydroxycoumarin, II (umbelliferone) (see Fig. 1).

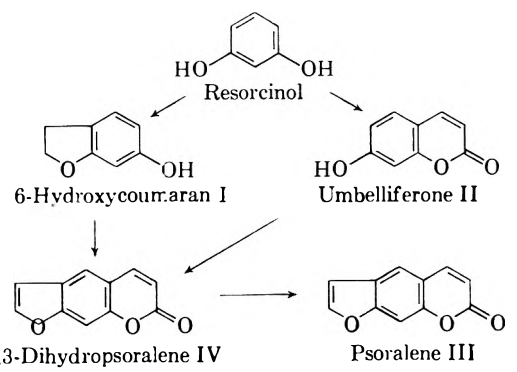

Fig. 1. Synthesis of psoralene from resorcinol

(1) This work was supported in part by grants from the Division of Research Grants and Fellowships, National Institutes of Health, Public Health Service. Published with the approval of the Monographs Publications Committee, Oregon State College as Research Paper No. 381, School of Science, Department of Chemistry.

(2) M. B. Salzberger and B. Lerner, *J. Am. Med. Assn.*, **167**, 2077 (1958). A. B. Lerner, J. Invest. Dermatol., **25**, 1 (1955). T. B. Fitzpatrick, *et al.*, J. Invest. Dermatol. **25**, 187 (1955). T. B. Fitzpatrick, J. D. Imbrie, and D. Labby, *J. Am. Med. Assn.*, **167**, 1586 (1958).

The earliest work was that of Späth,[3] who in a one step operation condensed malic acid with 6-hydroxycoumaran in a sulfuric acid medium to yield 2,3-dihydropsoralene IV from which psoralene III was obtained by dehydrogenation (see Fig. 2). Later Horning and Reisner[4] made this approach more attractive by devising an improved synthesis of the key intermediate 6-hydroxycoumaran. Furthermore, these workers found that 6-acetoxycoumaran (an intermediate for the preparation of 6-hydroxycoumaran) could be used directly for the synthesis of the 5-substituted 2,3-dihydropsoralenes and by condensing it with a variety of β-ketoesters, they obtained a series of 5-substituted 2,3-dihydropsoralenes.

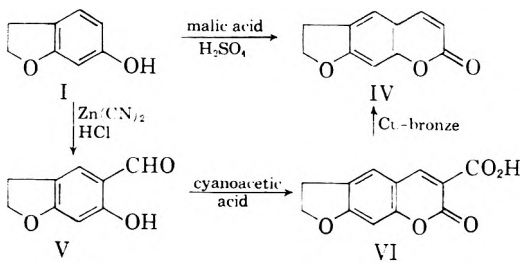

Fig. 2. Synthesis of psoralene from 6-hydroxycoumaran

Robinson, *et al.*[5] also using 6-hydroxycoumaran as the key intermediate devised an alternate route for the synthesis of psoralene. This group formylated I in the 5-position and then condensed the product V with cyanoacetic acid to yield a psoralene compound (see Fig. 2). The resulting 6-carboxy-2,3-dihydropsoralene VI was then decarboxylated and dehydrogenated to yield psoralene itself.

Ray, *et al.*[6] have approached the problem of furocoumarin synthesis from the coumarin moiety of the psoralene molecule and report the synthesis of 3-methylpsoralene. In this procedure 7-acetonyloxycoumarin, VIII, was prepared by treating umbelliferone with chloroacetone. Cyclization of this intermediate to IX was accomplished in an ethanolic medium using sodium ethoxide as the condensing agent; in this respect the ring closure was markedly different from the usual pattern (see Fig. 3).

An alternate route employing a coumarin intermediate was devised by Rodighiero and Antonello[7] for the synthesis of xanthotoxin, IX. These workers converted 7-hydroxy-8-methoxycoumarin to the 6-formyl derivative which in turn was cyclized to the psoralene using ethyl bromoacetate to effect ring closure. The four synthetic routes to the psoralenes of which two are based on the use of umbelliferone and two on the use of 6-hydroxycoumaran are illustrated in Figs. 2 and 3.

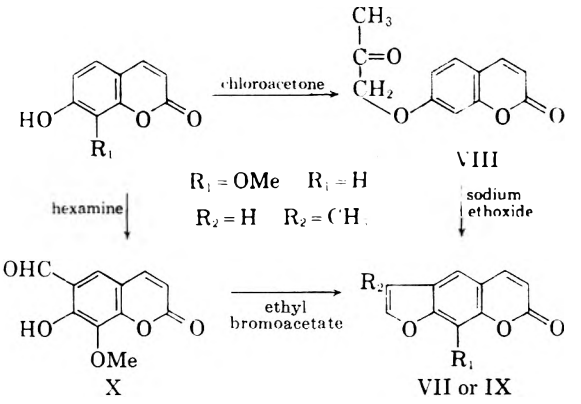

Fig. 3. Synthesis of psoralene from umbelliferone

Three of the routes (see Figs. 2 and 3 — the two employing formylation procedures and the third, the β-ketoester condensation) are long and involved. On the other hand the fourth procedure, as reported by Ray,[6] requires only three steps from resorcinol to a 3-substituted psoralene (see Fig. 3). This method is also attractive in that an umbelliferone is an intermediate rather than 6-hydroxycoumaran. Umbelliferones can be synthesized both easily and in some variety.[8]

The second step of Ray's procedure simply involves the coupling of an α-haloketone and an umbelliferone (see Fig. 3) to form an ether *via* the Williamson procedure. The formation of the keto derivative proceeds smoothly; the ring closure, however, in our hands was not satisfactory giving at best only 4% yield (Ray did not report yield data for this step).

Even if ring closure were to proceed in good yield, Ray's method is restrictive in that it yields 3-methylpsoralene (see VII, Fig. 3). To prepare the unsubstituted psoralene by the Ray procedure it would be necessary to start with 7-(2-oxoethoxy)-coumarin.

Although monochloroacetone reacted with umbelliferone *via* a Williamson synthesis to yield the desired intermediate, chloroacetaldehyde would not react under similar conditions with 4-methylumbelliferone. For this reason the 7-(2-oxoethoxy)-4-methylcoumarin was prepared by oxidative procedures from both 7-(allyloxy)- and 7-(2,3-dihydroxypropoxy)-4-methylcoumarin.

Cyclization experiments using 7-(2-oxoethoxy)-4-methylcoumarin were undertaken using both acid and basic catalyst, all of which led to either (1) recovery of starting material, (2) an uncharacterizable tar, or (3) ether cleavage with the recovery of 4-methylumbelliferone. One experiment

(3) E. Späth and M. Pailer. *Ber.*, **67**, 1212 (1934).

(4) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **70**, 3619 (1948).

(5) R. T. Foster, A. Robinson, and (in part) A. Bushra, *J. Chem. Soc.*, 2254 (1948).

(6) N. Ray, S. S. Silooja, and V. R. Vaid, *J. Chem. Soc.*, 812 (1935).

(7) G. Rodighiero and C. Antonello, *Annali di Chimica (Rome)* **46**, 960 (1956) [abstracted in *Chem. Abstr.*, **51**, 6616 (1957)].

(8) S. Sethna and R. Phadke, *Org. Reactions*, **7**, 1 (1953).

using acetic anhydride with 48% hydrobromic acid yielded the acylal derivative of 7-(2-oxoethoxy)-4-methylcoumarin. In connection with these ring closure studies both 7-bromoethoxy-4-methylcoumarin and 7,8-di(2-oxoethoxy)-4-methylcoumarin were synthesized and their preparations are included herewith for purposes of documentation.

For this reason a new series of experiments were undertaken using 6-acetoxycoumaran as the intermediate and based on the procedures described by Horning and Reisner.[4] A series of 6-alkyl-2,3-dihydro-5-methylpsoralenes were prepared by condensing the appropriate α-alkyl-β-ketoesters with 6-acetoxycoumaran. With the exception of 2,3-dihydro-5-methyl-6-myristylpsoralene, all of these compounds were dehydrogenated by refluxing in phenyl ether in the presence of 10% palladium on charcoal. Repeated and prolonged attempts to remove hydrogen from the myristyl derivative invariably resulted in the recovery of the unchanged starting material

In an attempt to prepare 5-carboxy-2,3-dihydropsoralene, XI, the sodium salt of diethyl oxalacetate was treated with 6-acetoxycoumaran in the presence of 75% sulfuric acid, following the usual procedure. For some unknown reason, all initial attempts were unsuccessful; a tarry product resulted, from which no pure component could be isolated. However, as the authors became more experienced with the reaction, conditions were discovered by which the condensation was successfully completed in a 75% sulfuric acid medium.

In the meantime, because of these initial failures and in view of the tarry nature of the reaction product, the concentration of the sulfuric acid in the reaction medium had been reduced to 60% in several of the experiments. The use of the more aqueous medium yielded a product having a sharp melting point which was not the desired compound. Carbon and hydrogen analysis indicated the empirical formula to be $C_{10}H_7O_3$. A molecular weight determination (Rast) showed the molecular formula to be $C_{20}H_{14}O_6$.

An examination of the infrared spectrum of this compound revealed the presence of two carbonyl groups and the absence of either hydroxyl or carboxylic acid substituents. Treatment of this product by the usual dehydrogenation procedures yielded a dehydrogenated product with a molecular formula $C_{20}H_{10}O_6$, which indicated that the compound may have possessed two dihydrofuran ring systems. Furthermore, when $C_{20}H_{14}O_6$ was subjected to the aforementioned treatment in 75% sulfuric acid medium, the *desired compound*, 5-carboxy-2,3-dihydropsoralene, was isolated from the reaction mixture. Speculations based on this data indicated that the sequence of reactions responsible for these changes may be that shown in Fig. 4. However, experiments designed to confirm the hypothesis that $C_{20}H_{14}O_6$ was the ester 6-coumaranyl

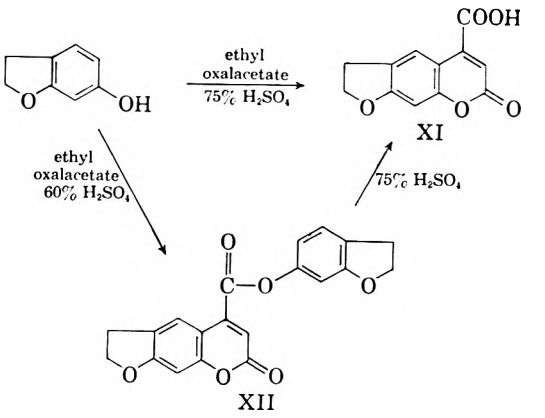

Fig. 4. 5-Carboxy-2,3-dihydropsoralene *via* the $C_{20}H_{14}O_6$, XII, compound

2,3-dihydropsoralene-5-carboxylate, XII, were inconclusive. Repeated attempts to saponify the compound under various conditions of basic hydrolysis were unsuccessful thus leaving the question of structure unsettled.

Horning and Reisner[9] have obtained psoralene by the simultaneous decarboxylation and dehydrogenation of 6-carboxy-2,3-dihydropsoralene. Similar treatment of the 5-carboxy-2,3-dihydropsoralene prepared in this laboratory yielded the expected, unsubstituted psoralene.

5-Hydroxypsoralene was one of the psoralenes desired for research purposes by this laboratory. Horning and Reisner[9] had succeeded in preparing the 2,3-dihydro-5-hydroxypsoralene from a phloroglucinol intermediate (in place of resorcinol—see Fig. 1) but were unable to dehydrogenate the compound. In this laboratory the 2,3-dihydro-5-hydroxypsoralene was converted to both the 5-acetoxy- and 5-methoxy- derivatives and each subjected to dehydrogenation operations. The 5-acetoxy derivative was stable under the conditions of dehydrogenation, but the 5-methoxy derivative responded readily to yield one of the desired isomers of xanthotoxin.

EXPERIMENTAL

7-(2,3-Dihydroxypropoxy)-4-methylcoumarin. 7-Allyloxy-4-methylcoumarin (4.32 g.) was dissolved in 75 ml. acetone. To this acetone solution was added, with rapid stirring, over a 10-min. period, a chilled solution of potassium permanganate (2.1 g.) in water (400 ml.). An excess of ice was maintained in the reaction mixture during oxidation to assure a low reaction temperature. Upon completion of the permanganate addition, the stirring was continued for an additional 10 min. Sulfur dioxide was then bubbled into the brown mixture until all color had been discharged. Upon filtration of the mixture 2.2 g. of unchanged starting material was recovered. The filtrate was concentrated to a volume of 150 ml. and then extracted with three 60-ml. portions of ethyl acetate. The combined ethyl acetate fractions were evaporated to dryness and the residue recrystallized from water; yield 1.3 g. (26%), m.p. 108–110°.

(9) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.4; H, 5.65. Found: C, 62.6; H, 5.76.

7-(2-Oxoethoxy)-4-methylcoumarin. A. 7-Allyloxy-4-methylcoumarin (2 g.) was dissolved in 80 ml. of ethylene chloride. The solution was cooled to 0° in an ice bath and a stream of approximately 3% ozonized oxygen was passed through the solution at a rate of about 50 ml. per min. for 3 hr. The solution was then added to 100 ml. of 10% acetic acid containing zinc dust (0.8 g.). The ethylene chloride was removed by evaporating the solution on a hot plate and the remaining hot aqueous solution filtered to remove the unused zinc. The product was collected from the thoroughly chilled filtrate; yield 1.4 g. This material contained approximately 1 mole of water. It was recrystallized, and at the same time dried by dissolving the hydrate in 50 ml. of xylene, followed by boiling the solution until it was concentrated to two-thirds of its original volume. The product was improved by treatment with decolorizing charcoal; yield 0.9 g. (45%), m.p. 150–152°.

Anal. Calcd. for $C_{12}H_{10}O_4 \cdot H_2O$: C, 61.0; H, 5.13. Found: C, 61.8; H, 5.08.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.62. Found: C, 66.1; H, 4.62.

The *2,4-dinitrophenylhydrazone* melted at 229–231°.

Anal. Calcd. for $C_{18}H_{14}O_7N_4$: C, 54.3; H, 3.54; N, 14.1. Found: C, 54.6; H, 3.71; N, 14.3.

B. One gram of 7-(2,3-dihydroxypropoxy)-4-methylcoumarin was dissolved in 250 ml. of warm water. This solution was cooled to room temperature and a solution containing 0.92 g. of periodic acid in 25 ml. of water was added. After stirring this mixture for 1.5 hr. the white product which formed was removed by filtration and crystallized from dilute ethanol to yield 0.73 g. (77%) of the aldehyde. The product from this reaction, as judged by carbon and hydrogen analysis, appeared to be hydrated. It was dissolved in 30 ml. of xylene and the solution boiled on a hot plate until one-third of the xylene had evaporated. The hot xylene solution was then filtered. Analysis of the product crystallized from the chilled filtrate showed the compound to be anhydrous.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.62. Found: C, 66.2; H, 4.63.

7-(2-Oxoethoxy)coumarin. 7-Allyloxycoumarin (1 g.) was dissolved in 40 ml. of ethylene chloride. The solution was cooled to 0° with an ice bath and a stream of approximately 3% ozonized oxygen allowed to bubble through the solution at a rate of about 50 ml. per min. for 1.5 hr. The ethylene chloride solution was then added to 50 ml. of 10% acetic acid containing zinc dust (0.4 g.). The ethylene chloride was removed by evaporation on a hot plate and the remaining hot aqueous solution filtered to remove the unused zinc. The product was collected from the thoroughly chilled filtrate; yield 0.65 g. This material contained approximately 1 mole of water. It was recrystallized, and at the same time dried by dissolving the hydrate in 30 ml. of xylene, followed by boiling the solution until it was concentrated to two-thirds of its original volume. The product was improved by treatment with decolorizing charcoal; yield 0.37 g. (37%), m.p. 130–131°.

Anal. Calcd. for $C_{11}H_8O_4 \cdot H_2O$: C, 59.4; H, 4.04. Found: C, 60.2; H, 4.52.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.95. Found: C, 64.8; H, 4.06.

7,8-Diallyloxy-4-methylcoumarin. 7,8-Dihydroxy-4-methylcoumarin (3.84 g.) was dissolved in acetone (80 ml.). Potassium carbonate (8.0 g.) and allyl bromide (5.32 g.) were added to the solution and the resulting mixture was stirred and refluxed for 18 hr. The acetone was removed by placing the open beaker containing the mixture in front of a hot air fan. The residue was dissolved in water and acidified with dilute hydrochloric acid. The solid which formed was removed from the aqueous phase by extraction with three portions of ethyl acetate. The ethyl acetate fractions were evaporated and the residue crystallized from ethyl alcohol. The chilled (−10°) alcohol solution yielded 4.2 g. of product, m.p. 50–51°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.93. Found: C, 70.6; H, 6.06.

7-(2-Bromoethoxy)-4-methylcoumarin. Absolute ethanol (150 ml.) containing sodium ethoxide prepared from 1.15 g. of sodium was added to a 150 ml. anhydrous alcoholic solution in which were dissolved 4-methylumbelliferone (9.5 g.) and ethylene bromide (9.4 g.). This mixture was stirred and refluxed for 18 hr.; the hot solution was then filtered and the filtrate added to twice its volume of water. The aqueous solution was then acidified with dilute hydrochloric acid to precipitate the product, which was then collected. The product was recrystallized from 40% ethanol; yield 2.5 g. (20%), m.p. 109–110°.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.9; H, 3.92. Found: C, 51.1; H, 3.99.

7,8-Di(2-oxoethoxy)-4-methylcoumarin. 7,8-Diallyloxy-4-methylcoumarin (1.5 g.) was dissolved in ethylene chloride (60 ml.) and the solution cooled to 0° with an ice bath. Approximately 3% ozonized oxygen was bubbled through the solution for 4 hr. at the rate of about 50 ml. per min. This solution was poured into 50 ml. of 10% acetic acid containing 0.6 g. of zinc dust and the ethylene chloride layer was removed by evaporation on a hot plate. The remaining hot, aqueous solution was filtered and chilled. The product was collected and recrystallized from water; yield 0.82 g. (54%), m.p. 95–97°.

Anal. Calcd. for $C_{14}H_{12}O_6$: C, 60.8; H, 4.38. Found: C, 61.2; H, 4.51.

7-(2,2-Diacetoxyethoxy)-4-methylcoumarin. A solution containing 7-(2-oxoethoxy)-4-methylcoumarin (0.5 g.), acetic anhydride (5 ml.), and 48% hydrobromic acid (0.5 ml.) was refluxed for 3.5 hr. The mixture was then added to 20 ml. of water, brought to a boil, decolorized with charcoal, filtered, and cooled. The rapidly formed crystals were collected and recrystallized from ethanol; yield 0.4 g. (55%), m.p. 129–130°.

Anal. Calcd. for $C_{16}H_{16}O_7$: C, 60.0; H, 5.04. Found: C, 60.2; H, 5.15.

2,3-Dihydro-5,6-dimethylpsoralene. A mixture containing 6-acetoxycoumaran (1.78 g.) and ethyl α-methylacetoacetate (1.42 g.) was placed on a steam bath; 10 ml. of 75% sulfuric acid was added with stirring over a 10-min. period. Heating and stirring were continued for an hour; the reaction mixture was then cooled and poured onto ice. The mixture was placed overnight in a refrigerator and then filtered and washed with cold water. The crude product was decolorized with charcoal and recrystallized, first from ethyl acetate and then from ethanol; yield 0.45 g. (21%), m.p. 186.5–187.5°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.60. Found: C, 72.2; H, 5.60.

2,3-Dihydro-6-ethyl-5-methylpsoralene. 6-Acetoxycoumaran (1.78 g.) and ethyl α-ethylacetoacetate (1.58 g.) were treated in the same manner as in the above experiment. The crude product was decolorized with charcoal and recrystallized twice with ethanol, yield 0.80 g. (35%), m.p. 143–144°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.13. Found: C, 72.5; H, 6.12.

2,3-Dihydro-6-isopropyl-5-methylpsoralene. 6-Acetoxycoumaran (1.76 g.) and ethyl α-isopropylacetoacetate (1.72 g.) were treated in the same manner as that employed for the preparation of 2,3-dihydro-6-ethyl-5-methylpsoralene. The yield was 0.60 g. (25%), m.p. 183–185°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.7; H, 6.61. Found: C, 73.6; H, 6.84.

2,3-Dihydro-5-methyl-6-myristylpsoralene. Eight milliliters of 75% sulfuric acid was added dropwise to a stirred mixture of 6-acetoxycoumaran (0.89 g.) and ethyl α-myristylacetoacetate (1.63 g.). The reaction was started at room temperature and gradually brought to 65°. After 2 hr. the mixture was cooled and poured onto ice. The precipitate was

TABLE I

5,6-Dialkylpsoralenes

Psoralenes	Yield, %	M.P.	Formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
5,6-Dimethyl-	45	235–236°	$C_{13}H_{10}O_3$	72.9	72.9	4.71	4.61
6-Ethyl-5-methyl-	55	179–180°	$C_{14}H_{12}O_3$	73.7	73.4	5.30	5.40
6-Isopropyl-5-methyl-	44	145–147°	$C_{15}H_{14}O_3$	74.3	74.0	5.83	5.89

collected, decolorized with charcoal, and recrystallized twice from dilute ethanol; yield 0.76 g. (38%), m.p. 96–97°.

Anal. Calcd. for $C_{26}H_{38}O_3$: C, 78.4; H, 9.62. Found: C, 77.9; H, 9.54.

Dehydrogenation of the 5,6-dialkyl-2,3-dihydropsoralenes. One gram of the compound to be dehydrogenated was added, together with 10% palladium on charcoal (0.5 g.), to 15 ml. of phenyl ether, and the mixture was then refluxed for 8 hr. The hot solution was filtered to remove the catalyst, which was washed with 5 ml. of hot phenyl ether. The phenyl ether was removed from the product by a steam distillation. The nonvolatile residue was collected, decolorized with charcoal, and crystallized from ethanol. See Table I.

Reaction product of 6-acetoxycoumaran and diethyl sodiooxalacetate (6-coumaranyl 2,3-dihydropsoralene-5-carboxylate, XII). 6-Acetoxycoumaran (5.24 g.) was melted in a flask on a steam bath. The sodium salt of diethyl oxalacetate (6.9 g.) was added and the mixture stirred into a paste. The heating was then stopped and 30 ml. of 60% sulfuric acid was added over a 30-min. period. Stirring was continued for another 30 min. and the mixture then replaced on a steam bath for an additional 15 min. The reddish mixture was cooled, poured onto ice, and left in a refrigerator overnight. The product was then collected and washed with cold water. The dry, crude product was improved by washing with very small portions of ethyl ether. Decolorization with charcoal and recrystallization from ethanol gave 2.95 g. (56%) of pale yellow needles, m.p. 209–210°.

Anal. Calcd. for $C_{20}H_{14}O_6$: C, 68.6; H, 4.03. Found: C, 68.4; H, 4.23.

Dehydrogenation product (6-benzofuranyl psoralene-5-carboxylate). The condensation product $C_{20}H_{14}O_6$ (0.5 g.) was refluxed in phenyl ether (10 ml.) with 10% palladium on charcoal (0.25 g.) for 5 hr. The hot solution was filtered to remove the catalyst, which was washed with a small amount of acetone. The acetone washings and phenyl ether were removed by steam distillation, and the dried, nonvolatile residue was recrystallized from ethanol; yield 0.25 g. (49%), m.p. 228–230°.

Anal. Calcd. for $C_{20}H_{10}O_6$: C, 69.4; H, 2.91. Found: C, 69.1; H, 3.19.

2,3-Dihydropsoralene-5-carboxylic acid, XI. A. 6-Acetoxycoumaran (3.56 g.) was melted and stirred into a paste with the sodium salt of diethyl oxalacetate (4.60 g.). Twenty milliliters of 75% sulfuric acid was added over a 30-min. period. The temperature was then raised to 80° and the stirred mixture maintained at this temperature for an additional 30 min.; it was then cooled, poured onto ice, and set in a refrigerator overnight. The product was filtered, washed with water, and dissolved in 100 ml. of hot 1% sodium hydroxide solution. The basic solution was filtered and the product precipitated from the filtrate with dilute hydrochloric acid. The product was collected and recrystallized from ethanol; yield 0.71 g. (20%), m.p. 254–256°.

Anal. Calcd. for $C_{12}H_8O_5$: C, 62.1; H, 3.48. Found: C, 62.2; H, 3.73.

B. The compound $C_{20}H_{14}O_6$, XII (0.5 g.), was added to 75% sulfuric acid (3 ml.) and the mixture was stirred for 25 min. at room temperature. The temperature was then raised to 80° and maintained at this temperature while stirring was continued an additional 25 min. The reaction mixture was cooled and poured onto ice. The product was filtered and washed with cold water. Recrystallization from dilute ethanol yielded 110 mg. (15%), m.p. 253–255°.

Anal. Calcd. for $C_{12}H_8O_5$: C, 62.1; H, 3.48. Found: C, 62.5; H, 3.69.

Psoralene. 2,3-Dihydropsoralene-5-carboxylic acid, XI (0.5 g.), and 0.25 g. of 10% palladium on charcoal were refluxed in 10 ml. of phenyl ether for 5 hr. The mixture was filtered while hot to remove the catalyst, which was washed with 5 ml. of hot phenyl ether. The solution was added to 200 ml. petroleum ether (b.p. 60–71°) and cooled at −10° overnight. The amorphous product was collected and recrystallized from ethanol; yield 0.18 g. (85%), m.p. 155–160°. Sublimation at 150°, 12 mm., gave a material melting at 160–161°. A mixed melting point with an authentic sample of psoralene gave no depression of the melting point.

Anal. Calcd. for $C_{11}H_6O_3$: C, 71.0; H, 3.25. Found: C, 70.6; H, 3.42.

The infrared spectrum was identical with that of an authentic sample of psoralene.

Ethyl α-myristylacetoacetate. Ethyl acetoacetate (6.5 g.) together with 100 ml. of absolute ethanol and 1.15 g. of sodium (converted to sodium ethoxide) were placed in a three necked flask, equipped with stirrer, reflux condensor, and separatory funnel. This solution was stirred, brought to a boil, and *n*-myristyl bromide (13.9 g.) was added over a 2-hr. period. The reaction was continued until the solution was neutral to litmus. When the reaction was complete, the cooled solution was decanted from the sodium bromide. The alcohol was removed by a simple distillation and the product was then distilled under reduced pressure. The fraction collected boiled at 180–185° at about 0.5 mm.; yield 12.9 g. (79%), n_D^{23} 1.4510.

Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.6; H, 11.75. Found: C, 73.5; H, 11.41.

2,3-Dihydro-6-acetoxypsoralene. 2,3-Dihydro-5-hydroxypsoralene (0.53 g.) was refluxed with 10 ml. acetic anhydride and 0.5 ml. pyridine for 3 hr., after which the solution was poured into water. The product was collected and recrystallized from ethanol; yield 0.35 g. (55%), m.p. 225–227°.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.4; H, 4.10. Found: C, 63.4; H, 4.27.

2,3-Dihydro-5-methoxypsoralene. One and a half grams of 2,3-dihydro-5-hydroxypsoralene[8] in 50 ml. of acetone was refluxed with potassium carbonate (3.75 g.) and dimethyl sulfate (1.5 ml.) for 18 hr. The mixture was poured into 200 ml. of water, cooled, and the product collected, and recrystallized from ethanol; yield 0.9 g. (56%), m.p. 209–210°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.62. Found: C, 66.0; H, 4.78.

5-Methoxypsoralene. 2,3-Dihydro-5-methoxypsoralene (0.63 g.) was dehydrogenated by the general procedure as given. The crude product was recrystallized from ethanol; yield 0.41 g. (65%), m.p. 216–217°.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.7; H, 3.73. Found: C, 66.5; H, 3.91.

CORVALLIS, ORE.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

Pyrazolono(3,4-d)pyrimidines. I. The Preparation of 6-Methylthiopyrazolono-(3,4-d)pyrimidines[1,2,3]

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Received February 15, 1960

The synthesis of 6-methylthiopyrazolono(3,4-d)pyrimidines from 2-methylthio-4-chloro-5-carbethoxypyrimidine and hydrazines is described. When hydrazine, methylhydrazine, *p*-nitrophenylhydrazine, and 2,5-dichlorophenylhydrazine were used, intermediate 4-hydrazino-5-carbethoxypyrimidines were isolated. With 1,2-dimethylhydrazine, isopropylhydrazine, phenylhydrazine, *p*-tolylhydrazine, *p*-halophenylhydrazines, and *p*-carboxyphenylhydrazine, the intermediate hydrazinopyrimidines were not isolated.

Systems composed of fused pyrazole and pyrimidine rings recently have received considerable attention as potential antagonists to natural purines. Robins[5] reported the preparation of a number of 1,4-disubstituted and 1,4,6-trisubstituted pyrazolo(3,4-d)pyrimidines by the action of formamide or ureas on 1-substituted 4-cyano-5-aminopyrazoles. Falco and Hitchings[6] synthesized 4,6-dihydroxypyrazolo(3,4-d)pyrimidine by treating 4,5-pyrazoledicarboxamide with sodium hypochlorite. Schmidt and Druey[7] also prepared a number of 1,4,6-trisubstituted pyrazolo(3,4-d)-pyrimidines both by treating 2-substituted 3-amino-4-carbethoxypyrazoles with urea and substituted ureas and by the cyclization of 4-hydrazino-5-pyrimidinecarbonitriles.

Relatively little work has been reported on systems with the pyrazolone and pyrimidine rings fused. Siewert[8] described the synthesis of 2-phenyl-5,7-dihydroxypyrazolono(4,3-d)pyrimidine by the action of potassium cyanate on 1-phenyl-3-carbethoxy-4-amino-5-pyrazolone. Taylor[9] reported the formation of 6-aminopyrazolono(3,4-d)pyrimidine along with 2-amino-8-hydroxypurine when 2,4-diamino-5-pyrimidinecarboxamide was treated with sodium hypobromite.

The 3-oxo group makes the 6-substituted pyrazolono(3,4-d)pyrimidines attractive intermediates for the synthesis of 3,6-disubstituted pyrazolo(3,4-d)pyrimidines which bear some structural relationship to the natural purines. This paper describes the preparation of 2-methylthio-4-hydrazino-5-carbethoxypyrimidines (I–V) and 6-methylthiopyrazolono(3,4-d)pyrimidines (VI–XVII). The synthetic route employed was quite similar to that of Michaelis[10] who prepared pyrazolonolutidines and to that of Kenner[11] who reported several indazolones. Michaelis treated 4-chloro-5-carbethoxylutidine with hydrazine and several arylhydrazines. With the former, he isolated pyrazolono(4,3-c)lutidine, and with the latter, the corresponding 4-arylhydrazino-5-carbethoxylutidines. These hydrazinolutidines on heating cyclized to 2-substituted pyrazolono(4,3-c)lutidines.

When Kenner treated methyl 2-chloro-3,5-dinitrobenzoate with phenylhydrazine, he obtained 5,7-dinitro-2-phenyl-3-indazolone. With hydrazine, 5,7-dinitro-3-indazolone was the product. When ethyl 2-chloro-5-nitrobenzoate underwent the same reaction, the uncyclized products, ethyl 2-(2-phenylhydrazino)-5-nitrobenzoate and ethyl 2-hydrazino-5-nitrobenzoate, were isolated. These both readily underwent base-catalyzed cyclization to the corresponding indazolones. The position of the phenyl group in the phenylhydrazinobenzoate was established by mercuric oxide oxidation to 4-nitro-2-carbethoxyazobenzene.

In the present investigation, when hydrazines were treated with 2-methylthio-4-chloro-5-carbethoxypyrimidine (XVIII),[12] 4-hydrazinopyrimidines or pyrazolono(3,4-d)pyrimidines were formed, depending on the hydrazines used. Hydrazine, methylhydrazine, *p*-nitrophenylhydrazine, and 2,5-dichlorophenylhydrazine formed the corresponding hydrazinopyrimidines (I–IV, Table I).

(1) Supported by a grant, CY-2857, from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) In part from a thesis submitted by Martin Hauser to the Graduate School of Arts and Sciences, The University of Buffalo, in partial fulfillment of the requirement for the degree of Master of Arts.

(3) Presented at the 137th Meeting of the American Chemical Society in Cleveland, Ohio, April, 1960.

(4) Present address: Deering Milliken Research Corporation, Spartanburg, S. C.

(5) H. C. Koppel, E. O'Brien, and R. K. Robins, *J. Org. Chem.*, **24**, 259 (1959), and preceding papers.

(6) E. A. Falco and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3142 (1956).

(7) P. Schmidt, K. Eichenberger, E. Wilhelm, and J. Druey, *Helv. Chim. Acta*, **42**, 763 (1959), and preceding papers.

(8) G. Siewert, *Arch. Pharm.*, **278**, 327 (1940).

(9) *Cf.* discussion of E. C. Taylor in *The Chemistry and Biology of Purines*, a Ciba Foundation Symposium (Wolstenholme and O'Connor, editors), Little, Brown and Company, Boston, (1957), p. 36.

(10) A. Michaelis, *Ann.*, **366**, 324 (1909).

(11) J. Kenner, *J. Chem. Soc.*, 2732 (1914). J. Kenner and E. Witham, *J. Chem. Soc.*, 1053 (1921).

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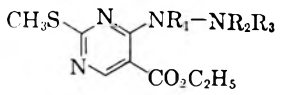
TABLE I

2-METHYLTHIO-4-HYDRAZINO-5-CARBETHOXYPYRIMIDINE

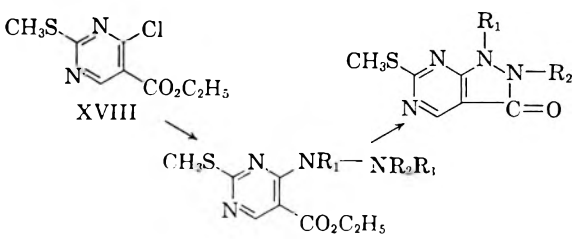


Compound	R_1	R_2	R_3	M.P.,[19]	Yield, %	Formula	Calcd. C	Found C	Calcd. H	Found H	Calcd. N	Found N
I	H	H	H	100–101	79	$C_8H_{12}N_4O_2S$	42.09	42.57	5.30	5.39	24.54	24.32
II	CH_3	H	H	107–109	85	$C_9H_{14}N_4O_2S$	44.60	44.31	5.82	5.66	23.12	23.51
III	H	H	p-$NO_2C_6H_4$	171–173	70	$C_{14}H_{15}N_5O_4S$	48.13	48.20	4.33	4.28	20.05	20.00
IV	H	H	2,5-$Cl_2C_6H_3$	146–148	88	$C_{14}H_{14}Cl_2N_4O_2S$	45.05	45.20	3.78	4.02	15.01	14.95
V	H	C_6H_5	$COCH_3$	137–138	27	$C_{16}H_{18}N_4O_3S$	55.47	55.32	5.24	5.22	16.17	16.18

In the conversion of halogenated pyrimidines to hydrazinopyrimidines with alkyl and arylhydrazines, it is usually assumed that reaction takes place at the nitrogen not bonded to the substituent.[13] Hinman[14] has pointed out that this assumption is not justified in many reactions of hydrazines. Schmidt and Druey[7] treated isopropylhydrazine with 2-dimethylamino-4-chloro-5-pyrimidinecarbonitrile and obtained 1-isopropyl-3-amino-6-dimethylaminopyrazolo(3,4-d)pyrimidine. The identical compound was obtained by hydrolysis of 2-dimethylamino-4-(1-isopropyl-2-acetylhydrazino)-5-pyrimidinecarbonitrile, confirming the position of the isopropyl group. We have found evidence to indicate that in the reactions of XVIII with hydrazines reaction occurs at the α-nitrogen of the alkylhydrazines and the β-nitrogen of the arylhydrazines.

A red to violet color developed when I and II were treated with sodium pentacyanoamineferroate. The test was negative with III and IV. Hydrazines of the type RNH—NH_2 and R_2N—NH_2 are reported to give a red to violet color with this reagent.[15] The infrared spectra of I and II show a medium peak at 1650–1625 cm.$^{-1}$ ascribed to the free amino group at the end of the hydrazine group.[16] This peak is absent in the spectra of III and IV. Although II formed an oil when treated with acetone, it reacted with propionaldehyde to give a solid hydrazone. It was not possible to heat II with these reagents; cyclization occurred to form VII. I formed solid hydrazones with acetone and benzaldehyde. III and IV did not form hydrazones.

Cyclization of I–IV to the corresponding pyrazolonopyrimidines, (VI, VII, XVI, and XVII, Table II) was effected by heating briefly in base.



Treatment of XVIII with isopropyl, 1,2-dimethyl-, phenyl-, p-tolyl-, p-bromophenyl-, p-chlorophenyl-, p-fluorophenyl-, and p-carboxyphenylhydrazine gave the pyrazolonopyrimidines, (VIII–XV, Table II) directly. In these cases, under the conditions used, the intermediate hydrazinopyrimidines were not detected.

Based on the data for hydrazinopyrimidines, it is probable that VII and VIII are 1-substituted pyrazolono(3,4-d)pyrimidines, while X–XV are 2-substituted. In addition, hydrolysis of 2-methylthio-4-(2-acetyl-2-phenylhydrazino)-5-carbethoxypyrimidine (V), prepared from XVIII and 1-acetyl-1-phenylhydrazine,[17] gave a compound identical with X.

In the aromatic series, of phenylhydrazine and the six *para*-substituted phenylhydrazines treated with XVIII, only p-nitrophenylhydrazine did not form a pyrazolonopyrimidine directly. This suggests that the high electronegativity of the nitro group sufficiently reduced the nucleophilicity of the 2′-nitrogen to prevent immediate cyclization. The weaker electron-attracting groups (p-bromo, p-chloro, p-fluoro, and p-carboxy) and the electron-releasing p-methyl group allow cyclization. The

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(14) R. L. Hinman, *J. Org. Chem.*, **23**, 1587 (1958).

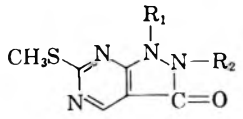
(15) F. Feigl, V. Anger, and O. V. Frehden, *Mikrochemie*, **15**, 184 (1934). F. Feigl, *Spot Tests in Organic Analysis*, Elsevier Publishing Co., New York (1956), p. 292.

(16) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York City, (1958), pp. 255–256.

(17) H. Behrend and W. Reinsberg, *Ann.*, **377**, 189 (1910).

TABLE II

6-METHYLTHIOPYRAZOLONO(3,4-D)PYRIMIDINES



Compound	R_1	R_2	M.P.,[19]	Yield, %	Formula	Calcd. / Found C	H	N
VI	H	H	340 dec.	75	$C_6H_6N_4OS$	39.55	3.32	30.75
						39.22	3.38	31.01
VII	CH_3	H	273–275	97	$C_7H_8N_4OS$	42.84	4.11	28.55
						42.70	4.24	28.43
VIII	$(CH_3)_2CH$	H	209–210	67	$C_9H_{12}N_4OS$	48.22	5.39	24.98
						48.31	5.15	25.10
IX	CH_3	CH_3	173–175	68	$C_8H_{10}N_4OS$	45.69	4.79	26.65
						45.55	4.70	26.38
X	H	C_6H_5	275–277	83	$C_{12}H_{10}N_4OS$	55.80	3.90	21.69
						55.79	3.89	21.65
XI	H	*p*-$CH_3C_6H_4$	300–302	88	$C_{13}H_{12}N_4OS$	57.33	4.44	20.57
						57.17	4.53	20.79
XII	H	*p*-BrC_6H_4	330 dec.	64	$C_{12}H_9BrN_4OS$	42.74	2.69	16.62
						42.70	2.75	16.64
XIII	H	*p*-ClC_6H_4	340 dec.	62	$C_{12}H_9ClN_4OS$	49.23	3.10	19.14
						49.21	3.48	19.53
XIV	H	*p*-FC_6H_4	310 dec.	65	$C_{12}H_9FN_4OS$	52.16	3.28	20.28
						52.04	3.57	20.29
XV	H	*p*-$HOOCC_6H_4$	360 dec.	77	$C_{13}H_{10}N_4O_3S$	51.65	3.33	18.53
						51.50	3.87	18.33
XVI	H	*p*-$NO_2C_6H_4$	315 dec.	82	$C_{12}H_9N_5O_3S$	47.52	2.99	23.09
						47.35	3.18	23.03
XVII	H	2,5-$Cl_2C_6H_3$	300 dec.	57	$C_{12}H_8Cl_2N_4OS$	44.05	2.46	17.13
						43.96	3.10	17.19

failure of IV to cyclize is also explained on the basis of low nucleophilicity of the 2′-nitrogen.

In the series of aliphatic-substituted hydrazinopyrimidines, the 1′-substituent does not greatly increase the nucleophilicity of the 2′-nitrogen. Further, there is a possible steric effect. Construction of the 5-carbethoxy-4-hydrazinopyrimidines with Courtauld Atomic Models[18] indicates that the preferred conformation, in those cases where a bulky group is located on the 2′-nitrogen, is that which places this nitrogen in a position favorable for nucleophilic attack on the carbonyl carbon. With the unsubstituted I and 1′-substituted II this conformation is not necessarily preferred. However, in VIII, the substituent, although on the 1′-position, is sufficiently bulky to promote cyclization when combined with the electron-release properties of the isopropyl group.

EXPERIMENTAL[19]

2-Methylthio-4-hydrazino-5-carbethoxypyrimidine (I). A solution of 2.0 g. (0.088 mole) of hydrazine in 25 ml. of absolute alcohol was added, with stirring and cooling, to a solution of 10 g. (0.043 mole) of XVIII[12] in 150 ml. of absolute alcohol at such a rate that the temperature did not rise above 25°. After standing for 2 hr. at room temperature, the solution was diluted with an equal volume of water. 1,2-Bis(2-methylthio-5-carbethoxy-4-pyrimidyl)hydrazine precipitated. This was immediately removed by filtration and treated as described below. The solid obtained by evaporation of the filtrate was washed with water and recrystallized from benzene-ligroin (b.p. 30–60°).

1,2-Bis(2-methylthio-5-carbethoxy-4-pyrimidyl)hydrazine. This material, a by-product in the preparation of I, was recrystallized from ethylbenzene to give 1.0 g. of yellow solid, m.p. 240–242°.

Anal. Calcd. for $C_{16}H_{20}N_6O_4S_2$: C, 45.27; H, 4.75; N, 19.80. Found: C, 45.94; H, 4.76; N, 19.67.

2-Methylthio-4-isopropylidenehydrazino-5-carbethoxypyrimidine. A solution of 2.0 g. (0.0088 mole) of I in 50 ml. of acetone was refluxed for 90 min. and the acetone evaporated at room temperature. The residue was recrystallized from benzene-ligroin (b.p. 30–60°) to give 2.3 g. (96%) of white solid; m.p. 164–166°.

Anal. Calcd. for $C_{11}H_{16}N_4O_2S$: C, 49.23; H, 6.01; N, 20.88. Found: C, 49.49; H, 5.75; N, 20.41.

2-Methylthio-4-benzylidenehydrazino-5-carbethoxypyrimidine. A solution of 1.5 g. (0.0066 mole) of I and 0.75 g. (0.0071 mole) of benzaldehyde in 50 ml. of absolute alcohol was refluxed for 2 hr. The hydrazone precipitated after cooling to room temperature and diluting with an equal volume of water. It was recrystallized from alcohol-water to give 1.9 g. (92%) of white solid; m.p. 148–149°.

Anal. Calcd. for $C_{15}H_{16}N_4O_2S$: C, 56.93; H, 5.10; N, 17.71. Found: C, 56.43; H, 4.94; N, 17.77.

2-Methylthio-4-(1-methylhydrazino)-5-carbethoxypyrimidine (II). A solution of 4.1 g. (0.087 mole) of methylhydrazine in 25 ml. of absolute alcohol was added slowly to a solu-

(18) The Ealing Corporation, Natick, Mass.

(19) Melting points are uncorrected. Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.; Geller Microanalytical Laboratories, Bardonia, N. Y.; and Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

tion of 10 g. (0.043 mole) of XVIII in 100 ml. of absolute alcohol cooled to 15° at such a rate that the temperature remained at about 15°. After standing for 1 hr. at 15°, the precipitate was filtered, washed thoroughly with water, and recrystallized from benzene-ligroin (b.p. 30–60°).

2-Methylthio-4-(1-methyl-2-propylidenehydrazino)-5-carbethoxypyrimidine. A solution of 0.50 g. (0.0021 mole) of 2-methylthio-4-(1-methylhydrazino)-5-carbethoxypyrimidine and 0.50 g. (0.0086 mole) of propionaldehyde in 25 ml. of absolute alcohol was allowed to stand overnight at room temperature. The solution was then evaporated to dryness in a stream of dry air and the residue recrystallized from ligroin (b.p. 30–60°) to give 0.37 g. (62%) of white solid; m.p. 66–67°.

Anal. Calcd. for $C_{12}H_{18}N_4O_2S$: C, 51.04; H, 6.43; N, 19.85. Found: C, 50.99; H, 6.42; N, 19.38.

2-Methylthio-4-(2-arylhydrazino)-5-carbethoxypyrimidines (III–IV). *General method.* A solution of 10 g. (0.043 mole) of XVIII in 150 ml. of absolute alcohol was added to a solution of 0.088 mole of the arylhydrazine in the minimum amount of absolute alcohol. The resulting solution was heated at 50° for 30 min., then allowed to stand 4 hr. at room temperature. It was next diluted with twice its volume of water and refrigerated overnight at 1°. The precipitate was filtered, triturated with 300 ml. of 5% hydrochloric acid, washed thoroughly with water, and recrystallized from alcohol-water.

2-Methylthio-4-(2-acetyl-2-phenylhydrazino)-5-carbethoxypyrimidine (V). To a solution of 2.3 g. (0.015 mole) of 1-acetyl-1-phenylhydrazine[16] in 55 ml. of absolute alcohol was added a solution of 1.8 g. (0.0075 mole) of XVIII in 25 ml. of absolute alcohol. The resulting solution was allowed to stand 4 hr., diluted with an equal volume of water, and refrigerated overnight at 1°. The precipitate of 2-phenyl-6-methylthiopyrazolono(3,4-d)pyrimidine (X) was removed and 150 ml. of water was added to the solution. After several hours of refrigeration, the solution was filtered and the precipitate recrystallized from water.

Cyclization of hydrazinopyrimidine (I–IV) *to pyrazolono (3,4 d)pyrimidines* (VI, VII, XVI, and XVII). *General method.* A solution of 1 g. of the hydrazinopyrimidine in 10 ml. of 10% potassium hydroxide was boiled for 15 min., cooled, and acidified with 25% acetic acid. The precipitate was washed with water and recrystallized from *n*-butyl alcohol.

1-Isopropyl-6-methylthiopyrazolono(3,4-d)pyrimidine (VIII). A solution of 3.3 g. (0.020 mole) of isopropylhydrazine oxalate, 35 ml. of water, and 2.8 g. of potassium hydroxide was diluted with 350 ml. of alcohol and the precipitate of potassium oxalate removed by filtration. To the filtrate was added a solution of 2.3 g. (0.010 mole) of XVIII in 50 ml. of alcohol and the solution warmed at 60° for 30 min. After cooling, the solution was diluted with 500 ml. of water and placed in the refrigerator at 1°. The precipitate was filtered and recrystallized from *n*-butyl alcohol.

1,2-Dimethyl-6-methylthiopyrazolono(3,4-d)pyrimidine (IX). A solution of 5.3 g. (0.088 mole) of 1,2-dimethylhydrazine in 25 ml. of absolute alcohol was added slowly, with stirring, to 10 g. (0.043 mole) of XVIII dissolved in 125 ml. of absolute alcohol. The temperature was maintained at 25° by cooling. When the reaction subsided, the solution was allowed to stand for 4 hr. and diluted with three volumes of water. After overnight refrigeration at 1°, the precipitate was filtered, washed thoroughly with water, and recrystallized from benzene-ligroin (b.p. 30–60).

2-Phenyl-6-methylthiopyrazolono(3,4-d)pyrimidine (X). *From* XVIII. A solution of 9.5 g. (0.088 mole) of phenylhydrazine in 25 ml. of absolute alcohol was added slowly, with stirring, to 10 g. (0.043 mole) of XVIII dissolved in 200 ml. of absolute alcohol. After standing 2 hr., the solution was poured into three times its volume of 5% hydrochloric acid and stirred for 1 hr. The precipitate was filtered, washed with water, and recrystallized from alcohol.

From V. A solution of 0.5 g. (0.0015 mole) of V in 30 ml. of 2% hydrochloric acid was refluxed for 30 min., cooled, and made just basic to litmus with 10% sodium hydroxide. After 1 hr. in the refrigerator at 1°, the precipitate was filtered, washed with water, and recrystallized from alcohol to give 0.21 g. (56%) of white solid; m.p. 276–278°. Mixed melting points, infrared and ultraviolet spectra showed this material to be identical with that from the preceding preparation.

2-Aryl-6-methylthiopyrazolono(3,4-d)pyrimidines (XI–XV). *General method.* A solution of 2.3 g. (0.01 mole) of XVIII in 25 ml. of absolute alcohol was added to a solution of 0.02 mole of the arylhydrazine in the minimum amount of absolute alcohol. The resulting solution was warmed at 50–60° for 30 min. and allowed to stand for 4 hr., diluted with three times its volume of water and refrigerated overnight at 1°. The precipitate was filtered, washed with water, and recrystallized from *n*-butyl alcohol.

BUFFALO 14, N. Y.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXV. Preparation of 6-Alkoxy-2-aminopurines[2]

RUDOLF W. BALSIGER AND JOHN A. MONTGOMERY

Received February 8, 1960

Some 6-alkoxy-2-aminopurines have been prepared from 2-amino-6-chloropurine.

As a part of our general program to investigate purines in search of more effective anticancer agents, a number of 6-alkoxy-2-aminopurines (I) (Table I) have been prepared. Although they are closely related to guanine(2-amino-6-purinol) (II), they cannot be prepared from this substance directly. Traube and Dudley[3] found that treatment of guanine in aqueous-alcoholic sodium hydroxide solution with iodomethane gave 7-methyl- and 1,7-dimethylguanine.

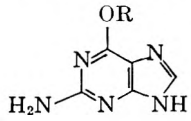
(1) Affiliated with Sloan-Kettering Institute.

(2) This work was supported by funds from the National Institutes of Health, Contract No. SA-43-ph-1740, and from the C. F. Kettering Foundation. For paper XXIV of this series see J. A. Montgomery and C. T. Temple Jr., *J. Am. Chem. Soc.*, in press.

(3) W. Traube and H. W. Dudley, *Ber.*, **46**, 3844 (1913).

TABLE I

6-ALKOXY-2-AMINOPURINES



Compound[a]	R	Solvent for Recrystallization	Yield, %	M.P.[b]	Analyses						Ultraviolet Spectra[c]							
					Carbon, %		Hydrogen, %		Nitrogen, %		pH 1		pH 7		pH 13		CH_3OH	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	mμ	(ε × 10^{-3})	mμ	(ε × 10^{-3})	mμ	(ε × 10^{-3})	mμ	(ε × 10^{-3})
Ia	CH_3—	H_2O	85	>260	43.63	43.18	4.27	4.44	42.41	42.56	286	(11.2)	240	(7.86)	246[f]	(4.49)	242	(8.73)
													280	(7.88)	284	(7.86)	282	(8.06)
Ib	C_2H_5—	H_2O	69.5	293[d,e]	46.92	46.68	5.06	5.15	39.09	38.56	286	(11.7)	240	(8.20)	246[f]	(4.07)	241	(8.83)
													280.5	(8.27)	284	(8.19)	282	(8.40)
Ic	C_3H_7—	H_2O	52	208	49.73	49.31	5.74	5.80	36.25	36.22	286	(11.5)	241	(7.96)	246[f]	(4.35)	241	(8.90)
													281	(8.40)	283	(8.31)	282	(8.66)
Id	iso-C_3H_7—	H_2O	58.5	177	49.73	49.80	5.74	5.83	36.25	35.64	286	(12.2)	240	(8.06)	246.5[f]	(3.78)	241	(8.78)
													281	(8.50)	285	(8.05)	282	(8.78)
Ie	n-C_4H_9—	H_2O/C_2H_5OH	40	175	52.16	51.90	6.32	6.24	33.80	34.38	286	(11.7)	240	7.73	246[b]	(3.79)	241	(8.86)
													281	(8.37)	285	(8.18)	282	(8.66)

[a] Compound II, R = OH; III, R = Cl; IV, R = SH. [b] Except where indicated, melting points were determined on a Kofler Heizbank. [c] Determined with a Beckman model DK-2 spectrophotometer, but the optical densities at the maxima were measured with a Beckman DU. [d] Capillary in aluminum block, not corrected. [e] Decomposition. [f] Shoulder.

The work of Huber[4] on 6-alkoxypurines suggested that 6-alkoxy-2-aminopurines (I) could be obtained readily from 2-amino-6-chloropurine (III).

The classical chlorination procedure using phosphoryl chloride has only recently been successfully applied to guanine to give III[5]; we obtained III by treating thioguanine (2-amino-6-purinethiol) (IV) in methanolic suspension with chlorine, a slight modification of a process described in a British patent.[6] This procedure permitted us to isolate the hydrochloride of III in 50–60% yield from the reaction mixture. The free base could be obtained by treating an aqueous suspension of the hydrochloride with sodium hydroxide solution.

2-Amino-6-chloropurine (III) is more resistant to hydrolysis than is 6-chloropurine[7]: The conversion to guanine (II) is complete after six hours in boiling 0.1*N* hydrochloric acid, whereas after boiling in 0.1*N* sodium hydroxide solution, more than 75% of III (by ultraviolet absorption) remained unchanged; the corresponding figures for the hydrolysis of 6-chloropurine to 6-purinol(hypoxanthine) are one hour in boiling 0.1*N* hydrochloric acid and four hours in boiling 0.1*N* sodium hydroxide.[7]

However, boiling the hydrochloride of III in methanol in the presence of a catalytic amount of water leads to the formation of 2-amino-6-methoxypurine (Ia) (identified by ultraviolet absorption spectrum).

For the preparation of 6-alkoxy-2-aminopurines (I) we treated the hydrochloride of III with a solution of a ten-fold excess of sodium alkoxide in the corresponding alcohol. After the solutions had been refluxed for eighteen hours, the compounds listed in Table I were isolated in yields ranging from 40% (Ie) to 85% (Ia) (yields of purified product). The 6-alkoxy-2-aminopurines are crystalline, white materials, soluble in alcohols and hot water; the lower members do not melt without decomposition.

(4) G. Huber, *Chem. Ber.*, 90, 698 (1957).

(5) M. H. von Saltza, Ph. D. thesis, University of Wisconsin 1958.

(6) Wellcome Foundation, Ltd., British Patent, 767,216, Jan. 30, 1957. Note Added in Proof: R. K. Robins has recently published a similar procedure for the preparation of 2-amino-6-chloropurine from 2-amino-6-methylthiopurine [*J. Am. Chem. Soc.*, 82, 2633 (1960)].

(7) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, 76, 6073 (1954).

EXPERIMENTAL

2-Amino-6-chloropurine (III) *hydrochloride.* A suspension of thioguanine (500 mg. 3.3 mmoles) in methanol (25 ml.) was cooled to 2° in an ice bath. Dry chlorine gas was bubbled through the mixture at such a rate that the temperature did not rise above 15°. As soon as the temperature began to drop, the stream of chlorine was replaced by a stream of dry nitrogen. When the clear solution was almost colorless, it was filtered and evaporated until crystallization set in. The crystals were collected, washed with ether, and dried *in vacuo* over phosphorus pentoxide; yield, 415 mg. (61%). *Spectral data:* λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 239 (6.32), 318 (6.80); *p*H 7, 242 (6.06), 308 (6.80); *p*H 13, 309 (5.82); CH_3OH, 243 (6.68), 314 (6.37).

Anal. Calcd. for $C_5H_4ClN_5 \cdot HCl$: C, 29.15; H, 2.44; Cl, 34.42; N, 33.99. Found: C, 29.22; H, 2.76; Cl, 34.26; N, 33.74.

2-Amino-6-chloropurine (III). 2-Amino-6-chloropurine hydrochloride (1.1 g., 5.3 mmoles) was suspended in 10 ml. of water; aqueous sodium hydroxide solution was added dropwise until the reaction mixture was slightly basic. The clear solution was filtered and neutralized with hydrochloric acid. The precipitate was recrystallized from aqueous ethanol, yielding 880 mg. (97%) of the free base (III). *Spectral data:* λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 238 (6.83), 316 (7.25); *p*H 7, 241 (6.23), 308 (6.96); *p*H 13, 273 (3.25), 309 (6.30); CH_3OH,2 43 (7.10), 309 (7.16).

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.41; H, 2.38; N, 41.30; Cl, 20.91. Found: C, 35.48; H, 2.58; N, 41.56; Cl, 20.51.

6-Alkoxy-2-aminopurines. 2-Amino-6-chloropurine hydrochloride (500 mg., 2.4 mmoles) was added to a solution of metallic sodium (550 mg., 24 mmoles) in the appropriate alcohol (20 ml.) and the mixture kept at reflux temperature for 18 hr. The reaction mixture was cooled to room temperature, the calculated amount of glacial acetic acid (1.2 ml. 20 mmoles) was added, and the volatile material were removed *in vacuo*. The residue was recrystallized from the solvent specified in Table I. The physical constants of the compounds and their analyses are summarized in Table I.

Acknowledgment. The authors are indebted to Mr. J. P. Holmquist and Mr. J. W. Murphy for the microanalytical results reported; to Miss V. Jackson and Mr. J. B. Hostettler for the spectral determinations; and to Mr. G. S. McCaleb for technical assistance.

BIRMINGHAM 5, ALA.

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

Synthesis of Potential Anticancer Agents. III. Nitrogen Mustards Derived from 8-Aminoquinolines[1-3]

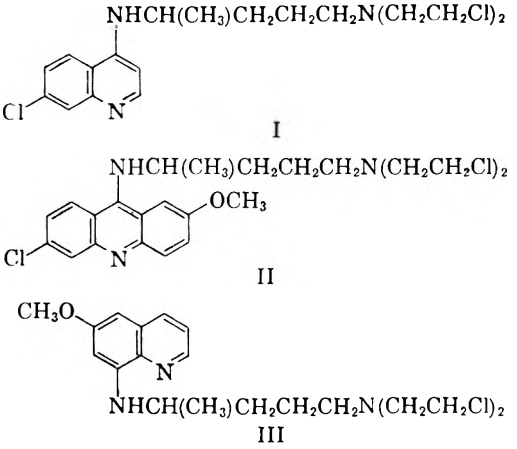
ROBERT C. ELDERFIELD AND ERNEST F. LEVON[4]

Received February 15, 1960

A series of 8-[3-bis(2-chloroethylamino)propionamido]quinolines has been prepared for evaluation as anticancer agents. 8-Amino-6-methoxyquinoline apparently cannot be reductively alkylated with acetals or aldehydes. Certain aspects of the synthesis of 8-(3-aminopropylamino)-2-methoxyquinoline have been clarified.

In recent years considerable interest has been displayed in the so-called antimalarial mustards as possible chemo-therapeutic agents in the management of neo-plastic disease. These substances may be broadly defined as embracing standard antimalarial drugs into the molecules of which an alkylating function such as the bis-2-chloroethylamino (nitrogen mustard) is incorporated. The rational underlying this approach was based on the hope that the antimalarial moiety of the molecule would act as a carrier to localize the action of the alkylating function.[5-7]

Fulton and co-workers[8] prepared the 2-anilino and 2-methyl derivatives of 4-[2-bis(2-chloroethylamino)ethyl]quinoline as candidate amebocides. The compounds showed no outstanding properties in this regard and apparently have not been examined as anticancer agents. Creech[6] has reported a derivative of 7-chloroquinoline carrying the same side-chain among several antimalarial mustards which showed appreciable activity against ascites tumors in mice. Creech also noted that antitumor activity in animals was retained in the 4-aminoquinoline mustards through various alterations in the side-chain and nuclear substitution. Jones[7,9] has reported the results of preliminary clinical trials of the nitrogen mustard analogs of chloroquine (I), quinacrine (II), and pamaquine (III), which although quite favorable were not conclusive.



In their syntheses Jones, Price, and Sen[7] were unable to obtain salts which analyzed for sufficient chlorine. Their 4-aminoquinoline and 9-aminoacridine mustards were prepared by a fundamentally different series of reactions and also gave somewhat unsatisfactory analytical data. Thus one would expect to encounter difficulty in the preparation and handling of compounds of this type.

Neeman[10] has prepared several amide analogs of the 8-amino-6-methoxyquinoline (IV) antimalarials carrying the carbonyl group in the side-chain, either at the 8-nitrogen or at the terminal end. Snyder and Freier[11] prepared several 3-dialkylaminopropionyl derivatives of IV. These as well as other acylated antimalarials had essentially no antimalarial activity.[12] Buchi[13] and Gaind and coworkers[14] have reported dialkylaminopropionyl derivatives of the other aminoquinolines as potential local anesthetics and several workers have described α-aminoacetamidoquinolines as spasmolytics or local anesthetics. The interesting point in

(1) This investigation was supported in part by Research Grant CY-2961 from the National Cancer Institute to the University of Michigan.

(2) For paper II in this series see *J. Org. Chem.*, **24**, 1410 (1959).

(3) This work is based on a dissertation submitted by Ernest F. LeVon in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(4) Dow Chemical Company Fellow, 1955-1957. U.S. P.H.S. Predoctoral Fellow, 1958.

(5) R. Jones, Jr., C. C. Price, and A. K. Sen, *J. Org. Chem.*, **22**, 783 (1957).

(6) H. J. Creech, *Ann. N. Y. Acad. Sci.*, **68**, 868 (1958).

(7) R. Jones, Jr., U. Jonsson, M. Browning, H. Lessner, C. C. Price, and A. K. Sen, *Ann. N. Y. Acad. Sci.*, **68**, 1133 (1958).

(8) J. D. Fulton, L. P. Joyner, H. King, J. M. Osbond, and J. Wright, *Proc. Roy. Soc. (London)*, B, **137**, 339 (1950).

(9) R. Jones, Jr., H. J. Creech, C. C. Price, A. K. Sen, R. M. Peck, R. F. Nankwitz, Jr., R. Rhines, D. McKenzie, and W. F. Dunning, *Proc. Am. Assoc. Cancer Research*, **2**, 132 (1956).

(10) M. Neeman, *J. Chem. Soc.*, 2525 (1955).

(11) H. R. Snyder and H. E. Freier, *J. Am. Chem. Soc.*, **68**, 2485 (1946).

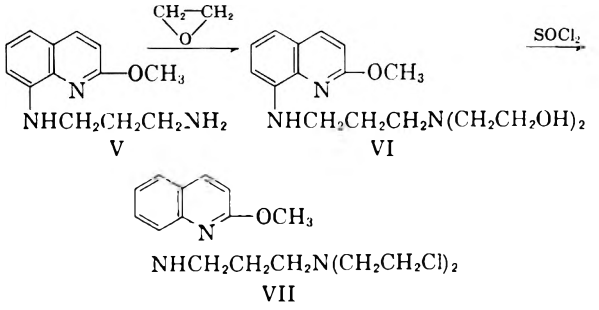
(12) *A Survey of Anti-malarial Drugs*, **1941-1945**, F. Y. Wiselogle (Editor), J. W. Edwards, Inc., Ann Arbor, Mich., 1946.

(13) J. Buchi, R. Lieberherr, and L. Ragaz, *Helv. Chim. Acta*, **34**, 1380 (1951).

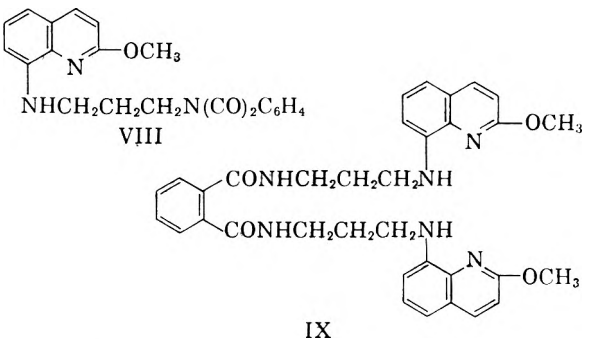
(14) K. N. Gaind, J. N. Ray, and B. Sarin, *J. Indian Chem. Soc.*, **17**, 619 (1941).

this connection is that the introduction of the amide function resulted in sharply reduced toxicity.[11] It therefore was desirable to prepare representative acylamido derivatives of 8-aminoquinolines which also carried the nitrogen mustard function. Interest in these compounds is two-fold. It was hoped that anticancer activity would be retained with lower toxicity and, secondly, that the compounds, or their precursors, might provide a better route to compounds of the type of III than that used by Jones and co-workers.[5] The first of these goals has apparently been achieved, as preliminary data with experimental animal tumors have shown a high order of activity coupled with relatively low toxicity for many of the substances.[15] Results of the approach to the second objective will be reported subsequently.

At the outset, attention was directed toward possible modifications of the Jones, Price, and Sen procedure[5] (V–VII) or alternate procedures for the preparation of anlogs of III. Initial effort was devoted to the preparation of 8-[3-bis(2-chloroethylamino)propylamino]-2-methoxyquinoline (VII) on the basis of preliminary pharmacological data on 8-(3-aminopropylamino)-2-methoxyquinoline and 8-(3-diethylaminopropylamino)-2-methoxyquinoline[16] which indicated that VII might be the compound of choice in this series.



A supply of crude 2-methoxy-8-(3-phthalimidopropylamino)quinoline (VIII) was available from other work. Fractional crystallization of this resulted in the isolation of a small amount of 8-bis(3-phthalimidopropylamino)-2-methoxyquinoline. Hydrazinolysis of VIII was accomplished by the method of Ing and Manske[17] and V was characterized as its dibenzenesulfonyl derivative. As a side-product in the hydrazinolysis a small amount of what is believed to be phthalobis[3-(2-methoxy-8-quinolylamino)propyl]amide (IX) analogous to the 6-methoxy derivative reported by Barber and Wragg[18] from a similar reaction. IX showed carbonyl absorption in the infrared at 1665 cm.$^{-1}$ similar to that of phthalamide and phthalhydrazide and a strong band at about 1522 cm.$^{-1}$ which probably corresponds to the band at 1538 cm.$^{-1}$ in VIII. Conversion of IX to a benzenesulfonyl derivative eliminated the band at 1522 cm.$^{-1}$ and regenerated carbonyl bands at 1705 and 1768 cm.$^{-1}$ typical of phthalimides. Barber and Wragg[18] noted that the 6-methoxy analog of IX regenerated the phthalimide corresponding to VIII by elimination of a molecule of primary amine. In view



of the difficulty encountered in handling V and its derivatives attention was shifted to 8-amino-6-methoxyquinoline (IV).

Mild conditions of hydroxyethylation of primaquine[6-methoxy-8-(4-amino-1-methylbutylamino)-quinoline] gave no isolatable products and in one instance resulted in no reaction. The forcing conditions used by Jones[5] were not employed because of the danger of alkylating the secondary 8-amino group as well as the terminal primary amine. Reductive alkylation offered an alternative means of introducing the side-chain as a preformed moiety. This has been accomplished by various workers from 8-aminoquinolines and ketals[19–22] or enol ethers derived from ketals.[23] 1-Bis(2-hydroxyethylamino)-4-pentanone[6] failed to yield the ketal under conditions which are successful with 1-diethylamino-4-pentanone. When 3-chloropropionaldehyde diethyl acetal was allowed to react with diethanolamine, the expected 3-diethanolaminopropionaldehyde acetal was obtained in good yield. However, attempted condensation of this acetal and IV failed. The mixtures obtained when the reaction was carried out in the presence of various acidic catalysts did not absorb catalytically activated hydrogen under conditions which are successful with ketals and infrared spectra, indicated only the recovery of starting materials. When the reaction of IV with butyraldehyde was

(15) Private communication from Dr. Ralph Jones, Jr., Jackson Memorial Hospital, University of Miami, Miami, Florida.

(16) H. B. Hughes and L. H. Schmidt, *Proc. Soc. Exp. Biol. Med.*, **73**, 581 (1950).

(17) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

(18) H. J. Barber and W. R. Wragg, *J. Chem. Soc.*, 1331 (1947).

(19) R. C. Elderfield, W. R. Vaughan, B. B. Millward, and J. H. Ross, *J. Org. Chem.*, **23**, 1378 (1958).

(20) H. J. Barber, D. H. O. John and W. R. Wragg, *J. Am. Chem. Soc.*, **70**, 2282 (1948).

(21) S. Tatsuoka, J. Ueyanagi, and T. Kinoshita, *J. Pharm. Soc. Japan*, **69**, 33 (1949).

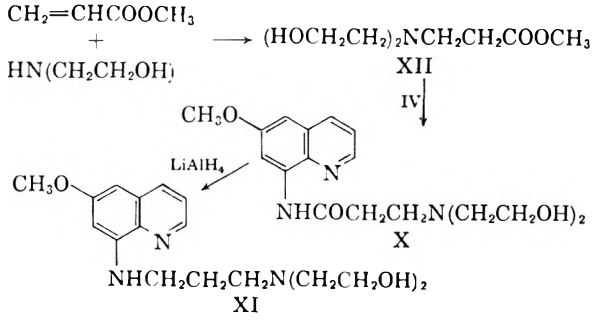
(22) K. S. Topchiev and M. B. Braude, *Compt. rend. acad. sci., U.R.S.S.*, **52**, 593 (1946).

(23) D. Shiho, *J. Chem. Soc. Japan*, **65**, 135 (1944).

attempted, it occurred readily even in the absence of acidic catalysts. However, the product did not undergo catalytic reduction (as judged by hydrogen absorption) and no pure products could be isolated. We therefore conclude that preparation of aminoalkyl derivatives of IV cannot readily be accomplished by reductive alkylation with acetals or aldehydes.

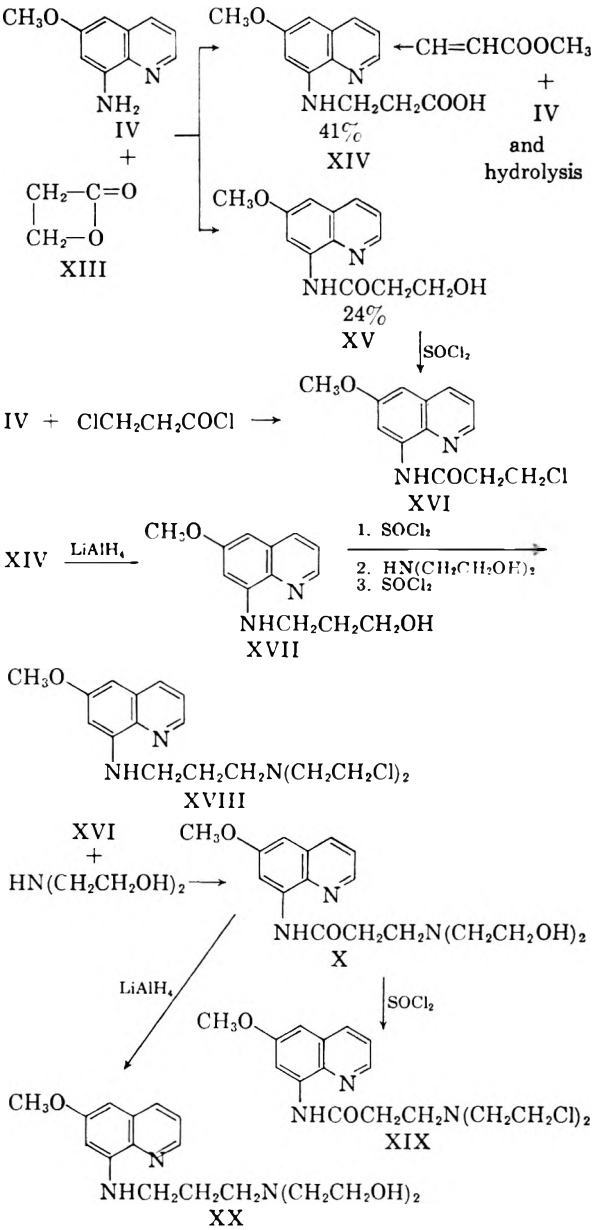
The Leuckart method for reductive alkylation with formic acid as the reducing agent was also investigated with butyraldehyde and IV. The only pure product isolated was the previously known formyl derivative of IV. Tomita[24] has reported that only low yields of pamaquine result from a modification of the Leuckart reaction under rather severe conditions.

Elderfield and co-workers[25] have suggested that alkyl derivatives of IV might be obtained by acylation of IV followed by reduction of the amide with lithium aluminum hydride. However, this approach was carried only through the acylation step and the proposed reduction was never carried out. It was hoped that aminolysis of a suitably substituted ester by IV would give a mustard diol carrying an amide function such as X which could be reduced to XI with lithium aluminum hydride. Addition of diethanolamine to methyl acrylate appeared to form methyl 3-bis(2-hydroxyethylamino)propionate (XII) very smoothly. Although XII dissociated on attempted distillation at 0.4–0.8 mm., it might have been useful as a crude product. Similar instability has also been reported for the adduct of diethanolamine and acrylonitrile.[26] Hydrolysis of crude XII gave 3-bis(2-hydroxyethylamino)-propionic acid which was also prepared from diethanolamine and propiolactone.[27] Because of the



instability of XII, exploratory attempts to acylate IV with ethyl butyrate were made. Several attempts under a variety of conditions gave no recognizable sign of the formation of the butyryl derivatives of IV. We therefore conclude that ester aminolysis with IV does not proceed readily.

Propiolactone (XIII) reacts with aromatic amines to give β-alanines and hydracrylamides.[27–29] The ratio of the products apparently varies with the amine and the conditions of the reaction. Reaction of IV with XIII in boiling benzene gave a mixture from which was isolated 41% of *N*-(6-methoxy-8-quinolyl)-β-alanine (XIV) and 24% of 6-methoxy-8-hydracrylamidoquinoline (XV). The reaction was very slow in boiling ether. The β-alanine (XIV) was identical with the product obtained by hydrolysis of the crude adduct of IV and methyl acrylate. Chlorination of XV with



(24) M. Tomita, S. Uyeo, H. Otaya, H. Maekawa, M. Fukuda, S. Echigo, S. Mizukami, and T. Matsui, *J. Pharm. Soc. Japan*, **71**, 829 (1951).

(25) R. C. Elderfield *et al.*, *J. Am. Chem. Soc.*, **77**, 4819 (1955).

(26) H. A. Bruson, *Org. Reactions*, 80 (1949).

(27) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorek, *J. Am. Chem. Soc.*, **73**, 3168 (1951).

(28) T. L. Gresham and F. W. Shaver, U. S. pat. 2,568,621 (1951).

(29) C. D. Hurd and S. Hayao, *J. Am. Chem. Soc.*, **74**, 5889 (1952); **76**, 5562 (1954).

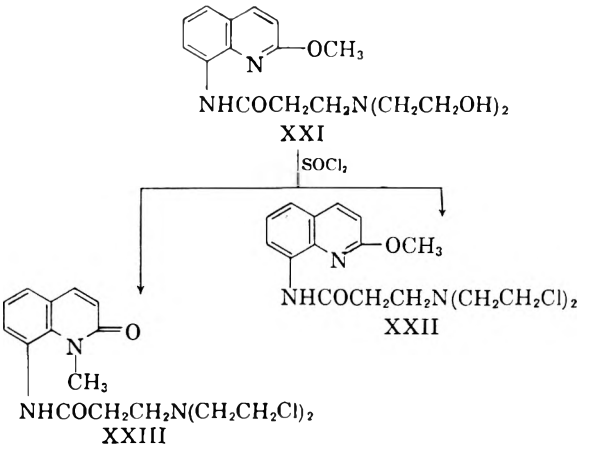
thionyl chloride gave 8-(3-chloropropionylamido)-quinoline which was identical with the product of the reaction of IV with 3-chloropropionyl chloride. When the reaction of IV with XIII was carried out in hot toluene or xylene substantial amounts of polymeric material resulted. However, XIV and XV were formed but in lower yields than was the case when the reaction was carried out in benzene.

The β-alanine (XIV) was reduced by lithium aluminum hydride in ether to give 8-(3-hydroxypropylamino)-6-methoxyquinoline (XVII) identical to the substance previously prepared by an alternate route.[30,31] This may possibly serve as an intermediate in the synthesis of the mustard derived from plasmocid (XVIII).

Reaction of XVI with two moles of diethanolamine gave up to 95% of the dihydrochloride of XIX which was in turn converted by thionyl chloride into 8-[3-bis(2-chloroethylamino)propionylamido]-6-methoxyquinoline (XX) an amide mustard analog of XVIII. Reduction of XIX with lithium aluminum hydride in tetrahydrofuran gave the mustard diol (XXI), which should be the ideal precursor to the plasmocid mustard (XVIII). Isolation and purification of XX as the dihydrochloride was easily accomplished in yields as high as 80% based on the amount of IV taken.

Contrary to the smooth reaction which we have noted between XVI and diethanolamine, Bergmann and Schapiro[32] report that reaction of XVI with diethylamine results in dehydrochlorination and that the crude product gives 8-(acrylamido)-6-methoxyquinoline on distillation. On the other hand, Gaind, Ray, and Sarin[15] found that 8-(3-chloropropionylamido)quinoline reacted with diethylamine without dehydrochlorination in the presence of sodium carbonate. They did not, however, distill the product, but isolated it as the picrate. Snyder and Freier[12] obtained Bergmann's acrylamide from IV and acrylolyl chloride and succeeded in adding diethylamine smoothly to the vinyl linkage. Again, the product was not distilled but isolated as the salt. Thus it is probable that Bergmann and Schapiro actually had 8-(3-diethylaminopropionylamido)-6-methoxyquinoline in hand but that this lost diethylamine on distillation.

In view of the encouraging results of preliminary screening data for XX against animal tumors,[15] the series was extended to include derivatives of 5,6-dimethoxyquinoline, 6-methoxylepidine, and 2-methoxyquinoline analogous to XVI, XIX, and XX. These all proceeded smoothly with the exception of the conversion of the mustard diol (XXI) derived from 2-methoxquinoline to the mustard (XXII). When XXI was treated with thionyl chloride in chloroform, two main products were isolated as the hydrochlorides. Recrystallization of the higher melting fraction gave a product which melted sharply at about 200° and furnished analytical data in substantial agreement with those



demanded by XXII. However, the infrared spectrum showed two carbonyl bands at 1705 and 1670 cm.$^{-1}$ and methoxyl analyses indicated the absence of the 2-methoxyl function. Sheinker and Pomerantsev[33] report infrared absorption in the carbonyl region at 1650 and 1655 cm.$^{-1}$ for carbostyril and 1-methyl-2-quinolone respectively. 1-Methyl-8-nitro-2-quinolone absorbs at about 1665 cm.$^{-1}$. Therefore the mustard melting at 200° is probably the isomeric 1-methyl-2-quinolone (XXIII). The first carbonyl absorption (1705 cm.$^{-1}$) is probably due to the side chain amide and the other (1670 cm.$^{-1}$) to the 2-quinolone. Other amides prepared in the course of this work showed carbonyl absorptions from 1660 to 1700 cm.$^{-1}$ However, none having the 1-methyl-2-quinolone structure were available. Recrystallization of the second hydrochloride gave the salt of XXII. This showed the presence of the methoxyl group on analysis and showed only one carbonyl band in the infrared at 1680 cm.$^{-1}$. On the other hand reaction of the hydrochloride of XXI with thionyl chloride gave XXII smoothly.

Details as to the physiological properties of these compounds will be reported elsewhere.

EXPERIMENTAL[34-36]

2-Methoxy-8-(3-phthalimidopropylamino)quinoline (VIII) *and 2-methoxy-8-bis(3-phthalimidopropylamino)quinoline.* The

(30) J. Crum and R. Robinson, *J. Chem. Soc.*, 561 (1943).

(31) W. H. Yanko, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, 67, 664 (1945).

(32) F. Bergmann and D. Schapiro, *J. Org. Chem.*, 7, 419 (1942).

(33) Y. N. Sheinker and Y. I. Pomerantsev, *Zhur. Fiz. Khim.*, 30, 79 (1956).

(34) All melting points and boiling points are uncorrected unless noted otherwise.

(35) Infrared spectra were taken as nujol mulls on a Perkin-Elmer double beam recording spectrophotometer, Model 21.

(36) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan, Mrs. Anna Griffin of the University of Michigan, Drs. Weiler and Strauss, Oxford, England, or Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

crude phthalimide[37] prepared from 8-amino-2-methoxyquinoline[38] and 3-phthalimidopropyl bromide according to the general procedure of Baldwin,[39] was separated by repeated recrystallization from benzene or acetone-alcohol into pure VIII, m.p. 113–114.5° and a small amount of the bisphthalimidopropylamino compound, m.p. 137–138°. Melting point previously reported for VIII is 112–114.5°.[37] The disubstituted material was analyzed.

Anal. Calcd. for $C_{32}H_{28}N_4O_5$: C, 70.06; H, 5.14. Found: C, 70.13; H, 4.96.

The infrared spectra were complementary with respect to the absence of a strong band at 1538 cm.$^{-1}$ in the spectrum of the 2-methoxy-8-bis(3-phthalimidopropylamino)-quinoline which was present in the spectrum of VIII. This band was probably due to the 8-nitrogen-hydrogen bond. The carbonyl bands were at 1715 and 1765 cm.$^{-1}$ in the monosubstituted compound and at 1705 and 1760 cm.$^{-1}$ in the other. VIII also showed an N—H band at about 3380 cm.$^{-1}$

Hydrazinolysis of VIII. 8-(3-Aminopropylamino)-2-methoxyquinoline has been the subject of pharmacological study[16] but its chemistry has not been recorded.[37] Pure VIII (25.0 g.) was suspended in 250 ml. of ethanol, hydrazine hydrate (3.8 g.) was added, and the mixture was refluxed gently for 3.5 hr. After cooling in the refrigerator, the nearly solid cake was filtered, washed, and dried to give 24.2 g. (89%) of the intermediate phthalhydrazide salt, m.p. 185–195°, of 8-(3-aminopropylamino)-2-methoxyquinoline; reported[37] m.p. 178.5–181°. In another run the intermediate was recrystallized from a large volume of alcohol without appreciably altering its melting point. The recrystallized material was suspended in water, made basic with *N* sodium hydroxide, and extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and acidified by dropwise addition of an alcoholic solution of hydrogen chloride. The hydrochloride of V (11.6 g.) melted at 156–159° dec., solidified and remelted at 245–251°. This salt has been reported as melting at 240–245° after sintering at 140–144°.[37]

In another run, the reaction mixture was acidified while still hot with 6*N* hydrochloric acid and the phthalhydrazide was filtered. However, when the hydrochloride of V was allowed to crystallize directly from the filtrate, it still contained up to 11% of phthalhydrazide. In view of this and the susceptibility of the 2-methoxyl group to acid, this method of working up the reaction mixture was abandoned.

When 250 ml. of absolute alcohol was substituted for 95% alcohol in the above hydrazinolysis, some difficulty with bumping caused by separated solid was encountered. After refluxing for 3 hr. most of the alcohol was distilled, the residue was mixed with excess sodium hydroxide solution and the free amine (V) was extracted with ether. After washing with water, the combined ethereal extracts were dried over anhydrous potassium carbonate. Acidification of the basic aqueous solution from the ether extraction gave 9.2 g. (82%) of phthalhydrazide, m.p. 343–344° dec. During the drying of the ether extracts, a colorless precipitate separated and was filtered off with the potassium carbonate. Acidification of the ether filtrate with 2*N* alcoholic hydrogen chloride (prepared from concd. aqueous hydrochloric acid) gave 15.6 g. of the hydrochloride of V, m.p. 159–160° dec., solidifying and remelting at 248–254°. The carbonate residue from the ether filtrate was washed with water leaving 2.1 g. of insoluble base, m.p. 147–150°. After six recrystallizations from ethanol it melted at 148–152°.

Anal. Calcd. for $C_{34}H_{36}N_6O_4$: C, 68.90; H, 6.12; N, 14.18. Found: C, 68.64; H, 5.92; N, 14.02.

A hydrochloride which decomposed before it could be analyzed darkened at about 174° and melted at 176–177.5° dec. On the basis of comparative infrared data[40] and by analogy with the corresponding derivative of 8-amino-6-methoxyquinoline[18] this compound is assigned the structure of phthalobis[3-(2-methoxy-8-quinolylamino)propyl]amide (IX).

The hydrochlorides of 8-(3-aminopropylamino)-2-methoxyquinoline. The double-melting hydrochloride continued to decompose at about 160° and remelt at about 250° dec. after recrystallization from alcohol even in the presence of excess acid. The lower melting point was eliminated on heating at 95° for 48 hr. during which a strong carbonyl band appeared in the infrared at 1660 cm.$^{-1}$ Titration with silver nitrate indicated an equivalent weight of about 190 (18.7, 18.8% Cl) which corresponds to 1.5 equivalents of hydrogen chloride per molecule of quinoline. It has been frequently observed that derivatives of 8-aminoquinoline do not react with stoichiometric amounts of acid.[41] We interpret this behavior as indicating that the original 2-methoxyquinoline derivative (V) rearranges to the *N*-methylquinolone under the influence of heat.

The unrearranged hydrochloride was also titrated against silver nitrate after only brief heating.

Anal. Calcd. for $C_{13}H_{17}NO_3 \cdot HCl$: Cl, 13.24; for $C_{13}H_{17}NO_3 \cdot 1.5\,HCl$: Cl, 18.60; for $C_{13}H_{17}NO_3 \cdot 2HCl$: Cl, 23.30; for $C_{13}H_{17}N_3O \cdot 2HCl \cdot 2H_2O$: Cl, 20.84; for $C_{13}H_{17}NO_3 \cdot 2HCl \cdot C_2H_5OH$: Cl, 20.24. Found: 20.5.

A monohydrochloride was obtained as a hygroscopic tan powder, m.p. 188–194°, when the free base was acidified with the calculated amount of alcoholic hydrogen chloride (based on the original hydrochloride as $C_{13}H_{17}N_3O \cdot 2HCl \cdot 2H_2O$).

Anal. Found: Cl, 13.0.

The monophosphate of 8-(3-aminopropylamino)-2-methoxyquinoline. When an aliquot of the free base in ether was acidified with an equivalent of alcoholic phosphoric acid a monophosphate, m.p. 240–250° with sintering at about 180°, was obtained in 97% yield. Recrystallization from ethanol changed the melting point to 206–225°.

Anal. Calcd. for $C_{13}H_{17}N_3O \cdot H_3PO_4$: C, 47.42; H, 6.08; N, 9.42. Found: C, 48.09; H, 6.40; N, 9.56.

The hydrochloride of V was treated with benzenesulfonyl chloride in aqueous sodium hydroxide. After several recrystallizations from ethanol the bissulfonamide melted at 146–148°.

Anal. Calcd. for $C_{26}H_{25}N_3O_5S_2$: C, 58.69; H, 4.93; N, 8.22; S, 12.53. Found: C, 58.79; H, 5.02; N, 8.01; S, 12.25.

3-(2,2-Dihydroxyethylamino)propionaldehyde diethyl acetal. A solution of 12.5 g. of diethanolamine and 10 g. of 2-chloropropionaldehyde diethyl acetal in 25 ml. of absolute ethanol was refluxed for 21 hr. After removal of volatile material at the water pump, the residue was dissolved in 10 ml. of water and extracted with four 25-ml. portions of chloroform. After drying the combined chloroform extracts over anhydrous potassium carbonate, the residue after removal of the solvent was distilled under reduced pressure to give 53% of an oil, b.p. 130–133° (0.5 mm.), n_D^{25} 1.457. Titration with hydrochloric acid to a methyl red end point gave a neutral equivalent of 232, calcd. 235.3. No solid derivative could be prepared.

Anal. Calcd. for $C_{11}H_{25}NO_4$: C, 56.14; H, 10.71; N, 5.95. Found: C, 56.38; H, 10.87; N, 6.11.

Reaction of propiolactone with 8-amino-6-methoxyquinoline. A. *In ether.* To a solution of 12.1 g. of IV in 100 ml. of ether cooled to 5°, 5 g. of propiolactone was slowly added. There was no evidence of a spontaneous reaction and the mixture was allowed to stand overnight. Addition of a solution of 2 g. of sodium hydroxide in 30 ml. of water caused a moderately vigorous reaction (hydrolysis of unchanged lactone). The ether layer was separated, washed with water, and dried.

(37) R. C. Elderfield and H. E. Mertel, unpublished work.

(38) K. Mislow and J. B. Koepfli, *J. Am. Chem. Soc.*, **68**, 1553 (1946).

(39) A. W. Baldwin, *J. Chem. Soc.*, 2959 (1929).

(40) See ref. (3) for details.

(41) R. C. Elderfield, *et al.*, *J. Am. Chem. Soc.*, **68**, 1524 (1946).

Evaporation of the ether left 12 g. of fairly pure unchanged IV. Neutralization of the basic solution with 5 ml. of concd. hydrochloric acid gave 0.25 g. (1.5%) of *N*-(6-methoxy-8-quinolyl)-β-alanine (XIV), m.p. 142–144° after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.33; H, 5.72; N, 11.35.

When the reaction mixture was refluxed for 45 hr., the yield of XIV was 15%.

B. *In benzene.* To a solution of 92 g. of IV in 600 ml. of warm benzene 39 g. of propiolactone was added. After refluxing for 70 hr. the cooled solution was extracted with an aqueous solution of 22 g. of sodium hydroxide. The aqueous solution was extracted with five 50-ml. portions of benzene. Concentration of the combined benzene solution and extracts left 45 g. of dark viscous oil. Crystallization from 100 ml. of benzene with charcoal gave 10.7 g. (8.2%) of 6-methoxy-8-hydracrylamidoquinoline (XV), m.p. 97.5–98.5°. The mother liquors contained further amounts of XV along with unchanged IV.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.39; H, 5.74; N, 11.51.

The hydrochloride of XV melted at 179–184° dec. after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{13}H_{14}N_2O_3 \cdot HCl$: N, 9.91. Found: N, 9.86.

When the reaction was run in refluxing xylene, it darkened rapidly in 5–10 min. Therefore it was allowed to stand overnight at room temperature during which a dark precipitate appeared. Addition of aqueous sodium hydroxide dissolved the precipitate and the mixture was continuously extracted with benzene for 24 hr. From the extracts 6% of XV was obtained. Careful acidification of the aqueous layer gave 34% of XIV along with a lump of black tar which was picked out manually.

When the reaction was run in toluene by gradually raising the temperature to 105° over 90 min., 13% of XV and 30% of XIV were obtained.

8-(3-Hydroxypropylamino)-6-methoxyquinoline (XVII). Absolute ether (200 ml.) containing a few mg. of lithium aluminum hydride was placed in a flask connected to a Soxhlet extractor and a condenser protected by a calcium chloride tube. After standing for a few minutes to insure dryness, 2.0 g. of hydride was added to the ether and 5 g. of XIV was placed in the thimble which was then filled with sand. Additional ether was added from time to time to maintain the volume. After a few days all the XIV had been extracted and the Soxhlet was replaced by a reflux condenser protected by a calcium chloride tube. After refluxing for 13 days, excess hydride was decomposed by successive addition of ethyl acetate and water. After filtering, the ether layer was separated, washed with water until neutral, and dried over anhydrous sodium carbonate. Cautious acidification of the aqueous solution gave no unchanged XIV. To the dried ether solution 50 ml. of absolute ethanol was added followed by 25 ml. of 1.5*N* alcoholic hydrogen chloride. The hydrochloride of XVII crystallized as clumps of orange needles, m.p. 170–177° dec. in 60% yield. After recrystallization from absolute ethanol and dry ether containing a little hydrogen chloride it melted at 178–180° dec. with preliminary sintering. Reported melting point for material prepared by another method is 178°[30] and 171–172°.[31]

Anal. Calcd. for $C_{13}H_{16}N_2O_2 \cdot HCl$: C, 58.10; H, 6.38; Cl, 13.19. Found: C, 58.08; H, 6.24; Cl, 13.00.

