THE JOURNAL OF Organic Chemistry®

VOLUME 28, NUMBER 11

NOVEMBER 12, 1963

Bridged Lactones and Bridged Carbocyclic Systems from 2-(3,4,5-Trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic Acid. Novel Mescaline Analogs[1]

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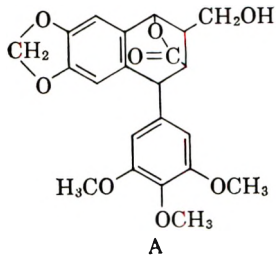
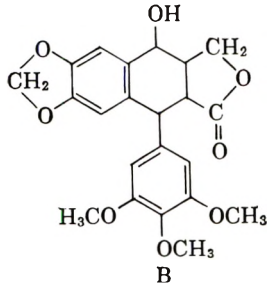
Received April 22, 1963

Treatment of 2-(3,4,5-trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic acid (C) with methanesulfonic acid yielded a mixture of the γ- and δ-lactones D and E, and a mixture of bridged ring acids, consisting principally of trimethoxybenzodimethyl[2.2.2]bicyclooctanecarboxylic acid (F). The structure of F was established by conversion of the amine F-5 (which is a mescaline analog of unusual type), degradation of the amine *via* the oxide, and pyrolysis to 1,2,3-trimethoxy-8-methylnaphthalene (M). This was synthesized by an unambiguous method. The dimethoxyphenyl analog of C was converted by methanesulfonic acid to a similar mixture of compounds.

This work was commenced with the idea of making bridged lactones as analogs of podophyllotoxin, which at that time was assigned structure A; the activity of podophyllotoxin in inhibiting experimental tumors suggested the synthesis and screening of related compounds. Since that time, podophyllotoxin has been shown to have structure[3] B by degradation and synthesis. The study of lactones related to structure A has led to some bridged carbocyclic structures and to some novel compounds containing the mescaline structure, which are described in the present paper.

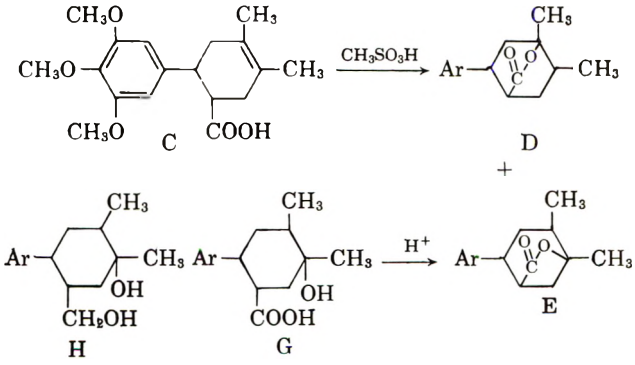


A



B

3,4,5-Trimethoxybenzaldehyde, prepared far more readily by treatment of N,N-dimethyl-3,4,5-trimethoxybenzamide with lithium diethoxyaluminum hydride[4] than by Rosenmund reduction of the acid chloride, was condensed with malonic acid to yield 3,4,5-trimethoxycinnamic acid[5]; 2,3-dimethylbutadiene added to this under pressure at 175° to form 2-(3,4,5-trimethoxyphenyl)-4,5-dimethyl-Δ^4-cyclohexenecarboxylic acid (C). Attempts to lactonize C with sulfuric acid, phosphoric acid, or hydrobromic acid were unsuccessful, but treatment with methanesulfonic acid yielded a mixture of lactones D and E and an acidic material, isomeric with the starting acid C.



Ar = 3, 4, 5-trimethoxyphenyl + isomeric acid F

The lactone mixture could be crystallized, but the melting point was not changed from 135–140° by further crystallization; the infrared spectrum (in Nujol) showed two peaks of nearly equal intensity at 1753 and 1725 cm.$^{-1}$. Chromatography on activity II alumina gave a homogeneous lactone, m.p. 156–157°, which, from its carbonyl band at 1720 cm.$^{-1}$, was given the δ-lactone structure D. When the two lactones are

(1) Taken from the Ph.D. theses of R. G. Nelb (1949), Leo Zeftel (1951), and T. J. Perun (1963), University of Rochester. Aided in part by Grant E-1138 of the U. S. Public Health Service.

(2) National Science Foundation Cooperative Fellow, 1961–1962.

(3) J. L. Hartwell and A. W. Schrecker, *J. Am. Chem. Soc.*, **73**, 2909 (1951); **75**, 5916 (1953); **77**, 432 (1955); W. J. Gensler, C. M. Samour, S. Y. Wang, and F. Johnson, *ibid.*, **82**, 1714 (1960); W. J. Gensler and C. D. Gatsonis, *ibid.*, **84**, 1748 (1962).

(4) K. I. H. Williams, Ph.D. thesis, University of Rochester, 1959; H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **81**, 502 (1959).

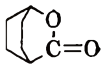
(5) K. H. Slotta and H. Heller, *Ber.*, **63**, 3042 (1930).

present in equal amounts a complex is formed which melts at 139–140° and which is not separated by chromatography on alumina.

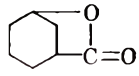
Saponification of the lactone mixture by base, followed by acidification, gave a 60% yield of a hydroxy acid, m.p. 191–193°; the fact that this hydroxy acid was converted to the γ-lactone E, m.p. 150–151°, with a carbonyl band in Nujol at 1753 cm.$^{-1}$, indicated that it was probably the γ-hydroxy acid G.

The n.m.r. spectra of the lactones D and E showed that they were indeed bridged across a dimethylcyclohexane ring. Both spectra showed one unsplit methyl peak, at about 8.55 τ, and one methyl peak split into a doublet at 8.95 τ. The presence of the two methyl peaks in both lactones showed that no skeletal rearrangement had occurred during the acid-catalyzed cyclization. The γ-lactone E was reduced by lithium aluminum hydride to a diol, m.p. 158–159°, presumably H, which also showed two methyl groups in the n.m.r. spectrum, one unsplit (8.48 τ) and one a doublet (8.83 τ).

The model bridged lactones I and J were prepared; their carbonyl frequencies, and those of D and E, are give in Table I.[6]



I



J

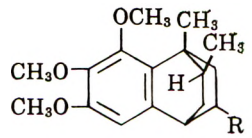
TABLE I

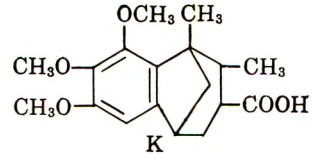
Lactone	Carbonyl absorption in CCl_4, cm.$^{-1}$
D	1748
E	1773
I	1754
J	1773

The treatment of C with reagent grade methanesulfonic acid for three hours gave approximately equal amounts of the lactone mixture D and E and of the isomeric acid F; the latter melted, after crystallization from ethanol–water, at 155–157°, and, after a further crystallization from carbon tetrachloride, at 159–160°.

The proportion of the lactone mixture and of the isomeric acid obtained depended on the conditions; the amount of isomeric acid was decreased by short reaction times, and increased, most strikingly, by the use of practical, instead of reagent grade methanesulfonic acid. The latter gave no lactone.

The n.m.r. spectrum of the isomeric acid showed the absence of vinyl protons and the presence of only *one* aromatic proton. One methyl group appeared as a singlet (8.46 τ), but the other methyl was present as a doublet (9.40 τ). The only structures consistent with the n.m.r. data are the bridged structures F and K. These structures can arise by nuclear alkylation by the tertiary carbonium ions formed by protonation at the two olefinic carbons in the cyclohexene ring.[7] The



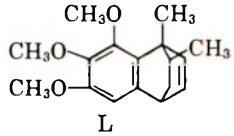


K

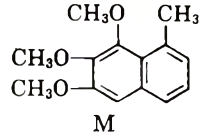
F-1, R = COOH
F-2, R = CON_3
F-3, R = N=C=O
F-4, R = $NHCOOCH_3$
F-5, R = NH_2
F-6, R = $NHCH_3$
F-7, R = $N(CH_3)_2$

melting point of the once crystallized acidic material showed that the material was not pure; the methyl ester was therefore prepared, and it was found by gas chromatographic analysis that two components were present in a 9:1 ratio. It is possible that the 9:1 ratio was different in the mixture before recrystallization. It was expected that the 2,2,2-bicyclooctane system F would be favored over the 3,2,1 system K, and this expectation was supported by degradation; F was found to be the major component.

The degradation was planned to consist of conversion of the carboxyl group in F to a tertiary amine, removal of the amino group to give the unsaturated compound L, and conversion of this by a reverse Diels–Alder reaction to the substituted naphthalene M and propylene.[8]

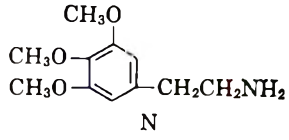


L

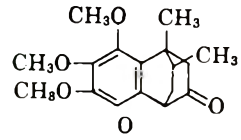


M

Conversion of the acid F-1 to the amine F-5 by the Schmidt reaction gave only a 38% yield. In an alternative procedure, the acid was converted to the azide F-2 through the mixed carboxylic–carbonic anhydride[9]; the azide was rearranged to the crystalline isocyanate F-3 by refluxing in toluene in 86% over-all yield from the acid, without the isolation of any intermediates. Acid hydrolysis of the isocyanate, which appeared to be unusually unreactive, gave a 47% yield of the crude amine F-5. The isocyanate was converted to the urethan F-4 in 97% yield by heating the toluene solution with methanol for five hours with triethylamine as catalyst. The slow rate of reaction of the isocyanate group with methanol required the use of the basic catalyst and of the long time of heating to complete the reaction. The urethan was hydrolyzed only slowly to the amine. The bridged amine F-5 is an analog of the hallucinogenic amine mescaline (N).



N



O

The samples of the amine F-5 obtained by various procedures were not homogeneous; the melting points varied, even after purification by sublimation. Thin layer chromatography of amine obtained by isocyanate hydrolysis showed two spots very close together, with

(6) The preparation of the crystalline lactone I is described by N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1950); J was obtained crystalline by E. J. Boorman and R. P. Linstead, *ibid.*, 258 (1935); see also M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.*, **75**, 1846 (1953).

(7) For analogous ring closures, see R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); C. Schöpf, *Experientia*, **5**, 201 (1949); G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Ann.*, **572**, 7 (1951).

(8) *Cf.* C. A. Grob, H. Kny, and A. Gagneux, *Helv. Chim. Acta*, **40**, 130 (1957); O. Diels and K. Alder, *Ber.*, **62**, 2343 (1929).

(9) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961); *cf.* D. S. Tarbell and J. A. Price, *ibid.*, **22**, 245 (1957).

the estimated ratio of areas about 4:1 or 5:1. It is unlikely that the Curtius rearrangement of F-2 to F-3 involves rearrangement of the carbon skeleton[10]; the variation in composition of the amine is probably due to differing rates of the various reactions involved, with compounds derived from the parent structures F and K.

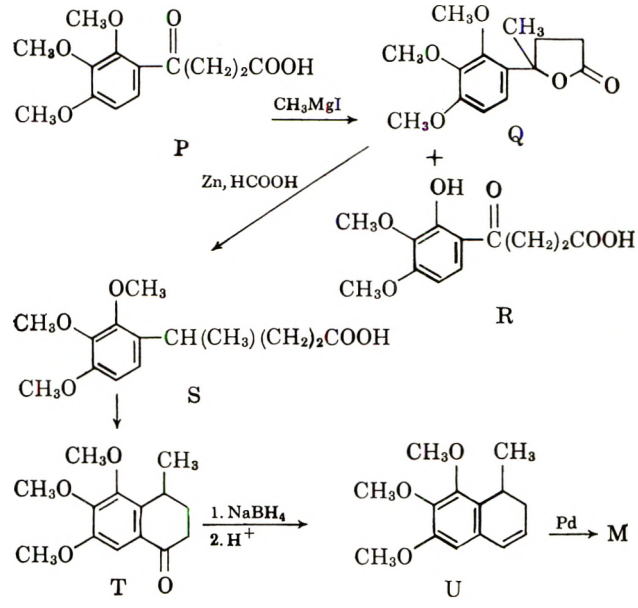
The primary amine was treated with formaldehyde–formic acid,[11] followed by refluxing with concentrated hydrochloric acid, to prepare the tertiary amine F-7. This yielded a mixture of amine salts, probably the hydrochlorides of trimethylamine and of F-7, and in addition 30% of a neutral oil, with a carbonyl band at 1710 cm.$^{-1}$ in the infrared, which was probably the ketone O. Milder reaction conditions with omission of the refluxing with concentrated acid yielded approximately equal amounts of the tertiary amine F-7 and the ketone O. This hydrolysis of the amino group during Clarke–Eschweiller methylation has been observed in other cases of bridged amines.[12] A mechanism has been suggested, involving hydrolysis of the imine.

Because the primary amine F-5 could not be converted to the tertiary amine F-7 in good yield, an alternative procedure was followed. The urethan F-4 was reduced by lithium aluminum hydride to the monomethylated amine F-6 in 75% yield, and this was converted to the tertiary amine by Clarke–Eschweiler methylation. The compounds F-6 and F-7 were not crystalline, but could be distinguished from each other and from the primary amine by thin layer chromatography.

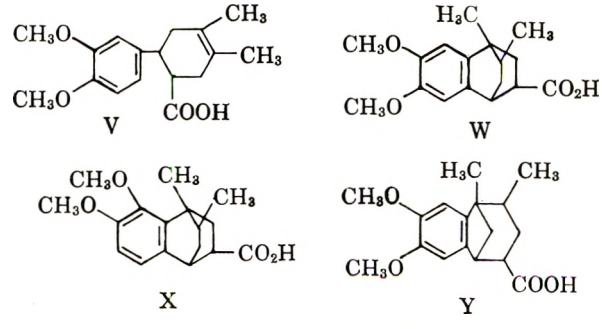
The N-oxide was prepared from F-7 by treatment with 30% hydrogen peroxide for two days, and was degraded by the Cope procedure[13] by heating at 170° for five hours *in vacuo;* dimethylhydroxylamine was isolated as the hydrochloride in 40% yield. The neutral material (isolated in 50% yield) was obtained crystalline after chromatography on alumina, m.p. 75–76°; the trinitrobenzene complex had m.p. 94–95°. The ultraviolet spectrum indicated that the material was a naphthalene derivative, and its analysis and melting point, and the melting point of the trinitrobenzene complex indicated that it was the known[14] 1,2,3-trimethoxy-8-methylnaphthalene (M). A sample of Haworth's material was not available for comparison, and the required trimethoxymethylnaphthalene was, therefore, synthesized.

The isolation of the naphthalene M in good yield from the degradation establishes the structure of the main component of the isomeric acid as F-1; it is unlikely that the amine oxide derived from K would aromatize to a naphthalene derivative under the conditions (170°) involved in the Cope degradation.

The naphthalene M was synthesized as follows. β-(2,3,4-Trimethoxybenzoyl)propionic acid (P)[15] was treated with methylmagnesium iodide to give the expected lactone Q, a viscous liquid with carbonyl absorption at 1770 cm.$^{-1}$. Some of the demethylated acid R was formed along with Q. Reduction of the lactone Q, which may have contained some demethylated acid, with zinc and formic acid[16] gave the valeric acid S, which could be obtained crystalline and analytically pure. The crude S could be used for cyclization with polyphosphoric acid to the tetralone T; this was reduced with sodium borohydride to the alcohol, which was dehydrated under acidic conditions to the dihydronaphthalene U. This material was treated with dimethyl sulfate and alkali to replace any methyl groups lost during the cyclization of S or in the later stages. Then it was aromatized by heating for two hours at 300° with palladium on charcoal; the product, after chromatography on alumina, melted at 73–74°, and showed no depression on mixture melting point withthe naphthalene M, obtained by degradation of the acid F-1. Identity of the two samples of M was also indicated by the infrared and ultraviolet spectra.



A less extended examination was made of the products from the action of methanesulfonic acid on the dimethoxyphenylcyclohexenecarboxylic acid V, which was prepared in a manner similar to that used for C.



The acid V was obtained as a monohydrate; the water of hydration could be removed *in vacuo*, and treatment of the anhydrous acid with methanesulfonic acid gave a lactone mixture and an acidic material. The lactone mixture showed carbonyl bands in the same region in the infrared spectrum as the mixture of D and E, and hence was considered to be a mixture of the γ- and δ-lactones. The acidic material contained water of hydration, and melted, when anhydrous, at 135–145°;

(10) E. S. Wallis and J. F. Lane, *Org. Reactions*, **3**, 272 (1946).

(11) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(12) W. E. Parkam, W. T. Hunter, R. Hanson, and T. Lahr, *ibid.*, **74**, 5646 (1952).

(13) A. C. Cope, T. T. Foster, and P. H. Towle, *ibid.*, 3929 (1949).

(14) R. D. Haworth, B. P. Moore, and P. L. Pauson, *J. Chem. Soc.*, 3271 (1949).

(15) P. D. Gardner, *J. Am. Chem. Soc.*, **76**, 4550 (1954); R. H. F. Manske and H. L. Holmes, *ibid.*, **67**, 95 (1945).

(16) R. L. Letsinger, J. D. Jamison, and A. S. Hussey, *J. Org. Chem.*, **26**, 97 (1961); M. S. Newman and K. Naiki, *ibid.*, **27**, 863 (1962).

its analysis showed it was isomeric with V. The n.m.r. spectrum showed that the two components were not the 2-position isomers W and X; there were two aromatic protons occurring in a single peak, indicating that the aromatic protons were in nearly identical environments. Therefore, the mixture was not a mixture of W and X, but more probably a mixture of W and Y.

It appears that a larger proportion of the 3,2,1 ring system was formed with the dimethoxy compound V than with the trimethoxy analog C. The methyl ester, prepared from a recrystallized sample of the mixture was shown by v.p.c. analysis to be a 55:45 mixture of two components, presumably W and Y. It appeared, however, that the original mixture was closer to a ratio of 2:1.

Experimental[17]

N,N-Dimethyl-3,4,5-trimethoxybenzamide.[4]—The crude 3,4,5-trimethoxybenzoyl chloride[18] from 76 g. of 3,4,5-trimethoxybenzoic acid was dissolved in 160 ml. of benzene, and the solution was cooled in an ice bath. Excess anhydrous dimethylamine (80 g., 1.8 moles) was distilled into the stirred solution through a delivery tube which extended below the surface. Water was added to dissolve the amine hydrochloride, the layers were separated, and the water layer was extracted with three portions of benzene. The combined benzene solution was dried and evaporated. The residue was dissolved in a mixture of 225 ml. of heptane and 70 ml. of benzene, and the solution was treated with Norit and allowed to cool. The white crystalline product obtained amounted to 65 g. (76%). The melting point was 76–77°.

3,4,5-Trimethoxybenzaldehyde.—A solution of lithium aluminum diethoxydihydride was prepared following the procedure of Brown.[4] The ethyl acetate used was dried over potassium carbonate and distilled. A solution of 15.5 ml. of ethyl acetate in 170 ml. of anhydrous ether was added to a stirred and cooled solution of 6.0 g. of lithium aluminum hydride in 170 ml. of anhydrous ether over a period of 2 hr. The resulting solution was then forced up into a long-stemmed dropping funnel by the use of nitrogen pressure. This solution was added dropwise to a well stirred suspension of 63 g. (0.26 mole) of N,N-dimethyl-3,4,5-trimethoxybenzamide in 500 ml. of anhydrous ether over a period of 2 hr. while the reaction flask was cooled in an ice bath. The reaction mixture was allowed to warm to room temperature and was refluxed for 2 hr. It was then poured over a mixture of 700 g. of ice and 700 ml. of 10% sulfuric acid. Benzene (350 ml.) was added to dissolve the product, the layers were separated, and the aqueous phase was extracted with three 350-ml. portions of benzene. The benzene extracts were added to the benzene–ether solution, and this solution was dried and evaporated, leaving an orange oil residue. The residue was dissolved in hot ethanol–water (1:1), and the solution was treated with Norit and cooled. The colorless plates obtained amounted to 30.6 g. (60%) with m.p. 73–74°; lit.[19] m.p. 74–75°.

2-(3,4,5-Trimethoxyphenyl)-4,5-dimethyl-Δ⁴-cyclohexenecarboxylic Acid (C).—In a high-pressure hydrogenation bomb was placed 60 ml. of anhydrous xylene, 24.6 g. of 3,4,5-trimethoxycinnamic acid,[5] 24.6 g. of 2,3-dimethylbutadiene, and 0.3 g. of hydroquinone. The bomb was heated at 175° in a rocker for 12 hr. The bomb was cooled, the contents poured out, and the inside washed out with portions of warm xylene. The combined xylene solution was heated on a steam bath, treated with Norit, and the filtered xylene solution was extracted with three 70-ml. portions of 10% sodium bicarbonate. In some runs a colloidal dispersion resulted. The bicarbonate solution was cooled in ice and acidified with dilute hydrochloric acid. The solid material obtained was recrystallized from ethanol–water (1:1) to give 21 g. (66%) of white, finely crystalline product with m.p. 137–138°.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.42; H, 7.48.

The **methyl ester** melted, after crystallization from dilute methanol, at 74.5–75.5°.

Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.91; H, 7.39.

The ***p*-nitrobenzyl ester** melted at 118.5–119.5°.

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42. Found: C, 65.53; H, 6.28.

Reaction of 2-(3,4,5-Trimethoxyphenyl)-4,5-dimethyl-Δ⁴-cyclohexenecarboxylic Acid with Methanesulfonic Acid.—To 1.0 g. of 2-(3,4,5-trimethoxyphenyl)-4,5-dimethyl-Δ⁴-cyclohexenecarboxylic acid (C) was added 6 ml. of reagent grade methanesulfonic acid. The solid dissolved quickly to give a reddish brown solution which was allowed to stand at room temperature for 3 hr. The reaction mixture was then poured onto 15 g. of cracked ice, and a white solid precipitated immediately. This material was filtered off, washed with water, and the sticky solid obtained was dissolved in about 20 ml. of ether.

A. The Tricyclic Acids (F and K).—The ether solution from the foregoing procedure was extracted with three portions of 10% sodium bicarbonate solution; the extracts were combined and acidified with dilute hydrochloric acid to give a sticky solid. This material was recrystallized from ethanol–water (1:1) to give 0.3 g. of white crystals with m.p. 155–157°. A second recrystallization from carbon tetrachloride gave fine white needles with m.p. 159–160°. The analysis was carried out on a sample of F recrystallized from dilute acetic acid.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.29; H, 7.45.

The ***p*-nitrobenzyl ester** melted at 156–157° after crystallization from ethanol.

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42. Found: C, 65.68; H, 6.37.

Saponification of this ester produced the same acid from which it had been prepared.

The n.m.r. spectrum of the tricyclic acid F showed that there was only one aromatic hydrogen in the compound, and that the two methyl groups were not equivalent. One methyl group was unsplit, and the other was split into a doublet. The spectrum also showed the absence of vinyl protons.

The ultraviolet spectrum contained a maximum at 278 mμ (log ε 3.17) and end absorption at 210 mμ.

The methyl ester of the once-recrystallized tricyclic acid was prepared by refluxing a solution of the acid in methanol containing 2% sulfuric acid. The colorless needles obtained after recrystallization had m.p. 109–110°. A gas chromatographic analysis of the ester on a 5-ft. SE-30 column at 200° showed the presence of two compounds, presumably the methyl esters of F and K, in a 9:1 ratio.

B. The Mixture of δ- and γ-Lactones (D and E).—The ether solution remaining from the bicarbonate extraction was dried over magnesium sulfate and evaporated to give 0.35 g. of a sticky solid. This material was recrystallized from diluted methanol to give 0.2 g. of colorless crystals with m.p. 132–134°. Repeated recrystallizations from methanol gave nicely formed prisms which melted between 135 and 140°.

An infrared spectrum of this material in solution (1% in carbon tetrachloride) contained two peaks in the carbonyl region at 1775 and 1755 cm.$^{-1}$. An infrared spectrum of a Nujol mull contained carbonyl peaks at 1753 and 1720 cm.$^{-1}$. Elementary analysis of the lactone mixture agreed with the expected value for D or E.

The mixture of δ- and γ-lactones (200 mg.) was dissolved in a petroleum ether–benzene solution and chromatographed on a 30-g. column of activity grade II neutral alumina. Elution with 2% ether in benzene gave 85 mg. of material in seven fractions. The material in the early fractions (40 mg.) consisted of a single lactone D with m.p. 156–157°. The infrared spectrum (Nujol mull) contained a single carbonyl peak at 1720 cm.$^{-1}$. A solution infrared spectrum (carbon tetrachloride) contained a carbonyl peak at 1748 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found (D): C, 67.65; H, 7.85.

Formation of the Hydroxy Acid G by Saponification of the Lactone Mixture.—Some of the recrystallized mixture of δ- and γ-lactones (170 mg.) was heated on the steam bath in 10 ml. of 2

(17) All melting points are uncorrected. Microanalyses are by V. Landeryou in this laboratory and by Micro-Tech Laboratories. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. The ultraviolet spectra were taken on a Beckman DU spectrophotometer. Nuclear magnetic resonance spectra were obtained on a 60-Mc. Varian instrument. We are indebted to Dr. L. D. Colebrook for the n.m.r. spectra and for assistance in their interpretation.

(18) Prepared following Rapoport, *et al.*, *J. Am. Chem. Soc.*, **73**, 1414 (1951).

(19) D. S. Tarbell, H. T. Huang, and H. R. V. Arnstein, *ibid.*, **70**, 4181 (1948).

N sodium hydroxide until it all dissolved (2.5 hr.). The cooled solution was then acidified with dilute hydrochloric acid, and the precipitate was collected and washed with portions of warm ether. The amount of hydroxy acid obtained was 110 mg., m.p. 191–193°.

Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.89; H, 7.75. Found: C, 63.56; H, 7.52.

Lactonization of the Hydroxy Acid G.—The hydroxy acid (100 mg.) was dissolved in 2 ml. of glacial acetic acid while warmed on a steam bath. Five drops of 10% sulfuric acid was added, and the solution was heated on the steam bath for 30 min. The solution was diluted with 2 ml. of water and cooled in the refrigerator. The colorless crystals that formed were filtered off to give 50 mg. of the **γ-lactone E**, m.p. 150–151°. The melting point of this lactone was depressed by mixture with the δ-lactone D.

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 67.48; H, 7.55. Found (E): C, 67.77; H, 7.52.

The infrared spectrum of lactone E showed a single carbonyl peak at 1753 cm.$^{-1}$; in carbon tetrachloride the carbonyl peak was at 1775 cm.$^{-1}$ when measured on a Perkin-Elmer Model 21 spectrometer; with a Perkin-Elmer Model 421, the compound in carbon tetrachloride showed a doublet at 1787 and 1775 cm.$^{-1}$.

Preparation of the Tricyclic Amine F-5 from the Tricyclic Acid F-1 by a Schmidt Reaction.—The reaction was conducted in a 100-ml. three-neck flask equipped with a stirrer, dropping funnel, and reflux condenser. A gas outlet tube was connected to the top of the condenser, and the tube led to a column of water in a graduate cylinder inverted in a beaker of water. The tricyclic acid F-1 (1.0 g.) was dissolved in 10 ml. of chloroform and to the stirred and cooled solution was added 2 ml. of concentrated sulfuric acid. The hydrazoic acid solution[20] (3.0 ml.) was then added dropwise to the reaction mixture. The mixture was allowed to warm to room temperature, and the reaction was stopped when 140 cc. of gas was collected in the water column. At this time the sulfuric acid layer was colored dark brown. The acid layer was separated from the chloroform and poured into 15 ml. of ice–water. The brown precipitate which formed was collected, and it amounted to 0.67 g. (m.p. 180–185°).

The solid was placed in an aqueous sodium hydroxide solution, ether was added, and the mixture was stirred with a magnetic stirrer. The yellow ether layer was separated and the brown aqueous solution was extracted with two more portions of ether. The ether extracts were combined, dried, and evaporated to give 0.35 g. (38%) of yellow oil which solidified overnight in the refrigerator. This material was sublimed under aspirator vacuum at an oil-bath temperature of 140° to give fine white crystals with m.p. 112–115°.

The hydrochloride of this amine was prepared, and it was recrystallized from ethyl acetate–methanol to give colorless needles with m.p. 204–208°.

Anal. Calcd. for $C_{17}H_{26}O_3NCl$: C, 62.28; H, 7.99. Found: C, 62.17; H, 8.05.

Reaction of the Tricyclic Amine F-5 with Formaldehyde and Formic Acid.[21]—A round bottom flask containing 110 mg. of the crude tricyclic amine was cooled in ice, while 0.2 ml. of 90% formic acid and 0.2 ml. of 38% formaldehyde were added separately. The reaction mixture was then heated on a steam bath under a reflux condenser for 20 hr. At the beginning of the last hour of heating, 0.04 ml. of concentrated hydrochloric acid was added. The solvent was removed under vacuum and a 25% sodium hydroxide solution was added to the yellow residue. A volatile amine was produced, and a yellow solid remained undissolved in the basic solution. Ether was added to dissolve the solid, and the aqueous solution was extracted with two more portions of ether. The ether solution was extracted with three portions of 10% hydrochloric acid and then dried over sodium sulfate. The ether solution was evaporated to give 33 mg. of a pale yellow oil which showed carbonyl absorption in the infrared at 1710 cm.$^{-1}$. A small portion of this neutral material was treated with 2,4-dinitrophenylhydrazine reagent. A precipitate was formed, but it could not be purified.

The acid extract was evaporated and the residue was treated with ethyl acetate to give a white solid which gave a positive chloride test with silver nitrate. A recrystallization from ethyl acetate–methanol gave colorless needles with m.p. 170–175° dec.

Another batch of crude tricyclic amine was treated with formaldehyde and formic acid for 10 hr., and the reaction was not heated with hydrochloric acid during the last hour. Work-up of this reaction gave nearly equal amounts of the ketone and the N,N-dimethyltricyclic amine F-7.

Preparation of the Tricyclic Isocyanate F-3.—The procedure used was similar to one used by Weinstock.[9] The tricyclic acid F-1 (1.3 g.) was placed in 1.0 ml. of water and acetone was added until solution occurred. The solution was stirred with a magnetic stirrer and cooled in an ice–salt bath while triethylamine (0.73 ml.) in 10 ml. of acetone was added. A solution of ethyl chloroformate (0.50 ml., 0.005 mole) in 2.0 ml. of acetone was then added slowly. During this addition, the solution became milky white. The mixture was stirred for 0.5 hr. while cooled at 0°, and then a solution of sodium azide (0.34 g.) in 2.0 ml. of water was added. The reaction gave good yields only with sodium azide purchased from Matheson Coleman and Bell. The reaction mixture first became clear and then became milky white again. The mixture was stirred at 0° for 1.5 hr. and then poured into ice–water. An oil first separated from the cloudy solution, and it then solidified. The azide was extracted from the aqueous mixture into three portions of toluene and the combined toluene extracts were dried. The toluene solution was then added slowly to a flask equipped with a stirrer while the flask was heated on a steam bath. When the evolution of gas had ceased, the toluene solution was evaporated to give 1.1 g. (86%) of pale yellow plates with m.p. 105–109°. The infrared spectrum (Nujol) of this material contained a peak at 2222 cm.$^{-1}$ due to the isocyanate group.[22]

Preparation of the Methylcarbamate F-4.—The toluene solution obtained in a preparation of the isocyanate was concentrated to about 25 ml., and 10 ml. of methanol and 1 drop of triethylamine were added. The solution was heated on the steam bath under a reflux condenser for 5 hr. Evaporation of the solution left 1.18 g. of viscous pale yellow material. The infrared spectrum contained an N–H peak at 3260 cm.$^{-1}$ and a carbonyl peak at 1690 cm.$^{-1}$. The material later crystallized to give almost colorless prisms with m.p. 115–120°. The yield was 97%.

Preparation of the Tricyclic Amine F-5 from the Isocyanate.—The tricyclic isocyanate F-3 (1.1 g.) was refluxed for 2.5 hr. in 8 ml. of 20% hydrochloric acid. The solid went into solution after a short time during the heating. Evaporation of the solution gave 1.2 g. of a glassy material, which was dissolved in water and the solution filtered. The aqueous solution was then stirred with ether and enough 20% sodium hydroxide was added to make it strongly basic. The basic solution was extracted twice more with ether and the pale purple ether solution obtained was dried over magnesium sulfate. Evaporation of the ether solution gave 0.47 g. (47%) of viscous yellow-orange liquid which solidified after standing a few days. After some seed crystals of the amine were placed on the cold finger of the sublimation apparatus, the material was sublimed under aspirator vacuum at an oil-bath temperature of 140°. The material was sublimed in batches totaling 0.3 g. to give 0.2 g. of fine white crystals with m.p. 104–109°.

Anal. Calcd. for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65. Found: C, 70.06; H, 8.57.

Thin-layer chromatography of this amine (1% in ethanol) on silica gel G, using 1-butanol–acetic acid–water solvent, produced a separation of the two isomers. The ratio of the areas of the spots appeared to be 4:1 or 5:1. The R_f values were 0.65 and 0.69, respectively.

Preparation of the Tricyclic Amine F-5 from the Methylcarbamate.—The crude methylcarbamate (1.1 g.) was placed in 5 ml. of 10% sodium hydroxide, and 5 ml. of ethanol was added to give a clear solution. The solution was refluxed for 4 hr., and the ethanol was evaporated to leave an oil in the reaction solution. The mixture was extracted three times with ether and the ether was dried. Evaporation gave an oil which showed carbonyl absorption in the infrared.

The oil was redissolved in basic aqueous ethanol and refluxed for 12 hr. more. Work-up as before gave 0.5 g. of oil which solidified overnight. This material still showed some carbonyl absorption in the infrared. The material was sublimed to give white crystals with m.p. 110–114°. Treatment with phenyl isothiocyanate gave the phenylthiourea derivative, which was recrystallized to give fine white needles with m.p. 185–188°.

(20) H. Wolff, *Org. Reactions*, **3**, 327 (1946).

(21) M. L. Moore, *ibid.*, **5**, 323 (1949).

(22) H. Hoyer, *Chem. Ber.*, **89**, 2677 (1956).

Preparation of the N-Methyl Tricyclic Amine F-6.—The methylcarbamate F-4 (1.05 g.) was dissolved in 15 ml. of anhydrous ether, and the solution was added dropwise to a stirred solution of 0.23 g. of lithium aluminum hydride in 15 ml. of anhydrous ether. The reaction mixture was refluxed for 21 hr. and was decomposed with wet ether. Enough 50% potassium hydroxide solution was added to form an aqueous layer containing the aluminum salts. The ether solution was separated and the aqueous layer was extracted with two more portions of ether. The ether solution was dried over potassium carbonate and evaporated to give 0.7 g. of viscous orange liquid. An attempt to sublime some of this material failed to give any crystalline product. The material gave a positive Hinsberg test for a secondary amine but failed to give a derivative with phenyl isothiocyanate. Thin-layer chromatography of this amine (1% in ethanol) using the 1-butanol–acetic acid–water solvent gave a single spot with R_f value 0.58.

Preparation of the N,N-Dimethyl Tricyclic Amine F-7.—The N-methyl tricyclic amine F-6 (0.5 g.) was placed in a flask with 0.45 ml. of 90% formic acid and 0.3 ml. of 38% formaldehyde. This mixture was heated on a steam bath under a reflux condenser for 8 hr. The flask was cooled, 0.28 ml. of 6 *N* hydrochloric acid was added, and the excess of formaldehyde and formic acid was removed under vacuum. Water was added to the residue and the aqueous solution (containing some insoluble material) was extracted with two portions of ether. This ether solution was dried and evaporated to give 0.06 g. of neutral oil which was not characterized.

The aqueous solution was stirred with ether, while enough sodium hydroxide solution was added to make it strongly basic. The solution was extracted with two more portions of ether and the ether solution was dried. Evaporation of the ether gave 0.4 g. of pale yellow viscous liquid.

Thin layer chromatography of this material (1% in ethanol) using the 1-butanol–acetic acid–water solvent gave a single spot with R_f value 0.46.

Thin layer chromatography of mixtures of the tricyclic amine, N-methyl tricyclic amine, and N,N-dimethyl tricyclic amine gave three distinct spots at precisely the same R_f values as determined individually.

Preparation and Decomposition of the N-Oxide of the N,N-Dimethyl Tricyclic Amine F-7.—The N,N-dimethyltricyclic amine F-7 (350 mg.) was dissolved in 1 ml. of methanol, 0.45 ml. of 30% hydrogen peroxide was added to the cooled solution, and the reaction solution was allowed to stand for 24 hr. at room temperature. Another 0.45 ml. of 30% hydrogen peroxide was added, and the solution was allowed to stand for 24 hr. more. The excess peroxide was decomposed with platinum foil (1 cm.^{2}). When the decomposition slowed down after standing overnight, a small drop of an aqueous solution of catalase was added.

The solution was transferred to a flask connected to a vacuum distillation apparatus. The methanol was removed under vacuum at room temperature and then the remaining solution was heated at 75° under 15-mm. pressure to remove the water (collected in a Dry Ice trap). The remaining material was heated for 5 hr. at 170° under 15-mm. pressure; it became brown during this time. Colorless material was collected in the Dry Ice trap. Nothing was collected in the receiving flask from the water condenser.

Ether and a 2 *N* solution of hydrochloric acid were added to the material in the trap and the two layers were shaken and separated. The ether solution was shaken with another portion of 2 *N* hydrochloric acid, and the combined acid solutions were extracted with two portions of ether. This procedure was also followed in working up the material in the pot.

The dried ether solution from the trap was evaporated, leaving no material. The acid solution was evaporated to give 33 mg. of white solid, m.p. 100–103°. Recrystallization from ethanol–ether gave colorless rods of N,N-dimethylhydroxylamine hydrochloride with m.p. 107–108°.[23] The yield of this material was 40% based on recovered starting material.

The acid solution from the pot was evaporated to give a glassy material. This was dissolved in water, and the solution was made strongly basic and extracted with ether. The dried ether solution was evaporated to give 70 mg. of the amine starting material.

The dried ether solution from the pot was evaporated to give 100 mg. of orange oil which showed mainly carbon–hydrogen peaks in the infrared. The ultraviolet spectrum contained maxima at 236 mμ (log ε 4.42), 280 (3.46), 312 (2.75) sh, and 328 (2.67). A 35-mg. portion of this material was chromatographed on activity grade II alumina, and 25 mg. of colorless oil was obtained. A portion of this material was crystallized from hexane to give 5 mg. of colorless prisms, m.p. 75–76°; lit.[14] melting point of 1,2,3-trimethoxy-8-methylnaphthalene is 73–75°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.23; H, 7.05.

A derivative with *s*-trinitrobenzene was prepared and crystallized from methanol to give orange plates with m.p. 94–95°; lit.[14] m.p. 91.5–93°.

Reaction of β-(2,3,4-Trimethoxybenzoyl)propionic Acid (P) with Methylmagnesium Iodide.—To 0.5 g. of magnesium turnings was added 15 ml. of anhydrous ether and 5 g. of methyl iodide. When the reaction was complete, the solution was added dropwise to a stirred solution of 2.0 g. of β-(2,3,4-trimethoxybenzoyl)propionic acid[15] in 50 ml. of dry benzene. A yellow complex separated as the Grignard reagent was added. The reaction mixture was stirred at room temperature for 4 hr. and then refluxed for 3 hr. The complex was decomposed with 10% hydrochloric acid. The organic layer was separated, and the aqueous solution was extracted with four portions of ether. The organic solutions were combined and extracted with three portions of 10% sodium carbonate solution. The organic solution was dried over anhydrous copper sulfate and evaporated to give 0.8 g. of viscous orange liquid which showed lactone carbonyl absorption in the infrared at 1770 cm.$^{-1}$. This lactone Q of γ-hydroxy-γ-(2,3,4-trimethoxyphenyl)valeric acid was not purified further but was used directly in the next reaction.

The combined sodium carbonate extracts were acidified with hydrochloric acid to give 0.25 g. of brown solid. This material was recrystallized from water–ethanol with Norit treatment to give pale yellow needles of β-(2-hydroxy-3,4-dimethoxybenzoyl)-propionic acid (R) with m.p. 154–155°; lit.[24] m.p. 152°.

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.63; H, 5.62.

γ-(2,3,4-Trimethoxyphenyl)valeric Acid (S).—The crude lactone of γ-hydroxy-γ-(2,3,4-trimethoxyphenyl)valeric acid (0.2 g.) was refluxed for 12 hr. with 3 ml. of 90% formic acid, 0.5 ml. of water, and 0.5 g. of zinc dust, then cooled and filtered. The formic acid solution was diluted with water and was placed in the refrigerator. After about 7 days a colorless crystalline solid separated. The amount was 70 mg. with m.p. 75–76°.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.64; H, 7.55.

4-Methyl-5,6,7-trimethoxy-1-keto-1,2,3,4-tetrahydronaphthalene (T).—The crude γ-(2,3,4-trimethoxyphenyl)valeric acid (300 mg.) was heated with 10 g. of polyphosphoric acid at 70–80° for 30 min. At the end of this time the color of the reaction mixture was an orange-brown. The reaction mixture was worked up with 30 g. of ice–water, and the cloudy solution was allowed to stand in the refrigerator for a few days. The aqueous solution was then poured off, and the remaining sticky material was dissolved in ether.

The ether solution was extracted with three portions of 10% sodium carbonate solution and then dried over magnesium sulfate. Evaporation of the ether gave 60 mg. of a yellow oil which contained a carbonyl peak in the infrared spectrum at 1670 cm.$^{-1}$. The infrared spectrum also contained a broad hydroxyl peak at 3390 cm.$^{-1}$. This indicated that the product was partially demethylated. The material could not be purified by chromatography or attempted crystallization.

1-Methyl-6,7,8-trimethoxy-1,2-dihydronaphthalene (U).—The crude tetralone (60 mg.) was dissolved in 5 ml. of methanol, and to this solution was added 100 mg. of sodium borohydride in aqueous methanol. The reaction mixture was stirred at room temperature for 14 hr. and then refluxed for 30 min. To this solution was added 4 ml. of 1 *N* hydrochloric acid, and the solution was stirred for 1.5 hr. The methanol was removed under vacuum and ether was added to the cloudy solution. The layers were separated and the aqueous solution was extracted with three portions of ether. The ether solutions were combined, dried, and evaporated to give 50 mg. of semisolid. The infrared spectrum contained no carbonyl peak and had two broad hydroxyl peaks at 3400 and 3240 cm.$^{-1}$. This hydroxy compound (50 mg.) was placed in 5 ml. of 10% sulfuric acid, and enough ethanol was added to effect solution. The solution was heated on a steam

(23) A. C. Cope, R. A. Pike, and C. F. Spencer; *J. Am. Chem. Soc.*, **75**, 3212 (1953).

(24) P. Mitter and S. De, *J. Indian Chem. Soc.*, **16**, 35 (1939).

bath under a reflux condenser for 4 hr. Most of the ethanol was then removed under vacuum leaving a milky white aqueous solution.

A solution of sodium hydroxide in water was added to the mixture until the oily material dissolved and the solution was basic. Dimethyl sulfate (5 drops) was then added and the solution was heated on a steam bath for 30 min. Enough sodium hydroxide solution was added to make the reaction solution basic again, 5 drops more of dimethyl sulfate were added, and the solution was heated for 30 min. more. At the end of this time an oil had separated from the reaction mixture. The basic solution was extracted with three portions of ether, and the ether solution was dried and evaporated to give 35 mg. of an orange oil which had only a small hydroxyl peak in the infrared. The ultraviolet spectrum contained maxima at 224 mμ (log ε 4.34), 269 (3.88), 276 (3.87) sh, and 307 (3.22) sh.

1,2,3-Trimethoxy-8-methylnaphthalene (M).—The dihydronaphthalene was heated with 5 mg. of 10% palladium on charcoal under nitrogen for 2 hr. at 280–310°. The product was dissolved in benzene, the solution was filtered, the charcoal was washed with more benzene, and the combined benzene solution was evaporated to give 18 mg. of orange oil. The infrared spectrum of this material was essentially identical to the infrared spectrum of the crude material obtained in the decomposition of the N-oxide from F-7. The ultraviolet spectrum of this material showed maxima at 235 mμ (log ε 4.55), 280 (3.59), 313 (3.06) sh, and 328 (2.95). The material was dissolved in benzene–petroleum ether and eluted through activity grade II alumina. A yellow oil (9 mg.) was obtained which was crystallized from hexane to give 4 mg. of yellow crystals, m.p. 73–74°; lit.[14] m.p. 73–75°. A mixture melting point of this material with the recrystallized material from the N-oxide decomposition was 73–74°.

2-(3,4-Dimethoxyphenyl)-4,5-dimethyl-Δ⁴-cyclohexenecarboxylic Acid (V).—In a small high-pressure hydrogenation bomb were placed 60 ml. of anhydrous xylene, 24 g. of 3,4-dimethoxycinnamic acid,[25] 23.8 g. of 2,3-dimethylbutadiene, and 0.3 g. of hydroquinone. The bomb was heated at 175° in a rocker for 13 hr. The bomb was then opened, the contents poured out, and the solid remaining in the bomb was washed out with portions of warm xylene. The solid was filtered off and the xylene solution was allowed to stand. More solid precipitated and this too was filtered off and added to the other solid material. This material was recrystallized from ethanol–water (1:1) to give white needles with m.p. 92–97°.