6-Methoxy-8-(3-chloropropionamido)quinoline (XVI). A. *From 6-methoxy-8-hydracrylamidoquinoline.* To a solution of 5.0 g. of XV in 50 ml. of chloroform dried over calcium chloride in a flask equipped with a dropping funnel, stirrer, and condenser, a solution of 3 ml. of pure thionyl chloride in 50 ml. of dry chloroform was added with stirring during 30 min. while the temperature was held at 10°. After standing 15 min. at room temperature the mixture was refluxed for 1 hr. After cooling 13 g. of anhydrous sodium carbonate was added and, after stirring for a few minutes, water was added cautiously. The chloroform layer was separated, filtered, and concentrated to give 5.7 g. of residue. Recrystallization from 2-propanol gave 86% of colorless needles, m.p. 104–105°; reported[32] m.p. 104°.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_2$: C, 58.98; H, 4.95; N, 10.58; Cl, 13.40. Found: C, 59.01; H, 4.93; N, 10.62; Cl, 13.02.

B. *From 8-amino-6-methoxyquinoline.* To a cooled solution of 10.0 g. of IV in 50 ml. of chloroform, previously dried over calcium chloride, and 5 ml. of pyridine 6 ml. of 3-chloropropionyl chloride was added gradually during 20 min. during which the temperature was maintained at 5–15°. After allowing the mixture to come to room temperature, a cold solution of 15 g. of potassium carbonate in 50 ml. of water was added with good stirring and cooling. The chloroform layer was separated and the aqueous layer was extracted with fresh chloroform. Concentration of the washed and dried chloroform solution gave 12.7 g. (84%) of XVI, m.p. 104.5–105.5° after recrystallization from 2-propanol.

8-[3-Bis(2-hydroxyethylamino)propionamido]-6-methoxyquinoline (X). To a solution of 8.0 g. of redistilled diethanolamine in 100 ml. of absolute ethanol was added 10.0 g. of XVI and the mixture was refluxed for 48 hr. After removal of the alcohol under reduced pressure, the residue was taken up in chloroform and the solution was washed with water until the wash water was neutral. After drying over anhydrous sodium carbonate, removal of the solvent left 16 g. of pale yellow viscous material which was perfectly satisfactory for the preparation of the mustard, XIX. For characterization the crude product was converted to the hydrochloride by solution in 150 ml. of absolute ethanol at 65° and acidification with 80 ml. of 1.5 *N* alcoholic hydrogen chloride. A copious precipitate (95%) of fine yellow needles formed which was collected and washed with absolute ethanol. It was recrystallized from methanol-ether. Physical constants and analytical data for this and related compounds are given in Table I.

The picrate, prepared in benzene and recrystallized from methanol, melted at 169–171°.

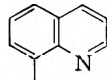
Anal. Calcd. for $C_{23}H_{26}N_6O_{11}$: C, 49.11; H, 4.66; N, 14.94. Found: C, 49.07; H, 4.54; N, 14.99.

8-[3-Bis(2-chloroethylamino)propionamido]-6-methoxyquinoline (XIX). Crude X prepared from 40 g. of XVI was cooled in an ice bath and 30 ml. of ice-cold purified thionyl chloride was added all at once. The flask was closed with a calcium chloride tube and kept in the ice bath for an hour with occasional swirling during which most of the diol dissolved. The mixture was allowed to come to room temperature overnight and concentrated under reduced pressure. The residue was warmed in 130 ml. of absolute ethanol and 20 ml. of 1.5*N* alcoholic hydrogen chloride was added during which the hydrochloride of XIX crystallized. After standing overnight the bright yellow granular crystals were collected and recrystallized by solution in 100 ml. of methanol and 20 ml. of 1.5*N* alcoholic hydrogen chloride, filtration and dilution with 100 ml. of absolute ether. The melting point varied somewhat with the rate of heating.

8-[3-Bis(2-chloroethylamino)propionamido]-5,6-dimethoxyquinoline. The chloroamide and diol were prepared from 5,6-dimethoxy-8-aminoquinoline[19] as in the preceding instance. Dry 8-[3-bis(2-hydroxyethylamino)propionamido]-5,6-dimethoxyquinoline hydrochloride (8.0 g.) was moistened with chloroform previously dried over calcium chloride and chilled in an ice-salt bath in a flask protected with a calcium chloride tube. To the mixture 16 ml. of purified thionyl chloride was added in one portion with swirling and cooling. The hydrochloride dissolved to give an orange solution in 5–10 min. The mixture was kept in the ice bath for 40 min. and then at room temperature for an hour after which the chloroform and excess thionyl chloride were removed under reduced pressure at 40°. The residue was crystallized from 80 ml. of absolute ethanol and 100 ml. of absolute ether. The very hygroscopic dihydrochloride was recrystallized from ethanol-ether in the presence of excess hydrogen chlo-

TABLE I

DERIVATIVES OF 8-AMINOQUINOLINE



NHCOCH$_2$CH$_2$R

R	Nuclear Substituent(s)	M.P. °	Yield, %	Analyses							
				Calcd.				Found			
				C	H	N	Cl	C	H	N	Cl
Cl	6-OCH_3	104.5–105.5	84	58.98	4.95	10.58	13.40	59.01	4.93	10.62	13.02
$N(CH_2CH_2OH)_2$[a]	6-OCH_3	175–178 (dec.)	95	50.25	6.20	10.34	17.45	50.24	6.28	10.14	17.31
$N(CH_2CH_2Cl)_2$[a]	6-OCH_3	184–187 (dec.)	80	46.07	5.23	9.48	32.00	46.16	5.40	9.58	31.84
Cl	5-OCH_3, 6-OCH_3	119–120	86	57.05	5.13	9.51	12.03	57.02	5.32	9.48	12.11
$N(CH_2CH_2OH)_2$[b]	5-OCH_3, 6-OCH_3	143–144	83	48.65	4.76	14.18		48.68	4.97	14.20	
$N(CH_2CH_2Cl)_2$[a]	5-OCH_3, 6-OCH_3	173–177	82	45.68	5.32	8.88	29.97	45.45	5.61	8.72	29.81
Cl	4-CH_3, 6-OCH_3	157.5–159	73	60.32	5.42	10.05	12.72	60.60	5.71	9.97	12.93
$N(CH_2CH_2OH)_2$	4-CH_3, 6-OCH_3	127.5–128.5	79	62.23	7.25	12.10		62.31	7.24	12.32	
$N(CH_2CH_2Cl)_2$[a]	4-CH_3, 6-OCH_3	176–178; 207–220[c]	83	47.28	5.51	9.19	31.02	47.28	5.57	9.24	31.24
Cl	2-OCH_3	113–114	83	58.98	4.95	10.58	13.40	59.13	4.88	10.89	13.39
$N(CH_2CH_2OH)_2$[d]	2-OCH_3	184.5–186 (dec.)	78	55.20	6.54	11.36	9.58	55.40	6.59	11.10	9.54
$N(CH_2CH_2Cl)_2$[d]	2-OCH_3	163–163.5 (dec.)	54	50.20	5.45	10.33	26.15	50.13	5.46	10.38	26.27[e]

[a] Isolated and analyzed as the dihydrochloride. [b] Isolated and analyzed as the picrate. The hydrochloride was amorphous. [c] Double melting point. [d] Isolated and analyzed as the monohydrochloride. [e] Calcd. CH_3O, 7.63. Found: 7.67.

ride. It showed a double melting point in an evacuated capillary, decomposing at about 106–107°, resolidifying and melting again at 183–177° dec.

8-[3-Bis(2-chloroethylamino)propionamido]-6-methoxylepidine. The chloropropionamide was prepared as in the above cases from 8-amino-6-methoxylepidine.[42] A solution of 15 g. of the chloropropionamide and 11.3 g. of redistilled diethanol amine in 225 ml. of absolute ethanol was refluxed for 40 hr. and concentrated to dryness. The residue was dissolved in chloroform and washed free of diethanolamine hydrochloride with water. After drying over anhydrous carbonate, the residue was crystallized from 150 ml. of absolute ethanol to give the diol as large prisms. The mustard was prepared in chloroform solution as described above. The dihydrochloride was recrystallized from methanol-ether with excess hydrogen chloride and showed a double melting point, decomposing at 178°, resolidifying as large plates, and melting again at 207–220° dec. in an evacuated capillary.

8-[3-Bis(2-chloroethylamino)propionamido]-2-methoxyquinoline (XXII) *and 8-[3-bis(2-chloroethylamino)propionamido]-1-methyl-2-quinolone* (XXIII). The chloropropionamide was prepared from 8-amino-2-methoxyquinoline as described above. The diol (XXI) was obtained as the monohydrochloride from methanol-ether with a slight excess of hydrogen chloride.

Direct treatment of the crude free base (XXI) with thionyl chloride gave no characterizable product. A solution of 2.0 g. of the monohydrochloride of XXI in water was made alkaline with sodium hydroxide and extracted with alcohol free chloroform. After drying the extract over anhydrous potassium carbonate, a solution of 10 ml. of redistilled thionyl chloride in 20 ml. of alcohol-free chloroform was gradually added. The mixture was protected by a calcium chloride tube. An oily precipitate that did not crystallize formed. Excess thionyl chloride was decomposed by addition of 10 ml. of methanol during which the oil solidified. It was too hygroscopic to collect on a filter satisfactorily. The tacky mass was dried in a desiccator to give a hard hygroscopic mass. Recrystallization from 2-propanol with excess alcoholic hydrogen chloride gave 112 mg. of material, m.p. 200–201.5° dec. The major portion of the product was recovered by concentrating the original chloroform-methanol filtrate and recrystallizing the residue from methanol-ether. This gave two slightly pink crops of 0.5 g. (46%) each. The first sintered from 180° and melted at 182–183° and the second melted at 163–164° dec. Recrystallization of the first fraction from methanol-ether gave material, m.p. 199.5–201.5° dec., which showed carbonyl absorption in the infrared at 1670 and 1705 cm.$^{-1}$ As no methoxyl was present on analysis, this is the *N*-methyl-2-quinolone (XXIII). Analytical data eliminate the carbostyril from consideration.

Anal. Calcd. for $C_{17}H_{21}Cl_2N_3O\cdot HCl$: C, 50.20; H, 5.45; N, 10.33; Cl, 26.15. Calcd. for $C_{16}H_{19}Cl_2N_3O_2\cdot HCl$: C, 48.93; H, 5.13; N, 10.70; Cl, 27.09. Found: C, 50.24; H, 4.99; N, 10.45; Cl, 25.95.

The second crop of crystalline material showed only a single carbonyl band in the infrared at 1680 cm.$^{-1}$ Recrystallization from methanol-ether left the melting point substantially unchanged. This was the monohydrochloride of the desired mustard (XXII).

When the hydrochloride of XXI was treated with thionyl chloride in chloroform as in the above examples, the hydrochloride of XXII was obtained in 54% yield with none of the quinolone being isolated.

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(42) K. N. Campbell, *et al.*, *J. Am. Chem. Soc.*, 69, 1465 (1947).

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

Synthesis of Potential Anticancer Agents. IV. Synthesis of Certain Substituted Amino- and Aziridinopyrimidines[1,2]

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Received March 7, 1960

Candidate cytotoxic agents have been prepared by condensation of 2,4-dichloro-6-methyl-5-nitropyrimidine with various cyclic amines. The relative activating influence of a nitro, chloro, and bromo substituent in the 5-position of 2,4-dichloro-6-methylpyrimidine toward nucleophilic displacement of the chlorines has been studied.

Since 1946, when Gilman and Philips[4] reported the cytotoxic activity of bis-β,β'-dichloroethylmethylamine (nitrogen mustard), a number of cytotoxic substances containing the bis-β,β'-dichloroethylamine functions have been reported.[5] Most of these, except for some derivatives of amino acids[6–8] and sugars[9] are derivatives of parent compounds which are not of natural occurrence. Curiously, attention to the biologically important purines and pyrimidines has been largely directed to the preparation of analogs of them as possible antimetabolites and, until comparatively recently, few reports of incorporation of alkylating functions such as the bis-β,β'-dichloroethylamino or aziridino groups into these parent molecules have appeared. The rationale underlying the present work, a portion of which is presented,

(1) This investigation was supported by Research Grant CY-2961 from the National Cancer Institute to the University of Michigan.

(2) For paper III in this series see *J. Org. Chem.*, 25, 1576 (1960).

(3) On leave of absence from the Chemistry Department, B. N. College, Patna University, India.

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(5) See *Comparative Clinical and Biological Effects of Alkylating Agents*, Annals of the New York Academy of Sciences, Vol. 68, Art. 3 (April 24, 1958) for an exhaustive review.

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(9) L. Varga, O. Feher, and S. Lendvai, *Acta Chim. Acad. Sci. Hung.*, 19, 308 (1959) and earlier papers.

therefore, is based on the concept that incorporation of such functions into a pyrimidine or purine might provide cytotoxic agents capable of acting in a dual capacity—as antimetabolites and as alkylating agents. Prior to the present investigation cytotoxic activity had been reported for 6-methyl-5-bis(β,β'-dichloroethylamino)-uracil[10] and during the course of this work similar activity was reported for 5-bis(β,β'-dichloroethylamino)uracil.[11] Hendry and co-workers[12] report the synthesis and anti-tumor evaluation of a number of aziridino derivatives of pyrimidine and conclude that, in general, these substances show no selective cytotoxic activity with respect to tumor cells as compared to normal cells. There thus appears to be a division of opinion as far as selective cytotoxic activity of pyrimidines carrying an alkylating function is concerned. In view of the known usefulness of 2,4,6-triaziridinotriazine in the management of certain cases of lymphatic and chronic myologeneous leukemia, it appeared that preparation of further representative aziridinopyrimidines was indicated.

2,4-Bisaziridino-6-methyl-5-nitropyrimidine (I) was readily prepared in 70% yield by condensation of aziridine with 2,4-dichloro-6-methyl-5-nitropyrimidine (II) in the presence of an equivalent amount of triethylamine. I is very susceptible to decomposition during purification especially in the presence of moisture. I was also prepared in low yield by adding an aqueous solution of aziridine and potassium hydroxide to an aqueous suspension of II and by successive reaction of II with sodium hydride and aziridine in ether or tetrahydrofuran.

Treatment of I with dry hydrogen chloride in ether resulted in opening of the aziridine rings and formation of a hydrochloride (III) for which a number of structures are possible. Cyclization to a piperazinium salt (IIIA) in a manner analogous to that noted by Golumbic[13] and Huber[14] with other β-chloroethylamines is suggested by the high decomposition point and insolubility of the salt in water. Reclosure of the opened aziridine ring on one of the pyrimidine nitrogens to give an imidazopyrimidine derivative (IIIB) is possible on the basis of the observation of Schaefer[15] that 1-aziridino-*s*-triazines rearrange in the presence of acid catalysts to dihydroimidazo[1.2-*a*]-*s*-triazines. It is impossible to distinguish between III, IIIA, and IIIB on the basis of elementary analyses. However, titration of the substance with 0.01*N* sodium hydroxide solution showed that it was a monohydrochloride which eliminates structure IIIA. The product of the titration without neutralization can then be represented by IV, IVA, or IVB. It was also obtained by the action of sodium methoxide in benzene on III. A substance of structure IV would be expected to be soluble in ether and insoluble in water which was found to be so. This, as well as elementary analyses, in all probability rules out structures IVA and IVB leaving III as representing the initial product of the action of anhydrous hydrogen chloride on I and IV as representing the product resulting from the action of base on III. We assume that the presence of the nitro group in the 5-position weakens the basicity of the nitrogens in the 2- and 4-positions sufficiently to render salt formation difficult.

Preliminary data on the action of I on animal tumors[16] was exceedingly encouraging. Since it was not known whether I was functioning as an alkylating agent, as an antimetabolite or in a dual capacity, it appeared to be of advantage to substitute other amines for aziridine in the reaction with II. Therefore II was condensed with azetidine, pyrrolidine, piperidine, and morpholine to give V, VI, VII, and VIII respectively. As the saturated heterocyclic ring system was expanded the color of the compounds changed progressively from light lemon yellow in the case of I to a very dark yellow in the case of VIII. All of the substances showed similar insolubility in water and solubility in most organic solvents.

A difference in reactivity of the chlorine atoms in II was noted and advantage was taken of this to introduce two different amine residues in the 2- and 4-positions. By analogy with the reaction of 2,4-dichloro-5-nitropyrimidine with ammonia under mild conditions to give 4-amino-2-chloro-5-nitropyrimidine[17] we assume that the 4-chlorine is most readily displaced in II. Thus when II was allowed to react with one equivalent of *p*-fluoroaniline at 0°, 2-chloro-4-(*p*-fluoroanilino)-6-methyl-5-nitropyrimidine (IX) was formed. When IX was treated with a second equivalent of an amine under more severe conditions 2,4-diaminopyrimidines (X, XI and XII) resulted.

On the other hand when II was allowed to react with excess representative amines, *p*-fluoroaniline and furfurylamine, in boiling ethanol both chlorines were replaced with the formation of diamino derivatives (X and XIII) respectively.

The reaction of II with 2-aminoethanol or 3-aminopropanol took a somewhat different course. On refluxing the reactants in ethanol the 4-chlorine of II readily underwent displacement by the amine, but the 2-chlorine was hydrolyzed, possibly

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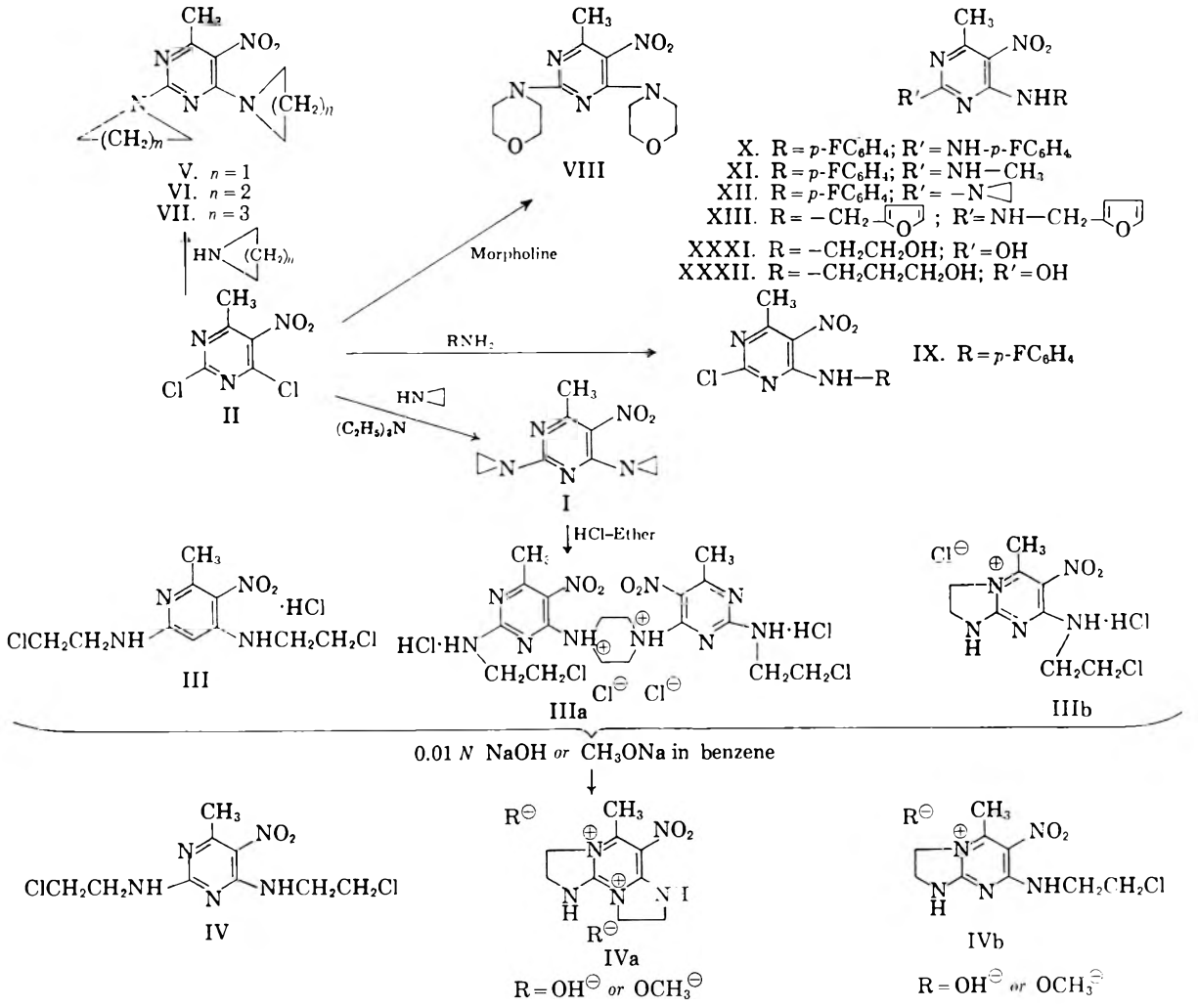
(16) Private communication from Dr. Ralph Jones, Jr., Jackson Memorial Hospital, University of Miami, Miami, Fla.

(17) D. Isay, *Ber.*, **39**, 250 (1906).



by water present in the system, with the formation of 2-hydroxy-4-(2-hydroxyethylamino)-6-methyl-5-nitropyrimidine and 2-hydroxy-4-(3-hydroxypropylamino)-6-methyl-5-nitropyrimidine respectively.

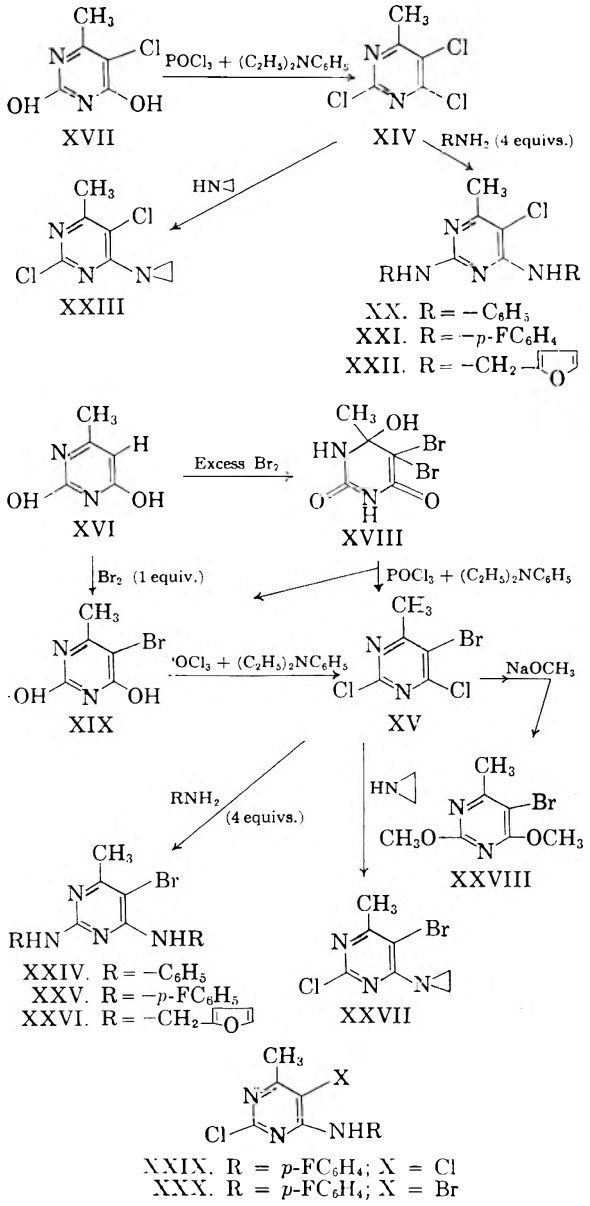
Finally, since the nitro group in II is obviously activating the chlorines in positions 2 and 4, it was of interest to study the effect of other substituents in the 5-position of the pyrimidine ring. For this purpose the 5-chloro- and 5-bromo- analogs (XIV and XV) of II were investigated. Behrend[18] prepared XIV by heating 6-methyluracil (XVI) with phosphorus pentachloride and phosphorus oxychloride in a sealed tube. We have obtained XIV in almost quantitative yield by heating 5-chloro-6-methyluracil (XVII)[19] with phosphorus oxychloride and diethylaniline. For the preparation of XV Behrend's method[20] was not followed. This was found to be lengthy and necessitates the initial formation of 5,5-dibromo-6-hydroxy-6-methyldihydropyrimidine-2,4-dione (XVIII) which has almost the same melting point as 5-bromo-6-methyluracil (XIX). Rather, essentially the procedure of Wang[21] for the bromination of uracil was applied to the bromination of XVI to give XIX which could be purified very easily from traces of XVIII by solution in a large volume of hot dilute potassium hydroxide solution and reprecipitation while still hot by acetic acid. Filtration of XIX from the acetic acid solution while still hot removed any unchanged 6-methyluracil (XVI) since the solubilities of XIX, XVIII, and XVI in the dilute acetic acid were roughly in the ratio 0.36:1.36:5.00. Actually treatment of XVIII with hot dilute potassium hydroxide probably results in extensive decomposition since no product could be isolated when XVIII alone was subjected to this procedure. XVIII with phosphorus oxychloride and dimethylaniline gave a poor yield of XV together with some XIX. The procedure of Overberger for the preparation of XV by treatment of XIX with phosphorous oxychloride alone[22] was improved by use of diethylaniline to provide an 85–95% yield of XV in less than three hours.

(18) R. Behrend, *Ann.*, **229**, 25 (1885).
(19) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1623 (1938).
(20) R. Behrend, *Ann.*, **236**, 57 (1886).
(21) S. Y. Wang, *J. Org. Chem.*, **24**, 11 (1959).
(22) C. G. Overberger, I. C. Kogen, and W. J. Einstman, *J. Am. Chem. Soc.*, **76**, 1953 (1954).

Nucleophilic displacement of the chlorines in positions 2 and 4 of XIV by aniline, *p*-fluoroaniline, and furfurylamine was easily accomplished to give XX, XXI, and XXII respectively. In general two equivalents of amine per atom of chlorine to be replaced were required. Thus, when only two equivalents of *p*-fluoroaniline per equivalent of trichloropyrimidine (XIV) were used only one chlorine was replaced with the formation of 2,5-dichloro-6-methyl-4-(*p*-fluoroanilino)pyrimidine. On the other hand reaction of XIV with two equivalents of aziridine in the presence of triethylamine in boiling ether resulted only in the displacement of the 4-chlorine and the formation of XXIII. When the reaction was carried out in boiling benzene there appeared to be some decomposition of the XXIII formed. From the amount of triethylamine hydrochloride recovered from the reaction mixture it appeared that only a trace of disubstitution product was formed.

The reactions of XV paralleled those of XIV. Displacement of both chlorines by aniline, *p*-fluoroaniline, and furfurylamine gave XXIV, XXV, and XXVI respectively. With aziridine only one chlorine was displaced to give XXVII. In contrast, sodium methoxide very readily gave 5-bromo-2,4-dimethoxy-6-methylpyrimidine (XXVIII).

We therefore conclude that a nitro group in the 5-position exerts a strong activating influence on chlorine atoms in the 2- and 4-positions, particularly on the 4-chlorine atom. Chlorine and bromine in the 5-position exert a much weaker activating influence as would be expected. However, the ease of displacement of the 2-chlorine seems to be dependent also on the nucleophilicity of the attacking reagent.



EXPERIMENTAL[23,24]

2,4-Bisaziridino-6-methyl-5-nitropyrimidine (I). *Procedure A.* Through a mixture of 2.4 g. of sodium hydride dispersion (courtesy of Metal Hydrides, Inc., Beverly, Mass.) in 20 ml. of freshly dried and distilled tetrahydrofuran and 2.15 g. of aziridine, dry nitrogen was passed for a few minutes. A solution of 5.2 g. of II in 50 ml. of tetrahydrofuran was slowly added and the gas which was immediately evolved was collected over water. Substantially the theoretical amount of hydrogen was liberated and the reaction mixture turned deep brown. After 1 hr. the mixture was hydrolyzed with water and extracted with four 50-ml. portions of ether. After drying the combined extracts over anhydrous magnesium sulfate, removal of the solvent left a yellow residue which, on recrystallization from petroleum ether (b.p. 90–100°) with Norit, gave 0.9 g. of light lemon-yellow needles, m.p. 120–122° dec. When anhydrous ether was substituted for tetrahydrofuran the yield was raised to 1.2 g.

Procedure B. An ice cold mixture of a solution of 3.0 g. of potassium hydroxide in 100 ml. of water and a solution of 2.15 g. of aziridine in 50 ml. of water was added to a well stirred ice cold suspension of II prepared by adding a solution of 5.2 g. of II in 50 ml. of acetone to 200 ml. of water. When the addition was complete (30 min.) the ice bath was removed and stirring was continued for 16 hr. during which a voluminous precipitate separated. The solid was filtered, washed with water, and dried. The yield was 1.3 g.

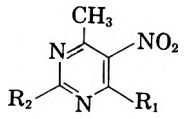
Procedure C. To a well stirred and chilled solution of 10.4 g. of II in 200 ml. of anhydrous ether was added dropwise a solution of 4.4 g. of aziridine and 10.2 g. of triethylamine in 200 ml. of dry benzene at a rate such that the temperature of the mixture did not exceed 10°. When the addition was complete (30–45 min.) 200 ml. of dry benzene was added to dilute the thick paste which formed. After stirring for an additional 30 min. below 10°, the ice bath was removed and the mixture was stirred for 12–15 hr. at room temperature. The mixture was filtered and the filtrate was evaporated to dryness below 40° under reduced pressure. The residue was crystallized from petroleum ether (b.p. 90–100°) to give 7.7 g. of lemon yellow needles, m.p. 122–123°. Concentration of the mother liquor gave additional material and raised the total yield to 8.2 g. Analyses for this and other pyrimidines prepared from II are given in Table I. Compound I is quite susceptible to light and slowly

(23) All melting points are uncorrected for stem exposure.

(24) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

TABLE I

DERIVATIVES OF 6-METHYL-5-NITROPYRIMIDINE



R_1	R_2	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
		$C_9H_{11}N_5O_2$	48.86	4.97	31.67	48.78	4.97	31.86
		$C_{11}H_{15}N_5O_2$	53.00	6.07	28.10	52.97	6.04	28.21
		$C_{13}H_{19}N_5O_2$	56.31	6.86	25.27	56.52	6.82	25.14
		$C_{15}H_{23}N_5O_2$	59.01	7.54	22.95	58.93	7.57	22.91
		$C_{13}H_{19}N_5O_4$	50.48	6.14	22.62	50.70	5.84	22.67
		$C_{15}H_{15}N_5O_4$	54.71	4.55	21.27	54.32	4.46	21.18
NH-*p*-FC_6H_4	NH-*p*-FC_6H_4	$C_{17}H_{13}F_2N_5O_2$	57.14	3.64		57.28	3.73	
$NHCH_2CH_2OH$	OH	$C_7H_{10}N_4O_4 \cdot 0.5H_2O$	37.66	4.93	25.11	37.67	5.03	24.72
$NH(CH_2)_3OH$	OH	$C_8H_{12}N_4O_4$	42.10	5.26	24.56	42.35	5.20	24.39
NH-*p*-FC_6H_4	Cl	$C_{11}H_8ClFN_4O_2$	46.72	2.83		46.78	2.98	
NH-*p*-FC_6H_4	$NHCH_3$	$C_{12}H_{12}FN_5O_2$	51.98	4.33	25.27	52.23	4.52	25.11
NH-*p*-FC_6H_4		$C_{13}H_{12}FN_5O_2$	53.97	4.15	24.22	54.32	4.36	23.89
$NHCH_2CH_2Cl$	$NHCH_2CH_2Cl$	$C_9H_{13}Cl_2N_5O_2 \cdot HCl$	32.67	4.23	21.18	32.38	4.05	21.26

turns brown with some decomposition. It can be stored indefinitely in a brown or green bottle even in full sunlight.

2,4-Bisazetidino-6-methyl-5-nitropyrimidine (V).[25] From a solution of 11.1 g. of moist azetidine[26] dried over potassium hydroxide according to Marckwald[27] and 11.1 g. of triethylamine in 50 ml. of dry ether and a solution of 10.4 g. of II in 700 ml. of dry ether, 7.83 g. of V was obtained by Procedure C above. The substance was recrystallized first from benzene–petroleum ether and finally from petroleum ether (b.p. 60–80°). It formed long bright yellow needles, m.p. 135°. One more recrystallization raised the melting point to 141–142°.

2,4-Bis-1'-pyrrolidino-6-methyl-5-nitopyrimidine (VI). A solution of 7.1 g. of pyrrolidine in 50 ml. of absolute ethanol was added with stirring during 45–60 min. to an ice cold solution of 8.32 g. of II in 100 ml. of absolute ethanol. When the addition was complete the mixture was heated gently on the steam bath for 24 hr. during which a light brown pasty mass was formed. The magma was triturated with acetone and filtered from 1.5 g. of high melting (256–258°) material which was not investigated further. The filtrate was concentrated to about 20 ml. and poured with stirring into 300 ml. of ice water. The pasty mass which separated solidified after standing at room temperature for 48 hr. yielding 5.5 g. (50%) of brownish yellow material, m.p. 146–148°. After two recrystallizations from aqueous acetone bright yellow granular crystals, m.p. 149–150°, were obtained. The same substance was obtained in 61% yield by Method C described above for the preparation of I.

2,4-Bis-1'-piperidino-6-methyl-5-nitropyrimidine (VII). Separate solutions of 5.2 g. of II in 60 ml. of benzene and 5.1 g. of triethylamine in 20 ml. of benzene were mixed. To the cold and well stirred mixture was added a solution of 4.25 g. of piperidine in 40 ml. of benzene over 15 min. After stirring for 16 hr. at room temperature the mixture was refluxed for 4 hr., filtered while still hot, and concentrated. The residual pasty mass was taken up in 100 ml. of hot ethanol and the solution was diluted with 200 ml. of water. On slow evaporation 4.8 g. (63%) of yellow crystals were obtained. After two recrystallizations from aqueous acetone bright yellow micro needles, m.p. 99–100°, resulted.

2,4-Bis-4-morpholino-6-methyl-5-nitropyrimidine (VIII). This was prepared by the method used for VII. The yield of material, m.p. 162–163°, after recrystallization from aqueous acetone was 64%.

2,4-Bisfurfurylamino-6-methyl-5-nitropyrimidine (XIII). To a cold solution of 7.8 g. of II in 100 ml. of absolute methanol 14.6 g. of freshly distilled furfurylamine (courtesy of the Quaker Oats Co.) was added dropwise over 15–20 min. during which solid material separated. The mixture was then refluxed gently on the steam bath during which the solids dissolved. After addition of 150 ml. of benzene the solution was boiled down to about half its volume and filtered while still hot. On cooling, the filtrate deposited 6.5 g. (52%) of light yellow solids. Recrystallization from ethyl acetate–petroleum ether (b.p. 90–100°) gave crystalline material, m.p. 115–116°.

2,4-Bis(β-chloroethylamino)-6-methyl-5-nitropyrimidine hydrochloride (III). Dry hydrogen chloride was passed slowly through a solution of 1.1 g. of I in 200 ml. of anhydrous ether chilled in an ice-salt bath for 30 min. The temperature of the solution was held below 10°. A voluminous white precipitate separated and further absorption of hydrogen chloride ceased. The solids were collected and washed thoroughly with cold anhydrous ether to give 1.63 g. (98%) of cream colored material which decomposed slowly above 200°. Two recrystallizations from anhydrous acetone–petroleum ether (b.p. 40–60°) gave an analytically pure sample although the melting point was still indefinite. III, however, was found to melt with decomposition at 175–177°, when put in a bath previously heated to 175°. If

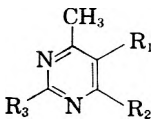
(25) This preparation was carried out by Dr. R. S. McElhinney of these laboratories.

(26) The azetidine was prepared in these laboratories by an improved procedure devised by Dr. W. R. Vaughan of these laboratories which will be described elsewhere.

(27) W. Marckwald and A. B. v. Droeste-Huelshoff, *Ber.*, **31**, 3264 (1898); C. C. Howard and W. Marckwald, *Ber.*, **32**, 2032 (1899).

TABLE II

DERIVATIVES OF 6-METHYL-5-BROMO- OR 5-CHLOROPYRIMIDINE



				Analyses, %					
				Calcd.			Found		
R_1	R_2	R_3	Formula	C	H	N	C	H	N
Cl	Cl	Cl	$C_5H_3Cl_3N_2$	30.37	1.51	14.17	30.46	1.53	14.19
Br	Cl	Cl	$C_5H_3BrCl_2N_2$	24.79	1.23		24.80	1.17	
Br		Cl	$C_7H_7BrClN_3$	33.80	2.81	16.90	33.84	2.65	16.88
Br	NHC_6H_5	NHC_6H_5	$C_{17}H_{15}BrN_4$	57.41	4.32	15.89	57.46	4.22	15.77[a]
Br	NH-*p*-FC_6H_4	Cl	$C_{11}H_8BrClFN_3$	41.70	2.52	13.27	41.82	2.68	13.10
Br	NH-*p*-FC_6H_4	NH-*p*-FC_6H_4	$C_{17}H_{13}BrF_2N_4 \cdot HCl$	47.71	3.27	13.07	47.24	3.33	12.94
Br			$C_{15}H_{15}BrN_4O_2$	49.58	4.13		49.17	4.20	
Br	OCH_3	OCH_3	$C_7H_9BrN_2O_2$	36.05	3.86	12.01	36.09	4.04	12.01
Br	OH	OH	$C_5H_5BrN_2O_2$	29.12	2.42		29.18	2.44	[b]
Cl		Cl	$C_7H_7Cl_2N_3$	41.17	3.43	20.58	41.20	3.47	20.62
Cl	NHC_6H_5	NHC_6H_5	$C_{17}H_{15}ClN_4 \cdot HCl$	58.76	4.61	16.13	58.95	4.68	15.72
Cl	NH-*p*-FC_6H_4	NH-*p*-FC_6H_4	$C_{17}H_{13}ClF_2N_5 \cdot HCl$	53.26	3.65	14.62	52.99	3.78	14.57
Cl	NH-*p*-FC_6H_4	Cl	$C_{11}H_8Cl_2FN_3$	48.52	2.94	15.44	48.72	3.09	15.41
Cl			$C_{15}H_{15}ClN_4O_2$	56.51	4.70	17.58	56.43	4.75	17.64

[a] Br: calcd. 22.52, found 22.53. [b] Br: calcd. 38.83, found 39.07.

the bath temperature was lower than 175°, the substance did not melt sharply but slowly decomposed up to 200°.

2,4-Bis(β-chloroethylamino)-6-methyl-5-nitropyrimidine (IV). *A. By the action of sodium hydroxide.* A suspension of 0.661 g. of III in 50 ml. of ice water was titrated with 0.01*N* sodium hydroxide solution to phenolphthalein end point. Calculated for one equivalent of sodium hydroxide: 200 ml. Found: 203 ml. The suspended yellowish solids were collected, washed thoroughly with water, and dried. The yield was 0.58 g. (98.6%). Recrystallization from ether–petroleum ether (40–60°) gave lemon needles, m.p. 145–146° dec. in a bath preheated to 145°. If the bath temperature was lower than 145°, the substance did not melt sharply but slowly decomposed up to 200°. The infrared spectrum was quite different from that of III.

Anal. Calcd. for $C_9H_{13}N_5O_2Cl_2$: C, 36.74; H, 4.40; N, 23.80; Cl, 24.16. Found: C, 36.76; H, 4.45; N, 23.92; Cl, 23.97.

B. By the action of sodium methoxide. To a suspension of 0.888 g. of III in 80 ml. of dry benzene was added dropwise with vigorous stirring a solution of 0.069 g. of sodium in 30 ml. of absolute methanol. The suspended solid went into solution and sodium chloride separated. After stirring for 2 hr. at room temperature, about 50 ml. of solvent was distilled off in the course of an hour. The mixture was then taken to dryness under reduced pressure and the residue was extracted with 300 ml. of ether in a Soxhlet extractor for 12 hr. The ether extract was boiled with carbon, filtered and, while still hot, was slowly added to 150 ml. of boiling petroleum ether (b.p. 40–60°). On cooling fine yellow needles separated. This substance was identical with that obtained by Procedure *A* as judged by melting point behavior and identical infrared spectra.

Anal. Found: C, 36.98; H, 4.53; N, 23.86; Cl, 24.24.

2,4-Bis(p-fluoroanilino)-6-methyl-5-nitropyrimidine (X). To a solution of 5.2 g. of II in 200 ml. of absolute ethanol was added 6.1 g. of *p*-fluoroaniline. There was an immediate separation of yellow solid. The mixture was heated on the steam bath on which the solid material went into solution but within 5 min. a precipitate reappeared. The mixture was refluxed for 1 hr. and allowed to stand overnight at room temperature. The solid material, 8.5 g., m.p. 215–220 dec., was collected and recrystallized from cyclohexane-benzene to narrow the melting point to 218–220° dec. On slow heating the substance melted at 185–187° dec.

2-Chloro-4-(p-fluoroanilino)-6-methyl-5-nitropyrimidine (IX). To a stirred solution of 5.2 g. of II chilled in an ice-salt bath was added dropwise a solution of 2.8 g. of *p*-fluoroaniline in 20 ml. of absolute ethanol. After stirring for 30 min. in the freezing bath, the mixture was stirred for an additional 30 min. at room temperature, cooled, and filtered to give 2.5 g. of dark yellow crystalline material. The filtrate on concentration gave an additional 3.0 g. of the same substance. (Total yield, 77%.) On recrystallization from methylcyclohexane, 4.2 g. of yellow woolly crystals, m.p. 152–154°, resulted.

4-(p-Fluoroanilino)-6-methyl-2-methylamino-5-nitropyrimidine (XI). A mixture of 2.8 g. of IX, 20 ml. of 40% aqueous methylamine, and 100 ml. of absolute ethanol was heated gently on the steam bath for 48 hr., without reflux. Substantially dry light yellow crystalline material, m.p. 165–175°, remained. This was triturated with dilute sodium hydroxide solution, collected, and washed thoroughly with water. After recrystallization from aqueous methanol and two recrystallizations from petroleum ether (b.p. 90–100°) fine yellow micro-crystals, m.p. 172–173°, were obtained.

4-(p-Fluoroanilino)-2-aziridino-6-methyl-5-nitropyrimidine (XII) To a well stirred solution of 2.82 g. of IX in 400 ml. of absolute ether was added gradually a solution of 0.53 g. of aziridine and 1.1 g. of triethylamine in 100 ml. of absolute ether, the temperature being maintained at 15–20°. After the addition was complete the mixture was stirred at room temperature for 18 hr. and the separated solid material was filtered. The filtrate was concentrated to about 50 ml. and added to a solution of 0.23 g. of aziridine and 0.5 g. of triethylamine in 100 ml. of benzene. The mixture was heated

at 60–70° for 3 hr., filtered through Norit and the filtrate was taken to dryness at a temperature below 35°. The oily residue was triturated with 60 ml. of anhydrous ether and the solution taken to dryness to give 2.0 g. (69%) of yellow crystalline material, m.p. 116–119° dec. Four recrystallizations from petroleum ether (b.p. 40–60°) gave an analytical sample, m.p. 135–137° dec. The substance gave a negative test for chlorine.

2-Hydroxy-4-(2'-hydroxyethylamino)-6-methyl-5-nitropyrimidine (XXXI). To a solution of 8.6 g. of II in 125 ml. of warm ethanol was added 6.1 g. of 2-aminoethanol. An immediate reaction occurred and the mixture turned yellow with evolution of heat. The mixture was heated gently on the steam bath without reflux for 48 hr. leaving a viscous residue. Trituration of the residue with dry acetone gave 11.5 g. of light brown material, m.p. 126–130°. Two recrystallizations from acetone and a little benzene gave 3.0 g. of shining orange needles, m.p. 147.5–148.5°.

2-Hydroxy-4-(3'-hydroxypropylamino)-6-methyl-5-nitropyrimidine (XXXII). The procedure was the same as the preceding one using 8.62 g. of II and 7.51 g. of 3-aminopropanol in 150 ml. of absolute ethanol. The crude product was triturated with methanol and an analytical sample was prepared by solution of the crude material in hot dilute hydrochloric acid, filtration and neutralization to about *p*H 8 with ammonium hydroxide. On cooling 1.0 g. of granular crystals, m.p. 244.5–245.5° dec. separated.

6-Methyl-2,4,5-trichloropyrimidine (XIV). A mixture of 1.2 g. of XVII,[19] 10 ml. of phosphorus oxychloride, and 2 ml. of diethylaniline was heated under reflux with stirring for 3 hr. After standing at room temperature for 24 hr., the light brown solution was poured cautiously onto chopped ice. (In larger scale runs the excess phosphorus oxychloride was distilled from the mixture under reduced pressure.) The mixture, from which solid separated, was extracted with five 60-ml. portions of ether and the combined extracts were washed with four 50-ml. portions of ice water. After drying over anhydrous magnesium sulfate, removal of the solvent left a colorless oil (1.5 g.), b.p. 55–56° (0.2 mm.); reported[18] b.p. 245–247°. Analytical data for XIV, XV, and substances prepared from them are given in Table II.

5-Bromo-6-methyluracil (XIX). To a stirred suspension of 3.15 g. of XVI in 100 ml. of water was added dropwise 4.0 g. of bromine over 15 min. After addition of 150 ml. of water the mixture was refluxed for 25 min. and cooled to 50–60°. Solid potassium hydroxide was added until a clear solution was obtained. The solution was boiled with carbon, filtered, and, while still hot, was acidified with acetic acid. The white crystalline precipitate was collected, triturated with 200 ml. of hot water, and collected. The cake was washed successively with hot water, alcohol, and ether to give 4.4 g. (86%) of material, m.p. 240–242° dec.; reported[20] m.p. 230° dec. In a 1 mole run the yield was 94%. The substance gave a negative test for halogen when boiled with nitric acid and silver nitrate for 1 min. In contrast 5,5-dibromo-6-hydroxy-6-methyldihydrouracil (XVIII), m.p. 234–235° dec. after crystallization from water, prepared by bromination of XVI with excess bromine in water, gave an immediate precipitate with silver nitrate in boiling nitric acid.

5-Bromo-2,4-dichloro-6-methylpyrimidine (XV). A mixture of 41.2 g. of XIX, 300 ml. of phosphorus oxychloride, and 80 ml. of diethylaniline was stirred and slowly heated for 30 min. and then refluxed for 90 min. The excess oxychloride was distilled from the brown mixture at reduced pressure and the residue was poured onto cracked ice with vigorous stirring. The pinkish-white solid was collected, washed thoroughly with water, and sucked as dry as possible. The moist filter cake was dried in a vacuum desiccator over phosphorus pentoxide and sublimed at 40–50° (0.2 mm.) during 20 hr. to give 44 g. (88%) of analytically pure material, m.p. 42°, b.p. 114° (0.3 mm.).

4-Aziridino-2,4-dichloro-6-methylpyrimidine (XXIII). The procedure was the same as Procedure *C* for the preparation of I. The product (78% yield) was recrystallized first from dilute methanol and finally from aqueous acetone. It melted at 115–116°.

5-Chloro-2,4-dianilino-6-methylpyrimidine (XX). A solution of 4.6 g. of aniline in 50 ml. of dry ether was added to a solution of 1.5 g. of XIV in 50 ml. of dry ether. On warming for 15 min. the mixture solidified. The solid was collected and triturated with 10 ml. of benzene to give 1.6 g. of the hydrochloride of XX. After recrystallization first from dilute methanol and then from methanol-benzene, analytically pure material, m.p. 284–285° dec. was obtained.

2,5-Dichloro-4-(p-fluoroanilino)-6-methylpyrimidine (XXIX). The procedure was substantially the same as that for the preparation of XX except that the reaction mixture was allowed to stand for 48 hr. at room temperature for completion. The yield of cream colored needles of the hydrochloride, m.p. 124–125° after recrystallization from ether–petroleum ether (b.p. 40–60°), was 50%.

2,4-Bis(p-fluoroanilino)-5-chloro-6-methylpyrimidine (XXI). To a solution of 1.97 g. of XIV in 20 ml. of ether was added a solution of 4.4 g. of *p*-fluoroaniline in 20 ml. of ether. After evaporation of the ether on the steam bath the residual pasty mass was mixed with 30 ml. of water and heated on the steam bath for 72 hr. The brown residual solid was triturated with ether and collected. The material was taken up in hot ethanol, benzene was added, and the solution was evaporated to incipient crystallization to give 2.6 g. (66%) of slate colored crystals, m.p. 275–280° dec. Further recrystallization from aqueous ethanol and from benzene–petroleum ether (b.p. 40–60°) after solution with the aid of a little methanol raised the melting point to 282–287° dec. This is the hydrochloride of XXI.

The ether from trituration of the crude material was boiled with carbon, filtered, and added to hot petroleum ether (b.p. 40–60°) to give 0.7 g. of crystalline material, m.p. 121–123°. Further recrystallization from the same solvent gave cream-colored needles of 2,5-dichloro-4-(*p*-fluoroanilino)-6-methylpyrimidine (XXIX), m.p. 124–125°.

4-Aziridino-5-bromo-2-chloro-6-methylpyrimidine (XXVII). To a stirred solution of 2.41 g. of XV in 100 ml. of anhydrous ether chilled in an ice bath was added a solution of 0.9 g. of aziridine and 2.1 g. of triethylamine in 50 ml. of anhydrous ether over 15 min. A further 50 ml. of anhydrous ether was added and the mixture was stirred at room temperature for 15 hr. The precipitated triethylamine hydrochloride was filtered and the filtrate was evaporated to dryness under reduced pressure. Two recrystallizations of the residue from aqueous methanol gave white needles, m.p. 127–128° dec.

2,4-Bisfurfurylamino-5-chloro-6-methylpyrimidine (XXII). To an ethereal solution of 3.95 g. of XIV was added a solution of 7.8 g. of furfurylamine in 30 ml. of dry ether. The reaction was vigorous and the ether boiled off quickly with the temperature rising to 60°. The clear residue was heated on the steam bath for an hour and left at room temperature for 24 hr. After trituration with dry ether and then with water, the residue was crystallized from aqueous methanol to give white flakes, m.p. 127–128°. Additional material was obtained from the mother liquor bringing the total yield to 4.6 g. (71%).

2,4-Bisfurfurylamino-5-bromo-6-methylpyrimidine (XXVI). To a stirred solution of 2.42 g. of XV in 50 ml. of dry ether was added a solution of 1.94 g. of furfurylamine and 2.02 g. of triethylamine in 100 ml. of dry ether. The mixture was stirred for 4 hr. and then slowly evaporated. The pasty residue was left at room temperature for 5 days during which it solidified. After trituration with water, reerystallization from ether–petroleum ether (b.p. 40–60°) gave the pure substance, m.p. 119–120°.

2,4-Bis(p-fluoroanilino)-5-bromo-6-methylpyrimidine (XXV). The procedure was the same as that for XXVI. The crude product was triturated with dry ether to give a slate-colored residue (57%) and a brown ether solution. Crystallization of the residue from aqueous methanol and

then from methanol-benzene gave the hydrochloride of XXV, m.p. 243–244° dec.

The brown ether solution was evaporated to dryness and the residue was recrystallized from benzene–petroleum ether and then from ether–petroleum ether (b.p. 40–60°) to give 25% of 5-bromo-2-chloro-4-(*p*-fluoroanilino)-6-methylpyrimidine as white needles (XXX), m.p. 143°.

5-Bromo-2,4-dianilino-6-methylpyrimidine (XXIV). The procedure was substantially the same as that for XXVI except that the reaction mixture was warmed in benzene for 24 hr. at 40–60°. The insoluble product was washed with ether, taken up in methanol, and precipitated by addition of benzene to give crystalline material, m.p. 247–249° dec. This was probably the hydrochloride of XXIV. The free base (50% yield) was obtained by recrystallization of the salt from dilute acetic acid. Further recrystallization from ether–petroleum ether (b.p. 40–60°) gave micro-needles, m.p. 111–112°.

5-Bromo-2,4-dimethoxy-6-methylpyrimidine (XXVIII). To a solution of 5.06 g. of sodium in 200 ml. of absolute methanol at 10–15° was added with stirring a solution of 13.3 g. of XV in 100 ml. of absolute methanol over 25 min. The mixture was refluxed for an hour and stirred at room temperature for 15 hr. The solid was filtered and washed with methanol. Carbon dioxide was passed into the filtrate until the *p*H was about 8. The separated solids (5.2 g.) were collected and the filtrate was taken to dryness. The residue was triturated with water leaving 10.0 g. (78%) of white insoluble material. Distillation gave 7.2 g. of material, b.p. 96–99° (0.5 mm.), m.p. 76–77°.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE SHELL DEVELOPMENT CO.]

Preparation and Infrared Absorption Spectra of Some Phenyl Ethers[1]

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Received July 27, 1959

The preparation and infrared absorption spectra of a number of aryl and alkyl-aryl ethers are recorded. In general, the assignments in the infrared regions of the spectra agree with those reported in the literature for benzene derivatives and aryl ethers. The *m*-disubstituted materials have their benzene-oxygen stretch band at a lower frequency than those previously reported.

A number of phenyl and alkyl-phenyl ethers were recently prepared for evaluation as radiation-resistant, high temperature lubricants.[2] Many of the products have not previously been reported. At the same time the infrared absorption spectra of both known and new compounds were recorded and the results compared with those of previous workers.[3–10]

Phenyl ethers and certain of their derivatives were prepared because, unlike alkyl ethers, they are very resistant to oxidation. Their thermal decomposition temperatures far exceed those of present synthetic lubricants and their resistance to radiolysis is excellent.

The high melting points of many of the products exclude them from consideration as lubricants for ordinary applications.[2] The literature shows that the better known *para*-linked polyphenyl ethers show a rise in melting point with increasing chain length. In the *meta*-linked series the melting point of certain compounds is surprisingly low. Thus, while *m*-diphenoxybenzene melts at 47° or 60° depending on crystal form, bis(*m*-phenoxyphenyl) ether (III) melts at 41°. The *meta*-linked ethers have a strong tendency to supercool; so far the higher members of the series (XI and XII) have not been obtained in crystalline form.

Most of the ethers were prepared by the Ullmann[11] ether synthesis. The exceptions (XXIX and XXX) were prepared from bis(chloromethyl)-durene and potassium *o*- or *p*-*tert*-butylphenate under milder conditions.

Synthetic problems arose only in the preparation of the *meta*-linked ethers. *m*-Dibromobenzene was prepared from *m*-bromoaniline *via* the Sandmeyer reaction. *m*-Bromophenyl phenyl ether was prepared either from *m*-phenoxyaniline by the same reaction or from phenol and *m*-dibromobenzene by the Ullmann procedure. *m*-Phenoxyphenol[12,13] was prepared by three different routes (Fig. 1), as stability problems connected with certain starting materials required clarification.

The most obvious method (A. R = H), reaction

(1) The greater part of this work was sponsored by Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

(2) C. L. Mahoney, E. R. Barnum, W. W. Kerlin, K. J. Sax, and W. A. Saari, "Polyphenyl Ethers as High-Temperature Radiation Resistant Lubricants," *J. Chem. Eng. Data Series*, Vol. 5, No. 2, 172.

(3) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen, London, 1954, p. 102.

(4) L. H. Briggs, L. D. Colebrook, H. M. Fales, and W. C. Wildman, *Anal. Chem.*, 29, 904 (1957).

(5) R. R. Randle and D. H. Whiffen, *Molecular Spectroscopy*, G. Sell, ed., Inst. of Petroleum, London, 1955, p. 111.

(6) F. S. Mortimer, unpublished work.

(7) J. E. Stewart and M. Hellman, *J. Res. Nat. Bur. Std.*, 60, 125 (1958).

(8) N. B. Colthup, *J. Opt. Soc. Amer.*, 40, 397 (1950).

(9) A. Stojilkovic and D. H. Whiffen, *Spectrochim. Acta*, 12, 47 (1958).

(10) Y. Mikawa, *J. Chem. Soc. Jap.*, 29, 110 (1956).

(11) F. Ullmann and P. Sponagel, *Ber.* 38, 2211 (1905); *Ann.* 350, 83 (1906).

(12) (a) G. Lock, *Monatsh.*, 55, 183 (1930); (b) H. Ungnade and K. T. Zilch, *J. Org. Chem.*, 15, 1108 (1950); (c) A. Luttringhaus, *Ann.*, 528, 181, 211, 233 (1937).

(13) G. Lock, *Monatsh.*, 55, 180 (1930).

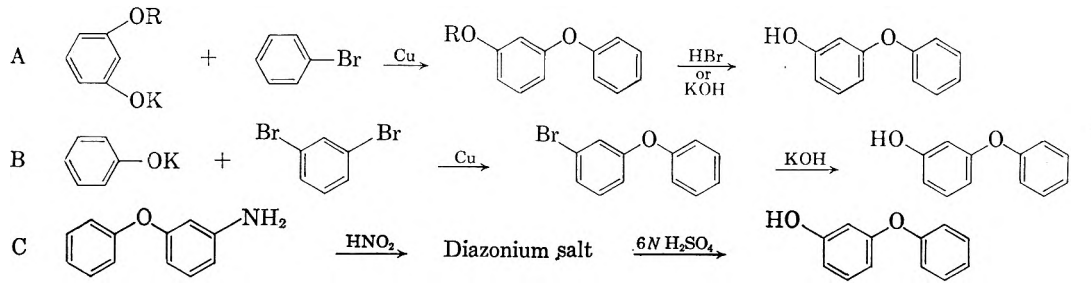


Fig. 1. Preparation of *m*-phenoxyphenol

of the monopotassium salt of resorcinol with bromobenzene, gives only tars. Method A (R = alkyl) gives pure *m*-phenoxyphenol after either acid[12a] or base[12b] hydrolysis unless the starting material contains ring-alkylated impurities. These impurities were demonstrated in a commercial sample of *m*-methoxyphenol by NMR spectroscopy,[14] although they could not be found by either gas-liquid chromatography or infrared absorption spectroscopy. The ring-substituted methyl absorption is easily distinguished from the methoxyl or any other methyl absorption and may be used for semi-quantitative work. No such absorption was found with materials of known purity. Thus no ring alkylation occurs during hydrolysis.

Ring alkylation of resorcinol during the preparation of its ethers has long been known.[15] It is usually connected with methyl iodide or dimethyl sulfate alkylations. However, *m*-ethoxyphenol and *m*-*n*-butoxyphenol, prepared from resorcinol, potassium hydroxide, and the appropriate alkyl bromide in aqueous ethanol, were free from ring-alkylated contaminants.

Base hydrolysis of *m*-ethoxyphenyl phenyl ether required a higher temperature than that needed for the methoxy compound. The *n*-butyl derivative could not be hydrolyzed by base without extensive decomposition.

Methods B and C were also investigated. Method B gave a 45% yield of *m*-phenoxyphenol. A 60% yield was obtained by method C. Both methods provided a route to the *meta*-linked ethers before the impurity problem connected with Method A was finally solved.

In preparations involving the Ullmann ether synthesis we have found that products prepared at 180–220° are generally purer than those prepared at higher temperatures. Although the usual copper catalyst was used during most of this work, cuprous oxide was used in some instances and was quite as satisfactory. The long reaction times used by some earlier workers and, in part, ourselves are usually unnecessary. However, presence of impurities in starting materials or low reactivity of certain compounds may require more vigorous conditions. The reaction is quite rapid; even two hours at reaction temperature is possibly excessive in many cases.

A number of new compounds were prepared from *p*-α-cumylphenol. Although these products and those prepared from *p*-*tert*-butylphenol lack the outstanding thermal and oxidation stability of the unsubstituted polyphenyl ethers, they are much more stable than present synthetic lubricants.[2]

The properties of the ethers prepared during this work are summarized in Table I.

As there is very little in the literature about these types of molecules, it was thought that a spectrum-structure correlation would be interesting. The spectra are a composite of the spectra of ethers and polyphenyl structures, with the exception that most of the ethers in this study exhibit their benzene-oxygen stretch band near 1215 cm.$^{-1}$ rather than near 1250 cm.$^{-1}$ as in vinyl and simple phenyl ethers. The absorption peaks that can be used to characterize the aryl ethers are given in the correlation chart in Table II.

The spectra were recorded on a Beckman IR-4 spectrophotometer equipped with sodium chloride optics. The samples were run in carbon disulfide solutions between 7.5 and 15 μ and in carbon tetrachloride solutions between 2 and 7.5 μ. A variable thickness cell was used to compensate for solvent absorption.

The compounds with an O—C (aliphatic) group have a strong band at 1040 ± 2 cm.$^{-1}$ which is not present in any of the other spectra. This supports the contention of Briggs, *et al.*[4] that the band near 1040 cm.$^{-1}$ rather than the 1120 cm.$^{-1}$ band is due to the O—CH_3 stretch vibration. The addition of bromine in the *para*-substituted compounds gives rise to a strong, sharp band at 822 ± 3 cm.$^{-1}$ and 1006 cm.$^{-1}$. Stojilkovic and Whiffen[9] mention that these bands are difficult to assign, but that the bands do indicate the presence of *para*-halogen substitution in aryl ethers. Characteristic absorption for mono-, *meta*- and *para*-substitution is found in the 860 cm.$^{-1}$ region. Two unique strong bands at 1132 ± 8 cm.$^{-1}$ and 977 ± 2 cm.$^{-1}$ are present only in 1,3-diaryloxybenzenes.

One of the strongest bands is due to the benzene-oxygen stretching mode. The majority of the samples have the band within the limits 1218 ±

(14) Spectra were obtained with a Varian Associates Model V-4300 High Resolution NMR Spectrometer at 40 megacycles per second.

(15) J. Herzig and S. Zeisel, *Monatsh.*, **10**, 144 (1889).

TABLE I

PHENYL ETHERS

	Compound	M.W.	KOH, Moles	Starting Materials: Phenol	Starting Materials: Bromo cpd.	Starting Materials: Moles
I	*m*-Diphenoxybenzene	262.3	1.6	Phenol	*m*-DBB[b]	0.64
II	Bis(*p*-phenoxyphenyl) ether	354.4	See general method in experimental			—
III	Bis(*m*-phenoxyphenyl) ether[d]	354.4	1.0	*m*-Phenoxy-	*m*-BPPE	0.933
IV	Bis(*o*-phenoxyphenyl) ether	354.4	0.1	*o*-Phenoxy-	*o*-BPPE	0.093
V	*o*-Phenoxyphenyl *p*-phenoxyphenyl ether	354.4	0.33	*o*-Phenoxy-	*p*-BPPE	0.33
VI	*m*-Phenoxyphenyl *p*-phenoxyphenyl ether	354.4	0.32	*p*-Phenoxy-	*m*-BPPE	0.31
VII	*m*-Phenoxyphenyl *o*-phenoxyphenyl ether	354.4	0.33	*o*-Phenoxy-	*m*-BPPE	0.33
VIII	*m*-Bis(*m*-phenoxyphenoxy)benzene[e]	446.5	0.4	*m*-Phenoxy-	*m*-DBB	0.19
IX	*p*-Bis(*m*-phenoxyphenoxy)benzene	446.5	1.08	*m*-Phenoxy-	*p*-DBB	0.64
X	*m*-Bis(*p*-phenoxyphenoxy)benzene	446.5	0.5	*m*(*p*-Phenoxy-phenoxy)-	*p*-BPPE	0.5
XI	Bis[*m*-(*m*-phenoxyphenoxy)phenyl] ether	538.6	0.27	*m*-(*m*-Phenoxy-phenoxy)-	1-*m*-BP-3-PB	0.27
XII	*m*-Bis[*m*-(*m*-phenoxyphenoxy)phenoxy]benzene[f]	630.7	0.35	*m*-(*m*-Phenoxy-phenoxy)-	*m*-DBB	0.17
XIII	*m*-Bis[*m*-(*p*-phenoxyphenoxy)phenoxy]benzene[g]	630.7	0.36	*m*-(*p*-Phenoxy-phenoxy)-	*m*-DBB	0.17
XIV	1-(*o*-Phenylphenoxy)-4-phenoxybenzene	338.4	See experimental			
XV	1-(*m*-Methoxyphenoxy)-4-phenoxybenzene	292.3	3.5	*m*-Methoxy-	*p*-BPPE	3.0
XVI	1-(*p*-*tert*-Butylphenoxy)-4-phenoxybenzene	318.4	0.8	*p*-*tert*-Butyl-	*p*-BPPE	0.7
XVII	Bis[*p*-(*m*-methylphenoxy)phenyl] ether	382.4	2.0	*m*-Cresol	Bis(*p*-BP)E	0.75
XVIII	Bis[*p*-(*p*-*tert*-butylphenoxy)phenyl] ether	466.6	1.0	*p*-*tert*-Butyl-	Bis(*p*-BP)E	0.35
XIX	Bis[*p*-(*p*-*tert*-amylphenoxy)phenyl] ether	494.6	1.0	*p*-*tert*-Amyl-	Bis(*p*-BP)E	0.35
XX	1-(*p*-α-Cumylphenoxy)-4-methoxybenzene	318.4	1.0	*p*-α-Cumyl-	*p*-Bromoanisole	0.85
XXI	1-(*p*-α-Cumylphenoxy)-4-ethoxybenzene	332.4	1.1	*p*-α-Cumyl-	*p*-Bromophenetole	1.0
XXII	*p*-(*p*-α-Cumylphenoxy)phenyl pivalate	388.5	See experimental			
XXIII	1-(*p*-α-Cumylphenoxy)-4-phenoxybenzene	380.5	1.0	*p*-α-Cumyl-	*p*-BPPE	0.84
XXIV	*m*-Bis(*p*-α-cumylphenoxy)benzene	498.6	0.67	*p*-α-Cumyl-	*m*-DBB	0.27
XXV	Bis[*p*-(*p*-α-cumylphenoxy)phenyl] ether	590.7	0.65	*p*-α-Cumyl-	Bis(*p*-BP)E Bis(*p*-BP)E	0.25 0.4
XXVI	Bis[*p*-(2-phenyl-4-*tert*-butylphenoxy)phenyl] ether	618.8	0.94	2-Phenyl-4-*tert*-butyl-		
XXVII	*p*-(*m*-Phenoxyphenoxy)bromobenzene	341.2	Obtained as a byproduct of IX			
XXVIII	*m*-(*m*-Phenoxyphenoxy)bromobenzene	341.2	See experimental			
XXIX	Bis(*p*-*tert*-butylphenoxymethyl)durene	458.7	See experimental			
XXX	Bis(*o*-*tert*-butylphenoxymethyl)durene	458.7	See experimental			

[a] Two crystal forms. [b] Abbreviations: DBB = dibromobenzene; BPPE = bromophenyl phenyl ether; Bis(*p*-BP)E = bis(*p*-bromophenyl) ether; 1-*m*-BP-3-BP = 1-(*m*-bromophenoxy)-3-phenoxybenzene. [c] These melting points were obtained from precision melting point curves. Calculated to be over 99.5% pure. [d] Density 1.18 g./ml. [e] Cuprous oxide catalyst. [f] Density 1.20 g./ml. [g] Purified by partial oxidation in a Dornte[17] apparatus followed by chromatography.

10 cm.$^{-1}$ which is lower than the values reported by Bellamy[3] and by Briggs, *et al.* but higher than those reported for vinyl ethers by Mikawa.[9] Thus the range quoted by Bellamy for the benzene-oxygen stretch frequency should be extended from 1230–1270 to 1210–1270 cm^{-1}.

Monosubstituted aryl ethers have their strong band near 1240 cm.$^{-1}$ but the addition of an oxygen to the *ortho* position moves the band to 1250 cm^{-1}. However, *meta*- or *para*-substitution shifts the band to near 1215 cm^{-1}.

Other bands, some almost as intense as those above, can be used for characterization. *Ortho*- and *para*-disubstitution results in a band at 1190 ± 10 cm.$^{-1}$ which is not present in the spectra of *meta* compounds. A strong, broad *meta* band appears near 1270 cm.$^{-1}$ and is very characteristic of this type of substitution.

The strong *meta* band near 1214 cm.$^{-1}$ is interesting. Even when the number of *m*-substituted rings increases from sample to sample (III, VIII, XI) the frequency does not change by more than one wave number. Thus for 1,3-disubstitution in aryl ethers, the frequency is depressed considerably below the limits for *m*-substitution set by Colthup.[8]

EXPERIMENTAL

Details of several experimental conditions used in the preparation of the ethers are reported. With the exception of XXII, XXIX, and XXX, the preparations reported in Table I were carried out essentially by the detailed procedure reported for bis(*p*-phenoxyphenyl) ether (II). An

TABLE I (*Contd.*)

PHENYL ETHERS

Catalyst, g.	Time, hr.	Temp.	Yield, %	M.P.°	B.P.°/mm.	n_D^{20}	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2	4	180–210	—	46.5–47.5[a] / 59.5–60	145–151/0.3	—	82.4	5.4	82.4	5.4
—	—	—	—	110.3[c]	245/2	—	—	—	—	—
5	20	230–250	74	41.1[c]	217–221/0.07	1.6234	81.3	5.1	81.4	5.1
3	10	250	22	122.0	185–215/0.4	—	81.3	5.1	81.5	5.2
3[e]	2	180–220	81	83.7[c]	209–219/0.8	—	—	—	—	—
3[e]	2	180–220	74	48.0[c]	230–235/0.15	—	—	—	—	—
3[e]	2	180–220	73	73.9[c]	207–213/0.15	—	—	—	—	—
3	6	210–240	54	oil	295–305/1.0	1.6322	80.7	5.0	80.8	5.0
7	6.5	210–230	39	77–79	290–307/1.0	—	80.7	5.0	81.0	5.0
5	4	250	39	88–89	287–293/0.3	—	80.7	5.0	80.8	5.0
4	5	240–245	42	oil	255–272/0.07	1.6380	80.3	4.9	80.5	4.9
5	8	205–208	35	oil	335–362/0.25–0.35	1.6420	80.0	4.8	79.9	4.8
	3	240–255								
6	2.5	250	22	87.5–88.5	337–375/0.2–0.6	—	80.0	4.8	80.0	4.8
				87–88	195–228/0.5	—	—	—	—	—
10	6	205–225	50	oil	190–200/0.7	—	78.1	5.5	78.2	5.5
10	2	240–260	61	53–55	182–186/0.5	—	83.0	7.0	83.0	6.9
10	2	250–300	56	58–60	250/1—	—	—	—	—	—
0.5	3.5	200–290	66	79.5–81	292–300/1	—	82.4	7.3	82.3	7.4
0.5	5	180–300	53	58–59	285–295/0.3	1.5823	82.6	7.7	82.6	7.8
20	3	200–250	66	oil	176–182/0.2 / 185–189/1—	1.5973 / 1.5971	83.0	7.0	83.1	7.0
5	4	220–280	76	oil	183–200/0.2	1.5888	83.1	7.3	83.0	7.3
				oil	204/0.25—	1.5633	—	—	—	—
15	3	200–250	59	55–56	230–234/0.5	—	85.2	6.4	85.2	6.4
1	2	210–290	73	oil	230–234/0.5	—	86.7	6.9	86.8	6.9
10	1	250	70	oil	300/0.5	—	85.4	6.5	85.4	6.6
5	2	270–340	40	oil	360/1 μ	—	85.4	6.8	85.5	6.9
			19	oil	170–177/0.15	1.6165	63.4	3.8	63.3	3.9
				oil	204–207/0.5	1.6257	—	—	—	—
				242–243.5	—	—	—	—	—	—
				217–218.5	—	—	—	—	—	—

[a] Two crystal forms. [b] Abbreviations: DBB = dibromobenzene; BPPE = bromophenyl phenyl ether; Bis(*p*-BP)E = bis(*p*-bromophenyl) ether; 1-*m*-BP-3-PB = 1-(*m*-bromophenoxy)-3-phenoxybenzene. [c] These melting points were obtained from precision melting point curves. Calculated to be over 99.5% pure. [d] Density 1.18 g./ml. [e] Cuprous oxide catalyst. [f] Density 1.20 g./ml. [g] Purified by partial oxidation in a Dornte[17] apparatus followed by chromatography.

excess of the reported phenol was used as solvent in these cases. No particular effort was made to obtain the best possible yield. Melting and boiling points are uncorrected except as indicated. Some boiling point ranges may have a wide spread from superheating near the end of the distillation.

Bis(p-phenoxyphenyl) ether[11] (II). A mixture of phenol (103 g., 1.1 moles) and 86% potassium hydroxide (65 g., 1.0 mole) was heated until potassium phenate formed. Water and phenol were removed under vacuum at 130–145°. When potassium phenate began to separate from the mixture, distillation was stopped. Two grams of copper powder[16] and 148 g. (0.45 mole) of bis(*p*-bromophenyl) ether were added. On further heating a very vigorous reaction raised the temperature to 220°. After 2 hr. at this temperature with occasional shaking, the reaction mixture was poured into xylene and the hot suspension was filtered. Excess phenol was extracted with 20% potassium hydroxide solution. After washing with water and drying over magnesium sulfate, the xylene was evaporated and the product distilled, b.p. 220–240°/1 mm. Recrystallization from acetone gave 115 g. (72%), m.p. 109.5–110°.

Anal. Calcd. for $C_{24}H_{18}O_3$ (354.4): C, 81.3; H, 5.1. Found: C, 81.2; H, 5.1.

1-(o-Phenylphenoxy)-4-phenoxybenzene (XIII). From 272 g. (1 mole) of 97% sodium *o*-phenylphenate tetrahydrate, 189 g. (0.8 mole) *p*-bromophenyl phenyl ether, and 10 g. of copper at 275–300° for 5 hr., 196 g. of product, b.p. 195–228°/0.5 mm. was obtained. Crystallization from acetone-methanol gave a 58% yield, m.p. 87–88°.

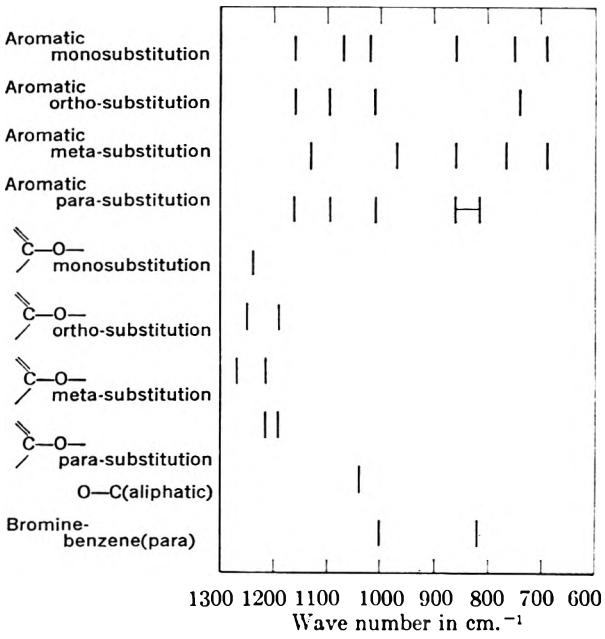
Anal. Calcd. for $C_{24}H_{18}O_2$ (338.4): C, 85.2; H, 5.4. Found: C, 85.2; H, 5.4.

p-(p-α-Cumylphenoxyl)phenyl pivalate (XXII). A mixture of 160 g. (0.53 mole) of *p*-(*p*-α-cumylphenoxy)phenol, 160 ml. of pyridine, and 150 ml. of toluene was treated with

(16) R. Brewster and T. Groening, *Org. Syntheses*, Coll. Vol. II, 445 (1943).

TABLE II

CORRELATION CHART, ARYL ETHERS



68 g. (0.57 mole) of pivalyl chloride and refluxed 6 hr. The mixture was poured into an ice–hydrochloric acid slurry and the organic layer was separated, washed with water, dilute sodium hydroxide solution, and water. It was dried over magnesium sulfate, filtered, and distilled. The fraction boiling at 204°/0.25 mm., 171 g. (83%) was collected.

Anal. Calcd. for $C_{26}H_{26}O_3$ (388.5): C, 80.4; H, 7.3. Found: C, 80.8; H, 7.3.

m-(m-Phenoxyphenoxy)bromobenzene (XXVIII). *m*-Phenoxyphenol (500 g., 2.67 moles) was heated to 130° and treated with 140 g. (2.12 moles) of 85% potassium hydroxide. Bis[2-(2-methoxyethoxy)ethyl] ether (200 ml.) was added as a solvent and water was removed under vacuum. The hot solution was added dropwise during 2 hr. to a rapidly stirred mixture of 1 kg. (4.24 moles) of *m*-dibromobenzene and 17 g. of copper catalyst at 180–200°. The mixture was stirred at 230–240° for 4 hr. and was cooled, filtered, diluted with toluene, and extracted with 10% aqueous potassium hydroxide solution. The product layer was washed with water and the solvent was evaporated. The oily residue was distilled through a 1″ × 30″ column packed with protruded stainless steel packing. A forecut of 485 g. of *m*-dibromobenzene was recovered. The product, 503 g., b.p. 204–207°/0.5 mm., n_D^{20} 1.6257, was obtained in 70% yield.

Anal. Calcd. for $C_{18}H_{13}O_2Br$ (341.2): C, 63.4; H, 3.8. Found: C, 63.5; H, 3.9.

Bis(o-tert-butylphenoxymethyl)durene (XXX). Bis(chloromethyl)durene (46 g., 0.2 mole) was refluxed with a mixture of 60 g. (0.4 mole) of *o-tert*-butylphenol and 26 g. (0.4 mole) of 86% potassium hydroxide in 500 ml. of acetone and 250 ml. of toluene for 8 hr. The product, which crystallized from the hot reaction mixture, was filtered and washed with acetone. It was boiled with 500 ml. of water for 0.5 hr. filtered, and washed with water and acetone. The product was dissolved in boiling toluene; the solution was filtered hot and concentrated to 300 ml. Cooling gave 61 g. (67%), m.p. 217–218.5°.

Anal. Calcd. for $C_{32}H_{42}O_2$ (458.7): C, 83.8; H, 9.2. Found: C, 83.8; H, 9.2.

Bis(p-tert-butylphenoxymethyl)durene (XXIX) was prepared as above without toluene in the reaction step, from bis(chloromethyl)durene and *p-tert*-butylphenol in 28% yield, m.p. 242–243.5°.

Anal. Calcd. for $C_{32}H_{42}O_2$ (458.7): C, 83.8; H, 9.2. Found: C, 83.8; H, 9.3.

o-Bromophenyl phenyl ether. o-Aminophenyl phenyl ether[18] (51 g., 0.275 mole) was converted to the diazonium bromide and added to a boiling mixture of 43.3 g. (0.3 mole) of cuprous bromide and 39 ml. of 48% hydrobromic acid during 45 min. The reaction mixture was refluxed an additional half hour. After cooling, the product was extracted with ether and the extract was washed with 5% hydrochloric acid, 10% potassium hydroxide, and water. The product was dried and distilled from a Vigreux-Claisen flask. The product was dried and distilled from a Vigreux-Claisen flask. The fraction boiling at 97–100°/0.1 mm. was recrystallized from methanol to give 47.4 g. (69%), m.p. 43.5–44.5°.

Anal. Calcd. for $C_{12}H_9OBr$ (249.1): C, 57.9; H, 3.6; Br, 32.1. Found: C, 57.9; H, 3.7; Br, 32.4.

m-Bromophenyl phenyl ether. This product was prepared from *m*-aminophenyl phenyl ether[13] by a procedure identical with that used for the preparation of *o*-bromophenyl phenyl ether. Distillation in a packed column gave a 58% yield, b.p. 156–158°/10 mm., n_D^{20} 1.6076.

Anal. Calcd. for $C_{12}H_9OBr$ (249.1): C, 57.9; H, 3.6; Br, 32.1. Found: C, 57.9; H, 3.7; Br, 32.4.

m-Phenoxyphenol.[12,13] (1) A mixture of 50 g. (0.25 mole) of 3-phenoxyanisole, 82 g. (0.5 mole) of 48% hydrobromic acid, and 200 ml. of glacial acetic acid was treated with 60 ml. of acetic anhydride and refluxed 5 hr. Most of the solvent was distilled. The residue was treated with water, extracted with xylene, and the xylene solution was extracted with aqueous potassium hydroxide solution. The aqueous layer was washed with xylene and the product was liberated with carbon dioxide. The ether extract of the product was dried and distilled to yield 35.5 g. (76%), b.p. 143–146°/2 mm., n_D^{20} 1.6005.

Anal. Calcd. for $C_{12}H_{10}O_2$ (186.2): C, 77.4; H, 5.4. Found: C, 77.4; H, 5.5.

(2) *m*-Phenoxyaniline (185 g., 1 mole) was diazotized with 700 ml. of 6*N* sulfuric acid and 71 g. (1 mole) of sodium nitrite. The solution was filtered to remove a small amount of unchanged amine sulfate. Excess nitrous acid was destroyed with urea and the diazonium salt was slowly poured into boiling 6*N* sulfuric acid. After an additional 5 min. the mixture was cooled, extracted with ether, and the product extracted from the ether with potassium hydroxide solution. The basic layer was washed with ether, acidified with acetic acid, and the product extracted with ether. On distillation, 112 g. (60%) of *m*-phenoxyphenol, b.p. 165–167°/7 mm., was obtained.

(3) *m*-Bromophenyl phenyl ether (87 g., 0.35 mole) was added to a solution of 65 g. (1 mole) of 86% potassium hydroxide in 600 ml. of diethylene glycol and the mixture was stirred at 200–205°. The reaction was followed by dilution of an aliquot with water and centrifugation. It was complete after 36 hr. The mixture was poured into water, extracted with toluene, and the aqueous layer was acidified with hydrochloric acid. The product was extracted with toluene and distilled to give a 60% yield, b.p. 157–159°/4 mm.

m-(p-Phenoxyphenoxy)phenol. 1-(*m*-Methoxyphenoxy)-4-phenoxybenzene (290 g., 1 mole) was refluxed with 600 ml. of 48% hydrobromic acid in 800 ml. of glacial acetic acid for 72 hr. The reaction mixture was diluted with water and the product was extracted with benzene. Distillation gave 245 g. (88%), b.p. 207–216°/1 mm. In another run the product boiled at 200–206°/0.5 mm.

m-(m-Phenoxyphenoxy)phenol. m-(m-Phenoxyphenoxy)-bromobenzene (450 g., 1.32 moles) was stirred with 218 g. (3.3 moles) of 85% potassium hydroxide and 1500 ml. of diethylene glycol at 230–240° for 2 hr. The reaction mixture was cooled, diluted with water, and extracted with

(17) R. W. Dornte, *Ind. Eng. Chem.*, 28, 26 (1936).

(18) C. M. Suter, *J. Am. Chem. Soc.*, 51, 2581 (1929).

toluene. The aqueous layer was acidified with hydrochloric acid and the product extracted with toluene. The toluene layer was washed with water; the toluene was evaporated and the product distilled, b.p. 222–230°/1 mm., 180 g., (49.5%), n_D^{25} 1.6188.

Anal. Calcd. for $C_{18}H_{14}O_3$ (278.3): C, 77.7; H, 5.1. Found: C, 77.4; H, 5.1.

Acknowledgment. The authors wish to thank J. J. Shook for the preparation of several of the compounds, C. A. Reilly for NMR spectra, F. S. Mortimer for aid in the evaluation of the infrared absorption spectra, E. R. Barnum for helpful discussions, and the Materials Laboratory, Wright Air Development Center for permission to publish this information.

EMERYVILLE, CALIF.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, PUREX CORPORATION, LTD.]

N-Halogen Compounds. II.[1,2] The N—Cl Stretching Band in Some *N*-Chloroamides. The Structure of Trichloroisocyanuric Acid

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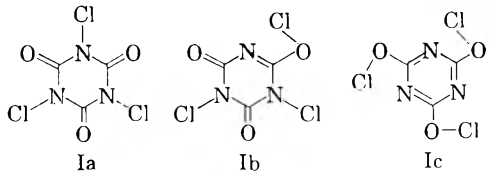
Received August 10, 1959

The infrared spectrum of solid trichloroisocyanuric acid is interpreted as confirming the keto structure Ia of Chattaway and Wadmore. The 650–900 cm.$^{-1}$ region of thirteen *N*-chloroamides and of some of their congeners was examined. All the chlorinated cyanuric acids and benzenesulfonamide derivatives studied as well as 1,3-dichloro-5,5-dimethylhydantoin contained a band between 762 and 803 cm.$^{-1}$ which is probably essentially an N-Cl stretching frequency. Compounds containing N-Cl attached to more weakly electronegative groups, such as *N*-chlorosuccinimide and *N*-chloroacetamide, did not have such a band. The preparation of some halogen derivatives of cyanuric acid is described.

As part of a program of examining solid compounds for bleaching activity we have run the infrared spectra of a number of *N*-chloroamides. The main object has been to build a library of reference spectra for identification purposes, but we have studied some of them in detail when structural questions arose, and have sought new spectra-structure correlations.

Early in the work it became of practical importance to know whether crystalline trichloroisocyanuric acid (I) was, as Chattaway and Wadmore[4] believed, all in the keto form Ia, or whether it was in some tautomeric form such as Ib or Ic, or was a mixture of two or more such forms.



Ia Ib Ic

The available chemical evidence,[1,4] which we confirmed by a molecular weight determination, make it quite certain that I is a trimer, $(CClNO)_3$. Estimates of bond and resonance energies definitely indicate that Ia should be the most stable form, thermodynamically. Nevertheless, in the absence of physical evidence for the location of the chlorine atoms, no definite conclusion could be reached.

No physical evidence for the location of the chlorine in any chloroamide has been found in the literature. However, the infrared spectra of six bromoamides reported by Lacher, Olson, and Park[5] were in accord with a keto-*N*-bromo structure, and a number of amides not containing positive halogen, including cyanuric acid, have been shown[6,7] to be completely in the keto form in the solid state by both x-ray and infrared studies.

The infrared spectrum of crystalline trichloroisocyanuric acid (Fig. 1 and Table I) turned out to be surprisingly simple, as it exhibited only six well-defined bands. In a twelve-atom molecule, this scarcity of bands indicates a symmetrical and probably a planar structure, and favors structure Ia or Ic over forms such as Ib. The strong band near 1740 cm.$^{-1}$ must be due to carbonyl absorption and the shift in its frequency from 1710 cm.$^{-1}$ in cyanuric acid[6] is in the direction expected. The frequency in cyanuric acid may be lowered by hydrogen bonding which is not possible for I, and it seems reasonable for an average of one chlorine substituent *alpha* to the carbonyl, and probably in the same plane, to raise the C=O stretching frequency

(1) Paper I, R. C. Petterson and U. Grzeskowiak, *J. Org. Chem.*, **24**, 1414 (1959).

(2) Presented before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, N. J., September 16, 1959.

(3) Present addresses: (a) Department of Chemistry, Imperial College, London S.W.7; (b) National Research and Chemical Co., Hawthorne, Calif.

(4) F. C. Chattaway and J. M. Wadmore, *J. Chem. Soc.*, **81**, 191 (1902).

(5) J. R. Lacher, G. G. Olson, and J. D. Park, *J. Am. Chem. Soc.*, **74**, 5578 (1952).

(6) R. Newman and R. M. Badger, *J. Am. Chem. Soc.*, **74**, 3545 (1952).

(7) S. Mizushima, T. Simanouti, S. Nagakura, K. Kuratani, M. Tsuboi, H. Baba, and O. Fujioka, *J. Am. Chem. Soc.*, **72**, 3490 (1950).

TABLE I

FREQUENCIES ($CM.^{-1}$) OBSERVED FOR TRICHLOROISOCYANURIC ACID

Film, evaporated on AgCl	1739	1360	1335	1154	800	696
Mull, in Nujol	1742	—	—	1153	800	698
Assignment	C=O		Ring stretching		N—Cl	?

TABLE II

FREQUENCIES IN THE 650–900 $CM.^{-1}$ REGION

Compound	Location of Bands							N-Cl Stretching
Cyanuric Acid Derivatives (See Figs. 2 and 3)								
Dichloroisocyanuric acid	790	748	709	699				790
Sodium dichloroisocyanurate	890	803	789	755	749	742		803,789
Sodium dichloroisocyanurate dihydrate	789	749	738	728	706			789
Potassium dichloroisocyanurate	787	764	746	740	699			787
Potassium dibromoisocyanurate	754	734						—
Benzenesulfonamide Derivatives (See Figs. 4 and 5)								
p-(Dichlorosulfamyl)benzoic acid	865	845	822	782	763	755	683	782 (755?)
p-Sulfamylbenzoic acid	864	767	687					—
N,N-Dichlorobenzenesulfonamide	891	851	771	749	683			771
Benzenesulfonamide	904	840	755	688				—
N,N-Dichloro-*p*-toluenesulfonamide	892	814	800	762	698			762 (800)
p-Toluenesulfonamide	809	704	667					—
N,N,N',N'-Tetrachlorotoluene-2,4-disulfonamide	889	849	842 sh.		774	744	[711]	774 (744?)
	696	666						
Toluene-2,4-disulfonamide	896	835	700	672				—
Hydantoin Derivatives (See Fig. 6)								
1,3-Dichloro-5,5-dimethylhydantoin	784	732	712					784?
1-Chloro-5,5-dimethylhydantoin	795	760	744	663				?
5,5-Dimethylhydantoin	801	769						—
1,3-Dibromo-5,5-dimethylhydantoin	855	770	734					—
Others								
N-Chlorosuccinimide	818	650 sh.						?
Succinimide	850	821	(733)					—
N-Bromosuccinimide	814	650 sh.						—
N-Iodosuccinimide	818							—
N-Chloroacetamide	826							?
Acetamide	876							—

by 25–30 $cm.^{-1}$[8] The strong doublet at 1335 and 1360 $cm.^{-1}$ and the weak band at 1154 $cm.^{-1}$ resemble fairly closely the main ring-stretching bands[6] of cyanuric acid, which has a strong band at 1470 $cm.^{-1}$ and a weak doublet at 1050 and 1065 cm^{-1}. *s*-Triazine differs greatly, having ring stretching frequencies at 1556, 1410, and 675 $cm.^{-1}$[9] Thus it seems almost certain that trichloroisocyanuric acid has structure Ia in the solid state.