The xylene solution was extracted with 10% sodium bicarbonate solution, but this was unsatisfactory because of the formation of colloidal dispersions. Extraction with lithium carbonate solution also produced the same results. The extract solutions that were obtained (after settling) were acidified to give a white solid. This was recrystallized from ethanol–water (1:1) to give the same white needles obtained previously.

The infrared spectrum of this material contained a strong hydroxyl peak at 3300 cm.$^{-1}$. The neutralization equivalent (308) and analysis indicated that the product was a hydrate.

Anal. Calcd. for $C_{17}H_{22}O_4 \cdot H_2O$: C, 66.21; H, 7.85. Found: C, 66.13; H, 7.73.

The total yield of this hydrated product was 19.2 g. (62%).

(25) Prepared in 60% yield by condensation of veratricaldehyde with malonic acid in pyridine with piperidine catalyst, m.p. 183–184°. G. Lock and E. Bayer, *Ber.*, **72**, 1070 (1939), report m.p. 181°.

A sample of this material was heated in a drying pistol with refluxing acetone under aspirator vacuum for 48 hr. The material obtained had m.p. 107–108°. The infrared spectrum contained no peak at 3300 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.82.

Reaction of 2-(3,4-Dimethoxyphenyl)-4,5-dimethyl-Δ⁴-cyclohexenecarboxylic Acid with Methanesulfonic Acid.—A 1.0-g. sample of the hydrate of 2-(3,4-dimethoxyphenyl)-4,5-dimethyl-Δ⁴-cyclohexenecarboxylic acid was heated in a drying pistol under aspirator vacuum for 48 hr. The material obtained (0.95 g.) melted at 107–108°.

The anhydrous acid was placed in 6 ml. of reagent grade methanesulfonic acid. The solid dissolved immediately to give a cherry red solution. The solution was allowed to stand at room temperature for 3 hr., during which time the color became dark brown. The reaction solution was poured over 15 g. of cracked ice, and the white precipitate was collected and dissolved in ether.

A. The Dimethoxy Tricyclic Acids W and Y.—The ether solution was extracted with three portions of 10% sodium bicarbonate, and the extracts were combined and acidified with dilute hydrochloric acid. The solid obtained was recrystallized from ethanol–water (1:1) to give 0.57 g. of white crystalline product. The material melted low and over a large range, and the infrared spectrum (Nujol) contained a peak at 3400 cm.$^{-1}$. Some of this material was heated under aspirator vacuum in a drying pistol for 60 hr., and the solid obtained had m.p. 135–145°. The infrared spectrum contained no peak at 3400 cm.$^{-1}$. Recrystallization of some of this acid from carbon tetrachloride gave colorless needles with m.p. 80–90°. When heating was continued with the melting point block, square crystals formed in the melt and these crystals remelted at 135–145°. Chromatography of the acid melting at 135–145° on silica gel gave material which had the same melting-point range as the unchromatographed material.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.61; H, 7.50.

The methyl ester of the dimethoxy tricyclic acid was prepared by refluxing a solution of the acid in methanol containing 2% sulfuric acid. The colorless liquid obtained was chromatographed on silica gel. All fractions of material obtained had identical infrared spectra. The chromatographed material was crystallized from an ethanol–water solution to give colorless prisms with m.p. 87–92°.

A gas chromatographic analysis of the ester on a 5-ft. SE-30 column at 195° showed the presence of two compounds in relative amounts of 45% and 55%.

The n.m.r. spectrum of the ester confirmed the ratio of the two compounds as determined by the gas chromatographic analysis.

B. The Lactone Mixture.—The ether solution remaining from the bicarbonate extraction was dried over magnesium sulfate and evaporated to give 0.05 g. of pale yellow oil which could not be crystallized.

When a sample of the hydrate of the cyclohexenecarboxylic acid was used in place of the anhydrous acid, 0.1 g. of neutral solid was obtained from the ether solution. A recrystallization of this material from dilute methanol gave white crystals with m.p. 138–143°. An infrared spectrum of this material as a Nujol mull contained a peak in the carbonyl region at 1722 cm.$^{-1}$, with a shoulder at 1755 cm.$^{-1}$.

Studies Directed toward the Total Synthesis of Azasteroids. I. 3,4-Cyclopenteno-5,6-dihydropyridines and 6,6-Tetramethylene-5,6-dihydro-1,3-oxazines[1-3]

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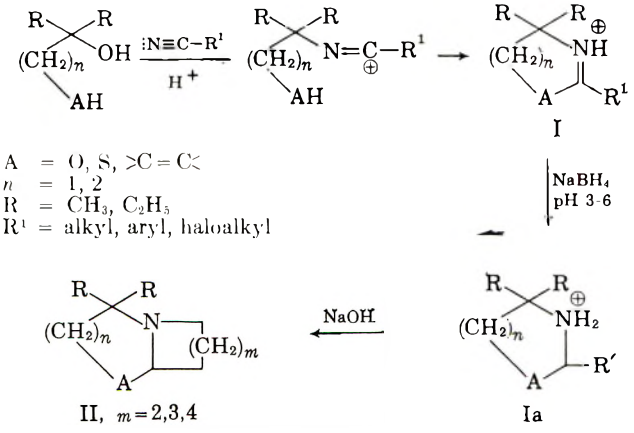
Received April 11, 1963

A study designed to obtain the azasteroid system by the condensation of suitably substituted nitriles with unsaturated tertiary alcohols in sulfuric acid has led initially to unexpected products identified as 2-substituted 6,6-tetramethylene-5,6-dihydro-1,3-oxazines (VII). The conditions favoring the formation of these products were found to be a function of the water activity in sulfuric acid. Decrease of the water activity led to exclusive formation of the desired azasteroidal precursor, a 3,4-cyclopenteno-5,6-dihydropyridine, presumably through the stabilized azocarbonium ion. The yield of the dihydropyridine was found to be quite low when the unsaturated alcohol XIIIb was employed (19%) but was increased to 76% when the corresponding glycol XVIII was the starting material. A study of the reduction products of the dihydropyridine was performed to test the feasibility of this ring system as a useful model in the steroid approach.

For several years, a study has been in progress which has extended the scope of the Ritter N-alkyl amide synthesis[4] to the preparation of a wide variety of N-heterocyclic compounds of the types I and II. The experimental conditions leading to I involved the treatment of a tertiary alcohol derivative containing an additional nucleophilic substituent with an alkyl or aryl nitrile in cold concentrated sulfuric acid. By employing β-, γ-, or δ-halonitriles with the tertiary alcohols, bicyclic bases II were produced by merely allowing the reaction to proceed to I followed by partial neutralization of the sulfuric acid solvent to a suitable pH (3–6) and adding sodium borohydride to obtain Ia. Alkaline treatment then gave II. The latter series of products were, therefore, produced in a single synthetic operation which did not require the isolation of intermediates I and Ia.



To date, this method has led to the convenient preparation of 5,6-dihydro-1,3-thiazines,[5] 5,6-dihydro-1,3-oxazines,[6,7] 2-thiazolines,[5,8] 5,6-dihydropyridines,[8] 1-pyrrolines,[8,9] and 1-azabicycloalkanes[10] in over-all yields of 40% or higher. The use of dinitriles[11] in this ring closure reaction led to α,ω-bis(N-heterocyclyl)alkanes derived from series I.

On the basis of the aforementioned studies, it soon became evident that this method could also be applied to the total synthesis of a variety of novel azasteroids if the proper starting materials could be obtained. A plan of approach (Chart I) was devised which required compounds containing relatively simple structural features. By treating *cis*-2-(2-cyanoethyl)chlorocyclohexane with the α-(1-cyclopentenyl)-*t*-alkanol in cold concentrated sulfuric acid, it was anticipated that the initial product would be the 3,4-cyclopentenodihydropyridine derivative III which could be reduced in a weakly acidic solution to the tetrahydropyridine IV. Further neutralization with sodium hydroxide would allow intramolecular alkylation to occur (presumably with some concurrent elimination) resulting in the racemic 9-azasteroid V possessing a *trans*-AB ring fusion. Examination of the structure of V indicates that it represents a molecule with several significant structural deviations from the natural steroids. This was of interest in view of the many recent efforts to modify the steroid nucleus in anticipation of enhanced biological activity.[12] Further modifications of V were considered as well as several other approaches which would place the nitrogen atom at any of the remaining ring junction positions. It was necessary, however, to test the feasibility of this scheme before proceeding to more complex structures.

A logical beginning to this approach appeared to be the study of the initial ring closure leading to the cyclopenteno-5,6-dihydropyridine III, using a simple nitrile. For this study, acetonitrile was chosen first to be followed by other nitriles of increasing complexity. The present paper will describe the results of reaction of simple nitriles with a cyclopentenyl-*t*-alkanol.

(1) A preliminary report of this study has already appeared: L. M. Trefonas, J. Schneller, and A. I. Meyers, *Tetrahedron Letters*, **22**, 785 (1961).

(2) Presented before the Organic Division at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November 1–3, 1962.

(3) Supported by funds granted by the National Institutes of Health, RG-6248(C2).

(4) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045, 4048 (1948).

(5) A. I. Meyers, *J. Org. Chem.*, **25**, 1147 (1961).

(6) (a) A. I. Meyers, *ibid.*, **25**, 147 (1960); (b) E. J. Tillmanns and J. J. Ritter, *ibid.*, **22**, 839 (1957).

(7) A. I. Meyers, *ibid.*, **25**, 218 (1961).

(8) J. J. Ritter and A. I. Meyers, *ibid.*, **23**, 1918 (1958).

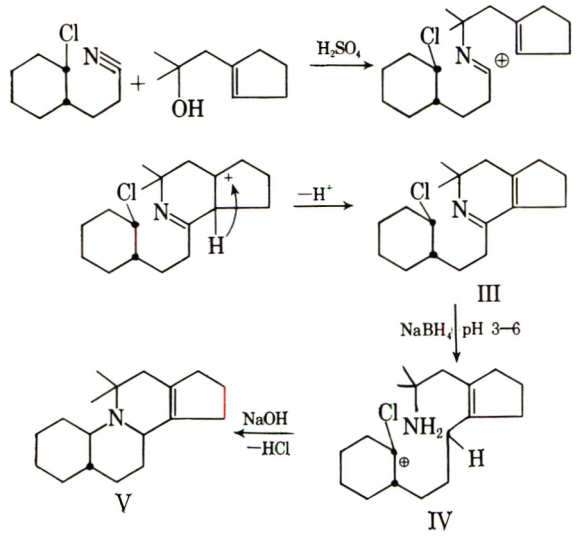
(9) A. I. Meyers, *ibid.*, **24**, 1233 (1959).

(10) A. I. Meyers and W. Y. Libano, *ibid.*, **26**, 1682, 4399 (1961).

(11) A. I. Meyers, *ibid.*, **25**, 2231 (1960).

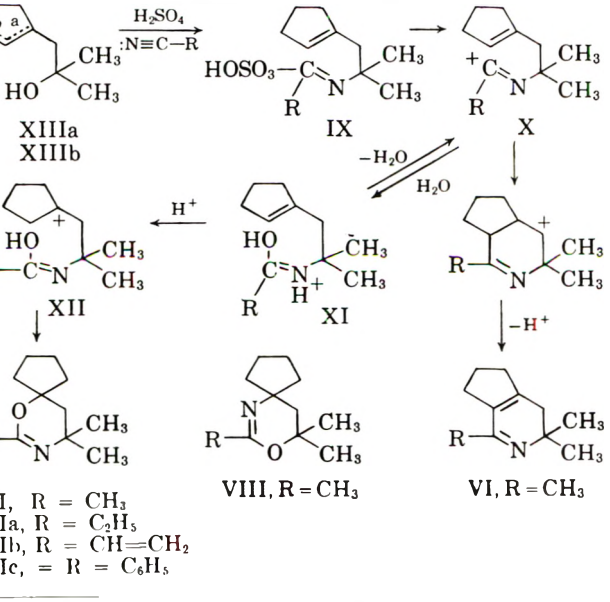
(12) To quote but a few: (a) C. W. Shoppee, *et al.*, *J. Chem. Soc.*, 1050 (1962), and earlier papers cited therein; (b) N. J. Doorenbos, *et al.*, *J. Org. Chem.*, **26**, 2546 (1961); (c) J. P. Kutney and R. A. Johnson, *Chem. Ind.* (London), 1713 (1961); (d) M. P. Cava and E. Moroz, *J. Am. Chem. Soc.*, **84**, 116 (1962); (e) J. Meinwald, G. G. Curtis and P. G. Gassmann, *ibid.*, **84**, 116 (1962); (f) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagen, *ibid.*, **82**, 1252 (1960); (g) P. B. Sallman, R. L. Elton, and R. M. Dodson, *ibid.*, **81**, 4435 (1959).

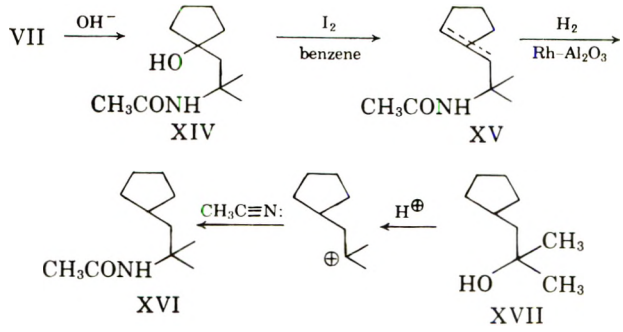
CHART I



Results and Discussion

When α-(1-cyclopentenyl)-*t*-butyl alcohol (XIIIa) was added to an ice-cold solution of acetonitrile in 96% sulfuric acid, extensive polymerization of the unsaturated alcohol resulted and no identifiable material was obtained. The fate of the entire program was altered, however, when the order of introducing the reactants was changed. Slow, dropwise addition of sulfuric acid to a cold solution of the alcohol in excess acetonitrile resulted in a basic product which exhibited a single strong band at 6.00 μ, yielded a pure picrate but did not show any signs of the C=C link which would be present in the cyclopentenodihydropyridine VI. Elemental analyses indicated that the compound possessed oxygen. The significant clue to the structure of the product was, however, the extremely strong absorption band at 6.00 μ which was reminiscent of the O—C=N stretching frequency observed by others[7,13] for dihydro-1,3-oxazines. On this basis a structure VII was advanced which was consistent with all the data at hand, and the path leading to its formation postulated as going through intermediates IX → X → XI → XII → VII. There also existed another possibility regarding the structure of the oxazine. If protonation of the double bond on the cyclopentenyl alcohol XIIIa occurred prior to that of the hydroxyl group, this would give rise to the isomeric oxazine VIII. Both of these structures would be consistent with all the data and their spectra would be indistinguishable. Evidence that VII was the correct structure was obtained by a degradation scheme which was initiated by alkaline hydrolysis of the oxazine to the hydroxyamide XIV, followed by dehydration with iodine to the unsaturated amides XV. Reduction, using rhodium catalyst, afforded a single saturated amide XVI. This amide was also prepared by the Ritter reaction[4] from α-cyclopentyl-*t*-butyl alcohol (XVII) and acetonitrile in sulfuric–acetic acid. The amides, as obtained from both routes were identical in every respect.[14]





The reaction was repeated using several other representative nitriles (VIIa–VIIc) all yielding the corresponding 2-substituted 6,6-tetramethylene-5,6-dihydro-1,3-oxazines. When the isomeric unsaturated alcohol, α-(3-cyclopentenyl)-*t*-butyl alcohol (XIIIb) was examined in this reaction, the products were identical to those obtained from the 1-cyclopentenyl alcohol and the yields were slightly higher (Table I) being accompanied by less polymeric material. By employing the the 3-cyclopentenyl alcohol, the reaction path leading to the oxazine, previously formulated, need not be altered other than considering an acid-catalyzed isomerization of the 3-olefin to the 1-olefin.

TABLE I

2-SUBSTITUTED 6,6-TETRAMETHYLENE-5,6-DIHYDRO-1,3-OXAZINES

Nitrile	% yield from α-substituted-*t*-butyl alcohol 1-Cyclopentenyl–	3-Cyclopentenyl–
Acetonitrile	41	63
Propionitrile	38	58
Acrylonitrile	29	57
Benzonitrile	39	72

The problem which now existed was to divert the sequence leading to oxazine formation to the desired cyclopentenopyridine derivative VI which is the necessary precursor in the proposed plan of approach to the azasteroid. It seemed reasonable that if the postulated reaction path (IX → X → XI → XII → VII) was essentially correct the equilibrium between X and XI was the critical factor in determining whether the oxazine or the pyridine would result. If reaction conditions could be arrived at which would decrease the ratio XI/X, this would then serve to enhance the formation

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 268.

(14) After the completion on this work, an X-ray crystallographic study on the hydrobromide of the spirooxazine was performed by Prof. L. M. Trefonas of this department. The result of this study also confirmed that VII was the correct structural assignment; *cf.* ref. 1.

of VI. It is presumably apparent from the equilibrium, X ⇌ XI that the water activity present in the solvent would determine which of these two species would predominate. Therefore, if the water activity in the acid could be diminished, this would increase the ion-solvating power of the solvent and decrease the ratio XI/X sufficiently to allow the reaction to proceed to the cyclopentenopyridine VI. Since the experimental conditions leading to the oxazine involved slow addition of twenty-five milliliters of sulfuric acid to a mixture of 0.25 mole of nitrile and 0.15 mole of the cyclopentenyl alcohol XIIIa, the water activity would be quite high during the initial stages of the acid addition. As the acid was added in excess, the water activity progressively decreased. This procedure led exclusively to the oxazine. Reversal of the order of addition, in which the same quantity of cyclopentenyl alcohol was added to the nitrile in twenty-five milliliters of sulfuric acid, gave, as previously mentioned, only polymeric products. The latter procedure, nevertheless, was still considered to be the only manner in which a minimum water activity could be maintained throughout the entire reaction period and shift the equilibrium in favor of X. This procedure was again applied but this time to the isomeric 3-cyclopentenyl alcohol XIIIb in the hope that polymerization would not be as extensive as in the previous case. It was observed that both XIIIa and XIIIb gave the same carbonium ion species in the sulfuric acid.[15]

The products obtained from the reaction included two basic fractions analyzed by gas chromatography to be a mixture containing 34% of the oxazine VII and 66% of a new substance possessing only the elements carbon, hydrogen, and nitrogen. The latter product was quite unstable, turning deep red after several hours' exposure to air. The ultraviolet spectrum of a freshly distilled sample exhibited a single peak, λ_{max} 263 mμ (ε 4260) typical of a 1,3-endocyclic conjugate system[16] in a six-membered ring. The infrared spectrum revealed a band of medium intensity at 6.00 μ and a strong, very sharp band at 6.25 μ indicative of the conjugated C=C and C=N stretching frequencies, respectively.[9,13] The n.m.r. spectrum (in deuteriochloroform) disclosed proton resonances which were all consistent with the structural assignment VI. That the C=C link was, in fact, located at the ring fusion was confirmed by: (a) the absence of the C=C—H stretching mode at 3.3 μ and the deformation modes at 11.9–12.4 μ; (b) the absence of a proton resonance signal at low field due to the C=C—H proton (lowest proton signal appeared at 7.6 τ); and (c) the high value of the λ_{max} since an exocyclic double bond would absorb at shorter wave length.[16]

By repeating the reaction of the 3-cyclopentenyl alcohol and acetonitrile in increasing amounts of sulfuric acid (such that the initial and final water activity was lowered) the *nearly exclusive formation* of the desired cyclopentenodihydropyridine was eventually achieved, thus validating the earlier postulate regarding intermediates X and XI (Table II).

TABLE II

FORMATION OF VI AND VII FROM α-(3-CYCLOPENTENYL)-*t*-BUTYL ALCOHOL AND ACETONITRILE AS A FUNCTION OF SULFURIC ACID CONCENTRATION[a]

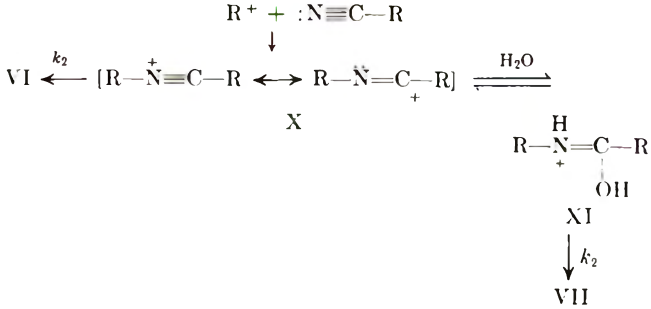
95.8% H_2SO_4 used initially[b]		Final % H_2SO_4[c]	Final water activity[d]	Total bases VI and VII	% Yield	
g.	ml.		(log a)		VI	VII
46.0	25.0	90.5	−3.66	41	66	34
92.0	50.0	93.1	−4.10	36	89	11
138.0	75.0	94.0	−4.26	27	98.5	1.5
184.0	100.0	94.4	−4.33	20	99.5	0.5
276.0	150.0	94.8	−4.40	19	99.8	0.2

[a] Analysis of this mixture was conveniently accomplished by gas chromatography using a 7-ft. column containing Chromsorb P coated with 5% KOH and 20% silicon oil (DC-710); *cf.* E. D. Smith and R. D. Radford, *Anal. Chem.*, **33**, 1160 (1961). [b] Each run was performed using 0.15 mole of α-(3-cyclopentyl)-*t*-butyl alcohol which yielded upon protonation 0.15 mole of H_3O^+. [c] These values were obtained from the following expression:

$$\text{Final \% } H_2SO_4 = 100\% - \frac{\text{wt. of } H_2O \text{ in 95.8\% } H_2SO_4 + \text{wt. of 0.15 mole } H_2O}{\text{wt. of 95.8\% } H_2SO_4 + \text{wt. of 0.15 mole } H_2O} \times 100$$

[d] The values were obtained by graphical interpolation from the expression derived by N. C. Deno and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **76**, 245 (1954): $\log a_{H_2O} = \log X_{H_3O^+} + H_0 + 5.00$, and assuming that the activity coefficient of water is essentially constant between 83–99.8% sulfuric acid.

It is evident from Table II that the azocarbonium ion X appears to be particularly favored in sulfuric acid concentrations above 93% since the pyridine VI is clearly the predominant product. More convincing evidence is indicated by the change in final water activity in the range 90–95% sulfuric acid which is *decreased by at least a factor of five*. The initial water activity would be much lower during the initial stages of the alcohol addition where the acid concentration is essentially 96% (log a_{H_2O} 4.62). This decrease in water activity would tend to enhance the ion-solvating power of the solvent and increase the amount of X in the following equilibrium.



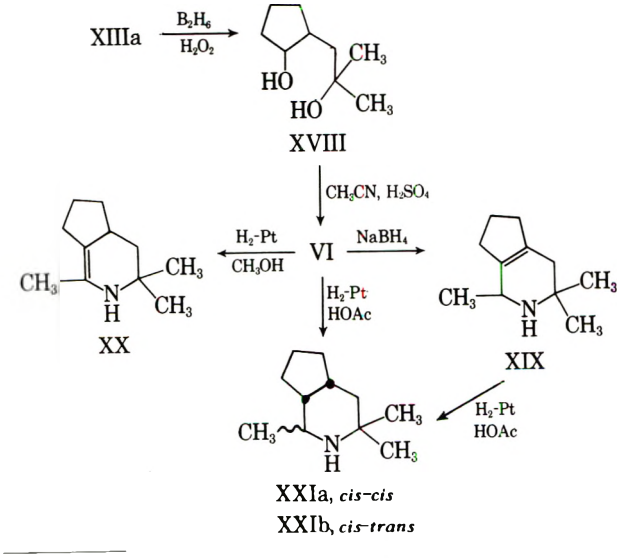
The results in Table II need not necessarily imply that the equilibrium lies heavily in favor of X at lower water activities since the rate constants k_1 and k_2 may be very different, that is to say, k_2 may be much greater than k_1, due to the fact that the azocarbonium ion is a much stronger acid than a proton and may add to the olefinic double bond at a much faster rate. Therefore, only appreciable (but not necessarily predominant) concentrations of X would be required for cyclopentenopyridine formation. The existence of the azocarbonium

(15) Dilute solutions (10^{-4} *M*) of each cyclopentenyl alcohol in concentrated sulfuric acid exhibited the same ultraviolet absorption spectrum, λ_{max} 303 mμ (ε 5500), which is characteristic of alkenyl carbonium ions; *cf.* N. C. Deno, H. G. Richey, Jr., J. D. Hodge, and M. J. Wisotsky, *J. Am. Chem. Soc.*, **84**, 1498 (1962).

(16) For an informative discussion of the ultraviolet maxima of alicyclic dienes and many leading references, *cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 15–21 (*cf.* E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, pp. 153–168).

ion species has been postulated[17] in the past as an intermediate both in the Schmidt reaction and the Beckmann rearrangement where concentrated sulfuric acid was employed. The rate of the Beckmann rearrangement was found to parallel the ion-solvating properties of the solvent medium.[18] Recently, Hill[19] has found that in some instances the Beckmann rearrangement, performed in concentrated sulfuric acid is actually a Ritter-type reaction,[5] where the nitrile formed *in situ* from the oxime, recombines with the carbonium ion, presumably to the azocarbonium ion. Subsequent dilution with water destroys this intermediate and yields the N-alkylamide.

Since the relatively low yield of I was accompanied by extensive polymerization of the cyclopentenyl alcohol in 96% sulfuric acid, the reaction was repeated in 98 and 100% sulfuric acid to determine if the quantity of water present in the acid performed any significant function regarding the polymerization. After four attempts in each acid medium, the yield of the pyridine and the quantity of polymerization was essentially unchanged. These results were considered to be due to the olefinic bond and dehydration to some diene species which extensively underwent acid-catalyzed polymerization. On this basis it was thought desirable to employ a starting compound which did not possess a double bond but one which could be converted to an olefin *in situ* during the course of the reaction. This technique has already been reported[20] to be advantageous in the formation of Δ^{-1} pyrrolines, prepared from ditertiary glycols and nitriles in much higher yields than those produced from the corresponding dienes.[21] By treating α-(1-cyclopentenyl)-*t*-butyl alcohol (XIIIa) with diborane according to the procedure of Brown and Zweifel[22] an 86% conversion to the glycol XVIII was realized. No trace of any isomeric product could be found during gas chromatographic analysis. The ultraviolet spectrum of this glycol in 96% sulfuric acid (10^{-5} *M*) was identical to that of both cyclopentenyl alcohols XIIIa and XIIIb [λ_{max} 303 mμ (ϵ 5400)] indicating that all three compounds gave identical carbonium ion species under these conditions. Addition of this glycol to a cold solution of acetonitrile in 98% sulfuric acid resulted in 76% yield of the cyclopenteno-5,6-dihydropyridine VI. The conditions under which this experiment was performed were identical to those employing the cyclopentenyl alcohol, yet the amount of polymerization was considerably less. This much more satisfactory procedure for obtaining the cyclopentenodihydropyridine then led to a study of the second step in the proposed steroid synthesis, that of reduction of the C=N link. The latter reduction would have to be carried out in acidic solution in order that the desired intermediates would react in the proper sequence. By adding an equimolar quantity of sodium borohydride to a solution of VI in dilute mineral acid solution, a quantitative reduction leading to XIX occurred. That the product was pure and free of any isomers was adequately demonstrated by gas chromatography. The infrared spectrum was very nondescriptive, showing only C—H stretching and long wavelength ring vibrations. The N—H group did not appear very distinctly in the spectrum, yet its presence was confirmed by a Zerewitinoff determination. The intensity of the stretching frequency of the tetrasubstituted C=C link was too weak to be detected.



The reduction using sodium borohydride was repeated on the dilution product of the glycol–acetonitrile–sulfuric acid mixture. After adjusting the quenched reaction mixture to pH 3.5 and adding sodium borohydride, the product thus obtained was identical to that prepared in the aforementioned experiment. Thus, it appeared that *for simple nitriles, at least, the first two operations of the proposed azasteroid synthesis were feasible.*

Further studies on the behavior of the cyclopentenopyridine toward reduction were undertaken in an effort to obtain an insight into the type of products which might be expected in the more complex steroid system.

Reduction of VI in absolute methanol using a platinum catalyst resulted in a very rapid uptake of one equivalent of hydrogen. An examination of the infrared spectrum of the product revealed that the C=N link was no longer present although this reduction method is known[23] not to reduce this group except when acetic acid is employed as the solvent. However, had the reduction occurred at the C=N link then the product would have been XIX. A mixture of the hydrochlorides of the reduced base (m.p. 195°) and that of XIX (m.p. 213°) gave a large depression in melting point. The position of the double bond (XX) was eventually confirmed by the enamine–imine tautomerism described by Leonard and Gash[24] where an absence of a band at 6.0–6.3 μ in the spectrum of the free base gave two sharp bands at 6.20 μ (C=N^+H) and 6.30 μ ($^+NH_2$) in the spectrum of its hydrosulfate salt.[25]

Repeating the catalytic reduction of I, in acetic acid, resulted in the absorption of two equivalents of hydro-

(17) (a) P. A. S. Smith, *J. Am. Chem. Soc.*, **70**, 320 (1948); (b) A. W. Chapman and C. C. Howis, *J. Chem. Soc.*, 806 (1933); (c) A. W. Chapman, *ibid.*, 1550 (1934).

(18) For numerous references pertaining to this system, *c.f.* J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 338, 339.

(19) R. K. Hill and O. J. Chartyk, *J. Am. Chem. Soc.*, **84**, 1064 (1962).

(20) A. I. Meyers and J. J. Ritter, *ibid.*, **23**, 1918 (1958).

(21) E. J. Tillmanns, Ph.D. thesis, New York University, 1954.

(22) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2550 (1961).

(23) (a) P. J. A. Demoen and P. A. J. Janssen, *ibid.*, **81**, 6283 (1959); (b) A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1920 (1958).

(24) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(25) Protonation of α,β-unsaturated amines in concentrated sulfuric acid was reported to give a mixture of 1- and 3-protonated amines; *cf.* R. L. Hinman and E. B. Whipple, *ibid.*, **84**, 2536 (1962).

gen and the production of two saturated bases, XXIa and XXIb. Analysis of this mixture by gas chromatography revealed that the ratio of products was 98 ± 0.5% to 2 ± 0.5%. Confirmation that the two peaks observed in the gas chromatogram were indeed those of two geometric isomers XXIa and XXIb and that the 98:2 ratio of peak areas was not a single compound and some impurity, the reduction products of XIX were examined under identical instrument conditions. This revealed approximately a 50:50 mixture of two saturated bases whose retention times were identical to the two products obtained by direct reduction of VI.

The high degree of stereoselectivity observed in the reduction of VI in acetic acid could lead to the assumption that the major product is the *cis–cis* isomer XXIa, and the minor product, the *cis–trans*. The reduction of 3,4-cyclopentenopyridine under the same conditions have been reported to yield exclusively 3,4-*cis*-cyclopentanopiperidine.[26] The validity of this analogy can be questioned if the presence of the methyl group in the dihydropyridine are considered important with respect to their effect upon direction of hydrogen addition. However, if the reduction of the tetrahydropyridine XIX in acetic acid involves *cis* addition then the resulting two products would be the *cis–cis* and the *cis–trans*. This fact is borne out upon gas chromatographic analysis of the products whose peaks are completely superimposable over those of the products from reduction of VI. Considering the possibility that the reduction of the dihydropyridine involved 1,4-addition then the tetrahydropyridine XX would presumably have to be an intermediate. This implies that the subsequent hydrogen addition would result in a *trans*-ring fusion as well as the *cis*-fusion.[27] Reduction of XX in acetic acid proceeded very slowly (fifty hours) and gave rise to a 55:45 mixture of bases of which the former was identical to XXIa, the latter *different* from XXIb.

This result is to be compared with the reduction of dihydropyridine VI in acetic acid which was complete within one hour. It is, therefore, difficult to account for the existence of XX as an intermediate in the reduction of the dihydropyridine. A further study has begun to substantiate these stereochemical results as well as the configuration of the 2-methyl group in XXIa and XXIb.

The present study has demonstrated that the first two steps of the planned azasteroid synthesis, (1) ring closure to the dihydropyridine and (2) borohydride reduction in acidic medium, were successful for simple nitriles. The next step, intramolecular alkylation to form the B ring remains to be examined. A study was therefore undertaken to employ halonitriles in this approach and the results are reported in the subsequent article.[28]

Experimental[29,30]

2,4,4-Trimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VII).—To a cold mixture of 21.5 g. (0.15 mole) of α-(2-cyclopentenyl)-*t*-butyl alcohol and 13.2 ml. (0.25 mole) of acetonitrile was added dropwise with stirring 25 ml. of 95.8% sulfuric acid. The mixture was kept below 10° during the addition of the acid which took about 0.5 hr. Due to the viscous nature of the resulting dark red solution an additional 25 ml. of concentrated sulfuric acid was added all at once and stirring continued for an additional 2 hr. at 8–12°. The reaction mixture was poured over 200 g. of chipped ice and stirred well. After standing at room temperature for several hours the aqueous acid solution was extracted three times with 75-ml. portions of chloroform. Upon neutralization with 35% sodium hydroxide an oil appeared which was taken up with ether and dried over potassium carbonate. Distillation of the residue from the ethereal solution gave 15.8 (63%) g. of a colorless oil, b.p. 77–79° (4 mm.); $n^{30}D$ 1.4694; $\lambda_{max}^{CCl_4}$ 6.00 (O—C=N).

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.92; H, 10.49; N, 7.73. Found: C, 73.12; H, 10.34; N, 7.75.

The **picrate** (from ethanol) melted at 154–155°.

The **hydrobromide** (from ethanol–ethyl acetate) melted at 173–174°.

2-Ethyl-4,4-dimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VIIa).—The method of preparation was similar to that of VII. After removal of the ether there was obtained a colorless oil (58%), b.p. 65–67° (1 mm.); $n^{30}D$ 1.4719.

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.80; H, 10.77; N, 7.18. Found: C, 73.98; H, 10.65; N, 7.14.

The **picrate** (from ethanol) melted at 105–106°.

2-Vinyl-4,4-dimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VIIb) was prepared in the usual manner yielding a colorless oil (57%), b.p. 68° (1 mm.); $n^{30}D$ 1.4848.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.68; H, 9.85; N, 7.25. Found: C, 74.46; H, 9.84; N, 7.09.

The **picrate** (from ethanol) melted at 156–158°.

2-Phenyl-4,4-dimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VIIc).—This compound was obtained as a brown solid after removal of the ether. Various attempts at recrystallization were fruitless. The pure oxazine (72%) was obtained by elution chromatography on a Florisil column using 20% petroleum ether–80% benzene as the eluent, m.p. 67–68°.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 79.10; H, 8.65; N, 5.77. Found: C, 79.11; H, 8.71; N, 5.62.

The **picrate** (from ethanol) melted at 143–144°.

α-(3-Cyclopentenyl)-*t*-butyl alcohol (XIIIb) was prepared (89%) by treating 3-cyclopentenylacetone[31] with methylmagnesium bromide in diethyl ether, b.p. 80–82° (10 mm.); $n^{30}D$ 1.4645.

Anal. Calcd. for $C_9H_{16}O$: C, 77.14; H, 11.42. Found: C, 76.90; H, 11.23.

α-(1-Cyclopentenyl)-*t*-butyl alcohol (XIIIa) was prepared (85%) by the action of methylmagnesium bromide on 1-cyclopentenylacetone (Aldrich Chemical Co.) in diethyl ether, b.p. 52–53° (0.5 mm.); $n^{30}D$ 1.4640.

Anal. Calcd. for $C_9H_{16}O$: C, 77.14; H, 11.42. Found: C, 77.03; H, 11.35.

2,6,6-Trimethyl-3,4-cyclopenteno-5,6-dihydropyridine (VI).

A. From α-(3-Cyclopentenyl)-*t*-butyl Alcohol (XIIIb).—To a cold solution of 4.1 g. of acetonitrile in 150 ml. of 95.8% sulfuric acid was added with stirring, 12.6 g. of α-(3-cyclopentenyl)-*t*-butyl alcohol at 5–7° during a period of 2 hr. After addition was complete the dark mixture was stirred for 3 hr. at 7–12° and then poured over 500 g. of chipped ice. The tarry material which appeared was removed by extraction with chloroform and the dark aqueous solution was made strongly basic by the careful addition of 35% sodium hydroxide. The red oil which then appeared was taken up in ether and dried with potassium carbonate. Distillation of the ether residue gave 2.9 g. (19%) of a light yellow oil which grew progressively darker when allowed to remain in contact with air; b.p. 61.5° (0.4 mm.); $n^{30}D$ 1.4925; λ_{max}^{EtOH} 263 mμ, (log ε 3.63); $\lambda_{max}^{CCl_4}$ 6.00 μ (C=C), 6.25 (—C=N).

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.99; H, 10.42; N, 8.58. Found: C, 81.06; H, 10.38; N, 8.61.

The **picrate** (from ethanol) had m.p. 144°.

Anal. Calcd. for $C_{17}H_{20}N_4O_7$: C, 52.10; H, 5.11; N, 14.29. Found: C, 52.06; H, 5.16; N, 14.10.

B. From α-(2-Hydroxycyclopentyl)-*t*-butyl Alcohol (XVIII).—The glycol (16.0 g.) was added slowly to a solution of 5.5 ml. of acetonitrile in 150 ml. of 98% sulfuric acid at 3–5° with good mechanical stirring. The solution took on color much more

(26) V. Prelog and V. Meltzer, *Helv. Chim. Acta*, **29**, 1170 (1946); G. G. Ayerst and K. Shofield, *J. Chem. Soc.*, 4097 (1958); K. Jewers and J. McKenna, *ibid.*, 1575 (1960).

(27) A referee has pointed out that Dreiding models of XX indicate that if the heterocyclic ring exists in the quasi chair form then a *trans*-ring fusion would predominate, whereas a quasi boat form would give the *cis*-product.

(28) A. I. Meyers and N. K. Ralhan, *J. Org. Chem.*, **28**, 2950 (1963).

(29) All boiling points and melting points are uncorrected.

(30) Microanalyses were performed by Alfred Bernhardt, Mulheim (Ruhr), West Germany.

(31) We wish to thank the Lilly Research Laboratories, Indianapolis, Ind., for a generous sample of this material.

slowly than experiments using the unsaturated alcohol. After the addition of the glycol was complete, however, the solution was a golden yellow. Stirring was continued at 5–7° for an additional 2 hr. and then the mixture poured on 350–400 g. chipped ice. The remainder of the procedure was identical with that described previously. Distillation of the ethereal residue gave 12.1 g. (76%) of VI.

Hydroboration of α-(1-Cyclopentenyl)-*t*-butyl Alcohol to the Glycol XVIII.—All reactants were distilled on the day of use. The apparatus employed consisted of a diborane generator containing 133 g. (0.89 mole) of boron trifluoride–ethyl ether complex and 120 ml. of diglyme into which a solution of 15.0 g. (0.43 mole) of sodium borohydride in 300 ml. of diglyme was slowly added. A slow stream of dry nitrogen continuously carried the diborane into a reaction flask containing 75 g. (0.54 mole) of α-(1-cyclopentenyl)-*t*-butyl alcohol dissolved in 250 ml. of tetrahydrofuran. The addition of diborane was complete within 3 hr., and the reaction mixture was allowed to remain at room temperature overnight. After adding 100 ml. of 10% sodium hydroxide at 0°, the mixture was heated to 50° for 1 hr. and cooled to room temperature, at which point 100 ml. of 30% hydrogen peroxide was cautiously added. An exothermic reaction ensued which was easily controlled by the rate of peroxide addition. The two layers which appeared were separated and the aqueous layer extracted several times with equal volumes of ether. Combination and drying of the organic layers gave a clear colorless solution. Removal of the mixture of solvents and distillation of the residue gave 73 g. (86%) of a viscous colorless oil, b.p. 110–112° (0.5 mm.); $n^{27}D$ 1.4735; infrared spectrum exhibited strong –OH (3.0 μ).

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.29; H, 11.39. Found: C, 68.09; H, 11.20.

2,6,6-Trimethyl-3,4-cyclopenteno-1,2,5,6-tetrahydropyridine (XIX). A. By Direct Reduction of VI.—A solution of 6.5 g. (0.04 mole) of I in 300 ml. of 0.25 *N* hydrochloric acid was adjusted to pH 3.5, and a solution of 1.48 g. (0.04 mole) of sodium borohydride in 30 ml. of 0.5% sodium hydroxide was added slowly maintaining the pH range of the solution between 3 and 4. After stirring for an additional hour at pH 4, the solution was neutralized and extracted with ether to remove the reduced base. Distillation of the dried ethereal extract resulted in 6.2 g. of a colorless oil, b.p. 53–55° (0.5 mm.); $n^{30}D$ 1.4810.

Anal. Calcd. for $C_{11}H_{19}N$: C, 80.00; H, 11.51; N, 8.49. Found: C, 80.21; H, 11.49; N, 8.39.

The **hydrochloride**, prepared by passing dry hydrogen chloride into an ethereal solution of the base and recrystallizing the crude salt with methanol–ethyl acetate, melted at 213°.

Anal. Calcd. for $C_{11}H_{20}NCl$: C, 65.51; H, 9.94; N, 6.98; Cl, 17.55. Found: C, 65.59; H, 9.92; N, 6.99; Cl, 17.47.

B. From α-(2-Hydroxycyclopentenyl)-*t*-butyl Alcohol and Acetonitrile.—The initial procedure is identical to that described for the formation of VIb, up to and including the chloroform extraction. The electrodes of a pH meter were inserted into the aqueous acid solution and the pH adjusted to 3–4 by the addition of sufficient 30% sodium hydroxide. The total volume of solution was approximately 800 ml. A solution containing 3.7 g. (0.1 mole) of sodium borohydride in 50 ml. of 0.5% sodium hydroxide was added dropwise to the weakly acidic solution keeping the pH between the range 3–4 by concurrent addition of 6 *N* sulfuric acid. After completion of the addition, stirring was maintained for 1.5 hr. and then the solution was neutralized. Extraction with ether, drying, and distillation resulted in 11.8 g. (72%) of the unsaturated base XIX.

Reaction Conditions Leading to Mixture of VI and VII.—This is a typical experiment in which the quantity of sulfuric acid employed led to a mixture of both products (Table II). To a solution of 8.2 g. of acetonitrile in 50 ml. of 95.8% sulfuric acid was added 24.6 g. (0.19 mole) of α-(3-cyclopentenyl)-*t*-butyl alcohol over a period of 2 hr. at 5–7°. After stirring for an additional 3 hr. the products were isolated in the usual manner. The infrared spectrum exhibited strong bands at 6.00 (—O—C=N and C=C) and 6.25 μ (conjugated C=N). Injection of 2.0 μl. of this mixture into the gas chromatograph at 145° on a Chromosorb P column coated with 5% potassium hydroxide and 20% silicon oil (DC-710)[32] gave two symmetrical peaks in the ratio 11% VII to 89% VI. These peaks were identified by employing pure samples of VI and VII under identical instrument conditions.

Alkaline Hydrolysis of VII to XIV.—A suspension of 6.0 g. of VII in 100 ml. of 30% sodium hydroxide was refluxed for 16 hr. and then extracted with ether. The removal of the ether left a viscous colorless oil, $\lambda_{max}^{CCl_4}$ 2.76 μ (–OH), 2.91 (NH), 5.89 (amide I), 6.61 (amide II).

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.45; H, 10.55; N, 7.05. Found: C, 66.60; H, 10.48; N, 6.90.

Dehydration of XIV to XV was accomplished by adding 0.05 g. of iodine to a solution of 5.4 g. of XIV in 100 ml. of benzene and removing the water in an azeotrope trap. After heating for 24 hr. the solution was filtered and the benzene evaporated *in vacuo*. The residue was washed with 0.1 *N* hydrochloric acid and then with water and dried, m.p. 84–92°. Attempts to separate the unsaturated amides by chromatography on alumina were not entirely successful, and the mixture was analyzed as such.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.92; H, 10.49; N, 7.73. Found: C, 73.05; H, 10.41; N, 7.70.

Hydrogenation of the Mixture of Unsaturated Amides to XVI.—A solution of 75 mg. of the amide mixture in 10 ml. of methanol containing 50 mg. of 5% rhodium on alumina[33] was subjected to 45 lb. hydrogen pressure for 20 min. at room temperature. Removal of the catalyst and evaporation of the solvent gave 65 mg. of colorless crystals, m.p. 73–75°.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.15; H, 11.48; N, 7.65. Found: C, 72.03; H, 11.33; N, 7.71.

α-Cyclopentyl-*t*-butyl alcohol was obtained quantitatively by hydrogenating a mixture consisting of 7.6 g. of α-(1-cyclopentenyl)-*t*-butyl alcohol, 75 ml. of methanol, and 0.5 g. 5% rhodium-on-alumina. The reduction, performed at room temperature under 40 lb. pressure, was complete within 2 min. After removal of the catalyst and solvent, there was obtained 7.5 g. of a colorless liquid, b.p. 59–60° (0.5 mm.); $n^{30}D$ 1.4536. The 3.25-μ band (C=C—H) was absent in the infrared spectrum.