The two remaining strong bands at 698 and 800 $cm.^{-1}$ are more difficult to explain. The former is, perhaps fortuitously, similar to an unidentified band at 695 $cm.^{-1}$ in cyanuric acid and no assignment can be made for it at present. The 800 $cm.^{-1}$ band is probably not related to the weak 807 $cm.^{-1}$ frequency of cyanuric acid which has been tentatively ascribed[6] to N-H bending; it might possibly be due to N-Cl stretching. The few known N-Cl bands have rather lower frequencies, *viz.* NH_2Cl, 686; $NHCl_2$, 687 and 666; and NCl_3, 652 $cm.^{-1}$,[10,11] but certain substituents on the nitrogen should cause an increase in an N-Cl stretching frequency. There is no obvious reason why N-Cl stretching should not vary at least as much as C-Cl stretching, which is found from 600 to 800 $cm.^{-1}$[12]

In the hope of verifying this tentative assignment the spectra of thirteen N-Cl compounds of several types and of some of their N-H and N-Br congeners were run as mulls and the curves examined for evidence of bands due to N-Cl. The frequencies of

(8) According to E. J. Corey and H. J. Burke, *J. Am. Chem. Soc.*, **77**, 5418 (1955), equatorial *alpha* substitution of chlorine in cyclohexanones raises the carbonyl frequency by 26–31 $cm.^{-1}$

(9) J. E. Lancaster and N. B. Colthup, *J. Chem. Phys.*, **22**, 1149 (1954).

(10) G. E. Moore and R. M. Badger, *J. Am. Chem. Soc.*, **74**, 6076 (1952).

(11) A. G. Pulford and A. Walsh, *Trans. Far. Soc.*, **47**, 347 (1951), state that a 595 $cm.^{-1}$ band in nitrosyl chloride corresponds essentially to N-Cl stretching.

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, N. Y., 2nd ed., 1958, p. 330.

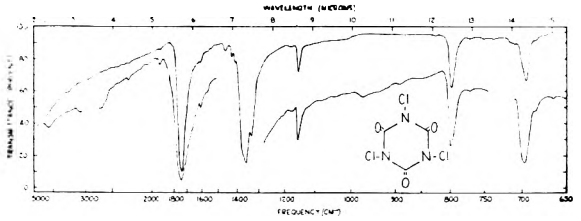


Fig. 1. Infrared spectrum of trichloroisocyanuric acid in Nujol mull (lower) and as a crystalline film (upper)

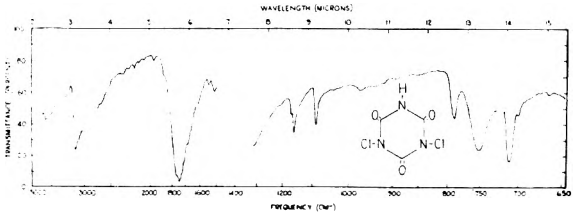


Fig. 2. Infrared spectrum of dichloroisocyanuric acid (Nujol)

bands found in the 650–900 cm.$^{-1}$ are listed in Table II. Bands near 720 cm.$^{-1}$ are unfortunately distorted or obscured by the Nujol peak in this region but no practical way of avoiding the use of the oil was found (see Experimental).

The spectra of six cyanuric acid derivatives are presented in Figs. 1–3. The N-Cl compounds all have a medium intensity band near 800 cm.$^{-1}$, which is at 800 cm.$^{-1}$ in trichloroisocyanuric acid, shifts to 787–790 cm.$^{-1}$ in dichloroisocyanuric acid (II) and its sodium and potassium salts, but is absent in potassium dibromoisocyanurate. In the anhydrous sodium salt this band has split into a 789, 803 cm.$^{-1}$ doublet, rather weaker than the single band in the dihydrate. In Figs. 1 and 2 I, with three N-Cl bonds, has a stronger peak, relative to the carbonyl stretching band, than II, which has only two N-Cl bonds. It seems likely that the N-Cl stretching frequencies for these chlorinated cyanuric acid derivatives lie between 785 and 803 cm.$^{-1}$.

Comparison of the spectra of four aromatic sulfonamides with those of their *N*-chloro derivatives (Figs. 4 and 5) reveals that all the bands present in the 650–900 cm.$^{-1}$ region of each sulfonamide seem to be present (slightly shifted) in the corresponding N-Cl compound. In addition, each chloro compound has a band between 762 and 782 cm.$^{-1}$, probably an N-Cl stretching frequency; three of them also exhibit another band in the 744–800 cm.$^{-1}$ region, which may be a second N-Cl band, namely *p*-(dichlorosulfamyl)benzoic acid (755 cm.$^{-1}$, Fig. 4), *N,N,N',N'*-tetrachlorotoluene-2,4-disulfonamide (744 cm.$^{-1}$, Fig. 5), and *N,N*-dichloro-*p*-toluenesulfonamide (800 cm.$^{-1}$, Fig. 5).

In the hydantoins (Fig. 6) the two possessing N-H groups have weak bands at 795–801 cm.$^{-1}$ which seem to be absent in the dichloro and dibromo compounds and may be caused by N-H. The medium intensity peak at 784 cm.$^{-1}$ in 1,3-dichloro-5,5-dimethylhydantoin may be an N-Cl

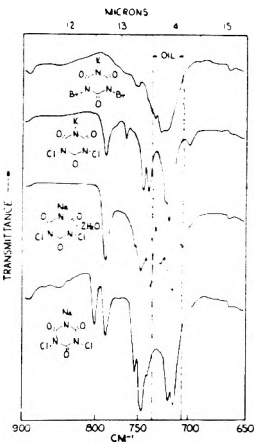


Fig. 3

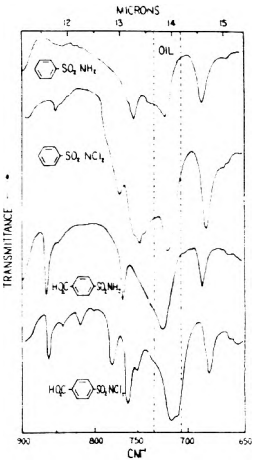


Fig. 4

Fig. 3. Infrared spectra of sodium dichloroisocyanurate and its dihydrate, potassium dichloroisocyanurate, and potassium dibromoisocyanurate (Nujol)

Fig. 4. Infrared spectra of *p*-(dichlorosulfamyl)benzoic acid, *p*-sulfamylbenzoic acid, *N,N*-dichlorobenzenesulfonamide, and benzenesulfonamide (Nujol)

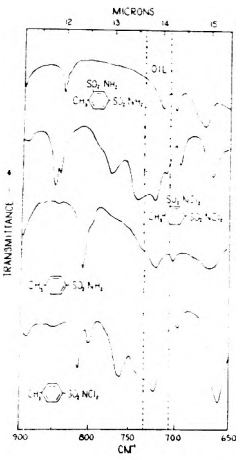


Fig. 5

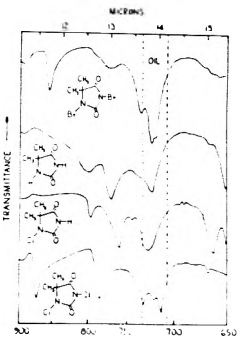


Fig. 6

Fig. 5. Infrared spectra of *N,N*-dichloro-*p*-toluenesulfonamide, *p*-toluenesulfonamide, *N,N,N',N'*-tetrachlorotoluene-2,4-disulfonamide, and toluene-2,4-disulfonamide (Nujol)

Fig. 6. Infrared spectra of 1,3-dichloro-5,5-dimethylhydantoin, 1-chloro-5,5-dimethylhydantoin, 5,5-dimethylhydantoin, and 1,3-dibromo-5,5-dimethylhydantoin (Nujol)

stretching frequency, although it may be related instead to the unidentified 760–770 cm.$^{-1}$ band present in the other three hydantoins. The spectrum of the 1-chloro derivative in this region seems to resemble that of the unhalogenated compound closely; no N-Cl assignment can be made.

In *N*-chlorosuccinimide no band attributable to N-Cl was found in the 650–900 cm.$^{-1}$ region. It has a strong peak at 818 cm.$^{-1}$ which is also present in the N-H, N-Br, and N-I derivatives (see Table II) and nothing else down to about 650 cm^{-1}. *N*-chloroacetamide does not show any bands in this region either except for a broad, weak absorption near 826 cm^{-1}.

From the rather large range of the frequencies which have been assigned to N-Cl stretching, it is obvious that the vibrations responsible are by no means localized completely in the N-Cl group. Motions of the other groups attached to nitrogen must be involved and the mass of such substituents ought to be an important factor. In the case of the chlorosulfonamides, other influences must be cancelling out the effect of the large mass of the sulfur atom relative to carbon for the frequencies for N-Cl in the chlorosulfonamides to come out in the same range as some of those in chloroamides.

Electronic effects must be quite important, as it is striking that only those compounds with rather strongly electronegative substituents on the N-Cl group show N-Cl bands in the region studied. For instance, although both trichlorocyanuric acid and *N*-chlorosuccinimide contain the —CON-ClCO— group, the fact that this group is bound to a highly electronegative —NClCONCl— grouping in the former but to the electropositive —CH_2-CH_2— group in the latter evidently results in a great difference in N-Cl frequency in the expected direction. On the other hand, it is surprising that the salts of dichloroisocyanuric acid have bands at only slightly lower frequencies than that of the parent acid.

Not much diagnostic use can be made of these empirical correlations at present. Fortunately, the presence of an N-Cl group in an amide can generally be readily detected iodometrically if it is assumed that the chlorine in chloroamides is always bound to nitrogen, a view which the foregoing evidence tends to support.

EXPERIMENTAL[13]

Infrared spectra. The infrared spectra described were run as mulls in Nujol between sodium chloride discs except for the crystalline film curve of I (Fig. 1). The latter is the spectrum of ten thin layers of crystals on a silver chloride disc deposited by rapid evaporation of successive drops of a fresh dilute solution of I in acetonitrile; a silver chloride disc was in the reference beam. No inert solvent capable of dissolving all the compounds of interest is known, and dispersions of N-Cl compounds in potassium bromide and potassium chloride pressed discs invariably gave spectra differing considerably from mull spectra. Decomposition was occurring in some cases, as the pellets sometimes developed orange (potassium bromide) or green (potassium chloride) colors. Deposition of crystalline films from solution without decomposition was not always possible, and, with dichloroisocyanuric acid, the spectra of films on silver chloride differed both from films on sodium chloride and from a mull but different from that of a film on sodium chloride. Mull spectra were always reproducible.

Materials. Pure *trichloroisocyanuric acid* was obtained by recrystallization of commercial material from warm ethylene chloride in the form of colorless needles, m.p. 246–247° dec., (lit.[4] m.p. about 245°).

Anal. Calcd. for $C_3N_3O_3Cl_3$: mol. wt., 232; Av. Cl, 91.53. Found: mol. wt. (cryoscopic, in benzene[14]), 237; Av. Cl, 91.13

Dichloroisocyanuric acid separated when an ice-cooled aqueous solution of its sodium salt was acidified with cold 3% sulfuric acid. It was collected, washed, and dried at 105° for 1.5 hr.; m.p. 226.4–226.7°. The absence of cyanuric acid as an impurity was shown by the complete solubility of the sample in acetonitrile.

Anal. Calcd. for $C_3HCl_2N_3O_3$: Av. Cl, 71.65. Found: Av. Cl, 71.58.

Crude sodium dichloroisocyanurate, kindly furnished by Westvaco Mineral Products Division, Food Machinery and Chemical Corp., crystallized from water as colorless needles which proved to be the *dihydrate.*

Anal. Calcd. for $C_3Cl_2N_3NaO_3.2H_2O$: Av. Cl, 55.41; water, 14.05. Found: Av. Cl, 55.42; weight loss in 45 min. at 105°, 13.95.

The solid remaining after heating was *sodium dichloroisocyanurate.*

Anal. Calcd. for $C_3Cl_2N_3O_3Na$: Av. Cl, 64.48. Found: Av. Cl, 64.37.

Potassium dichloroisocyanurate was prepared by dissolving potassium sulfate (4.36 g.) in an iced solution of sodium dichloroisocyanurate (11.0 g.) in water (60 ml.). The colorless crystals which separated were washed with water and dried at 115°.

Anal. Calcd. for $C_3Cl_2N_3O_3K$: Av. Cl, 60.08. Found: Av. Cl, 59.06.

To a solution of potassium bromide (23.8 g., 0.2 mole) in water (500 ml.) was added a solution of sodium dichloroisocyanurate (22 g., 0.1 mole) in water (200 ml.); crude *potassium dibromoisocyanurate* (26 g., 79% yield) was obtained by filtering, washing, and drying at 115° the colorless crystals which separated. Aqueous solutions of the substance liberated bromine on treatment with concd. hydrochloric acid. Recrystallization from water was accompanied by decomposition.

Anal. Calcd. for $C_3Br_2KN_3O_3$: Av. Br, 98.36. Found: Av. Br, 93.74.

p-Toluene-2,4-disulfonamide, obtained by reduction of its tetrachloro derivative with excess concd. aqueous ammonia, was recrystallized from water three times, m.p. 185–186° (with previous sintering near 174°) (lit.[15] m.p. 186–187°).

The samples of 5,5-dimethylhydantoin and its 1-chloro and 1,3-dichloro derivatives used have been described previously.[1] *N*-chloroacetamide, made by a known method,[16] melted at 110° (lit.[16] m.p. 110°).

The following compounds were dried *in vacuo* over phosphorus pentoxide, and used without further purification: benzene- and *p*-toluenesulfonamide, and *N*-bromosuccinimide (Eastman Kodak Co.); *N*-iodosuccinimide (Arapahoe Chemicals, Inc.); and *p*-(dichlorosulfamyl)benzoic acid (Dow Chemical Co.); 1,3-dibromo-5,5-dimethylhydantoin (Glyco Products Co., Inc.); *N,N*-dichlorobenzenesulfonamide and *N,N*-dichloro-*p*-toluenesulfonamide (Monsanto Chemical Co.); and *p*-sulfamylbenzoic acid (Boots Pure Drug Co., Ltd., England).

Acknowledgments. The authors are grateful to Dr. Robert C. Ferris for encouragement, and to the Purex Corporation, Ltd. for permission to publish.

South Gate, Calif.

(13) Melting points are uncorrected. The infrared spectra were run on a Perkin-Elmer Model 21 Spectrometer having a sodium chloride prism by Mr. Everett P. Honorof. It was frequently calibrated against ammonia. Some preliminary spectra were run at the University of Southern California by Mr. William J. Schenck to whom we are indebted for helpful advice on techniques.

(14) Determined by Mr. Laszlo L. Low.

(15) C. Fahlberg, *Ber.*, 12, 1048 (1879).

(16) A. Hantzsch and F. E. Dollfus, *Ber.*, 35, 252 (1902).

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

The Mechanism of the Oxidation of 2-Propanol by Peroxydisulfate Ion

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Received September 26, 1958

A reinvestigation of the kinetics and mechanism of the aqueous peroxydisulfate oxidation of 2-propanol has been carried out by two different experimental techniques. The direct interaction of the reagents can be studied only after oxygen inhibition and trace metal catalysis are eliminated. Mechanistic pathways for the reaction are discussed, and free radical chain sequences consistent with the data are presented.

The kinetics of the oxidation of alcohols by peroxydisulfate ion have been studied several times[2-6] but the results have not led to a satisfactory understanding of the reaction mechanism. In order to clarify the points of disagreement to be found in the literature and particularly to test the mechanisms postulated by Levitt[4,6] the present studies[1] were carried out, primarily on 2-propanol as the reductant.

EXPERIMENTAL

Materials. Two samples of 2-propanol were used with identical results. One sample, Eastman Spectro-Grade, was used without purification; the other, Union Carbide and Carbon 99%, was purified by refluxing over calcium oxide followed by distillation. The potassium peroxydisulfate, B & A Reagent Special Grade, was initially used without purification; careful recrystallization from conductivity water caused a significant decrease in rate (see below). Other materials including Na_2H_2Y (the disodium salt of ethylenediaminetetraacetic acid) were best grade available and were used without further purification. The early experiments were carried out with good quality distilled water; some later experiments were run with conductivity water.

Titration runs. Two methods for following the reaction were employed. The first method was by iodometric analysis of unchanged peroxydisulfate. As the reaction proceeds at a convenient rate, standard procedures for pipetting and analyzing aliquots were employed.

Spectrophotometric runs. Because of several difficulties (nonlinear plots, oxygen interference, catastrophes, etc.) which will be discussed below, it was desirable to find an alternative method for following the kinetics of this reaction. A spectrophotometric method was developed which involved the continuous measurement of absorbance at 2725 Å versus time with the Beckman DK-1 Recording Spectrophotometer. This wavelength was picked to give maximum change in absorbance during the course of a run. Acetone has a broad, rather weak absorption band centered at 2640 Å, while peroxydisulfate absorbs in a continuum from about 3600 Å out to beyond 2000 Å. With an initial peroxide concentration of 0.05*M* and a five-fold excess of alcohol (nonabsorbing) a change in absorbance ($A = \log I_0/I$) from about 0.45 to 0.90 was obtained over the course of the entire reaction. Normally the recorder was run at a chart speed of 0.5 inches per min. However, it was possible to interrupt a kinetic run at any point and rapidly scan the entire ultraviolet spectrum.

The early spectrophotometric experiments were made using a phosphate-sulfate buffer of *p*H 8.0 and ionic strength 0.5 as Levitt and Malinowski[4] had done. Comparable results were obtained, however, if the reaction were run in distilled water; thus the buffer was not employed in later runs. In all cases the reference solution was of the same composition as the reacting solution, with the omission of the peroxydisulfate. Matched ground-glass stoppered silica cells of 10-mm. path length were employed.

In the runs in which it was desired to exclude oxygen, the peroxide solution was saturated with nitrogen gas by bubbling the solution at 25° in an external Pyrex vessel for 2 hr. This 250-ml. vessel was equipped with a condenser jacket through which water from a constant temperature bath could be circulated to bring the solution up to temperature prior to the beginning of the run. The calculated amount of alcohol was added through a self-sealing rubber stopper with a hypodermic syringe at zero time and the solution rapidly mixed with a magnetic stirrer. The solution was then pumped under nitrogen into the spectrophotometer cell, which was equipped with a ground-glass adapter, allowing the cell to be thoroughly rinsed by several cell volumes of the reacting solution and filled without contacting the air. The solution remaining in the external vessel was used to follow the kinetics simultaneously by iodometric titration.

Temperatures within the spectrophotometer were maintained to ±0.5° by means of a thermostated cell holder through which constant temperature water was circulated. The entire mixing and transfer procedure took less than 1 min. A similar procedure was followed for the runs made in solutions saturated with oxygen. When the exclusion of air was not required, the solution of peroxydisulfate was allowed to come to temperature in the cell in the spectrophotometer. Alcohol was then added directly to the cell from a micropipette and the solution mixed by shaking; this procedure required about 15 seconds.

RESULTS

Stoichiometry. Yields of 88 ± 3% of acetone were isolated from the 2-propanol oxidation by precipitation of the ketone as its 2,4-dinitrophenylhydrazone. No other organic product could be found. In the ultraviolet spectra, an isosbestic point at 2570 Å persisted throughout the course of the reaction. Within the experimental error of the spectral method (0.01 absorbance units, or about ±2%), this plus the change in absorbance at 2725 Å confirm the stoichiometry of the reaction as

$$S_2O_8^{--} + R_2CHOH \longrightarrow 2SO_4^{--} + R_2CO + 2H^+$$

(1) (a) Ph.D. Thesis at Brown University (1956). (b) Ph.D. Thesis at Brown University (1960).

(2) P. D. Bartlett and J. D. Cotman, *J. Am. Chem. Soc.*, **71**, 1419 (1949).

(3) I. M. Kolthoff, E. J. Meehan, and E. M. Carr, *J. Am. Chem. Soc.*, **75**, 1439 (1953).

(4) L. S. Levitt and E. R. Malinowski, *J. Am. Chem. Soc.*, **77**, 4517 (1955); **78** 2018 (1956); **80** 5334 (1958).

(5) K. B. Wiberg, *J. Am. Chem. Soc.*, **81** 252 (1959).

(6) (a) L. S. Levitt, *Can. J. Chem.*, **31** 915 (1953); (b) L. S. Levitt, *J. Org. Chem.*, **20**, 1297 (1955).

TABLE I

SUMMARY OF TITRATION DATA ON THE PEROXYDISULFATE OXIDATION OF 2-PROPANOL AT 40°

pH	μ	[P(V)][a]	$[Na_2H_2Y]$	$[SO_4^{--}]_0$	$[R_2CHOH]_0$	$[S_2O_8^{--}]_0$	k, min.$^{-1}$
8	0.5	0.05M	0	0.10M	0.05M	0.02M	1.5×10^{-3}[b]
8	1.5	0.5	0	0	0.02	0.02	—
8	1.5	0.5	0	0	0.42	0.02	0.5×10^{-3}
3–2	0.06	0	0	0	0.42	0.02	1.0×10^{-3}
3–2	0.06	0	0	0	0.42	0.02	1.0×10^{-3}
3–2	0.06	0	0	0	0.42	0.02	0.5×10^{-3}
3–2	0.06	0	0	0	0.83	0.02	0.7×10^{-3}
8	1.5	0.5	$4 \times 10^{-4}M$	0	0.42	0.02	[c]
3	0.06	0	4×10^{-4}	0	0.42	0.02	[c]

[a] Concentration of total phosphate. [b] Value predicted by the data of Levitt and Malinowski.[4] [c] Observed decrease in $[S_2O_8^{--}]$ did not exceed the usual experimental error in the course of six hours. See text.

where R_2CHOH signifies 2-propanol and R_2CO signifies acetone.

Titration runs. A summary of kinetic experiments at 40° are presented in Table I. Generally the reaction was followed over the course of one half-life, and in such cases the reaction appeared to be first order in peroxydisulfate concentration. However, in runs carried over more than one half-life, the first order plots showed a small but significant sigmoid-shaped wiggle about the best straight line; this curvature, which was definitely outside the experimental error and will be mentioned later, is an indication of a complicated mechanism.

The possible effect of *p*H on the reaction was studied. Runs were made in solutions buffered by phosphate at *p*H 8 and in unbuffered solutions, in which the *p*H generally varied from 3 to 2 in the course of one half-life. Although there was a fairly wide variation (0.5×10^{-3} to 1×10^{-3} min.$^{-1}$) in the values of the apparent first order rate constants at 40°, no significant dependence on *p*H exists for the observed first order oxidation.

In their original study of the oxidation at 60°, Levitt and Malinowski[4] used an initial concentration of 0.02M for $S_2O_8^{--}$ and varied the initial concentration of R_2CHOH from 0 to 0.2M; a limiting first order rate was observed using an initial concentration of 0.05M for R_2CHOH. In the present titration study at 40°, the initial concentration of $S_2O_8^{--}$ was always 0.02M. When an initial concentration of 0.02M was used for R_2CHOH, there was no apparent reaction. No significant variation in the observed first order rate constant occurred when the initial concentration of R_2CHOH was varied from 0.42 to 0.83M.

A significant result of these data is the fact that the observed first order rate constants at 40° were sometimes less than the value predicted by Levitt and Malinowski (obtained using their observed value of 1.05 hr.$^{-1}$ for the limiting first order rate constant at 60° and their reported value of 26 kcal./mole for the Arrhenius activation energy). The kinetic studies of Levitt and Malinowski were made using reaction solutions containing rather large amounts (0.1M) of sulfate ion, to which those authors ascribed an inhibiting effect on the rate of the oxidation. The fact that slower rates were observed in the present study, even though no sulfate ion was added to the reaction solutions, is particularly noteworthy. Also, in the presence of small amounts ($4 \times 10^{-4}M$) of the powerful sequestering agent Na_2H_2Y the observed rate was markedly reduced; there was no apparent reaction during time intervals comparable to the time of one half-life in the absence of Na_2H_2Y.

In Fig. 1, data on the oxidation of three alcohols by peroxydisulfate ion are shown. Before the addition of Na_2H_2Y (shown by vertical bars) all three rates are identical within the experimental error; the first order rate constants are 2.1×10^{-3}, 1.9×10^{-3}, and 2.0×10^{-3} in units of min.$^{-1}$ for methanol, ethanol, and 2-propanol respectively. Also, these rates are not the same as those presented in Table I, for a different batch of buffer was employed. Although the rates after addition of Na_2H_2Y were too slow to be determined accurately, all three reactions are inhibited in the same way and to a similar degree by this sequestering agent.

Additional data, which were obtained at 50°, are presented in Table II; the results are similar to those obtained at 40°. It was observed, however, that the peroxydisulfate ion reacts with Na_2H_2Y. At 50° in solutions buffered at *p*H 8, about 5% of the peroxydisulfate (in the absence of alcohol) reacted during the first three hours of the run; subsequently, the observed first order rate slowed down to a value equal to that observed in the absence of Na_2H_2Y. The first order rate constant (k = *ca.* 0.8×10^{-4} min.$^{-1}$), observed at 50° at *p*H 8 in the absence of Na_2H_2Y, compares favorably with the value reported by Kolthoff and Miller[7] ($k = 0.87 \times 10^{-4}$ min.$^{-1}$ at *p*H 7 and at 50°) for the oxidation of water by peroxydisulfate ion. The rate of this oxidation has been shown[7] not to be explicitly dependent on *p*H (except in strong acid) or ionic strength. Returning to the peroxydisulfate reaction with Na_2H_2Y, the initial concentration of Na_2H_2Y was 0.0006M compared with 0.02M for $S_2O_8^{--}$; it is suggested that two peroxydisulfate

(7) I. M. Kolthoff and I. K. Miller, *J. Am. Chem. Soc.*, **73**, 3055 (1951).

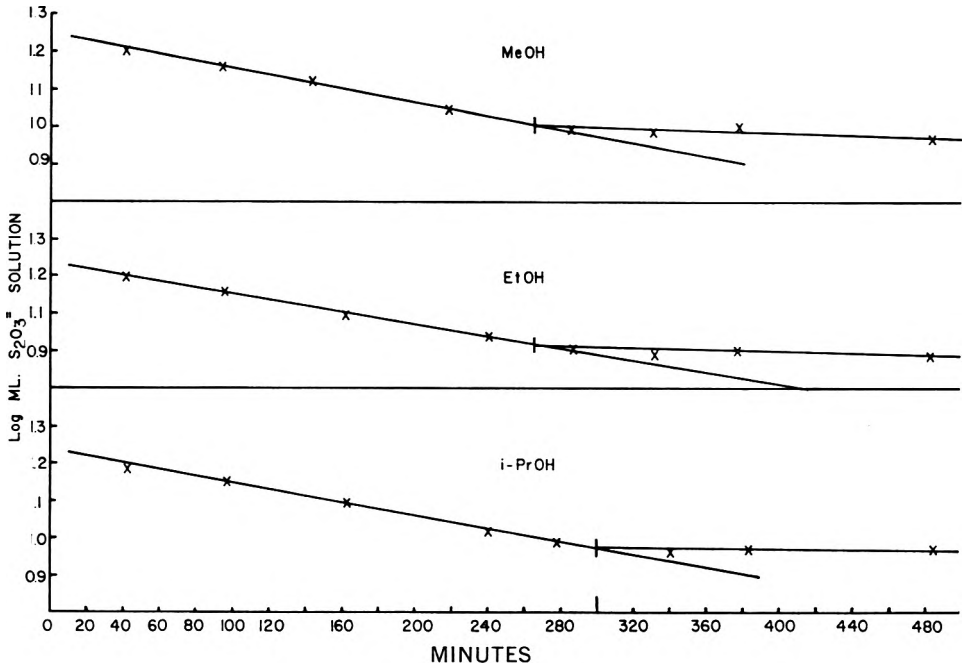

Fig. 1. Results obtained by the titration method for the oxidation of three alcohols (methanol, ethanol, and 2-propanol) by peroxydisulfate ion at 50°. The vertical bar indicates the point of addition of complexing agent

ions reacted with one molecule of Na_2H_2Y. Possibly oxidation occurs at the two amino nitrogens of the Na_2H_2Y molecule[8]

At *p*H 8 in phosphate buffer, which contains no Na_2H_2Y, $S_2O_3^{--}$ oxidizes R_2CHOH rapidly. The oxidation appears to be first order in the concentration of $S_2O_8^{--}$. A value of 2.0×10^{-3} min.$^{-1}$ for the first order rate constant was observed for the oxidation in the absence of Na_2H_2Y; the value for k predicted by the results of Levitt and Malinowski is 5.3×10^{-3} min.$^{-1}$

In the presence of Na_2H_2Y ($6 \times 10^{-4}M$), the oxidation proceeded slowly at first. These initial portions of the runs were plotted as first order in the concentration of $S_2O_8^{--}$ and the apparent rate constants listed in Table II. Variations in the initial concentration of R_2CHOH from 0.22 to 0.88M produced no apparent change in the indicated rate constant. However, after the passage of from three to six hours, a relatively rapid decrease (*ca.* $5 \times 10^{-3}M$) in the concentration of $S_2O_8^{--}$ occurred. Subsequently, the oxidation readopted an apparent first order behavior, but the reaction was somewhat less rapid than before the "catastrophe." Subsequent experiments, described below, revealed the cause of this behavior as interaction of dissolved oxygen with reaction intermediates.

Spectrophotometric data. The problem of the presentation of the experimental data obtained with the spectrophotometer is somewhat complicated by the complexity of the reaction. For this reason, the various factors affecting the reaction are discussed below in an order which attempts to be systematic (rather than chronological). Pertinent tables of data are included as needed. A complete summary of the experimental runs is given elsewhere.[1b]

Effect of oxygen. The most striking result obtained was the observation of a definite inhibition period, the length of which depended on the amount of dissolved oxygen present in the solution. When the solution was rigorously deprived of oxygen, a quite rapid reaction was observed which appeared pseudo-first-order in persulfate in the presence of a large excess of alcohol. When the reaction was run in the closed cell with solution which had been in equilibrium with the air, a much slower reaction with a rate which remained apparently constant was observed for a reproducible period of time lasting from 3 to 124 minutes (depending on conditions). At the end of this inhibition period there was a sudden significant increase in rate to the value found in the absence of oxygen, and pseudo-first-order kinetics ensued and continued until the completion of the reaction. When the reaction was run in a solution saturated with oxygen, the inhibition period continued until the persulfate was exhausted although after about one half-life the rate slowed down and approached higher order kinetics before completion. Spectrophotometer plots for these three cases in buffered solution at 60° are shown in Fig. 2. It is obvious from these results that at least two separate reactions are involved. For simplicity of discussion the slow, initial reaction involving oxygen will be called reaction A; and the rapid reaction which takes place in the absence of oxygen

(8) N. M. Beileryan, *Nauch. Trudy Erevan. Gosudarst. Univ. Ser. Khim. Nauk*, 60, 143 (1957); *Chem. Abstr.*, 53 11081 (1959).

TABLE II

SUMMARY OF TITRATION DATA ON THE PEROXYDISULFATE OXIDATION OF 2-PROPANOL AT 50°

pH	μ	[P(V)][a]	$[Na_2H_2Y]$	$[SO_4^{--}]_0$	$[R_2CHOH]_0$	$[S_2O_8^{--}]_0$	k, min.$^{-1}$ × 10^3
7	0.13	ca.0.04M	0	0	0	0.01M	0.087[b]
10	0.13	0	0	0	0	0.01	0.068[b]
8	1.5	0.5	0	0	0	0.02	ca. 0.08
8	1.5	0.5	0	0	0	0.02	ca. 0.08
8	0.5	0.05	0	0.1M	0.05	0.02	5.3[c]
8	1.5	0.5	0	0	0.42	0.02	2.0
8	1.5	0.5	$6 \times 10^{-4}M$	0	0.22	0.02	0.38
8	1.5	0.5	6	0	0.42	0.02	0.53
8	1.5	0.5	6	0	0.42	0.02	0.42
8	1.5	0.5	6	0	0.42	0.02	0.42
8	1.5	0.5	6	0	0.88	0.02	0.38
8	1.5	0.5	6×10^{-5}	0	0.05	0.02	0.38

[a] Concentration of total phosphate. [b] Data obtained by Kolthoff and Miller[7]; carbonate buffer used at pH 10. [c] Value predicted by data of Levitt and Malinowski.[4]

will be referred to as reaction B. The sudden transition from A to B apparently corresponds to the exhaustion of dissolved oxygen. After reaction B had begun, simply removing the stopper from the spectrophotometer cell for a second to admit air, followed by brief shaking, was sufficient to stop B and cause the rate of A to be reassumed.

The catastrophies found in the titration experiments can be explained as the rapid increase in rate observed at the transition from reaction A to B upon the exhaustion of dissolved oxygen. This sudden transition is quite striking on the continuous curves obtained from the spectrophotometer. In the runs with distilled water this transition is even more sharp than for the buffered solution, although it was observed in both cases. The catastrophies were observed (as discontinuous gaps in the titration data) only when EDTA was present, as under these conditions the rate of disappearance of persulfate was sufficiently reduced for dissolved oxygen to become exhausted between infrequent titrations. This was possible as, even though EDTA greatly decreased the rate of loss of persulfate during reaction A, it did not significantly affect the length of time required to exhaust the dissolved oxygen (see Table III). The implications of this observation will be considered later.

Comparison of methods. It is known that persulfate ion can decompose by a photochemical reaction to produce radicals, as well as by a thermal process.[9] In order to show that photochemical decomposition was not responsible for the complex kinetics observed in the spectrophotometer, the kinetics of the reaction in several runs were followed simultaneously by iodometric titrations of the solution remaining in the external thermostated cell. Care was taken to minimize the introduction of oxygen during sampling. Curves showing the results obtained by the two methods are given in Fig. 3. The curves labeled I were obtained from the same solution, in the presence of an excess of oxygen. The curves labeled II were obtained from another solution, which had been purged of most of its dissolved oxygen with nitrogen gas. Notice that the transition from reaction A to reaction B occurs at the same time in the external sample as in the sample receiving ultraviolet radiation in the spectrophotometer. Slight differences in the concentrations detected by the two methods are to be expected, as quenching of the reaction solution for the titrations was insufficiently fast compared to the rate of the fast reaction B. Also, despite precautions, oxygen seems to have been introduced into the titration experiment before completion. It is obvious, however, that the same major kinetic process is being monitored in both cases, and that the effects observed are not due to photochemical initiation of persulfate decomposition within the spectrophotometer.

From the comparison discussed in this section and from the results shown in Figs. 2 and 3, one definite conclusion can be drawn. The rates observed in the titration experiments were (excepting, of course, the catastrophies) those for reaction A. Therefore, the conclusions drawn from the results

TABLE III

THE EFFECT OF VARIOUS INHIBITORS ON REACTION RATES

Added Substance[a]	R(A)[b]	τ(A)[c]	$k_{1/2}$(B)[d]
None	1.8×10^{-3}	5.5	0.96
Triethylamine	2.0×10^{-3}	5.8	0.85
Triethylamine and acetic acid	2.2×10^{-3}	5.3	0.86
EDTA	0.40×10^{-3}	5.3	0.86
EDTA	0.50×10^{-3}	5.5	1.00
None[e]	0.59×10^{-3}	5.3	0.87
$[S_2O_8^{--}]_0 = 0.049M$; $[R_2CHOH]_0 = 0.39M$; unbuffered solution		60.0°;	

[a] Concentration = $10^{-5}M$. [b] Initial rate of reaction A in moles/l.$^{-1}$/min.$^{-1}$ [c] Inhibition period in minutes. [d] Rate of reaction B in l.$^{1/2}$/mole$^{-1/2}$/min.$^{-1}$ [e] Recrystallized potassium peroxydisulfate in de-ionized water.

(9) M. S. Tsao and W. K. Wilmarth, *J. Phys. Chem.*, **63**, 346 (1959).

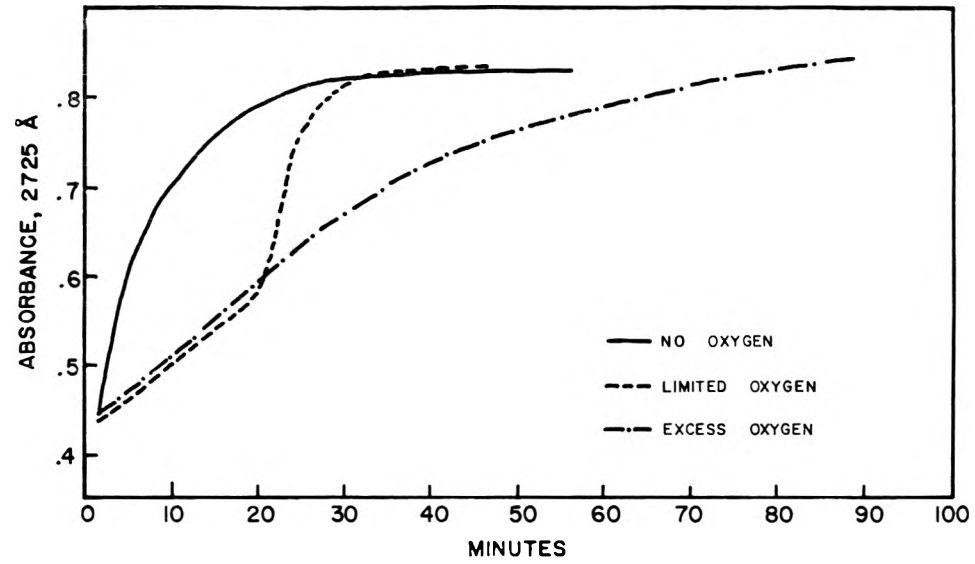

Fig. 2. Plots of absorbance at 2725 Å versus time for three runs with different initial amounts of dissolved oxygen at 60° in buffered solution

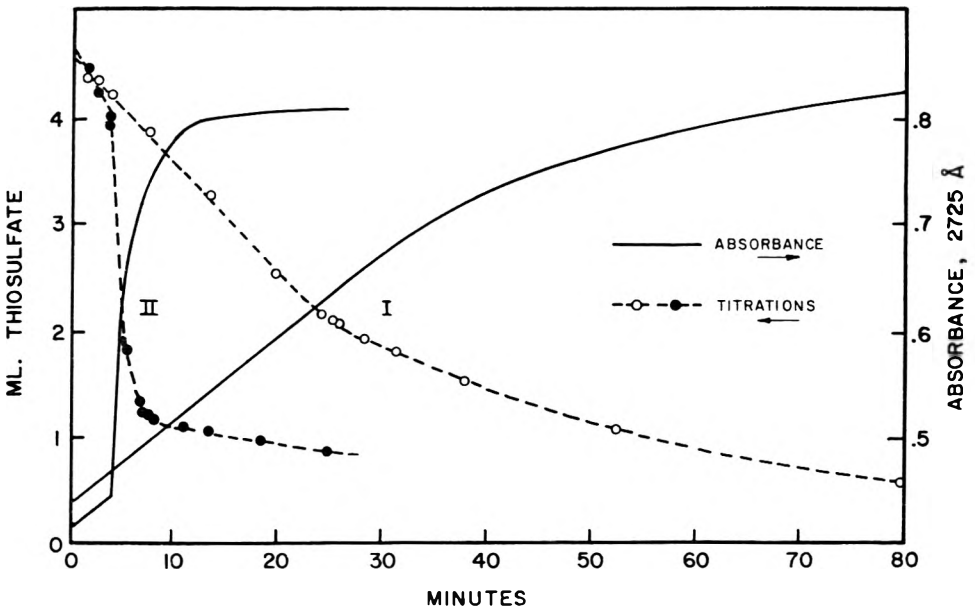

Fig. 3. Kinetic experiments to demonstrate that the two analytical methods give comparable results

of titration runs may be carried over to the sections below dealing with reaction A.

Reaction A orders. Reaction A is observed only in the presence of dissolved oxygen gas. A plot of absorbance *vs.* time is linear over as much as one half-life (see Fig. 2), making the reaction appear initially zero order in all reactants. At longer reaction time, however, the reaction slows down, approaching higher order kinetics. By varying the initial concentration of each component, the reaction was zero order in alcohol and zero order in oxygen, but not zero order in persulfate. The initially constant rate *vs.* time is then an indication of a complex reaction.

The usable absorbance range of the spectrophotometer so limited the range over which the initial persulfate concentration could be varied that it was difficult to define definitely the order with respect to persulfate concentration by this method. As mentioned earlier, if the titration data for the reaction A are plotted as first order (see Fig. 4), the resulting curve, which is reasonably fitted by the dotted straight line, actually has a soft sigmoid shape. This sigmoid shape was observed in spectrophotometric runs as well as titration runs. The spectrophotometric method, by providing a continuous curve rather than scattered points, emphasizes the deviations from linearity, which are definitely greater than the experimental error. Further discussion of this nonlinearity will be postponed until after the evidence for mechanistic complexities has been discussed.

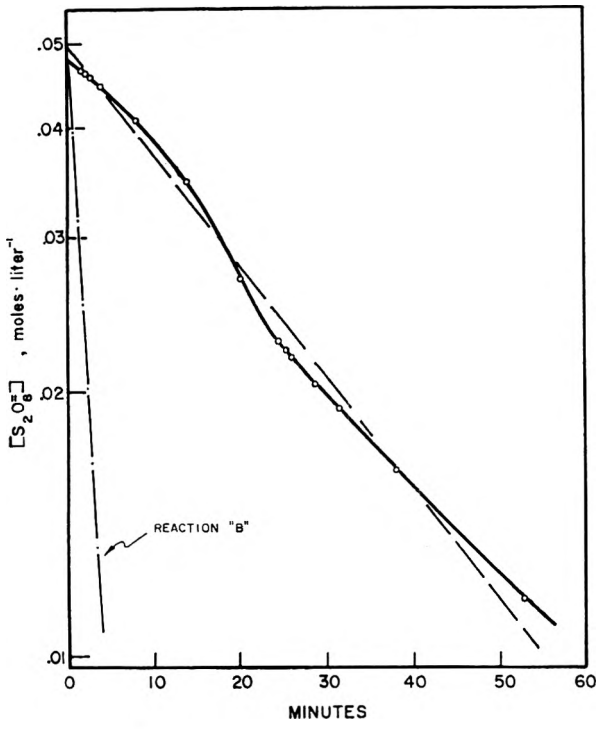

Fig. 4. Titration data demonstrating the sigmoid character of the first order plot for reaction A

Trace metal catalysis. The effect of EDTA on the rate is considered to be due to sequestration of trace metal impurities which exert a catalytic influence. Although it was observed that persulfate reacts slowly with higher concentrations of EDTA, probably by oxidation at nitrogen,[8] the inhibiting effect observed here with traces of EDTA is attributed to sequestration of trace metal catalysts rather than reaction with EDTA, as traces of substances with similar functional groups, but no strong chelating ability, gave no retardation of rate (see Table III).

In an attempt to discover the ion or ions responsible for the trace metal catalysis, a series of trace impurities were intentionally introduced into reacting solutions, and their effect on the rate of reaction A observed. From the series of ions—Ag^+, Ce^{+4}, Co^{+2}, Cr^{+3}, Cu^{+2}, Fe^{+2}, Fe^{+3}, Hg^{+2}, Mg^{+2}, Mn^{+2}, Ni^{+2}, Sn^{+4}, and Zn^{+2}—added so that their concentrations were approximately 10^{-5} *M*, only Cu^{+2} was observed to exert a noticeable catalytic effect. While this does not prove that Cu^{+2} is the only catalyst involved, it is certainly the most effective one observed. The presence of catalytic impurities was confirmed upon purification of the potassium peroxydisulfate by several recrystallizations from conductivity water. This reduced the initial rate of reaction A to a value approaching that observed in the presence of EDTA. Using recrystallized potassium peroxydisulfate, the initial rate of reaction A was then measured as a function of added Cu^{+2} ion. The data are summarized in Table IV. Assuming that Cu^{+2} is the impurity which is removed by the recrystallizations, the data allow estimates of the amount of Cu^{+2} originally present. Solutions of the unrecrystallized persulfate correspond to an added copper concentration of $10^{-5}M$. One recrystallization from conductivity water reduced the rate to that observed in the presence of 10^{-7} *M* Cu^{+2}, while two recrystallizations reduced the rate almost to that observed in the presence of EDTA.

TABLE IV

THE EFFECT OF RECRYSTALLIZED PERSULFATE AND ADDED CUPRIC ION ON THE INITIAL RATE OF REACTION A

$K_2S_2O_8$ Recrystallizations	Substance Added	Concentration Moles-l.$^{-1}$	Ratio Rate/Minimum Rate[a]
0	None	—	7.9
1	None	—	4.6
2	None	—	1.5
3	None	—	1.9
1	EDTA	10^{-5}	1.0
2	Cu^{+2}	10^{-8}	2.5
2	Cu^{+2}	10^{-7}	4.5
2	Cu^{+2}	10^{-6}	7.3
2	Cu^{+2}	10^{-5}	7.9
2	Cu^{+2}	10^{-4}	8.6
2	Cu^{+2}	10^{-4}	8.6

$[S_2O_8^{--}]_0 = 0.049M$; $[R_2CHOH]_0 = 0.39M$; temperature = 60.0°; unbuffered solution

[a] The minimum rate, observed with EDTA present, had an average value of 0.45×10^{-3} moles/l.$^{-1}$/min.$^{-1}$.

From the stability constant of the EDTA-Cu^{+2} complex[10] log K = 18.8, negligible free Cu^{+2} obviously is present in solution with added EDTA. Copper is a reasonable impurity to expect in persulfate, whose solutions are known to dissolve metallic copper.[11] The heavy metal analysis of potassium peroxydisulfate reported on the reagent bottle, if attributed entirely to copper, is of the right order of magnitude to account for the observed impurities. Other cases of trace copper catalysis in persulfate reactions are known.[12-15]

The data in Table IV show that the dependence on added Cu^{+2} is not a simple order. Although an added Cu^{+2} concentration of 10^{-7} *M* more than quadruples the rate observed in its absence, further increasing the Cu^{+2} concentration by a factor of one thousand increases the rate by a factor less

(10) R. W. Schmid and C. N. Reilley, *J. Am. Chem. Soc.*, **78**, 5513 (1956).

(11) G. C. Bond, B. M. Hill, and R. Tennison, *J. Chem. Soc.*, 33 (1959).

(12) T. L. Allen, *J. Am. Chem. Soc.*, **73**, 3589 (1951).

(13) C. H. Sorum and J. O. Edwards, *J. Am. Chem. Soc.*, **74**, 1204 (1952).

(14) O. A. Chaltykyan, A. N. Mamyan, and R. V. Mousesyan, *Nauch. Trudy Erevan. Gosudarst, Univ. Ser. Khim. Nauk*, **60**, 135 (1957); *Chem. Abstr.*, **53**, 10925 (1959).

(15) Y. K. Gupta and S. Ghosh, *J. Inorg. & Nuclear Chem.*, **11**, 62 (1959).

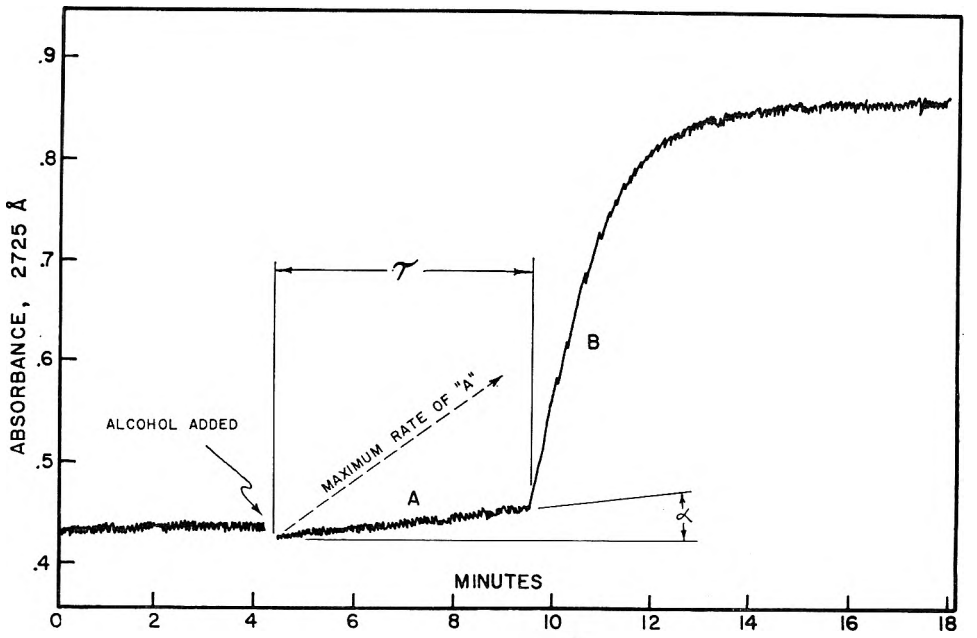

Fig. 5. A typical spectrophotometer trace at 2725 Å showing reaction A, reaction B, the induction period τ, and the initial angle α

than two. This indicates that the catalytic effect of Cu^{+2} reaches an upper limiting value at approximately 10^{-4} M. Reaction A must be zero order in copper ion above this concentration. This can account for the fact that previous workers have reported comparable rate constants, as at a Cu^{+2} concentration as low as 10^{-6} to 10^{-5} M, the rate is insensitive to small changes in copper concentration, although the small amount present has a very significant catalytic effect.

The length and rate of reaction A. A typical spectrophotometer trace is shown in Fig. 5 for a run at 60.0° in unbuffered solution using thrice recrystallized persulfate. Air is initially present, and the initial concentrations of persulfate and 2-propanol are $0.049M$ and $0.39M$, respectively. The maximum rate of reaction A, observed in the presence of added Cu^{+2}, is indicated by the dashed line. There are two important variables which were measurable for reaction A as it was normally observed on the spectrophotometer trace. The first is the length of time elapsed between the addition of alcohol and the sudden increase in rate at the onset of reaction B. This corresponds to the length of time required to use up the dissolved oxygen. This time will be referred to as the length of the inhibition period, and identified by the symbol τ. There was negligible air space above the solution in the stoppered spectrophotometer cells, and for short τ the rate of diffusion of additional oxygen, as it dissolved, may be ignored. Hence, for a given set of conditions, τ is a measure of the original concentration of dissolved oxygen. Conversely, for a given original concentration of dissolved oxygen, τ is inversely proportional to the rate at which oxygen is consumed. The second variable is the tangent of the angle α produced by the recorder trace with the horizontal. For measurements made at identical initial persulfate concentration, this value is proportional to the initial rate of reaction A. The factors affecting these two variables were studied.

Let us first consider τ. Table III shows that it is essentially independent of added EDTA. It increased slightly in the presence of the maximum effective concentration of Cu^{+2}. It was inversely related to the initial alcohol concentration as shown in Fig. 6. This effect reached a limiting value at high alcohol concentration. As might be expected, it was strongly dependent on temperature, as this affected not only the rate of loss of oxygen, but also the solubility of oxygen. The observed data are presented in Table V. It was also observed that τ was as much as twice as long in buffered solution as in unbuffered; the reason for this is not completely clear.

TABLE V

THE TEMPERATURE DEPENDENCE OF REACTION RATES[a]

Temperature	τ, min.	Tangent α[b]	$k_{3/2}(B)$[c]
40°	124	0.044	—
45°	32	0.070	0.30
50°	19.3	0.105	0.46
55°	8.6	0.194	0.76
60°	6.4	0.270	1.45
65°	3.2	0.374	2.14
70°	2.6	0.499	2.85

[a] $[S_2O_8^{--}]_0 = 0.049M$; $[R_2CHOH]_0 = 0.39M$; unbuffered solution initially in equilibrium with air at 25°. [b] Proportional to the initial rate of reaction A. [c] Reaction B, units are $l.^{1/2}/mole^{1/2}/min.^{-1}$.

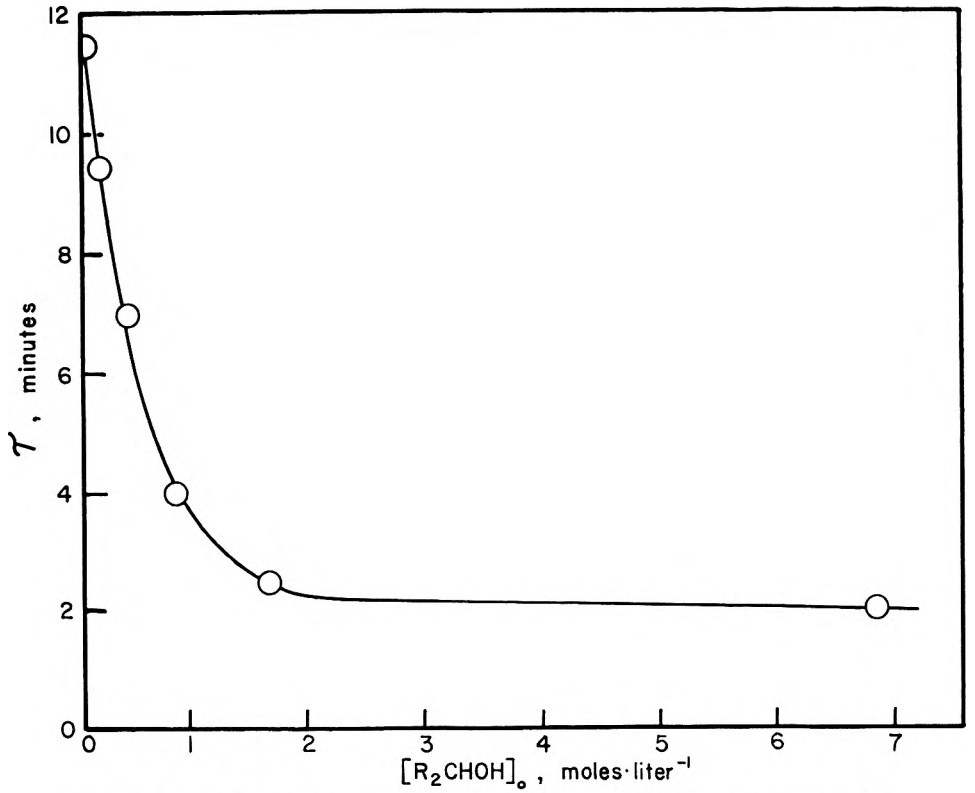

Fig. 6. Effect of alcohol concentration on the length of the induction period at 60°

The second variable, the initial rate of reaction A, was strongly dependent on the presence of EDTA or traces of Cu^{+2} as has already been discussed. The initial rate was independent of oxygen concentration. This may be seen in Figs. 2 and 3, as the initial rates are identical for different initial concentrations of dissolved oxygen. The sharp discontinuity in the spectrophotometer traces upon the exhaustion of dissolved oxygen provides additional evidence that the rate is independent of dissolved oxygen concentration until it is completely used up.

The initial rate was also independent of alcohol concentration, above $0.04M$, as demonstrated by the data of Table VI. This zero order behavior is consistent with the data of Tables I and II and with the findings of previous workers[4,5] under conditions where oxygen was not excluded. Although there is scatter in the measured initial rate values, there is clearly no rate dependence of the type of a kinetic order on alcohol concentration. Furthermore, this result predicts that the rate of reaction A should be independent of the nature of the alcohol; this was found in the experiments presented in Fig. 1.

The temperature dependence of the initial rate of A is included in Table V. It corresponds to an apparent activation energy of 18 kcal./mole. As $1/\tau$ is proportional to the rate at which dissolved oxygen is consumed, an approximate value for the activation energy of the reaction by which oxygen is lost may also be calculated. Although the solubility of dissolved oxygen varies with temperature, there was probably insufficient time for equilibrium solubility to be reached. The calculation was therefore made assuming identical initial oxygen concentration, regardless of temperature. A value of 25 to 27 kcal./mole was obtained from the resulting, approximately linear Arrhenius plot.

TABLE VI

The Effect of Alcohol Concentration on Initial Rates[a]

$[R_2CHOH]_0$, moles/l.$^{-1}$	Tangent α[b]	$k_{1/2}(B)$[c]
0.04	0.19	—
0.16	0.20	0.85
0.40	0.16	0.92
0.79	0.23	0.82
1.6	0.33	0.86
6.7	0.27	
	Avg. 0.23 ± 0.05	

[a] All measurements are at 60° and constant initial persulfate concentration (twice recrystallized). [b] Proportional to the initial rate of reaction A. [c] Rate constants units are $l.^{1/2}/mole^{-1/2}/min.^{-1}$

From the evidence which has just been presented, it may be seen that these two variables, τ and tangent α, which are related to the oxygen inhibition and the Cu^{+2} catalysis, respectively, are in some ways independent. The reaction with dissolved oxygen, which blocks the rapid reaction B, is not affected by the presence or absence of Cu^{+2} catalysis. The presence of oxygen, however, seems

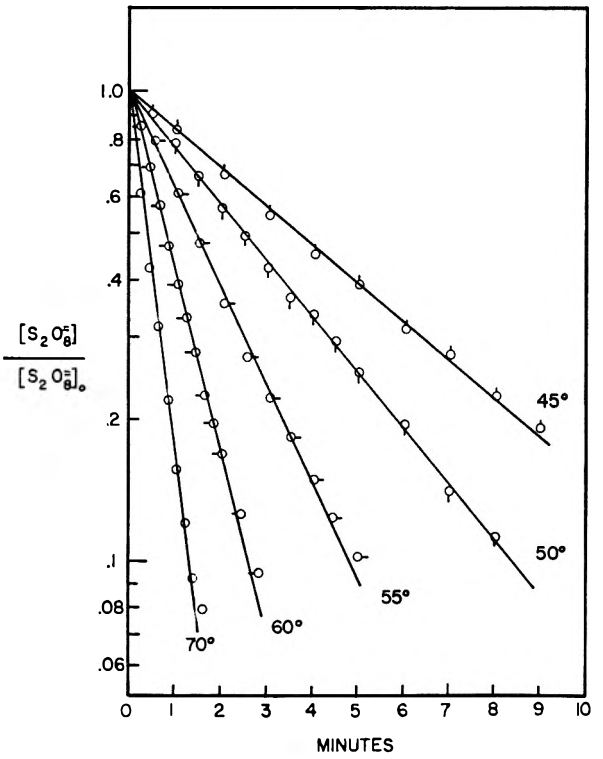

Fig. 7. Pseudo-first-order rate plots for reaction B at several temperatures; $[S_2O_8^{--}] = 0.049M$ and $[R_2CHOH] = 0.39M$

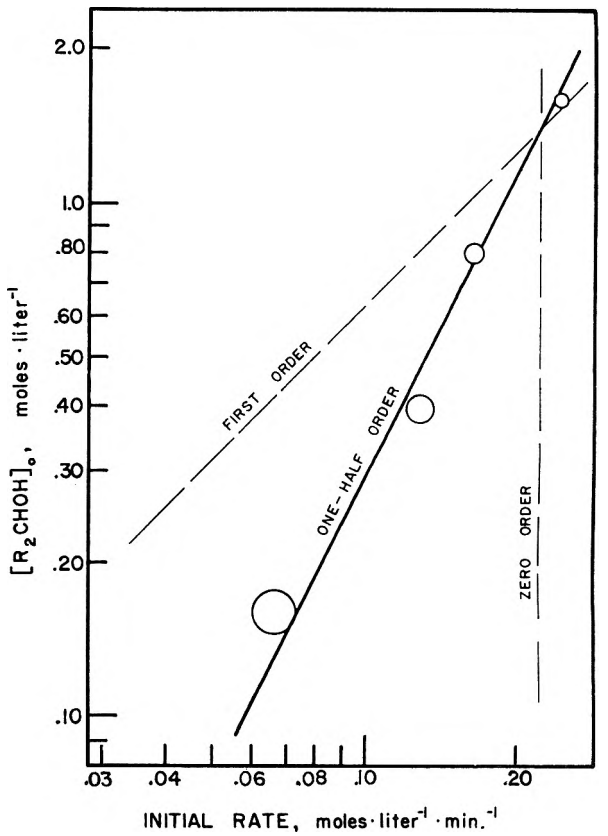

Fig. 8. Order plot demonstrating the dependence of the rate of reaction B on alcohol concentration

to be necessary for the metal catalysis, as reaction B is unaffected by Cu^{+2} or EDTA. There must be two reaction paths in reaction A. When the metal catalyzed path is removed by EDTA, the residual reaction—call it A_0—is simply the reaction by which dissolved oxygen is lost. Since the presence of Cu^{+2} catalysis does not shorten τ, the catalysis must proceed by a mechanism which does not introduce intermediates capable of increasing the rate of consumption of oxygen. This places rather stringent restrictions on the type of mechanisms which can be considered for reactions A and A_0. Unfortunately, neither EDTA nor recrystallization completely removed the influence of metal ions on the value of α, for this angle never decreased to the value predicted from the intrinsic rate of decomposition of persulfate. Therefore, in order to draw conclusions about reaction A_0, we limited ourselves to the information obtained from τ values.

Reaction B kinetics. Reaction B takes place only in the absence of oxygen. The introduction of a minute amount of oxygen into the reaction cell after B began immediately stopped B and the slower reaction A began again. As earlier workers apparently did not exclude oxygen, the kinetics of this reaction between persulfate and 2-propanol have not previously been studied.

Addition of EDTA or recrystallization of persulfate had no significant effect on the rate of reaction B as may be noted from the data of Table III. In experiments designed to test the influence of Cu^{+2} on the rate of reaction B, three runs with 0, 10^{-5}, and 10^{-4} M Cu^{+2} added were carried out with twice-recrystallized persulfate and de-ionized water. The rate constants obtained were 1.08, 1.07, and 1.06 $l.^{1/2}/mole^{-1/2}/min.^{-1}$, the variation observed therein is less than the expected error (see below).

The reaction appears pseudo-first-order in persulfate over four or five half lives when run in the presence of a large excess of alcohol. Pseudo-first-order rate plots for reaction B are shown in Fig. 7. The excellent linearity of the lines over 90% of the reaction confirms the order in persulfate. The observed rate constants are a function of the initial alcohol concentrations, however. By varying the initial alcohol concentration over a ten-fold range at constant initial persulfate concentration, the order in alcohol was shown to be one-half; some data are presented in Table VI. This one-half order behavior is demonstrated graphically in Fig. 8. The rate law for reaction B is therefore

$$\frac{d[S_2O_8^{--}]}{dt} = k[S_2O_8^{--}][R_2CHOH]^{1/2}$$

The apparent activation energy of reaction B was determined from runs at 45°, 50°, 60°, 65°, and 70° with the data presented in Table V. Within the experimental error, a linear Arrhenius plot was obtained, with a slope corresponding to an activation energy of 21 kcal./mole.

After our first trials dealing with the effect of

gases on rate, a procedure designed to minimize the diffusion of oxygen into the cell was worked out. Using this procedure, twenty-eight experiments at 60° giving values (from initial slopes) of the three-halves order rate constants were carried out. Values for initial rate constants between 0.70 and 1.08 $l.^{1/2}/mole^{-1/2}/min.^{-1}$ were obtained for twenty-six experiments; the other two were somewhat low (0.50 and 0.52), which suggests that oxygen was not completely excluded in these cases. The average constant and the average deviation for the twenty-six experiments was 0.91 ± 0.09 in units of $l.^{1/2}/mole^{-1/2}/min.^{-1}$ Although these rate constants from initial slopes of the B-part are not quite as accurate as those of Fig. 7 and 8, they show that the variation in $k_{3/2}$ is encouragingly small for such a complicated system; also, the inhibition period τ was never completely eliminated. However, the observed value of $k_{3/2}$ did not depend on the length of the inhibition period.

Comparison of reaction rates. Before proceeding to a discussion of possible mechanisms for these reactions, it will be helpful to make a summary comparison of the relative rates of all the reactions involved. This is given in Table VII below. The rates are based on the thermal decomposition of persulfate as unity. To make them consistent, they refer to initial rates which have been corrected to standard conditions of temperature and reactant concentrations. Due to changes in buffer, *p*H, trace impurities, etc. from one observer to another, the rate ratios may be expected to be only approximate. The fact that previous work lay in the range of the oxygen-inhibited, copper-catalyzed reaction is unmistakable, however.

TABLE VII

COMPARISON OF RELATIVE RATES[a]

Reactant	In Presence of	Observer	Relative Rate
H_2O	Air	Kolthoff[7]	1.000
H_2O	Air	Wiberg [5]	0.8
H_2O	Air	[b] 1b	1.1
R_2CHOH	Allyl acetate	Wiberg[5]	0.8
R_2CHOH	Air, EDTA	[b] 1a	5
R_2CHOH	Air, EDTA	[b] 1b	27
R_2CHOH	Air,[c]	[b] 1b	40
R_2CHOH	Air	[b] 1a	22–44
R_2CHOH	Air	Wiberg [5]	46
R_2CHOH	Air	Levitt [4]	65
R_2CHOH	Air; $10^{-4}M$ Cu^{+2}	[b] 1b	235
R_2CHOH	Nitrogen	[b] 1b	1800
R_2CHOH	Nitrogen, EDTA	[b] 1b	1800
R_2CHOH	Nitrogen; $10^{-4}M$ Cu^{+2}	[b] 1b	1800

[a] Based on initial conditions; $[S_2O_8^{--}]_0 = 0.049M$; $[R_2CHOH] = 0.39M$; 60°. [b] This study. [c] With twice recrystallized $K_2S_2O_8$.

DISCUSSION

Points of contention. Before the actual mechanistic steps for this oxidation reaction can be discussed, certain points of disagreement in the literature must be resolved. It is the purpose of this section to go over the evidence in order to arrive at a satisfactory conclusion on each point.

In this study, two previously unreported kinetic factors have been uncovered. The first of these is the catalysis up to a limiting rate of the persulfate-alcohol reaction by traces of copper ion. The evidence for this catalysis may be summarized as follows: a) Small amounts of Na_2H_2Y markedly slowed down the rates (in the A part) whereas comparable amounts of weakly coordinating reagents such as glycine or triethylamine had no effect on the rate, b) two recrystallizations of the potassium persulfate from conductivity water resulted in a decrease in rate approaching that observed in the presence of Na_2H_2Y, and c) addition of small amounts of copper ion caused a large increase in the rate when recrystallized persulfate was used.

The other factor, oxygen inhibition, is demonstrated by the following pieces of evidence: a) the sudden change in rate at the end of the A part is evidence for depletion of an inhibitor, b) the length of time of the A part (τ) varied directly with the initial oxygen concentration, c) shaking air into the cell after the B part has started causes the B part to cease and a new part A to begin, and d) the oxygen inhibition mechanism postulated below predicts a length of time for part A that agrees satisfactorily with the observed length.

It seems certain that the oxidation of alcohols by peroxydisulfate ion is a free radical reaction. In view of the fact that a polar mechanism has been put forth,[4,6] the evidence for the radical mechanism is worth reiterating: a) The rate of reaction is a sensitive function of the experimental conditions, b) the reaction is inhibited by oxygen which is normal for a chain reaction involving an organic radical, c) peroxydisulfate ion is known[7,9] to decompose by a radical mechanism, d) allyl acetate lowers the rate of loss of peroxydisulfate in the presence of alcohol to that observed for its free radical decomposition[5] thus no path independent of sulfate ion radicals can be present, e) Cu^{++} ion influences the rate of part A reaction, f) a one-half order as in the 2-propanol concentration dependence of the part B reaction is a characteristic of a radical reaction, and g) changes in order as concentrations vary[4] are found where several termination steps can compete.

One question which has been raised heretofore now seems answered: There seems to be no significant interaction of alcohol and peroxydisulfate in the initiation step. The reasons behind this conclusion are as follows: a) The overall order of the part B reaction is three-halves whereas it would have to be two if a bimolecular reaction constituted the initiation step, b) the rates of part A reactions are insensitive to alcohol concentration and to alcohol nature, c) the rate of loss of persulfate in

the presence of alcohol and allyl acetate agrees with the known decomposition rate for peroxydisulfate ion alone,[5] and d) no evidence for a bimolecular initiation step was found in the studies of Kolthoff, Meehan, and Carr[3] or of Bawn and Margerison.[16]

The present study and that of Wiberg[5] have brought forth considerable evidence which is contrary to the ionic mechanism postulated by Levitt for the peroxydisulfate oxidation of 2-propanol.[4,6] Some experimental points bearing on this matter are worth mentioning. a) There is no dependence of rate on sulfate ion concentration which would bear out the inverse first order dependence required by his mechanism. b) There has not been any evidence for a thermal peroxydisulfate–sulfate sulfur exchange[5,9,17] as required by his mechanism. c) The experimental observations of rate inhibition by allyl acetate[5] and by oxygen are positive proof that the rate constants found by Levitt must have arisen from a free-radical initiated mechanism. Any polar mechanism would be unaffected by these additives. d) Similarly the copper ion catalysis and the Na_2H_2Y inhibition are evidence against a polar displacement mechanism of oxidation. In view of the evidence, the mechanisms of Levitt[4,6] for the persulfate oxidation of 2-propanol must be considered incorrect. Indeed, the general applicability of any mechanism directly or indirectly involving a reversible, heterolytic reaction of persulfate such as proposed by Levitt for the oxidation of other substrates[6] also must be seriously questioned.

While we reject the mechanistic proposals of Levitt, we feel it is important to point out that the experimental data are not being questioned. Levitt and Malinowski[4] report and our results confirm that the reaction is zero order in alcohol concentration (when oxygen is present, of course). Also some of the kinetic plots of their latest paper seem to show the same soft sigmoid character that we have observed. Finally, the values for the first order rate constants which they reported are in the range of those rates we have observed for the A part of the reaction. For example we obtained initial rate values of 4.85×10^{-4} and 13.3×10^{-4} mole/l.$^{-1}$/min.$^{-1}$ for runs with no added copper and with 5×10^{-5} M cupric ion respectively, under a set of conditions (60°, $[S_2O_8^{--}] = 0.0485M$, $[R_2CHOH] = 0.396M$) for which the data of Levitt and Malinowski predict an initial rate value of 9.05×10^{-4}. Evidently, they never exhausted the oxygen supply nor did they remove the trace amounts of copper present in their reagents, and thus always observed the A portion of the reaction.

Mechanistic patterns. The results obtained here are surprisingly cleancut in that there are few kinetic patterns which can fit all of the data. Starting with reaction B which seems to be the least complicated part, the postulated chain mechanisms is

$$S_2O_8^{--} \xrightarrow{k_1} 2SO_4^{-}$$

$$SO_4^{-} + R_2CHOH \xrightarrow{k_2} HSO_4^{-} + R_2\dot{C}OH$$

$$R_2\dot{C}OH + S_2O_8^{--} \xrightarrow{k_3} R_2CO + HSO_4^{-} + SO_4^{-}$$

$$R_2\dot{C}OH + SO_4^{-} \xrightarrow{k_4} R_2CO + HSO_4^{-}$$

This predicts the rate law

$$R = \left(\frac{k_1k_2k_3}{k_4}\right)^{1/2} [S_2O_8^{--}][R_2CHOH]^{1/2}$$

in agreement with the observed expression. Since we have found that the chain length is greater than one thousand (see Table VII), the activation energies for k_2, k_3, and k_4 should be small; one predicts that the overall activation energy for the chain should lie between $^1/_2E_1$ and E_1 where E_1 is the activation energy of the k_1 step and has a value of about 31 kcal./mole^{-1}.[7,16] Our observed activation energy is 21 kcal./mole^{-1}, which is in good accord. Also, the rate constant observed for the B part should depend on the nature of the alcohol, as the ease of carbon-hydrogen bond breaking in the k_2 step would be expected to increase with methyl substitution on the carbinol carbon. Here again the agreement is excellent, for the rate of loss of persulfate in the B part is a factor of forty lower when methanol is oxidized than when 2-propanol is oxidized.[1b]

Rate inhibition by allyl acetate[5] and by oxygen must involve trapping of the radicals which carry the chain in the mechanism of part B. As persulfate has been reported to initiate polymerization of vinyl compounds through the sulfate ion radical,[18] it seems reasonable that allyl acetate reacts with the sulfate ion radical. Inhibition by oxygen, on the other hand, must involve the reducing radical $R_2\dot{C}OH$.

For the data of part A for the case of no contribution from metal ion catalysis, we postulate the following steps:

$$O_2 + R_2\dot{C}OH \xrightarrow{k_5} \cdot OOR_2COH$$

$$\cdot OOR_2COH + R_2CHOH \xrightarrow{k_6} HOOR_2COH + R_2\dot{C}OH$$

$$2 \cdot OOR_2COH \xrightarrow{k_7} O_2 + HOOR_2COH + R_2CO$$

The inhibition by oxygen can be traced to a very high rate constant for k_5 coupled with a low k_6 reactivity so that the peroxidic radicals build up in sufficient concentration to terminate the chain in the k_7 step. Such steps and their reactivities are

(16) C. E. H. Bawn and D. Margerison, *Trans. Faraday Soc.*, **51**, 925 (1955).

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discussed in the recent review on fundamental processes of autoxidation by Russell.[19]

Application of steady state treatment to the sequence k_1,k_2,k_5,k_6, and k_7 leads to the rate law

$$\frac{-d[O_2]}{dt} = k_1[S_2O_8^{--}] + k_6\left(\frac{k_1}{k_7}\right)^{1/2}[S_2O_8^{--}][R_2CHOH]$$

for the take-up of dissolved oxygen. As the inhibition period τ is related to the reciprocal of the rate, this law predicts that the value of τ should be related to the amount of oxygen initially present but not dependent on oxygen concentration as a kinetic order. The dependence on alcohol concentration also is as expected, for τ does decrease as alcohol concentration increases.

Using the step k_1 and the oxygen solubility in water for both of which we have values from the literature, one can compute an inhibition time using the mechanistic sequence, k_1,k_2,k_5, and k_7. For one experiment with an observed τ value of seventeen minutes, the calculated value was sixty minutes; considering that k_6 which would lower the τ value was not taken into account, the agreement is good.

It is worth noting here that step k_6 demands a dependence of slope α for reaction A_0 on both concentration and nature of alcohol. This was not observed as we were never able to eliminate completely the metal ion catalysis rate which swamps out A_0 because of its greater magnitude.

It would indeed be difficult to postulate a mechanism for the metal-catalyzed portion of the reaction but for the fact that the experimental data narrow down the number of possibilities. Criteria which must be satisfied in any mechanism postulated for the metal-catalyzed case include the following: a) The rate becomes independent of copper ion concentration above 10^{-4} M, b) the rate is independent of alcohol concentration or nature above 0.05 M, c) the inhibition time is not shortened (τ increases somewhat as copper concentration increases), d) some reactive species (from oxygen interaction?) other than those of the part B reaction must initiate the metal-catalyzed reaction as the part B rate is not affected by added copper or by added Na_2H_2Y, and e) no new free radicals can be formed.

We postulate the following steps:

$$H^+ + \cdot OOR_2COH + Cu^{+2} \xrightarrow{k_8} Cu^{+3} - HOOR_2COH$$

$$Cu^{+3} + R_2CHOH \xrightarrow{k_9} Cu^+ + R_2CO + 2H^+$$

$$Cu^+ + S_2O_8^{--} \xrightarrow{k_{10}} Cu^{+3} + 2SO_4^{--}$$

$$2Cu^+ \xrightarrow{k_{11}} Cu_0 + Cu^{+2}$$

$$Cu_0 + S_2O_8^{--} \xrightarrow{\text{fast}} Cu^{+2} + 2SO_4^{--}$$

In this sequence, step k_8 provides an entry into a cyclic redox chain involving Cu^+ and Cu^{+3}. Steps k_9 and k_{10} constitute the nonradical propagation steps which carry the main oxidation of alcohol in reaction A. Step k_{11}, which is the disproportionation of cuprous ion, acts as a chain termination step. The step k_{12} is postulated as a means of returning Cu^0 to Cu^{+2} without the formation of radicals.

The disproportionation reaction of cuprous ion (step k_{11}) is well known in aqueous solution.[20] The oxidation of zero valent copper to cupric ion (step k_{13}) is also known.[11] Knowledge of the tripositive oxidation state of copper is admittedly limited; the evidence has been summarized by Sneed, Maynard and Brasted[21] and Latimer[22] has given approximate oxidation potentials. Of particular pertinence to the presence study is the fact that a series of complex salts containing tripositive copper have been prepared by persulfate oxidation.[23] If these steps are combined with others already considered, the following rate law for the case of maximum copper-catalysis rate is derived:

$$R = \left(\frac{k_1}{k_{11}}\right)^{1/2} k_{10}[S_2O_8^{--}]^{3/2}$$

This rate law predicts a rate which is independent of alcohol and of metal in agreement with the experimental results. Further it suggests an explanation for the sigmoidal shape of the first order plots of part A. Often in reactions where intermediates are present, a finite time is required to reach the steady state concentration. Thus, the initial portion of the reaction indicates an autocatalysis. Toward the other end, however, the first order rate constant should fall off if the true order is greater than one. This combination of an initial build-up in intermediate concentration and a final order of three-halves can therefore give a first order plot that has a sigmoid appearance.

One surprising aspect of the experimental restrictions is that practically no alternative steps can be postulated for this reaction without contradicting some piece of experimental information. Particularly, reactions of the type

$$S_2O_8^{--} + Cu^{++} \longrightarrow SO_4^{-} + SO_4^{--} + Cu^{+3}$$

which have been proposed to explain catalysis by other metal ions of persulfate oxidations[16] must be excluded in our case. They predict a first order dependence on metal ion concentration, as well as produce additional SO_4^- radicals which would shorten τ.

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(20) T. Moeller, "Inorganic Chemistry," John Wiley and Sons, New York (1952); pg. 826.

(21) M. C. Sneed, J. L. Maynard, and R. C. Brasted, *Comprehensive Inorganic Chemistry*, Vol. II, D. Van Nostrand Co., Inc., New York (1954), pg. 111–113.

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(23) L. Malatesta, *Gazz. chim. ital.*, 71, 476, 580 (1941).

A possible alternative step for initiating the metal catalyzed chain is the reaction

$$HOOR_2COH + Cu^{+2} \xrightarrow{k_{8b}} Cu^{+} + H^{+} + \cdot OOR_2COH$$

which would replace k_8. While our data do not completely eliminate this as a possibility, it has the disadvantage that it would indicate a slight dependence of the metal-catalyzed rate on concentration and nature of alcohol (because of the k_6 step.) It is encouraging to note that all the types of steps and of intermediates are known types.

Acknowledgment. We wish to thank Miss Irma S. Silva for the product identification and Dr. D. V. Wells for careful perusal of the manuscript. A research grant from the BECCO Division of Food Machinery and Chemical Corp. aided in the purchase of the spectrophotometer. Fellowships from the Union Carbide and Carbon Corp. (DLB) and from the Monsanto Chemical Co. (MMC) are gratefully acknowledged.

PROVIDENCE, R. I.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, VETERANS ADMINISTRATION CENTER, WICHITA, KANSAS, AND THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF WICHITA]

The Reaction of Cholesteryl *p*-Toluenesulfonate with Dimethyl Sulfide and Methanethiol[1]

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Received February 23, 1960

Dimethyl sulfide reacts with cholesteryl *p*-toluenesulfonate to give 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate. Cholesteryl *p*-toluenesulfonate and methanethiol yield chiefly 3β-methylthio-5-cholestene together with small amounts of 3α-methylthio-5-cholestene and 3,5-cyclo-6-methylthiocholestene. Reasons for the structural and stereochemical assignments are given and some reactions of the compounds are described.

During recent years a number of investigations have been directed toward introducing sulfur-containing groups into natural steroids in order to study the effect of such substitution on physiological activity. Cholesterol has been converted to 5-cholestene-3β-thiol by reaction of cholesteryl *p*-toluenesulfonate with thiourea[2] or potassium thiocyanate[3,4] followed by hydrolysis. The conversion of steroidal ketones to thioketones has been accomplished recently[5,6] and alkanethiolic acids and mercaptans have been added to appropriately unsaturated steroidal ketones.[7,8]

Our interest in sulfur-containing steroids stems from a broad investigation being carried out in these laboratories into the chemical[9] and physiological properties of sulfur compounds, the sulfonium compounds in particular. Dodson and Riegel[10] have shown that the reaction product of thiourea with cholesteryl *p*-toluenesulfonate[2] is a 3β-thiouronium derivative. The reaction is very probably a nucleophilic attack by thiourea on a hybrid carbonium ion as depicted in formulas Ia→IIa.

I II

I, II. a, X = H_2NCNH_2 (with S)
I, II. b, X = CH_3SCH_3

The 3β-configuration (equatorial) for the introduced isothiouronium group is in accord with current views on the stereochemistry of reactions[11] involving nucleophilic displacements in homoallylic systems of the type found in 5-cholestenes.

Thus it seemed to us, that mechanistically it was possible to achieve a direct synthesis of 3β-dialkylsulfonio-5-cholestenes by the reaction of dialkyl sulfides with cholesteryl *p*-toluenesulfonate (Ib→IIb). Indeed, this proved to be the case. In nitromethane as a solvent, dimethyl sulfide reacted with cholesteryl *p*-toluenesulfonate to yield 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate (IIb) in 90% yield.

(1) Presented in part before the Fourth International Congress of Biochemistry, Vienna, Austria, September 1958.

(2) L. C. King, R. M. Dodson, and L. A. Subluskey, *J. Am. Chem. Soc.*, **70**, 1176 (1948). For the reaction of saturated steroidal tosylates with thiourea, see V. H. Turnbull, *Chem. & Ind. (London)*, 515 (1959).

(3) T. Wagner-Jauregg and T. Lennartz, *Ber.*, **74B**, 27 (1941).

(4) R. Bourbon, *Bull. Soc. Chim.*, 1117 (1958).

(5) R. M. Dodson and P. B. Sollman, U. S. Patent **2,840,577**, June 24, 1958.

(6) R. Bourbon, *Bull. Soc. Chim.*, 722 (1958).

(7) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959).

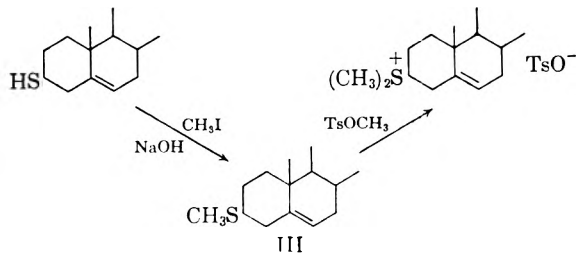
(8) J. W. Ralls, R. M. Dodson, and B. Reigel, *J. Am. Chem. Soc.*, **71**, 3320 (1949).

(9) N. F. Blau and C. G. Stuckwisch, *J. Org. Chem.*, **22**, 82 (1957).

(10) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).

(11) S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948).

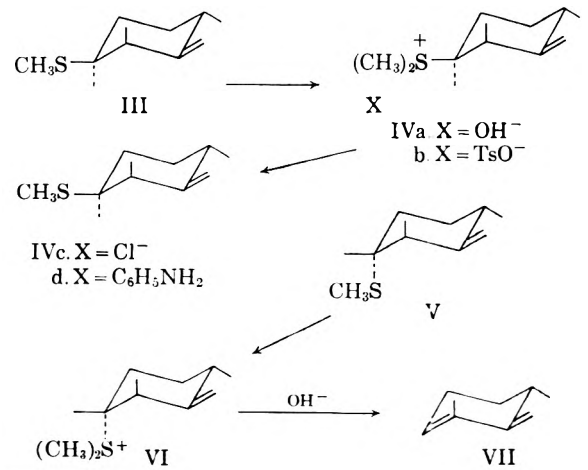
The structure and stereochemistry assigned to IIb followed from its mode of preparation, elemental analysis, desulfurization to 5-cholestene, and an independent synthesis from 5-cholestene-3β-thiol.



III

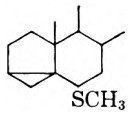
3β-Methylthio-5-cholestene (III) has been prepared by the alkylation of 5-cholestene-3β-thiol.[12] A more facile, one-step method of preparation is afforded by the reaction of methanethiol with cholesteryl *p*-toluenesulfonate. When the reaction is carried out in glacial acetic acid the product separates from the reaction mixture. Crystallization from ether-methanol and then acetone yields 3β-methylthio-5-cholestene (III), m.p. 125–126° in 80% yield.[13] From the mother liquors a small amount of the isomeric 3α-methylthio-5-cholestene (V), m.p. 110°, was isolated.

The configurational assignment for III is based on an independent synthesis from 5-cholestene-3β-thiol and on the reaction of its sulfonium derivative with various nucleophilic reagents, particularly hydroxide ion. Nucleophilic attack occurred exclusively on an *S*-methyl group giving the steroid sulfide with displacement of the methyl group. This was the case with hydroxide ion (IV)a, *p*-toluenesulfonate ion (IVb), chloride ion (IVc), and aniline (IVd).[14]



On the other hand, the sulfonium derivative (VI) of the axial isomer (V) reacts with hydroxide ion to give dimethyl sulfide and 3,5-cholestadiene (VII). These results are in agreement with earlier observations concerning quaternary ammonium hydroxides.[15,16] Hofmann elimination is favored by a *trans* coplanar arrangement in the transition state of the hydrogen atom, dimethylsulfide group and two carbon atoms going from sp^3 to sp^2 bonding. In such a transition state, the leaving hydrogen atom and the dimethyl sulfide group are axial. The equatorial 3β-sulfonium derivative lacks the steric requirements for facile Hofmann elimination, hence displacement at the *S*-methyl group is favored.[17] Attack at C_3 to give cholesterol would not be anticipated since, in addition to the statistical factor of two in favor of *S*-methyl attack, steric factors make S_N2 displacements at cyclohexyl-carbon atoms much slower.[18] A further consequence of the axial conformation in V is its much slower reaction with methyl iodide as compared to the rate of reaction of the equatorial isomer (III).[19]

When cholesteryl *p*-toluenesulfonate was treated with methanethiol in nitromethane the major product again was 3β-methylthio-5-cholestene. In addition to the major product a very small amount of a compound melting at 90–92° was isolated. We have tentatively assigned the *i*-cholestane structure, 3,5-cyclo-6β-methylthiocholestane (VIII) to this isomer.



VIII

This assignment is based on the following data: elemental analyses, reaction with methyl iodide to form a sulfonium derivative, rearrangement to cholesteryl acetate in acetic acid containing a few drops of sulfuric acid, and rearrangement to 3β-methylthio-5-cholestene in the presence of methanethiol and *p*-toluenesulfonic acid.[20] The β-conformation at C_6 is assigned on the basis of facile Hofmann elimination of dimethyl sulfide with alkali. This conformation is also in agreement with the orientation of 3,5-cyclo-6β-methoxycholestane obtained by

(12) A. S. Jones, F. Smith, and M. Webb, *Nature*, **162**, 857 (1948).

(13) Previous attempts to prepare alkylthiocholesterol derivatives by solvolysis of cholesteryl *p*-toluenesulfonate with boiling propane-1-thiol [H. McKennis, *J. Am. Chem. Soc.*, **70**, 675 (1948)] or with ethanethiol in acetone or dioxane [J. C. Colbert, Ph.D. thesis, Northwestern University, 1946, p. 51] have been unsuccessful.

(14) F. Challenger, R. Bywood, P. Thomas, and B. Hayward, *Arch. Biochem. Biophys.*, **69**, 514 (1957).

(15) D. Y. Curtin, R. D. Stolow, and W. Maya, *J. Am. Chem. Soc.*, **81**, 3330 (1959).

(16) R. D. Haworth, J. McKenna, and R. G. Powell, *J. Chem. Soc.*, 1110 (1953).

(17) For an excellent paper and leading references on the decomposition of sulfonium hydroxides see C. K. Ingold and K. C. Kurijan, *J. Chem. Soc.*, **136**, 991 (1933).

(18) A. Streitwieser, *Chem. Revs.*, **56**, 668 (1956).

(19) B. Gent and J. McKenna, *J. Chem. Soc.*, 573 (1956), have made a similar observation with tertiary amines.

(20) The conclusions drawn from the recorded observations are based on the assumption that the 3,5-cyclo-6-methylthiocholestene undergoes reactions similar to its oxygen analog. See L. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, N. Y., 1959, pp. 314–320.

methanolysis of cholesterol *p*-toluenesulfonate.[21]

At this point it is of interest to note tht the reaction of thiophenol with cholesteryl *p*-toluenesulfonate leads to 3,5-diphenylthiocholestane.[22] On the other hand extended treatment of cholesteryl *p*-toluenesulfonate with sodium thiophenoxide yields 3,5-cyclo-6-cholestene (8%), 6β-phenylthio-3,5-cyclocholestane (32%), and 3α-phenylthio-5-cholestene (13%). No detectable amount of 3β-phenylthio-5-cholestene is formed. Shoppee and co-workers have attributed these results to the abnormally great reactivity of the thiophenoxide ion in processes involving attack on covalently bound hydrogen and to the high nucleophilic power of this ion. In contrast, methanethiol and dimethyl sulfide, weak nucleophilic reagents, react chiefly by a unimolecular heterolysis leading to retention of configuration.

EXPERIMENTAL

3β-Dimethylsulfonio-5-cholestene p-toluenesulfonate (IV). (*a*) *From cholesteryl p-toluenesulfonate and dimethylsulfide.* Cholesteryl *p*-toluenesulfonate, 2.71 g. (0.005 mole), was suspended in 75 ml. of nitromethane contained in a pressure bottle (Fisher Scientific Co., Catalog No. 3-100), a large excess (10–15 ml.) of dimethyl sulfide was added, and the stoppered flask placed in an oven at 40°. The fine sterol particles gradually disappeared and were replaced by flat platelike crystals adhering to the wall of the flask. This transformation was usually complete at the end of the fourth day. The mixture was cooled at 0° and the crystals were washed with cold nitromethane, then with ether. The mother liquor and washings were evaporated *in vacuo*. The residue was dissolved in methanol and the small ether-insoluble component was added to the main crop of crystals. Recrystallized from methanol-ether, they weighed 2.78 g. (90%), m.p. 195–200°, $[\alpha]_D^{25}$ −15° in alcohol, $\lambda_{max}^{CH_3OH}$ 217 mμ, ε 13,000.

Anal. Calcd. for $C_{36}H_{58}O_3S_2$: C, 71.5; H, 9.62. Found: C, 71.34; H, 9.59.

When the reaction was run at 80° for 24 hr. two products were obtained: one melting at 200°, the other at 124–125°. The latter showed no depression in melting point when mixed with 3β-methylthio-5-cholestene.

(*b*) *From 3β-methylthio-5-cholestene and methyl p-toluenesulfonate.* A mixture of 2.1 g. (0.005 mole) of 3β-methylthio-5-cholestene, 2 ml. of methyl *p*-toluenesulfonate, and 25 ml. of nitromethane was heated at 40° for 10 days. The mixture was diluted with ether and filtered. The residue was crystallized from ethanol. The melting point of the product (204°) was undepressed when mixed with the product obtained from cholesteryl *p*-toluenesulfonate and dimethylsulfide.

3β-Methylthio-5-cholestene (III). (*a*) *From cholesteryl p-toluenesulfonate and methanethiol.* Cholesteryl *p*-toluenesulfonate, 2.71 g. (0.005 mole), was mixed in a pressure bottle with 25 ml. of glacial acetic acid and 5 ml. of methanethiol. After 4 or 5 days at 40° the long, needle-shaped, reddish colored crystals were separated from the cooled liquid and were washed with cold methanol until nearly white. Crystallization from ether-methanol and then from acetone gave 1.64 g. (79%) of needle-shaped crystals, m.p. 125–126°, $[\alpha]_D^{25}$ = −19° in chloroform, $\lambda_{max}^{Cyclohexane}$ 207 mμ, ε 6,270.

Anal. Calcd. for $C_{28}H_{48}S$: C, 80.79; H, 11.54. Found: C, 80.44; H, 11.48.

The mother liquor and washings from the above were concentrated and the sticky residue was dissolved in methanol. A small amount of crystals was obtained which melted at 110°. They were shown to be 3α-methylthio-5-cholestene, (VI). $[\alpha]_D^{25}$ = −24° in chloroform.

Anal. Calcd. for $C_{28}H_{48}S$: C, 80.79; H, 11.54. Found: C, 80.52; H, 11.44.

The reaction was carried out in a similar manner with 75 ml. of nitromethane as the reaction medium instead of glacial acetic acid. After the main product was removed from the mixture a small crop of crystals (70–100 mg.) melting at 90–92° precipitated from the concentrated mother liquor on standing at 0°. The *i*-cholestane structure (VIII) is tentatively assigned to this product. $[\alpha]_D^{25}$ = +15° in chloroform.

Anal. Calcd. for $C_{28}H_{48}S$: C, 80.79; H, 11.54. Found: C, 81.01; H, 11.67.

(*b*) *From 5-cholestene-3β-thiol and methyl iodide.* Two grams (0.005 mole) of 5-cholestene-3β-thiol[2] and 5 ml. of methyl iodide in 50 ml. of 2% alcoholic potassium hydroxide were placed in a pressure bottle and allowed to stand at 40° for 24 hr. with occasional shaking. The mixture was diluted with water, the solid product filtered and crystallized from acetone. The yield of 3β-methylthio-5-cholestene, melting at 126°, was 0.7 g. (85%).[23]

3β-Dimethylsulfonio-5-cholestene iodide.[12] A solution containing 700 mg. (1.7 mmoles) of 3β-methylthio-5-cholestene and 1 ml. of methyl iodide in 5 ml. of ether was allowed to stand at room temperature. After 4 hr. the crystalline mass which had separated was filtered and crystallized from methanol, m.p. 165°, yield, 95%.

3α-Dimethylsulfonio-5-cholestene iodide. The 3α-isomer was prepared from 3α-methylthio-5-cholestene by a procedure similar to that used for the 3β-isomer. The reaction time was 24 hr. The compound melted at 162°.

Anal. Calcd. for $C_{29}H_{51}SI$: I, 22.9 Found: I, 23.2.

Reaction of 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate with potassium hydroxide (IVa). A mixture containing 50 ml. of water, 50 ml. of ethanol, 10 g. of potassium hydroxide, and 1.5 g. (0.0025 mole) of 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate was refluxed for 2 hr. The cooled mixture was diluted with water and filtered. The residue, after crystallization from acetone, melted at 126°. No depression was observed in a mixed melting point with 3β-methylthio-5-cholestene.

When 3β-dimethylsulfonio-5-cholestene iodide[13] was treated with aqueous-alcoholic potassium hydroxide the resulting product again was 3β-methylthio-5-cholestene. On the other hand, treatment of 3α-dimethylsulfonio-5-cholestene iodide with aqueous-alcoholic potassium hydroxide yielded 3,5-cholestadiene (VIII), melting at 79–80° after crystallization from methanol. $[\alpha]_D^{25}$ = −91.5°.

Reaction of 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate with aniline. (IVd). One gram of the sulfonium compound and 1 g. of aniline were heated for 2 hr. at a bath temperature of 160°. The cooled mixture was dissolved in ether and extracted with 5% hydrochloric acid. The residue from the ether layer, crystallized from acetone, gave a product melting at 126°, which showed no depression on mixing with authentic 3β-methylthio-5-cholestene.

The hydrochloric acid extract from the above was made alkaline with 10% sodium hydroxide and treated with benzenesulfonyl chloride. The alkali-insoluble product was

(21) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(22) C. W. Shoppee, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 4817 (1956).

(23) Methylation of 5-cholestene-3β-thiol has been reported by Jones, Smith, and Webb (ref. 12) without experimental details. Their melting point, 141°, is at variance with our melting point of 126°. We prepared our compound in two different ways, each of which gave a product of correct analytical values for the substance sought. The melting point of our 3β-dimethylsulfonio-5-cholestene iodide of 165° agrees with that of Jones, Smith, and Webb.

extracted with ether, the ether evaporated, and the residual *N*-methylbenzenesulfonanilide crystallized from aqueous methanol, (m.p. 79°).[24]

Desulfurization of 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate and of 3β-methylthio-5-cholestene. Recently activated Raney nickel was filtered and rapidly washed with cold dioxane to remove water. Ten grams of the metal were added to an ice-cold solution of 1.0 g. of the sulfur-containing sterol in dioxane. The mixture was warmed cautiously, then refluxed gently for 7 hr. The residue on the filter was washed with ether and the ether dioxane filtrate distilled *in vacuo*. The solution of the residue in ether, treated with methanol, yielded a crystalline product. After several recrystallizations, this melted at 90–91° and showed a specific rotation of −56, values which agree with those given in the literature for 5-cholestene. The qualitative test for sulfur was negative. The sulfur-free products from both sulfur derivatives were identical as shown by mixed melting point determinations.

In both instances large losses of product occurred and no attempt was made at precise quantitative recovery.

Preparation of 3β-dimethylsulfonio-5-cholestene chloride from 3β-dimethylsulfonio-5-cholestene p-toluenesulfonate by ion exchange. Amberlite IRA-410 (Rohm & Haas), chloride form, was washed well with methanol and drained on a filter. To 90 g. of wet resin a methanolic solution of 6.5 g. of 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate was added and allowed to stand at room temperature for 48 hr. with occasional shaking.

After further mechanical shaking for 3 hr., 800 ml. of methanol were percolated through the resin bed supported on a filter. The concentrated percolate (ca. 25 ml.), treated with acetone, gave, on standing overnight in the refrigerator, 5.0 g. (theory 5.04 g.) of glistening plates melting at 185°. Recrystallization from methanol-ether raised the melting point to 187°.

Anal. Calcd. for $C_{29}H_{51}ClS$: Cl, 7.58. Found: Cl, 7.45.

On standing at room temperature the sulfonium chloride slowly decomposes as evidenced by a drop in melting point. The decomposition results probably from the attack of the chloride ion on the *S*-methyl group of the sulfonium ion (Xc). Recrystallization of the partially decomposed product from methanol-ether gave pure 3β-dimethylsulfonio-5-cholestene chloride and 3β-methylthio-5-cholestene, melting at 126°.

3,5-Cyclo-6β-dimethylsulfoniocholestane iodide. To 416 mg. (1.0 mmole) of 3,5-cyclo-6-methylthiocholestane in ether was added 1.0 ml. of methyl iodide. After 6 hr. the precipitate was collected, washed with ether, and dried, m.p. 148°.

Anal. Calcd. for $C_{29}H_{51}IS$: C, 62.6; H, 8.63; I, 22.8. Found: C, 62.41; H, 8.82; I, 22.5.

When the sulfonium compound was heated with potassium hydroxide in aqueous alcohol, dimethyl sulfide was eliminated and a hydrocarbon, m.p. 71–72°, was recovered. A mixed melting point with 3,5-cyclo-6-cholestene[25] was 72°.

Reaction of 3,5-cyclo-6β-methylthiocholestane with acetic acid. A mixture of 200 mg. (0.5 mmole) of 3,5-cyclo-6β-methylthiocholestane, 5 ml. of glacial acetic acid, and one drop of sulfuric acid was refluxed for 30 min. The mixture was diluted with water and extracted with ether. Evaporation of the ether and crystallization of the residue from acetone gave 50 mg. of cholesteryl acetate, m.p. 112°.

Rearrangement of 3,5-cyclo-6β-methylthiocholestane to 3β-methylthio-5-cholestene. A solution of 200 mg. (0.5 mmole) of 3,5-cyclo-6β-methylthiocholestane, 5 ml. of benzene, 5 ml. of methanethiol, and 0.1 g. of *p*-toluenesulfonic acid was allowed to stand at 50° for 48 hr. The solution was washed several times with 5% sodium bicarbonate, then evaporated to dryness. The residue, on crystallization from acetone, gave 50 mg. of 3β-methylthio-5-cholestene, melting point 126°, unchanged when mixed with an authentic preparation.

Acknowledgment. The authors are grateful to Mrs. Dorothy Churchwell for assistance with the analyses.

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(24) R. L. Shriner, R. C. Fuson, and D. Y. Curtin. *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley & Sons, New York, N. Y., 1956, p. 289.

(25) B. Riegel, G. P. Hager, and B. L. Zenity, *J. Am. Chem. Soc.*, 68, 2562 (1946).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, NATIONAL RESEARCH CENTRE, CAIRO]

Carbonyl and Thiocarbonyl Compounds. III.[1] Synthesis of Azines by the Reaction of Quinones with Hydrazones and Their Molluscacidal Activity

NAZIH LATIF AND IBRAHIM FATHY

Received December 3, 1959

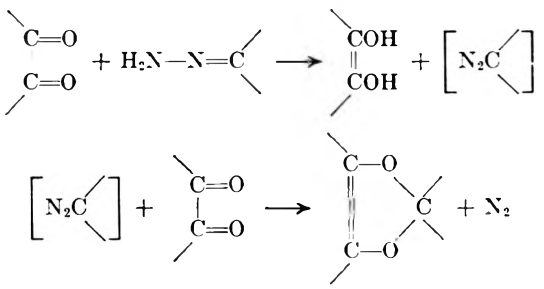
In contrast to other hydrazones previously investigated, benzophenone hydrazone reacts with tetrachloro- and tetrabromo-*o*-benzoquinone giving benzophenone azine in both cases. The nature of the products obtained by the action of *p*-benzoquinone on hydrazones in benzene depends on the molecular ratios of the reactants used. When using equimolecular amounts, the *p*-benzoquinoazines II, III, and IV are obtained from fluorenone, xanthone, and benzophenone hydrazones, respectively. Fluorenone and xanthone azines are produced when using two moles of the corresponding hydrazones, while with benzophenone hydrazone the condensation product V is obtained. The action of hydrazine hydrate on the quinoazines II, III, and IV is investigated and a reaction mechanism is suggested. *p*-Benzoquinone reacts with hydrazones in alcohol giving mainly the corresponding ketazines independent of the molecular ratios of the reactants used. Hydroquinone is obtained almost quantitatively by the action of hydrazine hydrate on *p*-benzoquinone. The molluscacidal activity of the quinone and derivatives is tested.

During our studies on the chemical constitution and biological activity of benzoquinones, it has been found necessary to prepare benzoquinoazines of the type $R_2—C=N—N=R'=O$. Gerhardt[2] has shown that phenanthraquinone condenses with

(1) Part II of this series, *J. Org. Chem.* 24, 1883 (1959).

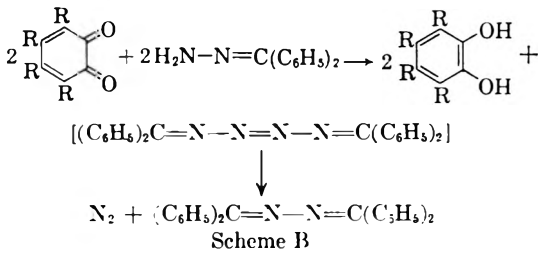
(2) O. Gerhardt, *Monatsh.*, 42, 70 (1921); *Chem. Abstr.*, 15, 3834 (1921).

aromatic hydrazones giving phenanthraquinoazines of the general formula I. In a previous article,[1] the authors have shown that tetrachloro- and tetrabromo-*o*-benzoquinone react with fluorenone and xanthone hydrazones giving the corresponding cyclic ethers according to Scheme A and no azines are produced.



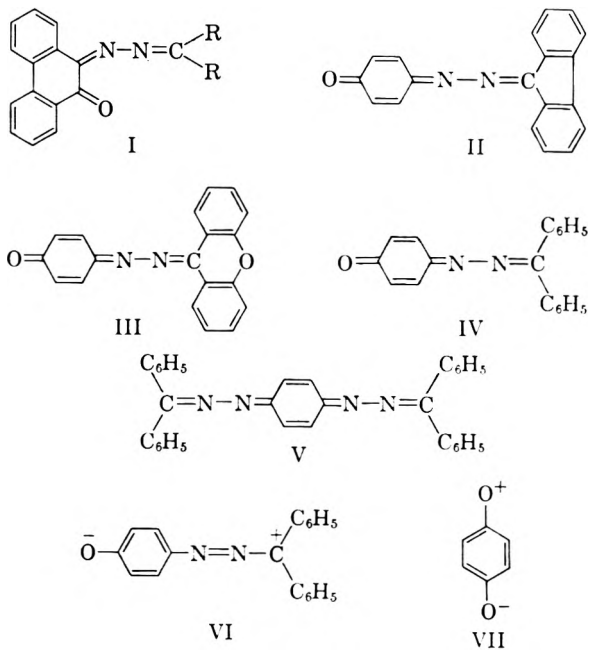
Scheme A

In trying to apply this reaction to benzophenone hydrazone, the corresponding cyclic ether is not obtained as would be expected, but instead, benzophenone azine is formed whether using tetrachloro- or tetrabromo-*o*-benzoquinone. The reaction takes place readily at room temperature and is greatly accelerated by heat, giving an almost quantitative yield of the azine. The reaction provides an easy and quantitative method for the preparation of benzophenone azine, the preparation of which has been found rather difficult by some authors.[3] It is thought that the reaction takes place through the intermediate formation of bisdiphenylmethylene tetrazone which is unstable in the presence of the high potential quinone. The formation of tetrazones by the oxidation of hydrazines is well known.[4]



Scheme B

In an attempt to obtain *p*-benzoquinoazines of the type $R_2—C=N—N=R'=O$, the action of *p*-benzoquinone on hydrazones was investigated. Wieland and Roseeu[5] found that the quinone reacts with fluorenone hydrazone in alcohol giving fluorenone azine. In contrast, it has been found that when the reaction is carried out in *dry benzene*, the nature of the reaction products depends mainly on the molecular ratios of the reactants. Thus, when equimolecular amounts are used, the *p*-benzoquinoazines II, III, and IV are obtained by the action of *p*-benzoquinone on fluorenone, xanthone, and benzophenone hydrazones, respectively, in boiling dry benzene. The azines are highly colored, insoluble in alkali, and exhibit the usual halochromism when added to concentrated sulfuric acid.[2] On the other hand, when two moles of fluorenone or xanthone hydrazones are used in this reaction, fluorenone and xanthone azines are mainly obtained while with benzophenone hydrazone the condensation product V is formed. This difference in the nature of the products of the reaction with



different hydrazones when two moles are used might be explained by assuming that the resonance structure (VI) contributes significantly to the actual state of the quinoazine molecule. In the case of II and III, the reactivity of the carbonyl group towards condensation with another molecule of the hydrazone is decreased and the carbonium ion stabilized by the strong resonance with the xanthylene and fluorenylidene residues. The formation of the azines is believed to be due mainly to the reaction between the *p*-benzoquinoazine first formed and the other molecule of the hydrazone. This is supported by the fact that when boiling a benzene solution of equimolecular amounts of III and xanthone hydrazone, the expected xanthone azine is obtained in amounts greater than would be produced from a simple oxidation of the hydrazone used. II reacts similarly with fluorenone hydrazone producing fluorenone azine. However, in the case of IV and benzophenone hydrazone, benzophenone azine together with V are obtained.

When the reaction of *p*-benzoquinone and hydrazones is carried out in alcohol instead of dry benzene, the corresponding ketazines are mainly obtained regardless of the molecular ratios of the re-

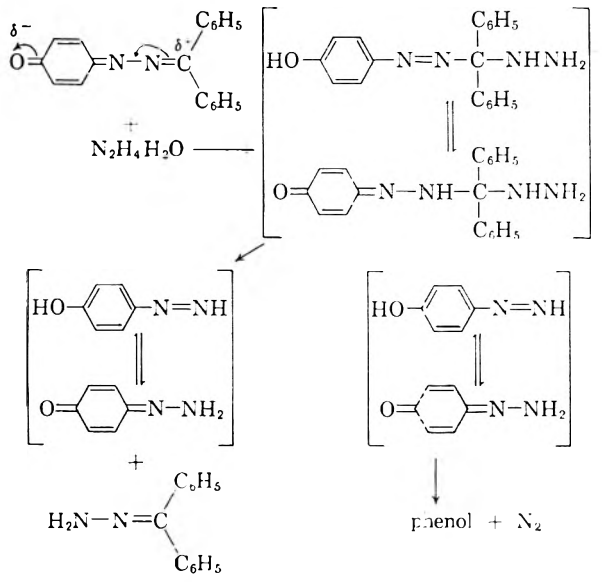
(3) *Cf.* H. Szmant and C. McGinnis, *J. Am. Chem. Soc.*, **72**, 2890 (1950).

(4) E. H. Rodd, *Chemistry of Carbon Compounds*, Elsevier Publishing Co., New York, Vol. IIIA, 379 (1954).

(5) H. Wieland and A. Roseeu, *Ann.*, **381**, 229 (1911).

actants used. It is thought that in this medium the zwitterion structure VII contributes largely to the actual state of the *p*-benzoquinone molecule.

In order to confirm the structure of the *p*-benzoquinoazines, their reaction with hydrazine hydrate was investigated. In contrast to the



Scheme C

action of hydrazones, it has been found that hydrazine hydrate reacts with these quinoazines in alcohol giving phenol, and the corresponding hydrazones and azines in all cases. For example, when IV is allowed to react with hydrazine hydrate in boiling alcohol, phenol and benzophenone hydrazone are mainly obtained according to Scheme C, together with a small amount of benzophenone azine, and no condensation products are obtained. This might be due to the relatively high basicity of hydrazine compared with hydrazones and in turn its great nucleophilic character. Staudinger and Kupfer[6] reported the formation of hydrazones from azines by the action of hydrazine hydrate under pressure and at elevated temperature.

p-Benzoquinone reacts with hydrazine hydrate at room temperature giving hydroquinone in an almost pure state. This obviates the formation of by-products usually met with in the reduction of the quinone by phenyl hydrazine[7] and in turn an almost quantitative yield is obtained.

The molluscacidal activity of p-benzoquinone and derivatives. Halawani and Latif[8] found that halogenated *o*-benzoquinone and benzodioxole derivatives are toxic to *Biomphalaria boissi* snails—the intermediate host of *Schistosoma mansoni* in Egypt—in high dilutions. Latif and Fathy[9] reported similar results with certain halogenated cyclic ethers. The molluscacidal activity of *p*-benzoquinone, hydroquinone, and *p*-benzoquinoazines was investigated. It was found that *p*-benzoquinone and the quinoazine (IV) kill the snails in concentrations down to 5 p.p.m. in water during a twelve-hours exposure period while the hydroquinone is less active. II and III could not be tested since they are almost insoluble in the solvents usually used for the test. Benzophenone azine is inactive in concentrations up to 20 p.p.m. This remarkable activity of the quinone and its azine (IV) might be due to their inhibition effect on the oxygen consumption of the snails. von Brand *et al.*[10] have shown that certain phenanthra- and naphthaquinones inhibit the oxygen consumption of *Australorbis glabratus* snails in high dilutions. Details of the experiments will be published separately.

EXPERIMENTAL

p-Benzoquinone was recrystallized from petroleum ether (b.p. 40–60°) and dried. "Analar" benzene which had been dried over sodium was used. Benzophenone hydrazone was prepared by the general method described by Schönberg *et al.*;[11] the hydrazone which separated on cooling was washed well with petroleum ether (b.p. 40–60°) and dried.

Reaction of tetrachloro-o-benzoquinone with benzophenone hydrazone. A solution of benzophenone hydrazone (1 g.) in dry ether (25 ml.) was added in portions to a boiling solution of the quinone (1.3 g.) in dry ether (25 ml.). A vigorous reaction took place after each addition and the red color of the quinone disappeared. The reaction mixture was refluxed for 30 min. and left to cool. The solid was filtered, crystallized from alcohol, and shown to be benzophenone azine (melting point and mixed melting point). The mother liquor was evaporated to dryness and another crop of benzophenone azine was obtained when a few ml. of alcohol was added to the residues (total yield 0.82 g., about 90%). The alcoholic solution, after separation of the azine, was poured onto ice cold water, and acidified with a few drops of dilute hydrochloric acid. The precipitate was filtered, dried, and dissolved in acetic anhydride. The mixture was refluxed for 30 min. then left to cool. The solution was then poured onto ice, left overnight, and the solid crystallized from alcohol as colorless crystals which proved to be the diacetate of tetrachlorocatechol (melting point and mixed melting point).

When tetrabromo-*o*-benzoquinone was used in the above experiment, benzophenone azine was similarly obtained.

Reaction of p-benzoquinone with benzophenone hydrazone. (a). *Preparation of N¹-p-benzoquinonylidene-N²-diphenylmethylenazine* (IV). A solution of benzophenone hydrazone (0.78 g., 1 mole) and *p*-benzoquinone (0.43 g., 1 mole) in dry benzene (15 ml.) was refluxed for 3 hr. on the water bath. The reaction mixture, which became red-brown, was filtered while hot and the benzene was evaporated to dryness under reduced pressure. Then a few drops of methyl alcohol was added to the oily residue. The solid IV, which separated on standing, was recrystallized from methyl alcohol as orange crystals m.p. 109–110° (yield 0.8 g.). It is insoluble in sodium hydroxide solution (10%) and gives a brick red color with conced. sulfuric acid.

Anal. Calcd. for $C_{19}H_{14}ON_2$: C, 79.72; H, 4.89; N, 9.78. Found: C, 79.14; H, 5.13; N, 10.09.

(6) H. Staudinger and O. Kupfer, *Ber.*, **44**, 2199, 2204 (1911).

(7) A. Giacolone, *Chem. Abstr.*, **23**, 599 (1929).

(8) A. Halawani and N. Latif, *J. Egypt. Med. Assoc.*, **37**, 957 (1954).

(9) N. Latif and I. Fathy, *Can. J. Chem.*, **37**, 863 (1959).

(10) T. von Brand, B. Mehlman, and M. O. Nolan, *Chem. Abstr.* **43**, 9352 (1949).

(11) A. Schönberg, A. Fateen, and A. A. Samour, *J. Am. Chem. Soc.*, **79**, 6022 (1957).

(b). *Preparation of* (V). A solution of benzophenone hydrazone (1.96 g., 2 moles) and *p*-benzoquinone (0.54 g., 1 mole) in dry benzene (20 ml.) was refluxed as above, then filtered while hot. The benzene was evaporated to dryness and a few drops of methyl alcohol was added. The solid which separated was extracted with acetone. The crystalline V left was filtered and recrystallized from benzene as orange-red crystals, m.p. 210° (yield 0.85 g.). It gives a crimson red color with concd. sulfuric acid.

Anal. Calcd. for $C_{32}H_{24}N_4$: C, 82.75; H, 5.17; N, 12.06. Found: C, 82.84; H, 5.36; N, 11.49.

The acetone extract was evaporated to dryness and a few drops of methyl alcohol was added. The crystals which separated were recrystallized from alcohol and shown to be benzophenone azine (0.25 g.).

Reaction of IV *with benzophenone hydrazone.* A solution of IV (0.71 g.) and benzophenone hydrazone (0.5 g.) in dry benzene (15 ml.) was refluxed as above. The reaction mixture was filtered while hot, concentrated, and left to cool. The orange crystals which separated were recrystallized from benzene and shown to be V (melting point and mixed melting point yield 0.2 g., about 25%). The mother liquor was then evaporated to dryness and methyl alcohol added to the oily residue. The crystals which separated on standing were recrystallized from alcohol and shown to be benzophenone azine (melting point and mixed melting point, yield about 50%).

Action of hydrazine hydrate on (IV). A mixture of IV (2 g.), hydrazine hydrate (about 95%, 4 ml.), and alcohol (25 ml.) was refluxed for 1 hr. The reaction mixture was filtered while hot, concentrated, and left to cool. The crystals were filtered, crystallized from alcohol, and proved to be benzophenone azine (0.14 g.). The filtrate was concentrated and left to cool; benzophenone hydrazone (0.9 g.) was obtained. The mother liquor was then poured onto ice and a 10% solution of sodium hydroxide was added. The alkaline mixture was extracted with ether and the aqueous layer was acidified with dilute hydrochloric acid and extracted with ether several times. The ethereal extract was washed with a small amount of water and evaporated to dryness. The oily residue was extracted with boiling water and the solution was left to cool. Bromine water was then added and the crystalline solid was filtered, dried, and recrystallized from petroleum ether (b.p. 40–60°) as colorless crystals (1.3 g.) which were shown to be tribromophenol (melting point and mixed melting point).

Reaction of p-benzoquinone with xanthone hydrazone. (a) *Preparation of N¹-p-benzoquinonylidene-N²-xanthonylidene azine* (III). A solution of xanthone hydrazone[12] (1.05 g. 1 mole) and *p*-benzoquinone (0.54 g., 1 mole) in dry benzene (15 ml.) was kept at room temperature (25°) for 1 hr. The bronze colored crystals were filtered, washed with acetone, and recrystallized from benzene giving III, m.p. 213–214° (1.2 g., about 80% yield). It gives a brown color with concd. sulfuric acid.

Anal. Calcd. for $C_{19}H_{12}O_2N_2$: C, 75.99; H, 4.03; N, 9.33. Found: C, 76.1; H, 4.05; N, 9.5.

(b). *Preparation of xanthone azine.* A solution of xanthone hydrazone (2.1 g., 2 moles) and *p*-benzoquinone (0.54 g. 1 mole) in dry benzene (20 ml.) was refluxed on the water bath. After 15 min., a crystalline solid separated and refluxing was continued for an additional 2 hr. The crystals were filtered, washed with acetone, and recrystallized from xylene as orange-yellow crystals which were shown to be xanthone azine (melting point and mixed melting point).

Reaction of III *with xanthone hydrazone.* A mixture of III (1.5 g.) and xanthone hydrazone (1 g.) in dry benzene (15 ml.) was refluxed on the water bath for 3 hr. The brown crystals which separated during the reaction were filtered and recrystallized from xylene as orange crystals which were shown to be xanthone azine (melting point and mixed melting point). The mother liquor was concentrated giving another crop of the azine (total yield 1.2 g.).

Action of hydrazine hydrate on III. To a suspension of III (2 g.) in boiling alcohol (75 ml.), hydrazine hydrate (5 ml.) was added and the mixture refluxed for 3 hr. The solid formed during the reaction was filtered and shown to be xanthone azine (identified as above). The filtrate was concentrated and left to cool, and the solid obtained was crystallized from alcohol and shown to be xanthone hydrazone (melting point and mixed point). The mother liquor was poured onto ice, and phenol was identified as in the case of IV.

Reaction of fluorenone hydrazone with p-benzoquinone. (a). *Preparation of N¹-p-benzoquinonylidene-N²-fluorenonylidene-azine* II. A solution of equimolecular amounts of fluorenone hydrazone[5] (1.94 g.) and *p*-benzoquinone (1.08 g.) in dry benzene was refluxed for 3 hr. The reaction mixture was concentrated, left to cool, and the solid which separated was crystallized from benzene giving II as orange crystals m.p. 160–161° (1.8 g., yield about 60%). It gives a brown-red color with concd. sulfuric acid.

Anal. Calcd. for $C_{19}H_{12}ON_2$: C, 80.28; H, 4.22; N, 9.85. Found: C, 79.93; H, 4.32; N, 9.97.

(b). *Preparation of fluorenone azine.* A solution of *p*-benzoquinone (0.54 g. 1 mole) and fluorenone hydrazone (1.94 g., 2 moles) in dry benzene (25 ml.) was refluxed for 3 hr. After filtration, concentration, and cooling the solid was crystallized from benzene and shown to be fluorenone azine (melting point and mixed melting point).

Reaction of II *with fluorenone hydrazone.* The reaction was carried out as in the case of III and fluorenone azine was similarly obtained and identified.

Action of hydrazine hydrate on II. The reaction was carried out as in the case of III and fluorenone azine, fluorenone hydrazone, and phenol were formed.

Reaction of p-benzoquinone with hydrazine hydrate. *p*-Benzoquinone (0.5 g.) in dry benzene (10 ml.) was added in portions to a solution of hydrazine hydrate (about 95%, 0.5 ml.) in absolute alcohol (5 ml.). A vigorous reaction took place after each addition. The solid which separated during the reaction was filtered off and crystallized from benzene; hydroquinone was obtained as colorless crystals (yield almost quantitative).

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(12) A. Schönberg and Th. Stolpp, *Ber.*, **63**, 3114 (1930).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, NATIONAL RESEARCH CENTER]

Carbonyl and Thiocarbonyl Compounds. IV.[1] Oxidations with Tetrahalo-o-benzoquinones: Synthesis of Cyclic Ethers

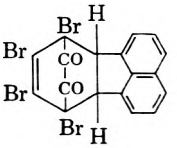
NAZIH LATIF, IBRAHIM FATHY, (MISS) NAWAL MISHRIKY, AND (IN PART) ADEL ATALLAH

Received December 29, 1959

Dehydrogenation of acenaphthene with tetrachloro-*o*-benzoquinone has been investigated by Braude, Brook, and Linstead. The low recovery of total hydrocarbons reported might be attributed, among other possible factors, to the formation of an adduct by the action of the quinone on the acenaphthylene formed. This side reaction should be considered in the dehydrogenating power of tetrahalo-*o*-benzoquinones.

The action of tetrahalo-*o*-benzoquinones on fluorene provides a simple and new method for the synthesis of fluorylidene cyclic ethers. The cyclic ethers Va and Vb are obtained by the action of tetrachloro- and tetrabromo-*o*-benzoquinone on thioxanthione in a carbon dioxide atmosphere. In the presence of air, thioxanthione is oxidized to thioxanthone under the effect of tetrahalo-*o*-benzoquinones. Va and Vb could also be obtained by the action of the corresponding tetrahalo-*o*-benzoquinone on thioxanthone hydrazone.

Braude, Brook, and Linstead[2] studied the dehydrogenating power of various high potential quinones using tetralin, acenaphthene, and dibenzyl as donors and found that the most effective was 2,3-dichloro-5,6-dicyano-1,4-benzoquinone followed by tetrachloro-*o*-benzoquinone. The extent of dehydrogenation was determined by isolating the mixture of unchanged and dehydrogenated hydrocarbons chromatographically from the light petroleum extracts of the reaction mixture, then estimating the percentage composition spectrometrically. When using tetrachloro-*o*-benzoquinone as the dehydrogenating agent and acenaphthene as donor, the total hydrocarbon recovered was only 45% with 60% dehydrogenation, whereas with tetralin, the recovery was 80% with 100% dehydrogenation. This remarkable low recovery reported in the case of acenaphthene might be attributed, among other possible factors, to the possible reaction between acenaphthylene formed and the chloroquinone. Horner and Merz[3] showed that an adduct of the formula $C_{18}H_8O_2Cl_4$ is formed in good yield by refluxing a benzene solution of tetrachloro-*o*-benzoquinone and acenaphthylene for one to two hours. Schönberg and Latif[4] have shown that tetrabromo-*o*-benzoquinone reacts similarly giving the adduct I. These adducts are almost insoluble in light petroleum. Thus the adduct $C_{18}H_8O_2C_4$, presumably formed during the dehydrogenation of acenaphthene by tetrachloro-*o*-benzoquinone, should be precipitated during the light petroleum treatment as described by Braude, Brook, and Linstead. In the present investigation it has been possible to separate this adduct in the form of its quinoxaline derivative during the dehydrogenation of acenaphthene with tetrachloro-*o*-benzoquinone. Under these conditions this side reaction should be taken into consideration when evaluating the dehydrogenating power of tetrachloro-*o*-benzoquinone.



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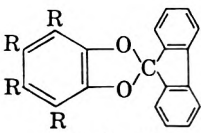
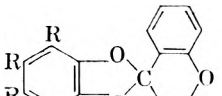
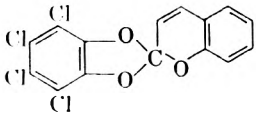


IIa. R = Cl
IIb. R = Br

Although quinones have been extensively used for the dehydrogenation of various hydrocarbons, the role of such quinones, as far as we are aware, involved only the removal of hydrogen without being incorporated into the molecules of the products formed. The authors have found, however, that tetrachloro- and tetrabromo-*o*-benzoquinone react with fluorene in boiling benzene giving the cyclic ethers IIa and IIb respectively. This reaction, which has not been described before, provides a simple and a new method for the synthesis of halogenated cyclic ethers derived from fluorene. IIa and IIb have been previously produced by the action of 9-diazofluorene on the corresponding quinones.[4]



IIIa. R = Cl
IIIb. R = Br



IV

The great reactivity of tetrahalo-*o*-benzoquinones has been previously utilized in the direct synthesis of halogenated cyclic ethers from certain thiones.[5] Thus, it has been found that tetrachloro- and tetrabromo-*o*-benzoquinone react readily with xanthione giving the cyclic ethers IIIa and IIIb respectively. The benzopyran derivative IV has been similarly obtained by the action of tetrachloro-*o*-benzoqui-

(1) Part III of this series, *J. Org. Chem.*, in press.

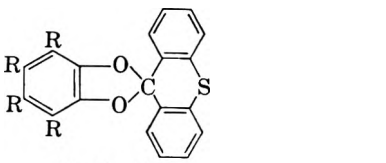
(2) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).

(3) L. Horner and H. Merz, *Ann.*, **570**, 89, (1950).

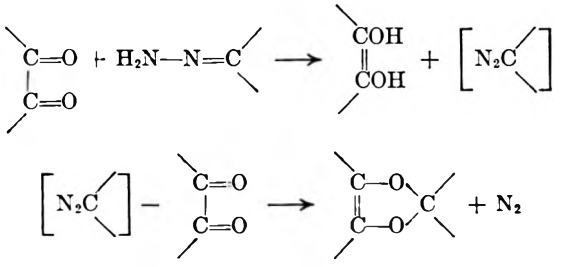
(4) A. Schönberg and N. Latif, *J. Chem. Soc.*, 446, (1952).

(5) N. Latif and I. Fathy, *Can. J. Chem.*, **37**, 863, (1959).

none on coumarin-2-thione. In trying to apply this reaction to other heterocyclic thiones, the action of tetrahalo-*o*-benzoquinones on thioxanthione is investigated. In contrast to xanthione, thioxanthione reacts in two different ways depending on the atmosphere in which the reaction is carried out. In a carbon dioxide atmosphere, tetrachloro-, and tetrabromo-*o*-benzoquinone react with the thione in boiling dry benzene giving the cyclic ethers Va and Vb respectively in good yield. If the reaction is carried out while passing dry air instead of carbon dioxide, the thione is almost completely oxidized to thioxanthone and only slight amounts of the corresponding cyclic ethers are formed. The constitution of Va and Vb is based on analogy[5] as well as on the fact that they are colorless, easily hydrolyzed with dilute mineral acids giving thixanthone and the corresponding tetrahalocatechol. Va could also be obtained by the reaction between tetrachlorocatechol and 9,9-dichlorothioxanthene. The readiness with which Va and Vb are hydrolyzed with dilute hydrochloric acid can be explained on similar lines previously suggested for IIIa and IIIb.[5] Va and Vb are also obtained easily by the action of tetrachloro- and tetrabromo-*o*-benzoquinone on thioxanthone hydrazone. The formation of methylenedioxy derivatives by the action of tetrahalo-*o*-benzoquinones on ketohydrazones has been previously described.[6] The reaction proceeds through the intermediate formation of the corresponding diazo-derivative as follows:



Va. R = Cl
Vb. R = Br



The great ease with which thioxanthione is oxidized to thioxanthone by the action of tetrahalo-*o*-benzoquinones in air even in the absence of sunlight is rather remarkable. Thioxanthione is resistant to oxidation by oxygen except in presence of light.[7]

(6) N. Latif, I. Fathy, and (in part) Miss N. Mishriky, *J. Org. Chem.*, 24, 1883, (1959).

(7) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 275 (1943).

EXPERIMENTAL

"Analar" benzene which had been dried over sodium was used in the reactions. The thioxanthione used was recrystallized to a sharp melting point 168°.

Reaction of tetrachloro-o-benzoquinone with acenaphthene. A solution of tetrachloro-*o*-benzoquinone (2.58 g.) and acenaphthene (1.54 g.) in benzene (15 ml.) was refluxed on the water bath for 10 hr. The reaction mixture was then filtered while hot, concentrated, and left to cool. On standing for about 24 hr. a solid separated from the viscid solution. This was filtered, washed first with a mixture of benzene and light petroleum (b.p. 40–60°), then with cold benzene and dissolved in the least amount of boiling glacial acetic acid. To the solution, a saturated solution of *o*-phenylenediamine in methyl alcohol was added, and the mixture boiled for about 5 min. The crystalline solid which separated was filtered and crystallized from benzene. It proved to be the quinoxaline of the adduct previously obtained by Horner and Merz[3] by the action of the quinone on acenaphthylene.

Action of tetrachloro-o-benzoquinone on fluorene. A solution of tetrachloro-*o*-benzoquinone (2.4 g.) and fluorene (1.8 g.) in benzene (30 ml.) was refluxed for 5 hr. on the water bath. The red color of the quinone disappeared and the reaction mixture became brown. This was filtered while hot and the benzene evaporated to dryness under reduced pressure. To the residue a few ml. of ether was added and the solid which separated was filtered and crystallized from acetone to give 9,9-(tetrachloro-*o*-phenylenedioxy)fluorene, IIa, as colorless crystals, m.p. 285° (undepressed when admixed with an authentic sample prepared by the action of 9-diazofluorene on the quinone. Both products have identical infrared spectra). Yield about 60%.

Action of tetrabromo-o-benzoquinone on fluorene. A solution of the quinone (4.2 g.) and fluorene (1.8 g.) in benzene (30 ml.) was refluxed as above. The product obtained was crystallized from xylene and shown to be 9,9-(tetrabromo-*o*-phenylenedioxy)fluorene, IIb, m.p. 338; yield about 50%.

Preparation of 9,9-(tetrachloro-o-phenylenedioxy)thiaxanthene, Va. A solution of tetrachloro-*o*-benzoquinone (2 g.) in benzene (10 ml.) was added dropwise to a boiling solution of thioxanthione (2 g.) in benzene (20 ml.) while passing dry carbon dioxide, and boiling was continued for 3 hr. The reaction mixture which became brown was filtered while hot and the solution was evaporated to dryness under reduced pressure. To the residue, acetone was added and the solid which separated was recrystallized from benzene to give Va as colorless crystals, m.p. 221°; yield about 70%.

Anal. Calcd. for $C_{19}H_8O_2Cl_4S$: C, 51.58; H, 1.81; Cl, 32.12; S, 7.24. Found: C, 51.74; H, 1.8; Cl, 31.8; S, 6.99.

Hydrolysis of Va. To a mixture of 1 ml. of concd. hydrochloric acid (sp. gr. 1.19) and dioxane (5 ml.) was added Va (0.2 g.) and the mixture boiled for 30 min., and left to cool. It was then poured onto ice and the yellowish precipitate formed was filtered, dried, and dissolved in the least amount of boiling methyl alcohol and left to cool. The solid which separated was recrystallized from alcohol and proved to be thioxanthone (by melting point and mixed melting point). The mother liquor was poured onto cold water which has been acidified with hydrochloric acid. The precipitate which formed was filtered, dried, dissolved in acetic anhydride, and the solution was refluxed for 30 min. It was then left to cool and poured onto ice. The solid which separated was crystallized from methyl alcohol and proved to be the diacetate of tetrachlorocatechol.

Reaction of tetrachlorocatechol with 9,9-dichlorothiaxanthene. To a solution of 9,9-dichlorothiaxanthene (0.1*M*, from thiaxanthone and thionyl chloride) in boiling benzene, a solution of tetrachlorocatechol in benzene (0.1*M*) was added dropwise while passing in a stream of dry carbon dioxide. A vigorous reaction took place with evolution of gas and the refluxing was continued for 5 hr. The reaction mixture was filtered while hot, and the benzene was evaporated to dryness under reduced pressure. To the residue obtained,

acetone was added and the solid which separated was crystallized from benzene and proved to be Va (undepressed when admixed with an authentic sample prepared by the action of tetrachloro-*o*-benzoquinone and thioxanthione. Both products have identical infrared spectra[8]).

Preparation of 9,9-(tetrabromo-o-phenylenedioxy)thiaxanthene, Vb. Thioxanthione (2.33 g.) and tetrabromo-*o*-benzoquinone (4.24 g.) were allowed to react as in the case of the chloro- analogue. Vb crystallized from ethyl acetate in colorless crystals m.p. 245° (yield about 70%)

Anal. Calcd. for $C_{19}H_8O_2Br_4S$: C, 36.77; H, 1.29; Br, 51.61; S, 5.16. Found: C, 36.87; H, 1.19; Br, 51.72; S, 4.00.

Hydrolysis of Vb. This was carried out as in the case of the chloroanalogue when thioxanthone and tetrabromocatechol (identified as the diacetate) were obtained.

Oxidation of thioxanthione in air. Tetrachloro-*o*-benzoquinone (0.5 g.) and thioxanthione (0.5 g.) in benzene (15 ml.) were refluxed on the water bath for 3 hr. while passing a stream of dry air. The reaction mixture was filtered while hot and the benzene was then driven off under reduced pressure. The residue was extracted with boiling methyl alcohol and the solid which remained was filtered and crystallized from benzene to give Va (about 0.5 g.). The alcoholic extract was concentrated and left to cool to give thioxanthone.

Reaction of tetrachloro-o-benzoquinone with thioxanthone hydrazone. A solution of tetrachloro-*o*-benzoquinone (0.5 g.) in dry ether (10 ml.) was added portionwise to a solution of the hydrazone (0.23 g.) in dry ether (15 ml.) at room temperature. A vigorous reaction with evolution of gas occurred after each addition and the color of the quinone disappeared. After all the quinone was added, a solid separated which was filtered, crystallized from benzene, and shown to be Va (melting point and mixed melting point); yield about 80%.

Reaction of tetrabromo-o-benzoquinone with thioxanthone hydrazone. The quinone (0.8 g.) and the hydrazone (0.23 g.) were allowed to react as in the case of the chloro- analogue. The solid which separated was crystallized from ethyl acetate and proved to be Vb (melting point and mixed melting point); yield about 75%.

Acknowledgment. The authors wish to express their appreciation to Professor F. G. Baddar, Faculty of Science, A' in Schams University, Cairo, for determination of infrared spectra.

DOKKI, CAIRO, U.A.R.

(8) Samples were dried under reduced pressure at 130° before infrared determination.

[CONTRIBUTION FROM THE EDGAR C. BRITTON RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

Amidation and Hydrazidation of *O*-Aryl Phosphorodichloridothioates[1]

E. H. BLAIR AND H. TOLKMITH

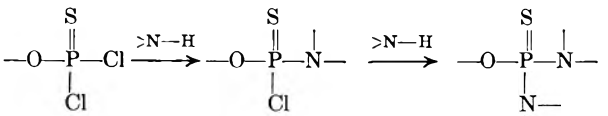
Received February 8, 1960

O-Aryl phosphorodichloridothioates on reaction with ammonia and aliphatic amines gave *O*-aryl phosphoramidochloridothioates and *O*-aryl phosphorodiamidothioates in high yields. *O*-Aryl phosphorodichloridothioates also react with substituted hydrazines to give *O*-aryl phosphorohydrazidochloridothioates and *O*-aryl phosphorodihydrazidothioates in high yields. The reactions were found to be dependent on temperature of reaction, mole ratio, and mode of addition of the reagents. Aromatic amines produced amido acid chlorides only, whereas hydrazine gave dihydrazides. *O*-Aryl phosphoramidohydrazidothioates were prepared by amidation of hydrazido acid chlorides and by hydrazidation of amido acid chlorides. A possible explanation of the difference observed in the reactions of the organophosphorus acid halides is presented.

The recent development of improved and convenient processes for the preparation of *O*-aryl phosphorodichloridothioates[2] prompted a study of the reactions of these phosphorus acid chlorides with compounds containing labile hydrogen atoms. The investigations described in this publication are concerned with the reactions of *O*-aryl phosphorodichloridothioates with ammonia, aliphatic and aromatic amines, hydrazine, and substituted hydrazines.

The first reported comprehensive study of the reactions of amines with phosphorus halides was by Michaelis.[3] *O*-Phenyl and *O*-tolyl phosphorodichloridothioates have been reported to form diamides and dihydrazides when treated with ammonia, benzylamine, hydrazine, and phenylhydrazine.[4-7] The patent literature cites examples of *O*-halophenyl phosphorodiamidothioates prepared from ammonia and amines.[8] However, no investigation has been reported on the stepwise substitution of the halogens in *O*-aryl phosphorodichloridothioates.

In the reaction I→III,



I II III

the logical pathway appeared to be through the partially amidated intermediate II. The remaining

(1) Presented before the Division of Organic Chemistry, 134th Meeting of the American Chemical Society, Chicago, Illinois, September, 1958, page 102P of Abstracts.

(2) H. Tolkmith, *J. Org. Chem.* **23**, 1685 (1958).

(3) A. Michaelis, *Ann.* **326**, 129 (1903).

(4) W. Autenrieth and W. Meyer, *Ber.* **58**, 840, 848 (1925).

(5) W. Autenrieth and O. Hildebrand, *Ber.*, **31**, 1094, 1111 (1898).

(6) E. Ephraim, *Ber.*, **44**, 3414 (1911).

(7) W. Strecker and H. Heuser, *Ber.*, **57**, 1368 (1924).

(8) L. R. Drake and A. J. Erbel, U. S. Patent **2,552,537** (1951); L. R. Drake and C. Moyle, U. S. Patent **2,552,538** (1951).

chlorine atom in II would then be less reactive toward further nucleophilic attack because of a decrease in the partial positive charge on the phosphorus atoms. This change in the electron density would result because of the displacement of the electronegative chlorine atom by the less electronegative amido group. As no successful preparation or isolation of an amido acid chloride (II) or a hydrazido acid chloride [—P(S)(NH—N—)Cl] had been reported in the literature, our main efforts were directed toward the preparation of such intermediates which would enable us to develop a scheme of reactions as outlined in Fig. 1.

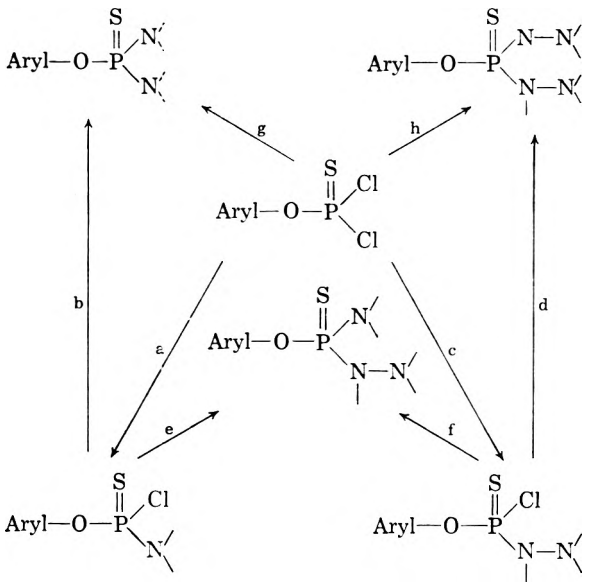


Fig. 1. Reaction scheme

Anhydrous ammonia and aliphatic amines underwent both reactions (a) and (g), Fig. 1. These reactions were determined by temperature, mole ratio and mode of addition of the reactants. The slow addition of two moles of an aliphatic amine to one mole of a well stirred solution of *O*-aryl phosphorodichloridothioate in ether or benzene at 0° to 10° gave the *O*-aryl phosphoramidochloridothioate and the amine hydrochloride, generally in high yields. Anhydrous ammonia added to *O*-(2,4,5-trichlorophenyl) phosphorodichloridothioate produced an amido acid chloride in satisfactory yield only at −20 to −30°. Attempts to prepare this particular amido acid chloride at higher temperatures were unsuccessful. The reverse addition, using the same amount of reactants as indicated above, always gave a mixture of diamide and unreacted acid chloride.

The amido acid chlorides were isolated by filtering from amine hydrochloride and removing solvent under reduced pressure. Amido acid chlorides could also be freed from amine hydrochlorides by a water wash. In many instances liquid products crystallized when stirred with cold low-boiling petroleum ether. The products which did not crystallize were purified by petroleum ether extraction, the amido acid chlorides being soluble whereas diamides were generally insoluble. The solid products were recrystallized from petroleum ether. Most of the amido acid chlorides prepared from aliphatic amines were white crystalline solids possessing well defined melting points. Although these acid chlorides did not decompose at their melting points, the amido acid chlorides prepared from primary amines might be expected to dehydrochlorinate at higher temperatures. No decomposition was ever encountered on storage at room temperature, however.

These phosphorus acid halides were relatively stable to hydrolysis. In many instances the crude amido acid chlorides were washed with water to free them from amine hydrochloride with no apparent decomposition. Aqueous isopropylamine was successfully employed in the preparation of *O*-(2,4,5-trichlorophenyl) isopropylphosphoramidochloridothioate (yield 80%). Evidently these phosphorus acid halides are considerably more resistant toward hydrolysis than phenylphosphonothioic dichloride, for Smith and Audrieth[9] have found the latter hydrolyzes so rapidly that aqueous amines are unsuitable for amidation.

The most interesting compound of this series was that prepared from anhydrous ammonia, for it represents the first reported phosphorus acid chloride containing the grouping [—P(S)(NH_2)Cl]. As might be expected, this amido acid chloride was not as stable as those prepared from aliphatic amines. While no decomposition was observed on taking the melting point, the compound did deteriorate in about two months on storage at room temperature.

Table I lists the physical and analytical data for an umber of *O*-aryl phosphoramidochloridothioates.

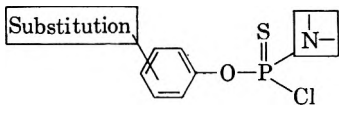
Symmetrical diamides were prepared by the reaction of *O*-aryl phosphorodichloridothioates with at least four equivalents of aqueous or anhydrous ammonia and aliphatic amines [route(g)]. A useful method for the preparation of unsymmetrical diamides was that of route (b). A definite decrease in the rate of formation of diamides was observed in going from ammonia and primary amines to the branched and bulkier amines. The unsymmetrical diamides described in this report were prepared from purified amido acid chlorides. All diamides reported herein were white crystalline solids with well defined melting points.

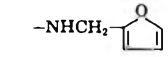
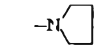
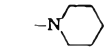
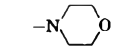
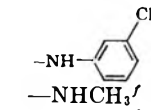
Further chemical evidence for the existence of the amido acid chlorides was established by the preparation of an unsymmetrical diamide from two different amido acid chlorides (Fig. 2). Preparations of the unsymmetrical diamide *O*-(2,4,5-trichlorophenyl) *N,N*-dimethylphosphorodiamido-

(9) W. Smith and L. F. Audrieth, *J. Org. Chem.* **22**, 265 (1957).

TABLE I

PHYSICAL AND ANALYTICAL DATA OF *O*-ARYL PHOSPHORAMIDOCHLORIDOTHIOATES



Substitution	—N< [a,b]	Reaction [c] Temp.	Yield, [d] %	M.P. [e]	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	—NHCH$_3$ [f]	15 ± 5	92.5	22–22.5 [g]	6.32	6.14	16.45	16.05
H [h]	—NHC$_6$H$_5$	40	85.8	[i]	4.93	4.82	12.49	12.10
2,4-Cl$_2$	—NHCH(CH$_3$)$_2$	0 ± 5	83	50.5–51	4.39	4.63	33.39	33.09
2,4,5-Cl$_3$ [h]	—NH$_2$ [f]	−25 ± 5	92	55–56	4.50	4.39	45.60	44.48
2,4,5-Cl$_3$	—NHCH$_3$ [f]	−5	99.5	61–62	4.31	4.27	43.64	43.56
2,4,5-Cl$_3$	—N(CH$_3$)$_2$ [f]	5 ± 10 [j]	54.6 [k]	49–50	4.13	4.13	41.60	41.77
2,4,5-Cl$_3$	—NHCH(CH$_3$)$_2$	−5 ± 5	83 [k]	51.5–52.5	3.97	3.75	40.17	40.13
2,4,5-Cl$_3$	—NHC$_6$H$_{11}$	0 ± 5	93.5	88–89	3.56	3.46	36.07	35.90
2,4,5-Cl$_3$	—NHCH$_2$C$_6$H$_5$ [l]	−5 ± 5	80 [k]	73–73.5	3.49	3.46	35.36	35.10
2,4,5-Cl$_3$		25 ± 5	48	[m]	3.58	3.15	36.28	36.54
2,4,5-Cl$_3$		25 ± 5	76	66–68	3.84	3.56	38.85	38.65
2,4,5-Cl$_3$		25 ± 5	80	40–43	3.68	3.58	37.42	37.40
2,4,5-Cl$_3$		25 ± 5	77	93–95	3.58	3.24	37.22	37.80
2,4,5-Cl$_3$	—NHC$_6$H$_5$ [l]	33 ± 8 [j]	70	[n]	3.62	3.60	36.64	36.20
2,4,5-Cl$_3$		82 ± 2 [j]	56.5	[o]	3.33	3.28	42.20	42.50
2,4,6-Cl$_3$	—NHCH$_3$ [f]	5	91.4	80–81	4.31	4.36	43.64	43.41
2-Cl,4-C(CH$_3$)$_3$	—NHCH$_3$ [f]	23 ± 1	90.5	[p]	4.50	4.48	22.71	21.25
3-Cl,4-NO$_2$	—NHCH$_3$ [f]	0 ± 5	74	[q]	9.35	9.15	23.55	23.41

[a] Prepared by addition of amine dissolved in ether or benzene to *O*-aryl phosphorodichloroidothioate dissolved in same solvent. [b] Amine hydrochloride removed by filtration. [c] Reaction time 1–4 hr. [d] Yield of technical grade material. [e] Recrystallized from petroleum ether (b.p. 60–70°). [f] Gaseous amine passed into the reaction mixture. [g] Recrystallized from petroleum ether (b.p. 30–60°); d_4^{25} 1.3195, n_D^{25} 1.5767. [h] Described in detail in Experimental section. [i] d_4^{25} 1.3091, n_D^{25} 1.6242. [j] Reaction time 6–8 hr. [k] Yield of purified product. [l] Amine hydrochloride removed by water wash. [m] n_D^{25} 1.606. [n] d_4^{25} 1.5140, n_D^{25} 1.6386. [o] d_4^{25} 1.5470, n_D^{25} 1.6318. [p] d_4^{25} 1.2547, n_D^{25} 1.5602. [q] n_D^{25} 1.6100.

thioate by the two routes differed in melting point by one degree (119–120° *vs.* 118–120°). A mixed melting point of 118–120° was obtained. Combustion analysis and infrared spectra substantiated the identity of the two diamides. Table II lists the physical properties and analytical data of a number of *O*-aryl phosphorodiamidothioates.

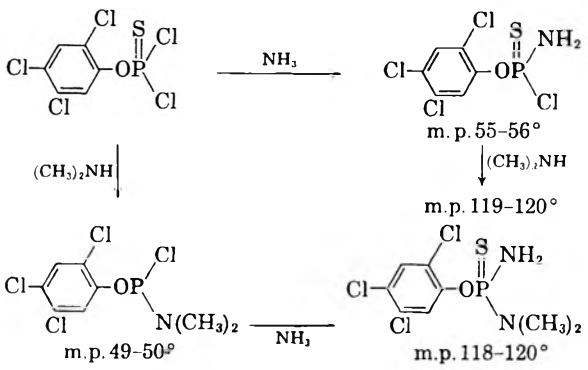


Fig. 2. Preparation of *O*-(2,4,5-trichlorophenyl) *N*,*N*-dimethylphosphorodiamidothioate

Amines containing an aromatic or heterocyclic group, linked through a methylene bridge such as benzylamine and furfurylamine, underwent reactions (a), (g), and (b) as expected. Secondary heterocyclic amines such as piperidine and morpholine likewise reacted exothermically along these routes.

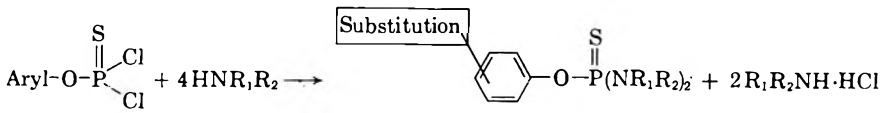
Amidation of *O*-aryl phosphorodichlorodothioates with aniline and *m*-chloroaniline in the absence of a separate hydrogen chloride acceptor reacted differently and unexpectedly, proceeding only to the extent of reaction (a), Fig. 1. This reaction required several hours of refluxing. Furthermore, it was not clear-cut and side reactions resulted—a marked contrast to the other amine reactions discussed.

The preparation of *O*-phenyl phenylphosphoramidochloridothioate from *O*-phenyl phosphorodichloridothioate and aniline in the presence of 10% sodium hydroxide has been described.[4] The reported melting point of 153° is abnormally high for such a compound. As it was isolated as a benzene insoluble material and only a sulfur analysis

TABLE II

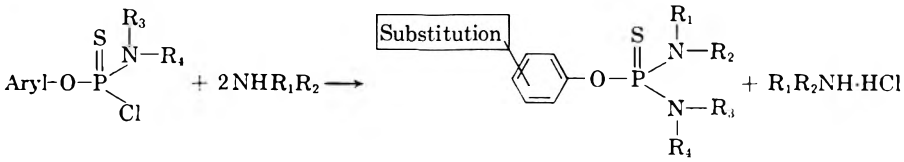
PHYSICAL AND ANALYTICAL DATA OF *O*-ARYL PHOSPHORODIAMIDOTHIOATES

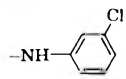
Symmetrical



Substitution	—NR_1R_2	Yield,[a] %	Crystallization Solvent	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
2,4,5-Cl_3	—NH_2[b]	95.9	Ethanol[c]	143.5–144.5	9.61	9.39	36.48	36.29
2,4,5-Cl_3	—$NHCH_3$[b]	95	Ethanol	116.5–117.5	8.76	8.73	33.28	32.91
2,4,5-Cl_3	—NHC_2H_5[b]	84	Cyclohexane	79–80	8.05	8.03	30.59	30.26
2,4,5-Cl_3	—$NHCH(CH_3)_2$[d]	93.5	Ethanol	90–91	7.46	7.45	27.99	28.31
2,4,5-Cl_3	—NHC_6H_{11}[d]	100	Propanol	124–124.5	6.15	6.28	23.33	23.12
2,4,5-Cl_3	—$N(CH_3)_2$[b]	97.8	Methanol	62.5–63	8.05	8.03	30.59	30.26
2,4,5-Cl_3[e]		39	Cyclohexane	99–101	7.03	7.06	26.61	26.80
2,4,5-Cl_3[e]		86.7	Propanol	156–157	6.49	6.71	24.64	24.40

Unsymmetrical[f]



Substitution	—NR_1R_2	—NR_3R_4	Yield,[a] %	Crystallization Solvent	M.P.	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H[e]	—$NHCH(CH_3)_2$	—NHC_6H_5	89	Methyl cyclohexane	96–97	9.14	8.99	10.11[g]	10.38
2,4,5-Cl_3	—NH_2	—$NHCH_3$	82	Ethanol	113–114	9.17	9.23	34.81	34.81
2,4,5-Cl_3	—$N(CH_3)_2$	—$NHCH_3$	85.9	Methanol	106–107.5	8.40	8.40	31.88	31.31
2,4,5-Cl_3	—NHC_2H_5	—$NHCH_3$	85.9	Methyl cyclohexane	91–92.5	8.40	8.41	31.88	32.00
2,4,5-Cl_3	—$NHCH(CH_3)_2$	—$NHCH_3$	85.5	Petroleum ether (60–70°)	88–89	8.05	8.00	30.59	31.15
2,4,5-Cl_3[h]		—$NHCH_3$	44	Cyclohexane	149–150	7.47	7.17	28.40	28.77
2,4,5-Cl_3[h]	—$NHCH_3$		46.5	Cyclohexane	132–133	6.73	6.69	34.10	33.76
2,4,5-Cl_3	—$N(CH_3)_2$	—NH_2	69.5	Methanol[c]	119–120	8.76	8.72	33.28	33.21
2,4,5-Cl_3	—NH_2	—$N(CH_3)_2$	92.8	Methanol	118–120	8.76	9.02	33.28	33.80
2,4,5-Cl_3	—$N(C_6H_{11})_2$	—NHC_2H_5	70	Methylene dichloride	144–145	5.79	5.70	21.98	22.10
2,4,6-Cl_3	—$NHCH_3$	—NHC_2H_5	86	Cyclohexane	106–107	8.40	8.30	31.88	31.47
2-Cl,4-NO_2[e]	—$NHCH_3$	—NHC_2H_5	80	Methyl cyclohexane	75–77	13.56	12.50	11.45	11.84

[a] Yield of technical grade material. [b] Gaseous amine passed into the dichloridothioate dissolved in methylene dichloride. [c] Described in detail in Experimental section. [d] Liquid amine added at room temperature, reaction mixture heated at 40° for 3–4 hr. and allowed to stand at room temperature overnight. [e] Benzene solvent. [f] Prepared by addition of gaseous or liquid amine at 25° to the amido acid chloride dissolved in methylene dichloride; reaction mixture then heated at 40° for 0.5–3.0 hr. [g] Phosphorus analysis. [h] Ether solvent.

was presented, there is some doubt as to the identity of the product. We prepared this compound, which was a dark brown oil. The infrared spectrum was in accord with the assigned structure. This amido acid chloride was further amidated with isopropylamine to give the unsymmetrical diamide *O*-phenyl *N*-isopropyl-*N'*-phenylphosphorodiamidothioate, m.p. 96–97°, in high yield.

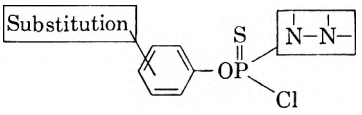
In order to allow the aromatic amines to react through route (g) to the dianilide, it was necessary to carry out a Schotten-Baumann reaction as suggested by Autenrieth and Hildebrand.[5]

In view of the results obtained from amidation studies, hydrazides offered an interesting challenge. Previous workers restricted themselves to the preparation of symmetrical dihydrazides and apparently made no attempt to isolate or identify intermediates such as a hydrazido acid chloride.[4–6] We approached the problem in a manner similar to that described for the amides, *i.e.* along routes (c), (d), and (h), Fig. 1.

1,1-Dimethylhydrazine reacted analogously to aliphatic amines. The slow addition of two moles of this hydrazine to one mole of dichloridothioate

TABLE III

PHYSICAL AND ANALYTICAL DATA OF *O*-ARYL PHOSPHOROHYDRAZIDOCHLORIDOTHIOATES



Substitution[a]	—N—N—	Yield,[b] %	M.P.	n_D^{25}	d_4^{25}	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	—NHN(CH$_3$)$_2$	97.1[c]		1.5663	1.2464	11.18	11.73	14.10	14.52
2-Cl	—NHN(CH$_3$)$_2$	95.8[c]		1.5701	1.3237	9.82	9.56	24.87	23.85
2,4-Cl$_2$[d]	—NHN(CH$_3$)$_2$	99.0	74–75			8.77	8.72	33.28	33.90
3,4-Cl$_2$	—NHN(CH$_3$)$_2$	84.0[c]		1.5794	1.4111	8.77	8.72	33.28	33.36
2,4,5-Cl$_3$	—NHN(CH$_3$)$_2$	100	76–78[e]			7.91	7.32	40.01	38.78
2,4,5-Cl$_3$[d]	–NH—NH– 	79	120–122	—		6.97	7.01	35.27	34.73

[a] Reactions carried out at 20–25° in ether or benzene unless otherwise noted. [b] Yield of technical grade material. [c] Product isolated by filtering 1,1-dimethylhydrazine hydrochloride and removing solvent under reduced pressure. [d] Described in detail in Experimental section. [e] Recrystallized from petroleum ether (b.p. 60–70°) then from methylcyclohexane.

in ether at 0° to 10° produced the hydrazido acid chlorides (route c) in nearly quantitative yields, again demonstrating a degree of difference in the ease of displacement of the phosphoryl halogen of $-OP(S)Cl_2$ and $-OP(S)(N-N)Cl$ by the nucleophilic reagent. Crystalline hydrazido acid chlorides were recrystallized from petroleum ethers and liquid products purified by extraction with petroleum ether. These acid chlorides were as stable as the amido acid chlorides toward hydrolysis and on storage. No decomposition was observed on melting.

Phenylhydrazine differed from 1,1-dimethylhydrazine only in that lower temperatures, −20 to −30°, were required to prepare the hydrazido acid chloride. As no solvent suitable for crystallization could be found, this hydrazido acid chloride was purified by dissolving in ether, precipitating insoluble material by the addition of petroleum ether (b.p. 30–60°), and removing the solvents under reduced pressure. This acid chloride was considerably less stable than the previously described acid chlorides. On standing at room temperature for a few weeks the sample deteriorated with sublimation of 2,4,5-trichlorophenol.

Attempts to prepare hydrazido acid chlorides from anhydrous hydrazine were unsuccessful. Failure to find nonreactive solvents compatible with anhydrous hydrazine and *O*-aryl phosphorodichloridothioates was a contributing factor. We were interested in the synthesis of amidohydrazides as additional proof for the existence of the disclosed amido and hydrazido acid chlorides. The reaction of *O*-(2,4,5-trichlorophenyl) 2,2-dimethylphosphorohydrazidochloridothioate with methylamine [route (f)] gave the same amidohydrazide (Fig. 3) as that obtained by hydrazidation of *O*-(2,4,5-trichlorophenyl) methylphosphoramidochloridothioate with 1,1-dimethylhydrazine [route (e)]. Physical properties and analytical data for *O*-aryl phosphorohydrazidochloridothioates are given in Table III.

Table IV lists the properties of *O*-aryl phosphoramidohydrazidothioates. The amidohydrazides were crystalline solids, recrystallizable from lower alcohols. All but one had melting points below those of the corresponding diamides and dihydrazides.

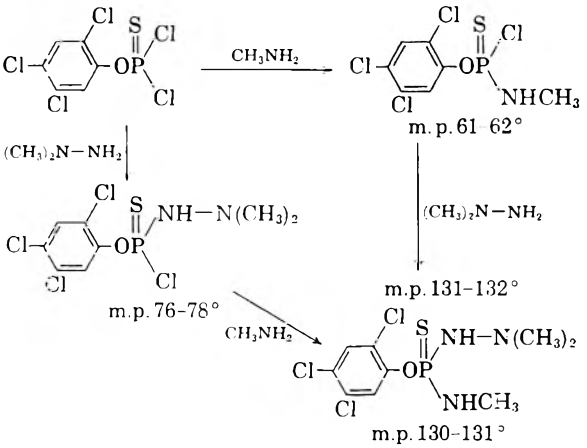


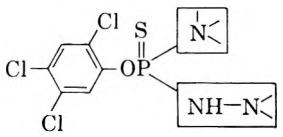
Fig. 3. Synthesis of *O*-aryl phosphorohydrazidochloridothioates

Dihydrazides were prepared, in high yields, from hydrazine hydrate, phenylhydrazine, and 1,1-dimethylhydrazine [route (h)], using four moles of hydrazine per mole of dichloridothioate. All were crystalline solids, insoluble in water and difficultly soluble in many organic solvents. These products were recrystallized from lower alcohols. The dihydrazides were higher melting than the diamides. Substitution of alkyl groups for hydrogens on the hydrazido groups lowered the melting points in much the same manner as alkyl substitution lowered the melting points of the diamides. Smith, Gher, and Audrieth[10] obtained phenylphosphonothioic

(10) W. C. Smith, R. Gher, Jr., and L. F. Audrieth, *J. Org. Chem.* 21, 113 (1956).

TABLE IV

PHYSICAL AND ANALYTICAL DATA OF *O*-ARYL PHOSPHORAMIDOHYDRAZIDOTHIOATES



—N< [a]	—NH—N< [b]	Yield, % [c]	M.P. [d]	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
—NH_2 [e]	—NH—NH_2	75	86–87 [f]	13.71	13.35	34.53	33.87
—NH_2	—NH—NH—C$_6$H$_5$	87	137–139 [g]	10.99	10.71	27.39	27.79
—$NHCH_3$	—NH—NH_2 [h]	90.5	104–105	13.13	14.79	33.10	33.10
—$NHCH_3$ [i]	—NH—$N(CH_3)_2$	100	130–131	12.04	11.48	30.51	30.39
—$NHCH_3$	NH—$N(CH_3)_2$	70.5	131–132	12.04	11.45	30.51	30.50
—$NHCH_3$ [j]	—NH—NH—C$_6$H$_5$	44 [k]	112–113	10.61	11.04	26.82	26.91

[a] Reactions carried out at 25–35° for 1 to 3 hr. [b] Prepared by addition of hydrazine reagent to the amido acid chloride unless otherwise noted. [c] Yield of technical grade material. [d] Recrystallized from ethanol or methanol. [e] Amido acid chloride in ether added to anhydrous hydrazine. [f] Purified by ether extraction and precipitation with petroleum ether (b.p. 30–60°). [g] Recrystallization from benzene prior to alcohol recrystallization. [h] Reaction carried out in methylene chloride with hydrazine hydrate. [i] Prepared by addition of a gaseous amine to hydrazido acid chloride in methylene chloride solvent described in detail in the Experimental. [j] Reaction carried out in benzene at 25–50° for 3 hr. [k] Yield of purified product.

dihydrazide by a similar type of reaction. Table V lists the analytical and physical properties of the *O*-aryl phosphorodihydrazidothioates.

The formation of the many products resulting from amidation and hydrazidation of *O*-aryl phosphorodichloridates can be related to electronic effects, steric effects, and base strength of the nucleophilic reagents as well as to reaction temperatures, mole ratios, and mode of addition of reagents.

In general diamide formation, (g) Fig. 1, results *via* two bimolecular reactions—(a) and (b). The phosphorus atom of the dichlorothioate is more susceptible to nucleophilic attack than the phosphorus atom of the amido acid chloride. When ammonia or an amine was added to a dichloridothioate, an amido acid chloride was generally obtained in high yields with little or no diamide. The amido nitrogen, following displacement of one of the two chlorine atoms attached to the phosphorus atom, decreases the positive charge on phosphorus *via* an inductive effect. This increase in electron density about the phosphorus atom causes the remaining chlorine atom to be less susceptible to further nucleophilic attack.

All of the nitrogen bases studied (except hydrazine) with *p*Ka values substantially higher than 5 gave a constant pattern of reaction; products *via* routes (a), (b), (g), (c), (d), and (h) in Fig. I were obtained in high yields.

Dostrovsky and Holmann,[11] in their kinetics studies on the amidation of dialkyl phosphorochloridates, showed that secondary amines, though stronger nucleophiles, reacted much more slowly than corresponding primary amines, indicating the operation of steric factors. These steric effects are also operative in the rate of formation of diamide *vs.* amidochloride. When ammonia gas was used to prepare the amidochloride, it was necesary to go to temperatures of −20° to −30° to obtain an amidochloride free of diamide, whereas isopropylamine gave the diamide only at temperatures above 30°.

Hydrazine gave the expected dihydrazide but failed to give a hydrazidochloride of sufficient purity and yield for identification, even at temperatues of −30° and −40°. Being a bifunctional material, hydrazine may behave anomalously on partial hydrazidation. The substituted hydrazines, having less bifunctional character and offering more steric interaction, did give the expected hydrazidochloride. Tolkmith and Britton[12] have found that the bifunctionality of amines such as ethylenediamine makes the isolation of an intermediate amido acid chloride improbable, for only the heterocyclic product resulting from complete dehydrochlorination was obtained.

Of the group of weak organic bases, aniline, *m*-chloroaniline, and phenylhydrazine reacted quite differently and unexpectedly. Independent of mole ratio of reactants and reaction conditions, the anilines did not react beyond the formation of aryl-OP(S)(Cl)NHC$_6$H$_5$, while phenylhydrazine readily produced aryl-OP(S)(NH—NH—C$_6$H$_5$)$_2$, and it was necessary to perform the reaction at −30° to obtain the product aryl-OP(S)(Cl)-NH—NH—C$_6$H$_5$. The lack of reactivity of aniline to form the diamido product was probably due more to its low basicity, *p*Ka = 4.58, than to steric

(11) I. Drostovsky and M. Holmann, *J. Chem. Soc.* 511 (1953).

(12) H. Tolkmith and E. C. Britton, *J. Org. Chem.* **24,** 705 (1959).

TABLE V

PHYSICAL AND ANALYTICAL DATA OF *O*-ARYL PHOSPHORODIHYDRAZIDOTHIOATES

Substitution	—N—N—	Solvent	Product Isolation Method[b]	Yield,[c] %	M.P.[d]	Nitrogen, % Caled.	Nitrogen, % Found	Chlorine, % Caled.	Chlorine, % Found
2-Cl	—NH—NH_2[e]	Methylene dichloride	A	93.7	145–147	22.17	22.02	14.03	13.25
2,4,5-Cl_3	—NH—NH_2[e]	Benzene	A	93.5	152–153	17.42	17.14	33.07	32.64
2,4-Cl_2	–NH–NH–	Methylene dichloride	A	96.7	156–157	12.76	12.92	16.14	15.47
2,4,5-Cl_3		Ether	B	73[f]	158–159	11.83	11.76	22.45	22.54
2-Cl, 4-C$(CH_3)_3$		Ether	B	92.3	151–153	12.15	12.10	7.61	7.66
2,4,5-Cl_3	NH—$N(CH_3)_2$	Methylene dichloride	C	93.5	123–125[g]	14.84	14.21	28.19	27.87

[a] Prepared by addition of acid chloride to excess hydrazine reagent at 5–15°, then heated to 35–40° for 1–2 hr. [b] A, product being insoluble in reaction solvent was isolated by adding water to reaction mixture, product filtered, and recrystallized; B, product being soluble in reaction solvent was isolated by filtering off the phenylhydrazine hydrochloride, removing solvent under reduced pressure, dissolving resulting solids in boiling ethanol or acetone, pouring into ice water, and recrystallizing filtered product; C, product being soluble in reaction solvent was isolated by washing with water to remove the 1,1-dimethylhydrazine hydrochloride, then proceeding as described under B. [c] Yield of technical grade material unless otherwise noted. [d] All recrystallizations from ethanol or methanol. [e] Hydrazine hydrate slurried in the solvent. [f] Yield of purified product described in detail in the Experimental. [g] Final recrystallization from methylcyclohexane.

interference of the bulky reagent for such behavior was not observed when cyclohexylamine was used.

The ease of reaction of phenylhydrazine, as evidenced by ready formation of aryl-OPS(Cl)-($NHNHC_6H_5$) as well as of aryl-OPS($NHNHC_6H_5$)$_2$, may be related to the fact that phenylhydrazine has a somewhat higher *p*Ka value (5.2) and a much more favorable steric factor than aniline.

EXPERIMENTAL[13]

Starting materials and procedures. All *O*-aryl phosphorodichloridothioates used have been previously described.[7] The liquid organic amines employed were freshly redistilled commercial products. Gaseous amines were volatilized into a chilled flask, then used. All hydrazines were used as commercial materials, except phenylhydrazine which was redistilled. The synthetic procedures for the preparation of the various amides and hydrazides are illustrated by the following examples.

1. *O-Aryl phosphoramidochloridothioates. O-(2,4,5-Trichlorophenyl) phosphoramidochloridothioate.* Two liters of ether containing 0.5 mole (165.2 g.) of O-(2,4,5-trichlorophenyl) phosphorodichloridothioate was cooled to −20° by means of an acetone-Dry Ice bath. Over a period of 3 hr., 1.0 mole (17.0 g.) of gaseous anhydrous ammonia was passed through a large-bore dip-pipe into the rapidly stirred reaction mixture which was maintained at −20° to −30°. After warming the mixture to room temperature the ammonium chloride was filtered and the ether removed under reduced pressure to give 138.0 g. (92% yield) of an oily product. The product solidified when stirred with 100 ml. of petroleum ether (b.p. 30–60°), m.p. 52–53°. The amidochloride after two recrystallizations from ethylcyclohexane melted at 55–56°.

O-(2,4,5-Trichlorophenyl) isopropylphosphoramidochloridothioate. To 0.15 mole (49.5 g.) of *O*-(2,4,5-trichlorophenyl) phosphorodichloridothioate dissolved in 300 ml. of methylene chloride was added a 50% aqueous solution containing 0.30 mole (17.7 g.) of isopropylamine. The addition was carried out at 0° and required 30 min. The mixture was stirred at 0° for 30 min. and allowed to come to room temperature. The aqueous phase was separated and the methylene chloride solution washed three times with water. The solvent was removed under reduced pressure leaving 44.5 g. (83% yield) of a liquid product. The liquid was dissolved in 70 cc. of petroleum ether (b.p. 30–60°) and cooled in an ice bath. A few seed crystals, obtained by freezing such a mixture in a Dry Ice-acetone bath, were added to induce crystallization. More petroleum ether was added and the amido acid chloride filtered, m.p. 51–53°, yield 60.4%. A sample when recrystallized from petroleum ether (b.p. 60–70°) melted at 51.5–52.5°.

O-Phenyl phenylphosphoramidochloridothioate. One mole (93.1 g.) of aniline was added at room temperature to 0.25 mole (56.7 g.) of *O*-phenyl phosphorodichloridothioate dissolved in 300 ml. of benzene. It was necessary to heat the solution at 40° for 24 hr. in order to obtain aniline hydrochloride equivalent to that required for monoamidation. The benzene solution was washed with 200 ml. of water, then with 200 ml. of 2.5*N* hydrochloric acid and twice with 100-ml. portions of 2.5*N* hydrochloric acid to remove excess aniline. The benzene solution was next washed twice with 100-ml. portions of aqueous 5% sodium carbonate to remove acidic materials. After four 250-ml. water washes the benzene solution was dried over Drierite. The benzene was distilled under reduced pressure, leaving 60 g. (85.8% yield) of clear light brown liquid, d_4^{25} 1.3091, n_D^{25} 1.6242.

(13) All melting points were determined on a Fisher-Johns block and are uncorrected.

This amido acid chloride on reaction with isopropylamine gave a solid diamide, *O*-phenyl *N*-isopropyl-*N'*-phenylphosphorodiamidothioate, in 89% yield, m.p. 96–97°.

2. *O-Aryl phosphorodiamidothioates. O-(2,4,5-Trichlorophenyl) phosphorodiamidothioate.* To 0.25 mole (82.6 g.) of *O*-(2,4,5-trichlorophenyl) phosphorodichloridothioate in 500 ml. of methylene dichloride was added, with stirring, an excess of gaseous anhydrous ammonia. The ammonia was passed into the reaction mixture through a large-bore dip-pipe. The exothermic reaction was kept at 15–25° by means of an ice bath. The product and ammonium chloride separated from the reaction mixture immediately upon formation. Following the addition of ammonia (0.5 hr.) the reaction mixture was stirred at room temperature for 1 hr. Water was added to dissolve the ammonium chloride and the product collected and air dried; m.p. 134–136°, yield 70.0 g. (95.9%). An analytical sample was obtained by recrystallizing from ethanol, m.p. 143.5–144.5°.

O-(2,4,5-Trichlorophenyl) N,N-dimethylphosphorodiamidothioate. An excess of dimethylamine was added as a gas through a wide-bore dip-pipe to 150 ml. of a stirred methylene dichloride solution containing 0.032 mole (10.0 g.) of *O*-(2,4,5-trichlorophenyl) phosphoramidochloridothioate. Addition was complete in 0.5 hr. The temperature of the reaction mixture increased from 25° to 29°. The reaction was heated with stirring at 50° for 20 min. and then cooled to room temperature. The reaction mixture was washed twice with 150-ml. portions of water. On distilling the solvent, 8.0 g. (39.5%) of product was obtained, m.p. 112–116°. An analytical sample was prepared by extracting the product with petroleum ether (b.p. 60–70°), evaporating the ether, and recrystallizing from methanol; m.p. 119–120°. The synthesis of the same chemical by the amidation of *O*-(2,4,5-trichlorophenyl) *N,N*-dimethylphosphoramido chloridothioate is recorded below.

O-(2,4,5-Trichlorophenyl) dimethylphosphoramidochloridothioate, 0.061 mole (20.0 g.), was treated with gaseous ammonia by the method described above and the product worked up in a similar manner yielding 18.0 g. (92.8%) of the desired product, m.p. 115–118°. An analytical sample crystallized from methanol melted at 118–120°. Mixed melting points with the previously prepared product gave no depression in melting point. Infrared analysis and combustion data gave added proof to the identity of the unsymmetrical diamide prepared from two different amidochlorides.

3. *O-Aryl phosphorohydrazidochloridothioates. O-(2,4-Dichlorophenyl) 2,2-dimethylphosphorohydrazidochloridothioate.* A solution of 0.6 mole (36.0 g.) of 1,1-dimethylhydrazine in 1.0 l. of ether was added dropwise over a period of 2 hr. to an agitated solution of 0.3 mole (89 g.) of O-(2,4-dichlorophenyl) phosphorodichloridothioate in 3.0 l. of ether cooled to a temperature of −20°. The reaction mixture was stirred at room temperature for 3 hr., filtered, and the solvent removed under reduced pressure. The solid product obtained as a residue was recrystallized from petroleum ether (b.p. 60–70°) to give 95.0 g. of colorless crystalline hydrazidochloridate, m.p. 74–75°, yield 99%.

This reaction was carried out at a temperature of −20° only to insure a hydrazidochloride of high purity. Other preparations of hydrazido acid chlorides prepared from 1,1-dimethylhydrazine were conducted at 0° to 10°. Infrared spectra of the 2,2-dimethyl phosphorohydrazidochloridothioates prepared at 0° to 10° compared favorably with those prepared at −20°.

O-(2,4,5-Trichlorophenyl) 2-phenylphosphorohydrazidochloridothioate. Freshly distilled phenylhydrazine (0.62 mole, 67.0 g.) in 1.0 l. of ether was added dropwise over a period of 12 hr. to a well stirred solution of 0.3 mole (102.3 g.) of *O*-(2,4,5-trichlorophenyl) phosphorodichloridothioate in 1.0 l. of ether cooled to −30° to −40°. The reaction mixture was stirred for an additional 8 hr. at −30°, allowed to warm gradually to room temperature, filtered to remove the phenylhydrazine hydrochloride, and the ether removed under reduced pressure, to give 93.4 g. of light brown crystals, m.p. 116–118°, yield 79.0%. An analytical sample was prepared by extracting with ether and filtering to remove insoluble material. Petroleum ether (b.p. 30–60°) was added to the ether solution to precipitate any dihydrazide formed. A small amount was formed; m.p. 152–154°. On evaporation of the ether solutions the desired product was obtained as a light gray solid, m.p. 120–122°.

4. *O-Aryl phosphorodihydrazidothioates. O-(2,4,5-Trichlorophenyl) 2,2-diphenylphosphorodihydrazidothioate.* O-(2,4,5-Trichlorophenyl) phosphorodichloridothioate (0.2 mole, 66.0 g.) in 200 ml. of ether was added to 0.8 mole (86.5 g.) of phenylhydrazine in 1.0 l. of ether at room temperature. The reaction mixture was heated to 35° for 0.5 hr., allowed to cool to room temperature, and stirred for an additional 1.5 hr. Phenylhydrazine hydrochloride was filtered and the solvent evaporated. The resulting solid was dissolved in acetone and poured into water. The brown solid which separated was filtered, dried (m.p. 149–152°), and recrystallized from 1.5 l. of ethanol to give a colorless crystalline solid, m.p. 158–159°, yield 73.0%.

5. *O-Aryl phosphoramidohydrazidothioates. O-(2,4,5-Trichlorophenyl) N,2,2-trimethylphosphoramidohydrazidothioate.* A slight excess of gaseous methylamine was passed into a stirred solution containing 0.05 mole (17.7 g.) of O-(2,4,5-trichlorophenyl) 2,2-dimethylphosphorohydrazidochloridothiolate in 150 ml. of methylene chloride. Addition was complete in 0.5 hr. The temperature of the reaction mixture increased to 42° during the addition. The mixture was stirred for 1 hr. and washed two times with 100-ml. portions of water. Evaporation of solvent left 18.0 g. of colorless solid product, m.p. 122–125°, yield 100%. The amidohydrazide after two recrystallizations from ethanol melted at 130–131°.

The same product was obtained by the hydrazidation of O-(2,4,5-trichlorophenyl) methylphosphoramidochloridothioate with 1,1-dimethylhydrazine. This reaction was carried out in ether at 35°. After two recrystallizations from ethanol the product melted at 131–132°, yield 70.5%. The mixed melting point obtained on these two products was 130–132°. A comparison of infrared spectra of the two samples showed them to be identical.

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

Synthesis of Fluorine-Containing Organosilanes

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Received December 8, 1959

Fluorine-containing organosilanes have been prepared by the interaction of vinylsilanes with fluoroolefins. Cyclic adducts of the type $CX_2—CF_2—CH_2—CH—(CH_2)_n—SiR_3$ (where X equals fluorine and/or chlorine, n equals 0 to 3, and R equals ethoxy, methyl, and/or chlorine) are obtained when trifluoroiodoethylene was used with the vinylsilanes.

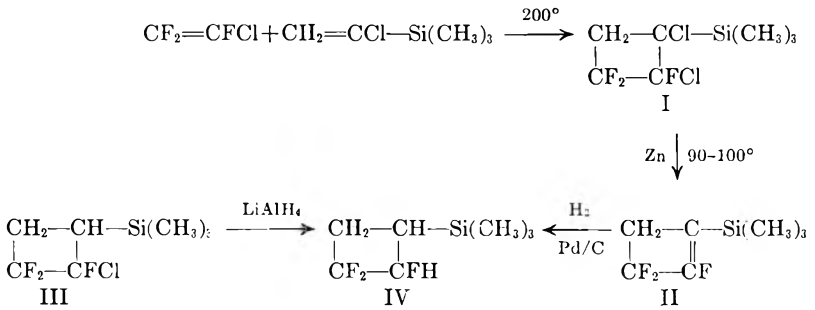
The thermal and chemical stability of the silicon polymers and tetraalkylsilanes[1,2] and the well known inherent stability of the polyfluorocarbons have led to attempts to incorporate the attributes of both systems into fluoroalkyl silicon compounds of high stability.

A number of new fluorine-containing cyclobutylsilanes have been prepared from fluoroolefins and alkenysilanes under conditions which generally favor cyclic codimer reactions rather than linear telomerization. All reactions were carried out in Pyrex combustion tubes at about 200° with hydroquinone and/or Terpene-B as free-radical inhibitors. The rationale for this study was based on the reasoning that the β-fluorine atoms of the cyclobutyl moiety in compounds of the type $CX_2—CF_2—CH_2—CH—SiR_3$ (where X is fluorine and/or chlorine) would be close enough to the silicon atoms to improve or enhance the thermal stability of the silicon-carbon bond. From steric considerations and the well known stability of fluorine-containing cyclobutanes toward alkaline hydrolysis, it was assumed that the fluorine-containing cyclobutyl group would be hydrolytically stable.

Thus, tetrafluoroethylene was codimerized with vinyltrimethylsilane in 82% yields to give $CF_2—CF_2—CH_2—CH—Si(CH_3)_3$. This fluorine-containing cyclobutylsilane was unaffected by dilute hydrochloric acid. Similarly, a 20% solution of potassium hydroxide at 70° for ten hours had no effect on the compound. On the other hand, α-fluorine-containing silanes while thermally stable undergo immediate hydrolysis in cold dilute alkali.[3]

The free radical additions of fluoroalkyl halides to vinylsilanes were also studied. Perfluorovinyl iodide added photochemically to vinyltrimethylsilane to give $CF_2=CF—CH_2—CHI—SiCl_3$ and $CF_2=CF—CH_2—CHI—Si(CH_3)_3$ in 56% and 16% yields, respectively. These yields are in line with the observation of Tarrant[4] that difluorodibromomethane added more readily to vinyltrichlorosilane than to vinyltrimethylsilane.

The structure of III was established chemically by the reduction of the chlorine atom by lithium aluminum hydride followed by the unequivocal synthesis of IV according to the following scheme:



The dechlorination of I with zinc in butyl cellusolve at 90–100° to the trimethylsilylcyclobutane (II) definitely proved the vicinal character of the chlorine atoms. The *cis-trans* relationship of the chlorine atoms in I is unknown.

The hydrogenation of II to IV with palladium-on-charcoal as a catalyst proceeded quantitatively at room temperature. The chlorine atom in III was reduced in 64% yield by lithium aluminum hydride to give IV. The infrared spectra of IV obtained by both methods were found to be identical.

(1) H. Rosenberg, J. D. Groves, and E. J. Bartholomew, WADC Technical Report 54-613 Part I (1955).

(2) H. Rosenberg, C. Tamborski, and J. D. Groves, WADC Technical Report 54-613 Part III, (1957).

(3) R. N. Haszeldine, and E. J. Marklow, *J. Chem. Soc.*, 962 (1956).

(4) P. Tarrant and G. W. Dykes, 128th Meeting American Chemical Society, Minneapolis, Minn., September 1955.

On the basis of the known structures of III and I, it is reasonable to assume that all fluoroolefins of the type, $CF_2 = CX_2$ (where X is fluorine and/or chlorine) codimerize with vinylsilanes to give products of similar structure (*e.g.*, $X_2C(F_2)C(H_2)CH(SiR_3)$).

This mode of addition seems quite reasonable and the reaction is diagnostic of the conjugative nature of a vinyl group joined to silicon,[5,6] but apparently of small importance in the cyclization reactions described here, as all the alkenylsilanes gave essentially the same kind of products.

The structure of the resultant cyclobutanes was consistent with other proved structures of various codimers of 1,1-difluoro-2,2-dihaloethylene and a conjugated, terminally unsaturated system. However, the activating influence of the silicon atom was more pronounced, the closer it was to the terminal double bond. This is shown by the respective yields in the following series: $CF_2(CF_2)CH_2CH(Si(CH_3)_3)$, 82%; $CF_2(CF_2)CH_2CH(CH_2Si(CH_3)_3)$, 73.4%; $CF_2(CF_2)CH_2CH(CH_2)_3Si(CH_3)_3$, 40%.

The influence of the trimethylsilyl group and the trichlorosilyl group on the double bond of the vinyl group was demonstrated to be in the same direction. Thus, when the trichlorosilylcyclobutane obtained from the codimerization of chlorotrifluoroethylene and vinyltrichlorosilane was treated with methyl magnesium bromide, a trimethylsilylcyclobutane was obtained which was identical to the one prepared from the codimerization of chlorotrifluoroethylene and vinyltrimethylsilane. This was also demonstrated in the codimerization reaction of chlorotrifluoroethylene and α-chlorovinyltrichlorosilane and α-chlorovinyltrimethylsilane.

The relative conjugative ability of the trimethylsilyl and the trichlorosilyl groups is less defined; however, it is theorized that the trichlorosilyl group might be more effective in increasing the reactivity of the double bond in the vinyl groups, as the chlorine atoms on the silicon atom would better stabilize the contributing form, $Cl_3Si{=}\overset{+}{C}H{-}CHR$ because of their electronegativity. This effect may be slight, however. Under the reaction conditions employed it was not surprising to observe no definite trends in the yields of products, when vinyltrichlorosilane or vinyltrimethylsilane was codimerized with 1,1-difluoro-2,3-dihaloethylenes.

EXPERIMENTAL

Preparation of vinyltrimethylsilane. Vinyltrimethylsilane was prepared in 40–45% yields by the method of Sommer,[7] from the reaction of vinyltrichlorosilane with methylmagnesium bromide.

Preparation of tetrafluoroethylene. Tetrafluoroethylene was prepared by the method of LaZerte[8] by the pyrolysis of sodium perfluorobutyrate. The yield in this reaction was not determined, as only a small amount of tetrafluoroethylene was prepared each time from a large quantity of sodium perfluorobutyrate.