Anal. Calcd. for $C_9H_{18}O$: C, 76.15; H, 12.68. Found: C, 76.00; H, 12.77.

Preparation of XVI *via* the Ritter Reaction.—A solution of 4.8 g. (0.034 mole) of α-cyclopentyl-*t*-butyl alcohol, 15 ml. of glacial acetic acid, and 2.0 ml. of acetonitrile in 20 ml. of concentrated sulfuric acid was allowed to stand in a stoppered flask at room temperature for 16 hr. The dark solution was then poured over 300 g. of chipped ice, which gave rise to a viscous oil which was extracted with ether, and dried with magnesium sulfate. Evaporation of the solvent left a tacky solid which could not be purified by recrystallization. Chromatography on alumina using petroleum ether as the eluent gave a light yellow solid, m.p. 50–65°. The crude amide was dissolved in 6 *N* hydrochloric acid and the solution extracted with chloroform until all the color was removed. Upon neutralization of the aqueous solution, a colorless powdery precipitate appeared, which after thorough washing and drying melted at 73–74°. A mixture of this product with that obtained by the reduction of XV, gave no depression in the melting point. Furthermore, the infrared spectra of both compounds were completely superimposable.

Reduction of VI to XX in Methanol.—A solution of 3.0 g. (0.018 mole) of VI in 30 ml. of absolute methanol containing 0.5 g. of platinum oxide was hydrogenated at 42 lb. at 25°. The absorption of 0.018 mole of hydrogen was complete within 15 min. Removal of the catalyst by filtration and concentration of the solution yielded an oil which distilled at 74° (3.5 mm.); $n^{30}D$ 1.4793. Examination of the product by gas chromatographic analysis (10% DC-710 silicon oil, 5% potassium hydroxide on Chromosorb P at 145°) indicated a single product. The infrared spectrum (carbon tetrachloride) exhibited very weak bands at 3.10 (NH) and 6.00 μ (C=C). The infrared spectrum in chloroform containing a drop of concentrated sulfuric acid exhibited medium bonds at 6.19 ($C=\overset{+}{N}H$) and 6.31 μ ($>\overset{+}{N}H_2$), indicative of the 3- and 1-protonated enamine.[10]

Anal. Calcd. for $C_{11}H_{19}N$: C, 80.00; H, 11.51; N, 8.48. Found: C, 79.94; H, 11.45; N, 8.45.

The **hydrochloride** melted at 194° (methanol–ethyl acetate).

Anal. Calcd. for $C_{11}H_{20}NCl$: C, 65.51; H, 9.94; Cl, 17.55. Found: C, 65.21; H, 10.05; Cl, 17.53.

Reduction of VI to XXIa and XXIb in Acetic Acid.—A solution of 3.0 g. (0.018 mole) of VI in 30 ml. of acetic acid containing

(32) We wish to thank Dr. E. D. Smith, University of Arkansas, Graduate Institute at Little Rock, for suggesting this column to us for use with basic compounds.

(33) Engelhard Industries, Newark, N. J.

0.45 g. of platinum oxide was reduced under a pressure of 45 lb. at 25°. The absorption of 0.036 mole of hydrogen was complete in 1 hr. The catalyst was removed and the solution neutralized with sodium hydroxide and extracted with ether. Distillation of the ether residue gave 2.8 g. of a colorless oil, b.p. 67–68° (1.5 mm.); $n^{30}D$ 1.4710. A sample injected into the gas chromatograph exhibited one strong peak (98%) and a small fore peak (2%). The mixture upon elemental analyses gave the following results.

Anal. Calcd. for $C_{11}H_{21}N$: C, 79.04; H, 12.57; N, 8.38. Found: C, 78.99; H, 12.48; N, 8.37.

A Zerewitinoff determination of active hydrogen gave 0.55% H (calcd., 0.61%).

The **hydrochloride** of the mixture, after a single recrystallization from methanol–ethyl acetate, melted sharply at 289° (sublimed at 240° at 1 atm.).

Anal. Calcd. for $C_{11}H_{22}NCl$: C, 64.86; H, 10.81; Cl, 17.44. Found: C, 65.10; H, 11.20; Cl, 17.80.

Hydrogenation of XIX to the Mixture XXIa and XXIb.—A solution of 6.0 g. of the tetrahydropyridine in 60 ml. of acetic acid and 1.5 g. of platinum oxide was hydrogenated at 60 lb. at 25° for 48 hr. After this period of time the theoretical uptake of hydrogen was complete. Removal of the catalyst, neutralization of the solution, and extraction with ether gave 5.8 g. of a colorless oil, b.p. 74–77° (3 mm.); $n^{30}D$ 1.4703; the analytical results were in accord with the calculated values. Gas chromatographic examination indicated that the sample was composed of two peaks in the ratio of 49.1% to 50.9%. Injection of the acetic acid reduction product of I under identical instrument conditions revealed that it was the same as one of the two reduction products of V. An attempt to separate the hydrochlorides of XXIa and XXIb was successful insofar as obtaining one of the isomers in a pure state, m.p. 289°. The other isomer could not be obtained without contamination, m.p. 235–260°.

N-2,6,6-Tetramethyl-3,4-cyclopentanopiperdine.—A solution of 4.0 g. of 2,6,6-trimethyl-3,4-cyclopentanopiperdine (XXIa) in 50 ml. of 98% formic acid and 30 ml. of 37% formalin solution was heated overnight on a steam bath. Upon cooling the solution was poured into 200 ml. of 25% sodium hydroxide and the resulting mixture extracted with ether. Distillation of the ethereal residue gave a colorless oil, b.p. 79° (1 mm.); $n^{30}D$ 1.4796.

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.55; H, 12.70; N, 7.75. Found: C, 79.63; H, 12.59; N, 7.81.

The **methiodide** recrystallized from methanol–carbon tetrachloride, melted at 253°.

Anal. Calcd. for $C_{13}H_{26}NI$: C, 48.37; H, 8.05; I, 39.36. Found: C, 48.16; H, 8.17; I, 38.99.

Studies Directed toward the Total Synthesis of Azasteroids. II. Cyclopenteno[*d*]-1-azabicycloalkanes as Precursors to Azasteroids[1,2]

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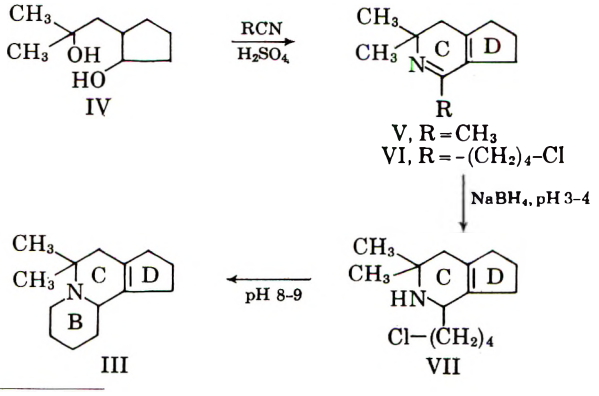
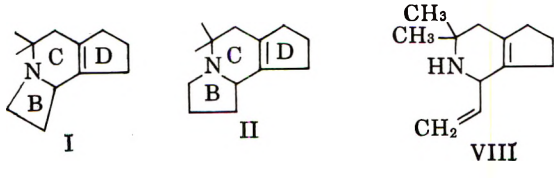
Received April 11, 1963

A study designed to obtain azasteroids by their total synthesis *via* a novel route has led to three new tricyclic bases, 2,2-dimethylcyclopenteno[*d*]-1-azabicyclo[4.2.0]octane (I), 2,2-dimethylcyclopenteno[*d*]-1-azabicyclo[4.3.0]nonane (II), and 2,2-dimethylcyclopenteno[*d*]-1-azabicyclo[4.4.0]decane (III). These systems were prepared from a single synthetic operation involving the appropriate chloroalkyl nitrile and α-(2-hydroxycyclopentyl)-*t*-butyl alcohol. The mechanism for the formation of these ring systems is consistent with previous studies which have led to related compounds.

The plan of approach for preparing azasteroids as described in an earlier publication[3] has now resulted in further related systems whose ease of preparation and structural features are of interest. These products (I–III) are results of a study whose main purpose was to determine the feasibility of applying the nitrile–glycol[4] condensation to the total synthesis of azasteroids. In a previous paper[3] the preparation of the model precursor (V, R = CH_3) was accomplished using acetonitrile. This product would ultimately represent the CD ring moiety of the azasteroid. In order to add the B ring it would be necessary to effect an intramolecular alkylation on the piperidine derivative VII using the appropriate halonitrile.



By treating α-(2-hydroxycyclopentyl)-*t*-butyl alcohol (IV) with δ-chlorovaleronitrile in cold concentrated sulfuric acid, there was obtained the cyclopentanodihydropyridine VI which was not isolated but reduced directly with sodium borohydride in weakly acidic solution. Attempts to isolate the cyclopentenopiperidine VII were never completely successful with regard to its purity, and, therefore, it was treated directly with base resulting in the steroidal precursor, III. When the entire sequence was performed without attempting isolation at any of the stages, a 46% yield of III based upon the glycol IV was obtained. The product, a light yellow oil, was found to be free of contaminants after a single distillation. By employing other chloronitriles,



(1) Presented before the Division of Organic Chemistry, 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963.

(2) This work supported by a grant from the National Institutes of Health (RG-6248).

(3) A. I. Meyers, J. Schneller, and N. K. Ralhan, *J. Org. Chem.*, **28**, 2944 (1963).

(4) A. I. Meyers and W. Y. Libano, *ibid.*, **26**, 1682, 4399 (1961), and earlier references cited therein.

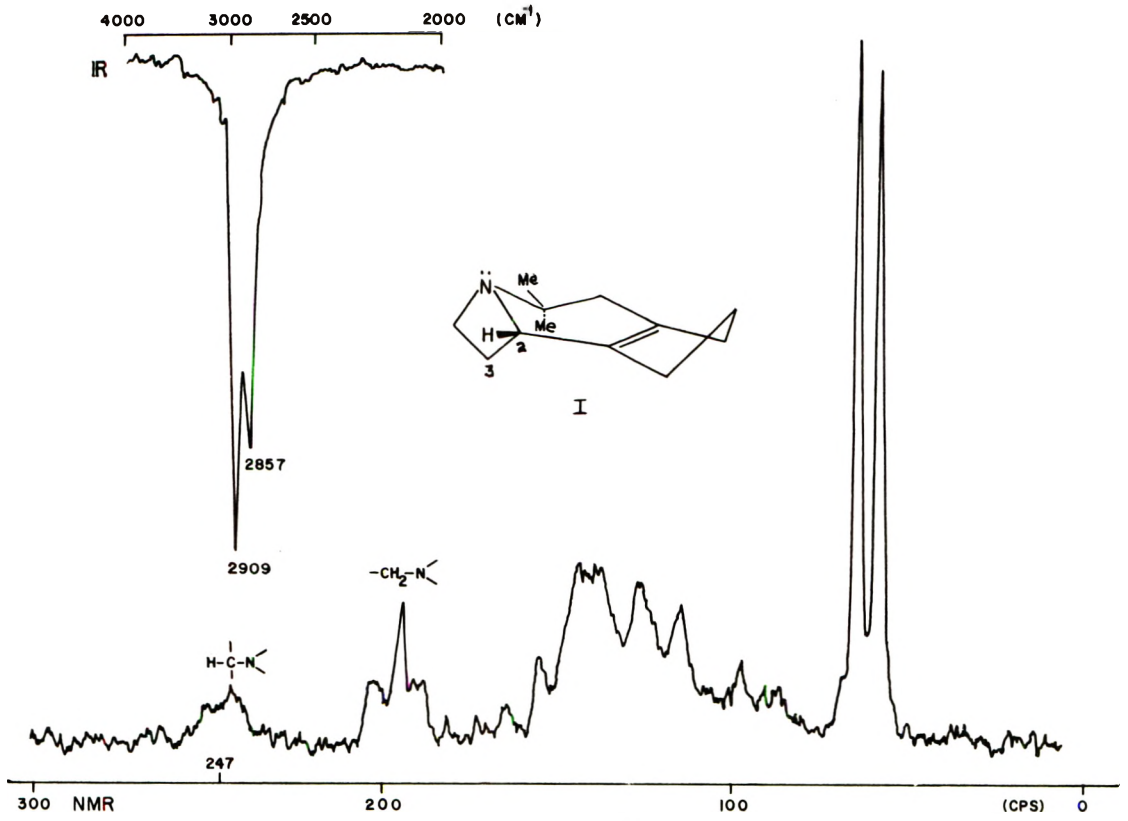


Fig. 1.—Infrared spectra were determined in carbon tetrachloride. N.m.r. spectra were performed on Varian A60 instrument using deuteriochloroform as a solvent and tetramethylsilane as an internal standard.

under essentially the same conditions, it was convenient to prepare the B-nor II and the bis-B-nor I derivatives from γ-chlorobutyronitrile and β-chloropropionitrile, respectively.

Isolation and purification of II presented no difficulty whatsoever, but I could not be purified by simple distillation or even careful fractionation. Gas chromatographic analysis of the distillate containing I indicated two close but well resolved peaks in the ratio 10.5:89.5. The component present in the smaller amount was believed to be the vinyl derivative VIII, which was finally removed by chromatography on a Florisil column. The vinyl derivative VIII undoubtedly was a product of elimination during the intramolecular ring closure.

The structures of I–III are supported by the absence of any infrared absorption bands in the region 3.5–6.9 μ. The tetrasubstituted double bond in these systems does not show any significant absorption in the 6-μ region. Ozonolysis of III, however, gave a basic compound which exhibited strong carbonyl bands at 5.90 μ.

The absence of the N–H stretching bands in the 3-μ region, the negative Zerewitinov determination, and the lack of deuterium exchange (n.m.r.) all supported the bridgehead nitrogen structure. The tetrasubstituted double bond is supported by its very weak infrared stretching band in the 6-μ region, the absence of a vinyl proton n.m.r. signal (lowest field signal, 247 c.p.s.), and the production of a basic product possessing strong carbonyl absorption at 5.9 μ. Attempts to reduce the double bond at the CD ring fusion under a variety of conditions were fruitless. The use of platinum, palladium, and rhodium in various solvents as well as pressures and temperatures ranging from 60 to 1500 p.s.i. and 25 to 180°, respectively, also failed to bring about reduction. The technique employing diborane and a carboxylic acid[5] under several different experimental conditions resulted in complete recovery of the starting material. Similar observations have been reported[6] in the attempted hydroboration of highly hindered double bonds in steroids.

The stereochemical assignments of the tricyclic bases, I–III, with respect to C-2 were made with the aid of the C–H stretch region (2700–2900 cm.$^{-1}$) and their n.m.r. spectra (Fig. 1). It can be seen that the infrared spectrum of III exhibits two sharp bands on the low frequency side of the major C–H absorption. These bands (2747 and 2825 cm.$^{-1}$) have been correlated with the presence of at least two α hydrogens *trans*-diaxial to the unshared electron pair on the bridgehead nitrogen.[7-10] The infrared spectrum of II also exhibits the two bands below 2900 cm.$^{-1}$ which indicates that the two α protons are in a *trans*-diaxial arrangement with the bridgehead nitrogen. Examination of the spectrum of I shows a rather simple C–H absorption and no distinct bands below 2857 cm.$^{-1}$. This, based on the preceding correlations, would place the proton at C-2 in a *cis* position relative to the electron pair. It is highly unlikely that the BC ring fusion in I would be other than *cis*. If I–III are represented in their most favored conformation, then the proton at C-2 should exhibit the characteristic axial and equatorial chemical shifts for a proton flanked both by a nitrogen atom and an olefinic linkage. Since it is well known that the equatorial protons produce n.m.r. signals at lower fields than their

(5) H. C. Brown and K. Murray, *J. Am. Chem. Soc.*, **81**, 4108 (1959).
(6) W. J. Wechter, *Chem. Ind.* (London), 294 (1959); M. Nussim and F. Sondheimer, *ibid.*, 400 (1960).
(7) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
(8) N. J. Leonard and W. K. Musker, *J. Am. Chem. Soc.*, **82**, 5148 (1960).
(9) E. Wenkert and D. Roychaudhuri, *ibid.*, **78**, 6417 (1956).
(10) W. E. Rosen, *Tetrahedron Letters*, No. **14**, 481 (1961).

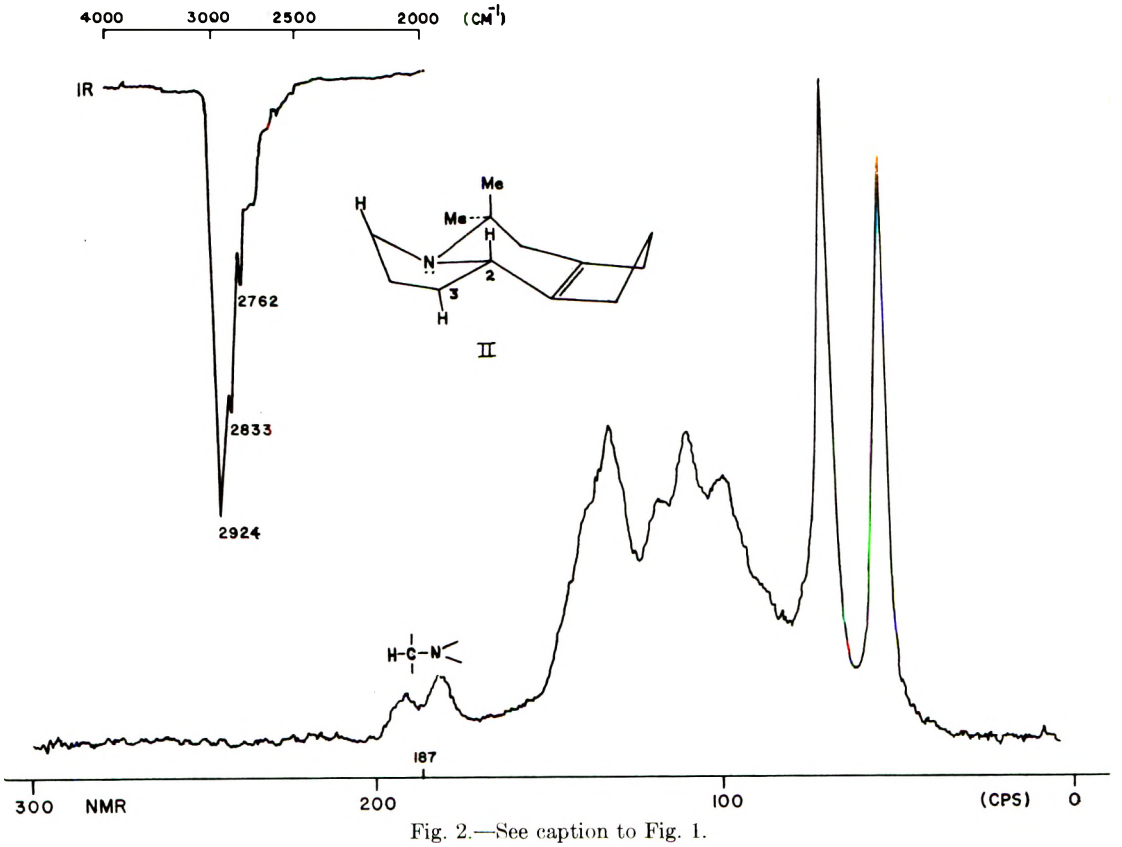


Fig. 2.—See caption to Fig. 1.

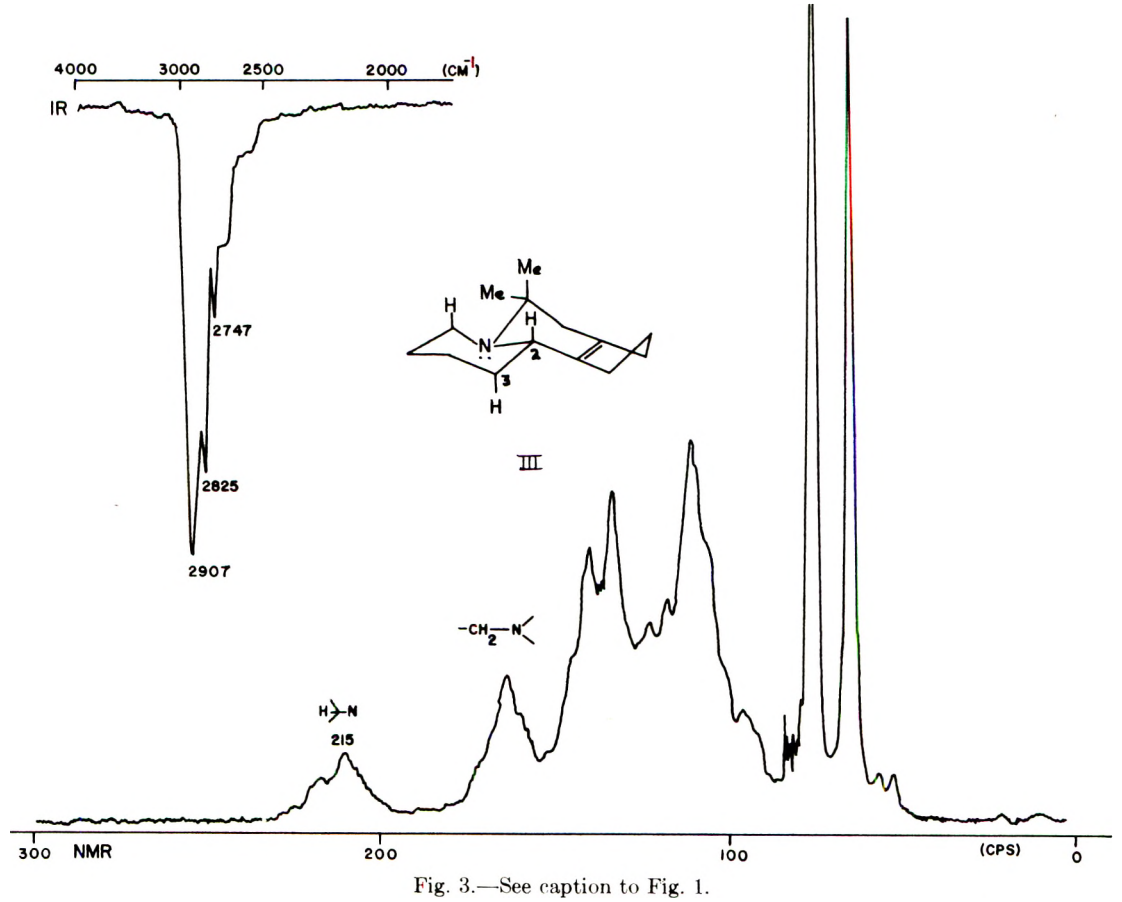


Fig. 3.—See caption to Fig. 1.

axial counterparts,[11] it is clear from Fig. 1 that the low field signal for I (247 c.p.s.) represents an equatorial C-2 proton, whereas the higher field signal in II (187 c.p.s.) and III (215 c.p.s.) reflect the presence of an axial C-2 proton. It also is seen that the C-2 proton signal in II and III is strongly coupled ($J_{H_2H_3}$II = 10 c.p.s. and $J_{H_2H_3}$III = 8.6 c.p.s.) and in I the poorly resolved C-2 proton signal appears to be similarly coupled ($J_{H_2H_3}$III

(11) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 116.

= 7.5 c.p.s.). The variation in spin–spin coupling constants has been correlated with the magnitude of the dihedral angle between two adjacent carbon atoms[12] and particularly in rigid ring systems.[13–15] Since in I–III the pair of C-3 protons will have at least one member whose dihedral angle with the C-2 proton will be in the vicinity of 150–180°, then this would account for the large coupling constants.[16]

The remainder of the n.m.r. spectrum for each of the tricyclic bases indicate the expected chemical shifts for the particular protons as well as the proper integrated proton counts

Experimental[17,18]

α-(2-Hydroxycyclopentyl)-*t*-butyl alcohol [b.p. 113–115° (0.55 mm.)] was prepared as previously described.[1]

2,2-Dimethylcyclopenteno[*d*]-1-azabicyclo[4.4.0]decane (III).—To a cold (0–3°) solution of 9.05 g. (0.077 mole) of δ-chlorovaleronitrile in 150 ml. of 98% sulfuric acid was added, dropwise, 11.06 g. (0.70 mole) of α-(2-hydroxycyclopentyl)-*t*-butyl alcohol (IV). The addition of the glycol was performed while efficient stirring was maintained, and the temperature of the mixture was kept below 10°. The time required for the complete addition of the glycol under these conditions was approximately 1.5 hr. The deep reddish-colored reaction mixture was slowly poured over 500 g. of chipped ice in a 2-l. beaker.[19] The aqueous acid solution was extracted several times with chloroform to remove insoluble polymeric material and then partially neutralized (pH 2–4) with 35% sodium hydroxide. The temperature was maintained below 40° during the neutralization with the aid of external cooling. The electrodes of a pH meter (Beckman Zeromatic) were inserted into the solution and the acidity adjusted to pH 3–4 by the addition of 4 *M* sulfuric acid and 6 *M* sodium hydroxide which were contained in burets situated above the beaker. The clear solution was cooled to room temperature and a freshly prepared solution of sodium borohydride (2.66 g., 30 ml. of water, and one drop of 35% sodium hydroxide) was added dropwise while stirring was supplied by a magnetic stirrer. The pH of the reaction, during the borohydride addition was constantly kept within the limits of pH 3–4 by the periodic addition of the sulfuric acid or the sodium hydroxide. The sodium borohydride addition was complete after 1 hr. at 25°. The solution was allowed to stir at room temperature overnight and then made acidic to pH 1 and stirred for 1 hr. which destroyed the excess sodium borohydride. After adding 300 ml. of water, the pH was again adjusted to 8–8.5 and allowed to stir for 5 hr. The oil which had separated was extracted with ether and dried over potassium carbonate. Removal of the ether on a steam bath and distillation of the residual oil gave 6.6 g. (46%) of the tricyclic base, b.p. 100–102° (1.0 mm.); $n^{30}D$ 1.5062. The infrared spectrum (carbon tetrachloride) showed only strong absorption at 3.4 (CH), 6.9 μ (CH_2 bending), and ring skeletal vibrations above 8 μ.

Anal. Calcd. for $C_{14}H_{23}N$: C, 81.94; H, 11.22; N, 6.83. Found: C, 81.71; H, 11.07; N, 6.81.

The **picrate** from methanol, melted at 191–193°.

Anal. Calcd. for $C_{20}H_{26}N_4O_7$: C, 55.30; H, 6.13; N, 12.90. Found: C, 55.08; H, 6.23; N, 12.83.

2,2,-Dimethylcyclopenteno[*d*]-1-azabicyclo[4.3.0]nonane (II).—A cold solution of 7.93 g. (0.077 mole) of γ-chlorobutyronitrile in 150 ml. of 98% sulfuric acid was treated with 11.06 g. (0.070 mole) of α-(2-hydroxycyclopentyl)-*t*-butyl alcohol as described previously. Distillation of the residue from the ethereal extracts afforded 7.2 g. (54%) of a light yellow oil, b.p. 73° (0.25 mm.); $n^{30}D$ 1.5025. The infrared spectrum (carbon tetrachloride) exhibited only CH stretching, CH_2 bending, and skeletal vibrations.

Anal. Calcd. for $C_{12}H_{21}N$: C, 81.67; H, 10.99; N, 7.33. Found: C, 81.62; H, 10.84; N, 7.28.

The **picrate**, from ethanol, melted at 188°.

Anal. Calcd. for $C_{19}H_{24}O_7N_4$: N, 13.33. Found: N, 13.32.

2,2-Dimethylcyclopenteno[*d*]-1-azabicyclo[4.2.0]octane (I).—This was obtained in essentially the same manner as described for III by treating a cold solution of 6.45 g. (0.77 mole) of β-chloropropionitrile in 150 ml. of 98% sulfuric acid with 11.06 g. (0.070 mole) of α-(2-hydroxycyclopentyl)-*t*-butyl alcohol. Removal of the ether left an oily residue which, although carefully fractionated [65–67° (1.0 mm.)], gave two peaks[20] in the ratio 89.5:10.5. A picrate, formed from this mixture, melted at 214° after two recrystallizations from ethanol. The infrared spectrum of the mixture exhibited a slight C=CH_2 stretching band at 3.25 μ and the corresponding bending frequency at 10.2 and 10.9 μ. This minor component was then assigned the structure VIII. The mixture (0.75 g.) was added to a Florisil column and eluted with petroleum ether–diethyl ether solvent pairs. The pure tricyclic base I was obtained (0.55 g.) and exhibited a single peak upon gas chromatographic analysis which corresponded to the 89.5% peak in the original mixture. The infrared spectrum showed the complete absence of the bands attributed to the vinyl derivative. The yield of I was 50%.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.36; H, 10.73; N, 7.91. Found: C, 81.25; H, 11.02; N, 7.72.

The **picrate**, from methanol, melted at 214°.

Anal. Calcd. for $C_{18}H_{22}N_4O_7$: N, 13.80. Found: N, 14.05.

Attempted Reduction of II by Hydroboration–Propionic Acid.—A solution of 5.0 g. of II in 50 ml. of anhydrous tetrahydrofuran was treated with diborane generated from another flask containing 3.5 g. of sodium borohydride and 20 g. of boron trifluoride–ethyl ether complex in 50 ml. of diglyme. After standing overnight the tetrahydrofuran was removed by distillation, and the residue was treated with 5.0 ml. of propionic acid and heated to 150° for 3 hr. The mixture was cooled, neutralized, and extracted with ether. The residue from the ethereal extract was distilled, b.p. 80° (0.5 mm.), amounting to 4.2 g. The picrate, infrared spectrum, and the refractive index were identical with the starting material.

Ozonolysis of II.—A solution of 2.0 g. of II in 100 ml. of dichloromethane was cooled in an ice bath and subjected to a stream of ozone for 2 hr. Work-up of the ozonized mixture gave a tarry mixture which was for the most part basic and whose infrared spectrum (carbon tetrachloride) showed a strong carbonyl absorption at 5.90 μ. Attempts to purify this substance were fruitless.

(12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(13) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).

(14) A. D. Cross, *ibid.*, **84**, 3207 (1962).

(15) D. J. Collins, J. J. Hobbs, and S. Sternhell, *Tetrahedron Letters*, No. **10**, 623 (1963).

(16) The n.m.r. spectra were determined both at 60 and 24 Mc. to ensure that these signals were coupling values rather than chemical shifts. We thank Dr. R. E. Glick, Florida State University, who determined this using the Varian HR-60 instrument.

(17) All melting points and boiling points are uncorrected.

(18) Microanalyses were performed by Alfred Bernhardt, Mulheim (Ruhr), West Germany.

(19) The following two reactions—*i.e.*, the sodium borohydride reduction and the intramolecular alkylation—were carried out in this vessel.

(20) Analyzed on a 6-ft. column coated with 10% Dow Corning 710 and 5% potassium hydroxide on Chromsorb P.

The Mechanism of Azo Ester Addition–Abstraction Reactions with Cyclic Dienes

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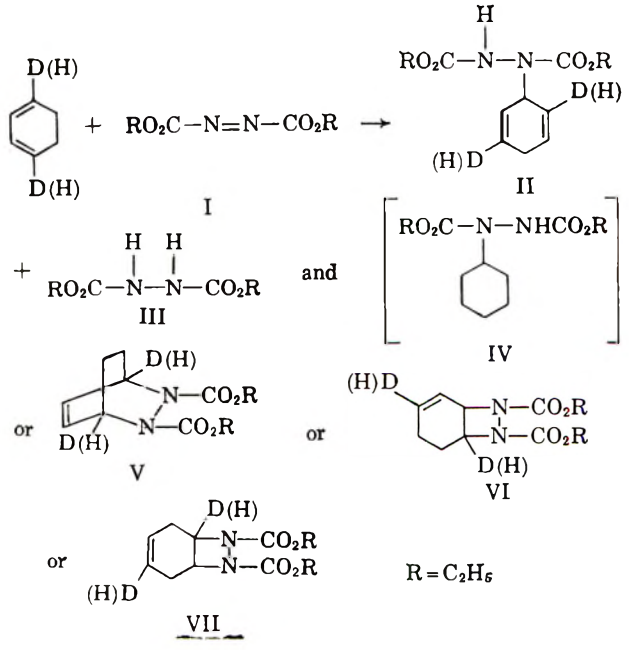
Received April 8, 1963

The structures of the Diels–Alder adduct and the addition–abstraction product from 1,4-dideuterio-1,3-cyclohexadiene and ethyl azodicarboxylate indicate that the formation of these compounds proceeds by entirely different paths. Lack of isomerization of both reactants and products and lack of deuterium exchange (in CH_3OD) for both reactants and products are consistent with a concerted cyclic process. These results are consistent with the energetics of the adduction reaction. Thus, the entropy of activation for the reaction of 1,3-cyclohexadiene and ethyl azodicarboxylate is -40.7 e.u., and it is -31.8 e.u. for ethyl azodicarboxylate and 1,4-cyclohexadiene. This high negative entropy of activation is consistent with a concerted process.

The reactions of ethyl azodicarboxylate with 1,3- and 1,4-cyclohexadienes[1a] and with sterically hindered conjugated dienes[1b] appear to proceed *via* an addition–abstraction mechanism. In order to verify the reaction path and to search more critically for the Diels–Alder adduct reported by both Cohen and Zand[2a] and Pirsch and Jorgl,[2b] an investigation on the mechanism of the reaction of ethyl azodicarboxylate with 1,3- and 1,4-cyclohexadienes was initiated.

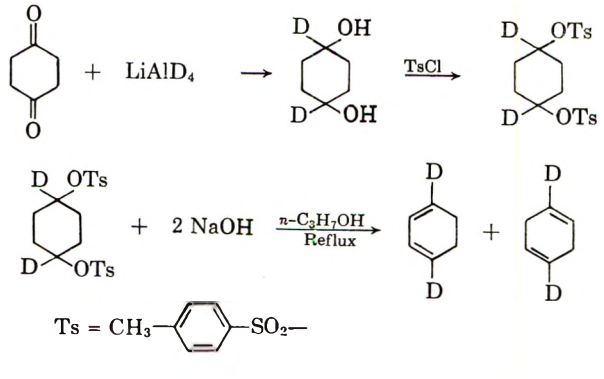
Vapor phase chromatographic analysis of the products from adduction of 1,3-cyclohexadiene with ethyl azodicarboxylate (I) indicated three compounds; the major product, the previously identified diethyl 2,5-cyclohexadien-1-yl-bicarbamate (II), has been further substantiated by Gillis and Beck.[1b] The formation of ethyl hydrazodicarboxylate (III) also had been substantiated by isolation of III from the reaction mixture.[1a] The third product, occurring only in 5 to 15% yields was tentatively identified as diethyl cyclohexylbicarbamate (IV) on the basis of similar v.p.c. retention times with an authentic sample.[1a] By column chromatography on an acid-washed alumina column, the third product has now been isolated and analyzed. The analysis does not agree with IV but is instead consistent with structures V, VI, or VII (without deuterium).



Since there was no N–H stretching at 3300 cm.$^{-1}$ in the infrared, and the n.m.r. indicated no hydrogen bound to nitrogen, this compound cannot be an addition–abstraction product. The relative hydrogen areas by n.m.r. are consistent with V, VI, or VII (nondeuterated). In Fig. 1a there can be seen six methyl hydrogens (triplet τ 8.7), two ring allyl hydrogens ($\tau \cong$ 8.1), four O–CH_2 hydrogens (τ 5.9), two hydrogens next to nitrogen (τ 5.2), and two vinyl hydrogens (τ 3.5).

The vinyl hydrogen triplet shown in Fig. 1a probably rules out VI as a possible structure but does not readily differentiate between compounds V and VII. The reaction of 1,4-dideuterio-1,3-cyclohexadiene with ethyl azodicarboxylate (I) could then have given rise to V, VI, or VII (with deuterium) along with ethyl hydrazodicarboxylate and a corresponding deuterated addition–abstraction product (II). The difference in the n.m.r. spectra of V *vs.* both VI and VII would be clearly demonstrated by a retention of vinyl hydrogen area and the complete disappearance of that peak due to the tertiary hydrogen next to the nitrogen. If, on the other hand, VI and VII were the product, both vinyl hydrogen and tertiary hydrogen would suffer a reduction in area to one-half of the original vinyl and tertiary hydrogen area. As is evident from Fig. 1b, the tertiary hydrogen next to nitrogen (τ 5.2) is no longer present, the vinyl hydrogen area is unchanged, and the vinyl triplet (τ 3.5) has collapsed to a singlet supporting only compound V, the Diels–Alder adduct. Thus the reaction of I and 1,3-cyclohexadiene does indeed give a 5–15% yield of Diels–Alder adduct (V), 5–15% of ethyl hydrazodicarboxylate (III), and about 80% of the addition–abstraction product (II).

The positional integrity of the deuterium in 1,4-dideuterio-1,3-cyclohexadiene was established in part by the synthesis of the diene and in part by the n.m.r. spectra of the resultant product.



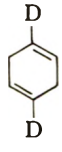
(1) (a) B. Franzus and J. H. Surridge, *J. Org. Chem.*, **27**, 1951 (1962); (b) B. T. Gillis and P. E. Beck, *ibid.*, **27**, 1947 (1962).

(2) (a) S. G. Cohen and R. Zand, *J. Am. Chem. Soc.*, **84**, 586 (1962); (b) J. Pirsch and J. Jorgl, *Ber.*, **68**, 1324 (1935).

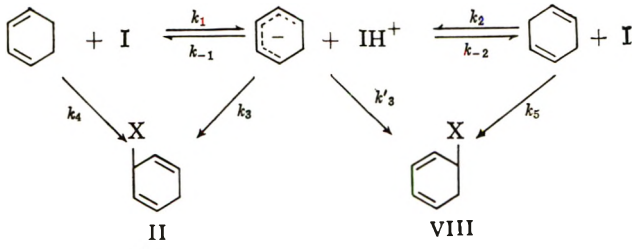
Reduction of 1,4-cyclohexanedione by lithium aluminum deuteride should involve no rearrangement[3] and the formation of the ditosylate involves no rearrangement.[4,5] Thus the only step of the synthesis which could conceivably give rise to deuterium scrambling is the elimination reaction since the dienes could isomerize in a basic media. If in a basic, protic media, proton abstraction occurs reversibly to form the carbanion of the cyclic diene, then not only would the 1,3- and 1,4-dienes interconvert but the resulting dienes would incur both deuterium scrambling and loss of deuterium to the protic solvent. However, the reaction of 1,4-cyclohexadiene and 1,3-cyclohexadiene with sodium hydroxide in 1-propanol gave no evidence of isomerization of the 1,4-diene to the 1,3-diene and vice versa. This means that the carbanion is not formed and the resultant 1,3- and 1,4-cyclohexadienes should be free of both deuterium scrambling and loss of deuterium. Final confirmation of structure resided in the analyses of the 1,4-dideuterio-1,3-cyclohexadiene and the 1,4-dideuterio-1,4-cyclohexadiene by n.m.r. as shown in Table I.

TABLE I

N.M.R. HYDROGEN AREAS FOR 1,4-DIDEUTERIO-1,3- AND -1,4-CYCLOHEXADIENES

	Calcd	Found
		
Allyl/vinyl	2.00/1	1.99/1
% Allyl-H	66.7	66.7
% Vinyl-H	33.3	33.3
		
Allyl/vinyl	2.00/1	1.92/1
% Allyl-H	66.7	65.7
% Vinyl-H	33.3	34.3

For the addition–abstraction reaction, the extent of carbon–hydrogen cleavage by the azo-nitrogen can be measured by the amount of isomerization of the starting dienes and by the final mixture of products.



X = $C_2H_5O_2CNNHCO_2C_2H_5$ ϵ_{max} 3760 (λ_{max} 258 mμ)

If proton abstraction by the azo-nitrogen is complete and the reaction with diene is reversible (k_1, k_{-1}, k_2, k_{-2}, fast), then starting with either 1,3- or 1,4-cyclohexadiene one would anticipate an equilibrium mixture of the 1,2- and 1,4-dienes. This was not observed; the starting diene was not isomerized. However,

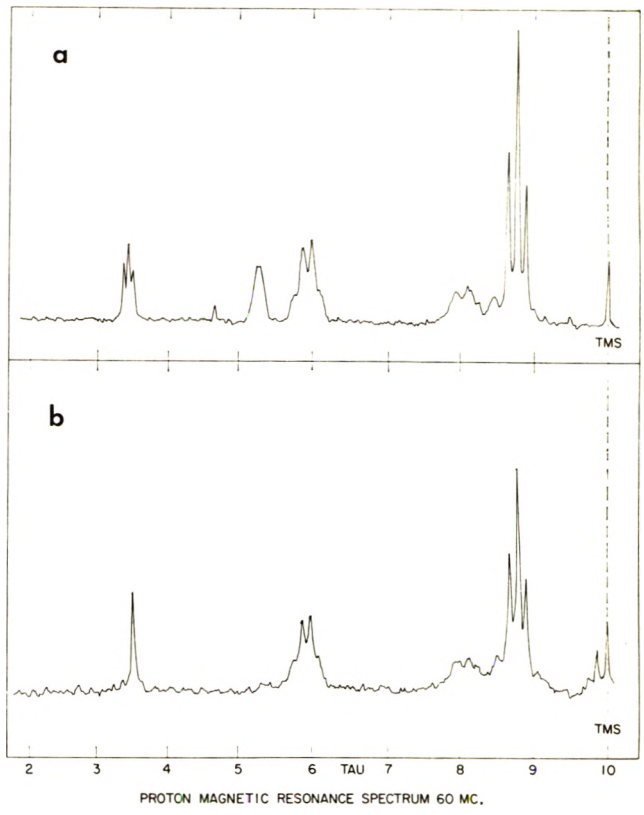


Fig. 1.—N.m.r. spectra of Diels–Alder adducts in CCl_4 at 25°: (a) Diels–Alder adduct from 1,3-cyclohexadiene and ethyl azodicarboxylate; (b) Diels–Alder adduct from 1,4-dideuterio-1,3-cyclohexadiene and ethyl azodicarboxylate.

one might anticipate that proton abstraction by the azo-nitrogen would be irreversible (also k_{-1} and k_{-2} are essentially zero), and this would be reflected by an equilibrium mixture of the final products (*via* k_3 and k'_3). This, too, was not observed. The 1,3-product VIII arising from 1,4-cyclohexadiene had a large molar extinction coefficient,[1a] and thus made traces of the 1,3-product easily detectable.

On the other hand, the 1,4-product II that arose from I and 1,3-cyclohexadiene was easily detectable by its n.m.r. spectrum shown in Fig. 2b. It will be noted that the hydrogens of the two ethyl groups of the azo ester are sufficiently different that a chemical shift is readily detectable by the two O–CH_2 quartets and the two CH_3 triplets. This n.m.r. spectrum is quite different from that of the 1,3-product VIII that arose from I and 1,4-cyclohexadiene (Fig. 2a). The latter n.m.r. spectrum (2a) only indicates one type of OCH_2 and CH_3. The observation that the 1,4-diene did not isomerize to the 1,3-diene and vice versa in the presence of I was further substantiated by the fact that *cis–trans* isomers also did not interconvert in their reactions with I.[6]

It became quite apparent that since both products and unchanged starting material did not undergo isomerization, complete removal of the proton by the azo-nitrogen did not occur. Furthermore, one can also rule out any solvated ion-pairs since there was no detectable deuterium in either unchanged starting diene or final product when I reacted with either 1,3- or 1,4-

(3) (a) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949); (b) M. S. Newman and R. Gaertner, *ibid.*, **72**, 264 (1950).

(4) H. Phillips, *J. Chem. Soc.*, **123**, 44 (1923).

(5) We are indebted to Prof. P. S. Skell for suggesting tosylate elimination as the best synthetic route to the dienes.

(6) Personal communication from Dr. W. A. Thaler of the Central Basic Research Laboratories, Esso Research and Engineering Co.