Preparation of 2-chloro-2,3,3-trifluorocyclobutyl trichlorosilane (I). Exactly 16.2 g. (0.10 mole) of vinyltrichlorosilane and 0.1 g. of hydroquinone were placed in a heavy-walled Pyrex combustion tube (19 mm. × 25 mm. × 700 mm.). After the contents of the tube had been frozen in liquid nitrogen, about 23.4 g. (0.20 mole) of chlorotrifluoroethylene was distilled into the tube. Vacuum was applied, the tube sealed, and placed in a steel-jacketed heating assembly and heated at 210° for 14 hr. After cooling in a Dry Ice–isopropyl alcohol mixture, the tube was opened. Vacuum distillation (through a 4-cm. glass helices-packed column) yielded 4.1 g. of vinyltrichlorosilane and 10.7 g. (51.0%) of I, b.p. 59–60° at 15 mm., n_4^{25} 1.4202, d_D^{25} 1.553, MR_D: calcd. 45.86; obsd. 46.15.

Anal. Calcd. for $C_4H_3Cl_4F_3Si$: C, 17.28; H, 1.08; Cl (hydrolyzable) 38.27; F, 20.50. Found: C, 17.36; H, 1.20; Cl, 38.16; F, 20.75.

2-Chloro-2,3,3-trifluorocyclobutyltrimethylsilane (II). *Method 1.* About 14.0 g. (0.141 mole) of vinyltrimethylsilane, 32.3 g. (0.28 mole) of chlorotrifluoroethylene, and 0.1 g. of hydroquinone were sealed in a heavy-walled Pyrex combustion tube and heated for 20 hr. at 210°. The tube was cooled and opened. Vacuum distillation of the product yielded 16.5 g. (54.5%) of II, b.p. 75° at 35 mm., n_D^{25} 1.4062, d_4^{25} 1.132, MR_D: calcd. 46.97, obsd. 47.02.

Anal. Calcd. for $C_7H_{12}F_3ClSi$: C, 38.79; H, 5.58; Cl, 16.36. Found: C, 38.81; H, 5.77, Cl, 16.15.

Method 2. To approximately 0.13 mole of methylmagnesium bromide in 80 ml. of anhydrous ether was added dropwise with stirring a solution of 10.0 g. (0.036 mole) of I in 15 ml. of anhydrous ether. A reflux temperature of 30° was maintained throughout the addition which was then refluxed for an additional 3 hr. The contents of the flask were poured into ice water and neutralized with 10% sulfuric acid. The layers were separated and the aqueous layer extracted three times with small portions of ether. The extracts were combined and dried over Drierite. Following removal of the solvent, vacuum distillation gave 4.95 g. (63.5%) of II, b.p. 85° at 50 mm., n_D^{25} 1.4062. The infrared spectrogram of this material was identical with that of the compound prepared by Method I.

1,2-Dichloroethyltrichlorosilane. The chlorination of vinyltrichlorosilane in silicon tetrachloride carried out according to the method of Wagner,[9] gave a 94% yield of 1,2-dichloroethyltrichlorosilane, b.p. 82–84° at 26 mm., (lit.,[9] b.p. 180–182° at 760 mm.)

α-Chlorovinyltrichlorosilane. Exactly 262.5 g. (1.13 moles) of 1,2-dichloroethyltrichlorosilane and 182.0 g. (1.41 moles) of quinoline were placed in a 500-ml. one-neck flask fitted with a reflux condenser. The temperature was slowly increased to 120°, at which stage a vigorous exothermic reaction took place. Heating was discontinued immediately and the temperature rose rapidly to 150°. After 40 min., the temperature dropped to 60°, and an amber semisolid mass was obtained. The condenser was fitted for downward distillation and the material boiling in the range of 40–125° was collected. Redistillation through a Todd Precise Fractionation Assembly gave 129.2 g. (58.6%) of an α-chlorovinyl-

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trichlorosilane, b.p. 117–119° at 626 mm., n_D^{25} 1.4615 (lit.,[10] b.p. 124° at 724 mm., n_D^{20} 1.4638. The above general procedure[7,10,11] was first used by Hurd[12] in the preparation of vinyltrichlorosilane from 2-chloroethyltrichlorosilane.

α-Chlorovinyltrimethylsilane. To approximately 0.43 mole of methylmagnesium bromide in 150 ml. of anhydrous ether was added dropwise with stirring, a solution of 23.0 g. (0.118 mole) of α-chlorovinyltrichlorosilane in 25 ml. of anhydrous ether. A reflux temperature of 30° was maintained throughout the addition which was completed in 45 min. The reaction mixture was then refluxed for an additional 2 hr. The contents of the flask were poured into ice water and neutralized with 10% sulfuric acid. The layers were separated and the aqueous layer extracted three times with small portions of ether. The extracts were combined and dried over Drierite. After removal of the solvent, vacuum distillation gave 9.9 g. (62.3%) of α-chlorovinyltrimethylsilane, b.p. 97° at 624 mm., n_D^{25} 1.4280, (lit.,[7] b.p. 104° at 730 mm., n_D^{20} 1.4299).

1,2-Dichloro-2,3,3-trifluorocyclobutyltrichlorosilane (III). Exactly 29.5 g. (0.15 mole) of α-chlorovinyltrichlorosilane, 34.95 g. (0.30 mole) of chlorotrifluoroethylene, and 0.1 g. of hydroquinone were sealed in a heavy-walled Pyrex combustion tube and heated at 220° for 33 hr. The tube was cooled and opened. Vacuum distillation of the amber liquid gave 38.3 g. (81.7%) of III, b.p. 45–46° at 2 mm., n_D^{25} 1.4493, d_4^{25} 1.644 MR_D calcd.: 50.70, obsd.: 50.97.

Anal. Calcd. for $C_4H_2F_3Cl_5Si$: C, 15.38; Cl, 56.70. Found: C, 15.38; Cl, 56.52.

1,2-Dichloro-2,3,3-trifluorocyclobutyltrimethylsilane (IV). *Method 1.* About 8.0 g. (0.0595 mole) of α-chlorovinyltrimethylsilane, 14.0 g. (0.12 mole) of chlorotrifluoroethylene, and 0.1 g. of hydroquinone were sealed in an air-free heavy-walled Pyrex combustion tube and heated for 28 hr. at 210°. The tube was cooled and opened. Vacuum distillation of the product yielded 7.6 g. (51.0%) of IV, b.p. 82° at 25 mm., n_D^{25} 1.4315, d_4^{25} 1.243, MR_D calcd.: 51.81, obsd.: 52.29.

Anal. Calcd. for $C_7H_{11}Cl_2F_3Si$: C, 33.47; H, 4.42; Cl, 28.23. Found: C, 33.87; H, 4.49; Cl, 28.11.

Method 2. To approximately 0.87 mole of methylmagnesium bromide in 500 ml. of anhydrous ether was added dropwise a solution of 75.2 g. (0.24 mole) of III in 100 ml. of anhydrous ether. A gentle reflux was maintained throughout the addition which was completed in 70 min. The reaction mixture was refluxed for an additional 9 hr. The excess Grignard reagent was decomposed by slowly pouring the contents of the flask into ice water, then neutralized with 10% sulfuric acid. The layers were separated and the aqueous layer was extracted four times with small portions of ether. The extracts were combined and dried over Drierite. After solvent removal, vacuum distillation yielded 50.4 g. (83.7%) of IV, b.p. 82–83° at 25 mm., n_D^{25} 1.4312. The infrared spectrogram of this product was identical with that of the compound prepared by Method 1.

2,3,3-Trifluoro-1-cyclobutenyltrimethylsilane (V). Approximately 3.3 g. (0.051 mole) of hydrochloric acid–activated zinc dust (activated prior to use by the addition of 1 ml. of concd. hydrochloric acid to 3.5 g. of the zinc dust in 5–10 ml. of solvent), 10.0 g. (0.04 mole) of IV, and 30 ml. of butyl cellosolve were placed in a 100-ml. three-neck flask fitted with a stirrer and reflux condenser. The temperature was slowly increased to 75°, and after 1 hr. the solution was only slightly turbid. The temperature was then gradually increased to 95° and maintained there for 4 hr. At the end of this time the stirred solution was light gray, indicative of some zinc chloride formation. The temperature was then raised to 105° and maintained for 1 hr.; the reaction mixture had turned white and contained only a small amount of unchanged zinc. The flask was cooled to 40° and a vacuum of 10 mm. was applied directly to the flask. Heating and stirring were resumed and at 60–75° about 5 ml. of a colorless liquid collected in a trap maintained at −70°. After washing with water, the condensate was taken up in 15 ml. of ether and dried over Drierite. Vacuum distillation yielded 3.2 g. (44.5%) of V, b.p. 40–41° at 29 mm., n_D^{25} 1.3878, d_4^{25} 1.010 MR_D calcd.: 41.66, obsd.: 42.08.

Anal. Calcd. for $C_7H_{11}F_3Si$: C, 46.64; H, 6.14; F, 31.62. Found: C, 46.89; H, 5.92; F, 31.30.

The preparation of V from IV proved the vicinal character of the chlorine atoms in IV. This reaction had been carried out a number of times with other solvents such as acetone and ethyl alcohol. The yields of V with these solvents were in the low range of 6.8–13.9%. These solvents were probably too low-boiling to effect the dechlorination.

2,3,3-Trifluorocyclobutyltrimethylsilane (VI). *Method 1.*[13,14] Exactly 10.0 g. (0.046 mole) of II in 15 ml. of anhydrous ethers was added slowly with heating to a suspension of 3.06 g. (0.0805 mole) of lithium aluminum hydride in 20 ml. of ether under reflux conditions. The addition was completed in 2 hr. and the mixture was then refluxed for an additional 2 hr. After cooling to 0°, about 50 ml. of 10% sulfuric acid was slowly added to decompose the excess lithium aluminum hydride. The ether layer was combined with two ether extracts and dried over Drierite. Vacuum distillation gave four fractions boiling in the range of 60–72° at 44 mm. Each of these fractions gave two peaks when further fractionated by gas chromatography at 140° (Aerograph Master A-100; Silicone Oil Column). The first fraction was identified at VI, and the second as II, n_D^{25} 1.4062. About 3.4 g. of unchanged II and about 3.75 g. (64.4%) of VI were recovered, b.p. (est.) 62–65° at 44 mm., n_D^{25} 1.3927, d_4^{25} 1.028, MR_D calcd.: 42.13; obsd.: 42.27.

Anal. Calcd. for $C_7H_{13}F_3Si$: C, 46.12; H, 7.19; F, 31.27. Found: C, 45.83; H, 5.07; F, 31.42.

Method 2. Exactly 2.75 g. (0.0153 mole) of V in an excess of ethyl alcohol was hydrogenated in a quantitative hydrogenating assembly utilizing 10% palladium-on-carbon as the catalyst. The absorption of 0.015 mole of hydrogen was complete in 15 min. The catalyst was filtered under suction through a fritted glass funnel. The filtrate was then shaken with water in a separatory funnel; the organic layer was separated and taken up in 10 ml. of ether and dried over Drierite. Following removal of the solvent, a pure sample of VI was obtained by gas chromatography. The infrared spectrogram of the material was identical with the compound prepared by Method 1.

The preparation of VI by the reduction of II definitely proved the structure of the latter.

2,2-Dichloro-3,3-difluorocyclobutyltrimethylsilane (VII). Exactly 37.2 g. (0.28 mole) of 1,1-difluoro-2,2-dichloroethylene, 14.0 g. (0.14 mole) of vinyltrimethylsilane, and 0.1 g. of hydroquinone were sealed in a heavy-walled Pyrex combustion tube and heated for 24 hr. at 220°. The tube was cooled and opened. Vacuum distillation of the product gave 23.0 g. (70.8%) of VII, b.p. 78° at 7 mm., n_D^{25} 1.4390, d_4^{25} 1.181, MR_D calcd.: 51.78; obsd.: 51.88.

Anal. Calcd. for $C_7H_{12}F_2Cl_2Si$: C, 36.06; H, 5.19; Cl, 30.42. Found: C, 36.03; H, 5.39; Cl, 30.25.

2,2-Dichloro-3,3-difluorocyclobutyltriethoxysilane (VIII). Approximately 26.6 g. (0.20 mole) of 1,1-difluoro-2,2-dichloroethylene, 19.0 g. (0.10 mole) of vinyltriethoxysilane and 0.1 g. of hydroquinone were sealed in a heavy-walled Pyrex combustion tube and heated at 200° for 26 hr. The tube was cooled and opened. Vacuum distillation of the material yielded 18.6 g. (57.5%) of VIII, b.p. 107–108° at 6 mm., n_D^{25} 1.4201, d_4^{25} 1.197, MR_D calcd.: 67.95, obsd.: 68.33.

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Anal. Calcd. for $C_{10}H_{18}F_2Cl_2O_3Si$: C, 37.15; H, 5.61; Cl, 21.94. Found: C, 36.93; H, 5.62; Cl, 21.74.

Allyltrimethylsilane. To approximately 0.36 mole of allylmagnesium chloride[15] in 100 ml. of anhydrous ether was added with stirring a solution of 32.6 g. (0.30 mole) of trimethylchlorosilane in 100 ml. of ether. A gentle reflux was maintained throughout the addition which was completed in 50 min. The solution was refluxed for an additional 4 hr. The reaction mixture was then poured into ice water and neutralized with 10% sulfuric acid. The ether layer was combined with three extracts and dried over Drierite. Following removal of the solvent, distillation of the light yellow oil through a Metroware Vigreux Fractionation Assembly gave 20.2 g. (59%) of allyltrimethylsilane, b.p. 77–79° at 628 mm., n_D^{25} 1.4042 (lit.,[16] b.p. 84.9° at 737 mm., n_D^{20} 1.4074).

α-(2,2,3,3-Tetrafluorocyclobutyl)methyltrimethylsilane (IX). Exactly 8.5 g. (0.075 mole) of allyltrimethylsilane, 10 g. (0.10 mole) of tetrafluoroethylene, 0.1 g. of hydroquinone, and 0.25 ml. of Terpene B were sealed in a heavy-walled Pyrex combustion tube and heated for 8 hr. at 150°, 10 hr. at 175°, and 20 hr. at 210°. The tube was cooled and opened. Vacuum distillation of the product yielded 1.5 g. of allyltrimethylsilane and 8.3 g. (63.4%) of IX, b.p. 62–63° at 25 mm., n_D^{25} 1.3828, d_4^{25} 1.058, MR_D calcd.: 46.99, obsd.: 47.21.

Anal. Calcd. for $C_8H_{14}F_4Si$: C, 44.84; H, 6.58; F, 35.47. Found: C, 44.64, H. 6.56; F, 35.20.

4-Pentene-1-ol. This alcohol was prepared from tetrahydrofurfuryl alcohol in 55% over-all yield by the method of Snyder and Brooks.[17]

5-Bromopentene-1. A solution of 74.0 g. (0.86 mole) of 4-pentene-1-ol and 24.0 g. (0.30 mole) of dry pyridine was placed in a 200-ml. three necked, round bottom flask fitted with a stirrer, a low temperature thermometer, and a dropping funnel with a pressure equalizing side-arm. The solution was cooled to −40° and 95.0 g. (0.35 mole) of phosphorus tribromide was added at such a rate that the temperature remained at −30° to −40°. The solution was stirred at −40° for an additional hour, then warmed to room temperature. The flask was heated to 60°, a vacuum of 1 mm. applied directly to the flask, and the crude bromide collected in a trap maintained at −70°. The crude product was washed with a cold 10% sodium bicarbonate solution, diluted with ether, and dried over Drierite. Distillation through a Todd Precise Fractionation Assembly gave 68.0 g. (53.2%) of 5-bromopentene-1, b.p. 118–120° at 625 mm., n_D^{25} 1.4600, (lit.,[15] b.p. 127° at 770 mm.).

4-Pentenyltrimethylsilane (X). A solution of 14.9 g. (0.10 mole) of 5-bromopentene-1 in 30 ml. of anhydrous ether was added with stirring at room temperature to 1.6 g. (0.23 g.-atom) of finely cut lithium metal in 100 ml. of ether. After initiation of the reaction the flask was cooled to 0 to −5°. The addition was completed in 1 hr. and the mixture stirred for an additional 30 min. at 5°.

To this solution of freshly prepared lithium reagent, a solution of 8.9 g. (0.90 mole) of trimethylchlorosilane in 20 ml. of ether was added under gentle reflux conditions. The addition was completed in 45 min. and thereafter the mixture was refluxed for an additional 8 hr. The reaction mixture was poured into ice water, neutralized with 10% hydrochloric acid, and extracted three times with small portions of ether. The extracts were combined and dried over Drierite. Following removal of the solvent, distillation gave 10.3 g. (80.5%) of X, b.p. 132° at 628 mm. n_D^{25} 1.4172, d_4^{25} 0.747, MR_D calcd.: 48.33, obsd.: 48.04.

Anal. Calcd. for $C_8H_{18}Si$: C, 67.52; H, 12.75. Found: C, 67.82; H, 12.55.

α-(2,2,3,3-Tetrafluorocyclobutyl)n-propyltrimethylsilane (XI). Exactly 8.8 g. (0.062 mole) of X, 10.0 g. (0.10 mole) of tetrafluoroethylene, and 0.1 g. of hydroquinone were sealed in a heavy-walled Pyrex combustion tube and heated at 24 hr. at 218°. The tube was cooled and opened. Vacuum distillation gave 2.5 g. of unchanged X and 4.24 g. (40.0%) of XI, b.p. 41–42° at 5 mm., n_D^{25} 1.3936, d_4^{25} 1.038, MR_D calcd.: 56.05, obsd.: 55.88.

Anal. Calcd. for $C_{10}H_{18}F_4Si$: C, 49.60; F, 31.36. Found: C, 49.86; F, 31.73.

1-Iodo-3,4,4-trifluoro-3-butenyltrimethylsilane (XII). Exactly 20.8 g. (0.10 mole) of perfluorovinyliodide and 10.0 g. (0.10 mole) of vinyltrimethylsilane were placed in an evacuated 2-l. Pyrex irradiation vessel. The vessel and reactants were irradiated with a 100-watt ultraviolet lamp for 18 days. The dark purple liquid was shaken with mercury to remove the free iodine and then filtered. Vacuum distillation of the light pink liquid gave a 5.0 g. (16.3%) of XII, b.p. 93–94° at 30 mm., n_D^{25} 1.4625. Vapor phase chromatography showed this fraction to be pure. An analytical sample collected from the chromatograph had the following physical properties: n_D^{25} 1.4630, d_4^{25} 1.4936, MR_D calcd.: 56.85, obsd.: 56.65.

Anal. Calcd. for $C_7H_{12}F_3ISi$: C, 27.28; H, 3.93; F, 18.49. Found: C, 27.42; H, 4.20; F, 18.79.

1-Iodo-3,4,4-trifluoro-3-butenyltrichlorosilane (XIII). Exactly 10.4 g. (0.05 mole) of perfluorovinyliodide and 8.06 g. (0.05 mole) of vinyltrichlorosilane were placed in an evacuated 2-l. Pyrex irradiation vessel. The vessel and its reactants were subjected to a 100-watt ultraviolet source for 12 days. The very dark purple liquid was shaken with mercury to remove the free iodine and then quickly filtered. Vacuum distillation gave 10.4 g. (56.2%) of XIII, b.p. 79–80° at 22 mm., n_D^{25} 1.4882, d_4^{25} 1.933, MR_D calcd.: 55.54, obsd.: 55.07.

Anal. Calcd. for $C_4H_3Cl_3ISi$: C, 13.00, H, 0.82; F, 15.43. Found: C, 13.29; H, 1.06; F, 15.72.

2,2,3,3-Tetrafluorocyclobutyltrimethylsilane (XIV). Approximately 20.0 g. (0.20 mole) of tetrafluoroethylene, 20.4 g. (0.20 mole) of vinyltrimethylsilane, and 0.2 g. of hydroquinone were sealed in a heavywalled Pyrex combustion tube and heated for 36 hr. at 210°. The tube was cooled, opened, and the nonvolatile liquid filtered. Vacuum distillation yielded 7.0 g. of vinyltrimethylsilane and 22.3 g. (82.0%) of XIV, b.p. 65–66° at 60 mm., n_D^{25} 1.3741, MR_D calcd.: 42.16, obsd.: 42.23.

Anal. Calcd. for $C_7H_{12}F_4Si$: C, 41.98; H, 6.04. Found: C, 41.98; H, 5.80.

Hydrolysis studies. A. Five grams of XIV and 50 ml. of dilute hydrochloric acid were placed in a 100-ml. flask and heated with stirring at 80° for 75 hr. The starting material was recovered unchanged.

B. Similarly, a 10-g. sample of XIV and 50 ml. of 20% solution of potassium hydroxide was heated with stirring at 70° for 10 hr. The starting material was recovered unchanged.

2,2,3,3-Tetrafluorocyclobutyldichloromethylsilane (XV). About 20.0 g. (0.20 mole) of tetrafluoroethylene, 28.2 g. (0.20 mole) of vinylmethyldichlorosilane, and 0.2 g. of hydroquinone were sealed in a heavy-walled Pyrex combustion tube and heated for 36 hr. at 210°. The tube was cooled and opened. Vacuum distillation gave 10.5 g. of vinylmethyldichlorosilane and 21.5 g. (71.2%) of XV, b.p. 65° at 39 mm., n_D^{25} 1.3943, d_4^{26} 1.382, MR_D calcd.: 42.42, obsd.: 42.10.

Anal. Calcd. for $C_5H_6F_4Cl_2Si$: C, 24.70; H, 2.47. Found: C, 25.00; H, 2.67.

Infrared spectra. A number of workers[18–21] have observed

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that cyclobutane and monosubstituted cyclobutanes absorb in the 10.85–11.10 μ region. These bands have tentatively been assigned to CH_2 rocking frequencies. If this assignment to the CH_2 modes of vibration is correct, absorption in this region would not be expected in fully substituted materials. Reid and Sack[22] confirmed this by the observation that fully substituted cyclobutanes absorb in the 11.25–11.65 μ region and not in the 10.85–11.10 μ range. Marrison[23] further pointed out that octafluorocyclobutane does not absorb in the 10.85–11.10 μ region.

In this work, the infrared spectra of fluorine-containing cyclobutylsilanes of the type, $CX_2—CF_2—CH_2—CH—(CH_2)_n$-$SiR_3$ (where R equals chlorine and/or methyl, n equals 0 to 3 and X equals fluorine and/or chlorine) have been studied. On the basis of the above discussion, these compounds would be expected to absorb in the 10.85–11.10 μ region, as one CH_2 group remains unsubstituted. In the twelve spectra studied this was found to be the case, however, in a somewhat wider region. Generally, a narrow range of absorption was observed for a particular cyclobutyl group as illustrated in the Table I.

TABLE I

TENTATIVE BAND ASSIGNMENTS TO THE CYCLOBUTYL GROUP

Structure	Number of Spectra	Assumed Ring Vibrations (μ)
$CH_2—CH—Si—$ $CF_2—CCl_2$	2	11.15–11.18
$CH_2—CH—Si—$ $CF_2—CFCl$	2	10.85–10.92
$CH_2—CCl—Si—$ $CF_2—CFCl$	2	11.07–11.10
$CH_2—CH—Si—$ $CF_2—CF_2$	2	11.27–11.30 (10.78–10.75)
$CH_2—CH—(CH_2)_n—Si—$ $CF_2—CF_2$	2	10.85–10.93
$CH_2—C—Si—$ $CF_2—CF$	1	10.93
$CH_2—CF—Si—$ $CF_2—CFH$	1	10.93

The spectra of two compounds having the $CF_2—CF_2—CH_2—CH—$ group, each exhibited two absorption bands in the 10.75–11.30 μ region. The proper assignment of the band attributable to the CH_2 rocking mode cannot be made, thus both absorptions are included in Table I. The intensity of the bands in the 10.85–10.93 μ region decreases as the number of insulating CH_2 groups between the $CF_2—CF_2—CH_2—CH—$ group and the silicon atom increases, as the contributory effect of the cyclobutyl group in the molecule is minimized.

The spectra of tetramethylsilane and the linear alkyltrichloro- and alkyltrimethylsilanes prepared in this work do not show unassignable absorption bands in the 10.85–11.25 μ region (*e.g.*, in the spectra of $CH_2=CH—(CH_2)_3Si(CH_3)_3$ the band at 11.00–11.05 μ is assigned to CH_2 out of plane bending of the vinyl group).[24] In addition, the spectra of a number of CH_2-containing fluorocyclobutanes have been found to absorb in the 10.94–11.06 μ region. In contrast, perhalocyclobutanes (without a CH_2 group) have no absorption bands in this region.[25]

The assignments made here are necessarily tentative, as they are based on the study of a limited number of compounds of a particular class.

Vibrations attributed to the Si—CH_3 group. There has been some dispute over the proper assignment (whether deformation or rocking) of the absorption bands at 11.75 and 8.0 μ, both arising from the vibrations of the methyl group bonded to silicon.[26–28] Recent evidence[26,28–30] indicates that the band in the 11.75 μ region is due to silicon-methyl unsymmetrical rocking and the band in the 8.0 μ region is attributable to symmetrical deformation vibrations of the methyl group attached to the silicon atoms. Both these bands were observed in the spectra of these fluorocyclobutyltrimethylsilanes. These bands were noticeably absent in the spectra of all monosubstituted trichlorosilanes studied.

Carbon-hydrogen deformation and stretching frequencies. The absorption band at 6.97 μ in the spectra of $CFCl—CF_2—CH_2—CH—SiCl_3$ and the band at 7.07 μ in the spectra of $CFCl—CF_2—CH_2—CCl—SiCl_3$ are attributed to bending modes of the CH_2 group in the cyclobutane ring. The shift to the longer wave length in the spectra of the latter is apparently due to the substitution of a hydrogen atom by a chlorine atom in the position adjacent to the CH_2 group in the ring.[23] The position of this band remains relatively constant (6.95–7.17 μ) throughout the remainder of the series. It is masked to a degree by the asymmetrical deformation of the methyl group on the silicon atom and by the CH_2 deformations in the ethyl group in $C_2H_5—O—Si$.

An absorption band in the 3.40 μ region is assigned the carbon-hydrogen stretching modes in the cyclobutyl group and in the methyl groups bonded to silicon, primarily the latter. Thus, this band appreciably decreases in the spectra of the fluorocyclobutyltrichlorosilanes with a shift to shorter wave lengths (3.1–3.3 μ).

Vibrations attributed to the Si—O—C and Si—Cl linkages. In the spectra of $CCl_2—CF_2—CH_2—CH—Si(OC_2H_5)_3$, there is a broad double band with peaks at 9.05 and 9.23 μ. One or both of these bands are attributed to the Si—O—C stretching vibration.

An assignment for the silicon-chlorine absorption was not attempted since it apparently occurs in a region beyond 15 μ.

Acknowledgment. We wish to express our gratitude to the U. S. Air Force, Wright Patterson Air Development Center, Ohio, and to the Minnesota Mining and Manufacturing Co., St. Paul, Minn., for their support of this work.

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[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

p-Phenylenedisilanes[1]

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Received January 6, 1960

A series of *p*-phenylenedisilanes with two or four silicon-attached alkoxy groups has been prepared. When these compounds were prepared through the intermediate bifunctional Grignard reagents, the over-all yield was determined by the choice of solvent, the presence of various reactants which can act as cosolvents, and the reactivity of the condensing silane. Methods for preparing the following *p*-phenylenedisilanes are discussed: *p*-Phenylenebis(diethoxymethylsilane), *p*-phenylenebis(ethoxydimethylsilane), *p*-phenylenebis(ethoxymethylvinylsilane), *p*-phenylenebis(diethoxyvinylsilane), *p*-phenylenebis(*p*-chlorophenyldiethoxysilane), *p*-phenylenebis(*p*-anisyldiethoxysilane), *p*-phenylenebis(diethoxyphenylsilane), *p*-phenylenebis-[diethoxy-*p*-(*N*,*N*-dimethylaminophenyl)silane], and 1-diethoxymethylsilyl-4-diethoxyphenylsilylbenzene.

Although a variety of totally alkylated or arylated derivatives of *p*-phenylenedisilane are described in the literature,[2-8] little is reported on the synthesis of *p*-phenylenedisilanes that can be hydrolyzed in aqueous media to yield hybrid arylenesiloxane polymers.

Condensation of trisubstituted silanes with benzene in the presence of aluminum trichloride or boron trichloride gave isomeric mixtures of the *meta* and *para* derivatives, particularly when the silane was present in large excess. The isolation of pure *p*-phenylenebis(trichlorosilane), *p*-phenylenebis(dichloromethylsilane,) and *m*-phenylenebis-(trichlorosilane) from the crude reaction products has been described.[9-11]

p-Phenylenebis(chlorodimethylsilane) and *p*-phenylenebis(chlorodiphenylsilane) were obtained by Sveda from the Grignard reagent of *p*-dibromobenzene in ether and the corresponding chlorosilanes, but no yields were reported.[12,13] From triethoxymethylsilane and the same Grignard reagent, Gainer obtained 9% of *p*-phenylenebis-(ethoxydimethylsilane) and 42% of *p*-bromophenyldiethoxymethylsilane.[14] Also, he condensed the Grignard reagent of *p*-bromophenyldimethylethoxysilane with triethoxymethylsilane to obtain 39% of 1-diethoxymethylsilyl-4-dimethylethoxysilylbenzene. Lewis prepared *p*-phenylenebis(ethoxydimethylsilane) from the Grignard reagent of *p*-dibromobenzene in ether and diethoxydimethylsilane. Although he did not report the yield of the pure material, repetition of the procedure in this laboratory gave a 31% yield of the phenylenedisilane. The synthesis of 1-trichlorosilyl-4-triethylsilylbenzene from *p*-triethylsilylphenylmagnesium bromide has also been reported.[2]

A series of *p*-phenylenedisilanes, each with two or four silicon-attached ethoxy groups, has been prepared (see Table I) in our laboratory. Because their preparation required the condensation of a bifunctional metallo-organic intermediate with a polyfunctional silane, reaction conditions were selected to avoid the formation of polymeric materials.

Grignard Syntheses. Yields of 30–40% of *p*-phenylene (diethoxymethylsilane) were obtained when the Grignard reagent of *p*-dibromobenzene was prepared in tetrahydrofuran, when this Grignard reagent was coupled with chlorodiethoxymethylsilane, and when the silane and bromide were added concomitantly to the magnesium.

The over-all yield of the various phenylenedisilanes from *p*-bromobenzene, as well as the identity of the by-products, was not limited by the ability of the dihalide to form the intermediate Grignard reagent, particularly when the dihalide and the silane are added concomitantly to the magnesium. The yield depended on factors that include the identity of the solvent, the presence of the various reactants that can act as cosolvents, and the reactivity of the condensing silane.

In ether the maximum yield of the Grignard reagent of *p*-dibromobenzene that may be expected is about 12%, unless entrainment procedures are used.[14-19] Also in ether, up to 70% of the mono-

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TABLE I

p-PHENYLENEDISILANES

Compound	Method of Preparation[a]	Yield, %
p-Phenylenebis(diethoxymethylsilane)	1. A and triethoxymethylsilane	11.5
	2. B and chlorodiethoxymethylsilane	
	a. Concomitant addition	33.3
	b. Normal addition	32–38
	3. *p*-Bromophenyldiethoxymethylsilane, chlorodiethoxymethylsilane, and sodium	27
1-Diethoxymethylsilyl-4-diethoxyphenylsilylbenzene	*p*-Bromophenyldiethoxymethylsilane, chlorodiethoxyphenylsilane, and sodium	6
p-Phenylenebis(ethoxydimethylsilane)	1. A and diethoxydimethylsilane	31
	2. B and chlorodiethoxymethylsilane	20
p-Phenylenebis(ethoxymethylvinylsilane)	B and diethoxymethylvinylsilane	9
p-Phenylenebis(diethoxyvinylsilane)	B and triethoxyvinylsilane	15
p-Phenylenebis(diethoxyphenylsilane)	B and chlorodiethoxyphenylsilane	
	a. Normal addition	29
	b. Concomitant addition	28
p-Phenylenebis(*p*-chlorophenyldiethoxysilane)	B and chloro(*p*-chlorophenyl)diethoxysilane	27
p-Phenylenebis(*p*-anisyldiethoxysilane)	B and *p*-anisylchlorodiethoxysilane	44
p-Phenylenebis[diethoxy-*p*-(*N*,*N*-dimethylaminophenyl)silane]	B and triethoxy-*p*-dimethylaminophenylsilane	44

[a] A = Grignard reagent of *p*-dibromobenzene in ether. B = Grignard reagent of *p*-dibromobenzene in tetrahydrofuran. Concomitant addition unless otherwise specified.

Grignard reagent is usually obtained. The reaction of *p*-dibromobenzene and magnesium in the presence of ethyl ether and diethoxydimethylsilanes gave, unexpectedly, about 30% of the *p*-phenylenebis(ethoxydimethylsilane), which was greater than the yield of the bifunctional Grignard reagent that is normally obtained in the absence of the silane. Substitution of the triethoxymethylsilane for diethoxydimethylsilane in the latter procedure gave the disilane in about the same proportion that would be predicted from the yield of the Grignard reagent formed in the absence of the silane. The cosolvent effect was apparently lost.

Although the conversion to the bifunctional Grignard reagent was higher in tetrahydrofuran,[20] the Grignard-tetrahydrofuran complex is less reactive toward alkoxysilanes than the Grignard-ethyl ether complex. When an attempt was made to react the bifunctional Grignard-tetrahydrofuran complex and triethoxymethylsilane, the complex was sufficiently stable that no condensation occurred. In tetrahydrofuran, it was necessary that the more reactive chlorodiethoxymethylsilane be substituted for the triethoxymethyl silane. With this change in the procedure, yields of 30–40% were obtained consistently in the preparation of *p*-phenylenebis(diethoxymethylsilane).

The presence of the chlorodiethoxymethylsilane did not materially affect the formation of the Grignard reagent. Similar yields were obtained when the silane was added concomitantly to the magnesium with the *p*-dibromobenzene or when the performed Grignard reagent was precipitated as the Grignard-tetrahydrofuran complex by external cooling, treated with the silane, and heated to effect condensation. In the latter procedure the reactivities of the various condensing groups permitted a mode of addition that would ordinarily be expected to yield only highly polymeric materials. This disilane was sufficiently stable against hydrolysis that the product could be worked up by pouring the reaction mixture over water.

The reactivity of the alkoxysilanes or the alkoxychlorosilanes was also increased by introducing groups into the condensing silane that could contribute a net increase in the electron density on silicon. Although triethoxymethylsilane and the phenylene-Grignard reagent failed to condense, diethoxymethylvinylsilane, whose structure is analogous to an allyl ether, gave a 9% yield of *p*-phenylenebis(ethoxymethylvinylsilane) and triethoxyvinylsilane gave 15% of the corresponding product.

Similarly, in the *p*-phenylenebis(diethoxyphenylsilane) series, substitution of a strong negative group *para* to silicon increased the yields, presumably through an increased reactivity of the silicon-attached chlorine. Yields of about 30% were obtained when chlorodiethoxyphenylsilane and chloro(*p*-chlorophenyl)diethoxysilane were condensed with the Grignard reagent of *p*-dibromobenzene in tetrahydrofuran. *p*-Anisylchlorodiethoxysilane gave 44% *p*-phenylenebis(*p*-anisyldiethoxysilane), and *p*-(triethoxysilyl)-*N*,*N*-dimethylaniline[21] gave 44% *p*-phenylenebis[diethoxy-*p*-(*N*,*N*-dimethylaminophenyl)silane]. The latter compounds are analogous to *p*-methoxy- and *p*-dimethylaminobenzyl derivatives in the carbon series.

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Aside from the improved yield, the Grignard-tetrahydrofuran procedure offers another advantage for the preparation of *p*-phenylenebis(diethoxymethylsilane). In ether, considerable unchanged *p*-dibromobenzene was recovered, as well as the *p*-bromophenyldiethoxymethylsilane. Avoiding the recovery of the solid and obtaining essentially a single volatile reaction product permitted the use of simpler distillation procedures. The chief products other than the *p*-phenylenedisilane were non-distillable polymeric products.

Sodium Condensations. Consistent with the results published by Clark, *et al.*,[22] *p*-dibromobenzene failed to condense with chlorodiethoxymethylsilane in the presence of sodium, either with toluene or diethyl ether as the reaction medium. When one bromine atom was replaced with the diethoxymethylsilyl group, however, *p*-phenylenebis(ethoxydimethylsilane) was obtained in a 27% yield. This yield is not significantly different from that reported for the condensation of *p*-bromophenyltrimethylsilane with chlorotrimethylsilane under similar conditions (30%).[22] The presence of silicon-attached alkoxy groups does not interfere with the normal course of the reaction, demonstrating the preferential reactivity of the arylsodium toward chlorine.[23]

The unsymmetrical compound, 1-diethoxymethylsilyl-3-diethoxyphenylsilylbenzene, was obtained in only a 6% yield when *p*-bromophenyldiethoxymethylsilane and chlorodiethoxyphenylsilane were condensed in the presence of sodium in refluxing toluene. Interaction with the solvent, always an important consideration in arylations with sodium in toluene, gave considerable diethoxymethylphenylsilane with the consequent loss in yield of the product.

Lithium intermediate. Although the dilithium derivatives form in good yields by an interchange reaction between *p*-dibromobenzene and butyllithium in petroleum ether,[24] these intermediates were not convenient for the preparation of polyfunctional phenylenedisilanes. Because of their great reactivity for both silicon-attached chloro and alkoxy groups, inverse addition of the preformed dilithium compound to the silane was required. Preparation of the lithium reagent by exchange precludes the formation of the intermediate in the presence of the silane. *p*-Phenylenedilithium is a gummy solid, insoluble in petroleum ether, and is not conveniently added to the silane.

EXPERIMENTAL

Alkoxychlorosilanes. Chlorodiethoxymethylsilane, prepared by the ethanolysis of trichloromethylsilane and subsequent fractional distillation, contained little dichloroethoxymethylsilane but some triethoxymethylsilane.[25] The chlorine equivalent was calculated on the basis of titration of a hydrolyzed aliquot of the silane.

Chloroethoxydimethylsilane was prepared by treating 903 g. (7.0 moles) of dichlorodimethylsilane with 323 g. (7.0 moles) of anhydrous alcohol and distilling the 32 g. of product that distilled below 72°. The residue, which had a neutralization equivalent of 139.1 (calcd. for $C_4H_{11}ClSiO$, 138.7), was used directly in the condensation with the Grignard reagent.

The syntheses of chlorodiethoxyphenylsilane, chloro-*p*-chlorophenyldiethoxysilane, and *p*-anisylchlorodiethoxysilane by ethanolysis of the chlorosilanes followed by fractional distillation were described earlier.[25] Pure *p*-(chlorodiethoxysilyl)-*N*,*N*-dimethylaniline was not obtained in the corresponding alcoholysis reaction, but the product which was mostly *p*-(triethoxysilyl)-*N*,*N*-dimethylaniline, was used in the Grignard synthesis.

A stirred mixture of 91 g. (0.36 mole) of *p*-(trichlorosilyl)-*N*,*N*-dimethylaniline 218 g. (2.16 moles) of triethylamine, and 600 ml. of toluene was treated with 32.7 g. (0.71 mole) of anhydrous ethanol by dropwise addition. The amine salts were removed by filtration and washed with a little toluene. Fractional distillation of the combined filtrate and washings gave 46 g. (45%) of the impure product boiling 135–143° at 2 mm. (164–165° at 5 mm.).

Anal. Calcd. for $C_{12}H_{20}ClNO_2Si$ *p*-(chlorodiethoxysilyl)-*N*,*N*-dimethylaniline: C, 52.63; H, 7.36; Si, 10.26; neut. equiv., 274. For $C_{14}H_{25}NO_3Si$ *p*-(triethoxysilyl)-*N*,*N*-dimethylaniline: C, 59.32; H, 8.89; Si, 9.91. Found: C, 57.95; H, 8.86, Si, 9.94, 9.76, neut. equiv., 2440.

p-Phenylenebis(diethoxymethylsilane) and p-bromophenyldiethoxymethylsilane. Grignard procedure in ethyl ether. In a series of experiments the best yields that were obtained following Gainer's procedure[14] were 11.5% of *p*-phenylenebis(diethoxymethylsilane) and 30.1% of *p*-bromophenyldiethoxymethylsilane. In this procedure, 4 moles of *p*-dibromobenzene, 5 g.-atoms of magnesium and 6 moles of triethoxymethylsilane were allowed to react. When most of the ether was not removed by distillation prior to filtering the product, unchanged Grignard reagent was collected in the filtration residue. Distillation of the product gave unchanged *p*-dibromobenzene in the forerun making it necessary to disassemble and clean the distillation apparatus before the products were collected. Redistillation of the higher boiling product from these experiments through an Oldershaw column with 15 plates gave *p*-phenylenebis(diethoxymethylsilane) boiling 128° at 2 mm., n_D^{25} 1.4614, d_4^{25} 0.9828.

Anal. Calcd. for $C_{16}H_{30}O_4Si_2$: C, 56.10; H, 8.83; Si, 16.40; MR_D, 95.24. Found: C, 56.08; H, 8.65; Si, 16.21; MR_D, 95.74.

The lower boiling fraction, 4-bromophenyldiethoxymethylsilane, was collected at 111–115° at 2.0 mm., n_D^{25} 1.4983.

Anal. Calcd. for $C_{11}H_{17}BrO_2Si$: C, 45.66; H, 5.94; Si, 9.71. Found: C, 45.94; H, 6.02; Si, 9.96.

Changing the stoichiometry of the reactants to 0.4 mole of *p*-dibromobenzene, 0.8 g.-atom of magnesium, and 1.0 mole of triethoxymethylsilane did not significantly alter the yields of either product.

p-Phenylenebis(diethoxymethylsilane). Grignard method in tetrahydrofuran. Concomitant addition of reactants. Magnesium, 53.5 g. (2.2 g.-atoms) and 16 g. of *p*-dibromobenzene,

(21) An attempt was made to prepare the *p*-(chlorodiethoxysilyl-*N*,*N*-dimethylaniline by the ethanolysis of *p*-(trichlorosilyl)-*N*,*N*-dimethylaniline in the presence of triethylamine, which was used as an acid acceptor. The triethylamine-chlorosilane complex was insoluble, even in a fairly large excess of toluene, and the low concentration of silane in solution gave mostly the trialkoxy product.

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(23) K. Hizdua, *et al.*, Japanese Patent **1,282** (1953).

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covered with 100 ml. of tetrahydrofuran and activated with a crystal of iodine, were treated with a solution of 220 g. (1 mole, total) of *p*-dibromobenzene, 338 g. (2 moles) of chlorodiethoxymethylsilane, and 450 ml. of tetrahydrofuran by dropwise addition over 2.5 hr. After the mixture was refluxed 3 hr., it was cooled and filtered. Several additional filtrations were required to remove salts that separated when the filtrate was concentrated by distillation. The product, fractionally distilled at 5.5 mm., gave 114 g. (33.3%) of *p*-phenylenebis(diethoxymethylsilane) at 16–°. Between 100–108°, 15.4 g. of a material was collected which could not be purified by additional distillation. Analysis by vapor phase chromatography showed that this fraction contained about 67% diethoxymethylphenylsilane, n_D^{25} 1.4664 (for an authentic sample, n_D^{20} 1.4684). The conversion was 4%.

When triethoxymethylsilane was substituted for chlorodiethoxymethylsilane, the product obtained from 5.3 g. (0.22 g.-atom) of magnesium, 23.4 g. (0.1 mole) of *p*-dibromobenzene, 28.5 g. (0.24 mole) of triethoxymethylsilane, and 90 ml. of tetrahydrofuran was refluxed for 8 hr. Distillation of a part of the tetrahydrofuran from the mixture gave two liquid phases. After 100 ml. of toluene was added, solvents were again distilled from the mixture. The residue, which gave a positive Gilman Color Test I, yielded only decomposition products during an attempted distillation.

Addition of silane to preformed Grignard reagent. The Grignard reagent, prepared in the usual manner from 10.6 g. (0.44 g.-atom) of magnesium, 100 ml. of tetrahydrofuran, and 47.2 g. (0.2 mole) of *p*-dibromobenzene, was diluted with 25 ml. of tetrahydrofuran and cooled to 20° to crystallize the Grignard-tetrahydrofuran complex. To the cold solution was added 75 ml. (0.44 mole) of chlorodiethoxymethylsilane in rapid drops. After the product was refluxed 2 hr., procedure A or B was used for purification. No *p*-bromophenyldiethoxymethylsilane was collected during the distillations.

A. The salts were removed by filtration and the filtrate was concentrated by distillation. Fractional distillation of the residue gave 26.6 g. (38%) of *p*-phenylenebis(diethoxymethylsilane).

B. The product was poured into a mixture of 200 ml. of water, 200 ml. of toluene, 25 g. of sodium bicarbonate, and ice. The organic phase, separated, and washed with three 100-ml. portions of water, was filtered and dried with Drierite. After the solvents were removed, 21.8 g. (32%) of *p*-phenylenebis(diethoxymethylsilane) was obtained by fractional distillation.

In larger scale experiments (for example, with 2.4 moles of *p*-dibromobenzene) formation of the Grignard reagent required 24 hr. The temperature could not be maintained at 20° during the addition of the silane because adequate stirring of the thick mixture was not obtained. The average yield for two batches was 11.8%.

Substitution of *p*-dichlorobenzene for *p*-dibromobenzene gave only the monosilane. From 29.4 g. (0.2 mole) of *p*-dichlorobenzene was obtained 16.0 g. (32.7%) of *p*-chlorophenyldiethoxymethylsilane boiling 74–75° at 0.1 mm. n_D^{22} 1.4841, d_4^{28} 1.069, when the product was purified by method A.

Anal. Calcd. for $C_{11}H_{17}ClO_2Si$: Si, 11.47; MR_D, 65.66. Found: Si, 12.19, 12.16; MR_D, 65.48.

p-Phenylenebis(diethoxymethylsilane). Sodium method. A mixture of 5.5 g. (0.24 g.-atom) of sodium and 30 ml. of toluene was heated to 112°, and then stirred at 600 r.p.m. to disperse the sodium. Dropwise addition of a mixture of 28.0 g. (0.093 mole) of *p*-bromophenyldiethoxymethylsilane and 20.0 g. (0.118 mole) of chlorodiethoxymethylsilane gave an exothermic reaction which maintained a refluxing mixture without external heating. The cooled product was filtered to remove the sodium halides and distilled at atmospheric pressure to remove the toluene and unchanged chlorodiethoxymethylsilane. Fractional distillation of the residue at 0.3 mm. gave 8.6 g. (27.0%) of phenylenebis(diethoxymethylsilane) boiling at 124–127°, n_D^{25} 1.4536.

When 13.0 g. (0.5 g.-atom) of sodium in 50 ml. of toluene was treated with a mixture of 29.5 g. (0.125 mole) of *p*-dibromobenzene, 42.3 g. (0.25 mole) of chlorodiethoxymethylsilane, and 50 ml. of toluene, a self-sustaining reaction could not be initiated even with the addition of small quantities of ethyl acetate. The results were the same when a threefold excess of the silane was used.

After 35.5 g. (0.15 mole) of *p*-dibromobenzene, 53 g. (0.30 mole) of chlorodiethoxymethylsilane, 15.2 g. (0.60 g.-atom) of sodium pressed into 1 mm. diameter wire, and 125 ml. of absolute ether were heated under reflux and stirred for 24 hr., the mixture became dark purple but an exothermic reaction could not be initiated. No *p*-phenylenebis(diethoxymethylsilane) was obtained when the product was fractionally distilled under reduced pressure.

1-Diethoxymethylsilyl-4-diethoxyphenylsilylbenzene. Sodium method. In a similar experiment, 5.1 g. (0.22 g.-atom) of sodium in 30 ml. of toluene, treated with 21.4 g. (0.11 mole) of chlorodiethoxyphenylsilane and 27.0 g. (0.093 mole) of *p*-bromophenyldiethoxymethylsilane, gave two materials when the product was fractionally distilled at 0.1 mm. One fraction, mostly *diethoxymethylphenylsilane*, was collected at 54–56°, n_D^{25} 1.4602, d_4^{25} 0.993.

Anal. Calcd. for $C_{11}H_{18}O_2Si$: C, 62.80; H, 8.62; Si, 13.35. Found: C, 61.95, 62.05; H, 7.95, 7.79; Si, 12.08, 121.15.

1-Diethoxymethylsilyl-4-diethoxyphenylsilylbenzene. 2.0 g. (5.7%) was obtained at 143–145°, n_D^{25} 1.4973, d_4^{25} 1.034.

Anal. Calcd. for $C_{21}H_{32}Si_2O_4$: C, 62.33; H, 7.97; Si, 13.89; MR_D, 115.0. Found: C, 61.95, 62.05; H, 7.95, 7.79; Si, 13.88, 14.10; MR_D, 114.6.

p-Phenylenebis(dichloromethylsilane). Attempted by the lithiation of p-dibromobenzene. A mixture of 0.122 mole of butyllithium in petroleum ether (b.p. 33–55°) and 14.4 g. (0.061 mole) of *p*-dibromobenzene, stirred at reflux for 24 hr., yielded a solid product. The liquid phase gave a negative Gilman Color Test I. Carbonation of the product gave 63% of the theoretical acids (calculated as terephthalic acid) with a neutralization equivalent 127.

When a similar lithium derivative, prepared from 0.115 mole of *p*-dibromobenzene, was added to a solution of 0.46 mole of trichloromethylsilane in 100 ml. of petroleum ether, distillation of the product gave 9.3 g. of an unidentified material boiling 150–153° at 26 mm.

Anal. Found: C, 62.59, 62.48; H, 7.57, 7.61; Si, 5.07, 5.14; neut. equiv., 309.

p-Phenylenebis(ethoxydimethylsilane). Grignard procedure in ether. Magnesium, 80.2 g. (3.3 g.-atoms), covered with 100 ml. of ether, was treated with a solution of 353.9 g. (1.5 moles) of *p*-dibromobenzene, 444.6 g. (3.0 moles) of diethoxydimethylsilane, and 500 ml. of anhydrous ether by dropwise addition over 2.5 hr. The product was heated and stirred for 15 hr., and then 400 ml. of ether was removed by downward distillation. After 400 ml. of heptane was added to the mixture, the salts were removed by filtration and the solvents were distilled from the mixture. Fractional distillation of the residue at 3.5 mm. gave four fractions: A, b.p. 64–123°, 49 g.; B, b.p. 123–125°, 26 g., n_D^{25} 1.4752; C, b.p. 127–128°, 131 g.; n_D^{25} 1.4752, d_4^{25} 0.9354; and D, b.p. 128–135°. Fraction C represented a 31% yield of the product.

Anal. Calcd. for $C_{14}H_{26}O_2Si_2$: Si, 19.88; MR_D, 84.46. Found: Si, 19.24, 19.14; MR_D, 85.19.

Grignard method in tetrahydrofuran. Addition of a mixture of 565 g. (5.0 moles, total) of *p*-dibromobenzene, 694 g. (5.0 moles) of chloroethoxydimethylsilane, and 1125 ml. of tetrahydrofuran to 134 g. (5.5 g.-atoms) of magnesium, which had been previously activated with 25 g. of *p*-dibromobenzene in 200 ml. of tetrahydrofuran, gave 139 g. (19.7%) of *p*-phenylenebis(ethoxydimethylsilane) boiling at 132–134°, n_D^{25} 1.4763, when the product was filtered and fractionally distilled at 4.5 mm.

p-Phenylenebis(ethoxymethylvinylsilane). When a mixture of 358 g. (1.56 moles) of *p*-dibromobenzene, 500 g. (3.12 moles) of diethoxymethylvinylsilane, and 400 ml. of tetrahydrofuran was added dropwise over 4 hr. to 83.4 g. (3.43

TABLE II

OTHER *p*-PHENYLENEDISILANES

Compound	B.P., Mm.	M.P.	Yield, %	Analysis					
				Calcd.			Found		
				C	H	Si	C	H	Si
p-[$C_6H_5Si(OC_2H_5)_2]_2C_6H_4$[a]	188–197 (0.30–0.07)	—	27.9	66.91	7.34	12.04	67.45	7.15	12.10
p-[4-$ClC_6H_4Si(OC_2H_5)_2]_2C_6H_4$	210–246 (0.25–0.8) 239–239 (1)	54–55[b]	26.5	58.30	6.02	10.49	58.14	5.82	10.35
p-[4-$(CH_3)_2NC_6H_4Si(OC_2H_5)_2]_2C_6H_4$	*ca.* 270 (0.1)	104–105[b]	43.5	65.17	8.02	10.16	65.57	7.83	10.56 10.16
				N = 5.07			N = 5.09		
p-[4-$CH_3OC_6H_4Si(OC_2H_5)_2]_2C_6H_4$	230–250 (0.2–0.6)	55–56[b]	43.9	63.84	7.27	10.67	63.52	7.21	10.68 10.74

[a] n_D^{25} 1.5345. [b] From anhydrous ethanol.

g.-atoms) of magnesium turnings, and the mixture was stirred at reflux for 7 hr., a negative Gilman Color Test I was obtained. After 500 ml. of heptane was added to the mixture, 400 ml. of the solvents were removed by distillation, and the salts were removed by filtration. When the product, containing 1 wt. % hydroquinone, was fractionally distilled at 3.3 mm. three fractions were obtained: A, b.p. 74–139°, 25 g.; B, b.p. 139–144°, 42 g.; n_D^{25} 1.4930, d_4^{25} 0.9605; C, b.p. 144–155°, 5 g., n_D^{25} 1.4958, d_4^{25} 0.9587. Fraction B represented a 9% yield of the product.

Anal. Calcd. for $C_{16}H_{26}O_2Si_2$: Si, 18.33; MR_D, 92.78. Found: Si, 18.75, 18.81; MR_D, 92.75.

p-Phenylenebis(diethoxyvinylsilane). Similarly, 5.3 g. (0.2 g.-atom) of magnesium, 23.6 g. (0.1 mole) of *p*-dibromobenzene, 38 g. (0.2 mole) of triethoxyvinylsilane, and 160 ml. of tetrahydrofuran gave 5.6 g. (15%) of *p*-phenylenebis(diethoxyvinylsilane), b.p. 125–129° at 0.15 mm.; n_D^{25} 1.4743; d_4^{25} 0.9852, MR_D calcd., 103.56, found, 104.63.

Other p-phenylene(disilanes). Compounds listed in Table II were prepared by the concomitant addition of mixtures of *p*-dibromobenzene and the appropriate dialkoxyarylchlorosilane in tetrahydrofuran to magnesium and were purified by fractional distillation.

p-Phenylenebis(diethoxyphenylsilane), prepared by treating a cooled, preformed Grignard reagent with chlorodiethoxyphenylsilane, was purified by method B. The product, 26.5 g. (28.5%), boiled at 160–170° at 0.1 mm.

When the reaction products were purified directly by filtration and distillation, the crude reaction mixtures were treated with an equal volume of heptane, and a large part of the tetrahydrofuran was removed by distillation. More complete precipitation of the magnesium halides was obtained, eliminating the necessity for several filtrations.

KANSAS CITY 10, MO.

[CONTRIBUTION FROM THE CORNING GLASS WORKS AND DOW CORNING CORP. MULTIPLE FELLOWSHIP AT MELLON INSTITUTE AND THE DOW CORNING CORP.]

Dehydration of 1,3-Bis(hydroxyalkyl)tetramethyldisiloxanes

JOHN L. SPEIER,[1] MARY P. DAVID, AND BENJAMIN A. EYNON[1]

Received February 16, 1960

Three 1,3-bis(hydroxyalkyl)tetramethyldisiloxanes of the formula $[(CH_3)_2Si(CH_2)_nOH]_2O$ were prepared in which n = 1, 2, or 3. When subjected to dehydration, each reacted differently. When n = 1, dehydration in the presence of sulfuric acid caused the formation of ethers having the formula, $[-(CH_3)_2SiCH_2OCH_2(CH_3)_2Si(O)-]_{1,2,\ldots x}$. The cyclic compound in which x = 1 was isolated. In the presence of lime, a product was obtained having the formula, $[-(CH_3)_2SiCH_2O-]_{2,3,\ldots x}$. Under either alkaline or acidic conditions, when n = 2, ethylene, water, and polydimethylsiloxanes formed. When n = 3, a reactive cyclic compound was formed having the formula $(CH_3)_2Si(CH_2)_3O-$.

The synthesis of a series of three *sym*-(hydroxyalkyl)tetramethyldisiloxanes of the formula $[HO(CH_2)_n(CH_3)_2Si]_2O$ has recently been completed with n = 1, 2 or 3, and the dehydration of these three structures has been studied. Although these three compounds form an homologous series, each loses water in a different manner.

1,3-Bis(hydroxypropyl)tetramethyldisiloxane, (I), prepared by the methanolysis of 1,3-bis(acetoxypropyl)tetramethyldisiloxane[2] lost water on distillation to form a cyclic structure (II) according to equation A:

$$O[Si(CH_3)_2(CH_2)_3OH]_2 \underset{}{\overset{\Delta}{\rightleftharpoons}} 2\ \underset{\text{II}}{\begin{matrix}(CH_3)_2 \\ | \\ Si{-}CH_2 \\ / \quad | \\ O \quad | \\ \backslash \quad | \\ CH_2{-}CH_2\end{matrix}} + H_2O \quad (A)$$

I

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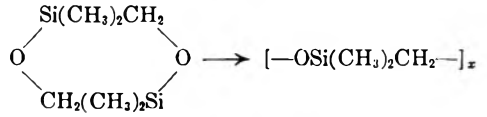
At room temperature the equilibrium is far to the left, but in the presence of a drying agent such as lime, 2,2-dimethyl-1-oxa-2-silacyclopentane (II) is obtained in good yield by distillation, b.p. 103°. In the absence of a drying agent, water and II codistilled and recombined on cooling to reform I.

The cyclic II polymerized readily at room temperature in the presence of minute amounts of water, presumably to form products of the formula $HO[(CH_3)_2Si(CH_2)_3O—]_nH$. In very carefully dried receivers, the polymer was of sufficiently high molecular weight so as to be somewhat rubbery. In the presence of the moisture in conventionally dried glassware, the polymers remained as extremely viscous liquids.

1,3-Bis(hydroxymethyl)tetramethyldisiloxane (III) was prepared by the method of Speier, *et al.*,[3] who noted that the compound was unstable even at room temperature and that heat caused the formation of water and a resinous mass which became quite fluid on exposure to water. Some years later, an opportunity arose to re-examine III somewhat more closely. Distillation from lime caused the formation of 40 to 60% of a volatile product, the properties of which changed rapidly at room temperature, much as described for II. The distillate reacted exothermally with very dilute hydrochloric acid or with glacial acetic acid. With the latter reagent 1,3-bis(acetoxymethyl)tetramethyldisiloxane formed. These phenomena are explained as being due to the changes summarized by Equations B.

$$O[Si(CH_3)_2CH_2OH]_2 \xrightarrow[CaO]{-H_2O}$$

III



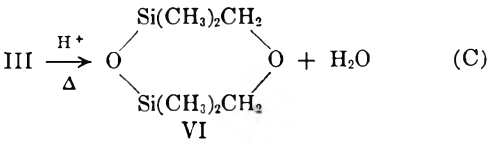
IV V

$$\downarrow x\ HOAc \qquad (B)$$

$$x/2\ H_2O + x/2\ [AcOCH_2(CH_3)_2Si]_2O$$

Dehydration of III in the presence of a small amount of sulfuric acid caused the formation of unreactive products, part of which (15%) was obtained as the cyclic ether, 2,2,6,6-tetramethyl-1,4-dioxa-2,6-disilacyclohexane (VI), with the remainder as a high boiling liquid polymer. These products were quite unlike those obtained with lime. Concentrated hydrochloric acid or refluxing dilute sodium hydroxide had no effect upon these products.

Proof of structure for the cyclic compound was obtained as outlined below.



VI (C)

$$3\ (VI) + 2\ BF_3.Et_2O \longrightarrow 3\ F(CH_3)_2SiCH_2OCH_2Si(CH_3)_2F + 2\ Et_2O + B_2O_3 \qquad (D)[4]$$

VII

$$VII + 2\ NaOH \longrightarrow VI + 2\ NaF + H_2O \qquad (E)$$

The cyclic VI and the polymer both had the same H^1 NMR spectra. The polymer also formed the precipitate of boric oxide (Eq. D) characteristically obtained from siloxanes. From these data, along with analyses and general behavior, we feel the polymer is probably linear forms of VI with hydroxymethyl end groups.

The infrared spectrum of VI showed two strong absorption maxima, one at 10.15 μ and one at 9.4 μ believed to be characteristic of the siloxane and ether bonds in a strained six-membered ring.

1,3-Bis(hydroxyethyl)tetramethyldisiloxane (VIII) was prepared by the methanolysis of 1,3-bis(acetoxyethyl)tetramethyldisiloxane. As isolated from the methanol, VIII was of reasonably high purity without further purification. When completely neutral, VIII was much more resistant to dehydration than I or III and distilled in the expected boiling range without change.

Elevated temperatures caused cleavage in VIII at the silicon-carbon bond of the hydroxyethyl group in the presence of even trace amounts of acid or base. Only dimethylpolysiloxanes remained after the rapid evolution of ethylene had ceased. Acid catalysis promoted a fairly rapid

$$[(CH_3)_2SiCH_2CH_2OH]_2O \xrightarrow[OH^-]{H^+} 2\ [(CH_3)_2SiO]_x + 2\ CH_2{=}CH_2 + H_2O \qquad (F)$$

reaction accurately described by Equation F. Potassium hydroxide was also an effective catalyst, but apparently promoted cleavage also by a second route leading to ethanol, according to Equation G. Freshly calcined lime was effective

$$\equiv SiCH_2CH_2OH \xrightarrow{OH^-} \equiv SiO^- + CH_3CH_2OH \qquad (G)$$

only at high temperatures and did not equal potassium hydroxide in promoting the formation of ethanol.

EXPERIMENTAL

1,3-Bis(hydroxypropyl)tetramethyldisiloxane (I) was prepared by methanolysis of 1,3-bis(acetoxypropyl)tetramethyldisiloxane[3] in an eight-fold excess of methanol with a small amount of potassium hydroxide as catalyst. After re-

(2) J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Am. Chem. Soc.*, **79**, 974 (1957).

(3) J. L. Speier, B. F. Daubert, and R. R. McGregor, *J. Am. Chem. Soc.*, **71**, 1474 (1949).

(4) L. H. Sommer and G. R. Ansul, *J. Am. Chem. Soc.*, **77**, 2482 (1955), have described this procedure for making fluorosilanes.

moval of methyl acetate by distillation, followed by removal of all volatile compounds, the product had the following properties[5]: n_D^{25}, 1.4472; d_D^{25}, 0.9531; R_D, 0.2804; calcd. R_D, 0.2817.

2,2-Dimethyl-1-oxa-2-silacyclopentane (II). Seventy-five grams of I was distilled at 50 mm. The vapor temperature varied erratically but remained much too low to be correct for the disiloxane (I). The distillate showed striations initially and became very viscous, but the striations disappeared on standing with no agitation. Soon after the distillation, the distillate had the physical constants of I. This behavior suggested that I decomposed on distillation and reformed in the receiver according to Equation A.

To verify this, a 40-g. sample of I was distilled through a small column packed with dehydrated alumina pellets. The alumina adsorbed much of the product as well as the water, so that only 10 g. of distillate was obtained. This distillate, however, was the heterocyclic II, b.p. 32° at 50 mm.; 103° at 740 mm.; n_D^{25}, 1.4415; d_4^{25}, 0.9178; R_D, 0.2880. Calcd. R_D, 0.2886. Infrared spectra showed no absorption maximum corresponding to hydroxyl.

Anal. Calcd. for $C_5H_{12}OSi$: Si, 24.2. Found: Si, 23.8.

The preparation was repeated more successfully by distillation of I from freshly calcined calcium oxide. Recovery was simplified by this technique and II was obtained in 93% yield, b.p. 102–103° at 740 mm.; n_D^{25}, 1.4409, d_D^{25}, 0.9180, R_D, 0.2876; % Si, 24.1.

The refractive index and density of this product changed rapidly after distillation. The indices reported above are those existing at the time the density was determined. The possibility of error cannot be disregarded. In 6 hr. the refractive index rose to 1.4503 in a tightly closed bottle. In 7 days it rose to 1.4535[6] as the product became a soft, gelatinous mass.

1,3-Bis(acetoxypropyl)tetramethyldisiloxane. A sample of II, 5.8 g., was mixed with 6.0 g. of glacial acetic acid and 0.36 g. of sulfuric acid at room temperature. After 24 hr. ether was added so that the mixture could be washed thoroughly with water. The product, free of ether and dry, was essentially pure diacetate ester of (I), $[Si(CH_3)_2(CH_2)_3OOCCH_3]_2O$,[7] n_D^{25}, 1.4323; d_4^{25}, 0.9747; R_D, 0.2663; sapon. equiv., 173.6. Calcd. sapon. equiv., 167.

2,2,5,5-Tetramethyl-1,4-dioxa-2,5-disilacyclohexane (IV). 1,3-Bis(hydroxymethyl)tetramethyldisiloxane (III) (150 g., 0.774 mole) was distilled at 100 mm. from calcined lime (45 g.). Three fractions were obtained: (a) 19.4 g.; b.p. 29–32° at 100 mm.; n_D^{25}, 1.3400; % Si, 3.50; % C, 36.9; % H, 12.6. This fraction was not identified. (b) 60.9 g. of sweet-smelling liquid; b.p. 95–104° at 100 mm. (c) A residue (115.7 g.) made up of the lime and an orange oil having n_D^{25}, 1.4259; d_4^{25}, 0.966.

Fraction (b) increased in viscosity and refractive index on standing in clean, tightly stoppered bottles under an atmosphere of nitrogen. The lowest index measured was n_D^{25} 1.4169, but after several days this value rose as high as 1.4290. The infrared spectrum of (b) was not that of the cyclic VI and showed no hydroxyl groups.

Anal. Calcd. for $[-(CH_3)_2SiCH_2O-]_x$: Si, 31.9; C, 40.9; H, 9.1. Found: Si, 32.0; C, 39.9; H, 9.6.

Boron trifluoride ethereate produced no precipitate of boric oxide from (b). At room temperature 2,4-dinitrobenzoyl chloride did not react with (b). With water, (b) reacted slowly. When a trace of acid was added, the reaction became noticeably exothermic.

To determine the stoichiometry of the reaction with water, 0.0001*N* hydrochloric acid was added to (b) in small portions and the change in viscosity of the solution was measured. From an original viscosity of 10.9 cs. at 25° (n_D^{25}, 1.4278) a smooth rise to a high of 29.4 cs. (n_D^{25}, 1.4309) was noted when 0.0108 mole of water per g. of sample had been added. Additional water caused the viscosity to decrease. Equation H requires 0.0114 mole of water per g. of sample for complete hydrolysis. The dehydration of III was repeated and the

$$[-(CH_3)_2SiCH_2O-]_x + H_2O \longrightarrow x\ HOSi(CH_3)_2CH_2OH \quad (H)$$

distillate was taken in two fractions: (a) 10 g.; b.p. 79° at 55 mm.; n_D^{25}, 1.4150, and (b) 70 g.; b.p. 79° at 55 mm. Fraction (b) was added directly to 100 g. of glacial acetic acid. A slightly exothermic reaction took place. The solution was heated to 115° for 2 hr. and distilled to remove 60 g. (59.7 calcd.) of water and acetic acid. The residue weighed 107 g. Distillation of the residue gave 89 g. (81%) of 1,3-bis(acetoxymethyl)tetramethyldisiloxane, b.p. 69–70° at 0.1 mm.; n_D^{25}, 1.4200; d_4^{25}, 0.999; R_D, 0.2533; calcd. R_D, 0.2514.[8] The infrared spectrum was that of authentic 1,3-bis(acetoxymethyl)tetramethyldisiloxane.

2,2,6,6-Tetramethyl-1,4-dioxa-2,6-disilacyclohexane (VI). With 15 drops of sulfuric acid III (509 g., 2.61 moles) was heated to reflux with a small amount of benzene under a trap for water. Water (34. g., 73%) was collected at a temperature of 180° in the flask. Distillation under vacuum removed the benzene followed by VI (52.5 g., 11%), b.p. 57–57.5° at 24 mm.; n_D^{25}, 1.4244; d_D^{25}, 0.9293; R_D, 0.2748; calcd. 0.2753. About 13.5 g., 4% of the same material (n_D^{25}, 1.4255), was caught in a Dry Ice trap along with water as ice (8 g., 17%).

The residue boiling above 250° at 24 mm., weighed 369 g., 81% of theory calculated as $[-(CH_3)_2SiCH_2O-]_x$, n_D^{25}, 1.4344; d_D^{25}, 0.9495; R_D, 0.2745; calcd. 0.2753.

Anal. Calcd. for $[(C_3H_8OSi)]_x$:Si, 31.8; OH, 0.00. Found: Si, 31.6; OH, 1.9.

Bis(dimethylfluorosilylmethyl)ether (VII). A mixture of 26.5 g. (0.15 mole) of VI and 15.6 g. (0.11 mole) of boron trifluoride etherate was placed in a 100-ml. round bottom flask attached to a small still head and heated. At 71°, ether started to distill. The temperature was gradually raised over a period of 3 hr. to the boiling point of the etherate (125°), during which time 7 g. of ether was collected (7.4 g. calcd.). The mixture was cooled and 3.2 g. (0.02 mole) of hexamethyldisiloxane added to react with the excess boron trifluoride ethereate. The mixture was heated again, and a total of 28.7 g. of volatile material was collected up to a flask temperature of 160°. The residue, 7 g., included the expected solid boron oxide, 3.8 g. theory. Fractional distillation through a small Podbielniak column gave 2 g. of ether, b.p. 28–30°; intermediate 1 g.; and 19 g. of VII, b.p. 144° at 738 mm.; n_D^{25}, 1.3795; d_4^{25}, 0.9444; R_D, 0.2450. Calcd. R_D, 0.2441. Residue, 5 g., n_D^{25}, 1.3820; neut. equiv., 99.8; was also calculated as VII, making the total yield 80%.

Anal. Calcd. for $C_6H_{16}F_2OSi_2$: neut. eq., 99.2. Found, 97.2.

Inspection of the H^1 NMR spectrum of V substantiated the structure assigned.

Preparation of VI *from* VII. Approximately 50 ml. of 1*N* sodium hydroxide was added to a stirred solution of 5 g. of VII in 25 ml. of benzene so that the solution became basic to phenolphthalein. The benzene solution was washed, dried over anhydrous sodium sulfate, filtered, and distilled. A quantitative yield of VI was obtained: b.p. 152.6° at 738 mm.; n_D^{25}, 1.4245; d_4^{25}, 0.926; R_D, 0.2759. Calcd. R_D, 0.2753.

Anal. Calcd. for $C_6H_{16}O_2Si_2$: Si, 31.8. Found, 32.0.

β-Acetoxyethyldimethylchlorosilane. A mixture of vinyl acetate (172.2 g., 2.0 moles) and 2.4 ml. of 0.1*M* chloroplatinic acid in isopropanol (2.4×10^{-4} mole of platinum) was heated to 72° and dimethylchlorosilane (208.3 g., 2.2 moles) was added during 7 hr. The addition of the chlorosilane was

(5) Ref. 2 cited n_D^{26}, 1.4470.

(6) W. H. Knoth, Jr., and R. V. Lindsay, Jr., *J. Am. Chem. Soc.*, 80, 4106 (1958), have synthesized II from 3-chloropropoxydimethylchlorosilane and sodium. They report b.p. 95°, n_D^{26} 1.4170 for a freshly distilled sample. They also observed that the cyclic formed polymers spontaneously on standing.

(7) Ref. 3 reported n_D^{25}, 1.4322; d_4^{25}, 0.9732; R_D 0.2666.

(8) Ref. 3 reported b.p. 250° at 760mm.; n_D^{25}, 1.4215; d_4^{25}, 0.993.

controlled so as to keep the temperature of reflux between 60 and 75°. Continued heating of the total quantities of reactants resulted in a maximum temperature of 108°. β-Acetoxyethyldimethylchlorosilane, $(CH_3)_2SiClCH_2CH_2OOCCH_3$, was obtained in 65% yield. The following properties were observed: b.p. 108–109.5° at 50 mm.; n_D^{25}, 1.4301; d_4^{25}, 1.031; R_D, 0.2506. Calcd. R_D, 0.2505.

Anal. Calcd. for $C_6H_{14}ClO_2Si$: neut. equiv., 180.8; sapon. equiv., 90.4; Si, 15.5. Found: neut. equiv., 180.1; sapon. equiv., 89.8; Si, 15.3.

A fraction (b.p. 60–75° at 50 mm.) representing approximately 10% by weight of the total product was observed during distillation. This impure fraction may have contained the α-adduct.

1,3-Bis(acetoxyethyl)tetramethyldisiloxane was prepared by hydrolysis of β-acetoxyethyldimethylchlorosilane in ice water. The hydrolyzate was washed with water and dilute sodium bicarbonate solution and fractionally distilled at reduced pressure; yield 93%. The properties observed were: b.p. 166–166.5° at 18 mm.; n_D^{25}, 1.4288; d_4^{25}, 0.9886; R_D, 0.2607; Calcd. R_D, 0.2609.

Anal. Calcd. for $C_{12}H_{26}O_5Si_2$: sapon. equiv., 153.2. Found: sapon. equiv., 151.

1,3-Bis(hydroxyethyl)tetramethyldisiloxane (VIII). 1,3-Bis(acetoxyethyl)tetramethyldisiloxane was dissolved in a 14-fold excess of methanol to which was added several drops of concd. hydrochloric acid. After several days, most of the methanol and methyl acetate were removed by distillation. The residue was freed of all volatile compounds by a sweep of dry nitrogen at 100 mm. pressure up to a temperature of 75°. A quantitative yield of clear, colorless, somewhat viscous VIII was obtained having these properties: n_D^{25}, 1.4432; d_4^{25}, 0.966; R_D, 0.2746. Calcd. R_D, 0.2745. The H^1NMR spectrum showed only β-product.

Distillation of neutral 1,3-bis(hydroxyethyl)tetramethyldisiloxane (VIII). In order to remove all traces of hydrochloric acid, 54 g. of VIII was dissolved in 35 ml. of benzene and washed with a mixture of 35 ml. of concd. sodium chloride solution and 25 ml. of saturated sodium bicarbonate solution. After a second washing with aqueous sodium chloride, the neutral organic solution was dried azeotropically, filtered to remove traces of inorganic salts, and rendered free of solvent. A final sweep with dry nitrogen at 70–80° and 100 m. pressure insured removal of the last traces of benzene; yield 50.3 g., n_D^{25}, 1.4438.

A small sample (4.8 g.) was flash distilled. At a pressure of 5 mm., distillation proceeded smoothly, and 2.0 g. of distillate (boiling range 151–159°; n_D^{25}, 1.4431) was collected before the temperature in the flask reached 200°. The residue, still clear and colorless, weighed 2.8 g.; n_D^{25}, 1.4475. Inspection of the H^1 NMR spectra of this distillate, and the residue showed all three samples to have identical curves. These data indicate that VIII when completely neutral may be distilled without change.

Cleavage of 1,3-bis(hydroxyethyl)tetramethyldisiloxane (VIII). a. *Slightly acidic with hydrogen chloride.* A sample of VIII containing a trace of hydrogen chloride decomposed when heated for distillation as above. No distillate was collected up to a temperature of 200° in the flask, and a loss in weight occurred equal to that calculated for complete cleavage of ethylene from the molecule (Equation F).

The experiment was repeated using 10.3 g. (0.046 mole) of VIII in a 50-ml. flask attached to a small condenser, a Dry Ice trap, and a gas collecting bottle in series. Evolution of gas commenced at 75° and a total of 1908 ml. (corr.), 92%, was collected up to a temperature of 220°, where the rate of evolution had essentially ceased. Most of the gas formed below 150°. The flask had lost 3.5 g. (theory for loss of ethylene and water, 3.4 g.) and contained 6.8 g. of a clear, colorless, viscous fluid: n_D^{25}, 1.4067; d_4^{25}, 0.972; R_D, 0.2531. Calcd. R_D, $[(CH_3)_2SiO]_x$, 0.2521.

Anal. Calcd. for (C_2H_6OSi)]: Si, 37.9. Found, 38.0. The trap contained 0.6 g. of ice (theory requires 0.8 g. water), n_D^{25}, 1.3421. The infrared spectrum of the gas was that of ethylene.

b. *Under alkaline conditions. Potassium hydroxide.* A mixture of 10 g. (0.045 mole) of VIII and 0.3 g. of crushed, dry potassium hydroxide was heated as in (a). The evolution of gas started at 80° and continued to a temperature of 218°.

Only 1260 ml. (corr.) of the calculated amount of 2016 ml. of gas was collected. Infrared analysis proved this to be ethylene. The cold trap contained 1.8 g., partly in the form of ice. Only 0.8 g. of water was expected. The contents of the cold trap smelled like ethanol, n_D^{25}, 1.3651. The colorless residue was dissolved in benzene and washed free of potassium hydroxide. It was then dried and devolatilized by a stream of nitrogen at 55° and 100 mm. It was essentially pure polydimethylsiloxane: n_D^{25}, 1.4037; d_D^{25}, 0.966; R_D, 0.2530 (calcd. R_D for $[(CH_3)_2SiO]_x$, 0.2521).

Anal. Calcd. for $(C_2H_6OSi)_n$: Si, 37.9. Found, 37.8.

From these data it appears likely that the cleavage in the presence of alkali formed both ethylene with water as well as ethanol as outlined in Equations F and G.

c. *With calcium oxide.* A mixture of 5 g. (0.0225 mole) of VIII and 2.5 g. of freshly calcined calcium oxide heated as above formed no gas until it reached 170°. The evolution of gas proceeded very slowly in this case. The experiment was continued up to a temperature of 218°, to obtain 780 ml. (corr.) of ethylene, 77% of theory according to Equation D. The trap contained only two drops of colorless liquid, n_D^{25}, 1.363, having the odor of ethanol. The residue weighed 6.5 g. The loss of 1.0 g. agrees with the 0.97 g. loss calculated for a 77% yield of ethylene, assuming that the lime would absorb the water also formed.

The residue was diluted with hexane, filtered free of the lime and worked up as in (a) and (b) above to give 3.0 g. of polysiloxane: n_D^{25}, 1.4175, d_4^{25}, 0.969; R_D, 0.2598. R_D calcd. for $[(CH_3)_2SiO]_x$, 0.2521.

The infrared spectrum of the gas was again that of ethylene.

Acknowledgments. The authors wish to thank Paul C. Lauterbur for the NMR data and for their interpretation, as well as the Physicochemical Research Service of Mellon Institute and the Spectroscopy Laboratory of Dow Corning Corporation for the infrared analyses.

MIDLAND, MICH.

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

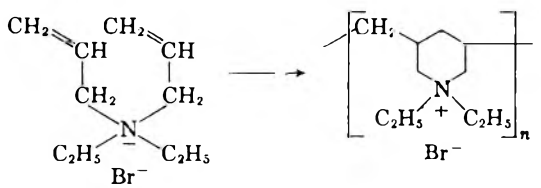
The Formation of a Cyclic Recurring Unit in the Polymerization of Diallyldimethylsilane[1]

C. S. MARVEL AND R. G. WOOLFORD

Received January 29, 1960

Diallyldimethylsilane has been polymerized with Ziegler-type catalysts to give soluble polymers containing cyclic recurring units.

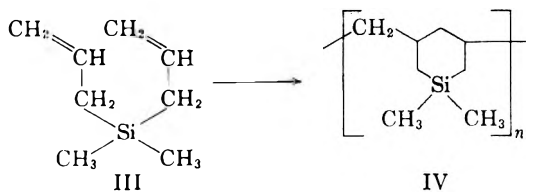
The formation of polymers containing cyclic recurring units by intermolecular-intramolecular polymerization of nonconjugated olefins is now well established. For example,[2] diallyl diethyl ammonium bromide (I) gives a soluble polymer containing recurring piperidine units (II). Similarly,



I

1,5-hexadiene,[3] 1,6-heptadiene,[3] and a series of 2,6-disubstituted 1,6-heptadienes[4] have been polymerized to give polymers containing cyclic recurring units.

It was thought that diallyldimethylsilane (III) might also polymerize to give such a polymer (IV) and such has been found to be the case. Using a



III IV

Ziegler-type catalyst of aluminumtriisobutyl and titanium tetrachloride in heptane solvent at 30°, soluble polymers ranging from moderately viscous oils to high-melting white solids have been obtained. From the preliminary experiments, it seems apparent that the polymerization conditions (amount of solvent, catalyst ratios, etc.) have a marked effect on both the yield and molecular weight of polymer produced. In each case, small amounts (0.9–10% yields) of insoluble, presumably cross-linked polymers, were obtained. Yields of the soluble polymers ranged from 13–91% and in most cases they were very sticky, glassy semisolids. These polymers dissolved completely in benzene, heptane, and chloroform. The results are tabulated in Table I.

The polymer sample from reaction 266A was purified thoroughly by four reprecipitations from benzene solutions into methanol. The soluble portion was able to be divided into two fractions: a white solid, completely insoluble in methanol-benzene solution but freely soluble in benzene (viscosity 0.22), and a viscous oil, moderately soluble in methanol-benzene (viscosity 0.04) which was recovered by boiling off the solvent. These fractions possessed identical infrared spectra (taken in 2.5% solution in chloroform), which contained the following bands (cm.$^{-1}$): 2905 (—C—H stretch); 1441 (—CH_2— deformation, normal); 1409 (—CH_2— deformation, lowered for CH_2 groups next to Si atom); 1339 (—CH< deformation); 1248, 838 (—$Si(CH_3)_2$—). In both cases, a very weak band was obtained at 1631 cm.$^{-1}$ (residual double bond). A quantitative comparison of these polymer samples with diallyldimethylsilane (2.5% solution in chloroform) showed that there were 6.0% of the monomer units incorporated in the polymer chain which still retained one double bond. The identical amounts of residual unsaturation in both fractions appear to indicate that, except for molecular weight, the same type of polymer linkage is present in each. The infrared studies are thoroughly consistent with polymer structure IV containing cyclic recurring units. The fraction with the higher viscosity was obtained analytically pure and, on heating, softened and shrank slightly between 100° and 300°. Above 300° it began to turn yellow and at 376° it formed a clear amber melt. When this sample was heated above 300° for more than a few minutes, it began to decompose noticeably.

At this point we learned that Dr. G. B. Butler of the University of Florida was working on this same general problem and we discontinued our work (9-20-58).[5]

(1) This work was sponsored by the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, Contract No. AF 33(616)-5486. Reproduction of this paper in whole or in part is permitted for any purpose of the United States Government.

(2) G. B. Butler and R. J. Angelo, *J. Am. Chem. Soc.*, **79**, 3128 (1957).

(3) C. S. Marvel and J. K. Stille, *J. Am. Chem. Soc.*, **80**, 1740 (1958).

(4) C. S. Marvel and R. D. Vest, *J. Am. Chem. Soc.*, **79**, 5771 (1957); also in press.

TABLE I

POLYMERIZATION OF DIALLYLDIMETHYLSILANE AT 30°

No. Sample	Heptane, G.	Aluminum Triisobutyl, G.	Titanium Tetrachloride, G.	Moles Aluminum Triisobutyl/Titanium Tetrachloride, Moles	Monomer, G.	Time, Hr.	Total Yield, %	Insol. Polymer, %	Sol. Polymer, %	η^a (25°)	Polymer Appearance
266A	7.5	0.15	0.144	1.0	4.0	48	32	2.1	30	0.22 (266A-1) 0.04 (266A-2)	White solid Viscous oil
266B	7.5	0.15	0.048	3.0	4.0	48	20	1.3	19	0.08	White solid
266C	15.0	0.15	0.048	3.0	4.0	48	13	0.9	12	0.09	White solid
266D	7.5	0.15	0.144	1.0	4.0	72	37	2.8	35	0.08	Glassy semisolid
266E	7.5	0.30	0.288	1.0	4.0	72	87	10	77	0.06	Glassy semisolid
266F	3.8	0.15	0.144	1.0	2.0	72	91	7.0	84	0.08	Glassy semisolid
266G	15.0	0.30	0.288	1.0	2.0	72	56	3.2	53	0.06	Glassy semisolid

[a] All viscosities were run on 0.25 g. polymer dissolved in 100 ml. of benzene solution.

EXPERIMENTAL[6]

Diallyldimethylsilane (III). A solution of allylmagnesium bromide was made in the usual manner[7] using the following quantities of reagents: allyl bromide (200 g., 1.66 moles), magnesium (97 g., 4.0 g.-atoms), and anhydrous ether (1.5 l.). This solution was decanted into another flask and a solution of allyldimethylchlorosilane (135 g., 1.0 mole) in 300 ml. of anhydrous ether was dropped in at reflux temperature. The reaction mixture was stirred for 12 hr. and hydrolyzed with a saturated solution of ammonium chloride. The ether layer was distilled three times through a 55-cm. packed glass column to yield diallyldimethylsilane (112 g., 80% yield) of b.p. 134–135° (at about 750 mm), n_D^{25} 1.4380. [Petrov *et al.*[8] give: b.p. 135.5° (760 mm.), n_D^{20} 1.4420.]

An infrared spectrum of this compound exhibited the following bands (cm.$^{-1}$): 3070, 2960, 2900 (C—H); 1632 (CH_2=CH—); 1423, 1395, 1300, 990, 925 (CH and CH_2 deformations); 1253, 830 (—$Si(CH_3)_2$—).

Gas chromatography indicated this silane was free from impurities.

Polymerization studies. Table I lists a series of polymerizations of diallyldimethylsilane. The reaction mixtures were made up in the usual manner.[3] The polymer obtained from reaction 266A was fractionated into two components by repeated reprecipitation from benzene solution into methanol. Fraction 266A-1 was a white, powdery solid, completely insoluble in methanol-benzene solutions, but soluble in benzene, chloroform, and heptane. Fraction 266A-2 was a moderately viscous oil, soluble in methanol-benzene and isolated by boiling off the solvent. This oily fraction represented approximately two thirds of the soluble polymer obtained. No effort was made to fractionate samples 266B–266G. The small amounts of insoluble polymer produced in each reaction were removed by filtering benzene solutions of the original crude polymers from the first reprecipitations. Fine mesh wire screening or ordinary filter paper were used. All samples were purified by reprecipitation and freeze-dried from benzene.

The following physical and chemical data on soluble polymers 266A-1 and 266A-2 were obtained:

266A-1 was a white solid which softened and shrank slightly from 100–300°, formed a clear amber melt at 376°, and was completely soluble in benzene, heptane, chloroform. X-ray diffraction studies indicated this polymer was amorphous.

Anal. Calcd. for $(C_8H_{16}Si)_n$: C, 68.48; H, 11.50; Si, 20.02. Found: C, 68.65; H, 11.48; Si, 19.26.

Infrared spectrum (2.5% in chloroform) (cm.$^{-1}$): 2905 (C—H); 1631 (weak) (residual C=C); 1441 (—CH_2— deformation, normal); 1409 (—CH_2— deformation for CH_2 groups next to Si atom); 1339 (—CH< deformation); 1248,

(5) Since this manuscript was written, the work of A. V. Topchiev, N. S. Nametkin, S. G. Durgar'yan, and S. S. Dyankov, *Khim i Prakt. Primenenie Kremneorg. Soedinenii, Trudy Konf. Leningrad*, No. 2, 118 (1958); *Chem. Abstr.*, **53**, 8686 (1959) has become available. They have obtained distillable liquids, presumably cyclic trimers and tetramers, by the action of aluminum triethyl/titanium tetrachloride catalysts on diallyldiethylsilane.

(6) We are indebted to Mr. J. Nemeth, University of Illinois and to Clark Microanalytical Laboratories, Urbana, Ill., for the microanalyses, to Mr. P. McMahon for the infrared determinations and to Mr. R. Greenley for the x-ray studies.

(7) O. Grummitt, E. Budewitz, and C. C. Chudd, *Org. Syntheses*, **36**, 60 (1956).

(8) A. D. Petrov, V. F. Mironov, and V. G. Glukhovtsev, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1123 (1954); *Chem. Abstr.*, **49**, 7510 (1955).

838 (—$Si(CH_3)_2$—). A quantitative comparison of this polymer with diallyldimethylsilane showed that there were 6.0% of the monomer units incorporated in the polymer chain which still retained one double bond.

266A-2 was a moderately viscous oil which was completely soluble in benzene, heptane, and chloroform. It had an infrared spectrum identical with that of 266A-1, including the amount of residual unsaturation in polymer.

URBANA, ILL.

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

The Formation of Linear Polymers from Diene Monomers by a Cyclic Polymerization Mechanism. VI. Polymerization Studies of Some Diallylsilanes[1]

GEORGE B. BUTLER AND ROBERT W. STACKMAN

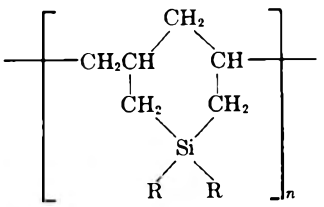
Received January 29, 1960

Diallyldimethylsilane and diallyldiphenylsilane have been polymerized with triethylaluminum–titanium tetrachloride complex catalyst to yield soluble polymers.

During the period following the original proposal[2] that 1,6-heptadienes can polymerize by an alternating intra-intermolecular mechanism to produce soluble, linear polymers, a wide variety of such monomers and the resulting polymers have been prepared and studied.[3] We now wish to report the synthesis and results of the polymerization studies of diallyldimethylsilane and diallyldiphenylsilane.

While both monomers studied in this work have previously been reported,[9,11] their significance was not realized until the advent of the intra-intermolecular mechanism for polymerization of 1,6-dienes and the Ziegler-type catalysts for polymerization of hydrocarbons. A kinetic study of radical catalyzed polymerization of allyltrimethylsilane and diallyldimethylsilane has been made,[4] and low molecular weight polymers were reported. More recently, polymerization of diallyldimethylsilane and diallyldiethylsilane by use of a triethylaluminum–titanium tetrachloride complex catalyst has been reported.[5] These authors reported that both liquid and solid polymers were obtained. From the liquids could be isolated trimers, tetramers, and pentamers; however, the solid polymers were insoluble in ether, benzene, and carbon tetrachloride, but swelled in heptane.

The polymers reported in this study are soluble in benzene. The absence of unsaturation in the polymers in conjunction with their solubility properties suggests the following structure for the polymers:



R = CH_3 or C_6H_5

The results of this study have been confirmed by Marvel and Woolford who independently studied polymerization of these and similar monomers.[6]

EXPERIMENTAL[7]

Diallyldimethylsilane. The allyl Grignard reagent was prepared from 208 g. (8.0 g.-atoms) of magnesium turnings, 448 g. (4.0 moles) of allyl bromide, and 4.0 l. of sodium-dried ether.[8]

Titration of the solution showed that it contained 3.7 equivalents (94% yield) of Grignard reagent. To 2.3 l. (2.3 equivalents) of the Grignard reagent was added 129 g. (1.0 mole) of dimethyldichlorosilane over a period of 4 hr.; the mixture was stirred for 20 hr. at room temperature. Hydrolysis was accomplished by pouring the contents of the reaction flask into a chilled hydrochloric acid solution. The ether layer and one 100-ml. ether extract of the aqueous phase were dried over calcium chloride; removal of the solvents by distillation left an oil which, when fractionated, gave 106 g. (76.3%) of diallyldimethylsilane, b.p. 135° (760 mm.), n_D^{20} 1.4405 [reported[9] b.p. 135.0–136.0° (760 mm.), n_D^{20} 1.4402]. The infrared spectrum of this compound[10] was identical with the spectrum of diallyldimethylsilane reported previously.[9]

(1) This research was supported by the United States Air Force through the Materials Laboratory, Wright Air Development Center of the Air Research and Development Command, under Contract Number AF 33(616)-5808. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) G. B. Butler and R. J. Angelo, *J. Am. Chem. Soc.*, 79, 3128 (1957).

(3) A previous paper in this series [M. D. Barnett, A. Crawshaw, and G. B. Butler, *J. Am. Chem. Soc.*, 81, 5946 (1959)] contains many pertinent references.

(4) O. Mikulasova and A. Hvirik, *Chem. zvesti*, 11, 645 (1957).

(5) A. V. Topchiev, N. S. Nametkin, S. G. Durgar'yan, and S. S. Dyankov, *Khim i Prakt. Primenenie Kremneorg. Soedinenii, Trudy Konf. Leningrad*, No. 2, 118 (1958).

(6) C. S. Marvel and R. G. Woolford, *J. Org. Chem.*, 25, 1641 (1960).

(7) All melting and boiling points are uncorrected.

(8) The procedure for the preparation of allyl Grignard reagent was obtained from Peninsular ChemResearch, Inc.

(9) L. D. Nasiak and H. W. Post, *J. Org. Chem.*, 24, 489 1959).

(10) The infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer by Mr. George Price and Mr. Leo Pijanowski.

TABLE I

POLYMERIZATION OF DIALLYLDIMETHYLSILANE

Heptane, ml.	$Al(C_2H_5)_3$, g.	$TiCl_4$, g.	Moles $Al(C_2H_5)_3$ / Moles $TiCl_4$	Monomer, g.	Temperature	Time, hr.	Polymer, g.	Conversion %
10	0.15	0.10	2.5	3	60	30	0.3	10
50	0.60	0.40	2.5	10	65	48	0.7	7
50	0.40	0.20	3.3	10	85	48	0.9	9
50	0.70	0.50	2.4	10	85	24	1.0	10

TABLE II

POLYMERIZATION OF DIALLYLDIPHENYLSILANE

Heptane, ml.	$Al(C_2H_5)_3$, g.	$TiCl_4$, g.	Moles $Al(C_2H_5)_3$ / Moles $TiCl_4$	Monomer, g.	Temperature	Time, hr.	Polymer, g.	Conversion, %
5	0.10	0.08	2.2	3	60	24	1.5	50
10	0.15	0.10	2.5	5	65	24	1.5	30
40	0.60	0.40	2.5	8	70	16	2.0	25
50	0.80	0.30	4.4	10	85	24	5.6	56

Diallyldiphenylsilane. The above procedure was repeated using 1.5 l. (1.5 equivalents) of allyl Grignard reagent and 126 g. (0.5 mole) of diphenyldichlorosilane. Fractionation of the product yielded 91 g. (71%) of diallyldiphenylsilane, b.p. 137–138° (1.5 mm.), n_D^{20} 1.5742 [reported[11] b.p. 140.5° (2 mm.), n_D^{20} 1.5750]. The previously reported spectrum of diallyldiphenylsilane[9] was identical with that obtained for this compound.

Polymerization studies. The catalyst for the polymerizations was prepared in a dry box. Triethylaluminum was dissolved in heptane; this was followed by the addition of a measured quantity of titanium tetrachloride which appeared to react immediately to give a brown suspension. After the flask was capped and removed from the dry box, the monomer was added, with stirring, to the suspension. The contents of the flask were then heated to the specified temperature. After varying intervals of time the polymerization mixtures were poured into methanol to decompose the catalyst.

Polydiallyldimethylsilane. Table I shows the results of the polymerization of diallyldimethylsilane. Purification of the polymers was accomplished by dissolving them in benzene; the resulting solution was poured into methanol from which the compounds precipitated. The analytical samples were obtained by repeating this process at least four times. The purified polymers melted between 80° and 110° and began to darken between 300° and 330° (open capillary). The infrared spectrum exhibits peaks for aliphatic hydrogen (2900–2800 cm.$^{-1}$) and for silicon dimethyl (1260–1240 cm.$^{-1}$, 815–800 cm.$^{-1}$). The bands for the double bond (1640 cm.$^{-1}$) and for the terminal methylene group (895 cm.$^{-1}$) are absent from the spectrum. An intrinsic viscosity determination in benzene gave a value of 0.13.

Anal.[12] Calcd. for $(C_8H_{16}Si)_n$: C, 68.52; H, 11.50; Si, 19.98. Found: C, 65.84; H, 10.95; Si, 19.73.

(11) A. D. Petrov, V. F. Mironov, and V. G. Glukhotsev, *Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 1123 (1954).

Polymerizations were also carried out using di-*t*-butyl peroxide as an initiator. The polymers were purified in a similar manner. The polymer obtained with 1.2% peroxide melted at 80–100° and began to darken at 280°. The infrared spectrum was similar to that of the Ziegler catalyst–initiated polymer but there were small peaks for the double bond (1640 cm.$^{-1}$) and for the terminal methylene group (895 cm.$^{-1}$) indicating some residual unsaturation.

Polydiallyldiphenylsilane. Table II shows the results of the polymerization of diallyldiphenylsilane. The method used for purifying the polymers was the same as that with polydiallyldimethylsilane. The polymers obtained melted from 125–155° and began to darken above 330° (open capillary). The weight-average molecular weight, as obtained by light scattering measurements,[13] was 6.0×10^4. A value of 0.065 was found for the intrinsic viscosity on a benzene solution of the polymer. The infrared spectrum possesses peaks for phenylsilicon (1430 cm.$^{-1}$, 1110 cm.$^{-1}$), aliphatic hydrogen (2900 cm.$^{-1}$), and aromatic hydrogen (3030 cm.$^{-1}$). The spectrum exhibits no absorption for the double bond (1641 cm.$^{-1}$) or for the terminal methylene group (895 cm.$^{-1}$).

Anal. Calcd. for $(C_{18}H_{20}Si)_n$: C, 81.78; H, 7.63; Si, 10.60. Found: C, 80.74; H, 7.60; Si, 10.40.

Polymerizations carried out on diallyldiphenylsilane with di-*t*-butyl peroxide gave similar polymers. A polymer prepared with 6% peroxide had a melting range of 115–140° and began to darken at 315°. An intrinsic viscosity of 0.04 was obtained for a sample of this polymer dissolved in benzene. The infrared spectrum of this polymer and the infrared spectrum of the Ziegler catalyst–initiated polymer are identical.

GAINESVILLE, FLA.

(12) Microanalyses were performed by Spang Microanalytical Laboratory and Clark Microanalytical Laboratory.

(13) The light scattering measurements were performed with a Brice-Phoenix Universal Light Scattering Photometer by Mr. Carey Rushing.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC CO.]

Chlorinated Aromatic Silicates and Related Compounds

P. D. GEORGE AND ARTHUR E. NEWKIRK

Received February 17, 1960

Twelve chlorinated aromatic silicates were synthesized from phenols with either chlorosilanes or ethyl orthosilicate, and from sodium phenates and silicon tetrachloride. Phenol and di-*t*-butoxydiaminosilane formed diphenoxydi-*t*-butoxysilane. All the compounds were white solids or colorless liquids having a wide liquid range, and they all had a strong phenolic odor even when highly purified. The hydrolytic stability of the chlorinated aromatic silicates, even those in which all *ortho* positions were blocked, was no better than that of unchlorinated aromatic silicates. The intrinsic thermal stability of 2-chlorophenyl orthosilicate was about the same as that of cresyl silicate, but was decidedly inferior to cresyl silicate in the presence of metals at 400°.

Although aromatic orthosilicates have been known since 1885[1] and have recently been offered commercially,[2] little has been reported about chlorinated aromatic silicates.[3-5] We have synthesized a variety of chlorinated aromatic silicates, including some with both *ortho* positions blocked, with the thought that these compounds might have enhanced hydrolytic stability.

The compounds prepared are listed in Table I together with their physical properties, analyses and methods of synthesis. All the materials were white solids or colorless liquids having a wide liquid range, and they all had a strong phenolic odor even when highly purified.

We applied conventional methods of synthesis to the preparation of these compounds, *i.e.*, reaction of: A) phenols with chlorosilanes[1,6]; B) sodium phenates with silicon tetrachloride[7]; C) phenols with ethyl orthosilicate; and D) one phenol with an aminosilane. The application of these methods to the preparation of analogous compounds has recently been described.[3]

The method of synthesis involving the reaction of silicon tetrachloride with chlorophenols proved quite satisfactory with those having no more than one *ortho* substituent. With 2,4,6-trichlorophenol, no reaction occurred with boiling silicon tetrachloride. The sodium salts of both 2,4,6-trichlorophenol and pentachlorophenol reacted satisfactorily with silicon tetrachloride to give the corresponding orthosilicates. The acid-catalyzed reaction of phenols with ethyl orthosilicate gave both chlorophenoxysilanes and chlorophenoxyethoxysilanes, depending on the molar proportions of the reactants.

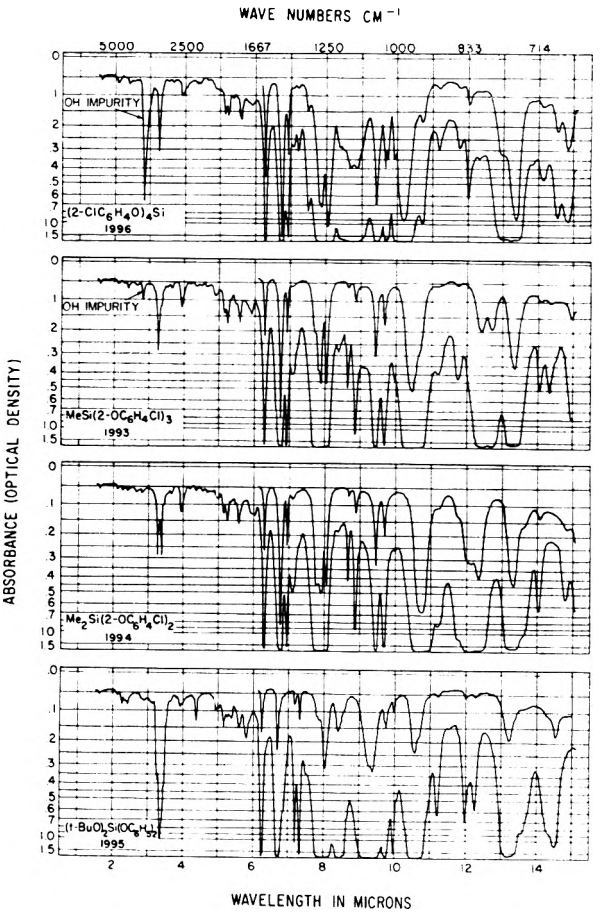


Fig. 1. Infrared spectra of representative compounds. Perkin Elmer Model 21 spectrometer with rock salt prism. Sample thickness: Upper curve a capillary layer; lower curve 0.030 mm.

The chlorinated aromatic silicates were no more resistant to hydrolysis than unsubstituted aromatic silicates. Extensive hydrolysis in boiling water occurred even with 2,4,6-trichlorophenyl orthosilicate, in which all *ortho* positions are blocked; the analogous borate appeared to be even more sensitive toward hydrolysis.[11] On the other hand, di-*t*-butoxydiphenoxysilane did exhibit improved hydrolytic stability; it was unaffected by boiling water,

(1) J. Hertkorn, *Ber.*, **18**, 1679 (1885).

(2) Notably by Monsanto Chemical Co., Oronite Chemical Co., Dow Corning Corp. and Kay-Fries Chemicals Inc. in the United States. Tonnage amounts are also said to be produced in Europe.

(3) J. L. Speier, Jr., *J. Am. Chem. Soc.*, **74**, 1003 (1952); U. S. Patent 2,611,778, September 23, 1952.

(4) R. Schwarz and W. Kuchen, *Ber.*, **86**, 1144 (1953).

(5) H. Jorg and J. Stetter, *J. fur Prakt. Chem.*, **117**, 305 (1927), have reported the synthesis of a number of bromophenoxy silicon compounds.

(6) L. H. Johnston, U. S. Patent 2,335,012, November 23, 1943.

(7) R. A. Thomson and F. S. Kipping, *J. Chem. Soc.*, 1176 (1929).

TABLE I

PROPERTIES OF AROMATIC SILICATES

Compound	Method	Yield, %	M.P.	B.P., 1 mm.	n_D^{20}	d^{20}	Analyses Calcd.	Analyses Found
$(2\text{-}ClC_6H_4O)_4Si$[a]	A	7[c]	−40[b]	287–290	1.5378	1.364[c]	R_D, 0.2447 Cl, 26.3	0.2467 25.9, 26.0
$(4\text{-}ClC_6H_4O)_4Si$[d]	A	76	74–75				Si, 5.21 Cl, 26.3	5.3, 5.4 26.0
$(2\text{-}ClC_6H_4O)_2(4\text{-}ClC_6H_4O)_2Si$[e]	A	89	−55[b,f]	280–293	1.5860	1.356	R_D, 0.2447	0.2475
$(2,4\text{-}Cl_2C_6H_3O)_4Si$	A[g]	59	198–199				Si, 4.16 Cl, 42.0	3.9, 4.2 40.1, 43.2
$(2,4,6\text{-}Cl_3C_6H_2O)_4Si$	B[h]	30	192–193	340–360			Si, 3.45 Cl, 52.4	3.6, 3.7 52.4, 52.4
$(Cl_5C_6O)_4Si$	B	30	285–286				Cl, 64.8	64.1, 60.2, 59.7[i]
$(2,4\text{-}Cl_2C_6H_3O)_2Si(OC_2H_5)_2$	C	23		[j]	1.5327		Cl, 31.8	31.0
$(2,4\text{-}Cl_2C_6H_3O)_3SiOC_2H_5$	C	11		273–275	1.5718		Cl, 37.8	36.5
$(2,4,6\text{-}Cl_3C_6H_2O)_2Si(OC_2H_5)_2$	C	26	68–69[k]	230–242			Si, 5.48 Cl, 41.6	5.4, 5.6 41.4, 41.5
$(2,4,6\text{-}Cl_3C_6H_2O)_3SiOC_2H_5$	C	24	81–82	288–293			Si, 4.22 Cl, 48.1	4.1 47.0, 47.2
$(2\text{-}ClC_6H_4O)_2Si(CH_3)_2$	A	32	2	127[l]	1.5482	1.227	R_D, 0.2586 C and H, 53.7, 4.5 Cl, 22.6	0.2588 53.1, 4.6 22.2
$(2\text{-}ClC_6H_4O)_3SiCH_3$	A	42		183	1.5742	1.318	R_D, 0.2498 C and H, 53.6, 3.6 Cl, 25.0	0.2504 53.9, 3.4 24.3
$(C_6H_5O)_2Si(OCMe_3)_2$	D	77		160	1.4905	1.029	R_D, 0.2791 C and H, 66.6, 7.8	0.2812 66.9, 8.0

[a] η(100°F) 21.6 cstks.; η(210°F) 3.8 cstks. ASTM flash point 276°; fire point 312°. [b] ASTM pour point. [c] Coefficient of expansion (25° to 350°): 0.00085 ml./g./°. [d] ASTM flash point 280°; fire point 312°. The synthesis of this compound was recently reported in references (3) and (4). [e] Made by the reaction of an equimolar mixture of 2-chlorophenol and 4-chlorophenol with silicon tetrachloride. η(100°F) 20.2 cstks.; η(210°F) 3.6 cstks. ASTM flash point 276°; fire point 314°. Probably a mixture of various *o*- and *p*-chlorophenoxysilanes. [f] Another sample had ASTM pour point −30°. [g] Also prepared by Method C in 25% yield, m.p. and mixed m.p. 198°–199°. [h] 2,4,6-Trichlorophenol did not react with silicon tetrachloride at reflux temperature. Refluxing with ethyl orthosilicate gave 90% of the theoretical amount of alcohol, but no effort was made to isolate the product. [i] A test with alcoholic silver nitrate proved the absence of hydrolyzable chlorine. The presence of silicon was qualitatively demonstrated. [j] Boiling point 227° to 231° at 5 mm. [k] This product depressed the melting point of 2,4,6-trichlorophenol. [l] Boiling point 269° to 270° at 149 mm.

but was hydrolyzed by boiling 10% sulfuric acid. Thus, the presence of *t*-alkoxy groups enhanced the hydrolytic stability of the neighboring phenoxy groups, just as it has been reported to stabilize alkoxy groups.[8] It seems probable that *t*-alkoxy groups would similarly impart enhanced hydrolytic stability to neighboring chlorophenoxy groups.

The thermal stability of 2-chlorophenyl orthosilicate was evaluated both in the presence and absence of air and metals. This compound proved to be superior to cresyl silicate and methyl silicone oil at 250° in the presence of air, and it was comparable to cresyl silicate in being superior to methyl silicone oil at 350° in the absence of air. However, 2-chlorophenyl silicate proved to be decidedly inferior to cresyl silicate in the presence of common metals at 350° to 400° in the absence of air.

EXPERIMENTAL

Starting materials. The chlorophenols used in this investigation were commercial materials whose properties after purification was as follows: 2-chlorophenol, redistilled b.p. 80° at 28 mm., m.p. 7°, n_D^{20} 1.5590; 4-chlorophenol, m.p. 42°; 2,4-dichlorophenol, m.p. 45° from heptane; 2,4,6-trichlorophenol, m.p. 69° after steam distillation and recrystallization from heptane; pentachlorophenol, m.p. 188° after decolorizing and recrystallization from benzene-heptane. Silicon tetrachloride from Stauffer Chemical Co. and ethyl orthosilicate from Carbide and Carbon Chemicals Corp. were used as received. The methylchlorosilanes were supplied by the Silicone Products Department of the General Electric Company. Di-*t*-butoxydiaminosilane was obtained from the Minnesota Mining and Manufacturing Co.

Methods of synthesis. The following are illustrative of the four methods used.[9] Specific details related to the various phenoxysilanes and chlorophenoxysilanes may be found in Table I.

A. *Chlorosilanes with phenols.* The simple apparatus con-

(8) C. S. Miner, Jr., L. A. Bryan, R. P. Holysz, Jr., and G. W. Pedlow, Jr., *Ind. Eng. Chem.*, **39**, 1368 (1947).

(9) Direct chlorination of phenyl orthosilicate also appeared feasible, but we did not use this method extensively because of the isomeric mixtures likely to be obtained. Bubbling chlorine through a carbon tetrachloride solution of phenyl orthosilicate for 10 hr. in the presence of ferric chloride gave dichloro derivatives, b.p. 230° to 237° at 1 mm., as a major product. *Anal.* Calcd. for $C_{24}H_{18}O_4Cl_2Si$: Cl, 15.1. Found: Cl, 14.3.

sisted of a round bottom flask fitted with a dropping funnel thermometer well, and tap-water cooled reflux condenser surmounted by a Dry Ice–trichloroethylene cold finger, from which an exit line led through a drying tube and a water scrubber to the atmosphere. The cold finger was necessary to prevent serious loss of volatile chlorosilane starting materials by entrainment with evolved hydrogen chloride.

The chlorosilanes were added gradually to the stoichiometric amount of molten phenol, and the temperature of the reaction mixture was raised to 200° to 300° over a period of 7 to 20 hr. as permitted by the rate of refluxing and hydrogen chloride evolution. The shorter reaction times were realized in syntheses involving *p*-chlorophenol. The presence of a single *ortho*-chloro substituent retarded the reaction considerably, and 2,4,6-trichlorophenol did not react with boiling silicon tetrachloride.

The reactions of phenols with chlorosilanes were considered complete when the evolution of hydrogen chloride ceased and the theoretical weight loss had been attained. Completeness of reaction was found to be essential; otherwise the products were contaminated with difficultly removable by-products containing hydrolyzable chlorine. Use of excess phenol would probably be of value in this connection. While we used stoichiometric amounts of reactants, an excess of phenol actually prevailed, because of slight losses of chlorosilane by entrainment with hydrogen chloride. Too large an excess, particularly of the more volatile phenols, might unduly restrict the final reaction temperature and thus lead to incomplete reaction.

Distillation and/or recrystallization from hexane or chlorobenzene produced, on a 0.5- to 5.0-kg. scale, yields of 60 to 90% of purified product.

B. *Silicon tetrachloride with sodium phenates.* The sodium phenate was prepared by portion-wise addition of the theoretical amount of freshly cut sodium to a stirred, refluxing solution of the phenol in xylene. The preparation usually required about 0.5 hr. per mole, and 500 ml. to 1000 ml. of xylene was used per 100 g. of phenol.

The theoretical amount of silicon tetrachloride was then added to the cold, stirred sodium phenate suspension, and the reaction mixture was refluxed for 6 hr. Negative halogen tests on the reflux indicated the absence of unreacted silicon tetrachloride.

The precipitated salt was removed by filtration, and xylene was removed by distillation. Vacuum distillation and/or recrystallization from heptane or chlorobenzene produced, on a 100-g. scale, yields of 30% of purified product.

C. *Ethyl orthosilicate with phenols.* The acid-catalyzed reaction of phenols with ethyl orthosilicate gave both tetra(chlorophenoxy)silanes and chlorophenoxyethoxysilanes, depending upon the molar ratio of reactants. The reactions were carried out on a 200-g. scale by heating a mixture of ethyl orthosilicate, chlorophenol, and a few tenths of a gram of *p*-toluenesulfonic acid. At pot temperatures of 170–320°, the theoretical amount of ethanol was removed by distillation over a period of 10 hr. The crude products were purified by distillation and/or recrystallization from heptane.[10]

D. *Di-t-butoxydiphenoxysilane* was prepared from 110 g., (0.53 mole) of di-*t*-butoxydiaminosilane refluxed for 4 hr. with 99.6 g., 1.06 moles, of phenol. The theoretical weight of ammonia was evolved. Distillation gave 1.46 g. (0.41 mole) 77% yield of di-*t*-butoxydiphenoxysilane, b.p. 158–165° at 1 mm., n_D^{20} 1.4899. A yellow color and amine odor were removed by a quick wash with 1*N* hydrochloric acid, drying over anhydrous potassium carbonate, and redistillation. The final product was a colorless liquid having a mild phenolic odor, b.p. 160° at 1 mm., n_D^{20} 1.4905, d^{20} 1.029.

Hydrolysis. The chlorinated aromatic silicates showed hydrolytic stability comparable to that of unsubstituted aromatic silicates.[11] Two gram samples of diethoxydi(2,4,6-trichlorophenoxy)silane and ethoxytri(2,4,6-trichlorophenoxy)silane were boiled with distilled water for 2 hr. and steam distilled. The steam distillate contained appreciable amounts of 2,4,6-trichlorophenol, m.p. and mixed m.p. 68–69°. The residue from the steam distillation contained silica, a white solid which was solvent-insoluble and did not fuse on being heated to 340°. Roughly the same sensitivity toward boiling water was observed with tetra(2,4,6-trichlorophenoxy)silane and tetra(pentachlorophenoxy)silane.

On the other hand, di-*t*-butoxydiphenoxysilane survived boiling with water, but was extensively hydrolyzed by boiling 10% sulfuric acid. The extent of hydrolysis was following by testing the steam distillate with bromine water, which is reactive toward phenol but was relatively inert toward *t*-butyl alcohol and di-*t*-butoxydiphenoxysilane. When the latter was boiled with water for half an hour, the steam distillate showed no reaction with bromine water. However, upon boiling witih 10% sulfuric acid, the steam distillate gave a strong test for phenol, and a gelatinous precipitate appeared in the reaction flask.

Thermal behavior of 2-chlorophenyl orthosilicate. This compound was selected for comparison with cresyl silicate. Tests were carried out at 250° to 400° both on the presence and absence of air and metals.

The first experiments were carried out by heating the substances in open Pyrex Petri dishes in the same oven. The results were as follows:

	12 Hr. at 250°		24 Hr. at 250°	
Compound	Weight Loss, %[a]	Appearance	Weight Loss, %[a]	Appearance
Cresyl silicate[b]	48	Black, skinned, gummy	66	Black, brittle, solid
2-Chlorophenyl silicate	30	No change	52	Amber liquid

[a] These losses probably included a major proportion of simple volatilization loss. [b] Both a commercial sample of cresyl silicate and a sample prepared from it by careful fractional distillation gave the same results.

Tests were then carried out at 350° by heating under dry nitrogen, in Pyrex flasks fitted with reflux condensers. After 10 hr., both commercial cresyl silicate and 2-chlorophenyl silicate showed only a slight darkening. In neither case were solid or gummy by-products formed. The heating of 2-chlorophenyl silicate at 350° was continued. After 45 hr., there was no weight loss or viscosity increase; after 114 hr. (which accidentally included 0.5 hr. at 450°), there was a 1.5% weight loss and a 2-centistokes increase in viscosity.

(10) E. Larsson, *Ber.*, **86**, 1382 (1953), has reported an analogous synthesis involving the preparation of dimethyldiphenoxysilane in 69% yield by heating dimethyldiethoxysilane with excess phenol and a small amount of sodium.

(11) Similar, if not more pronounced, hydrolytic instability was found in chlorinated aromatic borates. These were prepared by refluxing the appropriate chlorophenols with ethyl borate, which produced the theoretical amount of ethanol and substances presumed to be tri(2-chlorophenoxy)borane, b.p. 236–258° at 8 mm., and tri(2,4,6-trichlorophenoxy)borane, b.p. 267–271° at 10 mm. Both compounds were difficult to purify, presumably because of sensitivity to atmospheric moisture and traces of water. We were unable to obtain them pure in crystalline form in spite of efforts to exclude moisture. The synthesis of tri(2-chlorophenoxy)borane, b.p. 242° at 6 mm., m.p. 47–49°, has been reported; it was described as being very susceptible to hydrolysis by L. H. Thomas, *J. Chem. Soc.*, 820 (1946).

At the end of this treatment, the 2-chlorophenyl silicate was blackened but contained no sludge.

Thermal stability in the presence of metals was investigated by heating with metal strips under dry nitrogen in Pyrex flasks fitted with reflux condensers. Commercial cresyl silicate survived heating with black iron for 140 hr. at 350° substantially unchanged. Under the same conditions, 2-chlorophenyl silicate underwent a fivefold viscosity increase with black iron and a tenfold viscosity increase with cold-rolled steel and stainless steel. In another test at 400° for 50 hr. in the presence of cold-rolled steel, 2-chlorophenyl silicate decomposed to a black, sticky, solid mass while commercial cresyl silicate survived substantially unaffected.

Acknowledgment. We are grateful to the following for experimental assistance: A. D. Berry, G. Billuris, P. S. Flint, D. L. Harms, F. C. Kenyon, Jr., J. R. Ladd, A. J. Quant, J. T. Rossello, R. W. Trevithick, and M. Wasserman. Many of the analytical values and physical properties were obtained from the Materials and Processes Laboratory of the Large Steam Turbine and Generator Department and from the Analytical Chemistry Unit of our Laboratory.

SCHENECTADY, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Preparation of Polymeric Condensation Products Containing Functional Thiol Side Chains. Polyamides[1]

C. G. OVERBERGER AND HERBERT ASCHKENASY[2]

Received April 25, 1960

The purpose of this work was to develop a general method of synthesis for a polyamide containing free sulfhydryl groups. Polyamides from hexamethylene diamine and the acid chlorides of α,α'-dibenzylthioadipic acid, the cyclic disulfide of α,α'-dimercaptoadipic acid, and α,α'-dicarbobenzoxythioadipic acid were prepared by the interfacial polymerization technique. Successful preparation of the polyamide with free sulfhydryl groups was achieved by quantitative removal of the carbobenzoxy group from the polyamide from hexamethylene diamine and α,α'-dicarbobenzoxythioadipic acid.

The importance of the sulfhydryl compounds in biological systems is well known[3] In addition, their interest as reversible mercaptide-forming reagents as well as their recent applications as radioactive prophylactics has made synthesis of sulfhydryl-containing compounds of practical significance. We have reported[4] the synthesis of a polyurethan containing the sulfhydryl function in a structure of known constitution and environment and in this publication will describe the preparation of a sulfhydryl-containing polyamide.

The synthesis of polyamides requires, in general, exact molecular equivalence of reactants as well as very stringent reaction conditions, temperatures of 250° and above not being uncommon. The two synthetic approaches described, sought in the first instance to use a convenient method for obtaining the desired molecular equivalence, *e.g.*, intermediate salt formation, and in the second to employ a recently published[5] procedure for making high molecular weight polyamides under very mild reaction conditions, *i.e.*, interfacial polycondensation.

Benzylthiomethylsuccinic acid[4] would be expected to form a polymeric salt with a diamine suitable for subsequent polymerization by thermal dehydration. Only oils were obtained with hexamethylene diamine however, and with ethylene diamine a salt containing two acid molecules to one molecule of diamine was obtained. The unavailability of the second carboxyl group for salt formation is at present not understood.

We prepared *meso*-α,α'-dibenzylthioadipic acid by alkali-catalyzed displacement by benzyl mercaptan on *meso*-α,α'-dibromoadipic acid prepared by the method of Zanden[6] and found that it did not give a satisfactorily recrystallizable salt with ethylene diamine. A melting point range of 25° was observed even after five recrystallizations, as well as a small residue of the acid on addition of water.

The use of the *cis* cyclic disulfide of α,α'-dimercaptoadipic acid[7] prepared by Fredga, again did not yield a satisfactorily recrystallizable salt with hexamethylene diamine. Attempted thermal polymerization without recrystallization yielded an insoluble, infusible product. Cross-linking by a base catalyzed rupture of the disulfide bond[8] and/or

(1) This is the 20th in a series of papers on new monomers and polymers. For the previous paper in this series, see C. G. Overberger and Herbert Aschkenasy, *J. Am. Chem. Soc.*, in press.

(2) This paper comprises part of the thesis presented by Herbert Aschkenasy in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the graduate school of the Polytechnic Institute of Brooklyn.

(3) E. S. G. Barron, *Advances in Enzymology*, Vol. XI, Interscience Publishers, Inc., N.Y., 1951, pp. 219 *et seq.*

(4) C. G. Overberger and H. Aschkenasy, *J. Am. Chem. Soc.*, in press.

(5) P. W. Morgan and S. L. Kwolek, *J. Chem. Educ.*, **36**, 182 (1959) and previous references.

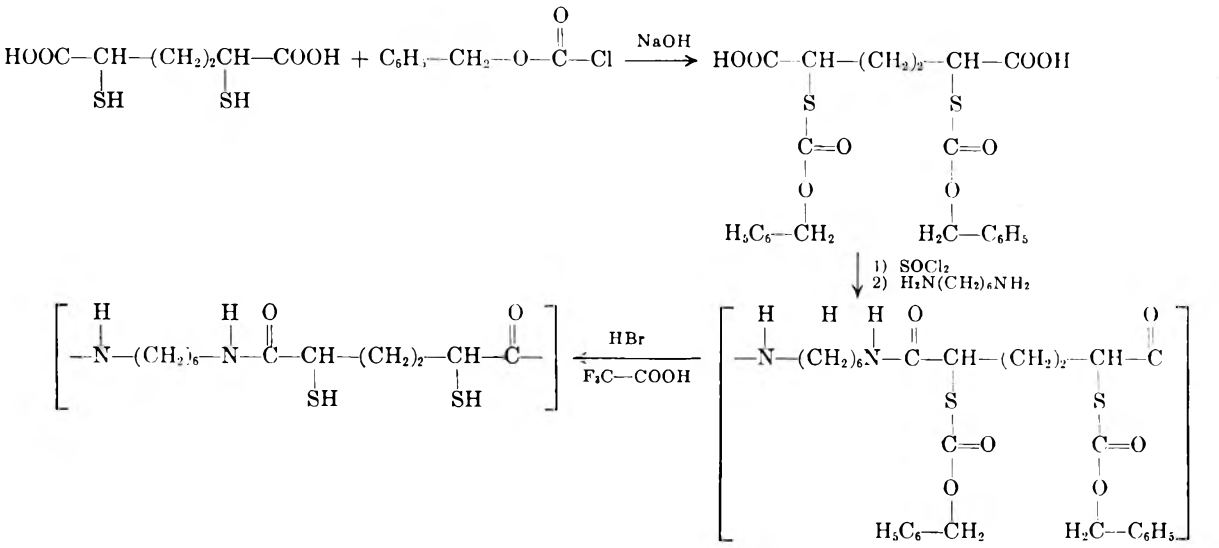
(6) J. M. Zanden, *Rec. trav. chim.*, **63**, 113 (1944).

(7) A. Fredga, *Ber.*, **71B**, 289 (1938).

(8) N. A. Rosenthal and G. Oster, *J. Soc. Cosmetic Chemists*, **5**, 286 (1954).

a disulfide interchange mechanism analogous to the thermal polymerization of lipoic acid[9] is possible here.

Interfacial polycondensation was then considered. This method depended only on the ability to prepare the necessary diacid chlorides. Neither benzylthiomethylsuccinic acid nor carbobenzoxymercaptosuccinic acid gave the desired compounds even by methods yielding the acid halides of related succinic acid derivatives.[10] The corresponding



anhydrides were predominantly obtained possibly by sulfur participation in the transition state. Standard methods did, however, convert α,α'-dibenzylthioadipic acid, the *cis* cyclic disulfide of α,α'-dimercaptoadipic acid, and a new acid, α,α'-dicarbobenzoxythioadipic acid to the corresponding acid chlorides. The acid halides were readily converted to their polyamides with hexamethylene diamine, by both a manually stirred and a film-forming interface method.

Neither the polyamide derived from the cyclic disulfide nor the α,α'-dibenzylthioadipic acid could be reductively cleaved to the desired free sulfhydryl compounds, presumably because of their insolubility in the reaction media. The polyamide derived from the α,α'-dicarbobenzoxythioadipic acid did, however, when treated with glacial acetic acid saturated with hydrogen bromide, yield an insoluble material which showed an absence of phenyl absorption in the infrared in what appeared to be a heterogeneous cleavage. A more rapid cleavage where subsequent oxidative coupling of the free thiol residues could be minimized was necessary and trifluoroacetic acid gave the desired results. Analysis indicated that up to 30% decarbobenzoxylation occurred in the trifluoroacetic acid alone on standing at room temperature overnight. When trifluoroacetic acid saturated with hydrogen bromide was employed the reaction was completed in half an hour yielding a base-soluble polyamide. The product was fusible and gave a weak but definitive absorption peak at 2550 cm.$^{-1}$, characteristic of the sulfhydryl function. Elemental analysis showed that 100% decarbobenzoxylation had been effected, a remarkable result for a polymeric reaction.

EXPERIMENTAL[11]

α,α'-Dibenzylthioadipic acid. A general method of Zanden[6], α,α'-dibromoadipic acid was used. To a stirred solution of 15.4 g. (0.05 mole) of the α,α'-dibromoadipic acid in 100 ml. of 1*N* aqueous sodium carbonate, was added dropwise a solution of 12.6 g. (0.1 mole) of benzyl mercaptan, and 5.6 g. (0.1 mole) of potassium hydroxide in 100 ml. of a 50% aqueous ethanol solution. The reaction mixture was warmed on a steam bath for 2 hr. and allowed to stir for 42 additional hours at room temperature. Addition of concd. hydrochloric acid to *p*H 1 yielded a white precipitate, which was recrystallized from a water-ethanol solution, 3.0 g. (20%), m.p. 161–163°. Infrared analysis gave a normal carboxylic acid and phenyl absorption.

This compound had previously been prepared by Fredga[7] by reaction of benzylbromide with α,α'-dimercaptoadipic acid in unspecified yield [m.p. 169° (*meso*); m.p. 130° (*dl* racemate)].

Anal. Calcd. for $C_{20}H_{22}O_4S_2$: C, 61.51; H, 5.68; S, 16.42; neut. equiv. 195. Found: C, 61.39; H, 5.99; S, 16.42; neut. equiv. 197.

Carbobenzoxymercaptosuccinic acid. A solution of 15 g. (0.1 mole) of recrystallized commercial grade mercaptosuccinic acid in 150 ml. of water containing 16 g. (0.4 mole) of sodium hydroxide was treated dropwise with 25 g. (0.15 mole) of carbobenzoxychloride. The solution was stirred at room temperature for 36 hr., extracted with two 50-ml. portions of ether, and acidified with concd. hydrochloric acid to *p*H 1. The resulting oil was extracted with two 100-ml. portions of ether, dried over anhydrous magnesium sulfate, and the ether evaporated. The residual yellow oil was cooled and macerated until it solidified. The solid was recrystallized from

(9) R. C. Thomas and L. J. Reed, *J. Am. Chem. Soc.*, **78**, 6148 (1956).

(10) J. Cason and R. D. Smith, *J. Org. Chem.*, **18**, 1201 (1953); W. Petri, *Ber.*, **14**, 1635 (1881); *Org. Synthesis*, **33**, 41 (1953).

(11) All melting points are uncorrected. Polymer melting points were determined on a Fisher-Johns block, all others by the capillary method.

boiling toluene yielding a white solid, 14 g. (56%), m.p. 147–148°. Infrared analysis showed the acid carbonyl at 1715 cm.$^{-1}$ and the carbobenzoxy carbonyl at 1710 cm.$^{-1}$ as well as phenyl absorption.

Anal. Calcd. for $C_{12}H_{12}O_6S$: C, 50.70; H, 4.26; S, 11.27; neut. equiv. 142. Found: C, 50.73; H, 4.39; S, 11.26; neut. equiv. 143.

Carbobenzoxymercaptosuccinic anhydride. Treatment of 2 g. (0.007 mole) of carbobenzoxymercaptosuccinic acid with 10 ml. of purified thionyl chloride at 60° until solution occurred gave a yellow solution from which excess thionyl chloride was removed under reduced pressure. The residue was solidified by cooling and recrystallized from hexane-benzene yielding a white solid, 1.2 g. (66%), m.p. 89–90.5°. Infrared analysis showed anhydride absorption at 1800 cm.$^{-1}$ and 1885 cm.$^{-1}$, carbobenzoxy carbonyl at 1710 cm.$^{-1}$, and phenyl absorption.

Anal. Calcd. for $C_{12}H_{10}O_5S$: C, 54.13; H, 3.78; S, 12.04. Found: C, 54.16; H, 3.98; S, 12.27.

α,α′-Dibenzylthioadipoyl chloride. A large excess of commercial grade thionyl chloride, 30 ml., was added in one portion to 2.6 g. (0.0066 mole) of α,α′-dibenzylthioadipic acid. Gentle warming at 50–60° for 0.5 hr. produced a vigorous evolution of hydrogen chloride and a yellow solution. The solution was allowed to stand at room temperature for 24 hr. and excess thionyl chloride removed under reduced pressure, after which 50 ml. of benzene was added and then removed under reduced pressure. The resulting solid, which could be converted to the starting acid with water, was recrystallized from petroleum ether (b.p. 30–60°), 2.2 g. (77%), m.p. 84.8–86.2°. Infrared analysis showed acid chloride carbonyl at 1778 cm.$^{-1}$, carbobenzoxy carbonyl at 1710 cm.$^{-1}$, and phenyl absorption.

Anal. Calcd. for $C_{20}H_{20}Cl_2O_2S_2$: C, 56.20; H, 4.72; Cl, 16.59; S, 15.00. Found: C, 56.25; H, 4.77; Cl, 16.70; S, 15.02.

α,α′-Dicarbobenzoxythioadipic acid. According to the method of Schotte,[12] α,α′-dimercaptoadipic acid was prepared. A solution of 6.4 g. (0.03 mole) of this acid in 200 ml. of water containing 8.4 g. (0.15 mole) of potassium hydroxide was treated with 15.3 g. (0.08 mole) of carbobenzoxy chloride. The mixture was cooled in an ice bath and stirred for 15 hr. The basic solution was extracted twice with 100-ml. portions of ether and acidified to *p*H 1 with concd. hydrochloric acid. The oil which precipitated could be solidified by cooling. Recrystallization from an acetone-benzene solution gave a white crystalline solid, 5.8 g. (41%), m.p. 180–182°. Infrared analysis showed acid carbonyl at 1715 cm.$^{-1}$, carbobenzoxy carbonyl at 1705 cm.$^{-1}$, and phenyl absorption.

Anal. Calcd. for $C_{22}H_{22}O_8S_2$: C, 55.22; H, 4.63; S, 13.40; neut. equiv. 239. Found: C, 55.06; H, 4.82; S, 13.20; neut. equiv. 236.

α,α′-Dicarbobenzoxythioadipoyl chloride. The diacid chloride was prepared by treatment of 4.8 g. (0.01 mole) of the corresponding acid with an excess (7:1 by weight) of commercial grade thionyl chloride. The mixture was gently refluxed until solution took place (about 0.5 hr.), cooled, and thionyl chloride removed under reduced pressure. The residual oil was dissolved in methylene chloride, filtered, and the methylene chloride evaporated. The oily residue was solidified by cooling and macerating. The solid was dried *in vacuo* for 4 hr. giving 4.9 g. (95%) of crude product. Infrared examination showed a peak at 1789 cm.$^{-1}$ corresponding to an acid halide carbonyl and at 1710 cm.$^{-1}$ corresponding to the carbonyl of the carbobenzoxy group. The material was not satisfactorily recrystallizable, m.p. 77–87°, but was identified by conversion to the diamide.

A mixture of 1 g. (0.0021 mole) of the acid in 5 ml. of thionyl chloride was refluxed until solution took place, cooled to room temperature, and added dropwise to 20 ml. of concd. ammonia cooled in an ice bath. The resulting solid material was filtered and recrystallized from dioxane-water, 0.76 g. (76%), m.p. 215–217°. Infrared analysis gave a normal unsubstituted amide curve with retention of the carbobenzoxy carbonyl at 1710 cm.$^{-1}$ and phenyl absorption.

Anal. Calcd. for $C_{22}H_{24}N_2O_6S_2$: C, 55.44; H, 5.08; N, 5.88; S, 13.46. Found: C, 55.60; H, 5.26; N, 6.01; S, 13.17.

Diacid chloride of cyclic disulfide from α,α′-dimercaptoadipic acid. The corresponding acid may be prepared by oxidation of the corresponding dimercapto acid with iodine–potassium iodide solution or 10% hydrogen peroxide, giving 63–74% of product, m.p. 196–198° (virtually quantitative, 199°).[7]

A mixture of 4.2 g. (0.02 mole) of the acid and an excess of commercial grade thionyl chloride (7:1 by weight) was refluxed until solution occurred (5–6 hr.), cooled, and excess thionyl chloride removed under reduced pressure. The oily residue was dissolved in methylene chloride, filtered, and the solvent evaporated. The residual oil was solidified by cooling and macerating and was dried *in vacuo* for 4 hr., giving 3.7 g. (75%) of crude material, m.p. 62–69°. The material could not be recrystallized satisfactorily. Infrared examination showed strong absorption at 1778 cm.$^{-1}$ indicating acid chloride carbonyl, and the material could be converted with water to a compound identical with that of the starting acid as shown by a mixed melting point determination. Attempts to form derivatives of the acid chloride *via* amide, anilide, and toluide formation did not give satisfactorily recrystallizable solids.

Polyamides. The compounds to be described were prepared by the technique of interfacial polymerization.[5] The two methods used were removal of the product as a continuous film from the interface, and manual or automatic stirring of the reaction mixture followed by isolation of the product by filtration.

A. Polymer from hexamethylene diamine and α,α′-dibenzylthioadipoyl chloride. 1. *Stirring method.* A solution of 4.27 g. (0.01 mole) of α,α′-dibenzylthioadipoyl chloride in 75 ml. of chloroform was overlaid with 1.85 g. (0.016 mole) of hexamethylene diamine in 75 ml. of water containing 0.8 g. (0.01 mole) of sodium hydroxide. The mixture was stirred for 1 hr. and the product isolated by filtration. The product was dissolved in a small volume of dimethylformamide and precipitated by dropwise addition to a large excess of benzene. The resulting white solid was filtered and dried over phosphorus pentoxide, m.p. 148–150°, $[\eta]$, 0.32 determined in dimethylformamide at 29.8°.

Anal. Calcd. for $C_{26}H_{34}N_2O_3S_2$: C, 66.34; H, 7.28; N, 5.95; S, 13.62. Found: C, 66.48; H, 7.43; N, 5.82; S, 13.57.

2. *Continuous film method.* A solution of 4.27 g. (0.01 mole) of the acid chloride in 75 ml. of purified carbon tetrachloride was carefully overlaid with a solution containing 7.54 g. (0.065 mole) of hexamethylene diamine and 0.8 g. (0.02 mole) of sodium hydroxide in 75 ml. of water. The film which formed immediately at the interface was separated from the walls of the beaker and withdrawn as a continuous filament. The product was washed with aqueous ethanol and with benzene and dried *in vacuo*. The resulting yellow tinged solid did not dissolve or swell in a variety of solvents and was infusible. It gave an infrared spectrum virtually identical with that of the previously described sample.

B. Polyamide from acid chloride of cyclic disulfide. 1. *Stirring method.* A solution of 2.45 g. (0.01 mole) of the crude cyclic acid chloride previously described was dissolved in 50 ml. of chloroform and overlaid with a solution containing 1.85 g. (0.016 mole) of hexamethylene diamine and 0.8 g. (0.02 mole) of sodium hydroxide in 50 ml. of water. A voluminous solid formed rapidly and after a few minutes of stirring was isolated by filtration. This material was totally insoluble in a variety of solvents and was infusible. When washed with benzene and dimethylsulfoxide and dried, the product gave an infrared spectrum consistent with the expected structure, but an elemental analysis which was not satisfactory, having low carbon and sulfur.

(12) L. Schotte, *Arkiv Kemi*, 9, 377 (1956).

2. *Continuous film method.* A solution of 2.45 g. (0.01 mole) of the acid chloride in 50 ml. of purified carbon tetrachloride was carefully overlaid with a solution of 7.54 g. (0.065 mole) of hexamethylene diamine containing 0.8 g. (0.02 mole) of sodium hydroxide in 50 ml. of water. The film which formed immediately was separated from the walls of the beaker and withdrawn continuously until the reaction was completed which generally coincided with the disappearance of the organic layer. This material was again insoluble and infusible. When washed with aqueous ethanol and benzene and thoroughly dried *in vacuo*, the resulting yellow solid gave an infrared spectrum consistent with the expected structure but an elemental analysis which was not satisfactory, having low carbon and sulfur.

3. *Solution method.* A solution of 2.45 g. (0.01 mole) of the acid chloride in 50 ml. of purified dioxane was rapidly mixed with a solution containing 1.16 g. (0.01 mole) of hexamethylene diamine and 1.12 g. (0.02 mole) of potassium hydroxide in 50 ml. of dioxane. A yellow solid formed almost immediately in a somewhat exothermic reaction. The product was isolated by filtration but proved to be totally insoluble in a variety of solvents and infusible.

4. *Salt formation method. (non-interfacial procedure).* A sample of the acid 131.7 mg. (0.64 mole) was dissolved in anhydrous tetrahydrofuran. A solution of hexamethylene diamine dissolved in tetrahydrofuran was added dropwise until no further precipitation occurred. The salt was filtered and dried *in vacuo* to constant weight, yielding a white solid which was completely water soluble, 212 mg. (102%), m.p. 188–194°. The material could not be recrystallized, however, from a variety of solvents. The crude material was heated at 200–205°, 1 mm., for 1 hr. The product was a somewhat yellowish solid which proved to be insoluble and infusible.

C. Polymer from hexamethylene diamine and α,α'-dicarbobenzoxythioadipoyl chloride. 1. *Stirring method.* A solution of 2.74 g. (0.0055 mole) of α,α'-dicarbobenzoxythioadipoyl chloride in 50 ml. of methylene chloride (chloroform gave a product of the same physical properties) was poured into a cold solution containing 1.6 g. (0.013 mole) of hexamethylene diamine and 0.67 g. (0.011 mole) of potassium hydroxide in 50 ml. of water. The reaction mixture was stirred for 6 hr. and the product isolated by filtration. The crude material could be separated into two fractions by extraction with dimethylformamide or trifluoroacetic acid. The soluble fraction isolated from the trifluoroacetic acid extract in no case exceeded 25% of total solids, m.p. 118–123°, $[\eta]$, 0.43 determined in dimethylformamide at 29.8°.

Anal. Calcd. for $C_{28}H_{34}N_2O_6S_2$: C, 60.19; H, 6.13; N, 5.02; S, 11.48. Found: C, 56.80; H, 7.04; N, 6.23; S, 11.48.

The dimethylformamide-insoluble fraction could not be dissolved with a variety of solvents and was also infusible. Infrared analysis gave virtually identical spectra for both the soluble and insoluble fractions, showing normal monosubstituted amide links, as well as phenyl and carbobenzoxy carbonyl absorption.

Anal. Calcd. for $C_{28}H_{34}N_2O_6S_2$: C, 60.19; H, 6.13; N, 5.02; S, 11.48. Found: C, 58.87; H, 6.88; N, 7.77; S, 11.74; nonalkaline ash, 1.39.

2. *Continuous film method.* A solution of 3.57 g. (0.007 mole) of the acid chloride in 50 ml. of purified carbon tetrachloride was carefully overlaid with a solution of 5.20 g. (0.045 mole) of hexamethylene diamine containing 0.56 g. (0.014 mole) of sodium hydroxide in 50 ml. of water. The film which formed almost immediately at the interface was separated from the walls of the beaker and pulled from the reaction mixture. The product was washed repeatedly with portions of aqueous ethanol and benzene, and dried *in vacuo*. The resulting light yellow solid could be separated into two fractions with hot dimethylformamide. The soluble fraction was reprecipitated by adding the dimethylformamide solution, dropwise, to a large excess of water giving 0.7 g. (16.6%) of material, m.p. 125–130°, $\eta_{inh.}$ 0.5 determined in dimethylformamide at 29.8° and a concentration of 5.8 mg./ml. The inherent viscosity showed a slight rise on dilution. The insoluble fraction which could not be dissolved in a variety of solvents was also infusible, but had the correct analysis. Infrared analysis gave a normal amide curve and was very similar to that given by the soluble fraction.

Anal. Calcd. for $C_{28}H_{34}N_2O_6S_2$: C, 60.19; H, 6.13; N, 5.02; S, 11.48. Found: C, 60.42; H, 6.44; N, 5.14; S, 11.43.

Decarbobenzoxylation of polyamide. A 1-g. sample of polyhexamethylene α,α'-dicarbobenzoxy adipamide obtained by the manual stirring method was finely subdivided in a mortar and pestle. The material containing both the soluble and insoluble fractions was then treated with 50 ml. of trifluoroacetic acid, which had been saturated with hydrogen bromide. The polymer, partly dissolved and partly dispersed in this solvent, was stirred by means of a magnetic stirrer at room temperature until the material appeared to agglomerate into large particles of crepe-rubber appearance and jelly-like consistency (in about 0.5 hr.). The polymer was isolated by filtration yielding a yellow solid, m.p. 183–201°.

The polymer was soluble in 10% aqueous sodium hydroxide and gave a strongly positive nitroprusside test for free mercaptan. Infrared analysis showed the presence of a weak sulfhydryl absorption at 2550 cm.$^{-1}$ and retention of the amide link. Elemental analysis indicated 100% decarbobenzoxylation.

Anal. Calcd. for $C_{12}H_{22}N_2O_2S_2$: C, 49.62; H, 7.63; N, 9.65; S, 22.08. Found: C, 49.84; H, 7.21; N, 9.45; S, 22.42.

Acknowledgment. We wish to acknowledge gratefully the support of this work by a grant from the Charles Pfizer Co. and the laboratory assistance of Martin Elsbach and Thomas Reilly.

BROOKLYN 1, N.Y.

[CONTRIBUTION FROM THE LEWIS RESEARCH CENTER, NATIONAL AERONAUTICS AND SPACE ADMINISTRATION]

Preparation and Properties of Some Trialkylboranes[1]

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Received December 2, 1959

Triethyl-, tri-*n*-propyl-, and tri-*n*-butylborane were prepared and fractionated under an inert atmosphere to prevent oxidation. Triethylborane and tri-*n*-propylborane were obtained in purities of 99.8 and 99.7 mole percent, respectively, while tri-*n*-butylborane underwent thermal decomposition during distillation. The following physical and thermodynamic properties of triethylborane and tri-*n*-propylborane were determined: freezing point, boiling point, refractive index, density, dielectric constant, and heat of combustion.

As part of an evaluation program of boron compounds as potential high-energy fuels, a survey was made of the properties of the trialkylboranes. It was noted that the literature offered values for only some of the properties of current interest[2-7] and that among these values there were occasional discrepancies. Since the trialkylboranes are extremely susceptible to air oxidation, it was felt that the discrepancies in the property values might well be due to the presence of small amounts of oxidation products in the material. With this in mind the preparation, purification, and measurement of several properties of triethyl-, tri-*n*-propyl-, and tri-*n*-butylborane were undertaken in an inert environment.

Triethyl- and tri-*n*-propylborane were prepared in purities of 99.8 and 99.7 mole percent, respectively. Tri-*n*-butylborane was not obtained in a pure form, since it readily decomposed during distillation.[8]

RESULTS AND DISCUSSION

Physical properties. Table I presents freezing points, boiling points, refractive indices, densities, and dielectric constants for triethyl- and tri-*n*-propylborane. The molar refractions were calculated by means of the Lorentz-Lorenz equation from the values for refractive index and density.

An examination of the values listed in Table I, when compared with the previous literature values (footnotes *a* to *h*), in several instances, shows discrepancies that cannot be explained in terms of experimental error. The probable cause of these discrepancies presents itself when the trends in the values are noted. The refractive index reported for tri-*n*-propylborane[7] is lower and the densities for triethylborane and tri-*n*-propylborane[5,7] are higher than the values obtained in this present investigation. When a trialkylborane is oxidized, the product is an alkyldialkoxyborane.[9] Although no refractive index and density data are available for these compounds where R = ethyl or propyl, there are data for the closely related trialkoxyboranes.[10] The trialkylboranes, when compared with the corresponding trialkoxyboranes, are found to have higher refractive indices (approx. 0.02 higher) and lower densities (approx. 0.15 g./ml. lower). The alkyldialkoxyboranes would be expected to have refractive index and density values between those of the trialkylboranes and the trialkoxyboranes. This contention holds for the case where R = butyl.[10] Therefore, it would be expected that contamination of the trialkylboranes with their oxidation products would tend to lower the refractive index and elevate the density values beyond those of the pure compound.

The above explanation was further substantiated by a crude experiment run on a sample of tri-*n*-propylborane. The sample was placed in a refractometer and then exposed to air. The refractive index was observed to decrease rapidly, over period of several seconds, as the sample oxidized.

Experimental values for the refractive index of triethylborane and the dielectric constant of triethyl- and tri-*n*-propylborane are reported here for the first time.

Thermodynamic properties. Heat of combustion. The values for the heats of combustion of triethyl- and tri-*n*-propylborane are listed in Table II. The uncertainty associated with the over-all raw heat-of-combustion determination was about 0.3%, and that associated with the estimation of unburned material and the corrections thereof was about 0.2%. The over-all uncertainty was therefore estimated to be 0.5%.

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TABLE I

PHYSICAL PROPERTIES OF TRIETHYLBORANE AND TRI-*n*-PROPYLBORANE

	F.P.	B.P.	Temp., *t*	Refractive index n_D^t	n_{Hg}^t	$n_{Hg,v.}^t$	Molar Refraction R_D	Density, d_4^t	Dielectric constant
$B(C_2H_5)_3$	−92.93[a]	95.0[b]	20	1.3971	1.3988	1.4060	34.46	0.6850[c]	1.974
			30	1.3920	1.3939	1.4013		0.6761[c]	1.962
$B(n\text{-}C_3H_7)_3$	−64.92[d]	159.6[e]	20	1.4143[f]	1.4164	1.4241	48.43[g]	0.7232[h]	2.026
			30	1.4099[f]	1.4119	1.4195		0.7158[h]	2.013

[a] Reported[3] m.p. −92.9°. [b] Reported[3] b.p. 95°. [c] Reported[3,5] d_4^{23} 0.6931 and d_4^{30} 0.6774, respectively. [d] Reported[6] m.p. −65.5°. [e] Reported[4,6] b.p. 156° and 164.5°, respectively. [f] Reported[4,7] $n_D^{22.5}$ 1.4135 and n_D^{20} 1.4090, respectively. [g] Reported[7] R_D 45.33. [h] Reported[4,7] $d_D^{24.7}$ 0.7204 and d_4^{20} 0.7639, respectively.

TABLE II

THERMODYNAMIC PROPERTIES, TRI-*n*-ALKYLBORANES

Compound, BR_3, R =	Heat of combustion, ΔH_c, kcal./mole	Heat of formation at 25°, kcal./mole: Liquid $\Delta H_{f(l)}$	Gas $\Delta H_{f(g)}$	Average bond energy, $\bar{D}$(B—R), kcal./mole
Methyl	−658.0[a]	−34.8	−30.1	88.1
Ethyl	−1096.9[b]	−51.4[b]	−42.6	86.0
n-Propyl	−1529.4	−74.4	−63.4	89.5
n-Butyl	−1965[c,d]	−94[d]	−80	92

[a] Footnote 11. [b] Calculated ΔH_c, −1101.5 from reported[15] value $\Delta H_{f(l)}$, −46.8. [c] Footnote 12. [d] Calculated ΔH_c, −1975.4 from reported[15] value $\Delta H_{f(l)}$, −83.9.

For purposes of comparison, the values of the heat of combustion, ΔH_c, for trimethylborane[11] and tri-*n*-butylborane[12] are also included. The average incremental contribution to the ΔH_c made by each CH_2 group is approximately 145.3 kcal./mole. As would be expected, this is about the same as the average CH_2 contribution (145.7 kcal./mole) in the normal paraffin series.[13]

Heat of formation and bond energy. The values listed in Table II for $\Delta H_f(l)$ were calculated for the reaction:

$$BR_3(l) + O_2(g) \longrightarrow B_2O_3\ (amorph) + CO_2(g) + H_2O(g)$$

The values for $CO_2(g)$ and $H_2O(g)$ were taken from NBS Circular 500[14] and for B_2O_3(amorph) from a report by Wagman *et al.*[15]

The values of $\Delta H_f(g)$ were calculated using the heats of vaporization of triethylborane[16] and tri-n-propylborane.[6]

The values for B—R average bond energy, $\bar{D}$(B—R), were calculated for the reaction:

$$BR_3(g) \longrightarrow B(g) + 3R(g)$$

The heat of formation of B(g) was from Searcy and Myers[17] and of R(g) was calculated from Stevenson's data.[18]

For comparison the $\Delta H_f(g)$, $\Delta H_f(l)$, and $\bar{D}$(B—R) for trimethylborane and tri-*n*-butylborane were calculated as above using the ΔH_c data of Long and Norrish[11] and Tannenbaum,[12] respectively. These values are listed in Table II.

EXPERIMENTAL

Materials. Ethyl, *n*-propyl, and *n*-butyl bromide were washed with water, dried over anhydrous sodium sulfate and distilled. The refractive indices of the purified bromides were n_D^{20} 1.4242, 1.4341, and 1.4399, respectively. Matheson boron trifluoride, 97% pure, was used directly from the cylinder. The ethyl ether was dried over calcium hydride. The butyl ether was percolated through a column packed with activated aluminum oxide and dried over calcium hydride.

Preparation. Tri-n-butyl and tri-n-propylborane. A modification of the procedure of Johnson, Snyder, and Van Campen[19] was used. The preparation of tri-*n*-butylborane is described to illustrate the procedure.

n-Butylmagnesium bromide was prepared in a 5-gal. stainless steel reactor by the addition of 20 moles of *n*-butyl bromide in 3 l. of ethyl ether to 20 moles of magnesium turnings in 2 l. of ethyl ether. The Grignard solution was stored in a 5-gal. tank under nitrogen until needed. An ether solution of boron trifluoride etherate was prepared by the slow addition, with stirring, of 6 moles of boron trifluoride to 2 l. of ethyl ether at 10°.

The apparatus for the preparation of tri-*n*-butylborane consisted of a 12-l. three-neck flask equipped with a stirrer, a large capacity stainless steel condenser, and a graduated

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(19) J. R. Johnson, H. R. Snyder, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.* **60**, 115 (1938).

dropping funnel. The entire apparatus was enclosed in a dry box under a nitrogen atmosphere.

Three liters of Grigard solution were siphoned into the 12-l. flask from the storage tank. Then boron trifluoride etherate solution was added with stirring at such a rate (about 250 ml./hr.) as to promote vigorous refluxing. After approximately 650 ml. of the boron trifluoride etherate solution had been added, the reaction mixture separated quite suddenly into two layers, the bottom layer apparently consisted of Grignard solution and magnesium salts. This layer, which was black with white saltlike solid suspended throughout it, reacted vigorously with water, evolving gas. The clear pale yellow top layer showed no reaction with water and was apparently an ether solution of tri-*n*-butylborane. This top layer was siphoned into a large separatory funnel through a tube having a sintered-glass disk fused on one end to act as a filter. When the entire top layer had been removed, another 3-l. portion of Grignard reagent was added to the reaction flask, and the entire procedure was repeated. A total of 8300 ml. of Grignard solution and 5.9 moles of boron trifluoride etherate was used. There was a slight excess of Grignard reagent remaining after the last of the boron trifluoride had reacted.

The top layers obtained from the above reaction were washed in the separatory funnel with a saturated aqueous solution of ammonium chloride and then with water. Finally the ether solution was transferred to a distillation flask, and the ether was removed by vacuum distillation. The liquid residue, which contained a small amount of salt, was filtered. The total weight of crude produce was 989 g.; the yield was 91% based on boron trifluoride.

Triethylborane. Ten moles of this compound were prepared in a 5-gal. reactor by the method of Krause and Nitsche.[4] Throughout the entire operation a positive pressure of helium was maintained in the reactor to exclude oxygen.

Purification. The crude reaction products were distilled through a 22-mm. by 6-ft. Podbielniak column. The entire distillation setup was enclosed in a dry box inerted with helium.

Triethylborane was distilled at atmospheric pressure, while tri-*n*-propylborane and tri-*n*-butylborane were distilled at pressures of 20 and 10 mm., respectively. Triethylborane and tri-*n*-propylborane were successfully distilled, but tri-*n*-butylborane decomposed during distillation. The decomposition products of tri-*n*-butylborane adulterated the distillate besides causing the column to flood continuously. Lowering the pot temperature about 20° by lowering the distillation pressure did not noticeably decrease the decomposition or the flooding. By rapidly distilling the tri-*n*-butylborane through an 18-in. glass-helix packed column, the amount of decomposition was reduced. However, the distillate was not considered to be sufficiently pure to warrant the measurement of its properties.

Physical properties. Samples of triethylborane and tri-*n*-propylborane of 99.8 and 99.7 mole % purity, respectively, were used to obtain values for the following physical properties.

Freezing point. The freezing points were determined by means of a solenoid-stirred freezing point apparatus charged with 10-ml. samples. The apparatus was loaded and sealed in a dry box inerted with helium; subsequent operations were conducted outside the box. The thermometric system consisted of a 25-ohm platinum resistance thermometer, a resistance bridge (Mueller type), and a highly sensitive galvanometer. The freezing point and the freezing point at zero impurity were obtained by analysis of the freezing curves.[20,21] These data, together with the values of the heat of fusion, were used to calculate the purity of the samples.[21] Duplicate determinations of the freezing point on a given sample differed by not more than 0.002°.

Boiling point. The boiling points were determined in an ebulliometer[22] equipped with a platinum resistance thermometer. The measurements were made in a helium atmosphere with an estimated accuracy of ±0.1°.

Refractive index. The refractive indices were measured with a Bausch and Lomb precision Abbé refractometer enclosed in a dry box with a helium atmosphere. Measurements were made at 20.0 ± 0.1° and 30.0 ± 0.1° and three wave lengths of light at each temperature. The spectral lines used were the sodium D (5893A), the mercury Hg_e (5460.7A), and the mercury $Hg_{b.v.}$ (4358.3A). The estimated accuracy of the measurements was ±0.0001.

Density. The densities were measured with a modified Lipkin pycnometer. The modification consisted of fusing a standard taper male joint onto the ends of the pycnometer. These ends could then be capped with a female joint equipped with a small stopcock. Once the pycnometer was filled, it could be closed off without disturbing the level of the sample in the arms. The pycnometer was loaded and sealed in a dry box inerted with helium. The densities were measured outside the box at 20.00° ± 0.05° and 30.00° ± 0.05° with an estimated accuracy of ±0.0002 g. per ml.

Dielectric constant. The dielectric constants were measured in a cell of 25-ml. capacity. After being filled in the dry box, the cell was sealed off and removed from the box for the capacity measurements. Measurements of the dielectric constant were made at 20.0° ± 0.1° and 30.0° ± 0.1° with a probable accuracy of ±0.2%. The dielectric constant apparatus has been previously described.[23]

Thermodynamic properties. Heat of combustion. Heats of combustion were determined for triethylborane and tri-*n*-propylborane in a Parr adiabatic calorimeter with an Illium constant-volume bomb.[24] Temperatures were measured with a mercury thermometer (calibrated by the Natl. Bur. of Standards) which could be read to ±0.005°F. The bomb was calibrated using standard benzoic acid supplied by the Parr Instrument Co. Because of their volatility and susceptibility to oxidation, the samples of trialkylboranes were introduced into the bomb in small thin-walled glass bulbs. In the first few runs the glass bulbs were suspended on an iron ignition wire, and the bomb was charged with 30 atm. of oxygen. Combustion was initiated by passing current through the iron wire. The heat generated ruptured the bulb and ignited the sample. Complete combustion was not realized with this method. Apparently the trialkylborane would flow out of a crack in the bulb and burn. The oxides formed would then impede sample flow and combustion would not be completed.

Better combustion was obtained by sealing the iron ignition wire through the wall of the glass bulb so that it passed through the interior of the bulb. The section of ignition wire inside the bulb was filed thin in one spot to ensure a hot spot at this point. Even with this method combustion often was poor. In over fifty runs only three were considered good.

Completeness of combustion was determined by visual inspection of the interior of the bomb and by analyses of the combustion gases for carbon dioxide and of the residue for boron oxide and boric acid. In the good runs the combustion of boron was 99 to 100% complete, and carbon was from 90 to 100% complete. Hydrogen combustion was assumed to be 100% in all cases. Corrections were made for unburned material on the assumption that it was exclusively

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elemental amorphous carbon and boron. Additional corrections were made to fit the bomb combustion to the over-all process at 25°:

$$BCH_{(liq.)} + O_{2(gas,\ 1\ atm)} \longrightarrow CO_{2(gas,\ 1\ atm)} + H_2O_{(gas,\ 1\ atm)} + B_2O_{3(amorph)}$$

Acknowledgment. The author wishes to thank Mrs. Patricia M. O'Donnell for performing the heat of combustion determinations and Mr. Harrison Allen, Jr., for his assistance in the measurement of certain of the physical properties.

CLEVELAND, OHIO

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE]

Compounds Related to 2,3,4-Triphenylbutyric Acid[1]

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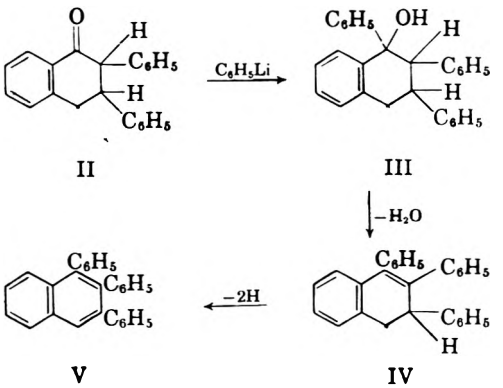
Received February 15, 1960

The structure of a by-product in the preparation of 2,3-diphenyltetralone from 2,3,4-triphenylbutyric acid, has been shown to be I. Various compounds related to the ester are described.

Several years ago, in the preparation of 2,3-diphenyltetralone[2,3] for use in other studies, traces of a compound I melting at 211–212° were obtained in several reactions. In one reaction in which the tetralone was prepared by treating 2,3,4-triphenylbutyryl chloride with anhydrous aluminum chloride, the yield of I was 18 g., 12% based on the weight of acid used. Analyses for carbon and hydrogen agreed with the values calculated for the tetralone but the molecular weight was much too high. Only one form of the tetralone, that melting at 147–148°, has been reported although many people have reported making it and diastereoisomers should be possible.

A series of reactions was planned which would test the hypothesis that I was an isomeric tetralone. The 147° tetralone II was treated with phenyllithium to give a new tertiary alcohol III. This alcohol was dehydrated to give the known 1,2,3-triphenyl-3,4-dihydronaphthalene[4] IV which was then dehydrogenated to give the known 1,2,3-triphenylnaphthalene[4] V. Earlier[3] the tetralone had been reduced to a secondary alcohol by aluminum isopropoxide and this alcohol had been dehydrated and dehydrogenated to give 2,3-diphenylnaphthalene.



These two series of reactions, applied to I, should have led to the same final products if I had been an isomeric tetralone. Aluminum isopropoxide was without effect on I. Phenyllithium reacted with I to give two products, neither of which could be dehydrated by heating with Lucas' reagent or with potassium hydrogen sulfate. Since I was not an isomeric tetralone, the problem was temporarily dropped.

Interest in I was aroused again when it was shown[5] that 2,3,4-triphenylbutyric acid could be cyclized by hydrogen fluoride to give a small amount of 2-phenyl-3-benzylindanone as well as the more common tetralone.

From the infrared spectrum of I, Dr. Gilbert Stork of Columbia University suggested to us that the carbonyl group might be presented as an ester. This proved to be the case. The ester resulted from the reaction of unconverted acid chloride with the enol form of the tetralone. The following chart shows the relationships of the compounds involved.

Hydrolysis of I led to the known acid VI and a neutral oil which could not be crystallized but whose infrared spectrum indicated that it was the known tetralone II. Reaction of I with phenyllithium gave the known ketone VIII[6] and a compound VII whose properties indicate that it may be isomeric with the ketone VIII. Ketone VIII was synthesized by the reaction of phenylmagnesium bromide on either the 87° or the 130° nitrile IX.[2,3] Mixed melting points showed no depression and the infrared spectra were the same. Under forcing conditions phenylmagnesium bromide also reacted with I to give VIII. The

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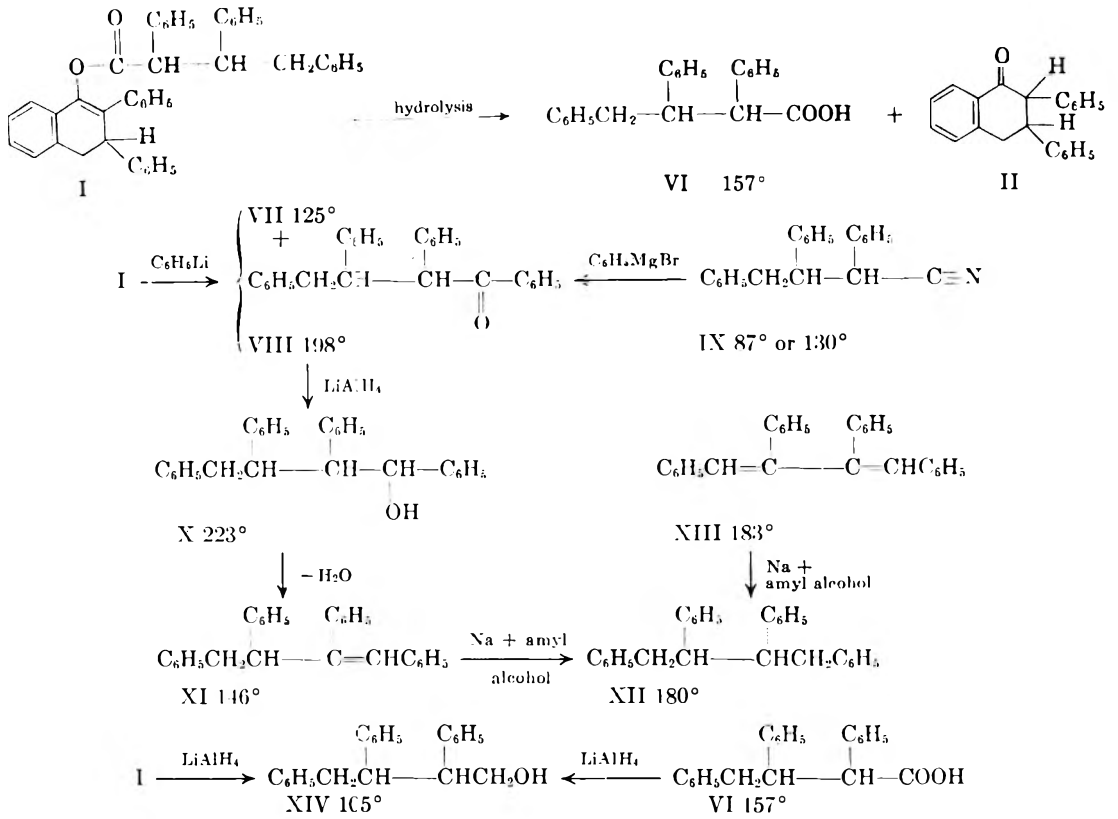
(6) E. Bergmann, D. Winter, and W. Schreiber, *Ann.*, 500, 122 (1933).



ketone VIII reacted with lithium aluminum hydride to give a new secondary alcohol X, which could be dehydrated to give the known hydrocarbon XI. This, in turn, was reduced to the known hydrocarbon XII, and a mixed melting point of this hydrocarbon with an authentic sample prepared from XIII[7] showed no depression. The reaction of lithium aluminum hydride on the ester I gave a new primary alcohol XIV which was identical with the alcohol prepared by the action of lithium aluminum hydride on the 157° acid VI.

EXPERIMENTAL

Preparation of the ester I. The ester I resulted in some of the reactions for the preparation[2,3] of 2,3-diphenyltetralone II. 2,3,4-Triphenylbutyric acid was converted to the acid chloride by phosphorus pentachloride. After the removal of phosphorus oxychloride, the acid chloride was treated with anhydrous aluminum chloride to form the tetralone. This tetralone is known[8] to enolize readily, and this enol form reacted with the acid chloride to form the ester I. The ester was only slightly soluble in ether, ethanol, and ethyl acetate but could be recrystallized from chloroform or dioxane. It crystallized as cottony, white needles, melting at 211–212°. Heating with chloranil failed to dehydrogenate it and treatment with aluminum isopropoxide did not reduce it. It was reduced by refluxing with lithium aluminum hydride and it reacted readily with phenyllithium and slowly with phenylmagnesium bromide.

The ester (1.5 g.) was heated with potassium hydroxide (1.3 g.) in diethylene glycol. The alkaline solution was extracted with ether. Evaporation of this ether solution did not yield any solid but the infrared spectrum of the oil was the same as that for the known tetralone. Small amounts of the tetralone are always difficult to crystallize, probably due to the tendency to enolize. The acid from the hydrolysis was isolated from the alkaline solution by acidifying and extracting with ether. The ether was evaporated and the acid crystallized from benzene–petroleum ether (b.p. 60–70°). It melted at 155–157° and a mixture of the hydrolysis product with a known sample of the acid VI melted at 155–157°. The yield was 84%. The infrared spectrum of I showed absorption at 5.75 μ and 8.95 μ.

Anal. Calcd. for $C_{44}H_{36}O_2$: C, 88.56; H, 6.08; Mol. Wt., 597. Found: C, 88.46; H, 6.48; Mol. Wt., 560.

Preparation of 1,2,3-triphenyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene, III. About 0.03 mole of phenyllithium in ether was added to an ether solution of 3 g. (0.01 mole) of the tetralone II. The ether boiled vigorously. After standing for 2 hr. the grey solution was decomposed with ice water. The ether layer was allowed to evaporate and the heavy oil was stirred with diisopropyl ether. The resulting solid was crystallized from ethanol–ethyl acetate to give colorless needles melting at 168.5–169.5°. The yield was 70%.

Anal. Calcd. for $C_{28}H_{24}O$: C, 89.32; H, 6.42. Found: C, 89.31; H, 6.30.

Preparation of 1,2,3-triphenyl-3,4-dihydronaphthalene, IV. One gram of the tertiary alcohol III was heated on the steam bath for 1 hr. with 10 ml. of benzene and 20 ml. of Lucas' reagent. The benzene layer, after washing with sodium carbonate solution, was heated and diluted with petroleum ether (b.p. 60–70°). The resulting solid (0.88 g., 92%) melted at 176–177°, the melting point recorded[4] for this compound.

Preparation of 1,2,3-triphenylnaphthalene V. Dehydrogenation of 0.5 g. of IV by heating at 280–300° for 22 hr. with 0.5 g. of selenium gave the known[4] 1,2,3-triphenylnaphthalene, melting at 153–154°.

Reaction of I *with phenyllithium and with phenylmagnesium*

(7) L. I. Smith and H. Hoehn, *J. Am. Chem. Soc.*, **63**, 1184 (1941). A sample of this compound was kindly supplied by Dr. Lee Irvin Smith.

(8) F. Bergmann and J. Szmuszkovic, *J. Am. Chem. Soc.*, **68**, 1662 (1946).

bromide. About 0.03 mole of phenyllithium was added to an ether suspension of 3 g. of I. The ether boiled vigorously and I dissolved. After standing for 2 hr. the mixture was decomposed with ice water. The ether layer was allowed to evaporate slowly. Two products could be isolated from the deep magenta colored solution by careful crystallization. The less soluble material, the ketone VIII, separated first and could be recrystallized from chloroform-methanol or from ethyl acetate to give white crystals melting at 198–199°. The more soluble compound VII could be crystallized from benzene–petroleum ether (b.p. 60–70°) and melted at 125–126°.

The ester I (2 g., 0.0033 mole) was treated with excess phenylmagnesium bromide in toluene and heated on the steam bath for 18 hr. after the ether had boiled off. The magnesium compounds were dissolved in ammonium chloride solution and the toluene layer was added to water and steam distilled to remove the toluene. An ether extract of the water layer gave 30% of VIII. None of the lower melting compound VII was isolated from this reaction. A mixed melting point of the ketone from the ester and the ketone made from IX showed no depression. Both VII and VIII gave identical infrared spectra with absorption at 6 μ characteristic of a conjugated ketone.

Anal. Calcd. for $C_{28}H_{24}O$: C, 89.32; H, 6.42; Mol. Wt., 376.5. Found: for VII: C, 89.26, 89.84; H, 7.03, 6.41; Mol. Wt., 381. Found: for VIII: C, 88.71, 89.82; H, 6.31, 6.55; Mol. Wt., 364.

Reaction of 2,3,4-triphenylbutyronitrile with phenylmagnesium bromide. Approximately 0.03 mole of phenylmagnesium bromide was added to 0.02 mole of either form[2] of 2,3,4-triphenylbutyronitrile and the mixture was refluxed for 2 hr. Dilute hydrochloric acid was then added, the ether evaporated, and the mixture heated on the steam bath for 1 hr. The solid was filtered from the cooled mixture and crystallized from ethyl acetate. It melted at 197–198° and a mixed melting point with the ketone made from the ester I was 197–198°. The yield was 56%. The infrared spectrum was the same as that for the ketone made from the ester. This compound was described earlier.[6] It was made by adding benzylmagnesium chloride to 1,2,3-triphenylpropen-2-one-1. The resulting ketone, melting at 178°, was isomerized to the form melting at 198°.

Reduction of 1,2,3,4-tetraphenylbutanone-1, VIII. A mixture of 1 g. of the ketone VIII and 0.75 g. of lithium aluminum hydride in 40 ml. of ether was refluxed for 1 hr. and allowed to stand overnight. The excess lithium aluminum hydride was decomposed with ethyl acetate, then water was added and the layers separated. Needles of the alcohol X began to separate from the ether solution at once. Recrystallization from ethanol-chloroform gave a quantitative yield of colorless needles melting at 223–225°. The infrared spectrum showed no carbonyl absorption at 6 μ but a broad band at 9 μ characteristic of a secondary alcohol group.

Anal. Calcd. for $C_{28}H_{26}O$: C, 88.84; H, 6.92. Found: C, 88.4; H, 6.86.

Dehydration of 1,2,3,4-tetraphenylbutanol-1, IX. This alcohol was not dehydrated by heating with Lucas' reagent but heating 2.5 g. of the alcohol in 50 ml. of benzene with 0.5 g. of *p*-toluenesulfonic acid for 4 hr. did bring about the loss of water. The benzene solution was washed with water and allowed to evaporate slowly. The resulting solid (0.9 g., 43%) was recrystallized from benzene-methanol and melted at 149–150°. This hydrocarbon has been described as melting at 147–148°.[9]

Reduction of 1,2,3,4-tetraphenylbutene-1, XI. Five hundred milligrams of the hydrocarbon XI, 1.5 g. of sodium, and 15 ml. of isoamyl alcohol were refluxed for 1.5 hr. and allowed to stand overnight. The solid which separated (0.36 g., 70%) was filtered and crystallized from benzene-methanol. It melted at 180–180.5° and the mixed melting point with a known sample of 1,2,3,4-tetraphenylbutane was not depressed. The known sample of XII was made by reducing 350 mg. of 1,2,3,4-tetraphenylbutadiene-1,3, XIII[7] with sodium and amyl alcohol.

Reduction of I *with lithium aluminum hydride.* One gram of lithium aluminum hydride and 1.5 g. of I were refluxed in ether for 3 hr. The excess lithium aluminum hydride was decomposed with ethyl acetate and water was then added. The ether solution gave 0.67 g. (88%) of colorless needles of XIV. The alcohol was very soluble in most solvents but could be crystallized from methanol and either water or petroleum ether (b.p. 60–70°). It melted at 105–106° and was identical with the 2,3,4-triphenylbutanol-1 prepared in 35% yield by reducing the 157° 2,3,4-triphenylbutyric acid VI. The mixed melting point was not depressed and both samples showed absorption in their infrared spectra at 9.7 μ, characteristic of a primary alcohol.

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.37; H, 7.33. Found: C, 86.82; H, 7.27.

Compound VII, whose analyses and infrared spectrum indicate that it is an isomer of VIII, was reduced by lithium aluminum hydride to a compound melting at 117–119°. Unfortunately most of this compound was lost. A less pure sample, after being heated with *p*-toluenesulfonic acid showed by infrared spectrum that it was a hydrocarbon. It contained 92.7% carbon and 6.7% hydrogen. This could be an isomer of XI.

Acknowledgment. The author wishes to thank the Department of Chemistry of Columbia University for the privilege of working in Havemeyer Hall in the spring of 1959 while she was on leave from Vassar College.

POUGHKEEPSIE, N. Y.

(9) F. Bergmann, *J. Org. Chem.*, 6, 543 (1941).

Notes

A department for short papers of immediate interest.

Reaction of β-Bromostyrene and Dinitrogen Tetroxide. A Radical Displacement

TRAVIS E. STEVENS

Received February 15, 1960

Addition of free radical reagents to halogenated olefins has been known to lead to adducts that have lost a halogen atom.[1] For instance, various alkyl radicals and 1,2-dichloroethylene interacted to produce 1-chloro-2-alkylethylenes,[2] and the dinitrogen tetroxide–allyl iodide reaction yielded 3-nitropropene.[3]

The addition of dinitrogen tetroxide to β-bromostyrene now has been found to give β-nitrostyrene as the major product, apparently by a radical path as outlined.[4] Slow addition of dinitrogen tetroxide to an ether solution of the bromostyrene produced the nitrostyrene (67%) and

$$NO_2 + C_6H_5{-}CH{=}CHBr \longrightarrow$$
$$[C_6H_5{-}\dot{C}H{-}CHBrNO_2] \longrightarrow C_6H_5{-}CH{=}CHNO_2 + Br.$$

even inverse addition of the styrene to the tetroxide in ether yielded β-nitrostyrene (47%). Formation of the relatively stable intermediate radical which may reversibly eliminate the NO_2 radical or which may eliminate a bromine atom to give the unreactive β-nitrostyrene makes this a favorable case for the observation of such a radical displacement reaction.

The other products of this β-bromostyrene reaction undoubtedly were the saturated compounds derived from the addition of bromine and dinitrogen tetroxide to β-bromostyrene. Only one of the possible adducts, a dibromonitrophenylethane, m.p. 73–74°, was isolated. The nitro group absorption at 1540 cm.$^{-1}$ in the infrared spectrum of this adduct indicated it was 1,1-dibromo-2-nitro-2-phenylethane; absorption at higher wave length would be expected for the isomeric 1,2-dibromo-1-nitro-2-phenylethane.[5]

(1) Several examples are given in C. Walling, *Free Radicals in Solution*, Wiley and Sons, New York, 1957, pp. 268–271.

(2) L. P. Schmerling and J. P. West, *J. Am. Chem. Soc.*, **71**, 2015 (1949); **75**, 6216 (1953).

(3) J. F. Brown, Jr., General Electric Company, personal communication.

(4) The homolytic nature of the dinitrogen tetroxide–olefin reaction appears to be well established; see H. Shechter, J. J. Gardikes, and A. H. Pagano, *J. Am. Chem. Soc.*, **81**, 5421 (1959) and T. E. Stevens, *J. Am. Chem. Soc.*, **81**, 3593 (1959).

(5) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **77**, 6341 (1955).

EXPERIMENTAL

Addition of dinitrogen tetroxide to β-bromostyrene. A solution of 4.3 g. (23.5 mmoles) of β-bromostyrene in 100 ml. of ether was stirred at 10° while 25 mmoles of dinitrogen tetroxide[6] was swept into the ether solution in a nitrogen stream over a 1-hr. period. The mixture was stirred for an additional hour at 15°. Water (100 ml.) then was added, and the ether layer was separated and washed with water and 10% sodium bicarbonate solution. Evaporation of the ether left 4.72 g. of residue. The residue was dissolved in methylene chloride–pentane and chromatographed on a silica gel column as described previously.[4] The first fraction eluted, 1.60 g., contained almost no β-nitrostyrene as evidenced by infrared spectra of the cuts. A 0.83-g. portion of this, probably 1,1-dibromo-2-nitro-2-phenylethane, solidified, and was recrystallized from hexane, m.p. 73–74°.

Anal. Calcd. for $C_8H_7Br_2NO_2$: C, 31.10; H, 2.28; N, 4.53. Found: C, 31.31; H, 2.39; N, 4.38.

The next fraction eluted was β-nitrostyrene, 2.36 g., (67%), m.p. 56–57°; the mixed melting point with an authentic sample of the same melting point was not depressed. The infrared spectrum was identical with that of an authentic specimen.

The last fractions eluted from the column, a total of 0.71 g. of oily material showing hydroxyl absorption in the infrared spectrum, were not characterized.

Addition of β-bromostyrene to dinitrogen tetroxide. A solution of 28 mmoles of dinitrogen tetroxide in 100 ml. of ether was stirred at 10° while 23.5 mmoles of β-bromostyrene in 15 ml. of ether was added over 20 min. The reaction mixture was stirred in a nitrogen atmosphere during this addition and for an additional hour at 15°. The reaction mixture then was worked up as described above. From 4.40 g. of crude residue was obtained 1.55 g. of material eluted prior to β-nitrostyrene; a 0.73-g. portion of this solidified and melted at 74° after hexane recrystallization. The β-nitrostyrene fraction weighed 1.66 g. (47%), m.p. 56–57°, identified as described above.

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(6) Obtained from the Matheson Co. and distilled before use.

The Hydrogenation of Nitriles to Primary Amines

FRANCIS E. GOULD, GRANNIS S. JOHNSON, AND ARTHUR F. FERRIS

Received March 3, 1960

The catalytic hydrogenation of nitriles to primary amines is a reaction of considerable importance in organic synthesis and has been the subject of many investigations because good yields of primary amines are frequently difficult to obtain. The difficulty apparently arises because the re-

TABLE I

HYDROGENATION OF NITRILES IN ACETIC ANHYDRIDE OVER RANEY CATALYSTS

Nitrile	Raney Catalyst	Co-catalyst	Product	Yield, %
$C_6H_5CH_2CN$	Ni	NaOAc	$C_6H_5CH_2CH_2NHAc$	97
C_6H_5CN	Ni	None	$C_6H_5CH_2NH_2 \cdot HCl$	91
$CH_3(CH_2)_{11}CN$	Ni	NaOAc	$CH_3(CH_2)_{12}NHAc$	100
$CH_3(CH_2)_{11}CN$	Ni—Cr	NaOAc	$CH_3(CH_2)_{12}NHAc$	89
$CH_3(CH_2)_{11}CN$	Co	NaOAc	$CH_3(CH_2)_{12}NHAc$	60
$CH_2{=}CHCN$	Ni	NaOAc	$CH_3CH_2CH_2NHBz$	92
$(CH_3)_2C(OH)CN$	Ni	NaOAc	$(CH_3)_2C(OH)CH_2NH_2 \cdot HCl$	40
$NC(CH_2)_4CN$	Ni	NaOAc	$AcNH(CH_2)_6NHAc$	100
$NC(CH_2)_4CN$	Ni	NaOH	$AcNH(CH_2)_6NHAc$	80
$NC(CH_2)_4CN$	Ni—Cr	NaOAc	$AcNH(CH_2)_6NHAc$	77
$NC(CH_2)_4CN$	Co	NaOAc	$AcNH(CH_2)_6NHAc$	25

duction proceeds stepwise through the aldimine, some of which condenses with primary amine already formed and ultimately leads to secondary amines.[1,2]

Recent work in this laboratory has shown that hydrogenation of ethyl 5-cyano-2-oximinovalerate in acetic anhydride over a Raney nickel catalyst in the presence of a basic cocatalyst, followed by hydrolysis with hydrochloric acid, gives DL-lysine monohydrochloride in almost quantitative yield.[3] It has been found now that hydrogenation in acetic anhydride in the presence of a Raney metal catalyst and a basic cocatalyst, a technique which appears never to have been applied to simple nitriles, is very effective for the reduction of a variety of nitriles to primary amines. In fact, this technique frequently may be the method of choice for carrying out this conversion in the laboratory because it gives very high yields simply and rapidly at moderate temperatures and low pressures. As an example of the very mild conditions which may be employed, with Raney nickel catalyst and sodium acetate cocatalyst hydrogenation of most nitriles is complete in 45–60 minutes at 50° and 50 p.s.i. hydrogen pressure. Lower temperature may be used but requires longer reduction time. Raney nickel–chromium appears to be as effective as Raney nickel, but Raney cobalt is somewhat less effective. Sodium acetate is a very mild cocatalyst suitable for most purposes, but strong bases such as sodium hydroxide give more rapid reduction. Caution should be exercised when strong bases are used, as very rapid reduction become vigorously exothermic. Catalyst life is affected strongly by the nature of the cocatalyst. With sodium acetate the activity of the Raney catalyst diminishes markedly with each use and is too low to be of practical value after three or four cycles, whereas with strong base recovered catalyst is as active as fresh and can be re-used repeatedly. With some nitriles such as benzonitrile no cocatalyst is necessary, but in general its presence gives better yields and purer products. Unsaturated nitriles are reduced to saturated primary amines by the new technique and, although the point has not been studied, it is likely that any other easily reduced group would also be attacked.

The amine products may be isolated in several ways, dependent in part on the nature of the particular amine. In many cases the *N*-acetyl derivative of the amine crystallizes from the reduction medium when it is cooled, and the solid may be obtained in a high state of purity by filtration and drying. In other instances it is convenient to subject the entire reduction mixture to acidic or basic hydrolysis and to isolate the amine as the hydrochloride or as the free base. Where a particular derivative is desired, it may be obtained frequently by treating the hydrolysis mixture with the appropriate derivatizing agent. Each of these methods has been used at least once to isolate the products reported in Table I, which lists the results obtained with six typical nitriles. The yield of 2-hydroxy-2-methylpropylamine hydrochloride from acetone cyanohydrin is not regarded as representative because the extremely hygroscopic nature of the product made isolation difficult.