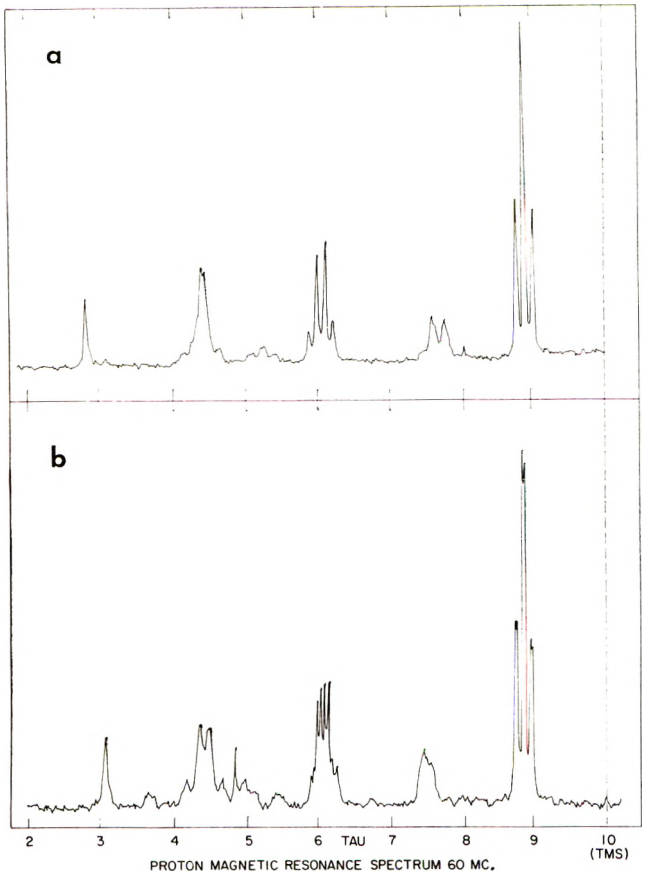


Fig. 2.—N.m.r. spectra of addition–abstraction products in CCl_4 at 25°: (a) compound VIII from 1,4-cyclohexadiene and ethyl azodicarboxylate; (b) compound II from 1,3-cyclohexadiene and ethyl azodicarboxylate [CH_3 (τ 8.8); ring alllyl hydrogens (τ 7.7 in a, τ 7.5 in b); OCH_2 (τ 6.1); vinyl hydrogens ($\tau \cong 4.4$); N–H ($\tau \cong 2.8$–3.1 dependent on concentration)].

cyclohexadiene in the presence of methanol-D.[7] Because the N–H bond in products II and VIII exchanged H for D with the deuterated solvent very slowly, the fact that there was essentially no N–D in the final product further eliminates the possibility of a solvated ion-pair. One must conclude that under these reaction conditions, lack of deuterium exchange infers that reaction of 1,3-cyclohexadiene with I (k_4) and 1,4-cyclohexadiene with I (k_5) proceeds through either an intimate ion-pair, ion-dipole, or *via* a concerted process. Hydrogen–deuterium exchange has been observed in other systems using stronger base, higher temperatures, and benzylic-type compounds.[8] This exchange apparently does not apply to the azo ester–diene system.

Kinetics of azo ester adduction with cyclic dienes should be second-order for a concerted process. As shown in Table II second-order kinetics is exactly what was observed. Kinetics were run both in cyclohexane and in ethanol with rate constants in ethanol being about twenty times greater than in cyclohexane. However, the data for the kinetics in ethanol are not reported here (except qualitatively) because competition

(7) Methanol-D was chosen because of its high dielectric constant ($D \cong 31$); however, in the presence of methanol the amount of oxidation–reduction increases at the expense of the addition–abstraction product. This was not true of solvents such as ethanol ($D = 24$), and dimethyl sulfoxide ($D = 46.7$) where the ratio of all three products remained essentially unchanged from those results obtained either in the absence of solvent or in cyclohexane as solvent.

(8) D. J. Cram, C. C. Kingsbury, B. Rickborn, *J. Am. Chem. Soc.*, **81**, 5835 (1959).

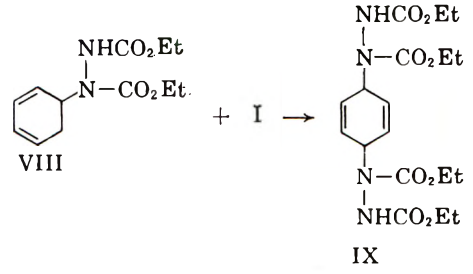
TABLE II

SECOND-ORDER RATE CONSTANTS IN CYCLOHEXANE AS FUNCTION OF CONCENTRATION

Cyclohexadiene	T, °C.	Diene	Azo ester	$10^5 k$ (l. mole^{-1} sec.$^{-1}$)
1,3	25	0.0615	0.0501	7.86
1,3	25	.0800	.0194	7.33
1,3	50	.1226	.0825	31.7
1,3	50	.2460	.0795	32.1
VIII	50	.166	.0974	6.99
1,4[a]	50	.1293	.1000	2.27
1,4	50	.2025	.0240	2.22
1,4	75	.0935	.0229	12.8
1,4	75	.1863	.0230	12.9

[a] Estimated from first 25% reaction, before reaction of VIII becomes dominant.

between I and the diene, and I and ethanol[9] caused difficulty in obtaining reproducible results. The results of the kinetics were surprising since it was assumed, *a priori*, that the loss or gain of resonance energy by 1,3- or 1,4-cyclohexadiene to 1,4- and 1,3-diene products (II and VIII, respectively) would be a large driving force in the azo ester cyclic diene adduction. Thus it was assumed that 1,4-cyclohexadiene should react faster than 1,3-cyclohexadiene. It is quite evident from Table II that at 50° the 1,3-diene reacts some fifteen times faster than the 1,4-diene. In fact, reasonable kinetics for the 1,4-diene were obtainable only by using a high concentration of 1,4-diene since the 1,3-product VIII also reacted faster than 1,4-cyclohexadiene to form compound IX. The data in Table II were finally ra-



tionalized by the observation that the 1,3-diene is only 600 calories more stable than the 1,4-diene as determined by the thermodynamic equilibration of the 1,3- and 1,4-dienes in the presence of strong base.

The kinetic data in Table III embrace three reaction rate constants for 1,3-cyclohexadiene; the addition–abstraction reaction (k_{AA}), an oxidation–reduction reaction ($k_{ox\text{-}red}$) and a Diels–Alder adduction (k_{DA}). Similarly a k_{total} for 1,4-cyclohexadiene is comprised of an addition–abstraction reaction (k_{AA}) and an oxidation–reduction reaction ($k_{ox\text{-}red}$). (See p. 2957, col. 1).

In the reaction of 1,3-cyclohexadiene with ethyl azodicarboxylate, the variation in product distribution as a function of temperature was determined by v.p.c. Since the differences in product distribution were of the same order of magnitude as the errors in the analytical

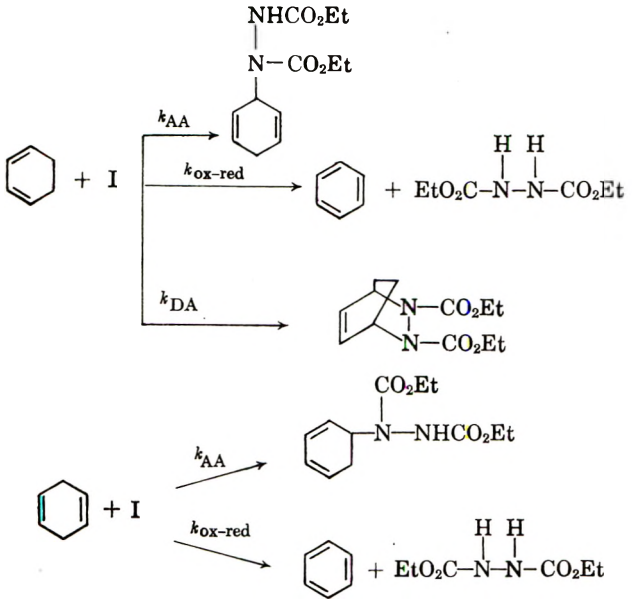
(9) O. Diels and C. Wulff, *Ann.*, **437**, 309 (1924).

TABLE III

PARTIAL AND RELATIVE RATES FOR 1,3- AND 1,4-CYCLOHEXADIENE AT 50°

Diene	$10^5 k_{total}$, l. mole^{-1} sec.$^{-1}$	$k_{1,3(total)}/k_{1,4(total)}$	$10^5 k_{AA}$, l. mole^{-1} sec.$^{-1}$	$k_{AA(1,3)}/k_{AA(1,4)}$
1,3-	31.9		24.0	
		14.5		18.5
1,4-	2.2		1.3	

Diene	$k_{ox\text{-}red}$ l. mole^{-1} sec.$^{-1}$	$k_{ox\text{-}red(1,3)}/k_{ox\text{-}red(1,4)}$	$10^5 k_{DA}$, l. mole^{-1} sec.$^{-1}$
1,3-	3.5		4.4
		3.9	
1,4-	0.9		



technique (±1%) an average product distribution was used for computation of k_{AA}, k_{DA} and $k_{ox\text{-}red}$. This same product distribution held (essentially unchanged) down to −25° both without solvent[1a] and in ethanol from room temperature to 62°. The addition–abstraction product from 1,4-cyclohexadiene forms a 1,3-product VIII with a reasonably large molar extinction coefficient so analyses of products were feasible even though the variation of product distribution as a function of temperature was small. These results are shown in Tables III and IV.

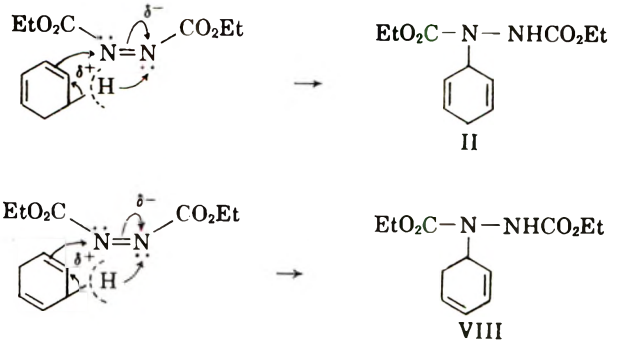
TABLE IV

ENTHALPY AND ENTROPY OF ACTIVATION FOR VARIOUS REACTION PATHS

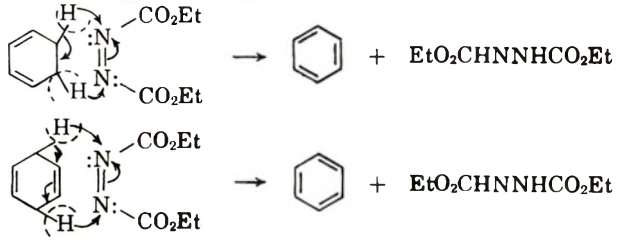
Diene	ΔH^* (total), kcal.	ΔS^* (total), e.u.	ΔH^* (A A), kcal.	ΔS^* (A A), e.u.
1,3-	10.9	−40.7	10.9	−41.0
1,4-	15.6	−31.8	14.4	−36.4

Diene	ΔH^* (ox-red), kcal.	ΔS^* (ox-red), e.u.	ΔH^* (D A), kcal.	ΔS^* (D A), e.u.
1,3-	10.9	−45.0	10.9	−44.5
1,4-	16.0	−32.3		

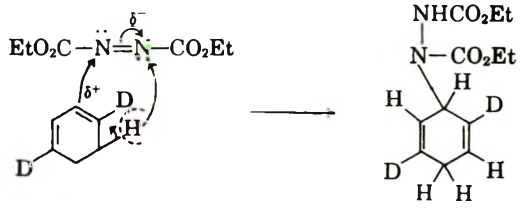
A favorable mechanism for the addition–abstraction reaction is *via* a concerted process with a partial charge development.[1a,b]



A similar mechanism also could be written for the oxidation–reduction reaction.

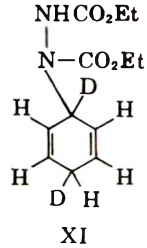


Consistent with these results is the rate enhancement in ethanol (over cyclohexane), the lack of hydrogen–deuterium exchange in reactants and products (when run in CH_3OD) and lack of isomerization of both starting dienes and final products. In addition, the observance of a kinetic isotope effect in the reaction of I with 1,4-dideuterio-1,4-dihydronaphthalene[10] also is consistent with a cyclic concerted mechanism. The high negative entropy of activation also fits the cyclic concerted mechanism just as it fits a Diels–Alder adduction. However, the addition–abstraction mechanism should not have the same transition state or go *via* the same intermediate as the Diels–Alder adduct. By a concerted cyclic mechanism, the product obtained by the reaction of ethyl azodicarboxylate with 1,4-dideuterio-1,3-cyclohexadiene (X), should have two vinyl hydrogens, two allyl hydrogens, and a tertiary hydrogen (next to nitrogen).



X

On the other hand, if one works out details, the addition–abstraction product one would obtain from a transition state (or intermediate) arising from a Diels–Alder adduct (after the appropriate hydrogen migra-



XI

(10) R. Huisgen and H. Pohl, *Ber.*, **93**, 527 (1960).

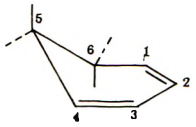
TABLE V

N.M.R. HYDROGEN AREAS OF X AND XI FROM 1,4-DIDEUTERIO-1,3-CYCLOHEXADIENE AND I

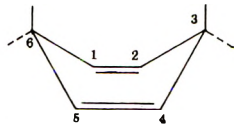
N.m.r. % area of hydrogens	% calcd. for X	% calcd. for XI	Found
CH_3	37.5	37.5	40.7
OCH_2	25.0	25.0	24.6
Ring CH_2	12.5	6.25	12.1
Vinyl	12.5	25.0	12.2
t-H (next to N)	6.25	0	5.2
N-H	6.25	6.25	5.2

tion) would have a structure corresponding to XI with four vinyl hydrogens and one allyl hydrogen. It is apparent from Table V that X is the observed product substantiating the concerted cyclic mechanism.

If one builds molecular models of the azo ester–cyclic diene system, one can rationalize the observed enthalpies and entropies of activation from the steric effects manifested by interactions of various atoms in the molecular models. Both Dreiding and Stuart–Briegleb models show that the two axial hydrogens (5 and 6 in 1,3-cyclohexadiene) extend in opposite directions perpendicular to the plane of the 1,3-cyclohexadiene ring (XII); axial hydrogens 3 and 6 in 1,4-cyclohexadiene extend in the same direction perpendicular to the plane of the 1,4-cyclohexadiene ring (XIII).[11]



XII



XIII

If one assumes that I approaches perpendicular to the cyclohexadiene rings to abstract an axial hydrogen, a steric effect from the other axial hydrogen is noted in the case of the 1,4-diene but not with the 1,3-diene. This effect could then show up in part in the ΔH^* term.[12] This could explain the greater reactivity of the 1,3-diene over the 1,4-diene since the entropy of activation for both the 1,3- and 1,4-dienes are very nearly the same. The oxidation–reduction rate constants for the 1,3- and 1,4-dienes are very nearly the same. Again the 1,3-diene has a lower ΔH^* than the 1,4-diene probably due in part to a hindering effect of the other axial hydrogen. The more favorable entropy for the 1,4-diene over the 1,3-diene could be rationalized by simultaneous abstraction of axial hydrogens 3 and 6 by I; this favorable conformation cannot be realized by the 1,3-diene.

Experimental

All melting points were corrected and were taken on a Fisher-Johns melting point apparatus. Infrared spectra were determined using a Beckman IR-5 spectrophotometer. Ultraviolet and visible spectra for the kinetic experiments were obtained using an Optika CF-4 double-beam recording spectrophotometer. N.m.r. spectra were determined with a Varian Associates A-60 spectrometer. Vapor phase chromatographic analyses were carried out on a Perkin-Elmer Model 154-D vapor fractometer. Elemental analyses were performed by both the Analytical Research Division of Esso Research and Engineering Company and by Galbraith Laboratories, Inc., Knoxville, Tenn. Molecular weight analyses were done by Galbraith Laboratories, Inc.

(11) F. H. Herbstein, *J. Chem. Soc.*, 2292 (1959).

(12) H. C. Brown and G. K. Barbaras, *J. Am. Chem. Soc.*, **75**, 6 (1953).

N,N-Dicarboxyethyl-1,4-*endo*-hydrazocyclohexene (V).—The reaction of I with 1,3-cyclohexadiene has been described elsewhere.[1a,b] Compound V, the Diels–Alder adduct, was separated from II the addition–abstraction product and ethyl hydrazodicarboxylate by chromatography on an acid-washed alumina column using methylene chloride as eluent. The Diels–Alder adduct (V) was the first compound to be eluted, followed by a mixture of II and ethyl hydrazodicarboxylate. The last compound to be eluted was ethyl hydrazodicarboxylate. Compound V is a viscous liquid whose infrared spectra differs mainly from compound II by the absence of the N–H stretching at 3300 cm.$^{-1}$.[13] The liquid chromatography samples were analyzed by v.p.c.[14] The Diels–Alder adduct (V) had a perfect analysis for a one-to-one adduct.

Anal. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.88; H, 7.13; N, 11.02. Found: C, 56.85; H, 6.93; N, 10.93.

1,4-Dideuterio-1,4-cyclohexanediol.—Into a dry 2-l. resin flask containing 5.0 g. (0.119 mole) of lithium aluminum deuteride, equipped with a vibromix stirrer, thermometer, and dropping funnel was distilled (from lithium aluminum hydride) 100 ml. of tetrahydrofuran. To this deuteride solution was slowly added 22.4 g. (0.2 mole) of 1,4-cyclohexanedione (Aldrich Chemical Co., Milwaukee, Wis.) in 300 ml. of dry tetrahydrofuran. Addition of the dione (which took 35 min.) was accompanied by slight heat evolution. Agitation was continued for 3 hr. after addition and the reaction mixture allowed to stand overnight. After decomposition of excess lithium aluminum deuteride with 200 ml. of methanol, all the solvent was removed (under aspirator vacuum) using a rotary evaporator. Extraction of the 1,4-diol was accomplished by dissolving the 1,4-diol from the combination of salts with tetrahydrofuran (150 ml.). This gave 6.0 g. of diol (after evaporation of the tetrahydrofuran). The solid was then further extracted with boiling tetrahydrofuran in a Soxhlet extractor to yield more 1,4-diol (6.4 g.). Finally the remaining solid was dissolved in dilute sulfuric acid, neutralized with sodium hydroxide, concentrated to dryness under vacuum on a rotary evaporator, and extracted with acetone to yield 1.9 g. of 1,4-diol. The yield of 1,4-dideuterio-1,4-cyclohexanediol (14.3 g., 0.133 mole) was 66.5%. The infrared and n.m.r. spectra of the 1,4-diol were consistent with deuteriums in the 1,4-position.

1,4-Dideuterio-1,4-cyclohexanediol-di-*p*-toluenesulfonate.—To 165 ml. (2.31 moles) of freshly distilled dry pyridine was dissolved 14.3 g. (0.133 mole) of 1,4-dideuterio-1,4-cyclohexanediol. To this solution was added (with stirring) 50.6 g. (0.266 mole) of *p*-toluenesulfonyl chloride. Exothermicity was apparent after 10 min., and a white crystalline precipitate appeared after 20 min. The mixture was allowed to stand at room temperature for 2 days after which the reaction mixture was poured into 1500 ml. of cold 2.0 *M* hydrochloric acid. The solid that precipitated was vacuum dried (35° at 1.0 mm.) for 20 hr. The weight of 1,4-dideuterio-1,4-cyclohexanediol-di-*p*-toluenesulfonate was 47.8 g. (0.1125 mole) representing an 84.5% yield.

1,4-Dideuterio-1,3- and -1,4-cyclohexadiene.—To a 500-ml. distillation flask containing 270 ml. of redistilled propanol and 9.9 g. (0.247 mole) of sodium hydroxide was added 47.8 g. (0.112 mole) of 1,4-dideuterio-1,4-cyclohexanediol-di-*p*-toluenesulfonate. The 500-ml. flask was the distillation pot of a Todd distillation assembly so that as the contents of the flask were heated to reflux, the condensate with boiling point less than 97° was collected. Four fractions of condensate were collected totaling 70 ml. To the condensate was added 50 ml. of water; this mixture extracted with *n*-pentane. The pentane layer was washed once with water and the combined water layers extracted with *n*-pentane. The combined pentane layers were washed twice with water. A total of 55 ml. of *n*-pentane was used for extraction; the final volume was 59 ml. Most of the pentane (after drying) was carefully distilled until 10 ml. of hydrocarbon (dienes and pentane) remained. The 1,4-dideuterio-1,3-cyclohexadiene was separated from the 1,4-dideuterio-1,4-cyclohexadiene by preparative gas chromatography. A 10 ft. × 0.5 in. column packed with 160 g. of a substrate consisting of Ucon nonpolar on acid-washed Chromosorb P was used at 65° in conjunction with a Perkin-Elmer Model 154-D vapor fractometer. Samples of 0.70 ml. were in-

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1957, p. 207.

(14) Obtained with a 1 m. × 0.25 in. column packed with 20% diethylene glycol succinate on acid-washed Chromosorb W at 170° and 210 cc./min. helium as carrier gas. The column packing was purchased from Wilkens Instrument and Research, Inc., Walnut Creek, Calif.

jected and the 1,3-diene (13.8 min. retention time from air) was collected first and the 1,4-diene (retention time 21.8 min. from air) was the second compound to be collected. The 2.3 g. (0.028 mole) of 1,4-dideuterio-1,3-cyclohexadiene represents a 25% yield.

Reaction of 1,4-Cyclohexadiene with Sodium Hydroxide in 1-Propanol.—To a distillation flask containing 125 ml. of 1-propanol, 4.6 g. (0.115 mole) of sodium hydroxide, and 19 g. (0.1 mole) of sodium *p*-toluenesulfonate was added 5.0 ml. (0.05 mole) of 1,4-cyclohexadiene. This mixture was refluxed for 2 hr. (on a Todd distillation assembly) after which condensate was collected and worked up as in the preparation of the deuterated dienes. The v.p.c. analysis[15] of the starting diene was 98.3% 1,4-cyclohexadiene, 1.6% benzene, and 0.1% cyclohexane. The v.p.c. analysis of the cyclohexadiene after refluxing with sodium hydroxide in propanol was 98.3% 1,4-cyclohexadiene, 1.6% benzene, and 0.1% cyclohexane. *No* 1,3-cyclohexadiene was formed.

Thermodynamic Equilibration of 1,3- and 1,4-Cyclohexadiene.—Using dimethyl sulfoxide as the solvent and potassium *t*-butoxide as the base, a solution 0.0402 *M* in base and 0.428 *M* in 1,4-cyclohexadiene (99.4% pure) was equilibrated at 35°. The system was in equilibrium in less than 5 min. since at 5, 15, 30, 60, 120, and 1180 min. the ratio of 1,3- to 1,4-cyclohexadiene was essentially unchanged. The analysis of the diene mixture by v.p.c.[15] gave a ratio of 1,3/1,4-cyclohexadiene of 1.86 ± 0.02. In an identical manner, 0.403 *M* 1,3-cyclohexadiene (analyzed[15] 96.0% 1,3-cyclohexadiene, 3.4% cyclohexene, 0.5% benzene, 0.1% 1,4-cyclohexadiene) and 0.033 *M* potassium *t*-butoxide in dimethyl sulfoxide was equilibrated at 35°. Again analyses[15] showed equilibration complete in less than 5 min. and the ratio of 1,3/1,4-cyclohexadiene was 1.84 ± 0.01.

Reaction of I and 1,3-Cyclohexadiene in Methanol-D.—Methanol-D was synthesized by cautiously adding 27 g. (0.5 mole) of sodium methylate to 33.5 ml. (1.175 moles) of 99.5% deuterium oxide. The whole operation was carried out in a dry-box in a 100 ml. flask with stirring. The methanol-D was distilled from the excess deuterium oxide under "anhydrous" conditions. The yield of CH_3OD was 17.5 ml. (0.42 mole) which represented an 84% yield. The isotopic purity of the methanol-D was 99.5% as determined by comparing the area of the hydrogen on the OH to the hydrogen area due to the splitting resulting from the natural abundance of C^{13}. Thus the $-C^{13}H_3-$ (1.1% abundance) area was compared to the OH area to determine isotopic purity.

In a typical experiment 4.3 g. (0.0246 mole) of ethyl azodicarboxylate (I), 5.0 ml. (0.050 mole) of 1,3-cyclohexadiene, and 5.0 ml. (0.122 mole) of methanol-D were added to a graduate which was then stoppered, and placed in a 62° bath until the yellow color of the azo ester had faded. The unchanged 1,3-cyclohexadiene, methanol-D, methanol, and benzene[1a] was stripped from the reaction mixture, analyzed by v.p.c.[15] and then analyzed by n.m.r. The allyl and vinyl hydrogens (n.m.r.) of the 1,3-cyclohexadiene are shifted widely from the OCH_3, OH, and benzene hydrogens. The areas of the allyl and vinyl hydrogens were equal indicating the lack of deuterium exchange. The products from the reaction were mixed with methylene chloride and filtered giving 2.2 g. of ethyl hydrazodicarboxylate and 1.7 g. of a viscous oil (after stripping the methylene chloride). V.p.c. analysis[14] indicated (by area per cent) 14% ethyl hydrazodicarboxylate, 53% of the Diels–Alder adduct (V), and 33% of the addition–abstraction product (II). Column chromatography as described in the isolation of the Diels–Alder adduct (V) was used to isolate the addition–abstraction product (II). The n.m.r. of compound II showed no deuterium incorporation; its n.m.r. spectra and infrared spectra were identical to authentic samples previously prepared.[1a]

In an identical experiment, 1,4-cyclohexadiene reacted with ethyl azodicarboxylate in the presence of methanol-D at 62°. Similarly the unchanged 1,4-cyclohexadiene had equal allyl and vinyl areas in the n.m.r. indicating no deuterium exchange. The product VIII was isolated in a manner similar to the isolation of II and in a manner previously described.[1a] This product had an n.m.r. and infrared spectrum identical to the product derived in the absence of any deuterium[1a] indicating no deuterium incorporation.

Preparation of Va and X from Reaction of 1,4-Dideuterio-1,3-cyclohexadiene with Ethyl Azodicarboxylate (I).—To 2.3 g. (0.028 mole) of 1,4-dideuterio-1,3-cyclohexadiene was added 4.5 g. (0.026 mole) of ethyl azodicarboxylate. The reaction mixture was kept at room temperature with stirring for 64 hr. after which time the reaction mixture had become colorless. As in the isolation of V, acid-washed alumina was the column packing and dichloromethane was the eluent. The first product off the column was V (analyses of fractions were done by v.p.c.).[14] This was then followed by compound X. Each of these compounds were then analyzed by n.m.r. and the results shown in Fig. 1b (for V) and Table V (for X).

Preparation of 1,4-Bis(1′,2′-dicarbethoxyhydrazyl)-2,5-cyclohexadiene (IX).—Compound VIII, diethyl 2,4-cyclohexadien-1-yl-bicarbamate (1.39 g. 0.0055 mole), was diluted with benzene so that the volume of solution was 3 ml. To this solution was added 0.95 g. (0.0055 mole) of ethyl azodicarboxylate. The solution was heated for 1 hr. on a steam bath, allowed to stand overnight, and once again heated on a steam bath for 45 min. Overnight a white solid had precipitated which did not redissolve on heating; this solid, after drying weighed 1.18 g. (0.00276 moles, 50% yield) had m.p. 155.5–157° and an n.m.r. consistent with IX.

Anal. Calcd. for $C_{18}H_{28}N_4O_8$: C, 50.45; H, 6.59; N, 13.08, mol. wt., 428. Found: C, 50.46, 50.32; H, 6.61, 6.52; N; 13.19; mol. wt., 395 (osmometer).

Determination of Rate Constants.—Purity of the cyclohexadienes was determined by v.p.c.[15] 1,3-Cyclohexadiene (purchased from Farchan Research Lab., Wickliffe, Ohio) was 99.1% pure; the other impurities were benzene and cyclohexane which did not react with ethyl azodicarboxylate. Similarly, analysis of 1,4-cyclohexadiene (purchased from Columbia Organic Chemical Co., Columbia, S. C.) indicated a purity of 99.5%; the impurity in the 1,4-diene was benzene. Both the dienes and the ethyl azodicarboxylate (purchased from Aldrich Chemical Co., Milwaukee, Wis.) were distilled prior to kinetic runs. Spectro Grade cyclohexane (as the solvent) carefully was redistilled from anhydrous calcium sulfate and analyzed at least 99.9% pure.[15] For the determination of rate constants for 1,3-cyclohexadiene, samples of 1,3-diene in about 80 ml. of cyclohexane (in a 100-ml. volumetric flask) were placed for 30 min. in a thermostated bath; a weighed amount of ethyl azodicarboxylate was added to the 100-ml. volumetric flask and the volume adjusted to 100.0 ml. at the desired temperature with thermostatted solvent (cyclohexane). Samples of the solution were removed from time to time, quickly brought to room temperature, and a known volume diluted (with cyclohexane) for measurement of optical density. Usually dilution was 1 to 5; however, it would vary with the concentration of azo ester. The concentration of azo ester was determined from the optical density at 403 mμ. The initial concentration of azo ester was determined both by optical density of a sample taken immediately after adding the azo ester to the diene, and by calculation from the weight of the added azo ester. Since Beer's law held at all concentrations from 0.025 *M* down, the reactions were followed to 50–80% completion. Plots of the rate data, using a standard equation for the second-order rate law[16] gave good straight lines. The determination of rate constant for compound VIII going to IX by reaction with I was done in the same way as the reaction of 1,3-cyclohexadiene with I except that optical density was measured at 258 mμ. The determination of rate constants for reaction of 1,4-cyclohexadiene with ethyl azodicarboxylate was done by making (at room temperature) a solution (100.0 ml.) 0.02 to 0.1 *M* in azo ester I and 0.1 to 0.2 *M* in 1,4-cyclohexadiene. Approximately 7 ml. of the solution was pipeted into each of nine tubes which were sealed and placed in a thermostated bath. Initial concentration of azo ester was determined both by the weight of the azo ester and by optical density at 403 mμ of an initial sample appropriately diluted. From time to time samples were removed from the bath, cooled to room temperature, opened and a known volume of solution diluted (usually about 1 to 5) for measurement of optical density. Usually after 20% reaction the amount of ethyl hydrazodicarboxylate formed was sufficient to cause cloudiness of the solution at room temperature; these solutions were filtered through sintered glass with a slight nitrogen pressure above the liquid. The concentration of reactants was corrected for the expansion of solvent[17] and the rate data plotted to good straight lines using the standard equation for a

(15) Analysis for 1,3- and 1,4-cyclohexadiene was done with a Perkin-Elmer 2-m. R column, at 55° on a Model 154-D Perkin-Elmer vapor fractometer.

(16) S. J. Cristol, *J. Am. Chem. Soc.*, **67**, 1494 (1945).

(17) G. Egloff, "Physical Constants of Hydrocarbons," Vol. II, Reinhold Publishing Corp., New York, N. Y., 1940, pp. 78–80.

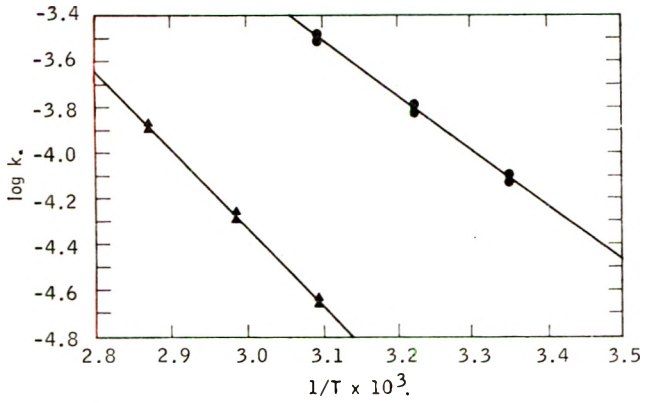


Fig. 3.—Enthalpy of activation from log k *vs.* $1/T$: ▲, 1,3-cyclohexadiene; ●, 1,4-cyclohexadiene.

second-order reaction.[16] Quantitative analysis for amount of compound VIII (from 1,4-cyclohexadiene and I) at different temperatures was based on the ultraviolet absorption of VIII at 258 mμ (ϵ_{max} 3760). After all solvent and unchanged diene were removed from the reaction mixture the product was diluted with ethanol and the concentration of VIII determined from the ultraviolet absorption. Reproducibility of results by this method was ±0.3%. Qualitative verification for the validity of this method was based on the analysis of benzene (and therefore ethyl hydrazodicarboxylate) by v.p.c.[15] Quantitative analysis for II, V, and ethyl hydrazodicarboxylate from the reaction of 1,3-cyclohexadiene and I was done by v.p.c.[14] Molar response data[18] from known mixtures of ethyl hydrazodicarboxylate and II and ethyl hydrazodicarboxylate and V were sufficient for the quantitative analysis of all three components. Reproducibility was good to ±1%. Reaction temperatures for 1,3-cyclohexadiene and I were 25.05 ± 0.05°, 37.07 ± 0.05°, and 49.96 ± 0.05°; for 1,4-cyclohexadiene and I reaction temperatures were 49.96 ± 0.05°, 61.86 ± 0.05° and 75.22 ± 0.05°. The plot of log k *vs.* $1/T$ is shown in Fig. 3 for the reaction of ethyl azodicarboxylate and both 1,3- and 1,4-cyclohexadiene. As can be seen from Fig. 3 the plots are quite good so that over-all enthalpies of activation are good to at least ±0.5 kcal.

Acknowledgment.—The author is greatly indebted to Mr. John H. Surridge for his invaluable assistance in the experimental work. Credit is given to my colleagues, Drs. W. A. Thaler, W. C. Baird, E. I. Snyder, and J. L. Kurz, along with Professors W. E. von Doering H. C. Brown, S. J. Cristol, and P. S. Skell for their helpful discussions and suggestions. The determination of the n.m.r. spectra is credited to Dr. Boyd E. Hudson, Jr.

(18) A. E. Messner, D. M. Rosie, and P. A. Argabright, *Anal. Chem.*, **31**, 230 (1959).

Synthesis of Bicyclic Nitriles and Related Compounds. II[1,2]

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Received January 10, 1963

A number of polynitriles and related compounds derived from bicyclic systems have been prepared *via* the Diels–Alder reaction. Of particular interest is the reaction of chloromaleic anhydride with 1-carbomethoxycyclohexa-1,3-diene, which affords but one of the two structurally possible isomers; chlorine appears in the 2-position of the adduct. The preparation of 2,3-diacetoxycyclohexa-1,3-diene is described, but the compound failed to react satisfactorily in the Diels–Alder synthesis.

A previous publication[1] in this series described the synthesis of a number of bicyclic nitriles and related compounds whose synthesis was stimulated by the unexpected antileukemia activity of the Diels–Alder adduct of fumaronitrile and cyclohexa-1,3-diene. The present paper is, in part, an extension of this exploratory synthesis and, in part, related to the broader problem of the scope and limitations of the Diels–Alder reaction with functionally substituted cyclic dienes and the steric course of this reaction.

Following up the reaction of fumaronitrile with cyclopentadiene[6] and cyclohexa-1,3-diene, it has been found that it is in general a practicable dieneophile, good yields of adducts being obtained with furan and cyclohepta-1,3-diene.[7]

A potential intermediate[8] in the preparation of fumaronitrile, α-chloroacrylonitrile, also proved to be a practicable dieneophile, with cyclopentadiene and cyclohexa-1,3-diene. The two purified adducts, which probably are the less soluble members of two epimeric pairs, surprisingly showed complete inertness to refluxing with silver nitrate solution. Thus, one may tentatively assign an *endo* configuration to the chlorine, for in the *exo* configuration one might reasonably expect comparatively labile chlorine.

An examination of the α-chloroacrylonitrile adducts by n.m.r. affords additional support for the *endo*-chlorine configuration: the vinyl protons in *exo*- and *endo*-bicyclo[2.2.1]hept-5-ene-2-carbonitrile appear as multiplets, respectively, at 3.83 and 3.72 τ (deuteriochloroform, internal tetramethylsilane reference, 60 Mc.), whereas in the 2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile, the vinyl protons appear as two multiplets at 3.79 and 3.52 τ suggesting that one of them (on C-6) is in approximately the same environment as in the unchlorinated compound while the other is less shielded due to the *endo*-chlorine. In 2-chlorobicyclo-[2.2.2]oct-5-ene-2-carbonitrile a multiplet for two protons falls at 3.64 τ, which suggests about the same environment as for the [2.2.1] analog.

Further evidence for the *endo*-chlorine configuration appears in the reduction of 2-chlorobicyclo[2.2.1]-heptane-2-carbonitrile by lithium aluminum hydride. The product, isolated as the hydrochloride, consists of

(1) Previous paper in this series: P. Scheiner and W. R. Vaughan, *J. Org. Chem.*, **26**, 1923 (1961).

(2) Work supported in part by a research grant (CY 5406) from the National Cancer Institute to The University of Michigan.

(3) National Institutes of Health Predoctoral Fellow, 1960–1961.

(4) Abstracted in part from a portion of the Ph.D. dissertation of P. Scheiner, The University of Michigan, 1961.

(5) American Cancer Society Institutional Research Grant Fellow, Summer, 1961.

(6) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).

(7) Hi-Laboratory, Whitmore Lake, Mich.

(8) D. T. Mowry and W. H. Yanko, to Monsanto Chemical Co., U. S. Patent 2,471,767 (1949).

more than 50% *endo*-2-aminomethylbicyclo[2.2.1]heptane.[9] If one allows inversion for replacement of the chlorine, this is the expected product. The alternative involving intermediate ethyleneimine formation followed by reopening of the aziridine ring, which would lead to the product isolated from the epimer, is not particularly attractive, since other work in this laboratory[10] has shown that the aziridine system is generally stable to lithium aluminum hydride.

Similar reduction of bicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarbonitrile afforded bis-2,3-*trans*-aminomethylbicyclo[2.2.2]oct-5-ene as the dihydrochloride. The double bond in the preceding initial adduct proved to be "normal" with respect to catalytic hydrogenation, epoxidation (*cf.* acrylonitrile adduct and fumaronitrile adducts with cyclopentadiene in Experimental part), and reaction with phenyl azide [*cf.* fumaronitrile adduct with cyclopentadiene, and norbornadiene (bis adduct) with phenyl azide in Experimental part].

Further structural isomers of the desired bicyclic dinitriles might be expected *via* the reaction of acrylonitrile with cyclohexa-1,3-diene and cyclopentadiene, each carrying an appropriate acid derivative (*e.g.*, ester) in the 1-position. To this end 1-carbomethoxycyclohexa-1,3-diene and 1-carbomethoxycyclopentadiene[11] were prepared. In addition, the preparation of 1-cyanocyclohexa-1,3-diene was attempted, but it appeared to be too unstable for analysis, and did not react satisfactorily with acrylonitrile, fumaronitrile, dimethyl maleate, or dimethyl fumarate, the only identifiable product (infrared spectrum) being benzonitrile at temperatures above 150°. However, adducts were obtained with tetracyanoethylene and maleic anhydride. The ultraviolet analysis of the former adduct showed conjugated nitrile. Therefore, instead of the expected diene, 2-cyanocyclohexa-1,3-diene was either obtained initially[12] or during the reaction.

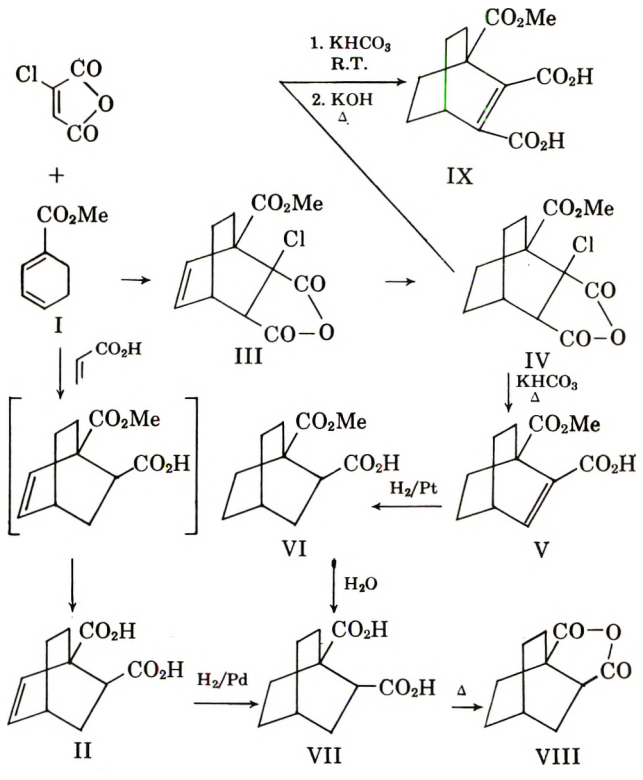
Carbomethoxycyclohexa-1,3-diene (I) also afforded a tetracyanoethylene adduct and a maleic anhydride adduct; in addition, adducts were obtained with acrylic acid and chloromaleic anhydride.

The problem of structure in the reactions of I was resolved in the following manner. I was allowed to react with both acrylic acid and with chloromaleic anhydride. In the former reaction only a dibasic acid was isolated (II), and in the latter only one characterizable product was obtained (55% yield, III). By the series of reactions, hydrogenation (IV), fragmentation (V) (dehalogenative decarboxylation), hydrogenation (VI), and hydrolysis (VII), the same product was obtained (VII) as by hydrogenation of II. The *ortho* relationship in VII was confirmed by anhydride formation, which was also achieved by heating VI. Thus the chloride in chloromaleic anhydride appears to provide a directive influence resulting in the chlorine assuming predominantly the *ortho* position in the adduct with I (*cf.* Chart I).

It is of interest to note that potassium bicarbonate at room temperature *does not* effect extensive fragmentation, but when followed with alkali produces, instead, dehydrohalogenation; thus IV → IX, and IX readily adds bromine to give a dibromide.

CHART I

EVIDENCE FOR STRUCTURE OF III



The corresponding 1-carbomethoxycyclopentadiene readily afforded a tetracyanoethylene adduct, but other derivatives were not investigated.

The problem of preparing 2,3-dicyanobicyclo[2.2.1]-hept-2-ene and the corresponding bicyclo[2.2.2]octene derivative required proceeding through the dimethyl acetylenedicarboxylate adducts with cyclopentadiene and cyclohexa-1,3-diene, respectively. Hydrogenation of the isolated double bond in each case proceeded satisfactorily, and conversion to the diamides was accomplished by methanolic ammonia catalyzed by sodium methoxide.[13] The diamides were then converted to the dinitriles by dehydration with phosphorus oxychloride.

It is appropriate to mention at this point two other bicyclic compounds available *via* a Diels–Alder reaction, of interest primarily for their potential resemblance to myleran (tetramethyleneglycolbismethanesulfonate): 2,3 - *trans* - bishydroxymethylbicyclo[2.2.1]hept - 5-ene[14] bismethanesulfonate and the corresponding saturated product obtained from it by hydrogenation.

It had been hoped to prepare a number of related functionally substituted bicyclic glycols for which 2,3-diacetoxycyclohexa-1,3-diene would be a desirable starting material, and to this end the diene was prepared from cyclohexane-1,2-dione and acetic anhydride with boron trifluoride etherate as catalyst. However, although a solid product was obtained with maleic anhydride and the new diene, it was not analytically satisfactory and proved to be too unstable to survive purification attempts.

(9) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958).

(10) J. R. Wood, "Potential Anticancer Agents," Ph.D. dissertation, The University of Michigan, 1962.

(11) J. Thiele, *Ber.*, **34**, 68 (1901).

(12) V.p.c. analysis indicated a mixture, but principally one component.

(13) P. B. Russell, *J. Am. Chem. Soc.*, **72**, 1853 (1950).

(14) K. Alder and W. Roth, *Chem. Ber* **87**, 161 (1954).

Finally, a further transformation of bicyclo[2.2.2]-oct-5-ene *trans*-2,3-dicarbonitrile[6] also was carried out: lithium aluminum hydride reduction to the corresponding bisaminomethyl dihydrochloride.

Experimental[15]

7-Oxabicyclo[2.2.1]heptane-*trans*-2,3-dicarbonitrile.—A solution of 5.4 g. of 7-oxabicyclo[2.2.1]hept-5-ene-*trans*-2,3-dicarbonitrile[16] (0.37 mole) in 130 ml. of ethyl acetate was hydrogenated at 3 atm. with 0.5 g. of 5% palladium-on-carbon catalyst. A quantitative yield of product, m.p. 110–114°, was obtained after filtration and evaporation. Five crystallizations from ethyl acetate–*n*-hexane gave a product melting at 124–125°.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.88; H, 5.43; N, 18.99.

Bicyclo[3.2.2]non-8-ene-*trans*-6,7-dicarbonitrile.—A solution of 7.8 g. (0.084 mole) of 1,3-cycloheptadiene[7] and 5.5 g. (0.071 mole) of fumaronitrile[17] in 27 ml. of xylene was refluxed for 48 hr. The dark reaction mixture was treated four times with Norit, then diluted with ethyl acetate and petroleum ether (b.p. 60–75°) and cooled, yielding 4.7 g. (38.5%) of a white camphor-like solid, melting above 128°. Recrystallization from petroleum ether (b.p. 90–100°) failed to change the melting point. Two vacuum sublimations at 80–90° (0.5 mm.), however, gave 3.6 g. (29%) of a white solid, m.p. 140.0–141.5°.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02. Found: C, 76.42; H, 6.70.

2-Chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile.—Freshly distilled cyclopentadiene (30 ml.) was added to a solution of 30 ml. of α-chloroacrylonitrile,[18] a small amount of hydroquinone, and 30 ml. of anhydrous diethyl ether. The reaction solution on standing 5 min., refluxed vigorously, and after moderation of the initial reaction, it was warmed over steam for 23 hr. After evaporation in an air stream, the resulting brown oil was sublimed at 85° (35 mm.). A fragrant white solid (41.0 g., 76%), m.p. 42–43°, was obtained. Two sublimations raised the melting point of the noncrystalline solid to 47–48° (34 g., 63%). V.p.c. analysis showed 10% of a second component. Microanalysis indicates the latter to be the epimer. N.m.r. showed vinyl protons at 3.52 and 3.79 τ.

Anal. Calcd. for C_8H_8ClN: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.70; H, 5.43; N, 9.07.