EXPERIMENTAL[4]

Pretreatment of Raney catalyst. The Raney catalysts were purchased in active form under water from the Raney Catalyst Co., Chattanooga, Tenn. Immediately before use the 2–3 g. (wet weight) of catalyst needed for the 0.10 mole scale

(1) H. Adkins and R. L. Shriner, *Organic Chemistry*, Vol. I, 2nd Ed., H. Gilman, ed., J. Wiley and Sons, New York, 1943, p. 809.

(2) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, J. Wiley and Sons, New York, 1953, p. 658.

(3) A. F. Ferris, G. S. Johnson, F. E. Gould, and H. Stange, *J. Org. Chem.*, **25**, 1302 (1960). References to the previous use of the combination of Raney nickel and acetic anhydride are given in this paper.

(4) All melting points are uncorrected.

reductions reported below was filtered from the water and washed with two 20-ml. portions of absolute ethanol and two 20-ml. portions of acetic anhydride. Catalyst so treated lost activity rapidly if allowed to stand under acetic anhydride.

Reduction of tridecanenitrile. A 2–3 g. portion of Raney nickel treated as described above and 12.0 g. of anhydrous sodium acetate were added to a solution of 19.5 g. (0.10 mole) of tridecanenitrile in 120 ml. of acetic anhydride. The resulting mixture was heated to 50° and shaken under hydrogen at an initial pressure of 50 p.s.i. After about 1 hr. hydrogen uptake was complete, and the catalyst was filtered from the hot solution. When the filtrate was cooled in ice, a white solid precipitated. After recovery and drying, this amounted to 24.1 g. (100%) of *N*-acetyltridecylamine, m.p. 57–58°.

Anal. Calcd. for $C_{15}H_{31}ON$; C, 74.62; H, 12.94; N, 5.80. Found: C, 74.62; H, 13.04; N, 5.44.

Reduction of benzonitrile. A mixture of 2–3 g. of treated Raney nickel, 10.3 g. (0.10 mole) of benzonitrile, and 120 ml. of acetic anhydride was shaken at 50° under an initial hydrogen pressure of 50 p.s.i. When the reaction was complete (1 hr.), the mixture was filtered hot and the filtrate was treated with 40 ml. of water. Then 180 ml. of concd. hydrochloric acid was added, and the mixture was heated under reflux for 16 hr. The resulting solution was cooled to 25°, made strongly basic with 5*N* sodium hydroxide solution, and extracted with two 100-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate, filtered, and treated with gaseous hydrogen chloride until no further precipitate formed. After recovery and drying, there was obtained 13.0 g. (91%) of benzylamine hydrochloride, m.p. 248–249° (lit.,[5] m.p. 248°).

Reduction of acrylonitrile. A mixture of 2–3 g. of treated Raney nickel, 5.3 g. (0.10 mole) of acrylonitrile, 12.0 g. of anhydrous sodium acetate, and 120 ml. of acetic anhydride was shaken at 25° under hydrogen at an initial pressure of 50 p.s.i. Hydrogen uptake was complete after 16 hr., and the catalyst was removed by filtration. The filtrate was treated with 40 ml. of water and the mixture was allowed to stand with occasional stirring for 3 hr. Then 180 ml. of concd. hydrochloric acid was added, and the mixture was heated under reflux for 16 hr. After cooling to 25° the solution was made strongly basic with 5*N* sodium hydroxide solution and was stirred for 2 hr. with 16.8 g. (0.12 mole) of benzoyl chloride. The solid which separated was recovered by filtration and dried. There was thus obtained 15.0 g. (92%) of *N*-propylbenzamide, m.p. 84–85° (lit.,[6] m.p. 84–85°).

Reduction of adiponitrile. A mixture of 10.8 g. (0.10 mole) of adiponitrile, 2–3 g. of treated Raney nickel, 4.4 g. of solid sodium hydroxide, and 120 ml. of acetic anhydride was shaken with hydrogen under 50 p.s.i. pressure, and the temperature was raised cautiously to 50°. At this point a vigorously exothermic reaction set in, and, although the heater was cut off, the temperature rose rapidly to 75° and then dropped slowly. Hydrogen uptake was complete in 15 min. The reaction mixture was filtered hot and the filtrate was cooled in ice to precipitate the product. After recovery and drying there was obtained 16.0 g. (80%) of *N*,*N*′-diacetylhexamethylenediamine, m.p. 125–126°. (lit.,[7] m.p. 125–126°).

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(5) I. Heibron and H. M. Bunbury, *Dictionary of Organic Compounds*, Vol. I, Oxford Univ. Press, N. Y., 1953, p. 270.

(6) I. Heibron and H. M. Bunbury, *Dictionary of Organic Compounds*, Vol. IV, Oxford Univ. Press, N. Y., 1953, p. 243.

(7) T. Curtius and H. Clemm, *J. prakt. Chem.*, 62, 210 (1900).

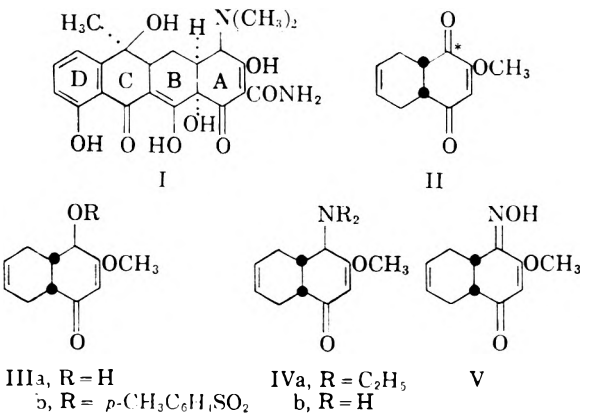
Selective Reactions of the Butadiene-Methoxybenzoquinone Adduct

GEORGE I. BIRNBAUM[1]

Received February 29, 1960

A recent publication by Barltrop and Burstall[2] prompts us to report our work with potential intermediates in a synthesis of tetracycline (I). We prepared 2-methoxy-4a,5,8,8a-tetrahydronaphthoquinone (II) in 85% yield. Further utilization of molecules of this type to elaborate rings A and B of tetracycline requires the introduction of the *N*,*N*-dimethylamino group in the place of the starred carbonyl. Selective reactions of this carbonyl were expected to be feasible since the other carbonyl group is deactivated by being conjugated with a free pair of electrons on the oxygen of the methoxy group. We were indeed successful in certain selective reactions. Compound II can be reduced selectively by sodium borohydride to give in 44% yield the keto alcohol IIIa. Its *p*-toluenesulfonate (IIIb) was prepared, but an attempt to prepare compound IVa by a displacement of the *p*-toluenesulfonate group was not successful as no reaction took place upon refluxing IIIb with diethylamine.

The monoxime of II, compound V, was also prepared in good yield. Catalytic hydrogenation of V with palladium-charcoal did not, however, yield the desired amine IVb.



EXPERIMENTAL[3]

2-Methoxy-4a,5,8,8a-tetrahydronaphthoquinone (II). Methoxybenzoquinone[4] (8.50 g.) and 15 ml. of dry benzene were placed in a heavy-walled glass tube cooled by Dry Ice. To

(1) Present address: Department of Biochemistry, College of Physicians and Surgeons, Columbia University, New York, N. Y.

(2) J. A. Barltrop and M. L. Burstall, *J. Chem. Soc.*, 2183 (1959).

(3) Melting points are uncorrected. Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) Prepared by the procedure of Ioffe and Sukhina, *J. Gen. Chem.*, 23, 295 (1953), [*Chem. Abstr.* 48, 2640d].

this suspension there was added 20 ml. of condensed butadiene and several crystals of hydroquinone to inhibit polymerization. The sealed tube was kept at 115° for 40 hr. After several crystallizations from ether 10.0 g. of white crystals, m.p. 126–127.5°, was obtained (85% yield). $\lambda_{max}^{CHCl_3}$ = 5.88 μ (unconjugated ketone), 6.04 μ (conjugated ketone), 6.24 μ (enol ether).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.30. Found: C, 68.36; H, 6.12.

2-Methoxy-4-oxo-1,4,4a,5,8,8a-hexahydro-1-naphthol (IIIa). Sodium borohydride (0.20 g.) was dissolved in 70 ml. of ethanol and a solution of 0.96 g. of II in 10 ml. of ethanol was added dropwise. The flask was allowed to stand for 3 hr., then water was added. The solution was saturated with sodium chloride and extracted with ether. Upon recrystallization from cyclohexane 0.20 g. (44% yield) of white, fibrous crystals, m.p. 134–135°, was obtained. $\lambda_{max}^{CHCl_3}$ = 6.05 μ, 6.20 μ.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.03; H, 7.27. Found: C, 68.06; H, 7.18.

The *p-toluenesulfonate* (IIIb) crystallized from methanol as white crystals, m.p. 93°.

Anal. Calcd. for $C_{18}H_{19}O_5S$: C, 62.23; H, 5.51. Found: C, 62.35; H, 5.60.

2-Methoxy-4a,5,8,8a-tetrahydronaphthoquinone-1-oxime (V). To a solution of 0.35 g. (0.005 mole) of hydroxylamine hydrochloride in 5 ml. of pyridine and 5 ml. of absolute ethanol there was added 0.96 g. (0.005 mole) of II. The solution was refluxed for 1 hr. After it had cooled the solvents were blown off by a stream of air. The residue was triturated with 5 ml. of cold water and filtered. The oxime was recrystallized from methanol to give white crystals which begin to decompose at 200°. The yield amounted to 0.65 g. (68%). $\lambda_{max}^{CHCl_3}$ = 6.08 μ, 6.28 μ.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 64.03; H, 6.28; N, 6.89.

Acknowledgment. The author wishes to express his gratitude to Professor Gilbert Stork for his interest in this work.

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Synthesis of Some Haloolefins. Addition of Dibromodifluoromethane and Bromotrichloromethane to Vinylidene Fluoride

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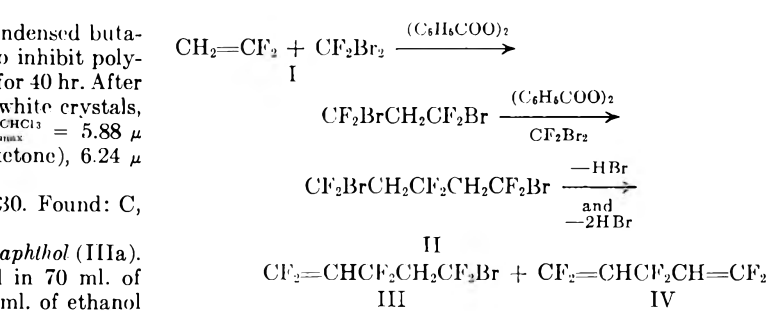
Received February 22, 1960

The addition reactions of dibromodifluoromethane to vinylidene fluoride, initiated by benzoyl peroxide, proceeded as described in the literature[1,2] and comparable yields were obtained. In addition to the simple one-to-one adduct (I) an approximately equivalent amount of the two-to-one adduct (II) was isolated. It is of interest to note that this



reaction occurred as it did, in spite of the fact that over 400% molar excess of the halomethane was used. The 1,5-dibromo-1,1,3,3,5,5-hexafluoropentane (II) was dehydrohalogenated to the unconjugated pentadiene (IV) 1,1,3,3,5,5-hexafluoropentadiene-1,4 and some pentene (III), the 5-bromo-1,1,3,3,5,5-hexafluoropentene-1. These results substantiate the work of Hauptschein, *et al.*,[3] on telomers of fluorinated olefins.

As a corollary of this work the polymerizability of the diene was studied.[4] While the diene did not homopolymerize, it formed copolymers with butadiene, styrene, and vinyl acetate. The diene is substituted with fluorine on the carbon atom *alpha* to the sites of unsaturation (CF_2=$CHCF_2CH$=CF_2) and thus not possessed of allylic hydrogen atoms. Therefore, it should not show the retarding influence of free-radical polymerization commonly associated with allylic compounds. This advantage was probably more than offset by the fact that free-radical attack would be predicted to occur at carbon atom 2 and would doubtlessly be sterically inhibited.

Another reaction investigated was that of the peroxide-initiated addition of bromotrichloromethane to vinylidene fluoride. Although this reaction has not been reported previously, it would be expected to occur quite readily. The complication of the formation of appreciable amounts of the two-to-one adduct should be lessened because of the high chain transfer tendency of bromotrichloromethane. This proved to be the case; yields of the adduct (V), 1,1,1-trichloro-3-bromo-3,3-difluoropropane, in the neighborhood of 60% were obtained consistently.

In attempting to dehydrohalogenate the halopropane, with aqueous and ethanolic base, no products could be isolated. In one reaction with aqueous sodium hydroxide, the reaction mixture sparked, possibly due to the formation of an unstable halogen substituted acetylene derivative. Triethylamine proved to be a useful reagent for effecting the dehydrohalogenation, although even here the high reactivity of the initial reaction prod-

(1) P. Tarrant, A. M. Lovelace, and M. R. Lilyquist, *J. Am. Chem. Soc.*, **76**, 944 (1954).

(2) P. Tarrant and M. R. Lilyquist, *J. Am. Chem. Soc.*, **76**, 944 (1954).

(3) M. Hauptschein, M. Braid, and F. E. Lawlor, *J. Am. Chem. Soc.*, **80**, 846 (1958).

(4) F. B. Jones, C. A. Lichtenwalter, P. B. Stickney, and R. G. Heiligmann, *Polymerization Studies on Monomers and Evaluation of Derivative Polymers*, Wright Air Development Center, Dayton, Ohio; Technical Report 57-110, Pt I (1957).

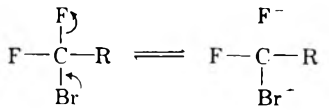
ucts caused the yield of olefin to be low. This reaction, however, was of interest in two respects. First, both possible dehydrohalogenation products were isolated (VI and VII). This is in contrast to

$$CH_2{=}CF_2 + CCl_3Br \xrightarrow{(C_6H_5COO)_2}$$

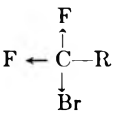
$$CCl_3CH_2CF_2Br \xrightarrow{(C_2H_5)_3N} CCl_3CH{=}CF_2 + CCl_2{=}CHCF_2Br$$

V VI VII

the results of Nesmeyanov[5] in the dehydrohalogenation with triethylamine of analogous compounds which contained no fluorine, when compounds of the type, $CCl_3CH{=}CHR$ were obtained from CCl_3CH_2CHBrR. This demonstrates the shielding effect afforded by adjacent fluorine atoms which arise, either through resonance of the type:



or a strictly inductive effect which results in a shortening of the bond between the electron-poor carbon atom and its bromine substituent:



Secondly, the structure of the initial adduct is shown to be 1,1,1-trichloro-2-bromo-3,3-difluoropropane, rather than 1,1,1-trichloro-2,2-difluoro-3-bromopropane, since removal of HX (X = Br or Cl) would yield only an olefin in the former case.

EXPERIMENTAL

Preparation of 1,5-dibromo-1,1,3,3,5,5-hexafluoropentane. A procedure similar to that of Tarrant, Lovelace, and Lilyquist[4] was used, in which a 5.2:1.2 ratio of the halomethane to the olefin was employed, with the exception that about three times as much benzoyl peroxide was used. These materials were combined in a 1.4 l. steel autoclave, cooled in Dry Ice, then heated and rocked for 6 hr. at 80°. Yields of the one-to-one adduct were 33–55% and the two-to-one adduct were 23–29%.

Anal. Calcd. for $C_5H_4F_6Br_2$: C, 17.7; H, 1.2; F, 33.7; Br, 47.3. Found: C, 17.4; H, 1.2; F, 33.8; Br, 46.7.

Dehydrohalogenation of 1,5-dibromo-1,1,3,3,5,5-hexafluoropentane. The method of Tarrant, Lovelace, and Lilyquist[4] was used. The haloalkane was added to 33% aqueous potassium hydroxide at 80° and the olefins distilled as they were formed. The 1,1,3,3,5,5-hexafluoropentadiene-1,3 (b.p. 44.6–45.1°/760 mm., n_D^{20} 1.3583, d_4^{20} 1.3935, $MR_{D(calcd.)}$ 24.36) and 5-bromo-1,1,3,3,5,5-hexafluoropentene-1 (b.p. 104–106°/738 mm., n_D^{20} 1.3583, d_4^{20} 1.7053, $MR_{D(calcd.)}$ 32.59) were obtained in a combined yield of 45%.

Anal. Calcd. for $C_5H_3BrF_6$: C, 23.4; H, 1.17; F, 43.4; Br, 32.0. Found: C, 25.4; H, 1.83; F, 43.1; Br, 32.6.

Anal. Calcd. for $C_5H_2F_6$: C, 34.1; H, 1.14; F, 64.8. Found: C, 34.1; H, 1.81; F, 64.8.

Preparation of 1,1,1-trichloro-3-bromo-3,3-difluoropropane. A 1.4 l. steel autoclave was charged with 990 g. (5.0 moles) of bromotrichloromethane and 12 g. (0.05 mole) of benzoyl peroxide, sealed, cooled in Dry Ice–acetone to −75°, and evacuated. Then 64 g. (1.0 mole) of 1,1-difluoroethylene was passed into the vessel. The vessel was rocked and heated at 90° for 8 hr. The autoclave was cooled, vented, and the contents distilled at 125 mm. to obtain 745 g. of unchanged bromotrichloromethane and 123 g. of product boiling at 90.5–94.5° with a yield of 62% based on unrecovered starting material. The product thus obtained was shown to be 95% pure by means of vapor phase chromatography. Upon careful redistillation through a Podbielniak Mini-cal column a cut was obtained which was shown to be essentially pure by the same means. The properties of this material were: b.p. 85.0°/100 mm., n_D^{20} 1.4678, d_4^{20} 1.8272, $MR_{D(calcd.)}$ 24.36.

Anal. Calcd. for $C_3H_2BrCl_3F_2$: C, 13.7; H, 0.76; Br, 30.5; Cl, 40.5; F, 14.5. Found: C, 13.7; H, 1.00; Br, 29.5; Cl, 39.7; F, 13.9.

Dehydrogenation of 1,1,1-trichloro-3-bromo-3,3-difluoropropane. In a three neck, 300-ml. flask equipped with stirrer, reflux condenser, thermometer, and funnel, the halopropane, 131 g. (0.5 mole) was added and heated to 70°. The triethylamine, 50.5 g. (0.5 mole) was added dropwise into the flask over a period of an hour. The temperature of the reaction was maintained between 70–90° during the addition. The mixture was stirred for 0.5 hr. after the addition was complete and then allowed to stand overnight. The reaction mixture was added to 300 ml. of water, the organic layer separated and dried over calcium chloride. The crude product weighed 98 g. Distillation gave 37 g. boiling from 94–125° and 58 g. of starting material boiling from 125–160°. Redistillation through the Podbielniak column gave 8 g. of 1,1,1-trichloro-3,3-difluoropropene-2, b.p. 96–97°, n_D^{25} 1.4273, d_4^{25} 1.5460; $MR_{D(calcd.)}$ 31.29 and 5 g. of 1-bromo-1,1-difluoro-3,3-dichloropropene-2, b.p. 116.1–116.3°; n_D^{25} 1.4568; d_4^{25} 1.8301; $MR_{D(calcd.)}$ 34.19.

Anal. Calcd. for $C_3HCl_3F_2$: C, 19.7; H, 0.55; Cl, 58.2; F, 20.8. Found: C, 20.2; H, 0.11; Cl, 57.1; F, 19.9.

Anal. Calcd. for $C_3HCl_2BrF_2$: C, 15.9; H, 0.44; Cl, 31.3; Br, 35.8; F, 16.8. Found: C, 16.2; H, 0.20; Cl, 31.8; Br, 35.4; F, 17.2.

MATERIALS CENTRAL
WRIGHT AIR DEVELOPMENT DIVISION
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(5) A. N. Nesmeyanov, R. Kh. FreIdlina, L. I. Zakharkin, and A. B. Belyavskii, *Zhur Obshchei Khim.*, 26, 1070 (1956); *Chem. Abstr.*, 50, 16658f (1956).

Some Reactions of Vinyl and Allyl Acetate with Haloalkanes

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Received February 22, 1960

In attempting to prepare polymers containing oxygen, either in pendant groups or in the polymer chain itself, several methods involving free radical additions were briefly investigated. The first attempt was the reaction of perfluoroalkyl radicals with ethylene oxide and the other involved the addition of haloalkanes to vinyl and allyl esters followed by conversion to the unsaturated epoxides. Although both methods were fruitless, some new materials were prepared and characterized.

The ability of ethylene oxide to enter into free radical polymerization processes with fluoroolefins was demonstrated by Hauptschein and Lesser.[1] It was thought that the reaction of perfluoropropyl iodide and ethylene oxide under free radical conditions might proceed to produce perfluoropropyl-β-iodoethyl ether, and subsequent dehydroiodination would give the corresponding vinyl ether. An exploratory reaction carried out at 200° gave a 15% yield of a liquid subsequently identified as 1-iodo-1,1,2,2-tetrahydroperfluoropentane. A repeat of this experiment gave a yield of 27% of the same alkane. Dehydrohalognation of the isolated product produced the corresponding olefin ($CF_3CF_2CF_2$-$CH{=}CH_2$). The fate of the oxygen in the original synthesis was not determined. Elucidation of the mechanism for the formation of the alkane was not undertaken.

The addition of haloalkanes to the vinyl and allyl esters should proceed analogously to the additions with bromotrichloromethane carried out by Kharasch[2] in which addition of the trichloromethyl group took place on the terminal methylene group. The additions were carried out and the products are listed below:

(a) $CH_3CO_2CH{=}CH_2 + CF_2Br_2 \xrightarrow[\text{or } \gamma]{(C_6H_5COO)_2}$ no product

(b) $CH_3COOCH{=}CH_2 + CF_2BrCFClBr \xrightarrow{(C_6H_5COO)_2}$

$$CF_2BrCFClCH_2CHBrOCCH_3$$

(c) $CH_3CO_2CH{=}CH_2 + CF_2Br_2 \xrightarrow[\text{or } \gamma]{(C_6H_5COO)_2}$

$$CF_2BrCH_2CHBrCH_2OCCH_3$$

(d) $CH_3CO_2CH{=}CH_2 + CF_2BrCFClBr \xrightarrow{(C_6H_5COO_2)}$

$$CF_2BrCFClCH_2CHBrCH_2OCCH_3$$

Yields in the region of 50% were obtained in three of the above reactions. In the case of (a) no product was obtained in either a benzoyl peroxide initiated reaction at 80° in a rocking autoclave or in a sealed tube exposed to a cobalt^{60} source. In the case of (b) a fair yield of crude product was obtained, but on redistillation, the material tended to decompose and only a small portion of the purified material could be obtained. It is interesting to note that the decomposition, which occurred at 100°, resulted in the formation of volatile products which could be condensed in a Dry Ice–acetone trap. The material formed had a pronounced aldehydic odor and was extremely lachrymatory. Kharasch[2] similarly reported the relative ease with which the bromotrichloromethane vinyl acetate adduct was converted to β,β-dichloroacrolein by the action of aqueous acid.

The additions of both dibromodifluoromethane and 1,2-dibromo-2-chloro-1,1,2-trifluoroethane to allyl acetate gave good yields of the desired adducts. Elementary analysis and the infrared spectra were consistent with the proposed structure. In the benzoyl peroxide initiated reaction product, it was obvious that there was an aromatic contaminant present which could not be removed by distillation. In order not to resort to purification by chemical means, analytical samples were obtained by irradiation of the materials in sealed glass vials until a specified dosage was obtained. This method was originally reported by Postelnek *et al.*[3,4] for the additions of bromotrichloromethane to various olefins. The allyl acetate adducts were separated by fractional distillation through the Podbielniak minical column. The spectra thus obtained were identical with the others, but no aromatic residues arising from the peroxide initiator were present.

Finally, the adduct of 1,2-dibromo-2-chloro-1,1,-2-trifluoroethane and allyl acetate was reduced with zinc dust to give the reported pentadiene, 1,1,2-trifluoropentadiene-1,4,[5] indicating that 2,5-dibromo-4-chloro-4,5,5-trifluoropentylacetate rather than 2,5-dibromo-5-chloro-4,4,5-trifluoropentyl acetate.

EXPERIMENTAL

Reaction of perfluoropropyl iodide and ethylene oxide. In a steel autoclave cooled to 5° were placed 59.2 g. (0.2 mole) of perfluoropropyl iodide and 8.8 g. (0.2 mole) of ethylene oxide. The autoclave was sealed and rocked while being rapidly heated to 200°. The pressure rose to 250 p.s.i. but dropped to 110 p.s.i. after 4 hr. At this time the autoclave was allowed to cool and the contents, which were somewhat carbonaceous and contained solid iodine, were fractionally distilled. The fraction boiling at 64.0 to 64.2°/108 mm. had the following properties: n_D^{20} 1.3787, d_4^{20} 1.9210, $MR_{D\,(obsd.)}$ 38.2, $MR_{D(calcd.)}$ 38.19.

Anal. Calcd. for $C_5H_4F_7I$: C, 18.5; H, 1.23; F, 41.0; I, 38.8. Found: C, 18.6; H, 0.60; F, 41.5; I, 38.8.

Dehydrohalogenation of 1-iodo-1,1,2,2-tetrahydroperfluoropentane. The adduct, 34 g. (0.1 mole) was added slowly to a solution of 12 g. (0.2 mole) of potassium hydroxide in 200 ml. of 95% ethanol kept at 0°. A white precipitate was formed immediately. Stirring was maintained for an hour after the addition was complete and then the reaction mass was added to 400 ml. of ice and water and the organic layer was separated and dried over calcium chloride. Upon distillation a cut was obtained, b.p. 32°/750 mm.; lit.[6] b.p. 31°, with the physical properties n_D^{20} 1.2752, d_4^{20} 1.3391, $MR_{D(obsd.)}$ 25.2, $MR_{D(calcd.)}$ 24.8.

Anal. Calcd. for $C_5H_3F_7$: C, 30.6; H, 1.53; F, 67.9. Found: C, 31.1; H, 1.52; F, 67.1.

(1) M. Hauptschein and J. Lesser, *J. Am. Chem. Soc.*, **78**, 676 (1956).

(2) M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Am. Chem. Soc.*, **69**, 1100 (1947).

(3) W. Postelnek, D. A. Rausch, and A. M. Lovelace, 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 1956.

(4) E. I. Heiba and L. C. Anderson, *J. Am. Chem. Soc.*, **79**, 4940 (1957).

(5) P. Tarrant and E. G. Gilman, *J. Am. Chem. Soc.*, **76**, 5423 (1954).

(6) O. R. Pierce, E. T. McBee, and C. F. Judd, *J. Am. Chem. Soc.*, **75**, 5618 (1953).

Dehalogenation of the product of the addition of 1,2-dibromo-2-chloro-1,1,2-trifluoroethane to allyl acetate. Zinc, 28.8 g. (0.44 g.-atom) and 150 cc. of dioxane were placed in a 500-cc. flask equipped with a stirrer, reflux condenser, and pressure-compensated addition funnel. A few drops of concd. hydrochloric acid were added, and the flask was stirred and heated to reflux. The addition product, 78 g. (0.2 mole) was placed in the addition funnel and slowly added. The condenser was allowed to warm to 40° and any material that passed through was collected in a cooled trap. About 10 ml. of product was obtained which on redistillation had a boiling point 37–38°, n_D^{20} 1.3424; reported[5] b.p. 38°, n_D^{27} 1.3435.

The peroxide initiated addition of dibromodifluoromethane to allyl acetate. The halomethane, 1110 g. (5.2 moles), allyl acetate, 130 g. (1.3 moles) and benzoyl peroxide, 8 g. (0.03 mole) were placed in a cooled 1.4-l. steel autoclave and sealed. After heating and rocking at 90° for 12 hr., the autoclave was cooled and the contents were distilled. Excess dibromodifluoromethane, 800 g., boiling at 22.5–24.5° was recovered, and then a product boiling at 95–109°/5 mm. This material was redistilled at 71–73°/2 mm. A yield of 163 g. (41%) was obtained. No reaction occurred under similar conditions with vinyl acetate.

The gamma radiation-induced reactions of 1,2-dibromo-2-chloro-1,1,2-trifluoroethane and dibromodifluoromethane with allyl acetate. In a 60-ml. glass tube (22 mm. in diameter) were sealed 77 g. (0.28 mole) of the haloethane and 7.0 g. (0.07 mole) of allyl acetate. The tube was wrapped with friction tape and the sample was then exposed to a cobalt^{60} source with a flux rate of 4.5×10^5 roentgens per hr. After exposure for an hour the tube was cooled and opened. Upon distillation 12 g. of pure product, b.p. 85–86°/3.5 mm., n_D^{25} 1.4654, d_4^{25} 1.8196, $MR_{D(obsd.)}$ 56.55, $MR_{D(calcd.)}$ 57.3, was obtained.

Anal. Calcd. for $C_7H_8BrClF_3O_2$: C, 22.3; H, 2.10; F, 15.1. Found: C, 21.4; H, 2.0; F, 15.3.

In the same manner, 100 g. (0.48 mole) of dibromodifluoromethane and 6 g. (0.06 mole) of allyl acetate were treated to give 8 g. of pure product boiling at 72°/2.5 mm. n_D^{20} 1.4631, d_4^{20} 1.8153, $MR_{D(obsd.)}$ 47.13, $MR_{D(calcd.)}$ 46.6.

Anal. Calcd. for $C_6H_8Br_2F_2O_2$: C, 23.2; H, 2.58; Br, 51.6; F, 12.52. Found: C, 23.7; H, 2.49; Br, 52.3; F, 12.0.

The gamma radiation-induced reactions of 1,2-dibromo-2-chloro-1,1,2-trifluoroethane and dibromodifluoromethane to vinyl acetate. These reactions were carried out in an identical manner with those in the previous section. The dibromodifluoromethane addition gave no higher boiling materials while the other addition product decomposed during distillation.

The peroxide initiated addition of 1,2-dibromo-2-chloro-1,1,2-trifluoroethane to vinyl acetate and allyl acetate. In a 500-cc. three-neck flask equipped with stirrer, reflux condenser, and pressure-compensated addition funnel were placed 10 g. (0.04 mole) of benzoyl peroxide and 400 g. (1.45 moles) of the perhalo compound, which had been prepared by the addition of bromine to chlorotrifluoroethylene, according to the method of Park, Lycan, and Lacher.[7] The flask was heated to 90° and 31 g. (0.36 mole) of redistilled vinyl acetate added at such a rate as to maintain mild reflux. The flask was heated an additional 4 hr. at 90° and then distilled at 150 mm. to recover the excess 1,2-dibromo-2-chloro-1,1,2-trifluoroethane, 200 g. boiling at 43.47° being obtained. The pressure was lowered to 2 mm. and 198 g. of material boiling from 72–85° (largely 78°) was distilled. Upon redistillation through a more efficient column the product obtained distilled at 73°/2 mm. and had the following physical properties: n_D^{25} 1.4531, d_D^{25} 1.9905, $MR_{D(calcd.)}$ 51.4.

Anal. Calcd. for $C_6H_6Br_2ClF_3O_2$: C, 19.9; H, 1.66; Br, 43.8; F, 15.8. Found: C, 20.4; H, 1.58; Br, 44.5; F, 15.6.

(7) J. D. Park, W. R. Lycan, and J. R. Lacher, *J. Am. Chem. Soc.*, **73**, 711 (1951).

A similar reaction using allyl acetate was also performed. Allyl acetate, 45 g. (0.45 mole) was slowly added to 500 g. (1.81 moles) of the haloethane and 10 g. (0.04 mole) of benzoyl peroxide. The product boiling at 84–88°/1.4 mm. was obtained, 128 g. (76%), n_D^{20} 1.4670. A solid had sublimed over the product. Upon drying this material melted at 110–112°.

MATERIALS CENTRAL
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Synthesis of 2,4-Dimethyl-3-hydroxy-6-oxoheptanal

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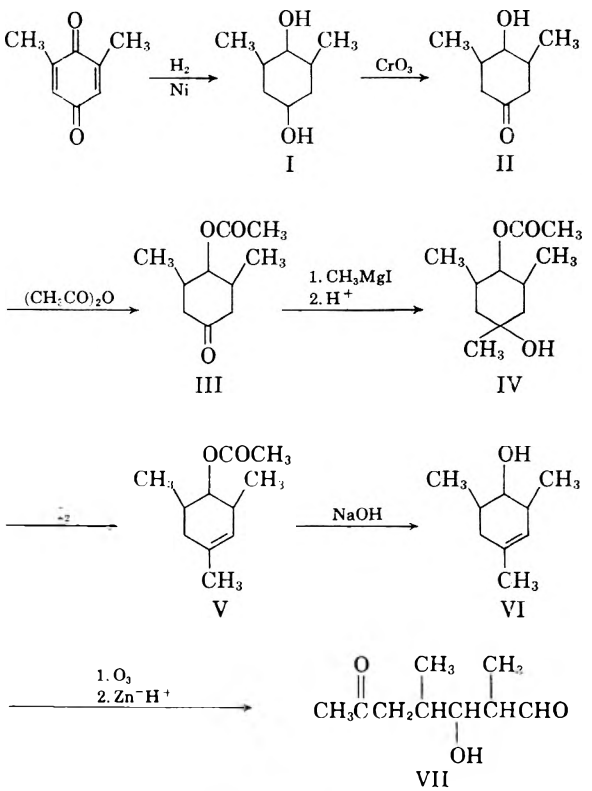
Received January 20, 1960

In connection with another problem 2,4-dimethyl-3-hydroxy-6-oxoheptanal was synthesized. The synthetic route used is outlined in the accompanying flow sheet. The reduction of *m*-xyloquinone was never very satisfactory. The crude product was a complex mixture, and purification resulted in low yields of I. It was assumed that use of a limited amount of chromic oxide would result in oxidation of I at the less hindered hydroxyl to give II rather than the isomeric hydroxyketone although this point was never unequivocally shown.



EXPERIMENTAL[1]

2,6-Dimethyl-1,4-cyclohexanediol (I). Ten grams of *m*-xyloquinone was reduced in ethanol over Raney nickel at 500 lbs. p.s.i. at 180°. The yield of product boiling at 85–90° at 0.3 mm. was 1.42 g. (13.5%). A redistilled sample was analyzed.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.70; H, 11.28.

3,5-Dimethyl-4-hydroxycyclohexanone (II). A solution of 0.9 g. (0.009 mole) of chromic oxide in 11 ml. of water was added dropwise to 2 g. (0.014 mole) of 2,6-dimethyl-1,4-cyclohexanediol in 95 ml. of glacial acetic acid. After the solution had stood for 2 hr. at room temperature and had been warmed for 15 min. on the steam bath, solvents were removed *in vacuo*. The residue was dissolved in water and extracted with chloroform. The chloroform extracts were washed with water and concentrated *in vacuo*. The residue was distilled at a bath temperature of 86° at 0.5 mm., n_D^{25} 1.4690. The ultraviolet spectrum showed absorption at 285 mμ, ε 25, the infrared spectrum at 2.80, 2.94, and 5.88 μ. The *2,4-dinitrophenylhydrazone* melted at 143–145° (from ethanol).

Anal. Calcd. for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.39. Found: C, 51.95; H, 5.69; N, 17.25.

The *p-toluenesulfonate* melted at 125–127° (from methanol).

Anal. Calcd. for $C_{15}H_{20}O_4S$: C, 60.78; H, 6.80; S, 10.82; mol. wt., 296.4. Found: C, 60.86; H, 7.04; S, 10.65; mol. wt. (ebull.), 266.8.

4-Acetoxy-3,5-dimethylcyclohexanone (III). A solution of 5.0 g. (0.035 mole) of 3,5-dimethyl-4-hydroxycyclohexanone and 35.8 g. (0.35 mole) of acetic anhydride in 120 ml. of dry pyridine was heated on the steam bath for 2 hr. The cooled solution was added to water which was then saturated with sodium bicarbonate. After evaporation of the solvent *in vacuo*, the residue was dissolved in water and extracted with ether. The ether extracts were dried and evaporated in *vacuo*. Distillation gave 3.33 g. (51%), b.p. 120° at 12 mm. The ultraviolet spectrum showed only end absorption; the infrared spectrum had bands at 5.78 and 5.83 μ.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76; $CH_3CO(1)$, 23.37. Found: C, 65.01; H, 8.80; CH_3CO, 15.57.

4-Acetoxy-1,3,5-trimethylcyclohexanol (IV). A solution of methylmagnesium iodide (from 0.82 g. of magnesium and 3 ml. of methyl iodide in 10 ml. of dry ether) and 3.2 g. (0.017 mole) of 4-acetoxy-3,5-dimethylcyclohexanone was refluxed, acidified with hydrochloric acid, and extracted with ether. The extracts were dried and concentrated *in vacuo*. Distillation gave 1.3 g. (38%) of diol monoacetate, b.p. 80° at 0.3 mm., n_D^{25} 1.4608. The infrared spectrum showed absorption at 2.82, 2.90, and 5.84 μ.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.96; H, 10.02; $CH_3C(4)$, 30.02; $CH_3CO(1)$, 21.49; mol. wt., 200.3. Found: C, 66.16; H, 10.59; CH_3C, 21.65; CH_3CO, 10.48; mol. wt. (ebull.), 184.3.

2,4,6-Trimethyl-3-cyclohexenyl acetate (V). A solution of 8.3 g. (0.041 mole) of 4-acetoxy-1,3,5-trimethylcyclohexanol and 0.55 g. of iodine in 70 ml. of dry toluene was refluxed for 4 hr. removing water continuously as formed. The toluene solution was washed with 5% sodium hydrosulfite solution and water and evaporated *in vacuo*. Distillation gave 3.48 g. (46%) of product, b.p. 82–93° at 11 mm., n_D^{25} 1.4638. This material gave the usual olefin tests, and the infrared spectrum no longer showed hydroxyl absorption but did show carbonyl absorption. A fractionated sample was analyzed.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96; $CH_3CO(1)$, 23.61; $CH_3C(4)$, 33.00; mol. wt., 182. Found: C, 72.12; H, 10.24; CH_3CO, 18.68; CH_3C, 25.19; mol. wt. (ebull.), 184.2.

2,4,6-Trimethyl-3-cyclohexenol (VI). A solution of 2,4,6-trimethylcyclohexenylacetate (prepared from 4.0 g. of IV and not distilled) and 10 g. of sodium hydroxide in 40 ml. of 50% alcohol was refluxed for 3 hr. The reaction mixture was diluted with water and extracted with ether. The ether extracts were dried, evaporated *in vacuo* and the residue was distilled. The yield of product boiling at 85–97° at 12 mm. was 0.8 g. The infrared spectrum showed absorption at 2.80 2.94, and 6.05 μ.

Anal. Calcd. for $C_9H_{16}O$: C, 77.10; H, 11.50; mol. wt., 140.2. Found: C, 77.96; H, 11.53; mol. wt. (ebull.), 131.

2,4-Dimethyl-3-hydroxy-6-oxoheptanal (VII). The 2,4,6-trimethyl-3-cyclohexenol from 2.0 g. of V was dissolved in 100 ml. of purified ethyl acetate. Ozone was bubbled through the cooled solution for 1.5 hr. After removal of the ethyl acetate *in vacuo* the residue was stirred for 18 hr. in 10 ml. of dry ether and 1.1 g. of glacial acetic acid with 0.8 g. of zinc dust. The zinc was removed and washed with ether which was added to the filtrate. This solution was washed with 5% sodium carbonate solution. The ether solution was dried and concentrated *in vacuo*. Attempted purification of the product was unsuccessful as distillation caused decomposition. The infrared spectrum had a band at 2.90 μ indicative of hydroxyl and carbonyl absorption bands at 5.82 and 5.88 μ.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.37; $CH_3C(3)$; 26.19. Found: C, 62.98; H, 9.31; CH_3C, 18.50.

Acknowledgment. The authors are grateful to Messrs. W. L. Brown, H. L. Hunter, and G. M. Maciak, and Miss Gloria Beckmann for microanalyses; and to Dr. H. E. Boaz and his staff for physical chemical data.

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(1) Melting points are uncorrected.

An Adduct of Hexachlorocyclopentadiene with Acenaphthylene

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Received January 26, 1960

Hexachlorocyclopentadiene has been shown to be an extremely versatile reactant in the diene synthesis.[1] During the course of a study involving Diels-Alder reactions of hexachlorocyclopentadiene, its addition to acenaphthene was tried. In view of the fact that naphthalene acts as a dienophile in this reaction,[2] it was expected that acenaphthene also might function in this manner, either through the five-membered ring or the naphthalene part of the molecule.

The reaction was effected by prolonged heating of the reactants and gave a monoadduct together with considerable tar. The properties and analysis of the product were best explained by assuming it was an addition product of acenaphthylene, the latter having been formed by the dehydrogenating action of hexachlorocyclopentadiene (chlorination followed by dehydrochlorination).

(1) H. E. Ungnade and E. T. McBee, *Chem. Revs.*, **58**, 249 (1958).

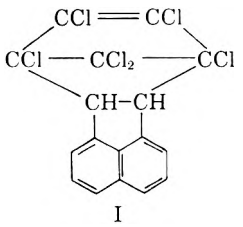
(2) A. A. Danish, M. Silverman, and Y. A. Tajima, *J. Am. Chem. Soc.*, **76**, 6144 (1954).

Accordingly, the addition of hexachlorocyclopentadiene to acenaphthylene was attempted and it was found that these interact readily in the cold to form the same adduct as is formed from acenaphthene but without tar production.

The adduct is a very stable substance, m.p. 192.5–194°, and unlike the naphthalene adducts[2] could not be cracked back to the components by pyrolysis under vacuum. Instead, it was distilled unchanged with slight decomposition at a low pressure.

The ultraviolet spectrum resembled that of a substituted acenaphthene, giving evidence that the five-membered ring only is attacked. The absorption peaks are given with ϵ values in parentheses: 225 (44,000), 268 (3710), 278 (6370), 288 (8020), 300 μ (5710). The corresponding figures for acenaphthene are: 227 (87760), 268 (3650), 279 (5780), 288 (6500), 300 μ (4150).

Structure I was thought to explain best the properties of the compound. The analytical values and the molecular weight are in agreement with this. The adduct undergoes nitration to give a mononitro derivative.



I

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns block.

Addition to acenaphthylene. A mixture of 5 g. (0.033 mole) of acenaphthylene and 10 ml. (0.063 mole) of hexachlorocyclopentadiene was warmed for solution and then left to stand at room temperature. Deposition of crystals began in a few hours and, after 2 days, the paste of product was worked up. It was stirred with a mixture of equal volumes of ether and peteroleum ether (b.p. 30–60°) (35 ml.) and filtered. The material was washed three times with this solvent mixture and dried; yield 11.45 g. (best obtained), 81.8%. Without recrystallization, this melted at 190.5–193° and, when mixed with the purified material from acenaphthene, it melted 191.5–193.5°.

Addition to acenaphthene. A solution of 25.4 g. (0.165 mole) of acenaphthene in 80 ml. (0.5 mole) of hexachlorocyclopentadiene was heated by a bath of boiling pinene (155–156°) for 130 hr. During this time, the mixture darkened and slow evolution of hydrogen chloride occurred. After cooling, the contents formed a nearly solid black mass. This was warmed, mixed with a little benzene to promote fluidity, and then stirred with a mixture of equal volumes of ether and petroleum ether (b.p. 30–60°). Crystalline grains soon formed and the suspension was left overnight. The product was filtered and washed with the same solvent mixture. Concentration of the filtrates and washings afforded a little more product. Yield of crude dark material was 49.1 g., 70%.

The compound was recrystallized a number of times from benzene-hexane and from ether with use of Norit. A pure white product was finally obtained, m.p. 192.5–194°. It forms characteristic sandy grains from these solvents.

Anal. Calcd. for $C_{17}H_8Cl_6$: Cl 50.12. Mol. wt.: 425. Found Cl 50.0. Mol. wt.: (Rast) 415.

In an attempt to crack the compound, it was heated with a free flame in a small flask at a pressure of 1 mm. A very high boiling material slowly distilled leaving a black tar in the flask. The solid distillate was recrystallized from benzene–petroleum ether (b.p. 30–60°) and formed grains, m.p. 187–190°. When mixed with the purest sample of starting adduct, the melting point was 188–191°.

Nitration. A solution of 2 g. of the adduct in 100 ml. of boiling glacial acetic acid was treated with 5 ml. of sulfuric acid. Then 4 ml. of concd. nitric acid was added cautiously, in portions. The orange solution was kept at 100–115° for 20–25 min. It was then cooled to about 80° and 10 ml. of water added, with stirring and cooling. The product separated as a yellow crystalline powder which was filtered, washed, and dried; yield 2.1 g. (95%). The nitro compound was recrystallized from acetone-water and from benzene–petroleum ether (b.p. 30–60°). On heating it sintered at 195–200° with melting point at 230.5–233°.

Anal. Calcd. for $C_{17}H_7Cl_6NO_2$: N 2.98. Found: N 2.83.

Acknowledgments. The author is indebted to W. Morgan Padgett II, Dietrich Heinritz, and Mrs. Jane Clark for spectral measurements and interpretations and analytical determinations, to H. P. C. Lee for assistance, and to Dr. Julius Hyman for encouragement during the work.

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Reaction of Isopropylzinc Iodide with Terebic Acid Chloride. A Suggested New Mode of Action of the Blaise Reagent

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Received February 8, 1960

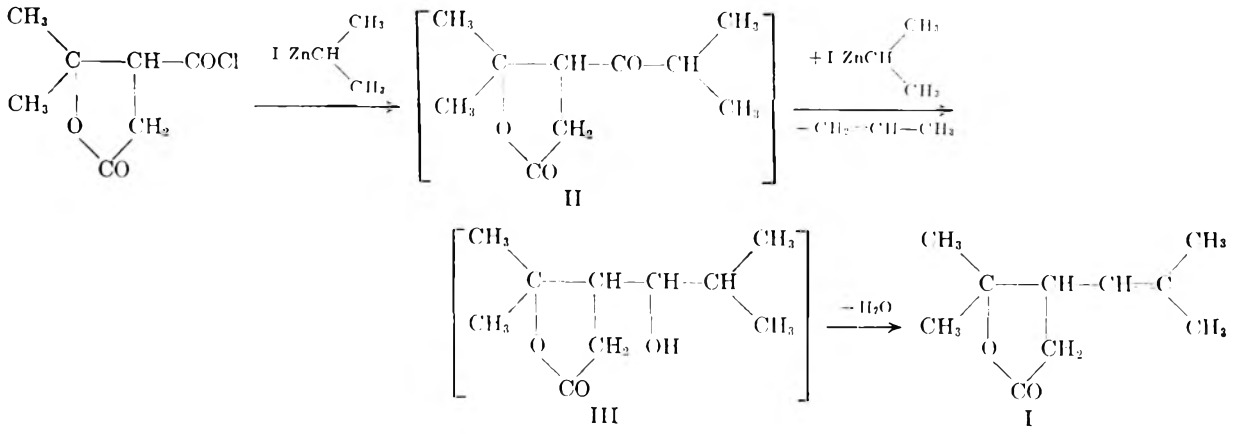
In the course of a study on the synthesis of a certain terpenoid compound, the authors became interested in the reaction of isopropylzinc iodide with terebic acid chloride. The reaction has been investigated by M. Matsui, *et al.*,[1] who by the reaction obtained pyrocin[2] (I), in 5% yield based on the acid chloride. They interpreted their unusual result by scheme A.

It is well known that a number of branched-chain Grignard reagents reduce carbonyl compounds to carbinols.[3] However, similar reduction by alkylzinc iodide seems never to have been described before the appearance of the above-cited work.[4] The present study was undertaken to ex-

(1) M. Matsui, T. Ohno, S. Kitamura, and M. Toyano, *Bull. Chem. Soc. Japan*, **25**, 210 (1952).

(2) Pyrocin was first isolated from the pyrolysate of pyrethrum flowers [M. Nagase and M. Matsui, *J. Agr. Chem. Soc. Japan*, **20**, 249 (1944)]. For structural studies, see S. H. Harper *et al.*, *J. Sci. Food Agr.*, **2**, 414 (1951).

(3) For a review, see M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall Inc., New York, 1954, pp. 147–165.



Scheme A

amine the property of the Blaise reagent as a reducing agent. This paper reports that the reagent possesses a fairly good reducing ability and that the above reaction does not proceed through a ketone (II).

In the original method,[1] the reaction was effected by condensing 0.25 mole of terebic acid chloride with the Blaise reagent prepared from 0.32 mole of isopropyl iodide. If the reaction follows the above presented scheme, at least two moles of the Blaise reagent should be used for one mole of the acid chloride. Simply by employing the molar ratio of 2:1 and by lengthening the reaction period as compared with the original method, a 49% yield of product I was easily obtained by distillation of the reaction mixture. In this case, as a by-product, a compound, m.p. 42.5–43.5°, was isolated from the higher boiling fraction by the countercurrent distribution method in 10% yield. The by-product possessed a molecular formula $C_{10}H_{16}O_4$ and exhibited infrared absorption bands at 1770 (γ-lactone) and 1720 cm.$^{-1}$ (C=O) and hence was formulated as isopropyl terebate. The validity of this conclusion was confirmed by comparison with an authentic sample. The ester seems to be formed as a result of air oxidation of the Blaise reagent. Thus a better yield of pyrocin may be obtained through complete exclusion of oxygen during the reaction. The presence of propylene in the gas evolved during the reaction was suggested by the reduction of the volume of the gas on treatment with concentrated sulfuric acid. It is therefore very probable that pyrocin is not formed as a result of complex side reactions and that the reaction path actually exists as stated above in the scheme A. However, the intermediate carbonyl compound (II) was not detected in the reaction mixture by dinitrophenylhydrazine, even when the starting materials were used in 1:1 molar ratio. In hope of proving the scheme A, preparation of the assumed ketone (II) was then attempted by the action of diisopropylcadmium upon terebic acid chloride in ether. The infrared spectrum of the reaction product however, revealed that an appreciable amount of isopropyl terebate was formed together with the desired ketone.[5] The presence of the ketone and of the ester was respectively confirmed by the isolation of dinitrophenylhydrazone and of the ester itself. However, as the separation of the two compounds was not so easy, the crude product was directly treated with isopropylzinc iodide. This treatment should afford pyrocin (I) and isopropyl terebate as a mixture, from which the two components may be separated by means of a combination of fractional distillation and countercurrent distribution. Contrary to expectation, the infrared spectrum of the reaction mixture, being almost identical with that of the starting material, strongly suggested that the material had been recovered unchanged. In fact the ketone (II) was isolated as dinitrophenylhydrazone. In the infrared spectrum of the reaction mixture no sign of the presence of pyrocin and its hypothetical precursor (III), which should exhibit an absorption band at 3300 cm.$^{-1}$ region, was indicated. The absence of pyrocin was confirmed by nuclear magnetic resonance absorption.[6] In Fig. 1 is depicted the NMR spectrum of the reaction mixture in carbon tetrachloride solution, taken on a Varian 40 MC machine.[7] The spectrum clearly demonstrates the absence of pyrocin[8] which should show two resonance lines due to one vinyl

(4) It was already known that diethylzinc reduces chloral to trichloroethanol. Gozarolli-Thurnlakh, *Ann.*, **210**, 63 (1881); **213**, 369 (1882); M. Delare, *Bull. soc. chim. France*, **48**, 784 (1887). Arylsulfonyl chlorides are reduced to sulfinic acids by mixed organozinc compounds. E. E. Blaise, *Bull. soc. chim. France*, 9 I (1911).

(5) Formation of the terebate may be due to air oxidation of diisopropylcadmium. Susceptibility of dialkylcadmium to oxidation was recently noted: A. G. Davies and J. E. Packer, *Chem. & Ind.*, **1958**, 1177. Ethyl terebate, which may be anticipated as a by-product [J. Cason and E. G. Reist, *J. Org. Chem.*, **23**, 1668 (1958) and previous papers of this series by J. Cason] was not detected by infrared spectrum. The ethyl ester shows characteristic absorption bands at 1162, 1038, and 1018 cm.$^{-1}$, while the mixture does not.

(6) Infrared spectrum alone does not provide a conclusive evidence for the absence of pyrocin, since its characteristic absorption band at 1665 cm.$^{-1}$ is weak.

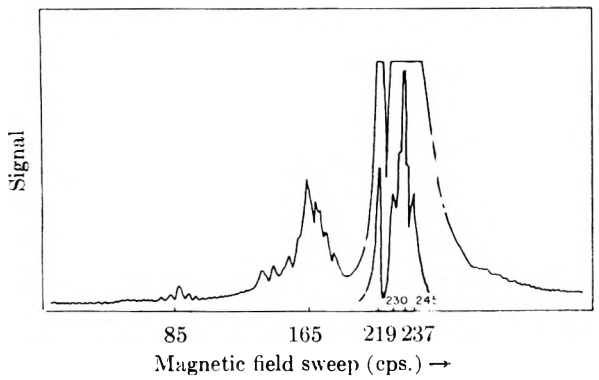


Fig. 1. Proton NMR spectrum at 40 mc in carbon tetrachloride of the product obtained from reaction of a mixture of II and isopropyl terebate with isopropylzinc iodide

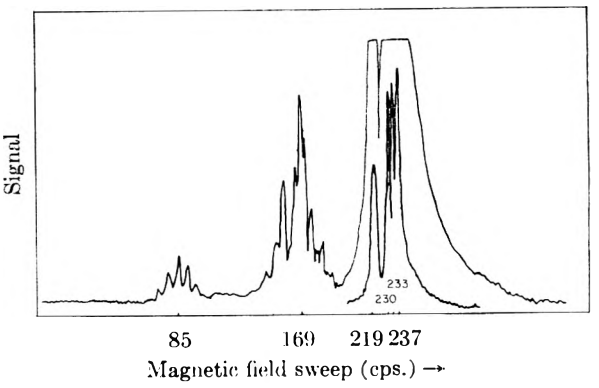
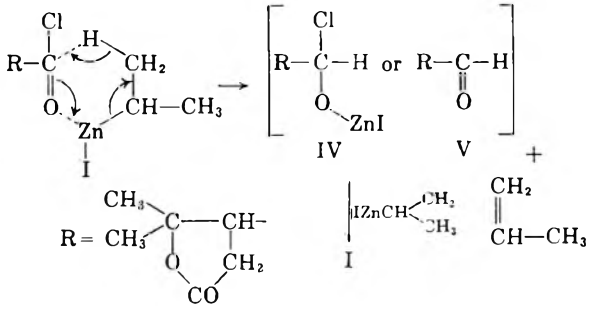


Fig. 2. Proton resonance spectrum of isopropyl terebate at 40 mc. in carbon tetrachloride

proton at lower magnetic field than 85 cps. (standard: benzene), on which the group of lines due to an α-proton of the isopropoxyl group of isopropyl terebate is centered.[9]

On the basis of the evidence presented above, it may be concluded that the reaction does not involve the ketone (II) as an intermediate. Probably, the reaction may proceed through the following route, the acid chloride being reduced *before* condensation rather than *after* condensation:



Scheme B

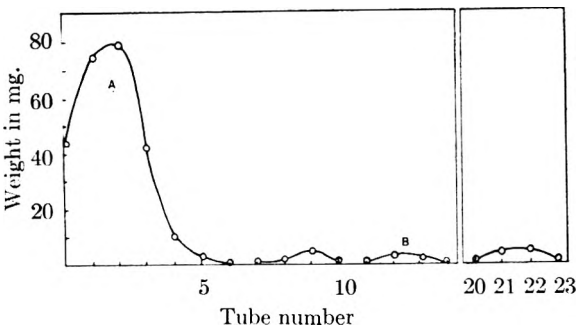


Fig. 3. Distribution curve of a high boiling fraction from reaction of terebic acid chloride and isopropyl zinc iodide

The intermediate may be either the α-haloalcoholate (IV) or the aldehyde (V). As the intermediates IV and V are anticipated to be reactive enough to combine easily with a further mole of the Blaise reagent, the suggested mechanism B affords a more reasonable explanation for the absence of any carbonyl compound in the reaction mixture. However, further studies are necessary before the detailed mechanism of the above reaction of the Blaise reagent can be elucidated. As a reaction similar to the first step of the scheme B, the reduction of acid chlorides to aldehydes and to the corresponding primary alcohols by the Grignard reagents may be mentioned.[10]

At an early stage of the present work, it was noted that treatment of terebic acid with thionyl chloride, which had been kept in the laboratory for over ten years, resulted in the formation of a compound $C_7H_8O_3$, m.p. 44°, and did not afford any detectable amount of the desired acid chloride. Similar observation has been made by Barbier and Loquin,[11] who regarded the product as caronic acid anhydride. However, the product has now been identified as teraconic acid anhydride by the melting point of

(7) The authors are very pleased to express sincere thanks to Prof. Genjiro Hazato of Tohoku University, Sendai, and his associates as well as to Dr. Ichiro Yamaguchi of Research Institute for Atomic Energy, Japan, for the measurement of the NMR spectra.

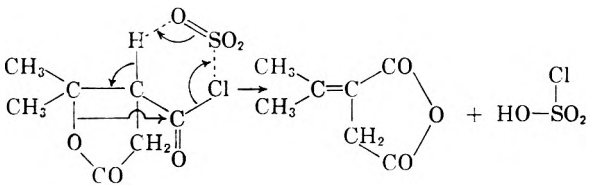
(8) Pyrocin exhibits double lines at 56 and 47.5 cps. Well defined methyl proton peaks appear at 190, 204, and 211 cps (Y. Ikenokami and A. Suzuki, unpublished observation).

(9) Comparison of the NMR spectra of the mixture with that of pure isopropyl terebate (Fig. 2) provides evidence for the ratio of the ketone (II) to the ester in the reaction mixture. As the line spacing between the septet due to α-proton of the isopropoxyl group is 7 cps., the peaks at 230 and 237 cps. (Fig. 2) with identical spacing may be ascribed to β-protons of the same isopropoxyl group. The remaining peaks at 219 and 233 cps. must then be due to the unequivalent geminal methyl groups on the lactone ring. Therefore, shifts at 237 (overlapped by methyl resonance of isopropoxyl group) and 245 cps. in Fig. 1 may be assigned to dimethyl protons of the isopropyl group of the ketone (II). The ratio of the area under the peak at 245 cps. to that under the peak at 230 cps. may therefore be regarded to present the approximate ratio of the ketone (II) to the ester.

(10) M. S. Kharasch and O. Reinmuth, *loc. cit.*, pp. 725–727.

(11) Ph. Barbier and R. Loquin, *Compt. rend.*, **153**, 188 (1911); *Bull. soc. chim. France*, **13**, 223 (1913).

the product as well as by melting and mixed melting point and infrared determination of the hydrolysis product, teraconic acid. As Barbier and Loquin's product melted at 44°, it actually may have been teraconic anhydride. The anhydride may be formed through the action of impurities such as sulfur trioxide in deteriorated thionyl chloride on the acid chloride as follows, as treatment of the acid chloride with a small amount of sulfur trioxide gave teraconic anhydride in excellent yield:



EXPERIMENTAL[12]

Terebic acid. The method of preparation described in the literature[1] gave a mixture of unidentified acids. It was modified as follows. To 108 g. of sodium methoxide in 400 ml. of anhydrous ether was added a mixture of 120 g. of acetone and 145 g. of methyl succinate under cooling with ice, and the resulting mixture was allowed to stand for 2 days at room temperature. Concd. hydrochloric acid (700 ml. rather than 350 ml.) and water (350 ml.) were poured into the mixture. After removal of ether, the residue was heated under reflux for 12 hr. Hot water (400 ml.) was added to the mixture, and the solution was decolorized with Norite and allowed to stand overnight. Terebic acid, which separated, was collected and recrystallized from water; yield 65 g.

Teraconic anhydride. A mixture of terebic acid (9 g.), thionyl chloride (15 ml., an old sample was used without purification) and dry benzene (40 ml.) was refluxed until no more hydrogen chloride gas evolved (for about 20 hr.). After removal of benzene and excess thionyl chloride, the residue was distilled *in vacuo* and a fraction boiling at 137–145° (9 mm.) was collected; yield 4.6 g. On being put aside, the distillate soon solidified. After recrystallization from carbon disulfide, the solid product melted at 44°.

Anal. Calcd. for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.15; H, 5.63.

Teraconic acid was obtained by hydrolysis of the anhydride with water. The acid decomposed at 160–161° when rapidly heated and at 154–156° on slow heating, and no melting point depression was observed on admixture with authentic sample.[13]

Terebic acid chloride. A mixture of thionyl chloride (30 ml.) purified by Fieser's procedure,[14] terebic acid (18 g.), and dry benzene (80 ml.) was heated under reflux until no more hydrogen chloride gas evolved (for about 9 hr.). The mixture was distilled and a fraction boiling at 123–129° (10 mm.) was collected; yield 17 g. ν_{max}^{film} 1785 cm.$^{-1}$ (C=O). Absence of absorption bands characteristic of the acid anhydride group indicated that no detectable amount of teraconic anhydride was produced in this case. Newly purchased, unpurified thionyl chloride gave an essentially same result. Addition of a small quantity of water or sulfur monochloride, a possible impurity of the commercial thionyl chloride, also did not alter the result.

The reaction of terebic acid chloride with sulfur trioxide was examined as follows. A mixture of terebic acid chloride (1.1 g.) and a small amount of sulfur trioxide in 4 ml. of benzene was heated under reflux for 13 hr. On removal of benzene, the residue was solidified, m.p. 41–43°. Recrystallization from carbon disulfide raised the melting point to 44°. No depression in melting point was observed on admixture with teraconic anhydride which was prepared above. When phosphorus trichloride was used instead sulfur trioxide, the acid chloride was recovered unchanged.

Reaction of isopropylzinc iodide with terebic acid chloride. Zinc-copper couple (60 g. weight ratio 10:1), isopropyl iodide (50 g.), and 25 ml. of ligroin (b.p. 87–95°) were placed in a three necked flask equipped with an inlet tube for nitrogen, a reflux condenser, and a mercury sealed stirrer. A slow stream of nitrogen was introduced and stirring and heating were continued for 10 hr. After cooling, dry benzene was added to the reaction mixture. A portion of the solution was submitted for analysis.[15] A portion of isopropylzinc iodide solution (containing 0.04 mole of the reagent) was placed in a flask equipped with a condenser, a mercury sealed stirrer, a dropping funnel and an inlet tube for nitrogen gas. Terebic acid chloride (3.6 g.; 0.02 mole) in 15 ml. of dry benzene was added with stirring and passing nitrogen, under cooling with ice. After the stirring had been continued for 2 hr., the reaction mixture was allowed to stand at room temperature for a week. The viscous mixture was hydrolysed with 70 g. of ice and 30 ml. of 6N hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed successively with water, 5% sodium carbonate solution, and again with water and dried with anhydrous sodium sulfate. In this way, 3.1 g. of a neutral product was obtained. Distillation of the product gave 1.7 g. of crude pyrocin, b.p. 135–145° (35 mm.) and 0.6 g. of an unknown product, b.p. 115–135° (6 mm.) The former fraction crystallized after being kept overnight at −35°. Recrystallization from petroleum ether (b.p. 30–60°) gave pure *dl*-pyrocin, m.p. 61–62° (lit.,[1] m.p. 61–62°). The fraction, b.p. 115–135° (6 mm.) was fractionated by countercurrent distribution in the glass apparatus designed by Craig with the system *n*-hexane and 85% aqueous methanol as solvents. The distribution curve was plotted with weight of material in each tube as ordinates and the tube numbers as abscissas. Fig. 3 illustrates the result obtained using this method on 0.47 g. of the above unknown substance. The material of the cut A became a scaly crystalline product. Recrystallization from *n*-hexane gave isopropyl terebate, m.p. 42.5–43.5°, ν_{max}^{nujol} 1770 cm.$^{-1}$ (γ-lactone) 1720 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.78; H, 8.12.

The cut B gave *dl*-pyrocin. An authentic sample of isopropyl terebate was prepared by the reaction of terebic acid with an excess of isopropyl alcohol in the presence of a small amount of concd. sulfuric acid; m.p. 43°, mixed m.p. 43°.

(12) All melting points and boiling points are uncorrected. Infrared spectra were taken on a Koken model DS-301 infrared spectrophotometer. The workers wish to thank Mr. O. Yonemitsu of the Pharmaceutical Institute of Hokkaido University for the spectral data and Miss N. Fujino for the microanalyses.

(13) H. Stobbe, *Ber.*, **36**, 197 (1903).

(14) L. F. Fieser, *Experiments in Organic Chemistry*, rev. 3rd ed., D. C. Heath and Company, Boston, 1955, p. 345.

(15) The analysis was effected by adaptation of H. Gilman's gas analysis method for Grignard Reagent (H. Gilman, P. D. Wilkinson, W. P. Fishel and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923)) and by the gravimetric determination of zinc in the solution by the pyrophosphate method (I. M. Kolthoff and E. B. Sandell, *Textbook of Quantitative Inorganic Analysis*, The Macmillan Company, London, 1936, p. 345). The two methods afforded consistent results.

Reaction of diisopropylcadmium with terebic acid chloride. An ether solution (47.5 cc.) of isopropylmagnesium bromide (0.065 mole[16]) was cooled to 0°, and 10 g. (0.037 mole) of powdered anhydrous cadmium bromide was added in several portions during about 5 min. The solution was stirred under ice-cooling until a negative Gilman test for Grignard reagent was obtained (usually in about 30 min.). A solution of 5.5 g. (0.031 mole) of terebic acid chloride in 20 ml. of benzene was added during about 5 min. After stirring has been continued for 4 hr. under ice-cooling and for 2 hr. at room temperature, the reaction vessel was kept air-tight and allowed to stand for a week. After addition of ice and 6*N* hydrochloric acid and extraction of the aqueous layer with ether, the total ether solution was successively washed once with water, twice with 5% sodium carbonate solution, and three times with sodium chloride solution; then it was dried. There remained 3.8 g. of a neutral product C; $\nu_{max}^{CCl_4}$ 1780 cm.$^{-1}$ (lactone), 1730 cm.$^{-1}$ (ester), 1710 cm.$^{-1}$ (ketone). Distillation gave 2.8 g. of colorless liquid, b.p. 138–141° (8 mm.). Upon seeding, it formed colorless crystals (2 g.; 32%), which were identified with isopropyl terebate by mixed melting point determination. When the oily portion of the distillate was allowed to stand for a long time (about 1 month) with Brady reagent in ethanol, a 2,4-dinitrophenylhydrazone (1.2 g.; 10.6% based on terebic acid chloride) was obtained. A sample for analysis was prepared by recrystallization from methanol; it formed orange needles, m.p. 175–176.5°.

Anal. Calcd. for $C_{16}H_{20}O_6N_4$: C, 52.74; H, 5.53. Found: C, 52.80; H, 5.67.

Reaction of the ketone (II) *with Blaise reagent.* The above mixture C (900 mg.; prepared in another run) containing the ketone (II) and isopropyl terebate was dissolved in 2 ml. of dry benzene. The solution was added with stirring under cooling with ice to 7.5 ml. of isopropylzinc iodide-benzene solution which contained 0.002 mole of the reagent. After the stirring was continued for 2 hr., the reaction mixture was allowed to stand at room temperature for 8 days. The reaction mixture was hydrolyzed with ice and 6*N* sulfuric acid; the separated organic layer and ether extracts were combined and washed successively with water, 5% sodium bicarbonate, and saturated sodium chloride aqueous solution. After having been dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure. A pale orange-red oily residue (750 mg.) was obtained. The residue was negative to Baeyer reagent to which pyrocin is positive. On treatment with Brady's Reagent, the residue afforded dinitrophenyl hydrazone of the ketone (II). The NMR spectrum of the residue was reproduced in Fig. 1.

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(16) Analysed by Gilman's method; *cf.* ref. 13.

The Preparation of Acetylated Aldonic Acids

ROBERT BARKER

Received March 7, 1960

The fully acetylated aldonic acids are important as intermediates in the synthesis of ketones[1] and some aldoses.[2] However, attempts to acetylate the aldonic acids or their salts have demonstrated that the yield of the desired product not only depends upon the stereochemistry of the acid but, with any given acid, varies markedly with the particular salt employed.[3]

The most generally applicable method for the preparation of acetylated aldonic acids involves formation of the amide, followed by acetylation, and then regeneration of the free acid from the amide,[4] although in some instances the use of this procedure has proved difficult.[5]

This report describes a method for the preparation of acetylated aldonic acids in good yields from the salts of the acids. The yields obtained are virtually independent of the salt used.

EXPERIMENTAL

A solution prepared at room temperature of 1.75 g. (12.9 mmoles) of fused zinc chloride in 25 ml. of acetic anhydride was cooled to −5° and 5 g. (24.3 mmoles) of finely divided potassium arabinonate was added. The suspension was then saturated with dry hydrogen chloride, care being taken to maintain a reaction temperature of less than 5°. When saturated, the mixture was set at room temperature and protected from atmospheric moisture by a calcium chloride tube. After standing at room temperature for periods varying from 5 to 18 hr. the reaction mixture was chilled in an ice bath and small portions of chipped ice were added cautiously to destroy the excess acetic anhydride. To ensure complete destruction of the anhydride, the reaction mixture was left at 0° for 1 hr., then diluted to approximately 100 ml. with water, and extracted six to eight times with 30-ml. portions of chloroform or dichloromethane. The extracts were dried over sodium sulfate, filtered from the drying agent, and concentrated *in vacuo* at 40° to a yellow sirup. This sirup was twice concentrated *in vacuo* with 40-ml. portions of toluene, then dissolved in 25 ml. of warm toluene, and the solution cooled. Crystallization occurred spontaneously within a few hours. The yield varied from 6.0 to 6.8 g. (74–84%) and the material melted at 135–136°, with $[\alpha]_D^{25}$ +32.0° (c 4.0, chloroform).

The yields of acetylated aldonic acids and their physical constants are listed in Table I. All of the acetates were prepared in a similar fashion to that described above except that the ammonium salts were allowed to react for a longer time because of their slower solubilization in the reaction mixture.

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(1) M. L. Wolfrom, D. I. Weisblat, E. F. Evans, and J. B. Miller, *J. Am. Chem. Soc.* 79, 6454 (1957) and previous communications in the series.

(2) E. W. Cook and R. T. Major, *J. Am. Chem. Soc.*, 58, 2410 (1936).

(3) K. Ladenburg, M. Tishler, J. W. Wellman, and R. D. Babson, *J. Am. Chem. Soc.*, 66, 1217 (1944).

(4) G. B. Robbins and F. W. Upson, *J. Am. Chem. Soc.*, 60, 1788 (1938).

(5) G. B. Robbins and F. W. Upson, *J. Am. Chem. Soc.*, 62, 1074 (1940).

(6) C. D. Hurd and J. C. Sowden, *J. Am. Chem. Soc.*, 60, 235 (1938).

(7) Crystallized from water as a monohydrate.

(8) E. W. Cook and R. T. Major, *J. Am. Chem. Soc.*, 58, 2474 (1936).

TABLE I

ACETYLATED ALDONIC ACIDS

Acid	Salt	Yield, %	Product M.P.	Product $[\alpha]_D^{20-25}$ in chloroform	Reported Constants M.P.	Reported Constants $[\alpha]_D$ in chloroform	Reference
Arabinonic	K^+	78					
	Ca^{++}	76	135–136°	+32.0°	135–136°	+32.5°	(5)
	Zn^{++}	78					
Gluconic	K^+	78					
	NH_4^+	65	110–112	+11.8	110–111	+11.5	(8)
	Ca^{++}	77					
Galactonic	K^+	76	129–130	+12.1	131.2	+12.0	(6)
	$Ca^{++}\cdot 5H_2O$	82					
Mannonic	NH_4^+	71	74–76[7]	+25.1	75–76[7]	+24.8	(5)

N-(β-Picolyl)glycine, *N*-(β-Picolyl)-β-aminopropionic Acid, and Their Methyl Derivatives

HARVEY N. WINGFIELD, JR.

Received February 15, 1960

The compounds *N*-(β-picolyl)glycine, *N*-(β-picolyl)-β-aminopropionic acid, and corresponding methyl derivatives were synthesized for comparison with the metabolic products of nicotine found in the urine of dogs after administration of nicotine. Since no reference to these compounds could be found in the literature, their synthesis is reported here.

EXPERIMENTAL

N-(β-Picolyl)glycine. Glycine ethyl ester hydrochloride (14 g., 0.1 mole) was dissolved in the minimum quantity of water and treated with 8.4 g. (0.1 mole) of sodium bicarbonate. Alcohol was added and the precipitated sodium chloride was removed by filtration, collecting the filtrate in a hydrogenation bottle. Pyridine-β-carboxaldehyde (10 g., 0.1 mole) was added and the mixture was hydrogenated, employing 100 mg. of palladium catalyst.[1] After the hydrogenation was completed the catalyst was filtered, and most of the solvent was evaporated under vacuum. The residual ester was washed with water, dissolved in acetone, and the insoluble material was removed by filtration. The acetone was evaporated under vacuum and the residue was dissolved in chloroform. After filtering and again removing the solvent, *N*-(β-picolyl)glycine ethyl ester remained as a viscous yellow oil. The yield of crude product was 50–60%. Attempts to distill the ester resulted in decomposition.

Several batches of the ester were combined in a flask, acidified with 15% sulfuric acid, and refluxed for 48 hr. The hydrolyzate was decolorized by boiling with activated charcoal and filtering. Sulfuric acid was removed by making the solution alkaline with barium hydroxide and filtering, and the excess barium hydroxide was removed by treating the solution with carbon dioxide, boiling, and filtering. Residual traces of barium were removed by treating the solution with a very small amount of cadmium sulfate, and precipitating the excess cadmium with hydrogen sulfide. The filtrate was evaporated under vacuum, the acid residue was dissolved in a minimum amount of water, and the *N*-(β-picolyl)lgycine was precipitated with alcohol-acetone. After several recrystallizations in this manner, the acid, m.p. 209–210° dec., was dried overnight for analysis.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 57.83; H, 6.02. Found: C, 57.71; H, 6.13.

The thiohydantoin, m.p. 176–177° dec., was prepared from azobenzene isothiocyanate by the method of Ramachandran and McConnell.[2]

Anal. Calcd. for $C_{21}H_{17}N_5OS$: C, 65.11; H, 4.39. Found: C, 64.94; H, 5.07.

N-Methyl-N-(β-picolyl)-glycine. A mixture of 0.2 mole of *N*-(β-picolyl)glycine ester and 100 ml. of formaldehyde was placed in a pressure bottle wth 70–75 g. Raney nickel catalyst and reduced with hydrogen at a gage pressure of 45 p.s.i. Absorption of hydrogen ceased after 3 hr. The catalyst was removed by filtration, and the solution evaporated to near dryness under vacuum. The residue was hydrolyzed by refluxing for several days with 15% sulfuric acid. After decolorization with activated carbon, the *N*-methyl-*N*-(β-picolyl)glycine was recovered by the same procedure employed with *N*-(β-picolyl)glycine. The yield of crude material was nearly quantitative. The methylated compound, m.p. 175–176°, was more soluble in alcohol than the unmethylated.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.00; H, 6.66. Found: C, 59.90; H, 7.03.

The chloroplatinate, m.p. 217° dec., was recrystallized from alcohol-water.

Anal. Calcd. for $C_9H_{14}N_2O_2Cl_6Pt$: C, 18.31; H, 2.37; Pt, 33.05. Found: C, 18.43; H, 2.98; Pt, 32.81.

N-(β-Picolyl)-β-aminopropionic acid (chloroplatinate and thioureide). β-Picolylamine (54 g., 0.5 mole) was chilled in an Erlenmeyer flask and 25 g. (0.47 mole) of acrylonitrile was added dropwise over a period of 2 hr. The mixture was allowed to come to room temperature and left standing for several days with occasional shaking. Fractional distillation of the mixture under 5 mm. pressure gave three fractions: (1) 95–96° (unchanged amine), (2) 165–170°, (3) above 170°. Fraction 2, which represented a yield of about 30%, was refluxed about 20 hr. with 15% sulfuric acid. The sulfuric acid was removed by treating with excess barium hydroxide and filtering. The filtrate was evaporated to a small volume and extracted three times with chloroform, thus removing a small amount of picolylamine. The aqueous solution was treated with carbon dioxide, boiled, and filtered to remove barium. The filtrate was evaporated to a small volume. After standing several weeks in a vacuum desiccator, the liquid solidified to a waxy mass. The material was dissolved in absolute alcohol and precipitated with acetone. The yield of a product, which still contained a

(1) Later, it was found that Raney nickel catalyst gave better results.

(2) L. K. Ramachandran and W. B. McConnell, *J. Am Chem. Soc.*, **78**, 1255 (1956).

trace of barium, was 10–12%. A satisfactory analysis could not be obtained even after repeated recrystallizations. The acid decomposed in the neighborhood of 270°. The chloroplatinate, decomposing above 250°, was prepared and recrystallized from alcohol-water.

Anal. Calcd. for $C_9H_{14}N_2O_2Cl_6Pt$: C, 18.31; H, 2.37; Pt, 33.05. Found: C, 18.71; H, 2.57; Pt, 33.19.

The thioureide, m.p. 174–176° dec., was prepared from azobenzene isothiocyanate.[2]

Anal. Calcd. for $C_{22}H_{21}N_5O_2S$: C, 63.01; H, 5.01. Found: C, 63.13; H, 5.29.

N-(β-Picolyl)-β-methylaminopropionitrile. β-Picolylmethylamine (25 g., 0.2 mole) was dissolved in 150 ml. of benzene contained in a three-necked flask fitted with stirrer, dropping funnel, and reflux condenser. Four or five pellets of potassium hydroxide were added and then a solution of 21.2 g. (0.4 mole) of acrylonitrile was added slowly while stirring. After 2 days at room temperature, the mixture was refluxed on the steam bath for several days. The insoluble material was removed by filtration, and the benzene was evaporated. On distillation of the thick residue in vacuum, the nitrile distilled as a slightly turbid liquid at 121–125° (1 mm.). The chloroplatinate, m.p. 228° dec., was recrystallized from alcohol-water.

Anal. Calcd. for $C_{10}H_{15}N_3Cl_6Pt$: C, 20.61; H, 2.58; Pt, 33.50. Found: C, 20.45; H, 2.57; Pt, 33.32.

N-(β-Picolyl)-β-methylaminopropionic acid. The nitrile, prepared above, was hydrolyzed by refluxing with 50% sulfuric acid. The hydrolyzate was treated with barium hydroxide, filtered, and the filtrate treated with carbon dioxide and again filtered to remove the barium. The filtrate was evaporated, and the residue dissolved in chloroform and filtered. Evaporation of the chloroform left the crude product that did not crystallize. Even after standing 6 months in a vacuum desiccator, it remained a viscous liquid. The dihydrochloride was prepared by the method of Liwschitz, Zilkha and Shahak.[3] This compound is a white crystalline solid, melting at 205–206° with slight decomposition.

Anal. Calcd. for $C_{10}H_{16}N_2O_2Cl_2$: C, 45.11; H, 6.01. Found: C, 44.97; H, 5.98.

The chloroplatinate, decomposing without melting, was recrystallized from alcohol-water.

Anal. Calcd. for $C_{10}H_{16}N_2O_2Cl_6Pt$: C, 19.96; H, 2.66; Pt, 32.45. Found: C, 19.61; H, 2.71; Pt, 32.44.

Acknowledgment. The author wishes to thank Mrs. Joyce Booth for the microanalyses.

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(3) Y. Liwschitz, A. Zilkha, and I. Shahak, *J. Org. Chem.*, 21, 1530 (1956).

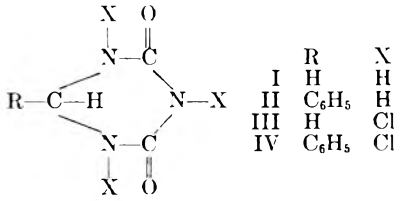
Chlorination of 2,4-Dioxohexahydro-1,3,5-triazines

FRANK B. SLEZAK, ALFRED HIRSCH, LEWIS I. KRIMEN,[1] AND HENRY A. MCELRAVY, JR.

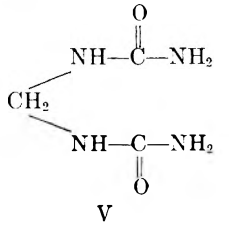
Received February 19, 1960

During the course of studying various *N*-halogen compounds, suitable methods of preparing *N*-chlorohexahydro-*s*-triazines became of interest to us.

(1) Present address: Nalco Chemical Co., Chicago, Ill.



	R	X
I	H	H
II	C_6H_5	H
III	H	Cl
IV	C_6H_5	Cl



V

Our attempts to prepare 2,4-dioxohexahydro-1,3,5-triazine (I) by previously described methods[2,3] were unsatisfactory because of low yield and purity of product. A far more convenient method was devised whereby crude, dry methylenediurea (V) was cyclized in a stirred, refluxing diluent such as nitrobenzene, *n*-hexyl ether, or the dibutyl ether of diethylene glycol (dibutyl Carbitol). Nitrobenzene seemed most convenient to use. The methylenediurea was prepared by a simplification of the method described by Kadowaki.[4] The method of Krassig and Egar[5] was used to prepare 6-phenyl-2,4-dioxohexahydro-1,3,5-triazine (II).

It was found that the efficiency of the halogenation in an aqueous medium was dependent on the *p*H and on the temperature at which the halogenation was carried out. Chlorination of I and II, to the novel III and IV respectively, gave the best results when the reactions were carried out in the range *p*H 1–3 and at ice temperatures. Chlorination at higher *p*H ranges and/or at higher temperatures resulted in diminished yields of product.

1,3,5-Trichloro-2,4-dioxohexahydro-1,3,5-triazine (III), in concentrations as low as 1 p.p.m., completely inhibited the growth of the test organisms *Erwinia amylovora*, *Xanthomonas phaseoli*, *Micrococcus pyrogenes* var. *aureus*, and *Escherichia coli*.[6]

EXPERIMENTAL[7]

Methylenediurea (V). Water (1500 ml.), urea (1200 g., 20 moles), 40% aqueous formaldehyde (250 ml., 3.32 moles),

(2) O. Diels and R. Lichte, *Ber.*, **59B**, 2778 (1926).

(3) H. Fahrenhorst and H. Scheuermann, German Patent **694,823** (1940).

(4) H. Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936); *Chem. Abstr.*, **30**, 5944.[6]

(5) H. Krassig and G. Egar, *Makromol. Chem.*, **18/19**, 195 (1956).

(6) Biological data provided by Dr. Paul H. Schuldt of the Boyce Thompson Institute for Plant Research, Inc., Yonkers, N. Y.

(7) All melting points are uncorrected. Elemental analyses by Diamond Alkali Company Research Analytical Laboratory. Available halogen determinations by sodium thiosulfate titration. The theoretical percent available halogen is taken as twice the weight percent of halogen attached to nitrogen.

and concd. hydrochloric acid (25 ml.) were stirred for 24 hr. The resulting solid was filtered and oven dried at 110°. Yields were of the order of 380–420 g. (88–98%) of material, melting at 210–220°, which was suitable for the preparation of I.

2,4-Dioxohexahydro-1,3,5-triazine (I). A stirred mixture of crude, dry methylenediurea (132 g., 1 mole) and 500 ml. of nitrobenzene was heated at a gentle reflux for 4–5 hr. After cooling and filtering, the tan residue was triturated with two 200-ml. portions of ethyl ether. The solid was extracted with three 1-l. portions of boiling water, the combined extracts decolorized with carbon, concentrated until crystals began to form, and cooled. Filtration and drying gave 80 g. (69.5%) of material decomposing above 300°.

Anal. Calcd. for $C_3H_5N_3O_2$: C, 31.3; H, 4.3. Found: C, 31.3; H, 4.4.

1,3,5-Trichloro-2,4-dioxohexahydro-1,3,5-triazine (III). I (23 g., 0.2 mole) was suspended in 500 ml. of water in a 1-l. beaker furnished with a gas dispersion tube, a mechanical stirrer, and an addition funnel, and cooled by an ice bath. The electrodes of a Beckman Model H-2 *p*H meter were so arranged that the *p*H of the contents of the beaker could be followed continuously. Chlorine (46 g., 0.648 mole) was passed in over a 2-hr. period while 6*N* sodium hydroxide was added at such a rate as to maintain the *p*H of the reaction mixture in the range *p*H 2.0–2.5. The solid was filtered, washed with two 50-ml. portions of water, and dried to give 31 g. (69%) of III containing 91% available chlorine (97.5% is theoretical). Recrystallization from chloroform–carbon tetrachloride gave white plates melting at 137–138°.

Anal. Calcd. for $C_3H_6Cl_3N_3O_2$: C, 16.5; H, 0.9; Cl, 48.7; N, 19.2. Found: C, 16.8; H, 0.8; Cl, 47.4; N, 19.4.

1,3,5-Trichloro-6-phenyl-2,4-dioxohexahydro-1,3,5-triazine (IV). II (15.2 g., 0.08 mole) was chlorinated, by the use of 18 g. (0.253 mole) of chlorine, and worked up in the manner described for III to give 21 g. (87%) of IV containing 70% available chlorine (72.4% is theoretical). Recrystallization from chloroform gave a white solid melting at 248–249°.

Anal. Calcd. for $C_9H_6Cl_3N_3O_2$: C, 36.8; H, 2.1; Cl, 36.2; N, 14.3. Found: C, 36.8; H, 3.0; Cl, 35.1; N, 14.5.

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Potential Anticancer Agents.[1] XXXVII. Monofunctional Aziridines Related to Tetramin

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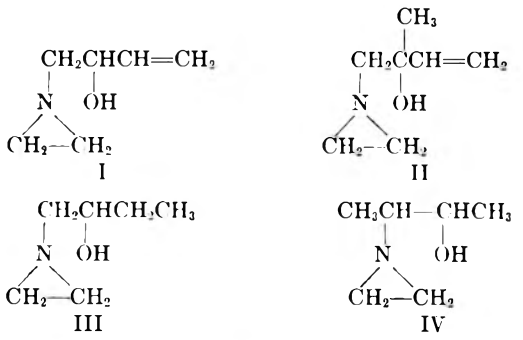
Received March 2, 1960

Tetramin [β-(1-aziridinyl)-α-vinylethanol] (I) is a broad spectrum anticancer agent which is active against a variety of transplanted animal tumors[2] as well as several human carcinomas.[2,3] Oettel[2] has reported that both the hydroxyl group and the double bond of Tetramin are necessary in order to maintain anticancer activity but did not cite evidence. Frohberg[4] reported that



β-(1-aziridinyl)-α-methyl-α-vinylethanol (II) showed reduced activity against Ehrlich Ascites-Carcinoma, Sarcoma 37, and Walker-Carcinosarcoma 256, as compared with Tetramin (I).

These results lead us to report our findings on the synthesis and activity of the Tetramin analogs (II–IV). These compounds were tested on the mouse tumors Sarcoma 180, Adenocarcinoma 755, and Leukemia L-1210. Tetramin has a substantial anticancer effect in all three of these systems.[3] However the three analogs (II–IV) were inactive at the maximum tolerated doses which were lower than the range where Tetramin showed activity. It is interesting to speculate that the possibility of biological oxidation of the secondary hydroxyl of Tetramin supplies the normal cell with a mechanism of detoxification which is apparently lacking in the cancer cell, thus accounting for the higher toxicity and resultant lack of activity of II–IV. Allylic alcohols are reported to be more easily oxidized to the carbonyl than the corresponding saturated alcohols,[5] thus offering a possible explanation for failure of the normal cell to detoxify the saturated analog (III) of Tetramin or the isomer (IV) by oxidation. The lowered activity of II compared with Tetramin observed by Frohberg[4] and the absence of selective activity of II observed in our laboratories is also understandable on the basis of an oxidative detoxification of Tetramin by the normal cell.

The synthesis of β-(1-aziridinyl)-α-methyl-α-vinylethanol (II) was accomplished in 70% yield by the addition of ethylenimine to 3,4-epoxy-3-methyl-1-butene. Although there is a possibility of obtaining two isomers from this addition, no isomeric β-(1-aziridinyl)-β-methyl-β-vinylethanol could be detected by vapor phase chromatography.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No: SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

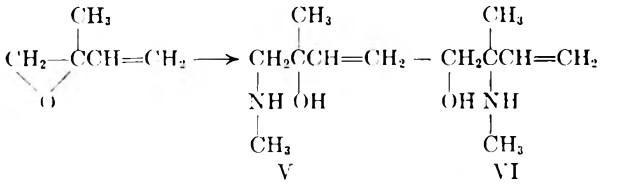
(2) H. Oettel, *Angew. Chemie*, **71**, 222 (1959).

(3) Cancer Chemotherapy Reports, issued by Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., August 1959, p. 52.

(4) H. Frohberg, *Arch. exp. Pathol. Pharmakol.*, **236**, 280 (1959).

(5) (a) H. Adkins, R. M. Elofson, A. G. Rossow, and C. C. Robinson, *J. Am. Chem. Soc.*, **71**, 3622 (1949). (b) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

This is somewhat surprising in view of the recent report[6] that the reaction of 3,4-epoxy-3-methyl-1-butene with methylamine gave a mixture of the primary (V) and secondary (VI) addition products in the ratio of 10 to 1. The addition of ethylenimine to 1,2-epoxybutane followed by distillation of the product, gave a 50% yield of a material which was 98% pure as shown by vapor phase chromatography and which is presumed to be β-(1-aziridinyl)-α-ethylethanol (III). Similarily, 2,3-epoxybutane gave a 45% yield of β-(1-aziridinyl)-α,β-dimethylethanol (IV) which was 93% pure according to vapor phase chromatography.



V VI

EXPERIMENTAL[7]

3,4-Epoxy-3-methyl-1-butene. To a vigorously stirred suspension of 67.3 g. (0.99 mole) of isoprene in 250 ml. of water was added 176.1 g. (0.99 mole) of *N*-bromosuccinimide at a rate which kept the temperature between 18–25°. After the addition (about 0.5 hr.) was complete, the mixture was stirred at 18–25° for 2–3 hr. by which time all of the *N*-bromosuccinimide was in solution and the solution gave a negative test with potassium iodide paper.

The organic layer was extracted with three 90-ml. portions of diethyl ether. The combined ether layers were dried over magnesium sulfate, then evaporated to dryness *in vacuo* to yield 151 g. of the crude bromohydrin of isoprene.

The isoprene bromohydrin was added over 20–30 min. to 270 g. of 30% aqueous sodium hydroxide which had been cooled to 10–15° in an ice bath. After the addition was complete, the reaction was stirred at about 10° for 2 hr., then the organic phase was separated from the aqueous layer. The aqueous layer was washed with 50 ml. of ether. The ether layer and organic layer were combined, dried over magnesium sulfate, then distilled through a small Vigreux column to yield 33.7 g. (41%) of 3,4-epoxy-3-methyl-1-butene, b.p. 78–82°, n_D^{26} 1.4139, which was 91% pure as shown by vapor phase chromatography;[8] $\lambda_{max(\mu)}^{film}$ 6.07 (C=C), 7.20 (CH_3), 10.08, 10.85 (—CH=CH_2), 11.25, 12.75 (epoxide).

Pummerer and Reindel[9] prepared this compound in 30–40% yield by the reaction of isoprene with perbenzoic acid. They reported b.p. 81° (735 mm.) and n_D^{19} 1.4179. Petrov[10] reported b.p. 78.5–79° and n_D^{20} 1.4142 for 3,4-epoxy-3-methyl-1-butene prepared using *N*-bromoacetamide, then 80% potassium hydroxide.