Attempted Reaction of the Adduct with Silver Nitrate.—A solution of 3.6 g. (0.024 mole) of 2-chlorobicyclo[2.2.1] hept-5-ene-2-carbonitrile, 100 ml. of 5% aqueous silver nitrate, and 100 ml. of acetone was refluxed for 24 hr. The resulting solution was entirely clear with no precipitated solid. Most of the acetone was boiled off and the solution then extracted three times with 50-ml. portions of ether. After drying over sodium sulfate and removal of ether, 2.9 g. (81%) of starting material was recovered. (Poor recovery undoubtedly was due to the volatility of the starting material.)

2-Chlorobicyclo[2.2.1]heptane-2-carbonitrile.—A solution of 9.9 g. (0.065 mole) of 2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile in 100 ml. of ethyl acetate was hydrogenated at 3 atm. over 0.9 g. of 5% palladium on carbon. The crude product, 9.5 g. (95%), was sublimed at 53° (0.3 mm.). Two additional sublimations gave a fragrant noncrystalline white solid (7.2 g., 72%), m.p. 48.0–49.5°. Analysis by v.p.c. indicates a second component in approximately the same proportions as for the unsaturated starting material, and microanalysis implies that it is the epimer.

Anal. Calcd. for $C_8H_{10}ClN$: C, 61.73; H, 6.48; N, 9.00. Found: C, 61.97; H, 6.53; N, 8.94.

The product was reduced in ether with excess lithium aluminum hydride, and from the reaction there was isolated unreduced starting material (infrared), an uncharacterized carbonyl compound (infrared), and 50% of *endo*-2-aminomethylbicyclo[2.2.1]-heptane hydrochloride,[9] identified by comparison of infrared spectrum with an authentic sample.[9]

2-Chloro-5,6-epoxybicyclo[2.2.1]heptane-2-carbonitrile.—A solution of 102 ml. of chloroform containing 9.5 g. (0.069 mole) of peroxybenzoic acid was added dropwise (0°) to 10.0 g. (0.069 mole) of 2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile. The clear solution was allowed to reach room temperature gradually, and the course of the reaction was followed titrimetrically. The reaction was completed in 24 hr. After washing with 55 ml. of 5% sodium hydroxide, followed by re-extraction of the aqueous layer with 50 ml. of chloroform, the combined organic layers were washed with 100 ml. of water and dried over magnesium sulfate. Evaporation in an air stream followed by sublimation of the fragrant oil over steam at 35–40 mm. produced 7.5 g. (68%) of a fragrant white, noncrystalline solid. The melting point of the compound, 90–96°, was not sharp, and did not improve on further sublimation. Analysis by v.p.c. indicated 20% of a minor component, and microanalysis implies an isomeric epoxide.

Anal. Calcd. for C_8H_9ClNO: C, 56.65; H, 4.76; N, 8.26; Cl, 20.90. Found: C, 56.91; H, 5.03; N, 7.91; Cl, 20.51.

5,6-Epoxybicyclo[2.2.1]heptane-2-carbonitrile.—A solution of 25 ml. of 40% peroxyacetic acid in acetic acid was added, in small amounts, to 11.9 g. (0.10 mole) of bicyclo[2.2.1]hept-5-ene-2-carbonitrile[19] cooled in an ice–salt bath. The vigorous reaction which occurred caused the solution to boil for a few minutes. The cooled, colorless reaction mixture was evaporated to a thick oil in an air stream, then diluted with 50 ml. of ether, and washed cautiously with 50 ml. of 5% sodium bicarbonate solution. After drying over sodium sulfate, the organic layer was evaporated, yielding 10.0 g. (74.0%) of a viscous, sweet-smelling oil. Sublimation at 75° (0.3 mm.) produced a fragrant, noncrystalline white solid, melting from 82–83°. Five additional sublimations did not change these physical properties.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.82; H, 6.63; N, 10.37.

5,6-Epoxybicyclo[2.2.1]heptane-*trans*-2,3-dicarbonitrile.—A 122-ml. chloroform solution containing 8.85 g. (0.064 mole) of peroxybenzoic acid was added to 7.2 g. (0.050 mole) of bicyclo-[2.2.1]hept-5-ene-*trans*-2,3-dicarbonitrile. The resulting solution remained at room temperature for 23 days, at which time standard thiosulfate indicated that reaction was complete. The solution was washed with 60 ml. of 5% sodium hydroxide, and the aqueous extract was extracted with 40 ml. of chloroform. The combined chloroform layers, washed with an equal volume of water, were dried over magnesium sulfate, filtered, and evaporated, yielding 7.8 g. (97.5%) of white solid, m.p. 160–165°. After four crystallizations from benzene–*n*-hexane, the compound melted at 184–185° (5.4 g., 68%).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.04; N, 17.49. Found: C, 67.88; H, 5.00; N, 17.39.

3a,4,5,6,7,7a-Hexahydro-5-(or 6)-chloro-1-phenyl-4,7-methano-1*H*-benzotriazole-5-(or 6)-carbonitrile.—A 70-ml. solution containing 9.7 g. (0.077 mole) of phenyl azide in carbon tetrachloride was mixed with 10.0 g. (0.065 mole) of 2-chlorobicyclo[2.2.1]-hept-5-ene-2-carbonitrile, and the resulting solution was allowed to stand at room temperature for 4 days. On evaporation, 12.5 g. (70.5%) of solid, melting at about 130°, was collected in five crops. Repeated recrystallization of this material from petroleum ether (60–75°)–benzene (4:1) gave material melting at 146–147° dec. (7.1 g., 40%).

Anal. Calcd. for $C_{14}H_{13}ClN_4$: C, 61.65; H, 4.80; N, 20.54. Found: C, 61.61; H, 4.95; N, 20.46.

5,6-Epoxybicyclo[2.2.2]octane-*trans*-2,3-dicarbonitrile.—Bicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarbonitrile[1] (12.0 g., 0.076 mole) was dissolved in 185 ml. of a chloroform solution containing 12.0 g. (0.087 mole) of peroxybenzoic acid. The course of reaction, completed after 9 days at room temperature, was followed titrimetrically. The reaction solution was washed with a solution of 4.0 g. (0.10 mole) of sodium hydroxide in 75 ml. of water. The aqueous layer was re-extracted with 70 ml. of chloroform and combined with the original organic layer. After two washings with water, the chloroform solution was dried over magnesium sulfate and evaporated, yielding 14.6 g. (110%) of a viscous yellow oil. Repeated crystallization from *n*-hexane–benzene gave a sticky white solid, m.p. 188.5–189.5° (8.1 g., 61%).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79; N, 16.08. Found: C, 69.06; H, 5.79; N, 15.97.

2-Chlorobicyclo[2.2.2]oct-5-ene-2-carbonitrile.—A solution of 14.6 g. (0.183 mole) of 1,3-cyclohexadiene,[20] 16.0 g. (0.183 mole)

(15) Melting and boiling points are uncorrected. Microanalyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich. N.m.r. spectra (Varian A-60) were obtained by Mr. B. E. Wenzel of this department (deuteriochloroform, internal tetramethylsilane, 60 Mc.).

(16) D. T. Mowry, *J. Am. Chem. Soc.*, **69**, 573 (1947).

(17) Kindly supplied by Monsanto Chemical Co.

(18) Kindly supplied by American Cyanamid Co.

(19) H. A. Bruson, *J. Am. Chem. Soc.*, **64**, 2457 (1942).

(20) A. T. Blomquist and J. Kwiatcek, *ibid.*, **73**, 2098 (1951).

of α-chloroacrylonitrile[21] (partially polymerized), a few crystals of hydroquinone, and 30 ml. of anhydrous xylene was refluxed for 24 hr. The clear solution was filtered away from the large amounts of polymer present in the original flask and evaporated to yield 2.8 g. (9.2%) of a fragrant white solid, m.p. 72.0–73.5°. Four sublimations at 110–120° (1.0–2.0 mm.) gave a noncrystalline solid melting at 84–85° (1.9 g., 6.3%). N.m.r. showed vinyl protons as multiplet at 3.64 τ.

Anal. Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 6.01; N, 8.36. Found: C, 64.22; H, 6.22; N, 8.15.

Treatment with silver nitrate as for the bicycloheptene analog also afforded no observable reaction and good recovery.

3a,4,5,6,7,7a-Hexahydro-1-phenyl-4,7-methano-1*H*-benzotriazole-*trans*-5,6-dicarbonitrile.—A 44-ml. solution of 5.8 g. (0.049 mole) of phenyl azide in carbon tetrachloride was mixed with 7.0 g. (0.049 mole) of bicyclo[2.2.1]hept-5-ene-*trans*-2,3-dicarbonitrile[1] and the resulting solution allowed to stand at room temperature for 40 hr. The precipitated solid, 7.1 g. (55.0%), was filtered and recrystallized from 95% ethanol, to give a white crystalline solid, m.p. 198° dec. Four further recrystallizations raised the decomposition point to 202° (4.6 g. 36%).

Anal. Calcd. for $C_{15}H_{13}N_5$: C, 68.42; H, 4.98. Found: C, 68.27; H, 4.87.

3-(6)-Bromocyclohexene-1-carbonitrile.—In a three-necked flask fitted with a condenser and stirrer was placed 58.6 g. (0.547 mole) of cyclohexene-1-carbonitrile[22] dissolved in 300 ml. of carbon tetrachloride. The stirred solution was refluxed gently while 97.4 g. (0.547 mole) of N-bromosuccinimide was added in small portions. An additional 100 ml. of carbon tetrachloride was used to transfer the N-bromosuccinimide to the flask. The reaction mixture was then refluxed with stirring for 5 hr. After cooling and filtration the solvent was removed under reduced pressure, yielding 99.9 g. (98.0%) of a sweet-smelling yellow oil. The crude product was distilled at 103–110° (1.5–2.0 mm.) and redistilled at 85.5–90.0° (0.8–0.9 mm.). The product decomposed with loss of hydrogen bromide on standing exposed to air. It was not analyzed but was dehydrohalogenated directly.

1,3-Cyclohexadiene-2-carbonitrile.—To 52.1 g. (0.280 mole) of 3-(6)-bromocyclohexene-1-carbonitrile, stirred and chilled in ice, 73 ml. of a methanolic solution containing 15.1 g. (0.280 mole) of sodium methoxide was added dropwise over 1 hr. The reaction mixture was then diluted with 300 ml. of water and extracted twice with 100-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, and the solvent was then removed under reduced pressure, leaving 21.6 g. (89.0%) of a fragrant yellow oil. On distillation, a colorless product was obtained, b.p. 70–75° (1.0 mm.), $n^{24}D$ 1.4898. V.p.c. analysis showed two components, one in considerable excess. This material was used directly in subsequent Diels–Alder reactions.

Bicyclo[2.2.2]oct-5-ene-2,2,3,3,5-pentacarbonitrile.—A mixture of 3.3 g. (0.031 mole) of 1,3-cyclohexadiene-2-carbonitrile and 4.0 g. (0.031 mole) of tetracyanoethylene was heated in a large test tube for 1 hr. at 85° and heated an additional hour at 115°. The dark reaction mixture, after remaining at room temperature for 13 hr., was filtered and the solid material thus obtained was washed liberally with toluene and carbon tetrachloride. A yield of 5.3 g. (72.6%) of washed product was collected. Two recrystallizations from benzene gave a white crystalline solid which melted at 214–215°, but with darkening above 205° (3.1 g., 42%). Four crystallizations from *n*-hexane–benzene failed to change the melting point. N.m.r. spectrum shows one vinyl proton, 3.00 τ (multiplet).

Anal. Calcd. for $C_{13}H_7N_5$: C, 66.94; H, 3.03. Found: C, 67.03; H, 3.14.

Ultraviolet (compensated absolute ethanol) showed log ε 3.286 at 22 mμ, absorption still increasing; acrylonitrile, log ε 1.69 at 215 mμ, absorption still increasing; saturated nitriles transparent in this region.

Bicyclo[2.2.2]oct-5-ene-*cis*-2,3-dicarboxylic Acid Anhydride-5-carbonitrile.—Maleic anhydride (1.3 g., 0.013 mole) and 2.8 g. (0.027 mole) of 1,3-cyclohexadiene-2-carbonitrile were heated at 150° for 25.5 hr. After cooling and dilution with 2 ml. of *n*-hexane and 10 ml. of benzene, 1.5 g. (57%) of crude product separated, m.p. 150–160°. Four crystallizations from *n*-hexane–benzene gave pure material melting at 185–186° (0.8 g., 30%).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.47; N, 6.81. Found: C, 65.26; H, 4.67; N, 6.93.

1-Carbomethoxybicyclo[2.2.2]oct-5-ene-2,2,3,3-tetracarbonitrile.—A solution of 6.4 g. (0.050 mole) of tetracyanoethylene and 7.0 g. (0.051 mole) of 1-carbomethoxy-1,3-cyclohexadiene[23] (I) in 20 ml. of anhydrous dioxane was heated for 2 hr. at 100°. After cooling, the dark reaction mixture was filtered (13.5 g.). The adduct, recrystallized from benzene, melted at 191–193° (8.2 g., 61%). Further crystallization from the same solvent did not change the melting point.

Anal. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.16; H, 3.85; N, 21.11.

Bicyclo[2.2.2]oct-5-ene-1,2-dicarboxylic Acid (II).—A mixture of 15.6 g. (0.216 mole) of acrylic acid, 36.2 g. (0.262 mole) of I, and a few crystals of hydroquinone was heated at 150–165° for 74 hr. On dilution with *n*-pentane and ether, and cooling, 10.5 g. (24.8%) of a white solid, m.p. 195–198°, was collected. The solution yielded no other characterizable material. Three crystallizations from benzene–*n*-hexane gave 3.7 g. of material, m.p. 202–204° (II).[24] The infrared spectrum indicated a dibasic acid. This was converted directly to VII by hydrogenation with Adams' catalyst.

1-Carbomethoxy-2-chlorobicyclo[2.2.2]oct-5-ene-*cis*-2,3-dicarboxylic Acid Anhydride (III).—A mixture of 61.8 g. (0.446 mole) of I and 52.7 g. (0.420 mole) of chloromaleic anhydride was heated at 155–165° for 20 hr. The dark brown reaction mixture was placed under aspirator pressure on a steam bath for 4 hr., then cooled. The resulting brown solid crystallized from 300 ml. of benzene–*n*-hexane, affording 62.5 g. (55.0%) of crystalline solid, m.p. 120–125°. Two recrystallizations from benzene–*n*-hexane gave material, m.p. 125–126° (31.6 g., 28%).

Anal. Calcd. for $C_{12}H_{11}ClO_5$: C, 53.24; H, 4.10; Cl, 13.10. Found: C, 53.38; H, 4.20; Cl, 13.20.

1-Carbomethoxy-2-chlorobicyclo[2.2.2]octane-*cis*-2,3-dicarboxylic Acid Anhydride (IV).—A solution of 7.2 g. (0.027 mole) of 1-carbomethoxy-2-chlorobicyclo[2.2.2]oct-5-ene-*cis*-2,3-dicarboxylic acid anhydride in 150 ml. of ethyl acetate was hydrogenated with 0.2 g. of Adams' catalyst under 3-atm. pressure. After the theoretical uptake of hydrogen, the catalyst was filtered, the solvent was evaporated, and 7.3 g. (100.0%) of white crystalline product was obtained, m.p. 136.5–138.0°. Further recrystallization from *n*-hexane–ethyl acetate failed to change the melting point.

Anal. Calcd. for $C_{12}H_{13}ClO_5$: C, 52.85; H, 4.80; Cl, 13.00. Found: C, 52.92; H, 4.96; Cl, 12.99.

1-Carbomethoxybicyclo[2.2.2]oct-2-ene-2-carboxylic Acid (V).—A solution of 10.4 g. (0.104 mole) of potassium bicarbonate in 40 ml. of water was added to 14.0 g. (0.0513 mole) of 1-carbomethoxy-2-chlorobicyclo[2.2.2]octane-*cis*-2,3-dicarboxylic acid (IV) at room temperature. It was then immediately heated on the steam bath for 20 min., during which time the initial carbon dioxide evolution moderated and finally ceased. After filtration, the solution was acidified with concentrated hydrochloric acid and cooled in the refrigerator for 2 hr. The resulting white solid was filtered, washed with water, and dried at 70° (30 mm.) for 2 hr.: yield, 9.5 g. (90.9%), m.p. 140.5–142.0°. Three crystallizations from *n*-hexane–benzene (2:1) gave material melting at 144–145° (6.7 g., 64%).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.75; H, 6.83.

1-Carbomethoxybicyclo[2.2.2]octane-2-carboxylic Acid. (VI).—A solution of 24.4 g. (0.116 mole) of 1-carbomethoxybicyclo-[2.2.2]oct-2-ene-2-carboxylic acid (V) in 220 ml. of ethyl acetate and 60 ml. of acetone was hydrogenated with 0.3 g. of 5% palladium-on-carbon at 3 atm. The hydrogenated solution was evaporated in an air stream to a viscous oil, 21.9 g. (89.0%). On standing, this oil solidified to a white powder, m.p. 66–67°. Two recrystallizaions from *n*-hexane gave material melting at 85–86° (10.4 g., 42%).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.69.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Acid (VII).—A solution of 1.07 g. (5.44 moles) of bicyclo[2.2.2]oct-5-ene-1,2-dicarboxylic acid (II) in 70 ml. of ethyl acetate was hydrogenated at atmospheric pressure with 0.10 g. of platinum dioxide. Work-up in the

(21) This compound was inert to silver nitrate in ethanolic solution at room temperature.

(22) O. H. Wheeler, and I. Lerner, *J. Am. Chem. Soc.*, **78**, 63 (1956).

(23) A. Sayigh, dissertation, Columbia University, 1952, p. 86.

(24) This compound corresponds in melting point to the same product prepared *via* a different route by J. Kazan and F. D. Greene. Results were kindly furnished prior to publication by Professor Greene.

usual manner gave 0.70 g. (65.4%) of product, m.p. 200–202°. Two recrystallizations from *n*-hexane–ethyl acetate (1:2) gave the pure acid, m.p. 200.5–201.0° (0.32 g., 33%).[24]

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.62; H, 7.09.

This compound was identical in melting point and infrared spectrum with the diacid resulting from either acidic or basic hydrolysis of VI. A mixture melting point determination of the two showed no depression.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Acid Anhydride (VIII).—In a small round-bottom flask 0.3 g. of bicyclo[2.2.2]octane-1,2-dicarboxylic acid (VII) was heated for 2.5 hr. at 200° (±3°). The sublimed material in the neck of the flask, m.p. 125–163°, was removed, boiled with 20 ml. of *n*-hexane, and filtered. On concentration, white crystals separated, m.p. 163–164°. Two subsequent recrystallizations gave material melting at 166–167°.[24] The infrared spectrum of this compound showed the characteristic cyclic anhydride doublet (1865 and 1779 cm.$^{-1}$), but no carboxylic acid adsorption in the carbonyl region.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.69; H, 6.76.

Distillation of VI at 140° (0.07 mm.) gave a mixture of anhydride and VI. Solid VIII separated from the mixture on cooling.

1-Carbomethoxybicyclo[2.2.2]oct-2-ene-2,3-dicarboxylic Acid (IX).—1-Carbomethoxy-2-chlorobicyclo[2.2.2]oct-2-ene-2,3-dicarboxylic acid anhydride (IV) (28.2 g., 0.107 mole), was treated with 21.4 g. (0.214 mole) of potassium bicarbonate in 87 ml. of water. The mixture was allowed to stand at room temperature until a clear solution was obtained, then heated 2–3 min. After acidification with concentrated hydrochloric acid and standing for 5.5 hr., a gummy white solid, 13.0 g., was obtained, m.p. 110–125°. This material was refluxed with 7.0 g. (0.125 mole) of potassium hydroxide in 40 ml. of 62% aqueous methanol for 2.5 hr. After concentration, acidification, and filtration, the resulting white solid was recrystallized from water, yielding 2.5 g. (9%) of solid, m.p. 221° dec. Two further crystallizations from 10% ethanol failed to change the melting point. The compound reacted immediately with potassium permanganate solution, and had an ester band in the infrared spectrum at 1739 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55; neut. equiv., 258. Found: C, 56.72; H, 5.48; neut. equiv., 254.

1-Carbomethoxy-*trans*-2,3-dibromobicyclo[2.2.2]octane-2-carboxylic Acid.—Bromine (4.8 g., 0.030 mole) in 25 ml. of chloroform was added slowly to a stirred solution of 6.3 g. (0.030 mole) of 1-carbomethoxybicyclo[2.2.2]oct-2-ene-2-carboxylic acid (V) in 25 ml. of chloroform. The reaction flask was illuminated with a 100-w. bulb for 10 hr., at which time the deep bromine color of the original solution was discharged. Evaporation gave a brown oil which did not crystallize from *n*-hexane–benzene mixtures. After standing 5 days, this oil partially crystallized and was found then to be recrystallizable from *n*-hexane–benzene. Three such crystallizations gave material melting at 170.0–171.5°.

Anal. Calcd. for $C_{11}H_{14}Br_2O_4$: C, 35.70; H, 3.81; Br, 43.19. Found: C, 35.74; H, 3.89; Br, 43.32.

1-Carbomethoxybicyclo[2.2.1]hept-5-ene-2,2,3,3-tetracarbonitrile.—A solution of 2.5 g. (0.020 mole) of freshly distilled 1-carbomethoxy-1,3-cyclopentadiene[11,25] and 2.6 g. (0.020 mole) of tetracyanoethylene in 16 ml. of dioxane was heated on the steam bath for 1.5 hr. After concentration in an air steam, 2.2 g. (43%) of the crude adduct was obtained. Three crystallizations from ethyl acetate gave pure product, m.p. 229–230° dec.

Anal. Calcd. for $C_{13}H_8N_4O_2$: C, 61.90; H, 3.20; N, 22.21. Found: C, 61.74; H, 3.32; N, 22.18.

***trans*-2,3-Dihydroxymethylbicyclo[2.2.1]hept-5-enebismethanesulfonate.**—A solution of 17.2 g. (0.150 mole) of methanesulfonyl chloride in 10 ml. of anhydrous chloroform was added slowly to a cooled solution of 11.7 g. (0.073 mole) of *trans*-2,3-dihydroxymethylbicyclo[2.2.1]hept-5-ene[14] and 11.9 g. (0.150 mole) of anhydrous pyridine in 20 ml. of chloroform. During the addition the temperature rose to 60°. After standing 20 hr. at room temperature, the colorless solution was poured onto a mixture of 90 g. of ice and 150 ml. of 10% hydrochloric acid. The organic layer was separated and the aqueous solution reextracted twice with 90-ml. portions of chloroform. The combined organic layers were separated and the aqueous layer re-extracted twice with 90-ml. portions of chloroform. The combined organic layers were then dried with magnesium sulfate and evaporated to yield 19.8 g. (85.0%) of a dark oil. Crystallization readily occurred from absolute methanol, the analytically pure compound being obtained after two such crystallizations (11.7 g., 50.2%), m.p. 66–67°.

Anal. Calcd. for $C_{11}H_{18}O_6S_2$: C, 42.57; H, 5.84; S, 20.66. Found: C, 42.59; H, 5.87; S, 20.71.

***trans*-2,3-Dihydromethylbicyclo[2.2.1]heptanebismethanesulfonate.**—A solution of 5.3 g. (0.017 mole) of *trans*-2,3-dihydroxymethylbicyclo[2.2.1]hept-5-enebismethanesulfonate in 70 ml. of ethyl acetate was hydrogenated with 0.4 g. of Adams' catalyst at 3 atm. Removal of the solvent gave 5.3 g. (quantitative) of pale yellow oil which, on cooling, and addition of a small amount of absolute methanol, crystallized. Two crystallizations from absolute methanol gave a white crystalline solid, melting at 83–84° (3.5 g., 70%).

Anal. Calcd. for $C_{11}H_{20}O_6S_2$: C, 42.29; H, 6.45; S, 20.53. Found: C, 42.40; H, 6.50; S, 20.53.

Bicyclo[2.2.2]oct-2-ene-2,3-dicarbonitrile.—Dimethyl bicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate[26] was subjected to partial hydrogenation with a 5% palladium-on-carbon catalyst, giving dimethyl bicyclo[2.2.2]oct-2-ene-2,3-dicarboxylate (quantitatively) which was then converted into bicyclo[2.2.2]oct-2-ene-2,3-dicarboxamide by methanolic ammonia containing a catalytic amount of sodium methoxide.[13]

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.96; H, 6.71; N, 14.50.

Initial attempts to prepare the dinitrile by dehydrating the amide with thionyl chloride yielded only a cyclic amide irrespective of whether solvent was used or not. However, phosphorus oxychloride was effective. Bicyclo[2.2.2]oct-2-ene-2,3-dicarboxamide (12.47 g. 0.0655 mole) was heated on a steam bath with phosphorus oxychloride for 4.5 hr. The cooled solution was slowly poured onto crushed ice (150 g.) with constant stirring and then extracted with benzene (300 ml.).

The benzene extract was washed with water till neutral, then with ice-cold 5% sodium hydroxide (45 ml.), then again with water; it was dried over magnesium sulfate and the benzene was evaporated through a fractionating column. The residue obtained was crystallized from petroleum ether (m.p. 60–75°) giving light cream needles (6.18 g., 61%), m.p. 93°.

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.03; H, 6.24; N, 17.61.

Bicyclo[2.2.1]hept-2-ene-2,3-dicarbonitrile.—The bicyclo[2.2.1]hept-2-ene-2,3-dicarboxamide was prepared in an analogous manner to the bicyclo[2.2.2]oct-2-ene-2,3-dicarboxamide.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.91; H, 6.71; N, 15.61.

The diamide (14 g. 0.078 mole) was heated with phosphorus oxychloride (100 ml.) on the steam bath for 4 hr. and was worked up as for the homolog, yielding a compound which was crystallized from petroleum ether (b.p. 60–75°) giving white plates (7.94 g., 70.6%), m.p. 42.5°.

Anal. Calcd. for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 74.86; H, 5.56; N, 19.46.

***trans*-2,3-Bisaminomethylbicyclo[2.2.2]oct-5-ene Dihydrochloride.**—A solution of bicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarbonitrile (10.9 g., 0.069 mole) in anhydrous ether (200 ml.) and benzene (100 ml.) was added dropwise with stirring to a slurry of lithium aluminum hydride (3 g., 0.34 mole) in anhydrous ether (100 ml.). During the addition which required 30 min., the reaction mixture was refluxed gently and the stirring was continued a further 30 min. Then water (5.5 ml.) was slowly added, followed by 10% sodium hydroxide (5 ml.) and the stirring was continued for a further 3 hr. The solution was filtered and the filtrate dried over potassium hydroxide for 18 hr. Anhydrous hydrogen chloride was then passed through the solution for 1 hr., during which time a bulky precipitate (16.3 g., 0.0683 mole, 99%) formed. The solid was recrystallized from ethanol–acetone (3:2) giving a pure white salt, m.p. 288.5° (9.6 g., 58%).

Anal. Calcd. for $C_{10}H_{18}N_2 \cdot 2HCl$: C, 50.20; H, 8.43; N, 11.71. Found: C, 50.16; H, 8.23; N, 11.58.

2,3-Diacetoxycyclohexa-1,3-diene.—Cyclohexane-1,2-dione, acetic anhydride, and boron trifluoride etherate were purified by distillation, then the dione (6.5 g. 0.058 mole) and acetic anhydride (15 ml.) were added to a dry, nitrogen purged flask and boron trifluoride etherate (1 ml.) was added to the solution

(25) K. Alder, F. H. Flock, A. Hausweiler, and R. Reeber, *Chem. Ber.*, **87**, 1752 (1954).

(26) O. Diels and K. Alder, *Ann.*, **490**, 236 (1931).

through which nitrogen was passed. The flask containing the solution, covered by an atmosphere of nitrogen, was tightly stoppered and allowed to stand at room temperature for 2 days.

The brown liquid was then distilled under nitrogen giving a clear liquid (4.35 g., 0.022 mole, 38%), b.p. 54° (1 mm.). The distillate showed only ester absorption in the infrared.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.10; H, 6.21.

Bis-2,3,5,6-(N-phenyl-*vic*-triazolino)bicyclo[2.2.1]heptane (Phenyl Azide–Norbornadiene Adduct).—A 76-ml. carbon tetrachloride solution containing 12.0 g. (0.10 mole) of phenyl azide was added to 4.6 g. (0.05 mole) of bicyclo[2.2.1]heptadiene. The pale green precipitate which first appeared after 12 hr. at room temperature was collected after 48 hr. A yield of 9.1 g. (55%), m.p. 229° dec., was obtained. This material proved insoluble in the usual solvents. Recrystallization was effected, however, in nitrobenzene (7.3 g., m.p. 229° dec.). The once recrystallized material was boiled with absolute ethanol and chloroform, to give analytically pure material (6.7 g., 41%), m.p. 229° dec.

Anal. Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49. Found: C, 69.07; H, 5.64.

This compound reacts to form a bright blue solution on treatment with glacial acetic acid.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Acid[1]

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Received March 14, 1963

Bicyclo[2.2.2]octane-1,2-dicarboxylic acid has been synthesized *via* the reaction of dimethyl 1,3-cyclohexadiene-1,6-dicarboxylate with maleic anhydride (Chart I) and *via* the reaction of ethyl 1,3-cyclohexadiene-1-carboxylate with ethyl acrylate (Chart II). The latter reaction affords the four possible Diels–Alder adducts in the ratio of 30 (head-to-head *endo*): 8 (head-to-tail *endo*): 5 (head-to-head *exo*): 1 (head-to-tail *exo*). Stereochemical and structural assignments for the intermediates in the syntheses are described.

As part of a program for the investigation of the behavior of cyclic diacyl peroxides,[2] an aliphatic six-membered cyclic diacyl peroxide was desired. Since peroxides prepared from the cyclohexane-1,2-dicarboxylic acids have been reported to be unstable,[3] a requirement placed on the system at the outset was a structure in which bisdecarboxylation would be difficult. The system selected was bicyclo[2.2.2]octane-1,2-dicarboxylic acid (**9**). The preparation and proof of structure of compounds in this series are reported in this paper.

Bicyclo[2.2.2]octane-1,2-dicarboxylic acid (**9**) was prepared by two routes. The chemical evidence for the structural assignments is summarized in Charts I, II, and III. A higher over-all yield of **9** was obtained from the (less direct) route shown in Chart I, patterned after a synthesis reported by Grob, Ohta, Renk, and Weiss.[4] However, the Diels–Alder reaction between ethyl 1,3-cyclohexadiene-1-carboxylate and ethyl acrylate (Chart II) shows a fourfold preference for the formation of head-to-head adducts over the head-to-tail adducts; and this preference for head-to-head reaction, coupled with the ease of separation of 1,2-diacid **9** from 1,3-diacid **17** by means of the cyclic anhydride **10**, renders route II a reasonable one for compound **9**.

A few aspects of structure require amplification: (a) the structure of the product **3** of the base-catalyzed isomerization of dimethyl 1,4-cyclohexadiene-1,2-dicarboxylate (**2**); and (b) the stereochemistry of **7**, **19**, and **4**.

Isomerization of 2.—Structure **2**, expected by the method of synthesis, is supported by the ultraviolet (λ_{max}^{MeOH} 239, ϵ 2259)[5] and n.m.r. data. The n.m.r. spectrum exhibits three regions of absorption of area ratio 2:4:6 at 4.21 τ [one band weakly split into a triplet (vinyl H)]; 7.06 τ [one band weakly split into a doublet (methylene)]; and 6.30 τ [singlet (methyl)]. Compound **2** is readily isomerized by base. Of the six possible diene diesters, the new isomer is assigned structure **3** on the basis of the n.m.r. spectrum (five regions of absorption of area ratio 1:2:6:1:2 at 3.02 τ [broadened triplet (1 vinyl H)]; 3.96 τ [multiplet (2 vinyl H's)]; 6.27 and 6.38 τ [two sharp singlets (6 methyl H's)]; 6.5 τ [multiplet, partly obscured by the methyl peaks (1 tertiary H)]; 6.83–7.98 τ [complex multiplet (2 methylene H's)]. Further support for this assignment is found in the infrared absorption at 1710 and 1735 cm.$^{-1}$ (both conjugated and unconjugated esters) and the ultraviolet absorption at λ_{max} 288 (ϵ 8120) [compare with ethyl 1,3-cyclohexadiene-1-carboxylate **14**, λ_{max} 292 (ϵ 8260)]. That no further isomerization of **3** occurs during the Diels–Alder reaction with maleic anhydride may be concluded from an examination of Charts I and III and the spectral data cited in the Experimental section.

The base-catalyzed isomerization of **2** to **3** rather than to either of the two conjugated isomers (1,2-dicarbomethoxy-1,3-cyclohexadiene or 2,3-dicarbomethoxy-1,3-cyclohexadiene) is probably associated with the unfavorable steric situation between the adjacent ester groups in the latter two cases. The ester groups in **3** may be staggered, permitting full conjugation of one of the groups with the diene system.[6a]

Stereochemistry of 7 and 19.—Compound **7** may be isomerized by sodium methoxide in methanol, affording a mixture in which the *endo* isomer **19** predominates over the *exo* isomer **7** by a ratio of 3.5 to 1.[6b] The assignment of the *exo* structure to **7** and the *endo* to **19** is based on the inability of the former, and the ability of the latter, to afford a bromo lactone (Chart III). In addition, examination of the n.m.r. and

(1) Supported in part by the research program of the Atomic Energy Commission under Contract No. AT(30-1)-905. Reproduction is permitted for any purpose of the U. S. Government.

(2) See F. D. Greene and W. W. Rees, *J. Am. Chem. Soc.*, **80**, 3432 (1958).

(3) W. von E. Doering, M. Farber, and A. Sayigh, *ibid.*, **74**, 4370 (1952).

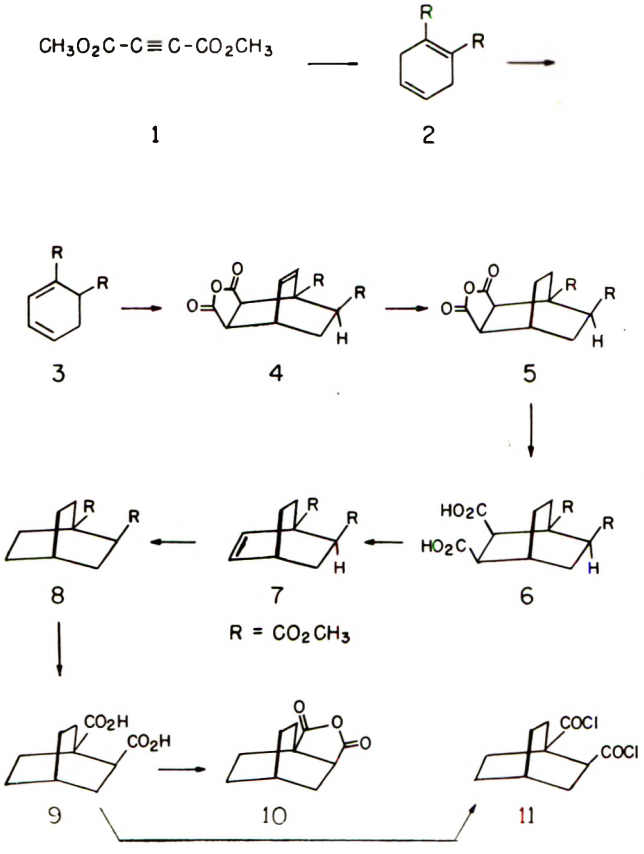
(4) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).

(5) For related cases, see A. T. Nielson, *J. Org. Chem.*, **22**, 1539 (1957).

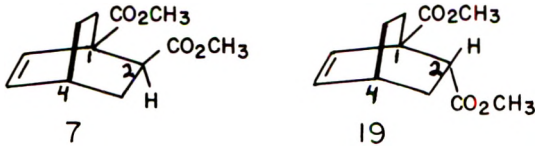
(6) (a) The positions of equilibria in cyclohexadienes present a number of points of special interest. W. von E. Doering, Abstracts, Carbanion Symposium, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963. (b) In methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate the *endo–exo* ratio is 51.5:48.5 [A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959)].

CHART I

SYNTHESIS OF BICYCLO[2.2.2]OCTANE-1,2-DICARBOXYLIC ACID AND ITS DERIVATIVES *via* MALEIC ANHYDRIDE ROUTE



mass spectra[7] of these isomers indicates that the stereochemistry also may be assigned by either of these physical methods.



(superimposed) 7.2–7.6 τ .... { H at C-2 ..... 6.8–7.1 τ quartet (four roughly equal peaks) / H at C-4 ..... 7.2–7.6 τ (broad)
(singlet) 6.32 τ . . . . H's of 1-$COOCH_3$. . 6.31 τ (singlet)
(singlet) 6.40 τ . . . . H's of 2-$COOCH_3$. . 6.46 τ (singlet)
(two unequal peaks) 3.65–3.8 τ . . . . vinyl H's . . . . . 3.34–4.0 τ (five major peaks)

The principal n.m.r. distinction between the *exo* and the *endo* isomers arises from the magnetic shielding effect of the 5,6-double bond at the region of C-2 that is *endo* to the double bond.[8] The methyl peak of the C-2 carbomethoxy group may be expected to appear at higher field in **19** than in **7** and the C-2 hydrogen may be expected to appear at higher field in **7** than in **19**. Such differences are seen in the n.m.r. spectra of the *endo* and *exo* isomers, and this assignment of configuration is in accord with the conclusion from the chemical data (Chart III). A further difference in the n.m.r. spectrum is seen in the vinyl region. This region is more complex and broad in **19** than in **7**, ascribed to the magnetic shielding effect of the carbon-oxygen double

(7) The mass spectral distinction was suggested and elucidated by Dr. Klaus Biemann of this department.

(8) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 129.

CHART II

SYNTHESIS OF BICYCLO[2.2.2]OCTANE-1,2-DICARBOXYLIC ACID *via* ETHYL ACRYLATE

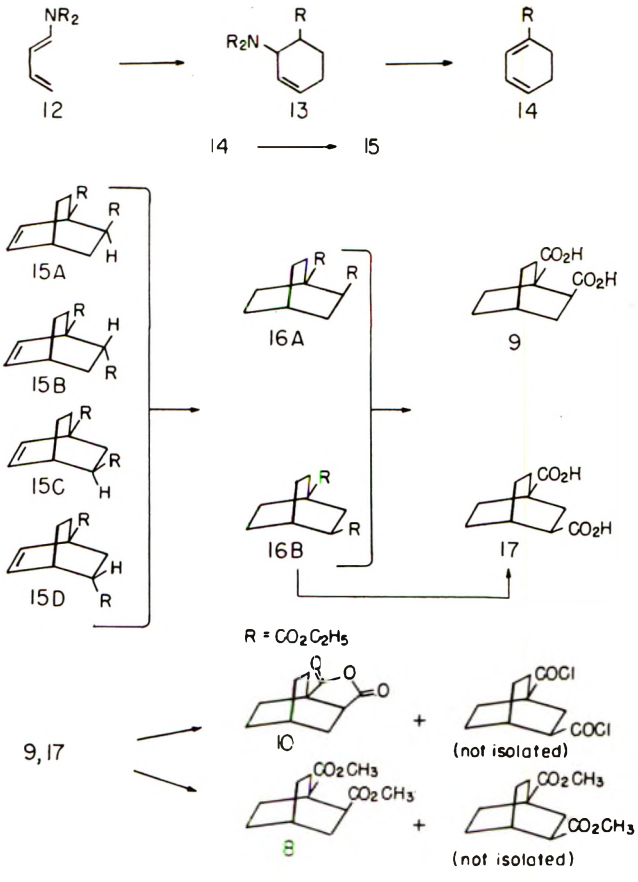
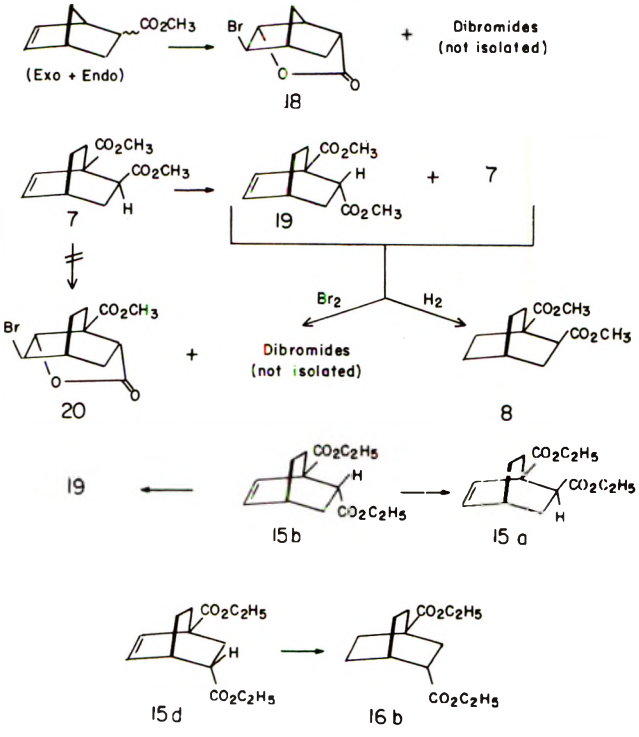


CHART III

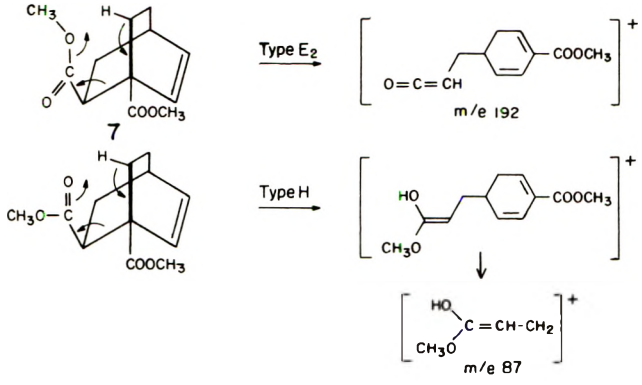
STRUCTURAL CONFIRMATION AND CORRELATION OF THE INTERMEDIATES OF THE TWO SYNTHESES



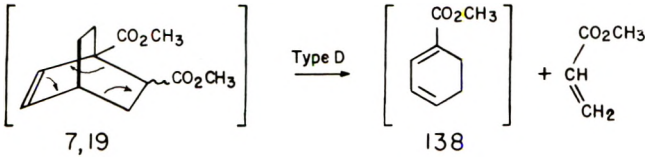
bond of the *endo*-carbomethoxy group on the C-6 hydrogen.

The mass spectrometric distinction between the two isomers is associated with the proximity in **7** of the 2-

carbomethoxy group to a hydrogen atom of the saturated bridge. The spectrum of **7** shows intense peaks *m/e* 192 (associated with type E_2 fragmentation leading to the M − 32 ion) and *m/e* 87 (associated with type H fragmentation). Both peaks are also present in **19** but at approximately one-fifth the intensity. These cases and others are discussed in more detail elsewhere.[9]



Both **7** and **19** exhibit strong peaks at *m/e* 138, associated with cleavage of type D, a process not appreciably influenced by the stereochemistry of the carbomethoxy group.



Stereochemistry of 4.—The orientation of the 2-carbomethoxy group *endo* to the double bond in compound **4** is derived from the assignment of the *exo* structure to **7** and is supported by n.m.r. analysis in two ways: (a) the methyl band for the 2-carbomethoxy group appears at higher field (6.38 τ) in the spectrum of compound **4** than in the spectrum of its hydrogenation product **5** in which it is found at 6.33 τ; (b) the vinyl region of **4** bears a strong resemblance to the vinyl region of compound **19** (*cf.* discussion of stereochemistry of **7** and **19**). The orientation of the anhydride group *endo* to the double bond in **4** is based on the Alder rule analogies.[10]

Stereochemistry of 15A–D.—The Diels–Alder reaction of ethyl 1,3-cyclohexadiene-1-carboxylate and ethyl acrylate (Chart II) affords all four possible isomers. The expected, and observed, major product is the 2-*endo* isomer **15B**, which constitutes 68% of the diester mixture. Diesters **15D, A,** and **C** constitute 18, 11, and 2.3% of the mixture. The basis for the assignment of structure and stereochemistry of the major product **15B** is shown in Charts II and III. The structural assignments of **15A, B,** and **D** rest on the chemical relations shown. The *endo* and *exo* distinction between **15D** and **C** is based on the Alder rule analogies.[10]

Experimental

The order of description of experiments parallels the order of presentation in Charts I, II, and III. All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird Model B, Perkin-Elmer Model 21, or Perkin-Elmer Infracord spectrophotometer; ultraviolet spectra were determined with a Cary recording spectrophotometer; n.m.r. spectra were determined on a Varian A-60 with internal reference by tetramethylsilane. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

Dimethyl acetylenedicarboxylate (**1**) was prepared[11] in 75% yield, b.p. 97–99° (23 mm.) [lit.[11] b.p. 95–98° (19 mm.)].

Dimethyl 1,4-cyclohexadiene-1,2-dicarboxylate (**2**) was prepared by the method of Sopov and Miklashevskaya[12] in 94% yield, b.p. 92–93° (0.3 mm.), $n^{25}D$ 1.4918, $n^{19}D$ 1.4941 [lit.[12] b.p. 138.5–139.5° (10 mm.), $n^{20}D$ 1.4950].

The ultraviolet spectrum of the product in methanol has a peak at 239 mμ (ϵ 2259); the infrared spectrum (CCl_4) exhibits bands at 1710 and 1660 cm.$^{-1}$.

Dimethyl 1,3-Cyclohexadiene-1,6-dicarboxylate (**3**).—To 100 ml. of absolute methanol–sodium methoxide [prepared from 0.87 g. (0.0307 g.-atom) of sodium] was added 30 g. (1.53 moles) of **2** under a nitrogen atmosphere. After 30 min. 2.53 g. (0.0422 mole) of glacial acetic acid was added to neutralize the base. The bulk of the methanol was removed under reduced pressure and the residue was extracted with 500 ml. of ether. The ethereal solution was washed with 275 ml. of water in two portions, and 75 ml. of saturated sodium bicarbonate, and then dried over anhydrous magnesium sulfate. The ether solution was separated from the drying agent, and the ether was removed by distillation. Fractionation of the residue gave 27.4 g. (91.5%) of dimethyl 1,3-cyclohexadiene-1,6-dicarboxylate (**3**) boiling at 85–93° (0 055 mm.); the refractive index of the fraction boiling at 90–93° (0.055 mm.) was $n^{25}D$ 1.5039. Gas–liquid phase chromatography (g.l.p.c.) indicated that the material was 92% **3**, 8% **2**. A sample of **3** was collected by g.l.p.c. for analytical and spectral data.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.19; H, 6.17. Found: C, 61.30; H, 5.96.

The ultraviolet spectrum of the product in methanol has a peak at 288 mμ (ϵ 8120); the infrared spectrum (CCl_4) exhibits bands at 1710, 1735 and 1650 cm.$^{-1}$ attributed to a conjugated ester group, unconjugated ester group, and carbon–carbon double bonds.

1-Carbomethoxy-2-*endo*-carbomethoxybicyclo[2.2.2]oct-5-ene-7,8-*endo*-dicarboxylic Anhydride (**4**).—To 6.38 g. (0.033 mole) of **3** was added 3.21 g. (0.033 mole) of maleic anhydride (crystallized from chloroform). The mixture was heated on a steam bath for 2 hr. The resulting yellow solution when cooled to room temperature solidified to a viscous semisolid material. An equal volume of ether was added, and the mixture was stirred and scratched, whereupon the substance crystallized to a white solid. Filtration gave 7.82 g. of crude material. Recrystallization from chloroform–hexane gave 7.21 g. (75%) of **4** in the form of colorless prisms, m.p. 125.5–127.5°. A portion of the material recrystallized three times from the same solvent mixture, melted at 126.5–127.5°.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.12; H, 4.80. Found: C, 57.09; H, 4.64.

The ultraviolet spectrum of the compound in methanol does not show a maximum above 210 mμ; the infrared spectrum ($CHCl_3$) exhibits bands at 1780 and 1860 cm.$^{-1}$ attributed to the anhydride group, and a band at 1740 cm.$^{-1}$ attributed to unconjugated ester groups.

1-Carbomethoxy-2-*endo*-carbomethoxybicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Anhydride[13] (**5**).—A sample of **4**, 27.5 g. (0.094 mole), was dissolved in 100 ml. of tetrahydrofuran (distilled from lithium aluminum hydride, b.p. 66°). The solution was added to a suspension of 2.8 g. of reduced platinum oxide in 50 ml. of tetrahydrofuran and the mixture was hydrogenated under atmospheric pressure. Hydrogen uptake amounted to 0.095 mole. Following the removal of the catalyst the solution was concentrated until crystallization occurred. Three crops of crystals were obtained, the last upon addition of hexane,

(9) K. Biemann, "Applications of Mass Spectroscopy to Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1962, p. 148–151.

(10) M. C. Kloetzel, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 10; I. N. Nazarov, A. I. Kuznetsova, and N. V. Kuznetsov, *J. Gen. Chem. USSR*, **25**, 75 (1955); J. C. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(11) E. H. Huntress, T. E. Lesalie, and J. Bornstein, *Org. Syn.*, **32**, 55 (1952).

(12) W. P. Sopov and V. S. Miklashevskaya, *J. Gen. Chem. USSR*, **26**, 2133 (1956).

yielding 25.8 g. (93%) of **5** in the form of colorless plates, m.p. 156.5–157.5°. Sublimation and crystallization from tetrahydrofuran–hexane of a portion of the product gave a material melting at 157.7–158°.

Anal. Calcd. for $C_{14}H_{16}O_7$: C, 56.73; H, 5.45. Found: C, 56.73; H, 5.58.

The infrared spectrum ($CHCl_3$) of the product exhibits bands at 1790 and 1860 cm.$^{-1}$ attributable to the anhydride group and a band at 1740 cm.$^{-1}$ attributable to the presence of unconjugated ester groups.

1-Carbomethoxy-2-*endo*-carbomethoxybicyclo[2.2.2]octane-5,6-*endo*-dicarboxylic Acid[13] (**6**).—To 96 ml. of 20% potassium carbonate was added 24 g. of **5**. The mixture was stirred and heated on a steam bath until a homogeneous solution was obtained. The solution was cooled to 0° and sufficient concentrated hydrochloric acid was added to make the mixture acidic. Filtration and crystallization of the material from water gave 23.1 g. (92%) of **6** in the form of colorless prisms, m.p. 150–152°. A sample of the material, heated and sublimed under reduced pressure, regenerated the anhydride **5** identical in infrared spectrum and showing no melting point depression. A sample of the material, recrystallized from chloroform–hexane, melted at 151–152°.

Anal. Calcd. for $C_{14}H_{18}O_8$: C, 53.48; H, 5.78; neut. equiv., 157. Found: C, 53.60; H, 5.81; neut. equiv., 154.

The infrared spectrum of the compound (KBr pellet) exhibits bands at 1700 (acid) and 1740 cm.$^{-1}$ (ester).

Dimethyl Bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (**7**).—To 83 ml. of anhydrous benzene under a nitrogen atmosphere was added 14.79 g. (0.0471 mole) of **6**, 5.59 g. (0.0707 mole) of anhydrous pyridine, and 22 g. (0.0471 mole) of lead tetracetate (crystallized from glacial acetic acid). The mixture was heated to the reflux temperature with stirring. Before this point was reached the solid dissolved, and a vigorous evolution of carbon dioxide occurred. The solution was refluxed for 2 hr. during which time a white precipitate formed. The solution was separated from the solid and washed with 30 ml. of 2 *N* sodium carbonate. 40 ml. of 2 *N* hydrochloric acid, and 10 ml. of water. The solution was dried over magnesium sulfate and the bulk of the benzene was removed by fractional distillation. Addition of ether to the residue precipitated 1.9 g. of **5**. Fractionation of the residue under reduced pressure gave 5.21 g. (50%) of **7** boiling at 86–87° (0.26 mm.), $n^{25}D$ 1.4838.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.24; H, 7.20. Found: C, 63.98; H, 7.25.

The infrared spectrum of the product exhibits bands at 1740 and 1620 cm.$^{-1}$ attributable to unconjugated ester groups and a carbon–carbon double bond.

Dimethyl Bicyclo[2.2.2]octane-1,2-dicarboxylate (**8**).—To 5 ml. of absolute methanol was added 0.25 g. of platinum oxide. The catalyst was reduced and 2.49 g. of **7** dissolved in 6 ml. of methanol was added. Upon completion of the hydrogenation (uptake 95%) the solution was separated from the catalyst and the bulk of the methanol was removed by fractional distillation. Fractionation of the residue under reduced pressure gave 2.34 g. (93%) of **8**, b.p. 84–85° (0.35 mm.), $n^{25}D$ 1.4778.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.68; H, 8.02. Found: C, 63.65; H, 8.34.

The infrared spectrum (CCl_4) exhibits a band at 1740 cm.$^{-1}$ attributable to the unconjugated ester groups.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Acid (**9**).—To 8 ml. of 75% methanol was added with stirring 1.49 g. (0.0265 mole) of potassium hydroxide. When the base had dissolved 2 g. (0.00885 mole) of **8** was added and the mixture was stirred and refluxed for 4 hr. After cooling the solution, the bulk of the methanol was removed under reduced pressure and the residue was diluted with 50 ml. of water. The resulting solution was cooled to ice-bath temperature and acidified with concentrated hydrochloric acid. The mixture was extracted with several portions of ether and the resulting ethereal solution was dried over anhydrous magnesium sulfate. The ether solution was separated from the drying agent and the solvent was removed on a steam bath. Recrystallization from water gave 1.49 g. (85%) of **9**, m.p. 188–190°. A sample of the material, recrystallized from water three times, gave colorless prisms, m.p. 200–201°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.57; H, 7.12. Found: C, 60.64; H, 7.20.

The infrared spectrum (KBr pellet) exhibits a broad band at 1700 cm.$^{-1}$ attributable to unconjugated acid groups.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Anhydride (**10**).—To 20 ml. of thionyl chloride, under anhydrous conditions, was added 1 g. of previously dried **9**. The mixture was stirred at reflux until solution occurred (1 hr.). The thionyl chloride was removed under reduced pressure. Crystallization of the residue from cyclohexane gave 0.82 g. (92%) of **10** in the form of colorless plates, m.p. 163.5–164.5°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.71. Found: C, 66.67; H, 6.76.

The infrared spectrum (CCl_4) exhibits bands at 1800, 1875, and 1200 cm.$^{-1}$ attributable to a cyclic 5-membered anhydride.

Bicyclo[2.2.2]octane-1,2-dicarbonyl Chloride (**11**).—To 15 g. (0.076 mole) of dry **9** under a nitrogen atmosphere was added 31.8 g. (0.152 mole) of phosphorus pentachloride. The solids were mixed by shaking, whereupon an exothermic reaction occurred, accompanied by the formation of a liquid. When the reaction had subsided the mixture was heated to 140° and kept at this temperature, with stirring, for 16 hr. Fractionation of the liquid under reduced pressure gave 16.7 g. (95%) of **11**, b.p. 121–122° (0.3 mm.), $n^{25}D$ 1.5199.

The infrared spectrum (CH_2Cl_2) showed a strong band at 1800 cm.$^{-1}$ attributable to the acyl chloride groups and weak band at 1870 cm.$^{-1}$ attributable to the small quantity of cyclic anhydride which codistills with the acid chloride.

1-Diethylaminobutadiene (**12**) was prepared by the method of Hünig and Kahanek[14] in 42% yield, b.p. 66–67° (9–10 mm.) [lit.[21] b.p. 64–66° (10 mm.)].

Ethyl *cis*-2-diethylaminocyclohex-3-ene-1-carboxylate (**13**) was prepared by the reaction of **12** with ethyl acrylate[14] in 72% yield, b.p. 70–76° (0.07–0.14 mm.) [lit.[14] b.p. 80–83° (0.2 mm.)].

Ethyl 1,3-cyclohexadiene-1-carboxylate (**14**) was prepared from **13** by the method of Grob, Ohta, Renk, and Weiss[4] in 50% yield, b.p. 98–100° (17 mm.), $n^{25}D$ 1.4988 [lit.[4] b.p. 90–92° (11 mm.)].

The ultraviolet spectrum of the product in ethanol has a maximum at 292 mμ (ε 8260); the infrared spectrum (CCl_4) exhibits bands at 1710 and 1640 cm.$^{-1}$ attributable to a conjugated ester and carbon–carbon double bonds.

***exo* and *endo* Isomers of Diethyl Bicyclo[2.2.2]oct-5-ene-1,2-(and 1,3)-dicarboxylate** (**15**).—To 75 mg. of hydroquinone was added 9.8 g. (0.0981 mole) of freshly distilled ethyl acrylate (b.p. 99°) and 5 g. (0.0327 mole) of **14**. The resulting solution was refluxed under nitrogen in the dark for 24 hr. and then was allowed to stand for 20 hr. at 0°. Fractionation gave 4.16 g. (50%) of a pale yellow liquid boiling at 90–94° (0.03 mm.). Gas–liquid chromatography indicated a mixture of four major components in the ratio of 5:30:1:8 (listed in the order of elution). They were assigned as follows: diethyl bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (**15A**), diethyl bicyclo[2.2.2]oct-5-ene-1,*endo*-2-dicarboxylate (**15B**), diethyl bicyclo[2.2.2]oct-5-ene-1,-*exo*-3-dicarboxylate (**15C**), and diethyl bicyclo[2.2.2]oct-5-ene-1,-*endo*-3-dicarboxylate (**15D**). The ratio of **A** + **B** *vs.* **C** + **D** was 3.9 to 1. The esters were separated on a preparative g.l.p.c. column containing 25% 550 silicone oil on 60–80-mesh Chromosorb P (Johns Mansville firebrick). Ester **15C** was not isolated.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.63; H, 7.99. Found for **15A**: C, 66.03; H, 8.16. Found for **15B**: C, 66.38; H, 8.02. Found for **15D**: C, 66.97; H, 8.11.

The infrared spectra of the esters (CCl_4) exhibit bands at 1730 and 1615 cm.$^{-1}$ attributable to unconjugated ester groups and a carbon–carbon double bond. The spectra of the three isolated esters were very similar with only minor differences in the fingerprint region.

Diethyl Bicyclo[2.2.2]octane-1,2(and 1,3)-dicarboxylate (**16**).—To 200 mg. of platinum oxide was added 5 ml. of 95% ethanol. The catalyst was reduced and 2 g. (0.00994 mole) of **15** was added in 5 ml. of ethanol. Upon completion of the hydrogenation (uptake 0.01 mole of hydrogen) the solution was separated from the catalyst and the solvent was removed under reduced pressure. Fractionation of the residue gave 1.82 g. (95%) of a colorless liquid, b.p. 110–113° (0.07 mm.). Two major components were shown by g.l.p.c. in the ratio of 3.8 to 1, assigned as **16A** and **16B**, respectively. The two components were separated on a

(13) The *endo* designation for **5** and **6** refers to a *syn* relation of a substituent to the *unsubstituted bridge*. In all other cases the *endo* designation refers to a *syn* relation of a substituent to an *unsaturated* bridge.

(14) S. Hünig and H. Kahanek, *Chem. Ber.*, **90**, 238 (1957).

g.l.p.c. column containing 25% 550 silicone oil on 60–80-mesh Chromosorb P.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.10; H, 8.73. Found for **16A**: C, 66.04; H, 8.81. Found for **16B**: C, 66.16; H, 8.75.

The infrared spectra of the esters (CCl_4) show a band at 1730 cm.$^{-1}$ (ester). The spectra of the two esters are very similar with only minor variations in the fingerprint region.

Bicyclo[2.2.2]octane-1,2(and 1,3)-dicarboxylic Acid (9, 17).—To a solution of 0.8 g. (0.00315 mole) of **16** in 8 ml. of absolute ethanol was added 0.53 g. (0.00945 mole) of potassium hydroxide and 2 ml. of water. The solution was refluxed for 4 hr. At the end of this period the bulk of the ethanol was removed under reduced pressure and 10 ml. of water was added. The resulting solution was acidified with concentrated hydrochloric acid and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration of the mixture and evaporation of the solvent gave 0.61 g. of a yellow solid, a mixture of **9** and **17**. A 95-mg. sample of this mixture was treated with 2.5 ml. of thionyl chloride for 2 hr. Evaporation of the excess thionyl chloride and recrystallization of the residue from cyclohexane afforded 31 mg. of bicyclo[2.2.2]octane-1,2-dicarboxylic anhydride (**10**), m.p. 163–164°, m.m.p. 163–164°, identical in infrared spectrum with the material prepared by the sequence of Chart I.

A second portion of the mixture of **9** and **17** (0.3 g.) was dissolved in ether and treated with ethereal diazomethane. Ether was removed through a Vigreux column and the residue was distilled to give 0.21 g. of a colorless liquid. Two components were indicated by g.l.p.c. in the ratio of 2 to 1. The compounds were separated on a g.l.p.c. column containing 25% 550 silicone oil on 60–80-mesh Chromosorb P. The major component had the same retention time and infrared spectrum as **8**.

Bicyclo[2.2.2]octane-1,3-dicarboxylic Acid (17).—To 42 mg. (0.000163 mole) of **16B** was added 1.24 ml. of absolute ethanol. To this was added 0.326 ml. of a solution of 8.3 g. of potassium hydroxide in 100 ml. of water (27.4 mg., 0.000489 mole). The resulting solution was refluxed for 4 hr. Water (10 ml.) was added and the solution was acidified with concentrated hydrochloric acid. The acidified solution was extracted with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave 62 mg. of a yellow semisolid material. Sublimation and crystallization from acetone–hexane gave 14 mg. (44%) of **17** in the form of colorless needles, m.p. 206–208°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.57; H, 7.12. Found: C, 60.44; H, 7.02.

The infrared spectrum (KBr) has a band at 1700 cm.$^{-1}$ attributable to carboxylic acid functions. The spectrum was similar to that of **9** with only minor differences in the fingerprint region.

Bromo Lactone in the Bicyclo[2.2.1]heptane System (18).—To a stirred solution of 5 g. (0.0328 mole) of a *endo* and *exo* methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate in 50 ml. of chloroform, cooled to 0°, was added dropwise 5.3 g. (0.0328 mole) of bromine. When the addition of the bromine was complete the solvent was removed under reduced pressure, giving a dark green oil (color developed during concentration). Decolorization with Norit and crystallization from ether–pentane gave 3.3 g. (62% based on the amount of *endo* isomer) of the bromo lactone of bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid in the form of colorless cubic crystals, m.p. 68–70°. A sample recrystallized from ether–pentane afforded material of melting point 67.5–69° (lit.[15] m.p. 67.5–68.5°).

The infrared spectrum ($CHCl_3$) has bands at 1775 and 1010 cm.$^{-1}$ attributable to the five-membered ring lactone.

Dimethyl Bicyclo[2.2.2]oct-5-ene-1,*endo*-2-dicarboxylate (19).—To 15 ml. of absolute methanol–sodium methoxide solution (from 51 mg. of sodium) under a nitrogen atmosphere was added 500 mg. (0.00233 mole) of **7**. The resulting pale yellow solution was refluxed under nitrogen for 13.5 hr., cooled, and 134 mg. (0.00223 mole) of glacial acetic acid was added. The methanol was removed under reduced pressure. Ether and water were added to the residue and the water solution was further extracted with ether. The combined ether extracts were washed with 10% sodium bicarbonate and water and dried over anhydrous magnesium sulfate. The solution was filtered and the ether was removed under reduced pressure. Distillation of the residue gave 352 mg. (70%) of a yellow liquid. Gas–liquid chromatography indicated two compounds in the ratio of 3.5 to 1. Comparison of retention indicated that the smaller peak was the starting material. Since, as indicated subsequently, reduction of the mixture gave only one component, **8**, the major component was designated as **19**. The two components were separated on a g.l.p.c. column containing 25% 710 silicone oil on 80–100-mesh Chromosorb P. The major component **19** crystallized and was recrystallized from pentane giving colorless cubic crystals, m.p. 44–45.5°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.24; H, 7.21. Found: C, 64.17; H, 7.21.

The infrared spectrum (CCl_4) of **19** had bands at 1730 and 1615 cm.$^{-1}$ attributable to an unconjugated ester group and a carbon–carbon double bond. The n.m.r. data are given in the discussion.

Dimethyl Bicyclo[2.2.2]octane-1,2-dicarboxylate (8).—Platinum oxide (10 mg.) was suspended in 1 ml. of absolute methanol, the catalyst was reduced, and 75 mg. (0.00334 mole) of the mixture containing **19** and **7** was added in 1.5 ml. of methanol. The amount of hydrogen absorbed was 0.0036 mole. Removal of the methanol under reduced pressure gave 72 mg. (94%) of a liquid, identical in infrared spectrum with **8**. Gas–liquid chromatography showed only one component which had the same retention time as **8**.

Bromo Lactone in Bicyclo[2.2.2]octane System (20).—To 2 ml. of methanol-free chloroform (passed through silica gel) cooled to 0° was added 100 mg. (0.000446 mole) of ester mixture **19** and **7** (80% **19**) and 71 mg. (0.000446 mole) of bromine in 2 ml. of chloroform. The reaction mixture was allowed to stand in the dark for 24 hr. at 0°. The resulting solution was washed with 5 ml. of 5% sodium sulfite, 5 ml. of water, and 5 ml. of saturated sodium chloride solution, and dried over magnesium sulfate. The chloroform was removed under reduced pressure leaving 172 mg. of a pale yellow oil. Addition of a small amount of ether caused the oil to crystallize to a white solid weighing 63 mg., m.p. 124–130°. Recrystallization from ether–pentane gave 43 mg. (44% based on the amount of *endo* isomer) of the bromo lactone of 1-carbomethoxybicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid, m.p. 128.5–129.5°. A sample recrystallized from acetone–hexane melted at 129–130°.

Anal. Calcd. for $C_{11}H_{13}O_4Br$: C, 45.67; H, 4.53; Br, 27.65. Found: C, 45.63; H, 4.52; Br, 27.92.

The infrared spectrum ($CHCl_3$) has bands at 1730 and 1790 cm.$^{-1}$ attributable to an unconjugated ester group and a 5-membered lactone.

Attempted Lactonization of Dimethyl Bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (7).—A sample of **7** was subjected to the preceeding bromination conditions, employing the same work-up procedure. Evaporation of the chloroform gave 165 mg. of a pale yellow oil which could not be crystallized. The infrared spectrum of the oil ($CHCl_3$) showed a band at 1730 cm.$^{-1}$ attributable to unconjugated ester groups. There was no band in the region where lactone absorption is expected.

Dimethyl Bicyclo[2.2.2]octane-1,*endo*-2-dicarboxylate (19) from Diethyl Bicyclo[2.2.2]octane-1,*endo*-2-dicarboxylate (15B).—To 75 mg. (0.000298 mole) of **15B** (containing 0.6% of **15A**) under a nitrogen atmosphere, was added 5 ml. of collidine and 399 mg. (0.00298 mole) of pulverized lithium iodide. The mixture was refluxed under nitrogen for 24 hr. After cooling, the reaction mixture was poured into a mixture of 5 ml. of concentrated hydrochloric acid and 5 g. of ice. The resulting yellow solution was extracted with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether under reduced pressure gave 65 mg. of a pale yellow semisolid material.

The crude solid was dissolved in 10 ml. of ether, cooled to 0°, and treated with an ethereal solution of diazomethane. The latter was added until a permanent yellow color occurred. The excess diazomethane was decomposed with 4 drops of glacial acetic acid. Evaporation of the ether under reduced pressure gave 74 mg. of a yellow oil. Gas–liquid chromatography of the liquid indicated two components in the ratio of 33 to 1. Comparison with mixture **19**, **7** indicated that the compounds had the same retention times. Purification of the major component on a column containing 25% 710 silicone oil on 80–100-mesh Chromosorb P gave a colorless oil which was crystallized from pentane. The infrared spectrum of the solid (CCl_4) was the same as the spectrum of **19**.

Diethyl Bicyclo[2.2.2]oct-5-ene-1,*exo*-2-dicarboxylate (15A) from Its *endo* Isomer 15B.—To 23.3 mg. (0.093 mmole) of **15B** under a nitrogen atmosphere was added 0.41 ml. of a 0.228 *M*

(15) C. D. VerNooy and C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **77**, 3583 (1955).

solution of ethanolic sodium ethoxide, and 7.5 ml. of absolute ethanol. The resulting solution was refluxed for 20 hr. under nitrogen. At the end of this period 5.6 mg. (0.093 mmole) of glacial acetic acid was added to neutralize the base. Evaporation of the solvent under reduced pressure left a small quantity of liquid which was extracted with two 10-ml. portions of ether. Drying of the ethereal solution over magnesium sulfate and evaporation of the solvent gave 10 mg. (43%) of a colorless oil. Gas–liquid chromatography of the oil on a column containing 20% XF-1150[16] on 80–100-mesh Chromosorb P showed two peaks in the ratio of 5 to 1. The lesser component was eluted first and had the same retention time as **15A**. The larger peak had the same retention time as **15B**.

Diethyl Bicyclo[2.2.2]octane-1,3-dicarboxylate (16B) from Diethyl Bicyclo[2.2.2]oct-5-ene-1,*endo*-3-dicarboxylate (15D).—A 12.5-mg. sample of **15D** (containing 4.2% of **15B**) was hydrogenated by platinum oxide in ethanol (1 ml.). Removal of the catalyst and evaporation of the solvent under reduced pressure gave 12.3 mg. (98%) of a colorless liquid giving two peaks on a g.l.p.c. column containing 25% 710 silicone oil on Chromosorb P. The two peaks were in the ratio of 23 to 1. The major component had the same infrared spectrum and retention time as **16B**-

(16) A nitrile–silicon polymer obtained from General Electric.

The Lactones of *cis*- and *trans*-2-Hydroxycycloheptaneacetic Acid[1]

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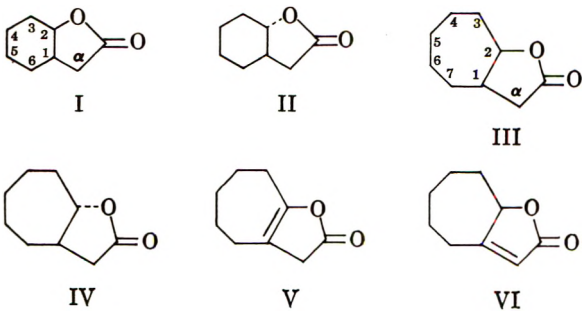
Received May 6, 1963

The *cis*- and *trans*-lactones of 2-hydroxycycloheptaneacetic acid have been prepared and equilibrated at various temperatures. The *cis* isomer predominates slightly in the temperature range 384–423°K. The thermodynamic quantities have been calculated and the conformations are discussed and contrasted with those of the cyclohexane analogs. Two examples of what appears to be partial *cis*-electrophilic addition to the cycloheptene double bond have been observed.

The lactone of *cis*-2-hydroxycyclohexaneacetic acid[3–6] (I) is more stable than the *trans* isomer (II),[7] the *trans* compound being convertible to the *cis* under the influence of sulfuric acid–acetic acid.[3,5] An analogous acid-catalyzed rearrangement is well known in the santonin series where the allylic position of the lactone ether oxygen renders the isomerization more facile,[8] but many other instances of this stability relationship among lactones of substituted 2-hydroxycyclohexaneacetic acid could be cited.[9]

In the last decade, a group of new sesquiterpene lactones has been discovered in which the γ-lactone ring is fused onto the seven-membered ring portion of perhydroazulene skeleton.[10] In discussions dealing with the stereochemistry of the new lactones, it has been tacitly assumed[11] that commonly accepted generalizations about γ-lactones fused onto six-membered rings can be extended to γ-lactones fused onto seven-membered rings. Because of our interest in naturally occurring perhydroazulenic lactones, we decided to examine this supposition by the synthesis and study of the previously unreported title compounds III and IV.



I II III IV V VI

The energetics of *cis*- and *trans*-ring fusion to cycloheptanes have, in the meantime, been considered by Hendrickson,[12] with particular reference to the *cis*- and *trans*-bicyclo[5.3.0]decanes (perhydroazulenes). The conclusion was reached that the energy difference between *cis*- and *trans*-perhydroazulene was likely to be virtually negligible, experimental support for this having been provided by Allinger and Zalkow.[13] When a lactone is substituted for a five-membered ring, inspection of Dreiding models suggests that in the *cis* isomer III the favored twist-chair conformation[12] of the cycloheptane ring may be destabilized somewhat because of angle strain. Of the two *trans*-forms of IV, the 2e-3e isomer appears to be affected only slightly, the 3e-4e isomer more so. The over-all effect is difficult to assess but would not be expected to alter the stability relationships significantly.

Lactone III was prepared from VI, or more conveniently from the mixture of V and VI prepared by cyclization of 2-oxocycloheptaneacetic acid.

Lactone IV was synthesized in a manner similar to that adopted by Newman and Vander Werf[3] for the preparation of II. However, the first step, the reaction of cycloheptene oxide with malonate ion, was exceedingly slow as compared with the analogous reaction of cyclohexene oxide which reacts at least 10 times as rapidly.

The reasons for this difference in reactivity are not quite clear. It has been shown that cyclohexene oxide reacts with methoxide ion about 1.5 times as fast as

(1) Supported in part by a grant from the National Science Foundation (NSF-G 14396).

(2) Abstracted from a thesis submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy, 1963.

(3) M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.*, **67**, 233 (1945).

(4) J. Klein, *J. Org. Chem.*, **23**, 1209 (1958).

(5) J. Klein, *J. Am. Chem. Soc.*, **81**, 3611 (1959).

(6) E. H. Charlesworth, H. J. Campbell, and D. L. Stachiw, *Can. J. Chem.*, **37**, 877 (1959).

(7) S. Coffey, *Rec. trav. chim.*, **42**, 387 (1923).

(8) Y. Abe, T. Miki, M. Sumi, and T. Toga, *Chem. Ind.* (London), 953 (1956); H. Ishikawa, *J. Pharm. Soc. Japan*, **76**, 504 (1956); M. Sumi, *J. Am. Chem. Soc.*, **80**, 4869 (1958); D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962); W. Cocker, B. Donnelly, H. Gobinsingh, T. B. H. McMurray, and M. A. Nisbet, *ibid.*, 1262 (1963).

(9) See, for example, M. Hinder and M. Stoll, *Helv. Chim. Acta*, **36**, 1995 (1953); W. Klyne, *J. Chem. Soc.* 3072 (1953).

(10) The most recent review of this rapidly moving field is already very much out of date, T. Nozoe and S. Ito, *Fortschr. Chem. Org. Naturstoffe*, **19**, 32 (1961).

(11) See, for example, J. W. Huffman, *Experientia*, **16**, 120 (1960). The complications have been recognized by J. B. Hendrickson and R. Rees, *Chem. Ind.* (London), 1424 (1962).

(12) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

(13) N. L. Allinger and V. B. Zalkow, *ibid.*, **83**, 1144 (1961).

cyclopentene oxide,[14] but no data are available on the reaction of cycloheptene oxide. However, a number of reactions are known in which cyclopentane and cycloheptane derivatives react at comparable rates which may be greater or less than the rate of the corresponding cyclohexane derivative.[15-17] The greater susceptibility of cyclohexane oxide to ring opening compared with that of cyclopentene oxide may be attributed to greater relief of eclipsed hydrogen interactions in the cyclohexane oxide system. A further effect is probably operative in cycloheptene oxide where Dreiding models indicate that there may be considerable steric hindrance to nucleophilic displacement of epoxide oxygen by the bulky malonate ion which would result in rate retardation.

Nuclear Magnetic Resonance Spectra.—Since the main objective of this work was the determination of the relative thermodynamic stabilities of lactones III and IV, a method for the analysis of mixtures of III and IV was necessary. In spite of prolonged and tedious efforts, artificial mixtures of III and IV could not be separated satisfactorily by gas liquid chromatography. Also, while the infrared spectra of III and IV were different, the distinguishing bands overlapped and the analysis by this method would have been difficult indeed.

A more than adequate solution to this problem was offered by n.m.r. spectroscopy. Table I lists important n.m.r. peaks of lactones I–IV, whose implications will now be discussed.

TABLE I[a]

Lactone	C_2-H[b]	H$_\alpha$[c]	CH$_2$[d]
I	4.60 q (4)	2.45 m	1.2–2.0 e, 1.55 s
II	3.97 h (10,4)	2.45 n,e	1.33–2.04 e
III	4.75 o	2.66 m	1.2–2.0 e
IV	4.25 n	2.42 m	1.62 s

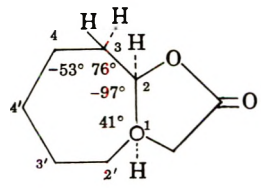
[a] Spectra were determined in CCl_4 solution on Varian HR-60 or A-60 spectrometers. Values in p.p.m. relative to tetramethylsilane as internal standard. Signals are described as follows: e, envelope; h, sextet; m, multiplet of uncertain multiplicity; n, unresolved multiplet; o, octet; s, relative sharp signal corresponding to several protons. Numbers in parentheses denote coupling constants in c.p.s. [b] Intensity one proton. [c] Intensity two protons. [d] Ring protons other than H_2.

C_2-H of I gives rise to a quadruplet at 4.60 p.p.m. characteristic of the A portion of an AX_3 system. The multiplicity indicates that the three adjacent protons have approximately the same dihedral angle, a situation which would prevail in a chair conformation in which C_1-H is axial and C_2-H is equatorial. The dihedral angles are then near 60°. This is in reasonable agreement with experimental values observed elsewhere.[18] However, the observed multiplicity of C_2-H could arise equally well from the time-averaged values of dihedral angles in a system which changes conformations rapidly compared with the spin frequency. Since the methylene region indicates a fair degree of flexibility (*vide infra*), it is not possible to decide between the two alternatives.

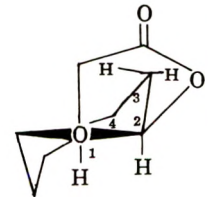
The two α-protons give rise to a complex system of bands centered at 2.45 p.p.m. which appears to contain two triplets at 2.51 (J = 3.5) and 2.38 p.p.m. (J = 2.2). The methylene region contains an envelope from which there projects a relatively sharp high-intensity band at 1.55 p.p.m. This suggests a certain amount of methylene proton equivalence and a reasonable degree of ring flexibility as would be expected from a *cis* isomer.

By contrast, the n.m.r. spectrum of II exhibits only a broad envelope extending from 1.33 to 2.04 p.p.m., but no strong projecting peak. This is consistent with the assumption of a more rigid ring system. The situation is reminiscent of that prevailing in *cis*- and *trans*-hydrindane,[19] with the lactone ring of I and II replacing the alicyclic five-membered ring. The α-protons of II are unresolved, but C_2-H gives rise to a sextet centered at 3.97 p.p.m. which corresponds to X of an A_2BX system (J_{AX} = 10). This indicates that II is a chair in which C_1-H and C_2-H are axial, in accordance with the required *trans*-diequatorial fusion of five- and six-membered rings. The shielding of C_2-H in II, as compared with C_2-H of I, is as expected; the coupling constants are in agreement with the assumption that the dihedral angles between C_2-H and the three adjacent protons are approximately 180, 180, and 60°.

Comparison of the n.m.r. spectra of I and II with those of III and IV reveals highly significant differences which point out the danger of drawing analogies between bicyclo[5.3.0] and bicyclo[4.3.0] ring systems. C_2-H of the *cis*-fused lactone III gives rise to a complex multiplet centered at 4.75 p.p.m. which can be analyzed as an octet closely approximating X of an ABCX system where J_{AX} = 10, J_{BX} = 7, and J_{CX} = 4 c.p.s. Dreiding models suggest that the most likely conformation is a chair in which C_1-H and C_2-H are quasi-axial and the five-membered ring is quasi-diequatorially oriented. This should give rise to dihedral angles of about 0, 82, and 158°.[12] A better fit is obtained by the twist-chair conformation advocated by Hendrickson[12]; this is shown in the appended formulae where the dihedral angles are marked.[20] III is quite rigid as shown by the envelope in the 1.2–2-p.p.m. region. The α-protons give rise to a multiplet which could not be analyzed satisfactorily.



H-H	angle	J_{H-H}
1α–2α	41°	7
2α–3α	97°	4
2α–3β	143°	10



(14) G. Gee, W. C. E. Higginson, P. Levesley, and K. J. Taylor, *J. Chem. Soc.*, 1338 (1959).

(15) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5727 (1959).

(16) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

(17) E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 121; E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 265–269.

(18) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(19) W. B. Moniz and J. A. Dixon, *J. Am. Chem. Soc.*, **83**, 1671 (1961).

(20) We wish to thank one of the referees for drawing our attention to this point.

The *trans*-lactone IV on the other hand is very flexible as shown by the strong relatively sharp band at 1.67 p.p.m. The flexibility of the seven-membered ring portion affects the dihedral angles and, hence, coupling of C_7-H. This proton which remains quasi-axial in all easily formed conformations gives rise to an unresolved multiplet at 4.25 p.p.m. The α-hydrogens are signaled by a multiplet centered at about 2.4 p.p.m. C_7-H of III and IV are apparently both axial, but Dreiding models of III indicated that C_7-H of III is less shielded by the C_3–C_4 and C_7–C_1 bonds than the corresponding proton of IV. This may account for the observed chemical shift.

The n.m.r. spectra of III and IV are in harmony with the suggestion[12] that there are two equal conformations for cycloheptane with a *trans*-fused ring while there is only one energetically preferred conformation of cycloheptane with a *cis*-fused ring.

Models[12] of *cis*- and *trans*-bicyclo[5.3.0]decane suggest that, just as in the case of lactones III and IV, the *trans* isomer may be more flexible also. If this were so, the explanation of the small entropy change in the equilibrium *cis*- $\rightleftharpoons$ *trans*-bicyclo[5.3.0]decane given by Allinger and Zalkow[13] would be in error. These workers assumed that the *cis* isomer was more flexible and that this was responsible for lowering the calculated entropy difference (1.4 e.u. greater for the *trans* isomer) to the observed small value of 0.3 ± 0.4 e.u.

Equilibration of III and IV.—Lactones III and IV were equilibrated under the influence of acid. The pronounced difference in the n.m.r. spectra of III and IV permitted the analysis of mixtures with an accuracy of ± 0.5% and a standard deviation of ± 0.24% using the H_2 signal. Heating III or IV with acetic acid at temperatures up to 473°K. resulted only in recovery of starting material. Equilibration with 5% sulfuric acid in acetic acid was quite incomplete, but use of 50% aqueous sulfuric acid in the temperature range 384–423°K. resulted in smooth equilibration. This suggests that the reaction involves hydronium ion catalysis. At lower temperatures the reaction was too slow to be useful; at more elevated temperatures extensive decomposition occurred.

Results for the equilibration at 384°K. for various times are tabulated in the Experimental section (Table II).

Equilibrium was approached from both sides but was reached only slowly at 384°K. After 48 hours, III yielded a mixture containing 41.8 ± 0.8% of IV. Similar treatment of IV yielded a mixture containing 44.7 ± 1% of IV. The average, 43 ± 1%, approximates the experimental errors and was used to calculate K_e 1.32 (384°K.) and ΔF −0.215 kcal./mole.

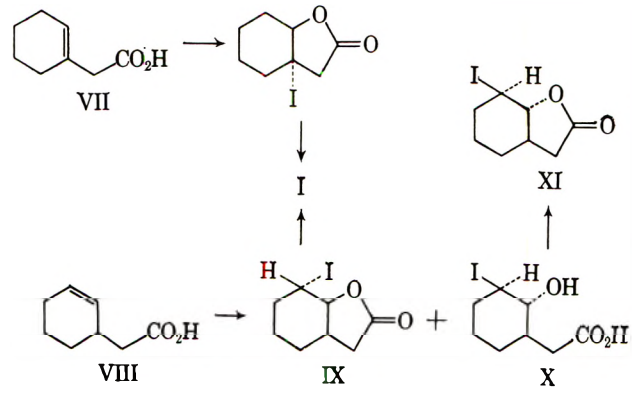
Measurements were also carried out at 401 and at 420°K. and ln K *vs.* $1/T$ was plotted. Intercept and slope of the line drawn through the experimental points by the least squares method gave, for the liquid phase isomerization of III $\rightleftharpoons$ IV, $K_{e\ 401°}$ 1.17 ± 0.05, ΔF −0.13 ± 0.03 kcal./mole, $\Delta H_{401°}$ −0.17 ± 0.06 kcal./mole, and $\Delta S_{401°}$ −0.13 ± 0.3 e.u.

The smallness of these quantities is surprising and is comparable to the values found by Allinger and Zalkow[13] for the isomerization *cis*- $\rightleftharpoons$ *trans*-bicyclo-[5.3.0]decane under conditions which were vastly different. At the higher temperatures at which their equilibrations were carried out, the *trans* isomer was more stable than the *cis*, but enthalpy and entropy differences were small. At the lower temperatures used in this study, *cis*-lactone III is slightly more stable than *trans*-lactone IV, but extrapolation indicates that the situation should be reversed at temperatures above 437°K.

The assumption that *cis*-lactones fused to seven-membered rings will necessarily be more stable than *trans*-lactones is, therefore, not supported by evidence. Minor changes in structure may easily change the relationship deduced for III and IV, particularly in complex systems like the guaianolides. The results offer a sharp contrast to the experiments reported by Klein[5] for the acid-catalyzed equilibration of I and II. His results indicated that less than 5% of the *trans*-lactone II was present at equilibrium. Recovery of only 50% of starting material was attributed to selective destruction of the more reactive II. If equilibrium was indeed attained, K_e for *cis*-I $\rightleftharpoons$ *trans*-II would be greater than 19 and ΔF < −2.2 kcal./mole.[21]

Cyclizations of Cycloheptenecacetic Acids.—Overwhelming predominance of I in the equilibrium mixture of I and II suggested[10] that the sole formation of the more stable isomer I on acid treatment of 1-cyclohexeneacetic acid (VII), originally[4] attributed to stereospecific protonation of the double bond, followed by cyclization, might conceivably involve an equilibration step. The existence of an equilibrium, however, does not necessarily eliminate stereospecific *trans*-addition as a possible mode of formation of the stable *cis* isomer as long as the *trans*-lactone equilibrates *via* the olefin acid VII which then undergoes stereospecific *trans*-addition to I,[23] and not by way of the carbonium ion.[23,24]

Stereospecific syntheses of I were achieved *via* the iodolactonization reactions of VII and VIII. Exclusive formation of I by the second sequence was explained in terms of *trans*-diaxial attack from the less hindered side of the molecule. Later work, however, has shown[25] that iodine also attacks VIII from the



(21) Professor E. L. Eliel has pointed out (private communication) that the claimed preponderance of I over II is somewhat surprising, since the results of Allinger and Coke on the relative stabilities of *cis*- and *trans*-hydrindane[22] do not differ materially from those on the bicyclo[5.3.0]-decanes.[13]

(22) N. L. Allinger and J. L. Coke, *J. Am. Chem. Soc.*, **82**, 2553 (1960).

(23) D. H. R. Barton, *J. Org. Chem.*, **15**, 466 (1950).

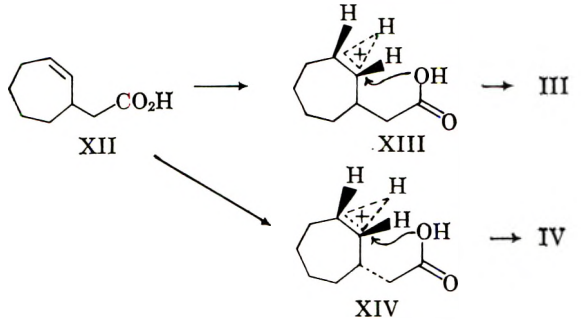
(24) C. H. Collins and G. S. Hammond, *ibid.*, **25**, 911 (1960).

(25) M. M. Shemyakin, Yu. A. Arbuzov, M. N. Kolosov, and Yu A. Ovchinnikov, *Dokl. Akad. Nauk SSSR*, 133, 1121 (1960); Yu. A. Arbuzov, M. N. Kolosov, Yu. A. Ovchinnikov, and M. M. Shemyakin, *ibid.*, 377 (1961).

more hindered side. The resulting iodo acid X was converted to the *trans*-lactone XI.

Since the composition of the equilibrium mixture of III and IV had been determined, it was now possible to study analogous cyclizations of the corresponding cycloheptaneacetic acids and to determine whether this results in a greater degree of selectivity than could be expected on the basis of the equilibrium studies. The results were also expected to have a bearing on the mode of addition to double bonds in seven-membered rings.

2-Cycloheptene-1-acetic acid (XII), prepared from 3-bromo-1-cycloheptene by condensation with diethyl malonate, hydrolysis to 2-cycloheptene-1-malonic acid, and decarboxylation, was refluxed with 50% aqueous sulfuric acid in acetic acid for 4 hours. The neutral product contained 53% ± 4% *cis*-lactone III and 47 ± 4% *trans*-lactone IV, a composition which closely resembles that of the equilibrium mixture. This suggests that equilibration is involved in the acid-catalyzed cyclization and that the unsaturated acid or the corresponding carbonium ion may be an intermediate in the acid-catalyzed equilibration of III and IV. If bridged ions are involved, little preference must be shown for the formation from XII to XIII or XIV, since rearward attack by the carboxyl group in XIII leads to III, and in XIV to IV.