β-(1-Aziridinyl)-α-methyl-α-vinylethanol (II). To a mixture of 10.0 g. (0.12 mole) of 3,4-epoxy-3-methyl-1-butene in 5 ml. of water was added dropwise with stirring 10.2 g. (0.24 mole) of ethylenimine dissolved in 5 ml. of water. The temperature was kept at 15–20° during the addition of the ethylenimine and for 3 hr. after the addition was complete. The reaction was left at room temperature for 16 hr. then evaporated to dryness *in vacuo*. The residue was distilled to give 10.6 g. (70%) of II b.p. 40–50° (0.1 mm.), n_D^{27} 1.4672; $\lambda_{max(\mu)}^{film}$ 2.95 (OH), 3.55 (aziridine CH), 6.07 (C=C). The vapor phase chromatogram[11] showed no detectable impurities.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.1; H, 10.3; N, 11.0. Found: C, 66.0; H, 10.5; N, 11.2.

By the same procedure *β-(1-aziridinyl)-α-ethylethanol* (III) was prepared from 10.0 g. of 1,2-epoxybutane[12] and ethylenimine; yield 8.0 g. (50%), b.p. 32–36° (0.1 mm.), n_D^{22} 1.4499; $\lambda_{max(\mu)}^{film}$ 2.97 (OH), 3.55 (aziridine CH). The product was 98% pure according to vapor phase chromatography.[11]

Anal. Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.4; N, 12.2. Found: C, 62.4; H, 11.4; N, 12.0.

β-(1-Aziridinyl)-α,β-dimethylethanol (IV). A mixture of 10.0 g. (0.14 mole) of 2,3-epoxybutane,[12] 12.0 g. (0.28 mole) of ethylenimine and 5 ml. of water was prepared as described in the preparation of β-(1-aziridinyl)-α-methyl-α-vinylethanol (II), then left for 72 hr. at room temperature. Distillation of the reaction mixture as described for II gave 7.15 g. (45%) of product (IV), b.p. 54–58° (3 mm.), n_D^{22} 1.4515; $\lambda_{max(\mu)}^{film}$ 2.97 (OH), 3.35–3.50 (aziridine CH). The vapor phase chromatogram showed that the distillate was 93% pure.

Anal. Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.4; N, 12.2. Found: C, 62.2; H, 11.6; N, 12.2.

A reaction time of 16 hr. gave only 5–10% yield.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra.

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(6) V. M. Al'bitskaia and A. A. Petrov, *J. Gen. Chem.*, **28**, 873 (1959), English translation.

(7) Boiling points are uncorrected.

(8) LAC column, 70°.

(9) R. Pummerer and W. Reindel, *Ber.*, **66**, 335 (1933).

(10) A. A. Petrov, *J. Gen. Chem.*, **13**, 581 (1943).

(11) DC-710 column, 170°.

(12) Farchan Research Laboratories, 28915 Anderson Road, Wickliffe, Ohio.

3α-Hydroxy-19-nor-5α-androstan-17-one and 19-Nor-5α-androstane-3α-17β-diol[1,2]

DAVID KUPFER, ENRICO FORCHIELLI, AND RALPH I. DORFMAN

Received February 8, 1960

These compounds were prepared for the purpose of identifying metabolites of 19-nortestosterone.[3,4] 3β-Hydroxy-19-nor-5α-androstan-17-one was converted to the 3β-*p*-toluenesulfonate. The tosylate was treated with potassium acetate in dimethylformamide and the resulting 3α-acetoxy-19-nor-5α-androstan-17-one hydrolyzed in methanolic sodium hydroxide to 3α-hydroxy-19-nor-5α-androstan-17-one. Reduction of 3α-hydroxy-19-nor-5α-androstan-17-one with sodium borohydride yielded 19-nor-5α-androstane-3α,17β-diol.

(1) This work was supported in part by a grant from U.S.P.H.S. No. A-2672.

(2) The C-10 hydrogen in all compounds reported here has the β-configuration.

(3) D. Kupfer and E. Forchielli, *Federation Proc.*, **19**, 1968 (1960).

(4) L. L. Engel, T. Alexander, and M. Wheeler, *J. Biol. Chem.* **231**, 159 (1958).

EXPERIMENTAL[5]

3β-Hydroxy-19-nor-5α-androstane-17-one-p-toluenesulfonate (I). A 17-mg. sample of 3β-hydroxy-19-nor-5α-androstan-17-one (m.p. 177–179°)[6] was dissolved in 2.0 ml. dry pyridine containing 500 mg. of freshly recrystallized *p*-toluenesulfonyl chloride.[7] The solution was allowed to stand at room temperature for 24 hr. About 15 ml. of ice water was added and the resulting suspension extracted with cold chloroform. The chloroform phase was washed with cold 0.2*N* hydrochloric acid, cold 5% aqueous sodium bicarbonate and cold water till neutral, dried over sodium sulfate, and evaporated under reduced pressure to dryness. A 28.2-mg. sample of solid resulted (I); λ_{max}^{KBr} 5.78 (cyclopentyl C=O), 6.25 (phenyl C=C) 7.4, 8.5, and 14.95 μ; no hydroxyl absorption was present. A similar spectrum was obtained with the tosylate of epiandrosterone.

3α-Hydroxy-19-nor-5α-androstan-17-one (II) *from* (I). The crude tosylate (I) was dissolved in 4.0 ml. of dimethylformamide containing 180 mg. of potassium acetate in 0.5 ml. of water. The resulting solution was refluxed for 3 hr., allowed to stand overnight, and refluxed for an additional hour. Twenty milliliters of water was added to the precooled solution and the resulting suspension extracted with ether. The ether phase was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The resulting brown oil was extracted with petroleum ether (b.p. 30–60°) and the extract evaporated to dryness. A light yellow oil resulted (14.2 mg.); λ_{max}^{film} 5.75 (cyclopentyl ketone), 6.05 (C=C), 8.05 μ (acetate) and no hydroxyl present. The complex band at 8.05 μ similar to that of androsterone acetate indicated the presence of an axial acetate (3α,5α).[8] The crude oil was dissolved in 4.0 ml. methanol containing 55 mg. of potassium carbonate dissolved in 1.0 ml. of water and the mixture refluxed for 2 hr. Water was added to form a suspension which was extracted with about 100 ml. of ether, the ether phase was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The colorless oil obtained (8.5 mg.) was chromatographed on a silica gel column and eluted with benzene and benzene–ethyl acetate mixtures. The 2.7-mg. sample of white amorphous material which was eluted with benzene gave no significant ultraviolet absorption in the region of 220–360 mμ: λ_{max}^{KBr} 5.75 (cyclopentyl ketone), 6μ (isolated double bond), and no hydroxyl or acetate absorptions. Based on the infrared spectra and on reactions carried out under similar conditions with epiandrosterone[9] and allopregnane-3α-ol,11,20-dione[7] which yielded the corresponding Δ^2-elimination products, the compound is tentatively assigned the structure of Δ^2-19-norandrostan-17-one (m.p. 115–121°). Elution with benzene–ethyl acetate 9:1 and 6:1 resulted in 3.7 mg. of white amorphous material which upon crystallization from acetone-hexane yielded (II) colorless needles with the double melt 148°, 164.5–167°; $[\alpha]_D^{21.7}$ +110, (c, 0.765 in chloroform); λ_{max}^{KBr} 2.75 (OH), 5.75 (cyclopentyl C=O), 9.0, 9.35, 9.49, 9.65, 9.81, 10 μ (axial OH).[8]

19-Nor-5α-androstane-3α,17β-diol (III) *from* (II). A 2.1-mg. sample of II was dissolved in 1.0 ml. of methanol containing 15 mg. of sodium borohydride. The solution was stirred overnight, water was added, and the resulting suspension extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated to dryness. Chromatography on silica gel yielded 1.3 mg. of white amorphous material (III). Crystallization from acetone-hexane produced colorless needles, m.p. 191–193°; $[\alpha]_D^{21.1}$ + 23.7 (c, 0.34 in chloroform); λ_{max}^{KBr} 2.90 (bonded OH), and 9.15, 9.40, 9.55, 9.90, 10.00 μ (axial OH).[8] Oxidation of the diol with chromic acid in acetic acid produced a dione (λ_{max}^{KBr} 5.80, 5.87 μ) identical to an oxidation product of 19-nor-5α-androstane-3β,17β diol and to an authentic sample of 5α-19-norandrostane-3,17-dione.[10,11]

Acknowledgment. The authors wish to thank Mr. Donald W. Parsons for his excellent technical assistance.

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(5) All melting points are uncorrected.

(6) D. Kupfer, E. Forchielli, and R. I. Dorfman, *J. Am. Chem. Soc.*, **82**, 1257 (1960).

(7) Von W. Nagata, C. Tamm, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1399 (1959).

(8) D. H. Barton, *J. Chem. Soc.*, 1027 (1953).

(9) J. Iriarte, G. Rosenkranz, and F. Sondheimer, *J. Org. Chem.*, **20**, 542 (1955).

(10) C. Chen, *Tetrahedron* **3**, 43 (1958).

(11) This compound was kindly supplied by Dr. Mika Hayano.

11-Oxygenated 17α-Acetoxy-9α-fluoro-6α-methyl-1,4-pregnadiene-3,20-diones

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Received February 10, 1960

Acylation of 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (I)[1,2] with acetic anhydride–*p*-toluenesulfonic acid[3] afforded 17α-acetoxy-9α-fluoro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (II) in 45% yield. The 11-keto analog III was obtained by the chromic acid oxidation of II.

Endocrine assays of these compounds are summarized in Table I.

TABLE I

CORTICOID AND PROGESTATIONAL ASSAYS OF COMPOUNDS I, II, AND III

Compound	Anti-Inflammatory Activity (X Hydrocortisone) Rats	Glycogen Deposition (X Hydrocortisone)	Progestational (X Progesterone)
I	131[4]	26[4]	60
II	170[5]	7[5]	60–80[5]
III	40		

Compound II is the only steroid described as effectively inhibiting both the C-3-II mammary

(1) J. A. Hogg, 6th National Medicinal Chemistry Symposium, ACS, Madison, Wis., June 23, 1958.

(2) The registered trademark of the Upjohn Company, Kalamazoo, Mich., for 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione is Oxylone.

(3) R. B. Turner, *J. Am. Chem. Soc.*, **75**, 3489 (1953).

(4) R. O. Stafford, A. Robert, S. C. Lyster, F. L. Schmidt, and W. E. Dulin, *Proc. Soc. Exptl. Biol. Med.*, **101**, 653 (1959).

adenocarcinoma in mice and the testosterone propionate-resistant mammary fibroadenoma in rats[5] (see Table II).

TABLE II

TUMOR INHIBITION BY COMPOUND II

Compound	Dose, mg./kg.	% Tumor Inhibition[a] TP-Resistant[b] (Rats)	% Tumor Inhibition[a] C-3-H (Mice)
Prednisolone	15	0–20	100
Testosterone propionate	5	0–15	0
Compound II	15	72	96

[a] Results derived from multiple assays, using 8–20 animals/group. The steroids were administered subcutaneously in a CMC vehicle. [b] E. M. Glenn, S. L. Richardson, and B. J. Bowman, *Endocrinology*, **64**, 379 (1959).

EXPERIMENTAL[6]

17α-Acetoxy-3α-fluoro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (II). A mixture of 5.0 g. of 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (I) in 625 ml. of glacial acetic acid, 125 ml. of acetic anhydride, and 2.0 g. of *p*-toluenesulfonic acid, monohydrate, was stirred vigorously at 26° until solution was completed (about 8 hr.). The reaction mixture was poured into a large volume of water containing 1 kg. of potassium bicarbonate. The product recovered by filtration, after drying, melted at 205–212° and constituted a quantitative yield. The crude product was recrystallized from ethyl acetate–Skellysolve B[7] to afford 2.5 g. (45.0% yield) of II, m.p. 225–228°, $[\alpha]_D$ + 49° (pyridine). The analytical sample, m.p. 230–232°, $[\alpha]_D$ + 50° (pyridine), was prepared by recrystallization from the same solvents.

Anal. Calcd. for $C_{24}H_{31}FO_5$: C, 68.89; H, 7.47; F, 4.54. Found: C, 68.90; H, 7.56; F, 4.7.

17α-Acetoxy-9α-fluoro-6α-methyl-1,4-pregnadiene-3,11,20-trione (III). To a solution of 1 g. of II in 50 ml. of acetone, 0.5 ml. of chromic acid solution[8] was added with stirring. After 5 min. the excess oxidizing agent was destroyed by the addition of a few drops of methanol. The reaction mixture was concentrated under vacuum and the product isolated by partition between methylene dichloride–water. The residue obtained from the methylene dichloride fraction when recrystallized from ethyl acetate–Skellysolve B weighed 300 mg. (30%) and melted at 273–275°. Recrystallization from the same solvents gave an analytical sample, m.p. 277–278.5°.

Anal. Calcd. for $C_{24}H_{29}FO_5$: C, 69.21; H, 7.07; F, 4.56. Found: C, 69.44; H, 7.36; F, 4.5.

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(5) Presented by E. M. Glenn, S. L. Richardson, B. J. Bowman, and S. C. Lyster at CCNSC Symposium titled, "Biologic Activities of Steroids in Relation to Cancer," Vergennes, Vt., Sept. 27–Oct. 2, 1959. (Abstracts of papers to be published.)

(6) The authors are indebted to G. E. VandenBerg of these laboratories for assistance in the preparation of these compounds.

(7) A saturated hydrocarbon fraction, b.p. 60–71°.

(8) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

The Preparation of 16-Methyl-Δ[16]-steroids Containing Ring C Substituents

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Received March 9, 1960

Research in this laboratory on C^{14}-substituted steroids[1] has been extended to include methyl substituents. In view of the recent publications,[2] especially that by Slates and Wendler,[2g] on C^{16}-methyl steroids we wish to report here on our work in this area. This note describes the preparation of 16-methyl-Δ[16]-steroids which contain substituents in the C-ring, in particular, on 21-acetoxy-9α-fluoro-11β-hydroxy-16-methyl-4,16-pregnadiene-3,-20-dione (VII).

Following the procedure of Wettstein[3] 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione[4] (Ia) on reaction with excess diazomethane gave 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4,9(11)-pregnadiene-3,20-dione (IIa).[5] A band attributable to —N=N—stretching[6] was observed at 1565 cm.$^{-1}$ in this and all the other pyrazolino-steroids herein prepared. Thermal decomposition of IIa readily afforded 21-acetoxy-16-methyl-4,9(11),16-pregnatriene-3,20-dione (IIIa).

N-bromoacetamide-perchloric acid treatment of 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4,9(11)-bromohydrin IV. This was converted, without further purification, in refluxing methanolic potassium acetate directly into 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-9β,11β-epoxy-4-pregnane-3,20-dione(V).

(1) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956), and subsequent papers.

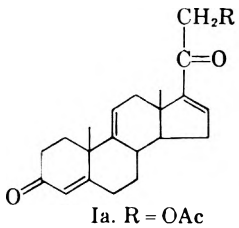
(2) (a) G. E. Arth, D. B. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958). (b) G. E. Arth, J. Fried, D. B. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958). (c) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958). (d) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4428 (1958). (e) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958). (f) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 6687 (1958). (g) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(3) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

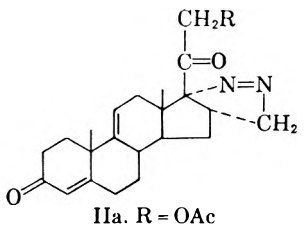
(4) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(5) This system of nomenclature for pyrazoline derivatives is according to that employed by G. P. Mueller and B. Riegel, *J. Am. Chem. Soc.*, **76**, 3686 (1954) for similar compounds.

(6) R. N. Jones and C. Sandorfy, *Techniques of Organic Chemistry*, **9**, 545 (1956).



Ia. R = OAc
Ib. R = H



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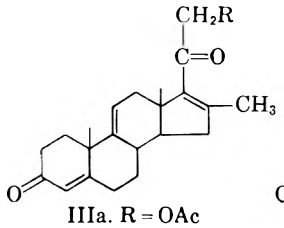
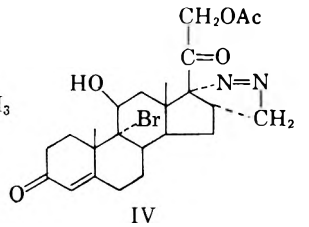
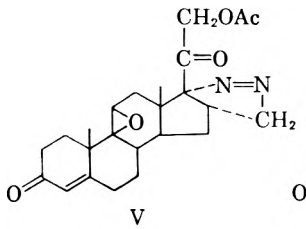
IIb. R = H



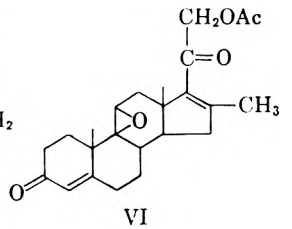
IIIa. R = OAc
IIIb. R = H



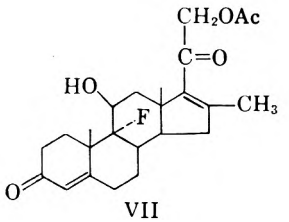
IV



V

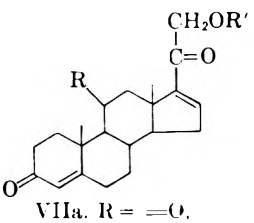


VI

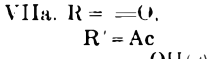


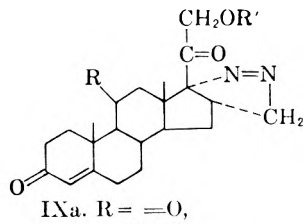
VII

An attempt to treat the epoxide V with anhydrous hydrogen fluoride was unsuccessful as the pyrazoline ring was attacked by the reagent. Accordingly, thermal decomposition of V was accomplished first to give 21-acetoxy-9β,11β-epoxy-16-methyl-4,16-pregnadiene-3,20-dione (VI) as a gum which then on treatment with hydrogen fluoride gave, after chromatography, crystalline 21-acetoxy-9α-fluoro-11β-hydroxy-16-methyl-4,16-pregnadiene-3,20-dione(VII).

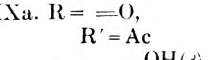


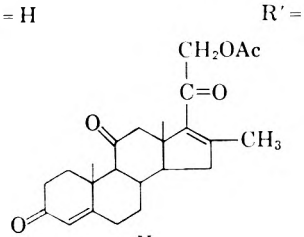
VIIa. R = =O,
R' = Ac

VIIIb. R = 
R' = H



IXa. R = =O,
R' = Ac

IXb. R = 
R' = H



X

By the same procedure[3] employed above, the pyrazoline derivatives (IXa) and (IXb) of 21 acetoxy-4,16-pregnadiene-3,11,20-trione[7] (VIIIa) and 11β,21-dihydroxy-4,16-pregnadiene-3,20-dione[7] (VIIIb) were formed. The former was converted to 21-acetoxy-16-methyl-4,16-pregnadiene-3,11,20-trione (X) by pyrolysis. In a similar sequence (Ib→IIb→IIIb) 16-methyl-4,9(11),16-pregnatriene-3,20-dione(IIIb) was obtained from 4,9-(11),16-pregnatriene-3,20-dione[8](Ib).

EXPERIMENTAL

All melting points are uncorrected. The optical rotations are for chloroform solutions and were determined at 25°. The ultraviolet spectra were determined in ethanol unless otherwise noted; the infrared spectra were determined in a potassium bromide disk. The petroleum ether used boiled at 60–70° (Skellysolve B).

21-Acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4,9(11)-pregnadiene-3,20-dione (IIa). Forty grams of a 50% potassium hydroxide solution and 40 ml. of ether were cooled in a separatory funnel at 5°. To this 1.84 g. of *N*-methyl-*N*-nitroso-*N'*-nitroguanidine was added portionwise with gentle agitation until solution was complete, and then the mixture was allowed to remain for an additional 15 min. The two layers were separated, and the ether layer was dried over sodium hydroxide pellets for 0.5 hr. and carefully decanted into a dry flask. A solution of 184 mg. of 21-acetoxy-4,9(11),-16-pregnatriene-3,20 dione (Ia) in 20 ml. of methylene chloride was added to the ether solution and the mixture was allowed to remain at room temperature for 4 days (loosely stoppered flask). On spontaneous evaporation a mixture of solid and gum remained. One crystallization from acetone–petroleum ether gave 191 mg. of yellow crystals (IIa), m.p. 158–159° dec.

A sample was dissolved in methylene chloride and filtered through magnesium silicate and evaporated to give white crystals, IIa, m.p. 164–166° dec. Recrystallization did not alter the melting point; λ_{max} 237–238 mμ (ϵ 17,900); ν_{max} 1760, 1725, 1675, 1615, 1560, 1225, 1075 cm.$^{-1}$; $[\alpha]_D$ +64°.

Anal. Calcd. for $C_{24}H_{30}N_2O_4$ (410.50): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.31; H, 7.49; N, 7.08.

21-Acetoxy-16-methyl-4,9(11),16-pregnatriene-3,20-dione (IIIa). Crude 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4,9-(11)-pregnadiene-3,20-dione (IIa) (206 mg.) was heated at 175° under reduced pressure (0.1 mm.) for 2 hr. A dark glass remained after cooling which was dissolved in acetone, and the solution was filtered through magnesium silicate and filter aid. The filtrate was evaporated *in vacuo* to give 203 mg. of a solid (IIIa), m.p. 133–139°. Three crystallizations from acetone–petroleum ether raised the melting point to 140–142.5°; λ_{max} 241 mμ (ϵ 22,600); ν_{max} 1755, 1675, 1640, 1605, 1226, 1080, 1035 cm.$^{-1}$; $[\alpha]_D$ +124°.

Anal. Calcd. for $C_{24}H_{30}O_4$ (382.48): C, 75.36; H, 7.91. Found: C, 75.55; H, 8.16.

21-Acetoxy-9α-bromo-11β-hydroxy-16α,17α-[3,1-(1-pyrazolino)]-4-pregnene-3,20-dione (IV). A solution of 90 mg. of 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4,9(11)-pregnadiene-3,20-dione (IIa) in 5 ml. of peroxide-free dioxane and 1 ml. of water was cooled to 15°. There was then added 42

(7) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **77**, 1028 (1955).

(8) S. A. Szpilfogel and V. Gerris, *Rec. trav. chim.*, **74**, 1462 (1955), and S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, **81**, 4596 (1959).

mg. of *N*-bromoacetamide and 0.20 ml. of 10% perchloric acid. After 15 min. at 15–20°, the reaction was quenched with saturated sodium sulfite and extracted with methylene chloride. The methylene chloride solution was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* at room temperature. The resulting white solid (110 mg.) was recrystallized twice from acetone–petroleum ether to give 23 mg. of crystals, IV, m.p. 172.5–174° dec.; $\lambda_{max}^{methanol}$ 242 mμ (ε 17,700); ν_{max} 3450, 1760, 1738, 1650, 1552, 1235, 1085, 1040 cm.$^{-1}$; $[\alpha]_D$ +252°.

Anal. Calcd. for $C_{24}H_{31}BrN_2O_5$ (507.43): C, 56.80; H, 6.16; Br, 15.75; N, 5.52. Found: C, 56.48; H, 6.32; Br, 15.97; N, 5.83.

21-Acetoxy-16α,17α-[3,1-(1-pyrazolino)]-9β,11β-epoxy-4-pregnene-3,20-dione (V). Crude 21-acetoxy-9α-bromo-11β-hydroxy-16α,17α-[3,1-(1-pyrazolino)]-4-pregnene-3,20-dione (IV, 2.8 g.) was dissolved in 225 ml. of refluxing methanol containing 6 g. of dry potassium acetate. After 3 hr. the solution was cooled and evaporated *in vacuo*. After trituration of the residue with cold water the product, V, was collected by filtration, dissolved in methylene chloride, dried over magnesium sulfate, and filtered through magnesium silicate. Evaporation of the methylene chloride provided a gum which crystallized from acetone–petroleum ether to give 1.0 g. of crystalline epoxide V, m.p. 163–166° dec. A 100-mg. portion was recrystallized twice from acetone–petroleum ether to give 30 mg., m.p. 173–175° dec.; λ_{max} 241 mμ (ε 16,000); ν_{max} 1765, 1740, 1675, 1634, 1560, 1230, 1085 cm.$^{-1}$; $[\alpha]_D$ +13°.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$ (426.50): C, 67.58; H, 7.09; N, 6.57. Found: C, 67.51; H, 7.28; N, 6.42.

21-Acetoxy-9β, 11β-epoxy-16-methyl-4, 16-pregnadiene-3, 20-dione (VI). 21-Acetoxy-16α,17α-[3,1-(1-pyrazolino)]-9β,-11β-epoxy-4-pregnene-3,20-dione (V) (200 mg.) was heated under reduced pressure (0.5 mm.) in an oil bath (temperature 140–170°). After gas evolution was complete, the cooled mass was dissolved in methylene chloride and filtered through magnesium silicate. The filtrate was evaporated *in vacuo* to give 119 mg. of VI was a yellow gum; λ_{max} 244 mμ (ε 21,500); ν_{max} 1755, 1680, 1625, 1230, 1075 cm.$^{-1}$

21-Acetoxy-9α-fluoro-11β-hydroxy-16-methyl-4,16-pregnadiene-3,20-dione (VII). A solution of 1.9 g. of 21-acetoxy-9β,11β-epoxy-16-methyl-4,16-pregnadiene-3,20-dione (VI) in 12.6 ml. of methylene chloride was cooled to −60° and added to a previously cooled (−60°) solution of 7 ml. of tetrahydrofuran, 2.5 ml. of methylene chloride, and 3.5 ml. of anhydrous hydrogen fluoride in a polyethylene flask. After 3.5 hr. at −5° the deep red solution was poured carefully into excess sodium bicarbonate solution. The methylene chloride layer was separated and washed with water until neutral, dried over magnesium sulfate, and evaporated *in vacuo* to give a glass (1.9 g.). A solution of this glass in benzene was added to a column of 100 g. of silica gel (>200 mesh) and was chromatographed successively with benzene, benzene-ether solution, and absolute ether. Elution with absolute ether afforded 1.2 g. of VII as white crystals, m.p. 175–179°. After two recrystallizations from acetone–petroleum ether the melting point was raised to 182–184°; $\lambda_{max}^{methanol}$ 241 mμ (ε 23,000); ν_{max} 3450, 1748, 1665, 1635, 1590, 1225, 1073, 1040 cm.$^{-1}$; $[\alpha]_D$ +119°.

Anal. Calcd. for $C_{24}H_{31}FO_5$ (418.48): C, 68.88; H, 7.47; F, 4.54. Found: C, 68.56; H, 7.63; F, 4.35.

21-Acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4-pregnene-3,11,20-trione (IXa). Twenty grams of a 50% potassium hydroxide solution and 200 ml. of methylene chloride were cooled in a separatory funnel immersed in an ice bath. To this was added portionwise 20 g. of nitrosomethylurea with gentle agitation until solution was complete, and then allowed to remain for an additional 15 min. The two layers were separated and the methylene chloride solution was dried over sodium hydroxide pellets for 0.5 hr. and carefully decanted into a dry flask. A solution of 2.8 g. of 21-acetoxy-4,16-pregnadiene-3,11,20-trione (VIIIa) in 28 ml. of methylene chloride was added to the diazomethane solution and then allowed to remain at room temperature for 18 hr. in a loosely stoppered flask. The methylene chloride was evaporated under a stream of air, and the resulting solid was crystallized from acetone–petroleum ether to give 2.2 g. of 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4-pregnene-3,11,20-trione (IXa), m.p. 182–183° dec. The melting point did not change on further recrystallization; λ_{max} 236 mμ (ε 16,600); ν_{max} 1765, 1740, 1715, 1685, 1625, 1555, 1235, 1220 cm.$^{-1}$; $[\alpha]_D$ +184°.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$ (426.50): C, 67.58; H, 7.09; N, 6.57. Found: C, 67.10, 67.41; H, 7.30, 7.24; N, 6.86.

21-Acetoxy-16-methyl-4,16-pregnadiene-3,11,20-trione (X). In an oil bath at 180–185°, 300 mg. of 21-acetoxy-16α,17α-[3,1-(1-pyrazolino)]-4-pregnen-3,11,20-trione (IXa) was heated until gas evolution ceased. The resulting glass was cooled and dissolved in methylene chloride. After filtration through filter aid, the methylene chloride was removed *in vacuo*, and the residue crystallized from acetone–petroleum ether to give 203 mg. of 21-acetoxy-16-methyl-4,16-pregnadiene-3,11,20-trione (X), m.p. 168–172°. Two further recrystallizations of a sample raised the melting point to 174–176°; λ_{max} 240 mμ (ε 23,500); ν_{max} 1755, 1705, 1675, 1615, 1380, 1225, 1075 cm.$^{-1}$; $[\alpha]_D$ +178°.

Anal. Calcd. for $C_{24}H_{30}O_5$ (398.48): C, 72.33; H, 7.59. Found: C, 72.14; H, 7.80.

11β,21-Dihydroxy-16α,17α-[3,1-(1-pyrazolino)]-4-pregnene-3,20-dione (IXb). To a dry diazomethane solution prepared as described previously from 3.3 g. of nitrosomethylurea, a solution of 500 mg. of 21-acetoxy-11β-hydroxy-4,16-pregnadiene-3,20-dione (VIIIb) in 2 ml. of methylene chloride was added. After 18 hr. the methylene chloride and excess diazomethane were removed by evaporation in an air stream, and the residue was crystallized from acetone–petroleum ether to give 460 mg. of 11β,21-dihydroxy-16α,17α-[3,1-(1-pyrazolino)]-4-pregnene-3,20-dione (IXb), m.p. 156–159° dec. Recrystallization from the same solvents raised the melting point to 165–167° dec.; λ_{max} 239 mμ (ε 15,700), 280 mμ (ε 280); ν_{max} 3450, 1725, 1675, 1635, 1555, 1100, 1045 cm.$^{-1}$; $[\alpha]_D$ +173°.

Anal. Calcd. for $C_{22}H_{30}N_2O_4$ (386.48): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.48; H, 8.16; N, 7.31.

16α,17α-[3,1-(1-Pyrazolino)]-4,9(11)-pregnadiene-3,20-dione (IIb). A solution of 155 mg. of 4,9(11),16-pregnatriene-3,20-dione (Ib) in 20 ml. of methylene chloride was added to a dry solution of diazomethane in ether (25 moles diazomethane per mole steroid). After 4 days at room temperature, evaporation in a stream of air gave a tacky solid which was dissolved in methylene chloride, the solution passed through magnesium silicate, and evaporated to give 89 mg. of crystalline product (IIb), m.p. 170–171° dec. Recrystallization from ether did not change the melting point; λ_{max} 237 mμ (ε 19,700); ν_{max} 1710, 1665, 1615, 1550 cm.$^{-1}$; $[\alpha]_D$ −138°.

Anal. Calcd. for $C_{22}H_{28}N_2O_2$ (352.46): C, 74.96; H, 8.01; N, 7.95. Found: C, 74.96; H, 8.22; N, 8.05.

16-Methyl-4,9(11),16-pregnatriene-3,20-dione (IIIb). The pyrazoline derivative IIb (100 mg.) was heated at atmospheric pressure in an oil bath at 170–180° until gas evolution was complete. The remaining gum was dissolved in methylene chloride and the solution was filtered through magnesium silicate. The filtrate was evaporated leaving a gum which gave 75 mg. of crystals, m.p. 135–138°, on trituration with ether. Two further recrystallizations from petroleum ether gave 15 mg. of IIIb, m.p. 142–144°; $\lambda_{max}^{methanol}$ 241 mμ (ε 22,900); ν_{max} 1668, 1645, 1610 cm.$^{-1}$; $[\alpha]_D$ +139°.

Anal. Calcd. for $C_{22}H_{28}O_2$ (324.44): C, 81.44; H, 8.70. Found: C, 81.58; H, 9.07.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analyses, and William Fulmor and associates for the infrared and

ultraviolet absorption spectra and optical rotation data.

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An Unexpected Reaction of 3,5-Di-*O*-benzoyl-2-deoxy-D-ribose

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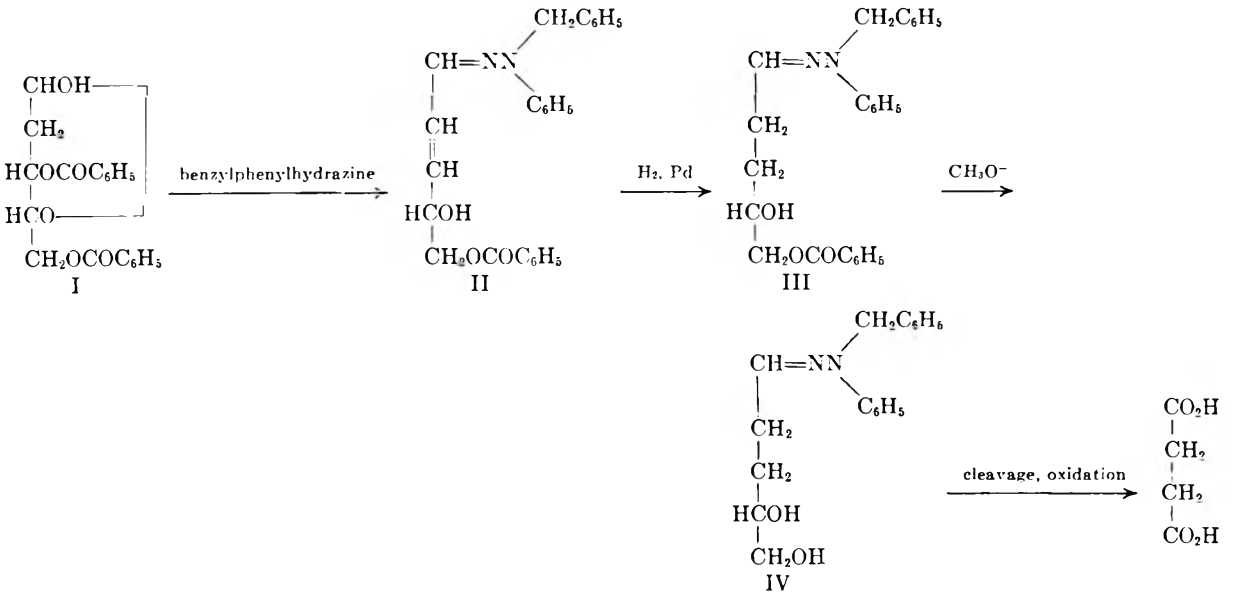
Received February 15, 1960

Relative to a synthetic program in the 2-deoxy-D-ribose series, we have prepared crude, amorphous 3,5-di-*O*-benzoyl-2-deoxy-D-ribose. An attempt was made to characterize this substance by converting it in the usual manner to a benzylphenylhydrazone. A crystalline hydrazone was indeed obtained, but its analysis revealed that loss of benzoic acid had accompanied the reaction. The product was shown to be 5-*O*-benzoyl-D-*glycero*-4,5-dihydroxy-2-pentenal benzylphenylhydrazone by reduction of the double bond, cleavage of substituents, and oxidation to succinic acid.

Acetylation of 3,5-di-*O*-benzoyl-2-deoxy-D-ribose in pyridine proceeded normally to give a crystalline monoacetate. This product conceivably could be either 4-*O*-acetyl-3,5-di-*O*-benzoyl-*aldehydo*-2-deoxy-D-ribose or the isomeric 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-D-ribose. Since the substance shows no mutarotation in USP chloroform, which contains ethanol, it has been assigned the latter structure.

EXPERIMENTAL

Methyl 3,5-di-O-benzoyl-2-deoxy-α,β-D-ribofuranosides. Three grams of 2-deoxy-D-ribose[1] in 60 ml. of absolute methanol was treated with 4.5 ml. of 0.14*N* hydrogen chloride in methanol and the resulting glycosidation was followed polarimetrically.[2] After 15 min., when a maximum positive specific rotation of +39.6° based on starting sugar had been reached, the solution was passed through a column containing 10 ml. of Duolite A-4 resin (wet with methanol) onto 2 ml. of pyridine. The solution was concentrated to dryness at reduced pressure and the resulting sirup was dried in high vacuum over phosphorus pentoxide. The dried sirup was dissolved in 33 ml. of dry pyridine and treated at 0° with 10.5 ml. of benzoyl chloride. After 1 day at room temperature, several drops of water were added and the solution was concentrated to a thin sirup in a stream of dry air. The residue was taken up in chloroform and washed successively with cold 3% sulfuric acid, water, saturated sodium bicarbonate solution, and water. After drying over sodium sulfate, the solution was concentrated at reduced pressure to a sirup (8.4 g.).



The unsaturated hydrazone was obtained readily in the presence of 1-benzyl-1-phenylhydrazine in aqueous ethanol, and somewhat more slowly with the hydrazine and acetic acid in aqueous ethanol. This unexpected, facile β-elimination of an ester group may be related to certain difficulties we have encountered in attempting to apply routine reaction conditions for syntheses based on 2-deoxy-D-ribose.

Fractional distillation of products prepared similarly gave about 70% of distillate, b.p. 135–138° (vapor temp.) at 10^{-4} mm., n_D^{25} 1.5456 to 1.5459, $[\alpha]_D^{33}$ +41° to +43° (*c* 1.5 in chloroform) and methoxyl content 8.47% to 8.65% (theory 8.71%). Qualitative paper chromatography, and the hydrolysis experiment described below, indicated such

(1) J. C. Sowden, *J. Am. Chem. Soc.*, **76**, 3541 (1954).
(2) R. E. Deriaz, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 2836 (1949).

products to be mixtures consisting of about 80% furanosides and 20% pyranosides.

Crude 3,5-di-O-benzoyl-2-deoxy-D-ribose, (I). The sirupy product described above (8.4 g.) was dissolved in 200 ml. of acetone, and 60 ml. of water followed by 45 ml. of 6*N* hydrochloric acid was added. After 2 days at room temperature, when the mutarotation had become essentially constant, the solution was deionized over Duolite A-4 (wet with 75% acetone) and concentrated at reduced pressure to a sirup. This was dissolved in chloroform, dried over sodium sulfate, and again concentrated to a sirup (7.2 g.). The methoxyl content of the sirupy product was about 1.8%, presumably due to unhydrolyzed methyl pyranosides.

5-O-Benzoyl-D-glycero-4,5-dihydroxy-2-pentenal benzylphenylhydrazone (II). The crude 3,5-di-*O*-benzoyl-2-deoxy-D-ribose (7.2 g.) was diluted with a small volume of ethanol and 4.7 g. of 1-benzyl-1-phenylhydrazine was mixed in to give a homogeneous solution. After 1 day the mixture was extracted by trituration with petroleum ether (b.p. 33–58°) and the residue was diluted with ethanol followed by water to give 3.4 g. of crystals in two crops. After recrystallization from benzene–ether, the 5-*O*-benzoyl-D-*glycero*-4,5-dihydroxy-2-pentenal benzylphenylhydrazone melted at 138–139°, $[\alpha]_D^{26}$ −14° in benzene, *c* 2.

Anal. Calcd. for $C_{25}H_{24}O_3N_2$: C, 75.0; H, 6.04; N, 7.00. Found: C, 74.7; H, 5.80; N, 6.97.

The same unsaturated benzylphenylhydrazone was formed, but somewhat more slowly, when an equivalent amount of acetic acid was added with the 1-benzyl-1-phenylhydrazine in the above reaction.

5-O-Benzoyl-D-glycero-4,5-dihydroxypentanal benzylphenylhydrazone, (III). The unsaturated benzylphenylhydrazone (3.4 g.) was hydrogenated at room temperature and atmospheric pressure in ethyl acetate solution in the presence of 0.5 g. of 10% palladium-on-carbon catalyst. The hydrogenation was complete in 2 hr. with the absorption of approximately one molecular equivalent of hydrogen. Filtration and evaporation gave a crystalline residue. Recrystallization from ether yielded 2.66 g. of 5-*O*-benzoyl-D-*glycero*-4,5-dihydroxypentanal benzylphenylhydrazone, m.p. 98–99°, $[\alpha]_D^{25}$ +3.7° in benzene, *c* 3.6.

Anal. Calcd. for $C_{25}H_{26}O_3N_2$: C, 74.6; H, 6.51; N, 6.96. Found: C, 74.6; H, 6.43; N, 7.15.

D-*Glycero-4,5-dihydroxypentanal benzylphenylhydrazone*, (IV). A solution of 1.5 g. of III in 300 ml. of methanol containing 0.3 g. of sodium was refluxed for 5 hr. The solution was then cooled, deionized, and concentrated, finally with water to remove methyl benzoate. The resulting crystals (1.05 g.) were recrystallized from ethanol–ether–petroleum ether (b.p. 32–37°) to give pure IV, m.p. 77–78°, $[\alpha]_D^{25}$ −14° in absolute ethanol, *c* 3.4.

Anal. Calcd. for $C_{18}H_{22}O_2N_2$: C, 72.5; H, 7.43; N, 9.39. Found: C, 72.5; H, 7.49; N, 9.31.

Degradation of IV *to succinic acid.* An amount of 570 mg. of III was shaken for 1 day with 1 ml. of benzaldehyde, 0.3 g. of benzoic acid, and 15 ml. of water. The mixture was then extracted three times with ether and the remaining aqueous phase was further treated with 5.3 ml. of 0.4*M* sodium metaperiodate solution for 7 hr. at room temperature. A few drops of ethylene glycol then were added, the solution was deionized, and the effluent and washings were treated with 1 g. of potassium permanganate. After 6 hr., excess permanganate was destroyed with acetaldehyde, manganese dioxide was removed by filtration and potassium ion by ion exchange, and the solution was concentrated to a semicrystalline residue. This was dissolved in dilute sodium hydroxide, extracted thoroughly with ethyl acetate, decolorized with carbon, again freed of sodium ion by ion exchange, and concentrated. The resulting crude succinic acid (m.p. 178–180°) was converted to the *p*-bromobenzyl pseudothiuronium salt,[3] m.p. 167°; yield, 100 mg.

The melting point of this product was undepressed by admixture with the *p*-bromobenzyl pseudothiuronium salt (m.p. 167°) prepared from authentic succinic acid, and the x-ray diffraction patterns given by the two preparations were identical.

1-O-Acetyl-3,5-di-O-benzoyl-2-deoxy-D-ribose. Thoroughly dried, crude 3,5-di-*O*-benzoyl-2-deoxy-D-ribose (840 mg.) was acetylated at 0° with acetic anhydride and pyridine in the usual manner. Addition of the reaction mixture to ice-water yielded a semicrystalline precipitate. This was separated by decantation, triturated with fresh ice-water, and recrystallized from ethanol to yield 205 mg. of crystalline product. Further recrystallization from ether–petroleum ether (b.p. 63–69°) yielded pure 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-D-ribose, m.p. 88–89°, $[\alpha]_D^{27}$ −23.7°, constant in USP chloroform, *c* 2.

Anal. Calcd. for $C_{21}H_{20}O_7$: C, 65.6; H, 5.25. Found: C, 65.7; H, 5.42.

Acknowledgment. The authors are pleased to acknowledge the generous support of the American Cancer Society, the Corn Industries Research Foundation, and the United States Atomic Energy Commission during the course of this work.

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(3) B. T. Dewey and H. G. Shasky, *J. Am. Chem. Soc.*, **63**, 3526 (1941).

The Structure and Synthesis of Rhetsinine (Hydroxyevodiamine)

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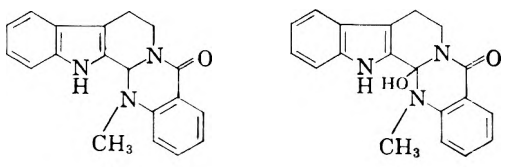
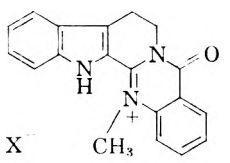
Received March 7, 1960

The chemistry of the alkaloid evodiamine (I), derived from the Chinese drug plant *Evodia rutecarpa* Benth. and Hook., was studied many years ago by Asahina and his co-workers. During the course of their investigations, a yellow base, $C_{19}H_{17}N_3O_2$, was derived upon potassium permanganate oxidation of the alkaloid.[1] The product was named hydroxyevodiamine and was assigned structure II. Later Ohta[2] observed that hydroxyevodiamine may react with acids with loss of water and suggested formula III for the salts. Upon addition



I II



X III

(1) Y. Asahina and T. Ohta, *J. Pharm. Soc. Japan*, **530**, 293 (1926); *Chem. Abstr.* **21**, 2134 (1927).

(2) T. Ohta, *J. Pharm. Soc. Japan* **65B**, 89 (1945).

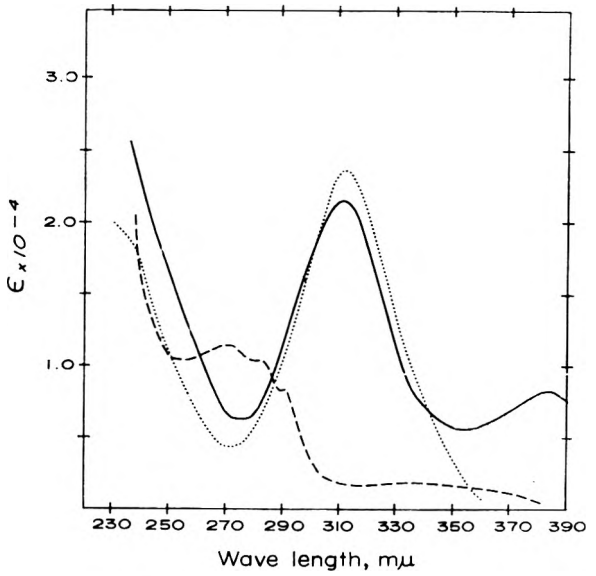
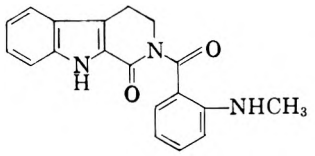


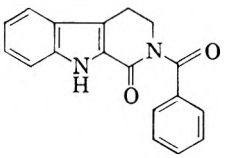
Fig. 1. Rhetsinine (hydroxyevodiamine), ————; evodiamine, - -; 2-benzoyl-1-oxo-1,2,3,4-tetrahydropyrid-[3,4-b]indole, ... Spectra in absolute acetonitrile

of base to III, he suggested, the quaternary base (III. X = OH) first arises and then forms II. Very recently Chatterjee and co-workers[3] proposed formula I for the alkaloid rhetsine and formula II for the alkaloid rhetsinine derived from *Xanthoxylum rhetsa* D.C.

It seemed probable to us, on the basis of some previous work in these laboratories, that the evodiamine oxidation product should be formulated as the dicarbonyl compound IV. A sample of the yellow substance was prepared from evodiamine[4] and was spectrally related, *in non-hydroxylic media*, to 2-benzoyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole (V) rather than to evodiamine (Fig. 1).



IV

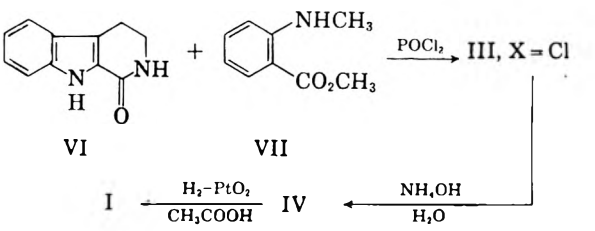


V

Its infrared spectrum in mineral oil mull, showing carbonyl bands at 5.97 and 6.05 μ and NH bands at 2.97 and 3.10 μ, also eliminates the quaternary base structure (III. X = OH) as a possible one for the *crystalline* alkaloid, since the quaternary chloride (III. X = Cl) shows only a single carbonyl band at 5.87 μ. Hydroxyevodiamine thus should be formulated as IV.

A sample of rhetsinine, isolated from *Xanthoxylum rhetsa* D.C. and kindly sent to us by Professor S. M. Kupchan of the University of Wisconsin, had infrared and ultraviolet spectra identical with those of hydroxyevodiamine and gave no depression of melting point upon admixture. Rhetsinine is a more suitable name for the compound than hydroxyevodiamine.

Rhetsinine was also synthesized through reaction of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole (VI), methyl *N*-methylanthranilate (VII), and phosphorus oxychloride followed by addition of base. The hydrolysis to IV may be reversed by dilute hydrochloric acid, which immediately reconverts IV to III (X = Cl). Catalytic reduction of rhetsinine in acetic acid yielded *dl*-evodiamine (rhetsine).



EXPERIMENTAL

2-Benzoyl-1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole. A mixture of 10 ml. of benzoyl chloride, 1 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole and 1 ml. of pyridine was heated under reflux for 1 hr. Excess benzoyl chloride was removed *in vacuo* and the residue was thoroughly triturated with 5% aqueous sodium carbonate. The solid was collected and recrystallized twice from chloroform–ethyl acetate to give 0.9 g. of product, m.p. 266.5–267.5°

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86. Found: C, 74.07; H, 4.95.

Synthesis of rhetsinine (hydroxyevodiamine). To 5.0 g. of 1-oxo-1,2,3,4-tetrahydropyrid[3,4-b]indole dissolved in 120 ml. of hot, dry toluene was added 3 ml. of freshly distilled phosphorus oxychloride. The reaction mixture was heated under reflux for 15 min. during which time a small second phase separated. A 7.5-g. portion of methyl *N*-methylanthranilate was then added. The reaction mixture was stirred vigorously under reflux for 2.5 hr. The toluene was then removed by distillation. The residue was cooled and treated with aqueous ammonia and chloroform. The chloroform layer was separated, concentrated, filtered, diluted with benzene, and treated with hydrogen chloride. A solid yellow hydrochloride separated and was recrystallized first from 300 ml. of water and then from 95% ethanol containing a little 5% hydrochloric acid to give 6.2 g. (68% yield) of *anhydrohetsinine hydrochloride* (III. X = Cl), m.p. 238° dec.

Anal. Calcd. for $C_{19}H_{16}N_2OCl$: C, 67.55; H, 4.77; N, 12.44. Found: C, 67.30; H, 4.84; N, 12.52

A sample of the hydrochloride was shaken with aqueous ammonia and chloroform. The red chloroform solution was concentrated, diluted with 80% ethanol, and allowed to stand. The color faded to pale orange and yellow crystals of rhetsinine, m.p. 196° dec. after turning red at *ca.* 175°, separated from solution.

Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.45; H, 5.37; N, 13.16. Found: C, 71.35; H, 5.25; N, 13.26.

dl-Evodiamine. To a solution of 2.3 g. of rhetsinine in 100 ml. of glacial acetic acid was added 65 mg. of platinum oxide catalyst. The mixture was shaken under 45 p.s.i. of hydrogen for 45 min. The product crystallized from solution during the reduction. The mixture was diluted with water and the product collected, dried, and recrystallized from a 1:1 mix-

(3) A. Chatterjee, S. Bose and C. Ghosh, *Tetrahedron* **7**, 257 (1959).

(4) We are indebted to Professor T. Ohta of the Tokyo College of Pharmacy, Tokyo, Japan, for providing an authentic sample of evodiamine.

ture of ethanol and ethyl acetate to give 1.9 g. of prisms which soften at 269° and melt at 275–277° when heated at a rate of 5° per min. The compound was compared with a specimen of natural evodiamine from Professor T. Ohta[4] and had the same ultraviolet and infrared spectral properties.

Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.22; H, 5.65. Found: C, 75.32, 75.25; H, 5.77, 5.85.

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Chlorination of Polyfluoroalkyl Borates[1a]

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Received February 5, 1960

In connection with recent studies on fluoro heterocycles an interest developed in the synthesis of perfluorinated *n*-alkyl borates. Orthoboric acid esters are generally prepared by reaction of the respective alcohol with either a boron halide, boron trioxide, or orthoboric acid. Perfluorinated alcohols were desired in this work, but primary perfluorinated alcohols are not isolable. However, work was started with alcohols of the type R_FCH_2OH which are commercially available. The orthoborates expected from these alcohols require final fluorination either by direct exchange of hydrogen for fluorine by silver difluoride or similar agents, or by halogenation with bromine or chlorine followed by replacement of bromine or chlorine by fluorine by means of an inorganic fluorinating agent such as silver fluoride.

Preliminary experiments showed that boron trifluoride etherate did not react with trifluoroethanol, pentafluoropropanol, and heptafluorobutanol even under reflux, whereas boron trichloride in petroleum ether solution reacted instantaneously at −20° to give the desired borates. Thus tris(trifluoroethyl)borate (I), tris(pentafluoropropyl)borate (II), and tris(heptafluorobutyl)borate (III) were obtained in a 60–70% yield.

While bromination was unsuccessful, compound I was chlorinated rapidly when exposed to ultraviolet light. Surprisingly, the absorption of chlorine never stopped and the volume of the reaction mixture started to decrease after a certain interval of time. The reaction mixture thus obtained was distilled under vacuum to give two compounds, bis(trifluoromonochloroethyl) chloroboronate (VII) and the higher boiling tris(trifluoromonochloroethyl)borate (IV).

This result proved that the chlorination first proceeds as desired with the substitution of three of the six available hydrogen atoms by chlorine. The resulting compound IV then chlorinates further, not by exchange of residual hydrogen for chlorine, but by splitting off an alkoxy group with the formation of VII.

$$\underset{\text{I, II, III}}{(R_FCH_2O)_3B} \xrightarrow{Cl_2,\ h\nu} \underset{\text{IV, V, VI}}{(R_FCHClO)_3B} \xrightarrow{Cl_2,\ h\nu} \underset{\text{VII, VIII, IX}}{(R_FCHClO)_2BCl}$$

I, IV, VII. $R_F = CF_3$
II, V, VIII. $R_F = C_2F_5$
III, VI, IX. $R_F = C_3F_7$

We assume that compound VII is also not stable to chlorine and is probably converted into trifluoromonochloroethyldichloroboronite (X) which in turn undergoes further reaction with chlorine to form boron trichloride.

Chlorination of II and III led to the corresponding compounds V, VI, VIII, and IX. Bis(heptafluoromonochlorobutyl)chloroboronate (IX) was obtained contaminated with heptafluoromonochlorobutyldiehloroboronite (XI).

For proof of structure, IX was also prepared from VI and boron trichloride as another method of preparation of dialkyl chloroboronates.[2] When

$$\underset{\text{VI}}{2\ (CF_3CF_2CF_2CHClO)_3B} + BCl_3 \longrightarrow \underset{\text{IX}}{3\ (CF_3CF_2CF_2CHClO)_2BC}$$

the preparation of XI, the monoalkoxy derivative, was attempted by using an excess of boron trichloride, surprisingly only the dialkoxy derivative, IX, was obtained.

Since bromination and chlorination had failed to produce a perhalogenated orthoborate, an attempt was made to prepare the desired perfluoroalkyl orthoborates by direct fluorination of the hydrogen atoms attached to the α-carbon atoms of the alkyl groups by means of silver difluoride. The only product obtained from III was a boron-free material, probably di-1,1-dihydroheptafluorobutyl ether.

EXPERIMENTAL[3]

Tris(heptafluorobutyl) borate (III). The solution of 23 g. of boron trichloride in 200 ml. of petroleum ether (b.p. 30–38°) was added dropwise to a stirred mixture of 100 g. of 1,1-dihydroheptafluorobutanol and 100 ml. of petroleum ether with ice-salt cooling during 40 min. To ensure complete reaction, the mixture was then kept for 20 min. at 20°. The separated solid, boric acid, was filtered off and the petroleum ether evaporated. Distillation of the residual product gave a forerun of heptafluorobutanol and then 66.5 g. of III (66%); b.p. 137° (200 mm.); n_D^{23} 1.2596. The use of pyridine as hydrogen chloride scavenger decreased the yield.

(1)(a) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by The Olin Mathieson Chemical Corporation, New York, N. Y. (1)(b) Present address: Olin Mathieson Chemical Corporation, New Haven, Conn.

(2) W. Gerrard and M. F. Lappert, *J. Chem. Soc.*, 501 (1957).

(3) Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Despite the fact that considerable care was taken in the purification of the reaction products, some variance was observed between the analyses and the calculated values which is typical of compounds containing high percentages of fluorine.

Anal. Calcd. for $C_{12}H_6BF_{21}O_3$ (608.0): C, 23.70; H, 0.99; F, 65.63. Found: C, 24.29, 24.48; H, 1.18, 1.19; F, 64.50, 64.33.

Tris(pentafluoropropyl) borate (II). The procedure given for III was followed exactly except treating 58 g. of 1,1-dihydropentafluoropropanol suspended in 60 ml. of petroleum ether with 17 g. of boron trichloride in 150 ml. of petroleum ether; yield of II, 39 g. (66%); b.p. 110° (200 mm.); n_D^{23} 1.2940.

Anal. Calcd. for $C_9H_6BF_{15}O_3$ (458.0): C, 23.60; H, 1.32; B, 2.36; F, 62.63. Found: C, 23.63, 23.89; H, 1.98, 2.18; B, 2.06, 1.96; F, 63.53, 63.89.

Tris(trifluoroethyl) borate (I) was obtained in analogy to the procedure given for III in 60% yield; b.p. 77° (200 mm.); n_D^{23} 1.2975.

Anal. Calcd. for $C_6H_6BF_9O_3$ (307.9): C, 23.40; H, 1.96. Found: C, 23.32, 23.19; H, 2.34, 2.55.

The following procedure is typical of the experiments performed.

Chlorination of tris(1,1-dihydrotrifluoroethyl) borate (I). Gaseous chlorine was passed slowly into 13.1 g. of I exposed to an ultraviolet lamp. When after 25 hr. the contents of the flask began to diminish, the reaction mixture was distilled at 200 mm. and 12.0 g. of products was obtained. Repeated fractional distillation gave 3.5 g. of IV and 3.0 g. of VII.

The *chlorination of 16 g. of tris(1,1-dihydropentafluoropropyl) borate* (II) afforded 14 g. of reaction products. Repeated fractional distillation yielded 5.5 g. of V and 1.5 g. of VIII.

The *chlorination of 15 g. of tris(1,1-dihydroheptafluorobutyl) borate* (III) gave 6 g. of VI and 2 g. of a mixture of IX and XI. Separation by distillation yielded 0.5 g. of IX.

Tris(trifluoromonochloroethyl) borate (IV) boiled at 100° (200 mm.); n_D^{25} 1.3405.

Anal. Calcd. for $C_6H_3BCl_3F_9O_3$ (411.3): C, 17.50; H, 0.73; B, 2.62; Cl, 25.87. Found: C, 16.87, 16.62; H, 0.93, 1.09; B, 2.87, 3.06; Cl, 25.93, 26.12.

Tris(pentafluoromonochloropropyl) borate (V) boiled at 117° (200 mm.); n_D^{25} 1.3262.

Anal. Calcd. for $C_9H_3BCl_3F_{15}O_3$ (561.3): Cl, 18.95. Found: Cl, 17.95.

Tris(heptafluoromonochlorobutyl) borate (VI) boiled at 150° (200 mm.); n_D^{25} 1.3250.

Anal. Calcd. for $C_{12}H_3BCl_3F_{21}O_3$ (711.3): C, 20.11; H, 0.42; B, 1.52; Cl, 15.00; F, 56.00. Found: C, 19.87, 19.80; H, 0.82, 0.91; B, 1.75, 1.86; Cl, 14.68, 14.52; F, 55.35, 55.14.

Bis(trifluoromonochloroethyl) chloroboronate (VII) boiled at 77° (200 mm.); n_D^{25} 1.3490. It is extremely sensitive to moisture, and fumes heavily in the open air.

Anal. Calcd. for $C_4H_2BCl_3F_6O_2$ (313.3): C, 15.34; H, 0.64; B, 3.45; Cl, 34.00. Found: C, 15.42, 15.28; H, 0.77, 0.96; B, 4.27, 4.40; Cl, 34.24, 34.49.

Bis(pentafluoromonochloropropyl) chloroboronate (VIII) is extremely sensitive to moisture; n_D^{25} 1.3330.

Anal. Calcd. for $C_6H_2BCl_3F_{10}O_2$ (413.3): Cl, 25.80. Found: Cl, 25.47, 25.25.

Bis(heptafluoromonochlorobutyl) chloroboronate (IX) is extremely sensitive to moisture; n_D^{20} 1.3360.

Anal. Calcd. for $C_8H_2BCl_3F_{14}O_2$ (513.3): C, 18.70; H, 0.39; B, 2.10. Found: C, 17.92, 17.80; H, 0.45, 0.49; B, 2.09, 1.96.

Di-1,1-dihydroheptafluorobutyl ether (XII). A 10-g. sample of III was added to 25 g. of silver fluoride in a 50-ml. reaction flask immersed in an ice bath and provided with a reflux condenser. A vigorous reaction started immediately, then 5.5 g. of reaction product was distilled. It was added to 10 g. of silver fluoride and the reaction yielded 3.2 g. of products. This amount was added to 5 g. of silver fluoride, scarcely causing a reaction. Distillation at 200 mm. gave 2.3 g. of XII, b.p. 65° (200 mm.), n_D^{25} 1.2890.

Anal. Calcd. for $C_8H_4F_{14}O$ (382.1): C, 25.14; H, 1.05; F, 69.61. Found: C, 25.13, 25.22; H, 1.10, 1.30; F, 66.56, 66.41.

Acknowledgment. The author is very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work. Furthermore, he wishes to thank Dr. C. J. Grundmann for his interest in the work and for stimulating discussions.

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Acylation and Alkylation of Aminoboronic Acids[1]

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Received January 18, 1960

The syntheses of organoboron compounds which we have carried out[2-4] have been based on their possible utilization in the therapy of brain tumors by neutron capture irradiation. The study in C_3H mice with subcutaneous brain tumors has shown[5,6] that organoboron compounds with hydrophilic groups offer the most promise for this type of treatment.

On this basis it seemed desirable to prepare boron compounds with carboxylic acid functions. Many with the carboxyl group attached directly to the aromatic ring[2,5,6] had been prepared and tested. Their utility prompted the synthesis of organoboron compounds containing an aliphatic carboxylic acid group.

Acylation and alkylation of a compound such as *m*-aminobenzeneboronic acid would permit the introduction of such a group. However, the stability of the boronic acid moiety in simple aromatic compounds has been shown[2,7-11] in a variety of systems to vary and to be dependent upon substituents. It was considered possible, therefore, that acylation and alkylation of aminobenzeneboronic acids might occur with loss of the borono group, even though acylations of such amines have been effected[9,12] in certain instances without cleavage of the carbon-boron linkage.

(1) This work was supported by grants from the National Cancer Institute C-3174 and from the Atomic Energy Commission AT(30-1)-1093.

(2) A. H. Soloway, *J. Am. Chem. Soc.*, **81**, 3017 (1959).
(3) E. Nyilas and A. H. Soloway, *J. Am. Chem. Soc.*, **81**, 2681 (1959).
(4) A. H. Soloway, *J. Am. Chem. Soc.*, **82**, 2442 (1960).
(5) A. H. Soloway, *Science*, **128**, 1572 (1958).
(6) A. H. Soloway, B. Whitman, and J. R. Messer, *J. Pharm. and Exp. Therap.*, **129**, 310 (1960).
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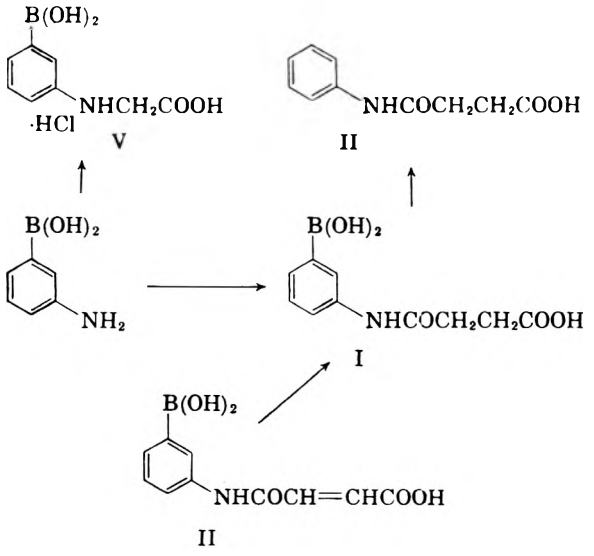
(8) H. Gilman, D. R. Swayampati, and R. O. Ranck, *J. Am. Chem. Soc.*, **80**, 1355 (1958).
(9) K. Torssell, *Arkiv Kemi*, **10**, 513 (1957).
(10) K. Torssell, *Svensk Kem. Tidskr.*, **69**, 34 (1957).
(11) H. G. Kuivila and L. E. Benjamin, *J. Am. Chem. Soc.*, **77**, 4834 (1955).

The reaction of 3-aminobenzeneboronic acid with succinic anhydride was carried out in refluxing ethylene glycol dimethyl ether to form 3-boronosuccinanilic acid (I). The product was characterized by deboronation with a silver salt[13] to succinanilic acid (II), identical in all respects with the compound which had been prepared from aniline and succinic anhydride. In a similar manner 3-amino-4-methylbenzeneboronic acid was converted to 2-methyl-5-boronosuccinanilic acid (III).

Maleic anhydride could replace succinic anhydride in this acylation reaction. In this way 3-boronomaleanilic acid (IV) was synthesized. This compound was characterized by analysis and by its absorption of one mole of hydrogen under catalytic reduction with platinum oxide to form 3-boronosuccinanilic acid. This was identical with the compound which was synthesized using succinic anhydride as the acylating agent.

The alkylation of 3-aminobenzeneboronic acid with chloroacetic acid occurred readily in an aqueous medium with sodium carbonate as a condensing agent. The product, 3-borono-*N*-phenylglycine (V), was very soluble and was isolated as the hydrochloride. In a similar manner 2-carboxy-5-borono-*N*-phenylglycine (VI) was synthesized from 2-amino-4-boronobenzoic acid. This compound was isolated as the free amino acid.

Screening of a variety of organoboron compounds resulted in attempts to prepare α-boronomalonic acid from ethoxymagnesium ethyl malonate. They were unsuccessful. However, it was possible to prepare *m*-trifluoromethylbenzeneboronic acid from *m*-bromo-α,α,α-trifluoromethylbenzene *via* the Grignard reagent.



EXPERIMENTAL

All melting points were determined in capillary tubes and are uncorrected.

m-Boronosuccinanilic acid (I). To a solution of 1.4 g. of *m*-aminobenzene-boronic acid[14] in 15 ml. of ethylene glycol dimethyl ether (Ansul Ether 121), was added 1.2 g. of succinic anhydride in 20 ml. of this ether. The solution was refluxed on a steam bath for 1 hr. and then concentrated to near dryness under reduced pressure. The solid residue was triturated with water, cooled and filtered. A 900-mg. sample of a brown solid was obtained, m.p. 185–189°. Successive recrystallizations from water, utilizing a decolorizing charcoal gave a white crystalline solid, m.p. 196–197°.

Anal. Calcd. for $C_{10}H_{12}BNO_5$: C, 50.66; H, 5.10. Found, C, 49.71; H, 5.17.

In 1.5 ml. of an ammoniacal silver nitrate solution[15] was added 100 mg. of *m*-boronosuccinanilic acid. The solution was warmed on a steam bath for 5 min. and allowed to remain at room temperature for 30 min. The mixture was acidified with 30% nitric acid and filtered. A 45-mg. sample of succinanilic acid (II) was obtained, m.p. 148–150°, which showed no melting point depression on admixture of succinanilic acid prepared from aniline. The melting point of a mixture of boronosuccinanilic acid with succinic acid was 174–178°, a lowering of the melting point of each by 15°.

2-Methyl-5-boronosuccinanilic acid (III). A 3.0-g. sample of 3-amino-4-methylbenzeneboronic acid[14] was dissolved in 25 ml. of ethylene glycol dimethyl ether. To this was added a solution of 2.2 g. of succinic anhydride in 40 ml. of the same solvent. The solution was refluxed on a steam bath for 35 min. Solid had already begun separating out of solution after 25 min. The mixture was cooled and filtered, yielding 1.6 g., m.p. 171–173°, of 2-methyl-5-boronosuccinanilic acid. The filtrate was refluxed an additional 35 min. After cooling, the solution was filtered and yielded a second amount, 1.9 g., of the product, m.p. 160–167°. The combined yield of crude boronic acid was 3.5 g. After successive recrystallizations from water a white crystalline product was obtained, m.p. 182–183°, which was analyzed.

Anal. Calcd. for $C_{11}H_{14}BNO_5$: C, 52.62; H, 5.62. Found: C, 52.90; H, 5.88.

m-Boronomaleanilic acid (IV). To a solution of 6.9 g. of 3-aminobenzeneboronic acid in 35 ml. of ethylene glycol dimethyl ether was added a solution of 30 ml. of this ether containing 4.9 g. of maleic anhydride. The solution was refluxed for 90 min. It was then concentrated to half its volume, cooled and filtered. A 4.5-g. sample of *m*-boronomaleanilic acid was obtained, m.p. 201–202°. From the filtrate a second crop of crystals were isolated, m.p. 201–202°. Successive recrystallizations from water gave pale yellow crystals, m.p. 209–211°.

Anal. Calcd. for $C_{10}H_{10}BNO_5 \cdot H_2O$: C, 47.46; H, 4.78. Found: C, 47.49; H, 5.11.

A solution of 1.0 g. of *m*-boronomaleanilic acid in 20 ml. of methanol was catalytically reduced in the presence of 10 mg. of platinum oxide. When the uptake of hydrogen was completed the solution was filtered, the catalyst was washed with water and the filtrate was concentrated to a small volume. On cooling, 850 mg. of a white precipitate settled out of solution. Its melting point, 190–192°, showed no depression on mixture with *m*-boronosuccinanilic acid but a definite lowering with *m*-boronomaleanilic acid.

3-Borono-N-phenylglycine (V). A mixture of 6.9 g. of *m*-aminobenzeneboronic acid, 11 g. of the monohydrate of sodium carbonate and 5 g. of chloroacetic acid in 100 ml. of water was heated on the steam bath for 3 hr. The solution was cooled and acidified carefully with concd. hydrochloric

(12) K. Torssell, H. Meyer, and B. Zacharias, *Arkiv Kemi*, **10**, 497 (1957).

(13) J. R. Johnson, M. G. Van Campen, and O. Grummitt, *J. Am. Chem. Soc.*, **60**, 111 (1938).

(14) R. Bean and J. R. Johnson, *J. Am. Chem. Soc.*, **54**, 4415 (1932).

(15) One gram of silver nitrate was dissolved in 8 ml. of water and this was diluted to 10 ml. with 28% aqueous ammonia.

acid. After remaining overnight in the refrigerator the solution was filtered and washed with a small amount of ice water. A 2.5-g. sample of white needles was obtained, m.p. >350°. This is the hydrochloride of the amino acid. The high solubility in aqueous solution of the free amino acid prevented its isolation when acetic acid was used as the acidifying agent. The hydrochloride was recrystallized three times from small amounts of water and the final solid analyzed.

Anal. Calcd. for $C_8H_{10}BNO_4 \cdot HCl$: C, 41.51; H, 4.79. Found: C, 41.15; H, 4.91.

2-Carboxy-5-borono-N-phenylglycine (VI). To a mixture of 6.0 g. of 2-amino-4-boronobenzoic acid[12] and 8.2 g. of sodium carbonate monohydrate in 50 ml. of water was added 3.1 g. of chloroacetic acid. There was an immediate reaction and following this, the solution was heated on the steam bath for 4 hr. The mixture was cooled, acidified with acetic acid, and filtered. The product, 2.3 g., m.p. >350°, was washed with a small amount of water and dried. Successive recrystallizations from water gave an analytical sample.

Anal. Calcd. for $C_9H_{10}BNO_6$: C, 45.23; H, 4.17. Found: C, 45.63; H, 4.82.

3-α,α,α-Trifluoromethylbenzeneboronic acid anhydride. m-Bromo-α,α,α-trifluoromethylbenzene (25 g.) was converted in the usual manner[2] *via* the corresponding Grignard reagent to 7.3 g. of 3-α,α,α-trifluoromethylbenzeneboronic acid anhydride, m.p. 161–164°. Successive recrystallizations from water gave a white crystalline product, m.p. 165–167°.

Anal. Calcd. for $C_7H_4BF_3O$: C, 48.90; H, 2.34. Found: C, 49.32; H, 2.65.

Acknowledgments. The authors are very grateful to Dr. William H. Sweet, Associate Professor in Surgery at the Harvard Medical School, for his encouragement and great interest.

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Observations on the Reaction between Triethylaluminum and Octene-1

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Received March 10, 1960

While attempting to measure the tritium isotope effects of the reactions between tritiated alcohols and organoaluminum compounds, the reaction between triethylaluminum and octene-1 was studied and the products identified. The products included 2-ethyloctene-1, a compound mentioned only briefly in the literature[1,2] and for which no reliable physical constants have been reported. Here we report briefly on the determination of the products of the reaction between triethylaluminum and octene-1, the measurement of some physical constants of 2-ethyloctene-1, and the determination of tritium kinetic isotope effects for methanol-*O-t* and isobutyl alcohol-*O-t* with the reaction mixture.

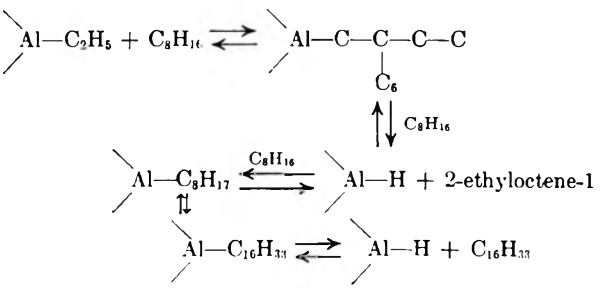
The complete distribution of products from the reaction between triethylaluminum and octene-1 is shown in Table I. The components which were determined as paraffins are expressed in the table arbitrarily as the corresponding pure organoaluminum compounds. While most of the products were identified by comparison with known infrared and mass spectra, no reference data were available for 2-ethyloctene-1. Carbon-hydrogen analysis and molecular weight measurements on this material indicated a composition of $C_{10}H_{20}$. The skeletal structure was determined by identification of its hydrogenation product as 3-methylnonane. Absorption bands at 890 cm.$^{-1}$ and 1650 cm.$^{-1}$, characteristic of vinylidene unsaturation, were observed in the infrared spectrum. For a molecule with the same skeletal structure as 3-methylnonane, vinylidene unsaturation is possible at only one position; therefore, 2-ethyloctene-1 was identified unambiguously.

TABLE I

COMPOSITION OF THE REACTION MIXTURE

Component	Mole Percent
Tri-*n*-octylaluminum	12.1
Octene-1	2.7
Tri-3-methylnonylaluminum	10.5
2-Ethyloctene-1	44.0
Trihexadecylaluminum	6.5
Hexadecene	24.3

The parachor calculated from measured physical constants, neglecting the vapor density, is 414 and compares well with that calculated from parachor equivalents,[3] 415. The components listed in Table I were the only ones formed in significant quantities as a result of the reaction between triethylaluminum and octene-1. One can deduce that the reaction proceeds as follows:



Other compounds, such as *n*-decene, *n*-decane, dodecanes, etc., which would have been expected from other reaction modes, were not found.

The tritium isotope effects (k_H/k_T), at 25° for isobutyl alcohol-*O-t* and methanol-*O-t*, with the organoaluminum compounds in the mixture shown in Table I, were 2.5 and 3.2, respectively.

Tritium isotope effects with Grignard reagents have been reported for a) methanol-*O-t* as 1.0-

(1) P. Bagard, *Bull. soc. chim.*, [4], 1, 346 (1907).
(2) B. Grédy, *Compt. rend.*, 195, 313 (1932).
(3) O. R. Quayle, *Chem. Rev.*, 53, 439 (1953).

1.2,[4] b) tritium oxide as 1.4–1.8,[5] c) phenol-*O-t* as 1.3,[6] and d) *tert*-butylcatechol-*O-t* as 3.0–3.5.[6] In the latter case, *n*-butyl ether was used as a solvent to prevent the formation of coordination compounds between the reactants, thus accounting for the greater isotope effect. The deuterium isotope effect between deuterium oxide and diethylzinc has been reported as 2.5.[7] In light of the above reports, the values reported herein are plausible. The higher tritium isotope effect found for methanol-*O-t* compared with isobutyl alcohol-*O-t* may result from the solubility of the reaction mixture in excess isobutyl alcohol and its insolubility in excess methanol.

EXPERIMENTAL

Materials. The materials used for these experiments included: Ethyl Corp. triethylaluminum (>95%), Phillips Pure grade octene-1 (>99%), argon, originally containing <20 ppm oxygen, <8 ppm water, dried further over Linde 5A molecular sieve, methanol (>99.85%), and isobutyl alcohol (98%). The tritiated alcohols were prepared by exchange with tritium oxide, followed by removal of water by distillation.

Reaction procedure and isotope effects. Triethylaluminum was mixed with octene-1 in a weight ratio of 1:3.5, corresponding to a ratio of 1.2 moles of octene-1 per ethyl group. The mixture was allowed to react under argon for 2 hr. at 145–160°. Then the temperature was raised to 195° in 1 hr. The reaction mixture was cooled to 25° and dropped slowly into a greater than ten-fold excess of either methanol-*O-t* or isobutyl alcohol-*O-t* at the same temperature. Inorganic products and excess alcohol were removed by extraction with dilute hydrochloric acid, dilute sodium hydroxide solutions, and distilled water. The paraffins in a portion of the product mixture were separated from the olefins using the fluorescent indicator adsorption technique.[8]

The average molecular weights of the saturated products were determined cryoscopically. The radioactivities of the reagent alcohols and the saturated reaction products were measured with a Packard Instrument Company Tri-Carb liquid scintillation counter, using a phosphor which consisted of 0.05 g./l. *p*-bis[2-(5-phenyloxazolyl)]benzene and 3.0 g./l. 2,5-diphenyloxazole dissolved in a xylene mixture.[9]

The tritium kinetic isotope effects (k_H/k_T), were calculated according to the equation:

$$\frac{k_H}{k_T} = \frac{A_a}{A_p} \cdot \frac{1}{M}$$

where A_a is the activity in counts per min. per mole for the alcohol, A_p is the activity in counts per min. per g. for the saturated products, and M is the cryoscopic average molecular weight.

A control determination to test the technique was carried out by adding the labeled alcohols slowly to part of the triethylaluminum and octene-1 reaction mixture held at 25°. Complete reaction was allowed to occur between incremental additions of alcohol. Separation and measurements of radioactivity and molecular weight were carried out as described above. An apparent isotope effect of unity for the control indicated that the reaction with alcohol was quantitative.

Analysis. The products which were recovered after treating the reaction mixture with alcohol were identified and determined quantitatively. Hexadecane and hexadecene were identified and determined directly by mass spectrometry; the distribution of C_{16} isomers was not determined. The other components were separated and measured quantitatively by gas chromatography at 80°, using a two-meter column packed with 20% *o*-xenyl-diphenyl phosphate on red Chromosorb. They were identified by infrared and mass spectra.

2-Ethyloctene-1. Several milliliters of pure 2-ethyloctene-1 were isolated from the product mixture using a large capacity gas chromatograph with a 14-foot, one-inch diameter column packed with the same substrate mentioned above. The isolated material, of high purity as determined by mass spectrometric analysis, was used for determination of physical constants. These were: n_D^{25}, 1.4231; d^{25}, 0.7438; b.p., 167.0–167.6°, surface tension at 25°, 22.9 dynes/cm.

Anal.[10]: Calcd. for $C_{10}H_{20}$: C, 85.71%; H, 14.29%; mol. wt., 140. Found: C, 85.81%, H, 14.55%, mol. wt., 138 ± 7.

The compound shows strong absorption in the infrared at 890, 1460, 2900 cm.$^{-1}$, medium bands at 730, 1380, 1650 cm.$^{-1}$, and weak bands at 775, 794, 962, 1060, 1120, 1780 cm^{-1}. A portion of the isolated material was hydrogenated, using a platinum dioxide catalyst, and the recovered hydrogenation product was identified through its infrared spectrum, which was identical with that of 3-methylnonane.[11]

Acknowledgment. Messrs. H. E. Clements and K. A. Pinkerton performed the cryoscopic and mass spectrometric measurements respectively. Prof. Z. W. Salsburg, of Rice University, allowed the use of his interfacial tensiometer.

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(4) L. O. Assarsson, *Acta Chem. Scand.*, 11, 1283 (1957).
(5) L. O. Assarsson, *Acta Chem. Scand.*, 10, 1509 (1956).
(6) L. O. Assarsson, *Acta Chem. Scand.*, 12, 1545 (1958).
(7) L. Friedman and A. P. Irsa, *Anal. Chem.*, 24, 876 (1952).
(8) *1958 Book of ASTM Standards, Part 7*, American Society for Testing Materials, Philadelphia, Pa., p. 756.
(9) H. Kallman and M. Furst, *Nucleonics*, 8, 32 (1951).
(10) Galbraith Microanalytical Laboratories, Knoxville, Tenn.
(11) American Petroleum Institute Research Project 44, Catalog of Infrared Spectral Data, Serial No. 609, 3-Methylnonane, contributed by the Naval Research Laboratory.

Communications TO THE EDITOR

Novel Rearrangement of 1,3-Glycols

Sir:

Recently, Gillis[1] has reported the isolation of small quantities of propionaldehyde from the attempted Bissinger rearrangement[2] of trimethylene sulfite in the presence of triethylamine. For some time we have been investigating the base catalyzed rearrangement of 1,3-glycols (Ia–c) and the corresponding cyclic sulfites (IIa–c). In each case studied, it has been observed that treatment of the glycol with strong base, sodium or potassium hydroxide, in the presence of sodium sulfite, arsenite, or phosphite has resulted in rearrangement to form the monoalcohols (IIIa–c) in good yields (approximately 50%). The corresponding cyclic sulfites[3] on rearrangement with sodium or potassium hydroxide alone gave comparable yields of the same monoalcohols as shown in Fig. 1.

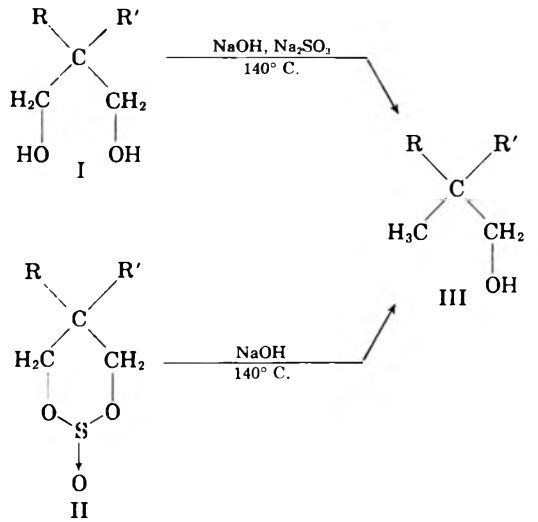

Fig. 1. Base catalyzed rearrangements of 1,3-glycols and cyclic sulfites

A. R = Methyl, R′ = Ethyl
B. R = Ethyl, R′ = Ethyl
C. R = Ethyl, R′ = Butyl

The reaction is experimentally quite simple to carry out and offers promise for the synthesis of a variety of neopentyl-type alcohols, difficult to obtain by other techniques. To a slurry of water (1.0 mole), sodium hydroxide (3.0 moles) and sodium sulfite (1.0 mole), the glycol (1.0 mole) was slowly added at a reaction temperature of 130–140°. After the addition was complete, the mixture was slowly cooled, water added, and the monoalcohol isolated by extraction in the normal fashion. Alternately, the cyclic sulfite was treated in a similar fashion with the exception that the sulfite was omitted. The yields obtained by either procedure were between 46 and 49%.

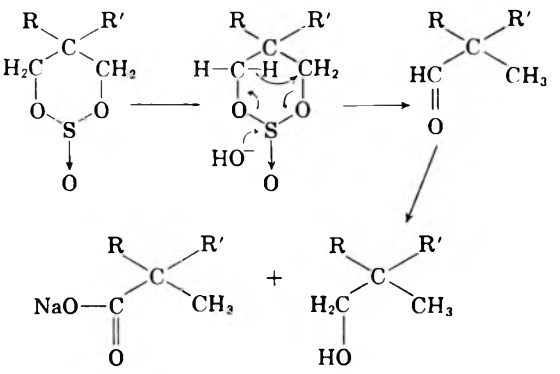

Fig. 2. Mechanism of 1,3-glycol rearrangement

Apparently, this is an extremely interesting example of a direct 1,3-hydride shift concurrent with the elimination of one of the hydroxyl groups. The resulting aldehyde, although not isolated among the reaction products, would be expected to undergo the Cannizzaro reaction in the strongly basic medium to yield the observed product, the monoalcohol. Basically, this mechanism is consistent for the rearrangement of either the cyclic sulfite or the glycol and can be visualized as indicated in Fig. 2. Using scale molecular models, the hydride migration postulated is easily visualized. In the case of the glycol, however, it must be assumed that only the monosulfite is formed and that the steric compression of the substituents on the *alpha*-carbon facilitates the rearrangement.

Further examples of this novel and interesting rearrangement are presently under investigation and a full account of this study with supporting data concerning the postulated mechanism will be published soon.

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Received June 15, 1960

(1) R. G. Gillis, *J. Org. Chem.*, **25**, 651 (1960).
(2) W. E. Bissinger, F. E. Kung, and C. W. Hamilton, *J. Am. Chem. Soc.*, **70**, 3940 (1948).
(3) For preparation see: A. C. Farthing, *J. Chem. Soc.*, 3648 (1955).

Synthesis of Ethyl 2- and 4-Pyridylpyruvates

Sir:

Considerable interest attaches to 2-pyridylpyruvic acid, 4-pyridylpyruvic acid, and their

simple esters and much work has gone into the investigation of possible synthetic methods.[1] To date the compounds have not been available. We wish to report the synthesis of esters of both the acids by a simple modification of the Claisen ester condensation of ethyl oxalate with α- and γ-picoline.

For reasons which will be given later, it appeared to us that previous attempts failed because of either too great or too little activity of the basic co-reactant used, and a metal derivative of the picolines of somewhat intermediate reactivity seemed to be indicated. If 2-picolyllithium is treated with anhydrous cadmium chloride and the resulting picolylcadium is treated at $-70°$ in ether with ethyl oxalate a 10% yield of easily purified ethyl 2-pyridylpyruvate is obtained as light-yellow crystals melting at 82.5–83.5° (*Anal.* Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.35; H, 5.85; N, 7.18).

Use of cadmium chloride was not effective in the case of 4-picoline but when mercuric chloride was substituted for it, under almost identical conditions, a 10% yield of ethyl 4-picolylpyruvate was obtained. This ester was also easily isolated and purified and appeared as an orange-yellow powder which melted at 138–139°. (*Anal.* Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.3; H, 5.95; N, 7.08).

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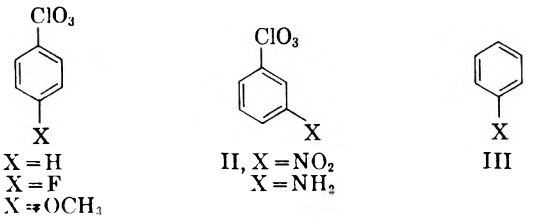
Received June 20, 1960

(1) C. R. Hauser and W. J. Humphlett, *J. Am. Chem. Soc.*, **72**, 3805 (1950); R. Adams and S. Miyano, *J. Am. Chem. Soc.*, **76**, 3168 (1954).

Hydrogenolysis of Perchloryl Aromatic Compounds

Sir:

When some representative perchloryl aromatic compounds, I and II, dissolved in glacial acetic acid, were stirred in contact with a palladium-on-charcoal catalyst and with hydrogen,[1] they absorbed the latter rapidly.[2] The products were identified by ultraviolet spectral data as being the



I, a. X = H
b. X = F
c. X = OCH_3

II, X = NO_2
X = NH_2

III

deperchlorylated compounds (III). The stoichiometry of the reaction corresponds generally to

$$ArClO_3 + 4H_2 \longrightarrow ArH + HCl + 3H_2O \qquad (1)$$

There are two qualifications we must offer to the above statements. First, *m*-nitroperchlorylbenzene absorbed not 4, but 7 moles of hydrogen corresponding to reduction of the nitro-group as well as hydrogenolysis of the perchloryl moiety. Second, our qualitative series of runs revealed no apparent structural influence on rate of hydrogenolysis, the uptake of hydrogen being quite rapid and essentially complete in 30 minutes at room temperature. The only exception was *m*-aminoperchlorylbenzene which as the free base readily underwent reaction (1) but which when placed in solution as its hydrochloride, was resistant to hydrogenolysis. The cause of this anomaly is being examined further.

When 95% ethanol was used as solvent the absorption of hydrogen observed was step-wise, one mole being taken up very rapidly and the other three much more slowly. These data suggest the following sequence for the overall hydrogenolysis (1).

$$ArClO_3 + H_2 \longrightarrow ArH + HClO_3 \qquad (2)$$

$$HClO_3 + 3H_2 \longrightarrow HCl + 3H_2O \qquad (3)$$

Calibrating experiments with chloric acid solutions in both glacial acetic acid (where reduction is rapid) and 95% ethanol (where reduction is slow) confirm this sequence of cleavage. In a critical experiment, a solution of Ia in 95% ethanol was allowed to take up one molar proportion of hydrogen, it was then filtered, extracted with ether, and the aqueous mother liquor was shown to contain 88% of the calculated chlorate content in accord with equation (2). An alternative mode of scission to the observed initial C—Cl rupture would involve initial Cl—O cleavages (to yield Ar—Cl) followed by its hydrogenolysis. This Ar—Cl intermediate in the case of Ia, *viz.* chlorobenzene was not hydrogenolyzed under our conditions.

These results also have some implication with regard to the structure of compounds of type (I). If the perchloryl compounds had the structure Ar—O—ClO_2 instead of the well established one, $ArClO_3$,[3] then one might anticipate their hydrogenolysis being akin to those of the analogous nitrate esters[4] and they should then proceed as follows:

(1) These hydrogenolyses were all run at room temperature and on a micro scale. The apparatus, technique, and catalyst used were as described by C. L. Ogg and F. J. Cooper, *Anal. Chem.*, **21**, 1400 (1949).

(2) An earlier probing experiment failed to reveal appreciable reaction between hydrogen with palladium catalyst and perchlorylbenzene [C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 5286 (1958)]. The present data now amend this erroneous impression. Other than the possibility that the earlier run may have contained some impurities which poisoned the catalyst, and the fact that it was not run on a quantitative scale, we cannot explain the negative result.

(3) See Inman, *et al.*, *J. Am. Chem. Soc.*, **80**, 5286 (1958).

(4) L. P. Kuhn, *J. Am. Chem. Soc.*, **68**, 1761 (1946).

$$ROClO_2 + 3H_2 \longrightarrow ROH + HCl + 2H_2O$$

Neither the observed stoichiometry nor the observed cleavage pattern of the perchloryl compounds conforms to this last equation. The present data thus support our earlier structural conclusions.[3,5]

(5) Another indication of the difficulty of Cl—O cleavage in the aromatic perchloryl compounds was given by a preliminary attempt at a polarographic assay. With a dropping mercury electrode from 0.0 to −2.0 v., an 0.05 *M* solution of perchloryl benzene in 50% aqueous ethanol with lithium chloride as supporting electrolyte gave no reductive wave in either neutral, weakly acidic or weakly alkaline solution.

The authors are deeply indebted to Messrs. H. Francis and E. Minnick for performing the microhydrogenolyses. This work was supported in part by the Air Research and Development Command.

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Received June 6, 1960