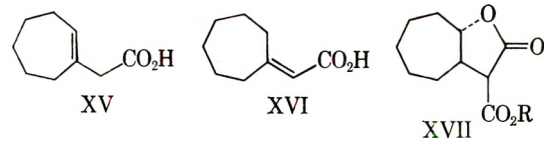


The mixture of 1-cycloheptene-1-acetic acid (XV) and $\Delta^{1,\alpha}$-cycloheptaneacetic acid (XVI) usually obtained by the literature method[26] was refluxed with acid for 11 hours in the usual way. The neutral product contained 26.3 ± 1.6% of the *trans*-lactone IV, a result which could not have arisen through prior formation of the *cis*-lactone III followed by partial equilibration, since (see Table II, Experimental) after 12 hours under these conditions, pure III yields only 17.5 ± 1% of IV. We, therefore, conclude that the acid-catalyzed cyclization of XV does probably not proceed stereospecifically toward the *cis*-lactone by *trans*-quasi-diaxial electrophilic addition, but does produce stereoselectively a preponderance of the *cis* isomer. The formation of 26% of the *trans* isomer requires an appreciable amount of *cis*-addition.[27]

The iodolactonization of acids XII and XV led to analogous results. Addition of the sodium salt of XII to iodine and potassium iodide furnished a noncrystallizable, easily decomposed mixture of iodolactones (82%) whose hydrogenolysis resulted in a fraction containing 54 ± 2% III and 46 ± 2% IV. Thus, iodination occurs from both sides of the cycloheptene ring system; the greater flexibility and more facile formation of a *trans*-lactone, compared with the situation prevailing in the iodolactonization of VIII, results in the formation of both III and IV, whereas in the cyclohexene system, one of the intermediate bridged iodonium ions (iodine *cis* to the side chain) undergoes hydroxylation rather than lactone ring closure to XI.

Iodolactonization of the mixture of acids XV and XVI led, in relatively low yield, to a mixture of iodolactones whose hydrogenolysis resulted in 66 ± 1% of III and 34 ± 1% of IV. Again, the formation of IV in appreciable amounts indicates that in the cycloheptene series *trans*-addition to the double bond is not the exclusive process demonstrated in the cyclohexene series.

The apparent nonstereospecificity of electrophilic additions to the cycloheptene ring system which has been observed in this study should be a source of caution to workers in this area. It appears that nucleophilic addition to activated double bonds, for example to 1-cyanocycloheptene, leads to *trans*-disubstituted compounds, but this is apparently due to the rapid base-catalyzed isomerization of the initially formed *cis*-1,2-disubstituted cycloheptane to the more stable *trans*-1,2-diequatorially substituted cycloheptane.[28,29] Thus both electrophilic and nucleophilic additions to cycloheptenes may lead to mixed products.



Experimental[30]

2-Oxocycloheptaneacetic Acid.—Ethyl 1-carbethoxy-2-oxocycloheptane-1-acetate[31], b.p. 133–140° (1 mm.), was hydrolyzed and decarboxylated by the literature method[31] to give 23.8 g. (71%) of acid, b.p. 125–130° (0.5 mm.), $n^{25}D$ 1.4873. In order to obtain this yield it was necessary to rehydrolyze the distillation foreruns.

Lactones of 2-Hydroxy-1-cycloheptene-1-acetic Acid (V) and 2-Hydroxycycloheptane-$\Delta^{1,\alpha}$-acetic Acid (VI).[32].—Treatment of 29.8 g. of the previous compound with acetic anhydride and a drop of acetyl chloride furnished, after removal of acetic anhydride 25 g. of crude lactone mixture. Distillation furnished three fractions: b.p. 93–105° (0.6 mm.), 4.6 g.; b.p. 105–113° (0.8 mm.), 11.2 g.; b.p. 113–121° (0.8 mm.), 5.1 g.; total yield, 22.7 g. (85%). Fraction 3 crystallized and fraction 2 crystallized on seeding. The solid material was taken up in ether, washed with dilute bicarbonate solution, water, dried, and the residue, 10.5 g. (39%), crystallized from hot pentane; yield,

(26) G. G. Ayerst and K. Schofield, *J. Chem. Soc.*, 3445 (1960). Since XVI should not cyclize unless prior rearrangement to XV occurs, its presence was not considered disturbing.

(27) A referee has commented that the results could be explained by assuming that XV (approximately 60% of the mixture) undergoes stereospecific *trans*-addition to *cis*-lactone which in the course of 11 hr. equilibrates to approximately 85% *cis*-lactone, while XVI (40% of mixture) is converted to A and then to B which immediately furnishes the equilibrium mixture of III and IV (41–45%) of *cis*-lactone.

(28) D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958).

(29) J. Sicher, F. Šipos, and J. Jonáš, *Collection Czech. Chem. Commun.*, **26**, 262 (1961).

(30) Melting points and boiling points are uncorrected. Analyses were by Drs. Franz Pascher, Bonn, Germany, and Weiler and Strauss, Oxford, England. N.m.r. spectra were run by Mr. Fred Boerwinkle and Mr. Gerald Caple on a Varian HR-60 or A-60 spectrometer. The A-60 instrument was purchased with the aid of a grant from the National Science Foundation. Infrared spectra were run in carbon tetrachloride solution unless otherwise specified. Ultraviolet spectra were determined in 95% ethanol solution on a Cary Model 14 recording spectrophotometer. Gas–liquid chromatograms were run on an F & M Model 500 instrument using 0.25 ft. × 2 ft. copper tubing programmed from 85–220° at 11°/min. and held at the higher temperature, carrier gas helium at 60 ml./min.

(31) Pl. A. Plattner, A. Fürst, and K. Jirasek, *Helv. Chim. Acta*, **29**, 730 (1946).

8.3 g. of VI; m.p. 52–55° (lit. m.p. 55–56°); infrared bands at 1760 and 1630 cm.$^{-1}$ The liquid fractions were redistilled; b.p. 83–93° (0.4 mm.); yield, 6.5 g. (24%). The infrared spectrum indicated that this material was a 3:2 mixture of V–VI, bands at 1800 and 1680 cm.$^{-1}$ corresponding to V and bands at 1760 and 1630 cm.$^{-1}$ corresponding to VI.

Lactone of *cis*-2-Hydroxycycloheptaneacetic Acid (III).—Small-scale hydrogenation of 0.47 g. (0.00312 mole) of VI in 30 ml. of ethanol with platinum oxide required 70 ml. (0.00312 moles) of hydrogen. The catalyst was filtered; titration of the filtrate with sodium hydroxide solution revealed the presence of 0.00018 equivalents (5–7%) of acid. Work-up in the usual manner furnished 0.3 g. of III, b.p. 94–96° (0.4 mm.); infrared band at 1780 cm.$^{-1}$ (γ-lactone); n^{25}D 1.4857.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.07.

The hydrazide, feathery needles from benzene, melted at 129–130.5°.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.78; H, 9.74; N, 15.10.

In a subsequent run, reduction of 2.97 g. of lactone mixture with W-2 Raney nickel in a Parr hydrogenator furnished 2.03 g. (68%) of III.

Lactone of *trans*-2-Hydroxycycloheptaneacetic Acid.—To a solution of sodium ethoxide (2.18 g. of sodium) in 70 ml. of ethanol was added with stirring 15.2 g. of malonic ester and then, after 15 min. and cooling to 17°, dropwise 9.8 g. of cycloheptene oxide[32] The mixture was stirred at 70° for 32 hr., decomposed with water, and made alkaline with 8.1 g. of potassium hydroxide. Solvent was partially evaporated, the remainder refluxed for one hour, cooled, and acidified to pH 4. The acid solution was continuously extracted with ether for 1 day and the ether extract concentrated. The residue, 6.8 g., was decarboxylated by heating at 185° for 2 hr., distilled, and the fractions, b.p. 92.5–98° (0.4 mm.), collected (3.05 g. 23%). The analytical sample boiled at 91–92° (0.3 mm.), n^{25}D 1.4826, infrared band at 1785 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.56.

The hydrazide was recrystallized from benzene, m.p. 131–132°, melting point depressed to 115–125° on admixture of the hydrazide of III.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 57.89; H, 9.64; N, 14.69.

In an attempt to increase the yield, the condensation of 16 g. of cycloheptene oxide with sodium malonic ester was carried out in refluxing amyl alcohol. The work-up was modified by cooling and acidifying with dilute acetic acid. Distillation furnished 1.51 g. of cycloheptene oxide, 3.3 g. of diethyl malonate, 1.09 g. of a mixture of diethyl malonate and lactone IV (1:1), 1.3 g. of a mixture of lactone IV,[33] and lactone ester XVII, and 3.0 g. of lactone ester XVII (mixture of ethyl and amyl esters), b.p. 128° (0.1 mm.).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.30; H, 9.29, 9.07.

The base-soluble fraction and water washings from this reaction were hydrolyzed with sodium hydroxide. The usual work-up, followed by distillation, furnished 3.71 g. of IV (25%).

Lactones of *cis*- and *trans*-2-Hydroxycyclohexaneacetic Acid (I and II).—These compounds were prepared by the method of Newman and Vander Werf[3]: lactone I, 57% yield, b.p. 105–108° (3.5 mm.); lactone II, 50% yield, b.p. 87–88° (0.3 mm.). Heating of 0.500 g. of I with 50% aqueous sulfuric acid in acetic acid as described by Klein[5] gave 0.282 g. of pure I in the neutral fraction. II furnished 0.240 g. of a 7:3 mixture of I and II, but more prolonged heating might possibly have caused complete conversion of II to I.[5] Analyses were carried out by n.m.r. spectroscopy which would have detected less than 5% of either isomer.

Equilibration of III and IV.—Artificial mixtures of III and IV were analyzed by n.m.r. spectroscopy, using neat samples in the Varian HR-60 n.m.r. spectrometer. There was a small overlap of the H_2 bands, but it was possible to cut out each band and weigh the pieces. Five to ten integrations of this type for each artificial mixture gave an accuracy of ± 1% with a standard deviation of 0.55–1.0%. For example, five spectra of a mixture containing 41.2% of IV gave a value of 41.3 ± 0.5% of IV. Machine integration of the same mixture in deuteriochloroform on a Varian A-60 spectrometer, which became available later, yielded the composition 41.6 ± 0.5% of IV with a standard deviation of the mean of ±0.24%.

Equilibrations were carried out by refluxing 0.500 g. of the lactone with 5 ml. of glacial acetic acid and 3 ml. of 50% aqueous sulfuric acid for the desired period. The mixture was cooled and extracted with three 10-ml. portions of benzene. The benzene was washed with 10- and 5-ml. portions of 5% sodium bicarbonate solution and dried. Removal of benzene typically yielded 0.40–0.45 g. of residue which, on distillation, furnished 0.25–0.3 g. of mixed lactones, b.p. 72–75° (0.2 mm.), which were analyzed neat by n.m.r. spectroscopy. Results are tabulated in Table II.

For equilibrations carried out at temperatures above the boiling point, the solutions were placed in Carius tubes (1 × 6 in. heavy wall), sealed under nitrogen, and heated in a sealed tube furnace for the desired period. The tubes were cooled, opened, and the contents worked up in the usual manner. By-product undistillable material was somewhat greater and total recovery smaller.

TABLE II

EQUILIBRATION OF THE LACTONES OF *cis*- AND *trans*-2-HYDROXYCYCLOHEPTANEACETIC ACID

Starting Material	Temp., °C.	Time, hr.	% *cis*	% *trans*	Intersection[a]
III	111	6	89.8 ± 0.8	10.2 ± 0.8	
					41% IV
IV	111	6	13.5 ± 2.0	87.5 ± 2.0	
III	111	12	82.5 ± 1.0	17.5 ± 1.0	
					41% IV
IV	111	12	25.8 ± 0.7	74.2 ± 0.7	
III	111	18	74.7 ± 1.7	25.3 ± 1.7	
					41% IV
IV	111	18	37.0 ± 1.3	63.0 ± 1.3	
III	111	48	58.2 ± 1.0	41.8 ± 0.8	
					43% IV
IV	111	48	55.3 ± 1.0	44.7 ± 1.0	
III	128	12	54 ± 1	46 ± 1	
					46% IV
IV	128	12	54 ± 1	46 ± 1	
III	147	3	52.3 ± 0.8	47.7 ± 0.8	
					47.6%
IV	147	3	52.5 ± 1.0	47.5 ± 1.0	IV

[a] Intersection of plot of composition *vs.* time at the indicated temperature.

2-Cycloheptene-1-acetic acid (XII).—To 100 ml. of sodium ethoxide solution (from 1.77 g. of sodium) was added 12.4 g. of diethylmalonate with stirring. After 15 min. the solution was cooled with ice and 13.5 g. of 3-bromo-1-cycloheptene[35] in 15 ml. of ethanol was added dropwise. Stirring was continued at room temperature for 16 hr., the solution filtered, diluted with water, and extracted with ether. The combined organic layers were dried and distilled; yield, 13.8 g. (71%); b.p. 105–106° (0.2 mm.).

The malonate, 12.0 g., was refluxed for 12 hr. with 8.05 g. of potassium hydroxide in 50 ml. of ethanol and 30 ml. of water. The base was neutralized with dilute hydrochloric acid and the solution evaporated at room temperature. The residue was thoroughly extracted with hot ethyl acetate and the extract concentrated; yield, 5.4 g. (58%) of 2-cycloheptene-1-malonic acid; m.p. 144–145° dec. Recrystallization from ethyl acetate furnished needles, m.p. 151–152 dec.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.52; H, 7.12.

2-Cycloheptene-1-acetic acid was prepared in 70% yield by heating the malonic acid at 180° for 1 hr. and distilling the product at 80–90° (0.2 mm.). Redistillation furnished the analytical sample, b.p. 85° (0.2 mm.).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.17.

Cyclizations of XII. (A).—A mixture of 0.7 g. of XII, 6 ml. of acetic acid and 4 ml. of 50% sulfuric acid was refluxed for 11 hr. and worked up as usual to yield 0.35 g. of neutral material (50%).

(32) P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, **24**, 555 (1959).

(33) The direct decarbethoxylation of the condensation product to IV on refluxing with alkoxide finds it parallel in a recently reported reaction of diethyl malonate with 1-cyclohexenecyanide.[34]

(34) R. A. Abramovitch, L. X. Mallavarapu, and D. L. Struble, Report No. 6, Petroleum Research Fund, American Chemical Society, 1961, p. 146.

(35) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 607 (1954).

The distillate, b.p. 75–80° (0.3 mm.), 0.19 g., was analyzed by n.m.r. spectroscopy, which indicated 46.7 ± 4.1% of IV and 53.3 ± 4.1 % of III.

(B).—To 3.5 g. of iodine and 6.8 g. of potassium iodide in 60 ml. of water was added the sodium salt of XII (from 1.0 g. of XII and 1.73 g. of sodium bicarbonate) in 30 ml. of water. A heavy oil which separated was extracted with ether. The extracts were washed with sodium bisulfite solution until colorless, sodium bicarbonate solution, and water and dried. Removal of ether furnished 1.5 g. (82%) of an undistillable (dec.) noncrystallizable oil which represented the iodolactone (infrared spectrum). Hydrogenolysis with W-2 Raney nickel in ethanol and triethylamine was only partially successful, whereas hydrogenolysis with nickel and sodium bicarbonate completed removal of iodine. Infrared and n.m.r. spectra of the product indicated that it was composed of III and IV; n.m.r. analysis indicated the presence of 54.2 ± 2% III and 45.8 ± 2% IV.

1-Cycloheptene-1-acetic Acid (XV) and Cycloheptane-$\Delta^{1,\alpha}$-acetic Acid (XVI).—Dehydration of the hydroxy ester, obtained in 67% yield by the Reformatsky reaction of cycloheptanone and ethyl bromoacetate, with thionyl chloride furnished a mixture of α,β- and β,γ-unsaturated ester; b.p. 71–82° (1.5 mm.); yield, 51%; infrared bands at 1740 (ester), 1715 (conjugated ester), and 1635 cm.$^{-1}$ (conjugated double bond) which contained 60% of the β,γ-unsaturated compound (v.p.c.). Hydrolysis gave a mixture of the title compounds, b.p. 110–114 (18 mm.), 74% yield, which was used directly for the following reactions.

(A).—Cyclization of the mixture with dilute sulfuric acid–acetic acid for 11 hr. and work-up in the usual manner gave 57% of a neutral fraction, b.p. 68–73° (0.15 mm.), whose n.m.r. analysis indicated that it was composed of 73.7 ± 1.6% *cis*-lactone III and 26 ± 1.6% *trans*-lactone IV.

(B).—Iodolactonization of the mixed acids yielded 26% of a noncrystallizable oil which decomposed on attempted distillation but was a mixture of iodolactones (infrared spectrum). W-2 Raney nickel hydrogenolysis in ethanol with sodium bicarbonate gave a mixture of lactones III and IV, b.p. 88–92° (0.6 mm.), 44% yield, which contained 66 1% of III ± and 34 ± 1% of IV.

The Reactions of Phosphonic Acid Esters with Acid Chlorides. A Very Mild Hydrolytic Route

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Received June 14, 1963

The reaction of trimethylchlorosilane with a number of dialkyl esters of phosphonic acids and the hydrolysis of the resultant silyl phosphonates was studied as a means of preparing the phosphonic acids under very mild conditions. 2-Vinyloxyethylphosphonic acid, β-cyanovinylphosphonic acid, and vinylphosphonic acid were successfully prepared and characterized as their dicyclohexylamine salts. The reaction of primary, secondary, and tertiary alcohols with bis(trimethylsilyl) methylphosphonate results in an equilibrium mixture containing starting materials, acidic products, and mixed ethers [$ROSi(CH_3)_3$]. Mercaptans do not react. The reaction of excess acetyl chloride with dimethyl methylphosphonate yields methyl chloride, acetic anhydride, and dimethyl dimethylpyrophosphonate. The stability of the latter in excess acetyl chloride is discussed. Mechanistic interpretations of all reactions are presented.

The conventional means of converting a phosphonic acid ester into the corresponding phosphonic acid is by refluxing in concentrated aqueous acid.[1] However, this method is not applicable to phosphonates containing acid or water sensitive groups like nitriles, vinyl ethers, acetals, etc. During an investigation of the preparation and reactions of bis(trimethylsilyl) benzylphosphonate it was noted that this compound was hydrolyzed in high yield to benzylphosphonic acid when shaken in water at room temperature. Furthermore, the liquid bis(trimethylsilyl) ethylphosphonate slowly dissolved in water to give a strongly acidic solution. This suggested that conversion of phosphonates of the general formula $RP(O)(O\text{-alkyl})_2$ where R contains an acid labile group, to the corresponding bistrimethylsilyl phosphonates and subsequent hydrolysis should result in the preparation of phosphonic acids which ordinarily would be difficult to obtain.

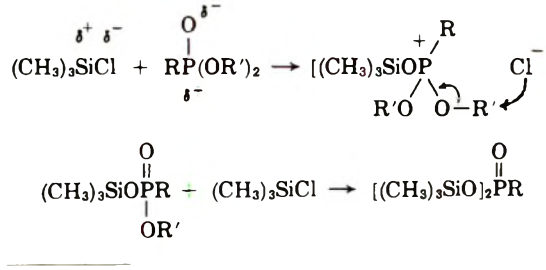
Diethyl β-cyanovinylphosphonate was converted in high yield to bis(trimethylsilyl) β-cyanovinylphosphonate. This was hydrolyzed in water, and a 30% yield of the β-cyanovinylphosphonic acid was isolated and characterized as the crystalline dicyclohexylamine salt. When the bis(trimethylsilyl) compound reacted with methanol, a quantitative yield of the phosphonic acid was obtained. Diethyl 2-vinyloxyethylphosphonate was converted in good yield into the corresponding bistrimethylsilyl compound which, upon reaction with methanol, gave the phosphonic acid as an oil. It was characterized as the crystalline dicyclohexylamine salt. Finally bis(β-chloroethyl) vinylphosphonate and diethyl vinylphosphonate were converted, using this procedure, to vinyl phosphonic acid. Vinyl phosphonic acid has been a rather elusive compound and was reported only recently.[2]

$$2ClSi(CH_3)_3 + NCCH{=}CHP(O)(OC_2H_5)_2 \longrightarrow 2C_2H_5Cl + NCCH{=}CHP(O)[OSi(CH_3)_3]_2$$

$$NCCH{=}CHP(O)[OSi(CH_3)_3]_2 \xrightarrow[\text{or } CH_3OH]{H_2O} NCCH{=}CHP(O)(OH)_2$$

Discussion

The reaction of trimethylchlorosilane with phosphonates as well as phosphates to yield the corresponding trimethylsilyl derivatives has been described.[3] Although no mechanism is proposed it appears likely



(1) G. M. Kosalapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950.

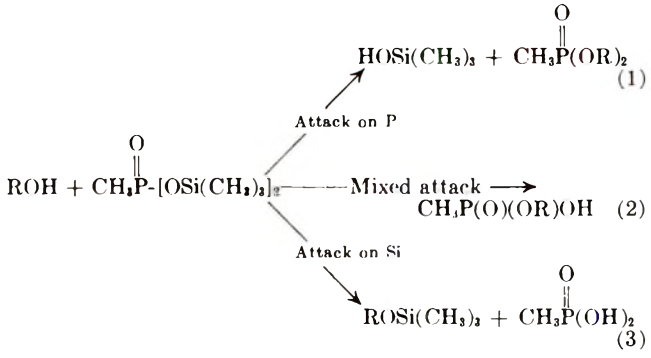
(2) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2142 (1959).

(3) H. W. Kohlschutter and H. Simoleit, *Kunststoffe—Plastics*, **6**, 9 (1959).

that a phosphonium-type Arbuzov intermediate is involved. (See p. 2975, col. 2, bottom.)

The reactions of the various phosphonates of this work with trimethylchlorosilane were all carried out by heating the phosphonate to approximately 120° and then adding trimethylchlorosilane until the reflux temperature of the system dropped to 70°. Additional quantities of trimethylchlorosilane were added periodically until it appeared that the reaction was complete. Even using a minimum temperature of 70°, the reaction in a number of cases required several days of attention. Dimethyl methylphosphonate was synthesized since it was presumed, on steric grounds, that this would be converted to the corresponding bistrimethylsilyl compound faster than any of the higher esters. Actually the reaction was complete in less than six hours, and a greater than 90% yield of product was obtained.

Aqueous hydrolysis of the bistrimethylsilyl phosphonates, whether water attack is on silicon or phosphorus, will yield the phosphonic acid. However, reaction with alcohols can lead to a phosphonate or a phosphonic acid or a mixed product depending on the position of attack (equations 1–3). The reaction of



bis(trimethylsilyl) methylphosphonate with a number of alcohols was studied with the aid of a Perkin-Elmer 154D gas chromatography apparatus. Qualitatively the results are as follows. Primary and secondary alcohols like methanol, ethanol, 1-butanol, 1-heptanol, cyclohexanol, and phenol react *instantaneously* to give an equilibrium mixture containing the alcohol and the mixed ether (reaction 3). The existence of an equilibrium was postulated on the basis that significant amounts of the alcohol and the mixed ether were present when less than half of the stoichiometric amount of alcohol was added to the phosphonate. Tertiary alcohols like *t*-butyl and *t*-amyl alcohol react very slowly at room temperature; however, when heated for a few minutes at 80–110°, equilibrium is rapidly established. Although the equilibrium must involve both the half-acid ester and the full acid, it is convenient to simply express the over-all equilibrium as shown.

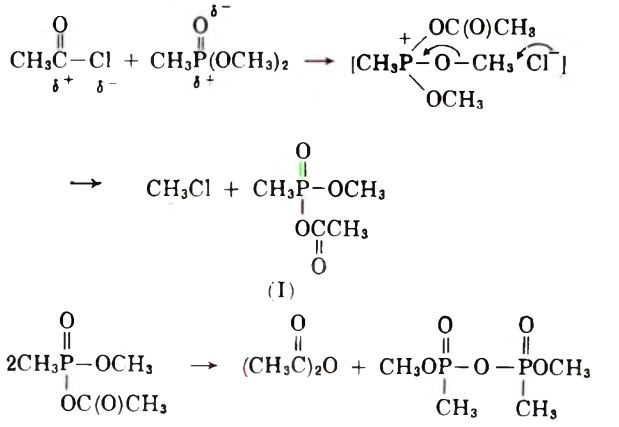
$$CH_3P(O)[OSi(CH_3)_3]_2 + 2ROH \rightleftharpoons 2ROSi(CH_3)_3 + CH_3P(O)(OH)_2$$

Further evidence for the existence of this equilibrium was obtained by adding *n*-propylamine to the reaction mixtures at equilibrium. This serves to remove the phosphonic acid or the half-acid ester as the salt, and as anticipated, the ratio of mixed ether to alcohol increased markedly as a result of the forward reaction proceeding in order to re-establish an equilibrium. Separately it was shown that *n*-propylamine does not react with bis(trimethylsilyl) methylphosphonate even at 100°.

Although the reaction of methanol or ethanol with a bistrimethylsilyl phosphonate reaches an equilibrium before complete reaction, this reaction can be used to convert the phosphonate completely to the phosphonic acid. This is possible by using a reasonable excess of the alcohol while taking advantage of the fact that the alcohol-mixed ether azeotrope always boils at a lower temperature than does the free alcohol.[4]

Amyl mercaptan and benzyl mercaptan do not react with bis(trimethylsilyl) methylphosphonate at room temperature. This was not surprising in view of the fact that the driving force of the reaction of alcohols with the phosphonate is the formation of the strong O–Si bond (89.1 kcal.)[5] while the corresponding S–Si bond is considerably weaker (60.9 kcal.).[5]

The scope of the reaction of acid chlorides like trimethylchlorosilane with phosphonates was investigated by studying the reaction of acetyl chloride with dimethyl methylphosphonate. The reaction was carried out in a large excess of acetyl chloride. The only products identified, besides methyl chloride, were acetic anhydride and dimethyl dimethylpyrophosphonate (49%). The course and proposed mechanism are the following.



These results are in agreement with recent studies[6] on the action of acetyl bromide, acetyl chloride, and benzoyl chloride on diethyl ethylphosphonate. This work was carried out on a mole-to-mole basis and the survival of the pyrophosphonate against further acid chloride attack is understandable. However, the isolation of significant amounts of dimethyl dimethylpyrophosphonate after having carried out the reaction using a large excess of acetyl chloride was, at first, difficult to rationalize. It is now felt that the stability of the mixed ester anhydride (I) and of the pyrophosphonate toward further rapid acetyl chloride attack is due to the fact that, according to the proposed mechanism, phosphorus must accept a positive charge in the transition state. This is not a favorable situation when the electron withdrawing –OC(O)– or OP(O)– groups are also attached to this phosphorus.

(4) R. O. Sauer, *J. Am. Chem. Soc.*, **66**, 1707 (1944).

(5) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. I, XXXI, Claredon Press, Oxford, 1950, p. 551.

(6) A. N. Pudovik, A. A. Muratova, T. I. Konnova, T. Feoktistova, and L. N. Levkova, *Zh. Obshch. Khim.*, **30**, 2624 (1960).

Experimental

Materials.—Dimethyl methylphosphonate and diethyl benzylphosphonate were prepared in high yields by treating trimethyl phosphite and triethyl phosphite with methyl iodide and benzyl chloride, respectively. Diethyl β-cyanovinylphosphonate[7] and diethyl 2-vinyloxyethylphosphonate[8] were available at this laboratory. Bis(2-chloroethyl) vinylphosphonate was obtained from the Monsanto Chemical Company. Trimethylchlorosilane was Anderson's "pure" grade. Diethyl vinylphosphonate was prepared by triethylamine dehydrobromination of diethyl 2-bromoethylphosphonate, the reaction product of triethyl phosphite and an excess of 1,2-dibromoethane.

Preparation of Bis(trimethylsilyl) Benzylphosphonate.—A solution of 35.8 g. (0.155 mole) of diethyl benzylphosphonate and 16.9 g. (0.155 mole) of trimethylchlorosilane was heated under a reflux condenser which was connected to a Dry Ice–trichloroethylene trap. The initial reflux temperature was 72°. Periodically during the next 4 days, when the reflux temperature was above 95°, a total of 29.4 g. (0.27 mole) of trimethylchlorosilane was added. Fractionation of the reaction mixture led to the recovery of 5 g. of trimethylchlorosilane and the isolation of 45.6 g. (93%) of bis(trimethylsilyl) benzylphosphonate, b.p. 96.5–98° (8 mm.).

Anal. Calcd. for $C_{13}H_{25}O_3PSi_2$: C, 49.4; H, 7.91; P, 9.80. Found: C, 50.2; H, 7.89; P, 10.10.

Hydrolysis of Bis(trimethylsilyl) Benzylphosphonate.—A mixture of 9.6 g. (0.030 mole) of bis(trimethylsilyl) benzylphosphonate and 75 ml. of water was shaken for 1 hr. At this point an oil floated on the water, whereas in the original mixture the bis(trimethylsilyl) benzylphosphonate was the lower layer. The mixture was extracted with three 50-ml. portions of chloroform, and the water layer was evaporated to dryness. The residue was a white solid, 4.1 g. (80%), which was recrystallized from 20 ml. of water. The crystalline product was collected and dried, m.p. 169–171°. This was identified as benzylphosphonic acid by comparison with an authentic sample.

Preparation of Bis(trimethylsilyl) Vinylphosphonate. A. From Bis(2-chloroethyl) Vinylphosphonate.—Using the procedure described for the synthesis of bis(trimethylsilyl) benzylphosphonate, 37.8 g. (0.162 mole) of bis(2-chloroethyl) vinylphosphonate reacted with a total of 56.1 g. (0.51 mole) of trimethylchlorosilane during a 30-day addition period. Fractionation yielded 32.6 g. (78%) of bis(trimethylsilyl) vinylphosphonate, b.p. 102.3–104° (14 mm.).

Anal. Calcd. for $C_8H_{21}O_3PSi_2$: C, 37.9; H, 8.3; P, 12.20; Si, 22.4. Found: C, 37.8; H, 8.65; P, 12.31; Si, 19.6.

B. From Diethyl Vinylphosphonate.—Using the procedure described previously, 42.3 g. (0.26 mole) of diethyl vinylphosphonate reacted with a total of 76.2 g. (0.70 mole) of trimethylchlorosilane during a five-day addition period. Fractionation yielded 60 g. (92%) of bis(trimethylsilyl) vinylphosphonate, b.p. 103–104° (14 mm.).

Anal. Calcd. for $C_8H_{21}O_3PSi_2$: C, 37.9; H, 8.3; P, 12.20. Found: C, 37.8; H, 8.7; P, 12.3.

Preparation of Vinylphosphonic Acid and Dicyclohexylamine Salt.—A solution of 7.0 g. (0.028 mole) of bis(trimethylsilyl) vinylphosphonate in 50 ml. of water was shaken for 16 hr. at room temperature. The oil floating on the water layer was extracted with three 50-ml. portions of chloroform. The water layer was devolatilized leaving 2.77 g. (93%) of very slightly yellow liquid residue, vinylphosphonic acid. One gram (0.0090 mole) of the vinylphosphonic acid was dissolved in 6 ml. of benzene and 4 ml. of acetone. This was added to a solution of 3.6 g. of dicyclohexylamine in 6 ml. of benzene and 4 ml. of acetone. Immediately a white solid precipitated which was collected and air-dried, 2.63 g. (100%). A portion of this was recrystallized from dilute water in acetone, and a white crystalline product was obtained, m.p. 210–215°.

Anal. Calcd. for $C_{14}H_{28}NO_3P$: C, 58.2; H, 9.7; N, 4.9; P, 10.7. Found: C, 58.0; H, 9.7; N, 4.9; P, 10.7.

Preparation of Bis(trimethylsilyl) 2-Vinyloxyethylphosphonate.—Using the procedure described previously, 50.0 g. (0.24 mole) of diethyl 2-vinyloxyethylphosphonate reacted with 89.5 g. (0.82 mole) of trimethylchlorosilane during a 48-hr. period. Fractionation of the reaction mixture gave 50 g. (72%) of bis(trimethylsilyl 2-vinyloxyethylphosphonate, b.p. 124–126° (5 mm.).

Anal. Calcd. for $C_{10}H_{25}O_4PSi_2$: C, 40.5; H, 8.43; P, 10.45. Found: C, 39.2; H, 7.83; P, 9.49.[9a]

Preparation of 2-Vinyloxyethylphosphonic Acid and Dicyclohexylamine Salt.—A solution of 12 g. (0.038 mole) of bis(trimethylsilyl) 2-vinyloxyethylphosphonate in 30 ml. of methanol was fractionally distilled,[9b] thus preferentially removing trimethylsiloxymethane and shifting the equilibrium continuously toward products. Finally all the remaining methanol was removed under reduced pressure leaving 5.5 g. (95%) of the phosphonic acid. A solution of 1.8 g. (0.012 mole) of the phosphonic acid in 5 ml. of methanol was added to a solution of 3.0 g. of dicyclohexylamine in 5 ml. of methanol. The temperature rose to 46°. The volume was reduced to 2–3 ml. and then the solution was diluted with 25 ml. of acetone. The solid which precipitated was collected and air-dried, 4.23 g. (106%). This was recrystallized from dilute methanol in acetone, m.p. 184–185°.

Anal. Calcd. for $C_{16}H_{32}NO_4P$: C, 57.8; H, 9.61; N, 4.21; P, 9.34. Found: C, 55.7; H, 9.63; N, 4.48; P, 10.0.[9a]

Reaction of Trimethylchlorosilane with Dimethyl Methylphosphonate. Preparation of Bis(trimethylsilyl) Methylphosphonate.—Using the procedure already outlined, 52.5 g. (0.423 mole) of dimethyl methylphosphonate reacted with 95.4 g. (0.88 mole) of trimethylchlorosilane during a 6-hr. period. Fractionation of the reaction mixture gave 92.0 g. (91%) of the desired product, b.p. 105–107.5° (27 mm.).

Anal. Calcd. for $C_7H_{21}O_3PSi_2$: C, 35.0; H, 8.73. Found: C, 35.6; H, 8.57.

Reactions of Bis(trimethylsilyl) Methylphosphonate with Alcohols.—The majority of these reactions were run on a qualitative basis using a Perkin-Elmer Model 154D gas chromatography (g.c.) apparatus for analysis. Usually the conditions were 180°, 20 lb./sq. in. He, silicone ("O") column (on Celite). The elution times for the silyl phosphonate, pure alcohol, trimethylsiloxymethane,[10] and trimethylsiloxyethane[10] were determined separately. The silyl phosphonate and the alcohol were mixed at room temperature and a sample immediately examined by g.c. The relative peak heights of the starting phosphonate, alcohol, and product ether were measured. Although the elution times of the majority of trimethylsiloxy compounds were not independently determined, the major new peak that appeared in the g.c. pattern of the alcohol–silyl phosphonate reaction mixture was presumed to be the ether. In this manner it was shown that methanol, ethanol, 1-butanol, cyclohexanol, 1-heptanol, and phenol *rapidly* equilibrated with bis(trimethylsilyl) methylphosphonate.

A. Demonstration of an Equilibrium.—When 0.33 cc. of bis(trimethylsilyl) methylphosphonate and 5 drops of cyclohexanol were mixed, the ratio of silyl ether to cyclohexanol peak heights was 1.58. Addition of 5 drops of *n*-propylamine resulted in the immediate increase of this ratio to 4.7.

B. Tertiary Alcohols.—When 0.33 cc. of the silyl phosphonate was contacted with 15 drops of *t*-butyl alcohol, the ratio of product ether to *t*-butyl alcohol was <0.0025. When this solution was heated for 10 min. at 110° this ratio increased to 0.30. An additional 8-min. heating at 110° had no further effect on the ratio.

When 0.33 cc. of the silyl ether was contacted with 15 drops of Eastman Practical *t*-amyl alcohol the ratio of product ether to *t*-amyl alcohol was 0.016. When the solution was heated for 15 min. at 80° the ratio increased to 0.25. An additional 27 min. at 80° and 10 min. at 110° had no effect on the ratio. When 9 drops of *n*-propylamine was added and the solution heated for 8 min. at 100°, the ratio increased to 0.56.

Attempted Reaction of Amines with Bis(trimethylsilyl) Methylphosphonate.—Examination of a solution of the phosphonate and diethylamine by g.c. indicated no reaction had occurred. Starting materials were the only peaks noted. Likewise, no reaction was evident between the phosphonate and *n*-propylamine even after heating at 100° for 20 min.

Reaction of Acetyl Chloride and Dimethyl Methylphosphonate.—A total of 122.2 g. (1.56 moles) of acetyl chloride was slowly

(7) This was prepared by Dr. F. Scotti of this laboratory by reacting triethylphosphite with β-chloroacrylonitrile.

(8) R. Rabinowitz, *J. Org. Chem.*, **26**, 5152 (1961).

(9) (a) Efforts to obtain a more satisfactory analysis were unsuccessful. (b) The first distillate boiled at 50°, the reported[4] boiling point of the methanol–trimethylsiloxymethane azeotrope. When a large-scale reaction of ethanol and the silyl phosphonate was carried out, the first fraction boiled at 67°. The reported[4] boiling point of the ethanol–trimethylsiloxyethane azeotrope is 66°.

(10) Samples were kindly supplied by Dr. Stanley H. Langer of this laboratory; see S. H. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958).

added to 74.9 g. (0.534 mole) of the phosphonate during a 5-hr. addition period while refluxing. The condenser was attached to a Dry Ice trap, which, after a total of 24 hr. of refluxing had condensed 51.7 g. (1.02 moles) of methyl chloride. Fractionation of the reaction mixture gave acetic anhydride and 26.4 g. (0.13 mole) of a liquid, b.p. 100–101.5° (0.4 mm.), which was identified as dimethyl dimethylpyrophosphonate. The infrared spectrum showed P–CH_3 at 1325 and 900, P–OCH_3 at 1190 and 1050, P–O–P at 960, and P=O at 1265 $cm.^{-1}$.

Anal. Calcd. for $C_4H_{12}O_5P_2$: C, 23.7; H, 5.93. Found: C, 24.2; H, 6.25.

The residue in the distillation flask was a brown tacky immobile material which reacted rapidly with water.

Acknowledgment.—We wish to thank Drs. Joseph Pellon and Richard W. Young for their helpful suggestions and interest.

The Ammonolysis of 1,6-Anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose and the Synthesis of 2,4-Diamino-2,4-dideoxy-D-glucose[1]

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Ammonolysis of 1,6-anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose afforded one diamino and two monoamino derivatives. The structure of the first product was established as a 2,4-diamino-2,4-dideoxy derivative of D-glucose by its independent synthesis from 2-acetamido-1,6-anhydro-3-*O*-benzoyl-2-deoxy-4-*O*-methylsulfonyl-β-D-galactopyranose. One of the two monoamino compounds is presumably a derivative of 4-amino-4-deoxy-D-glucose.

Numerous diamino derivatives of hexoses have been isolated from antibiotics in the last few years. In all these compounds, the amino groups are located at positions C-2 or C-3 and at position C-6 of the carbon chain. The recent isolation by Sharon and Jeanloz,[2] from a polysaccharide of *Bacillus subtilis*, of a diamino hexose in which the two amino groups are probably located at positions C-2 and C-4 of the carbon chain has aroused interest in this type of derivative. The synthesis of 2,4-diamino-2,4-dideoxy-D-glucose was, therefore, investigated.

Numerous studies on the opening of epoxide rings of carbohydrates with ammonia have shown that the transdiaxal conformation was greatly favored when the spacial configuration of the starting material was stabilized by the presence of a 1,6-anhydro or a 4,6-*O*-benzylidene ring. During ammonolysis of 1,6-anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (II), transdiaxal opening resulted in the preponderant formation of 2,4-diamino-1,6-anhydro-2,4-dideoxy-β-D-glucopyranose isolated as the fully acetylated derivative VII. The formation of this diamino product VII could proceed *via* either monoepoxide intermediate, 1,6;3,4-dianhydro-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose (I) or 1,6;2,3-dianhydro-4-*O*-*p*-tolylsulfonyl-β-D-mannopyranose (III). The presence of traces of water could result in the hydrolytic splitting of the *p*-tolylsulfonyl groups. Since the newly formed hydroxyl groups would be in *trans* position to the epoxide groups, a second nucleophilic displacement would result in the formation of 1,6;2,3-dianhydro-β-D-gulopyranose (V) from I and 1,6;3,4-dianhydro-β-D-altropyranose (IV) from III, respectively.[3] Formation of the epoxide III seems, however, not to be favored, since reaction of II with sodium methoxide, even for prolonged periods of time, gives a monotosyl monoepoxide product, which has been shown by Černý and Pacák[4] to be 1,6;3,4-dianhydro-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose (I). Additional evidence for the stability of I in the presence of alkali is shown by its formation during the reaction of 1,6-anhydro-2,3,4-tri-*O*-*p*-tolylsulfonyl-β-D-glucopyranose with a very large excess of barium hydroxide.[5]

In order to ascertain the *gluco* configuration of the diacetamido derivative VII, 2-acetamido-1,6-anhydro-3-*O*-benzoyl-2-deoxy-4-*O*-methylsulfonyl-β-D-galactopyranose (IX)[6] was treated with sodium azide, and the resulting azido compound VIII was hydrogenated and acetylated to give a compound VII inentical to the one obtained by ammonolysis of II. The displacement by an azide group of a sulfonyloxy group located in a pyranose ring in vicinal position to a *cis* hydroxyl group, with concomittant Walden inversion, has been reported recently.[7–9] Saponification of the 3-*O*-acetyl group gave crystalline VI.

Attempts to obtain 2,4-diamino-2,4-dideoxy-D-glucose as the dihydrochloride derivative by direct hydrolysis of VI were not successful. As had already been observed by Sharon and Jeanloz with the diamino sugar isolated from *Bacillus subtilis*[2] and more recently by Reist, *et al.*,[7] with derivatives of 4-amino-4-deoxy-D-glucose, hydrolysis of 4-amino-4-deoxy sugars results in extensive degradation. The hydrolysis of VI also was accompanied by much degradation and the hydrolyzate gave multiple spots on paper chromatograms. These

(1) Amino Sugars XXXV. This is publication no. 339 of The Robert W. Lovett Memorial Unit for the Study of Crippling Disease, Harvard Medical School at the Massachusetts General Hospital, Boston 14, Mass. This investigation has been supported by research grants from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, United States Public Health Service (Grant A-3564). This work was presented before the Division of Carbohydrate Chemistry, at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) N. Sharon and R. W. Jeanloz, *J. Biol. Chem.*, **235**, 1 (1960).

(3) W. H. G. Lake and S. Peat, *J. Chem. Soc.*, 1069 (1939); J. G. Buchanan, *Chem. Ind.* (London), 1484 (1954); F. H. Newth, *J. Chem. Soc.*, 441 (1956).

(4) M. Černý and J. Pacák, *Collection Czech. Chem. Commun.*, **27**, 94 (1962).

(5) R. M. Hann and N. K. Richtmyer, personal communication of Dr. N. K. Richtmyer.

(6) R. W. Jeanloz, *J. Am. Chem. Soc.*, **81**, 1956 (1959).

(7) R. D. Guthrie and D. Murphy, *Chem. Ind.* (London), 1473 (1962).

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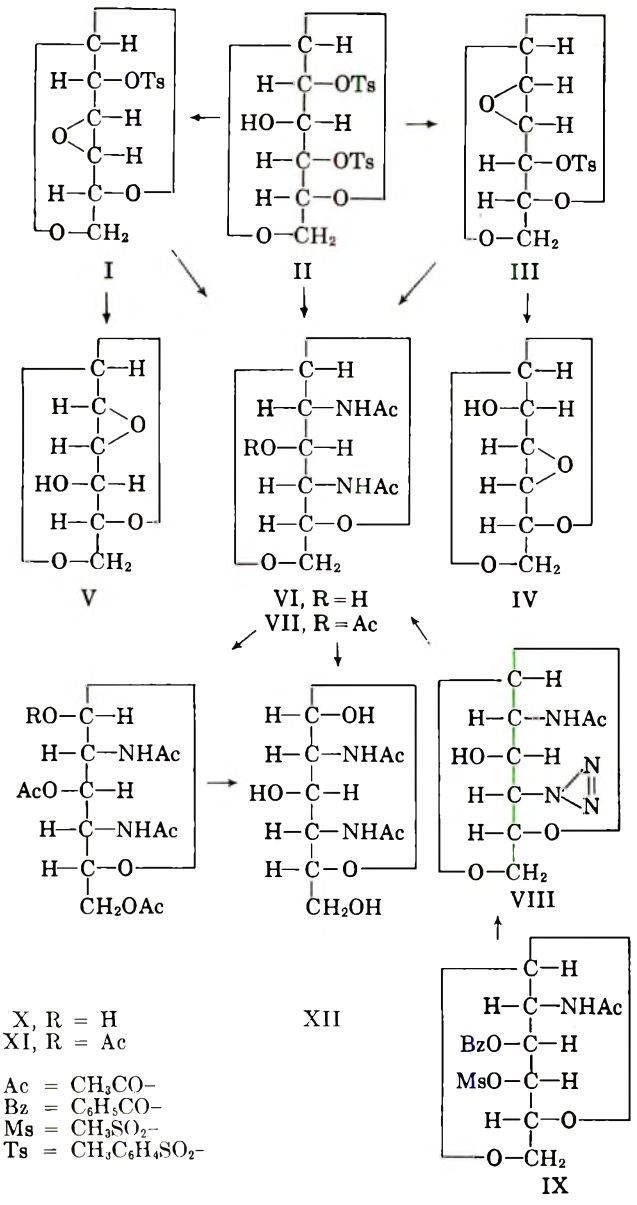
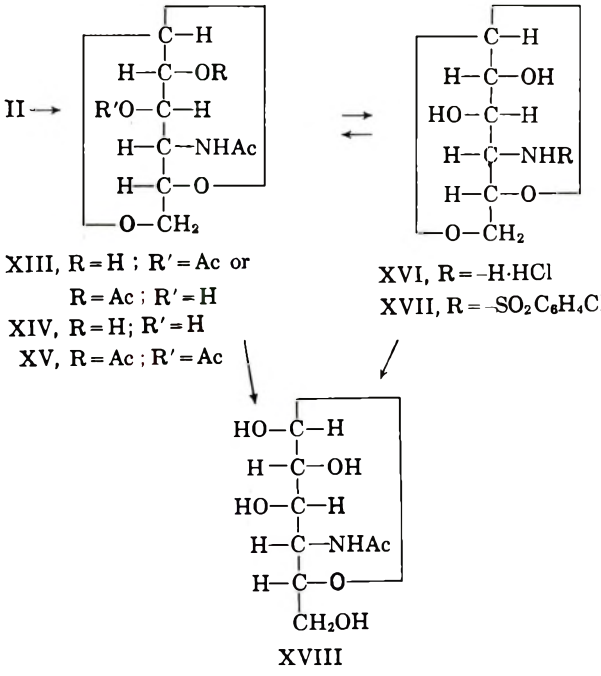


spots correspond to the various possible intermediates resulting from partial deacetylation at positions 2 and 4 with or without opening of the 1,6-anhydro ring.

Opening of the 1,6-anhydro ring of VI was effected by acetolysis. Crystalline mixtures were obtained, but these could not be resolved by crystallization or by chromatography. During purification, partial deacetylation had evidently occurred, giving a 3,6-di-*O*-acetyl derivative X as shown by mutarotation, elemental analysis, and color formation with the Morgan and Elson reagent. Reacetylation of X with acetic anhydride and pyridine gave in very small yield crystalline 2,4-diacetamido-1,3,6-tri-*O*-acetyl-2,4-dideoxy-β-D-glucose (XI). De-*O*-acetylation of mixtures of X and XI and of their anomers gave the crystalline 2,4-diacetamido-2,4-dideoxy-α-D-glucopyranose (XII). The same product was obtained in 16% yield by direct hydrolysis of VI, followed by *N*-acetylation and chromatographic separation of the resulting mixture of products. Hydrolysis of the diacetamido derivative XII was studied by paper chromatography, and the presence of a monoacetamido-monoamino hydrochloride derivative and of a diamino dihydrochloride derivative could be ascertained. On a preparative scale, however, all attempts to obtain these products in crystalline form failed.

Chromatographic separation of the mixture resulting from the ammonolysis of 1,6-anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (II) followed by acetylation gave an additional crystalline product, corresponding to a monoamino derivative. From the mode of preparation and from the course of the reaction most likely to take place, it is probable that this monoamino derivative resulted from traces of water, and that it corresponds to the 4-amino-4-deoxy derivative XIII. The very small yield of the compound, and the fact that the presence of a second monoamino derivative could be detected among the products of ammonolysis, raises some doubt about the validity of this structure. Various derivatives were prepared in order to confirm the proposed structure. The crystalline product XIII contained only one *O*-acetyl group at position 2 or 3 and could be de-*O*-acetylated into 4-acetamido-1,6-anhydro-4-deoxy-β-D-glucopyranose (XIV), which in turn could be fully acetylated to give XV. Attempts to hydrolyze XIV gave as the only crystalline product 4-amino-1,6-anhydro-4-deoxy-β-D-glucopyranose hydrochloride (XVI). *N*-Tosylation of this material gave a crystalline product LXVII different from 1,6-anhydro-2-deoxy-2-*p*-tolylsulfamido-β-D-glucopyranose prepared previously by Micheel and Michaelis,[10] thus establishing conclusively that, if the derivative XVI had the *gluco* configuration, the amino group could not be located at C-2. Acetolysis of XIV followed by de-*O*-acetylation gave in a 40% over-all yield the crystalline 4-acetamido-4-deoxy-β-D-glucose (XVIII), which showed no reaction in the Morgan and Elson test, a proof that it was not a 2-acetamido-2-deoxy sugar. Since the physical properties of XVIII or of 1,6-anhydro derivative XIV differ from those of seven of the 3-acetamido-3-deoxyhexoses or of their 1,6-anhydro derivatives[11–16]



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it can be safely assumed that it is a 4-acetamido-4-deoxy sugar and the *gluco* configuration seems to be the most logical one.[17] Attempts to obtain 4-amino-4-deoxy-D-glucose hydrochloride in crystalline form have failed up to now thus rendering impossible a comparison with the product prepared by Reist and associates.[8]

During the purification of XIII a sirupy fraction was isolated, which gave after de-*O*-acetylation a second crystalline 1,6-anhydromonoacetamidomonodeoxy-β-D-hexopyranose. Splitting of the acetamido group gave a crystalline free amino hydrochloride, but all attempts to open the 1,6-anhydro ring or to obtain other crystalline derivatives failed, and no structure can, therefore, be proposed for this product at the present time.

A 4-amino-4-deoxy sugar recently has been isolated by Wheat and associates[18] from *Chromobacterium violaceum*. This is the first time that a monoamino sugar with the amino group at position 4 has been isolated from a natural source, which points to the possible biological importance of this type of compound.

Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro or micro (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer Model 237. Chromatograms were carried out with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950, 60–200 mesh) used without pretreatment. The sequence of eluants was hexane, benzene or chloroform, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be absorbed to weight of adsorbent was 1 to 50–100. The proportion of weight of substance in grams to volume of fraction of eluent in milliliters was 1 to 100. The ratio of diameter to length of the column was 1 to 20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen. The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

Descending paper chromatograms were developed with a mixture of pyridine, ethyl acetate, acetic acid, water, 5:5:1:3,[19] on sheets of Whatman No. 1 and Whatman No. 54 paper, and the compounds were subsequently detected with ninhydrin or with aniline phthalate on no. 1 papers, and with the alkaline silver reagent on no. 54 papers.

Ammonolysis of 1,6-Anhydro-2,4-di-*O*-p-tolylsulfonyl-β-D-glucopyranose (II).—A solution of 5 g. of II[20] in 320 ml. of methanol was saturated with ammonia gas at 0°, in tubes which were sealed, and then heated for 48 hr. at 100°. After cooling, the reaction mixture was evaporated to dryness, and the residue was acetylated for 24 hr. at room temperature with 40 ml. of acetic anhydride and 120 ml. of anhydrous pyridine. The excess of anhydride was destroyed by adding methanol while cooling in ice, and the solution was evaporated, the last traces of pyridine being removed by codistillation with ethanol and toluene. The residue was dissolved in chloroform and the solution was chromatographed on 500 g. of silica gel. Mixtures of various concentrations of chloroform and ethyl acetate, and pure ethyl acetate eluted 1.34 g. of partially crystalline material which, upon de-*O*-acetylation with sodium methoxide, gave sirups from which no crystalline material could be isolated.

Mixtures of ethyl acetate and acetone, 9:1 and 4:1, eluted a partially crystalline material, which was purified by a second chromatography and recrystallized from a mixture of methanol, ethyl acetate, and pentane to give 140 mg. (5%) of **4-acetamido-1,6-anhydro-4-deoxy-2- or 3-*O*-acetyl-β-D-glucopyranose (XIII)**, m.p. 195–205°. After two recrystallizations, thin, rectangular plates, m.p. 203–204°, with sublimation from 190°, were obtained (the melting point varies with the method of crystallization and the speed of heating); $[\alpha]^{23}D$ −95° (*c* 1.24 in methanol).

Anal. Calcd. for $C_{10}H_{15}O_6N$: C, 48.97; H, 6.17; N, 5.71. Found: C, 48.91; H, 6.11; N, 5.72.

During the purification of XIII, a second monoacetamido compound was isolated. The study of this product is described at the end of this paper.

Elution of the original silica gel column with mixtures of ethyl acetate and acetone, 2:1, 3:2, and 1:1, gave 1.66 g. of partially crystalline material which, after two recrystallizations from a mixture of methanol, ethyl acetate, and pentane, gave 0.90 g. (30%) of **2,4-diacetamido-3-*O*-acetyl-1,6-anhydro-2,4-dideoxy-β-D-glucopyranose (VII)** as prismatic needles, m.p. 226–228°, with sublimation about 200°; $[\alpha]^{22}D$ −43° (*c* 1.04 in methanol).[21]

Anal. Calcd. for $C_{12}H_{18}O_6N_2$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.46; H, 6.31; N, 9.84.

Further elution of the silica gel column with pure acetone and with methanol gave 5.87 g. of side products which were not further investigated.

In another experiment where 4 g. of the ditosyl ester was treated as previously described, the yield of XIII was 35% for the crude material and 11% after recrystallization (m.p. 203–206°), whereas 52% of crude VII was obtained, giving 26% of pure material (m.p. 225–227°) after recrystallization.

2,4-Diacetamido-1,6-anhydro-2,4-dideoxy-β-D-glucopyranose (VI) from VII.—To a solution of 200 mg. of VII, in 13 ml. of methanol, cooled at 0°, was added 0.80 mmole (1.14 mole equivalent) of cold sodium methoxide, and the solution was kept at 0° for 3 days. After evaporation of the solvents, the residue was dissolved in 4 ml. of water, and deionized by passage through a short column of Dowex 50 (H^+ form). The effluent was concentrated to give a sirup which crystallized spontaneously. Recrystallization from a mixture of methanol, acetone, and ether gave 164 mg. (96%) of elongated prisms, m.p. 246–248° (with sublimation from 243°); $[\alpha]^{23}D$ −46° (c 0.96 in methanol).[21]

Anal. Calcd. for $C_{10}H_{16}O_5N_2$: C, 49.17; H, 6.60. Found: C, 49.17; H, 6.66.

2,4-Diacetamido-3-*O*-acetyl-1,6-anhydro-2,4-dideoxy-β-D-glucopyranose (VII) from IX.—A solution of 270 mg. of 2-acetamido-1,6-anhydro-3-*O*-benzoyl-4-*O*-methylsulfonyl-β-D-galactopyranose (IX)[5,22] and 150 mg. of sodium azide in 25 ml. of dimethylformamide was refluxed for 24 hr. The solution was then evaporated to dryness, and the residue was dissolved in 10 ml. of methanol. To the solution cooled at 0° was added 0.5 ml. of 1.75 *N* barium methoxide. After standing overnight at 0°, the solution was diluted with methanol and filtered through a double layer of Celite and Darco G-60. It was evaporated to dryness and the residue, dissolved in water, was passed through a column of Dowex 50 (H^+ form). After evaporation, the residue weighed 106 mg. and showed in the infrared spectra the typical adsorption at 2120 $cm.^{-1}$ for the azide group. The material was dissolved in 20 ml. of ethanol and the solution was filtered through Darco G-60 and hydrogenated in the presence of 20 mg. of platinum oxide under a slight pressure of hydrogen for 4 to 5 hr. After filtration, the solution was evaporated and the residue was acetylated overnight with 0.5 ml. of anhydrous pyridine and 0.3 ml. of acetic anhydride. The excess of anhydride was decomposed by addition of ice, and the solution was evaporated to dryness. The residue was dissolved in chloroform and chromatographed on silica gel. Elution with pure acetone gave 84 mg. of crystalline material which afforded, after recrystallization from a mixture of methanol, acetone and ether, 70 mg. (35%) of prismatic needles VII, m.p. 228–230°; $[\alpha]^{21}D$ −44° (*c* 0.94 in methanol). The product showed no depression of the melting point in admixture with the product prepared by ammonolysis of II, and the infrared spectra of both samples were identical.

Anal. Calcd. for $C_{12}H_{18}O_6N_2$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.25; H, 6.40; N, 9.54.

(17) The possibility of the formation of the *allo* configuration is very remote.

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(21) The first preparation of this product was carried out in this laboraby Dr. S. Hakomori.

(22) On large crystals and rapid heating, m.p. 221–222° dec., was observed.

Acetolysis of VI.—A solution of 50 mg. of VI in a mixture containing 3 ml. of acetic anhydride, 0.05 ml. of concentrated sulfuric acid, and 1.95 ml. of glacial acetic acid was kept at room temperature for 5 days, during which time the optical rotation changed from $[\alpha]^{28}D$ −37° (after 8 min.) to $[\alpha]^{28}D$ +125° (after 24 hr.), and $[\alpha]^{23}D$ +117° (after 5 days). The excess of acetic anhydride was decomposed by addition of a small piece of ice, and the reaction mixture was neutralized with 230 mg. of anhydrous barium acetate. The salts were eliminated by filtration through a double layer of Darco G-60 and Celite and, after evaporation of the solvents, the residue was dissolved in chloroform, and the solution was chromatographed on silica gel. Elution with pure ethyl acetate and mixtures of ethyl acetate and acetone, 7:1 and 3:1, eluted 58 mg. of a nearly colorless sirup. Crystallization of this sirup from a mixture of methanol and ether gave 24 mg. of microcrystals, m.p. 183–200°. Both crystals and mother liquor gave two spots on paper chromatography (Whatman No. 54), with $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.28 and $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.51. Complex mutarotations were observed in both cases; with the microcrystals, there was a change from $[\alpha]^{26}D$ +52° (after 12 min.) to $[\alpha]^{26}D$ +71° (after 60 min.) and $[\alpha]^{26}D$ +63° (after 24 hr., *c* 0.91 in methanol), whereas the mother liquor mutarotated from $[\alpha]^{27}D$ +79° (after 6 min.) to $[\alpha]^{27}D$ +85° (after 30 min.) and $[\alpha]^{27}D$ +65° (after 24 hr., *c* 0.74 in methanol).

Acetylation of 12 mg. of impure crystalline material was carried out with 0.3 ml. of acetic anhydride and 3 ml. of anhydrous pyridine in the usual manner to give 18 mg. of a brown sirup which was purified by chromatography on silica gel. Elution with mixtures of ethyl acetate and acetone, 3:1 and 3:2, gave 11 mg. of **2,4-diacetamido-3,6-di-*O*-acetyl-2,4-dideoxyglucose** (**X**), a colorless sirup which could not be crystallized, but which gave only one spot on paper chromatography (Whatman No. 54), R_f 0.91, $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.75.

Anal. Calcd. for $C_{14}H_{22}O_8N_2$: C, 48.55; H, 6.40. Found: C, 48.63; H, 6.45.

Acetylation of 21 mg. of the microcrystals obtained initially gave 14 mg. of the same tetraacetate X.

In another acetolysis experiment carried out on 165 mg. of VI, the colorless sirup isolated in the first chromatogram was immediately acetylated with acetic anhydride and pyridine, and care was taken to avoid moisture. This gave 120 mg. of partially crystalline material, which was purified by chromatography on silicic acid. Mixtures of ethyl acetate and acetone (4:1, 3:2, and 1:1) eluted 43 mg. of partially crystalline material which, after crystallization from a mixture of methanol, ethyl acetate, and ether, gave 15 mg. (7%) of **2,4-diacetamido-1,3,6-tri-*O*-acetyl-2,4-dideoxy-β-D-glucopyranose** (**XI**), transparent platelets, m.p. 263–265°; $[\alpha]^{22}D$ −8° (*c* 0.89 in methanol); no mutarotation was observed.

Anal. Calcd. for $C_{16}H_{24}O_9N_2$: C, 49.48; H, 6.23; N, 7.21. Found: C, 49.37; H, 6.24; N, 7.32.

The pentaacetate gave a weak Morgan–Elson reaction which intensified on standing. In paper chromatography, the sugar moved with R_f of 0.89 and 0.94, and $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.74 and 2.1 (on Whatman papers No. 1 and 54, respectively); it reacted very weakly with the alkaline silver reagent and gave a light pink spot with aniline phthalate. Further elution of the initial silica gel column with acetone and with methanol gave 177 mg. of sirup, giving a faintly positive Morgan–Elson reaction, and moving on paper chromatography with $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.06 and 1.35 (Whatman No. 54). This material could not be further purified, and it was de-*O*-acetylated as described in the next paragraph.

2,4-Diacetamido-2,4-dideoxy-α-D-glucopyranose (XII) from X and XI.—De-*O*-acetylation was carried out on a mixture of several more or less acetylated products obtained in the acetolysis experiment previously described; 210 mg. of sirupy material was dissolved in 2 ml. of methanol, and to this cooled solution was added 1.92 mmoles of cold sodium methoxide. The solution was kept at 0° overnight, then evaporated to dryness. The residue was dissolved in 1 ml. of water and deionized by passage through a short column of Dowex 50 (H^+ form). After concentration 126 mg. of sirup was obtained, which was chromatographed on silica gel. A mixture of ethyl acetate and acetone, 1:1, and pure acetone eluted 81 mg. of a sirupy product which, on paper chromatograms, could be detected neither with aniline phthalate nor with the silver reagent, and which is probably a 1,6-anhydro derivative. Further elution of the silica gel column with mixtures of acetone and methanol (19:1, 9:1, and 4:1) gave 50 mg. of sirup which, after two recrystallizations from a mixture of methanol, ethyl acetate, and ether, gave 10 mg. of XII, small prisms, decomposing without melting at about 233° (with partial transformation to needles at 210°). This compound was shown by paper chromatography (R_f 0.53, $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.04, on Whatman No. 1 and 54) to be identical with XII obtained by hydrolysis of VI followed by *N*-acetylation as described subsequently. Compound XII showed mutarotation in water, from $[\alpha]^{24}D$ +88° (after 7 min.) to $[\alpha]^{24}D$ +61° (after 3 hr. and after 24 hr., *c* 1.15).

2,4-Diacetamido-2,4-dideoxy-α-D-glucopyranose (XII) from VI.—A mixture of 82 mg. of VI and 1 ml. of 0.5 *N* hydrochloric acid was heated for 1 hr. at 100°, after which a large amount of absolute ethanol was added, and the solution evaporated, the last traces of acid being removed by codistillation with ethanol and toluene. A dark-colored sirup was obtained (107 mg.) which was shown by paper chromatography (Whatman No. 54) to contain at least 4 components: $R_{2\text{-amino-2-deoxyglucose}}$ 0.61, $R_{2\text{-amino-2-deoxyglucose}}$ 1.00, $R_{2\text{-amino-2-deoxyglucose}}$ 1.39, and $R_{2\text{-amino-2-deoxyglucose}}$ 1.96. No attempt was made to separate these products, and the crude hydrolysate was directly *N*-acetylated, by dissolving it in 2.5 ml. of methanol, and adding 284 mg. of silver acetate and 1.5 ml. of acetic anhydride to the solution. After standing overnight at room temperature, the mixture was refluxed for 5 min. and filtered while hot through a double layer of Celite and Darco G-60, and the salts were successively washed with hot methanol and hot water. To the filtrate was added 6 drops of 2 *N* hydrochloric acid, and, after 2 hr., the silver chloride precipitate was removed by filtration and washed with methanol. The filtrate was evaporated in the presence of toluene and absolute ethanol to give 104 mg. of dark brown sirup. It was chromatographed on silica gel, and pure acetone eluted 19 mg. (23%) of the starting material VI. Pure acetone, and a mixture of acetone and methanol, 19:1, eluted 17 mg. of a sirup showing an R_f 0.73 and an $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.26 on Whatman No. 1 paper; this material had a positive ninhydrin reaction but also gave a faint color in the Morgan–Elson reaction. The sirup could not be crystallized. Further elution of the silicic acid column with mixtures of acetone and methanol (19:1, 9:1, and 4:1) gave 32 mg. (36%) of partially crystalline material, which gave a very faint ninhydrin reaction. In the Morgan–Elson test, it gave a weak color which intensified on standing. Crystallization from a mixture of 95% ethanol, ethyl acetate, and ether gave 14 mg. (16%) of XII, small prisms, decomposing without melting at about 230°. This product had the same mobility on paper chromatograms as that obtained from XI (R_f 0.53, $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.04), and a mutarotation in water from $[\alpha]^{21}D$ +84° (after 30 min.) to $[\alpha]^{22}D$ +69° (after 2.5 hr. and 24 hr., *c* 0.32).

Anal. Calcd. for $C_{10}H_{18}O_6N_2$: C, 45.80; H, 6.92. Found: C, 45.86; H, 6.93.

Hydrolysis of VI.—Examination of the products resulting from the hydrolysis of VI with concentration of hydrochloric acid varying from 0.5 *N* to 3 *N* and time of reaction varying from 30 min. to 24 hr. was made by paper chromatography. It showed, in cases where hydrolyses had been carried out for 30 min. with 2 *N* or 3 *N* acid, and for 30 min., 1 hr., and 3 hr. with 0.5 *N* acid, the presence of five different products. The R_f values and properties of these products were as follows: R_f 0.19 ($R_{2\text{-amino-2-deoxyglucose}}$ 0.66), giving a purple spot with ninhydrin, a brown spot with aniline phthalate, and reducing silver nitrate; R_f 0.22 ($R_{2\text{-amino-2-deoxyglucose}}$ 0.76), blue with ninhydrin and not detected by the other two reagents; R_f 0.29 ($R_{2\text{-amino-2-deoxyglucose}}$ 1.00), purple with ninhydrin, brown with aniline phthalate, and reducing silver nitrate; R_f 0.37 ($R_{2\text{-amino-2-deoxyglucose}}$ 1.28), brownish yellow with ninhydrin, pink with aniline phthalate, and reducing silver nitrate; R_f 0.44 ($R_{2\text{-amino-2-deoxyglucose}}$ 1.52), purple with ninhydrin, but not detected with either aniline phthalate or silver nitrate. In addition, a pink spot of R_f 0.52 ($R_{2\text{-amino-2-deoxyglucose}}$ 2.00, $R_{2\text{-acetamido-2-deoxyglucose}}$ 1.01) was observed with aniline phthalate, but not with ninhydrin; this last named material must, therefore, correspond to the diacetamido glucose XII previously described. The five spots of ninhydrin positive material probably correspond to the various possible combinations of compounds having the 1,6-anhydro ring either present (compounds not reacting with silver nitrate and aniline phthalate) or opened (reducing compounds), and having either or both of the amino groups free or acetylated. All hydrolysates were found to be composed of complex mixtures and, even with strong acid and prolonged hydrolysis, the presumed 1,6-anhydro compounds were always found present.

Hydrolysis of XII.—Samples of XII were hydrolyzed with 0.5 *N* and with 2 *N* hydrochloric acid for 30 min., 2 hr., 6 hr., and 24 hr., and the hydrolysates were examined by chromatography on paper. Paper chromatography on Whatman No. 1 paper showed that the starting material (R_f 0.50 and $R_{2\text{-amino-2-deoxyglucose}}$ 1.82) had completely disappeared in less than 30 min. with 2 *N* acid, and in more than 2 hr. with 0.5 *N* acid. Two spots of ninhydrin positive material were observed in all cases: one with an R_f 0.17 and $R_{2\text{-amino-2-deoxyglucose}}$ 0.68, and a second having R_f 0.28 and $R_{2\text{-amino-2-deoxyglucose}}$ 1.12. The slower moving component seemed to be present in slightly larger amounts, and it was in the 2-hr. and the 6-hr. hydrolysates that the color obtained with ninhydrin was most intense. Since both compounds must be amino sugar hydrochlorides, it was assumed that one of them, probably the faster moving component, was **4-(or 2)-acetamido-2-(or 4)-amino-2,4-dideoxy-D-glucose hydrochloride** and the other was **2,4-di-amino-2,4-dideoxy-D-glucose dihydrochloride**.

Several attempts were made to hydrolyze XII on a preparative scale and to isolate the products, either by crystallization, or by elution from a Dowex-50 column (H^+ form) with 0.3 *N*, 0.5 *N*, and 1 *N* hydrochloric acid, according to the method described by Gardell[23] for the separation of glucosamine and galactosamine. In no case, however, could a good separation be obtained, nor any crystalline material be isolated.

4-Acetamido-1,6-anhydro-4-deoxy-β-D-glucopyranose (XIV).—To a cold solution of 102 mg. of XIII in 2 ml. of absolute methanol was added 1.15 mole equivalent of sodium methoxide. After standing overnight at 0°, the solution was evaporated to dryness and the residue dissolved in water, then deionized by passage through a short column of Dowex 50 (H^+ form). After evaporation, the crystalline residue was recrystallized from a mixture of methanol and ether to give 73 mg. (87%) of small prisms, m.p. 212–213° (with sublimation starting at 190°); $[\alpha]^{27}D$ −118° (c 0.73 in methanol).

Anal. Calcd. for $C_8H_{13}O_5N$: C, 47.29; H, 6.45. Found: C, 47.35; H, 6.63.

4-Acetamido-2,3-di-*O*-acetyl-1,6-anhydro-4-deoxy-β-D-glucopyranose (XV).—Acetylation of 24 mg. of XIV with acetic anhydride in pyridine solution in the usual manner gave, after crystallization from a mixture of methanol and ether, 25 mg. (73%) of small prisms, m.p. 181.5–182.5°; $[\alpha]^{27}D$ −62° (c 0.83 in methanol).

Anal. Calcd. for $C_{12}H_{17}O_7N$: C, 50.17; H, 5.96; CH_3CO, 44.95. Found: C, 50.10; H, 6.08; CH_3CO, 44.95.

The same product was obtained in 34% yield by acetylation of XIII. On paper chromatography (Whatman No. 54) XV had an R_f of 0.93, and $R_{2\text{ acetamido 2 deoxyglucose}}$ 1.71, giving a weak spot with the alkaline silver reagent.

4-Acetamido-4-deoxy-β-D-glucopyranose (XVIII).—A solution of 90 mg. of XIV in a mixture of 3 ml. of acetic anhydride, 0.05 ml. of concentrated sulfuric acid, and 1.95 ml. of glacial acetic acid was kept for 24 hr. at room temperature, during which time the optical rotation was observed to shift from $[\alpha]^{23}D$ +89° (23 min.) to $[\alpha]^{21}D$ +146° (19 hr. and 24 hr.). The acetolysis mixture was poured onto 10 ml. of crushed ice and then extracted with 200 ml. of chloroform. The organic layer was washed three times with saturated sodium bicarbonate and three times with water, then dried over sodium sulfate. The solution was evaporated to dryness, to give 164 mg. of a pale yellow sirup which could not be crystallized. It was directly de-*O*-acetylated by dissolving it in 2 ml. of absolute methanol, and adding to the solution cooled at 0°, 1.92 mmoles of cold sodium methoxide. The mixture was kept overnight at 0°, then evaporated to dryness, and the residue was dissolved in water and passed through a short column of Dowex 50 (H^+ form). The effluent was concentrated to give 100 mg. of yellow sirup. It was dissolved in a mixture of ethyl acetate and acetone, and the solution was chromatographed on silica gel. Mixtures of acetone and methanol (19:1, 9:1, and 4:1) eluted 97 mg. of partially crystalline material which, after two recrystallizations from a mixture of ethanol and ether, gave 37 mg. (40%) of very fine needles, m.p. 171–174° dec. The compound showed mutarotation from $[\alpha]^{23}D$ +12.5° (after 15 min.) to $[\alpha]^{26}D$ +19° (after 44 hr., at equilibrium) (c 0.79 in water).

Anal. Calcd. for $C_8H_{15}O_6N$: C, 43.42; H, 6.84. Found: C, 43.48; H, 6.81.

The product gave no color with the Morgan–Elson reagent. On paper chromatography (Whatman No.1) it migrated with an R_f of 0.44 ($R_{2\text{-amino-2-deoxyglucose}}$ 1.37, $R_{2\text{-acetamido-2-deoxyglucose}}$ 0.90), giving a reddish purple spot with aniline phthalate. When 3-acetamido-3-deoxy-β-D-glucose (*N*-acetylkanosamine) was chromatographed in the same solvent system, it moved with an R_f of 0.49, $R_{2\text{-amino-2-deoxyglucose}}$ 1.45 and $R_{2\text{-acetamido-2-deoxyglucose}}$ 0.95, giving a brownish red color with aniline phthalate.

Hydrolysis of 4-Acetamido-4-deoxy-β-D-glucopyranose (XVIII).—Samples of XVIII and 3-acetamido-3-deoxy-β-D-glucopyranose for comparison were heated with 1 *N* hydrochloric acid in sealed tubes at 100° for 2 hr. In the Elson–Morgan test the hydrolysate of XVIII gave no color, whereas that of *N*-acetylkanosamine gave a positive reaction. On paper chromatography (Whatman No. 1) the two hydrolyzates were found to migrate in the same way: R_f 0.32, $R_{2\text{-amino-2-deoxyglucose}}$ 1.07, $R_{2\text{-acetamido-2-deoxyglucose}}$ 0.64; but the hydrolysate of XVIII (4-amino-4-deoxy-D-glucose hydrochloride) gave a brown color with aniline phthalate, whereas 3-amino-3-deoxy-D-glucose hydrochloride gave a red-brown color.

Hydrolysis of XIV.—A solution of 70 mg. of XIV in 3.5 ml. of 0.5 *N* hydrochloric acid was heated for 15 hr. in a sealed tube at 100°. The brown hydrolyzate was evaporated, and the last traces of acid removed by codistillation with absolute ethanol and toluene. This gave 59 mg. of partially crystalline material which, after three recrystallizations from a mixture of aqueous ethanol and ether, gave 24 mg. (35%) of **4-amino-1,6-anhydro-4-deoxy-β-D-glucopyranose hydrochloride (XVI)**, small prisms decomposing without melting between 200 and 220°. The product had $[\alpha]^{26}D$ −103° (c 0.84 in water), and showed no mutarotation.

Anal. Calcd. for $C_6H_{12}O_4NCl$: C, 36.46; H, 6.12; Cl, 17.94. Found: C, 36.33; H, 6.31; Cl, 17.28.

On paper chromatography (Whatman No. 1) XVI gave a spot of R_f 0.37 and $R_{2\text{-amino-2-deoxyglucose}}$ 1.28, which could be detected both by ninhydrin and by the silver reagent (the starting material XIV had an $R_{2\text{-amino-2 deoxyglucose}}$ of 2.40). Both the Elson–Morgan and the Morgan–Elson tests were negative with compound XVI.

In another experiment, hydrolysis of XIV was carried out with 3 *N* hydrochloric acid and heating for 2.5 hr. at 100°. In this case a sirup was obtained which could not be crystallized. Paper chromatography (Whatman No. 1) of this sirup showed three spots of ninhydrin positive material, with the following $R_{2\text{ amino-2-deoxyglucose}}$ values: 0.87, 1.03, and 1.25. The fast moving material was the major component. The product with $R_{2\text{-amino-2-deoxyglucose}}$ 1.25 corresponds to XVI, while that with 1.03 is probably **4-amino-4-deoxy-D-glucose hydrochloride**. Acetylation of 13 mg. of the sirup with acetic anhydride in pyridine, in the usual manner, gave 25 mg. of a sirup from which 13 mg. of crystals, m.p. 160–172°, was obtained. After three recrystallizations from a mixture of methanol and ether, 7 mg. (37%) of **4-acetamido-2,3-di-*O*-acetyl-1,6-anhydro-4-deoxy-β-D-glucopyranose (XV)** was obtained; m.p. 179–181°; $[\alpha]^{23}D$ −62° (c 0.84 in methanol). The melting point was not depressed by admixture with the previously described XV.

1,6-Anhydro-4-deoxy-4-*p*-tolylsulfonamido-β-D-glucopyranose XVII.—A solution of 28 mg. of XVI, 27 mg. of crystalline sodium bicarbonate and 27 mg. (1.1 mole equivalent) of *p*-toluenesulfonyl chloride in 0.8 ml. of water was shaken for 6 hr. at room temperature. After addition of 2 ml. of water, crystals began to form. The mixture was left overnight at 0°, then poured into a large volume of chloroform, and the organic layer was washed three times with saturated sodium bicarbonate and three times with water, and finally dried over sodium sulfate. After evaporation of the solvent, 31 mg. (69%) of a sirup was obtained which, by crystallization from a mixture of acetone and ether, gave 17 mg. (38%) of fine needles, m.p. 187–188.5°; $[\alpha]^{22}D$ −52° (c 1.1 in methanol).

Anal. Calcd. for $C_{13}H_{17}O_6NS$: C, 49.54; H, 5.43; S, 10.17. Found: C, 49.28; H, 5.44; S, 10.00.

Monoamino-1,6-anhydro-monodeoxy-β-D-hexopyranose.—In the purification of XIII (which see), some sirupy material had been eluted from the second silicic acid column by mixtures of chloroform and ethyl acetate, and by acetone, either alone or mixed with methanol (whereas XIII was eluted by mixtures of ethyl acetate and acetone). This sirup was added to the mother liquors of XIII, to give a total of 1.17 g. of sirup which was dissolved in methanol and de-*O*-acetylated by adding 5.28 mmoles of sodium methoxide, and keeping overnight at 0°. The reaction mixture was deionized by dilution with water and passage through a column of Dowex 50 (H^+ form), and the effluent was concentrated to give 0.92 g. of sirup which was chromatographed on silica gel. Mixtures of ethyl acetate and acetone, 1:1, and pure acetone eluted 297 mg. of partially crystalline material from

(23) S. Gardell, *Acta Chem. Scand.*, **7**, 207 (1953).

which 186 mg. of pure XIV, m.p. 209–211°, was obtained after recrystallization from a mixture of methanol and ether.

Further elution of the silica gel column with pure acetone, and with a mixture of acetone and methanol, 19:1, gave 593 mg. of a pale yellow sirup which could not be crystallized; $[\alpha]^{23}D$ −175° (*c* 1.08 in methanol). The elemental analysis corresponded to that of a **monoacetamido-1,6-anhydro-monodeoxy-β-D-hexopyranose** with one mole of methanol added.

Anal. Calcd. for $C_8H_{13}O_5N \cdot CH_3OH$: C, 45.95; H, 7.28; N, 5.96. Found: C, 46.12; H, 7.38; N, 6.01.

On paper chromatography (Whatman No. 54) this product moved with an $R_{2\text{-amino-2-deoxyglucose}}$ 2.07 and reacted weakly with the alkaline silver reagent.

A solution of 80 mg. of this sirup in 3.5 ml. of 0.5 *N* hydrochloric acid was heated for 15 hr. at 100° in a sealed tube. The solution was then evaporated to dryness, the last traces of acid being removed by codistillation with ethanol and toluene. This residue was crystallized from a mixture of water, ethanol, and ether to give 34 mg. (51%) of elongated prisms, decomposing at 215–225° without melting. This compound had $[\alpha]^{26}D$ −169° (*c* 1.10 in water), and no mutarotation was observed. The elemental analysis corresponded to a **monoamino-1,6-anhydro-monodeoxy-β-D-hexopyranose hydrochloride**.

Anal. Calcd. for $C_6H_{12}O_4NCl$: C, 36.46; H, 6.12; Cl, 17.94. Found: C, 36.34; H, 6.15; Cl, 18.05.

This hydrochloride gave a positive ninhydrin reaction, but no color in either the Elson–Morgan or the Morgan–Elson test. By paper chromatography (Whatman No. 1 and 54) a single spot was obtained with R_f 0.32 and $R_{2\text{ amino-2 deoxyglucose}}$ 1.10.

Several attempts were made to obtain the free sugar by opening the 1,6-anhydro ring by hydrolysis with 2 *N*, 3 *N*, or 6 *N* hydrochloric acid, but this was always accompanied by much decomposition, as evidenced on paper chromatograms by trailing and multiple spots, and no pure material could be obtained. Attempts to obtain other crystalline derivatives by acetylation, tosylation, or acetolysis were also unsuccessful.

1,6;3,4-Dianhydro-2-O-p-tolylsulfonyl-β-D-galactopyranose (I).[21]—A solution of 300 mg. of II[20] in 10 ml. of methanol and 5.8 ml. of a solution of 0.43 *N* sodium methylate (3.7 moles) was refluxed for 24 hr. After concentration to 3 ml., the sirup was diluted with 30 ml. of water and 76 mg. of crystals were filtered. The filtrate was deionized by passage through columns of Amberlite IR 400 (OH^- form) and Dowex 50 (H^+ form) and evaporated to dryness. The residue was crystallized from methanol to give an additional yield of 9 mg. (total yield, 70%). Recrystallization from a mixture of methanol and pentane raised the melting point to 149–150°; $[\alpha]^{26}D$ −37° (c 0.56 in chloroform).[24]

Anal. Calcd. for $C_{13}H_{14}O_6S$: C, 52.34; H, 4.73; S, 10.75. Found: C, 52.42; H, 4.80; S, 10.59.

Acknowledgment.—The authors wish to thank Dr. R. B. Baker for providing before publication the experimental conditions for the replacement of a mesyloxy group with an azide group, and Dr. H. H. Baer for a sample of 3-acetamido-3-deoxy-D-glucose.

(24) Černý, Gut, and Pacák[25] reported m.p. 148–150°; $[\alpha]D$ −40° (*c* 1.4 in chloroform); Hann and Richtmyer[5] observed 149–149.5°; $[\alpha]^{20}D$ −41.7° (*c* 1 in chloroform).

(25) M. Černý, V. Gut, and J. Pacák, *Collection Czech. Chem. Commun.*, **26**, 2542 (1961).

The Synthesis of 2-Acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucose (*N*-Acetylmuramic Acid) and of Benzyl Glycoside Derivatives of 2-Amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose (Muramic Acid)[1]

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Received June 6, 1963

The synthesis of various derivatives of the benzyl α-D-glycoside of 2-amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose (muramic acid) and of the disaccharide benzyl 6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside is described. In addition, crystalline 2-acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucose (*N*-acetylmuramic acid) has been obtained.

In a previous paper,[3] the synthesis of the acetylated methyl α-glycoside of the disaccharide 2-acetamido-2-deoxy-D-glucopyranosyl-(1 → 6)-*N*-acetylmuramic acid has been described. This disaccharide has been postulated as one of the repeating units of the 2-amino-2-deoxyglucan, which constitutes the backbone of the cell wall of numerous Gram-positive and Gram-negative bacteria.[4–6] Since removal of the protective methyl α-glycosidic group cannot be accomplished without considerable degradation of the disaccharide linkage, the synthesis of the disaccharide was repeated using the protective benzyl α-glycoside group, which can be removed by catalytic hydrogenolysis. Starting from benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (I),[7] the synthesis proceeded along a route similar to the one described for the methyl α-glycoside derivative.[3] The various crystalline muramic acid derivatives II to VIII were obtained in yields quite similar to those obtained for the methyl α-glycoside derivatives. The condensation of benzyl 2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl] - α - D - glucopyranoside (VI) with 2-acetamido - 3,4,6 - tri - *O* - acetyl - 2 - deoxy - α - D - glucopyranosyl bromide (XI) proceeded, however, in very low yield, and only 3 to 4% of the desired disaccharide (XII) was obtained. Removal of the benzyl glycoside group of the deacetylated product XII by catalytic hydrogenation gave an amorphous disaccharide; its properties, compared to those of the disaccharide isolated from *Micrococcus lysodeikticus* cell wall, will be described in a forthcoming publication.

Removal of the benzyl glycoside group of benzyl 2-acetamido - 3 - *O* - (D - 1 - carboxyethyl) - 2 - deoxy-

(1) Amino Sugars XXXVII. This is publication no. 341 of The Robert W. Lovett Memorial Unit for the Study of Crippling Diseases, Harvard Medical School at the Massachusetts General Hospital, Boston 14, Mass. This investigation has been supported by research grants from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States Public Health Service (Grant E-4282) and the National Science Foundation (Grant 9-2312). It was presented before the Division of Carbohydrate Chemistry at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) On leave of absence from the Weizmann Institute of Science, Rehovoth, Israel.

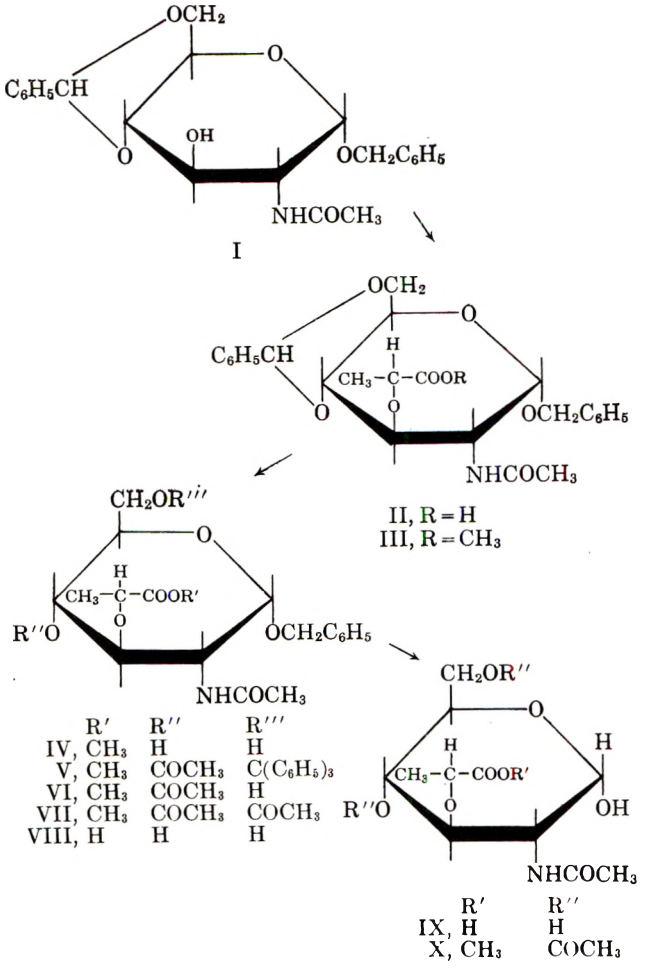
(3) H. M. Flowers and R. W. Jeanloz, *J. Org. Chem.*, **28**, 1564 (1963).

(4) M. R. J. Salton and J. M. Ghuysen, *Biochim. Biophys. Acta*, **36**, 552 (1959).

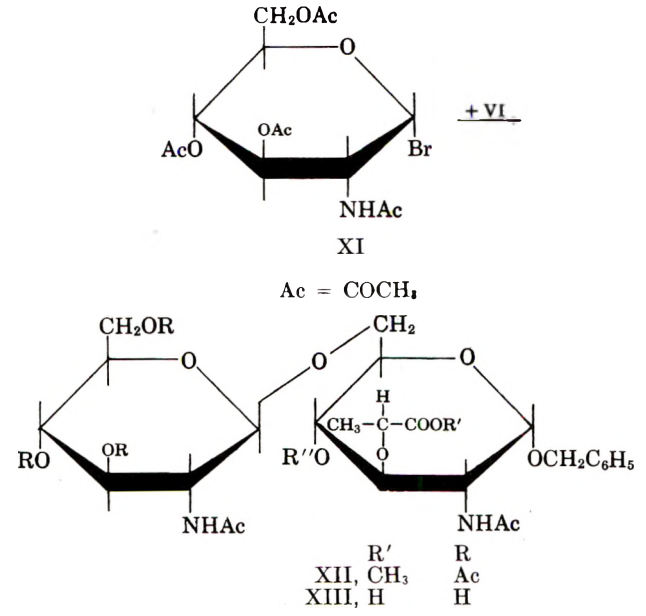
(5) M. R. J. Salton and J. M. Ghuysen, *ibid.*, **45**, 355 (1960).

(6) H. R. Perkins, *Biochem. J.*, **74**, 182 (1960).

(7) R. Kuhn, H. H. Baer, and A. Seeliger, *Ann.*, **611**, 236 (1958).



α - D - glucopyranoside (VIII) gave crystalline 2-acetamido - 3 - *O* - (D - 1 - carboxyethyl) - 2 - deoxy-α - D - glucose or *N* - acetylmuramic acid (IX). The preparation of a compound with a similar structure, but obtained in an amorphous form, recently has been reported.[8] The preparation of VIII in a pure state allows the determination of its physical and chemical properties, especially its reactions with the Morgan and Elson reagent[9] and with the periodate ion. These tests have been extensively used in the determination of the structure of the glucosaminyl–muramic acid derivative isolated from bacterial cell wall,[4–6] but no comparison of the results with those obtained with pure *N*-acetylmuramic acid has been reported.



Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro- or micro- (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer, Model 237. Chromatograms were made with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950, 60–200 mesh), which was used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluents was hexane, benzene or ethylene dichloride, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 50–100. The proportion of weight of substance in grams to volume of fraction of eluent in milliliters was 1 to 100. The ratio of diameter to length of the column was 1 to 20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen. The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (II).—A solution of 8 g. of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (I) dissolved in 500 ml. of dry dioxane was treated with sodium hydride and L-α-chloropropionic acid as described previously for the preparation of the corresponding methyl α-glycoside derivative,[3] except that the stirred mixture was maintained at 60° overnight to complete the reaction. After addition of 20 ml. of ice–water, the clear solution was cooled and acidified with cold 6 *N* hydrochloric acid. Addition of 1 l. of ice–water precipitated a white solid which was separated by filtration, washed thoroughly with water and dried, giving 8.9 g. melting at 227–230°. Recrystallization from methanol gave 7.2 g. (77%) of needles, m.p. 237–239°, $[\alpha]^{18}D$ +115° (*c* 1.28, in methanol); the melting point was unaffected by a second recrystallization.

Anal. Calcd. for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.64; H, 6.29; N, 3.00.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (III).—A solution of 140 mg. of II in the minimum of methanol was esterified by the addition of a slight excess of diazomethane in ether. Evaporation of the solution and recrystallization of the residue from methanol gave 115 mg. (80%) of needles, m.p. 212–213°, $[\alpha]^{21}D$ +94° (*c* 0.70, in chloroform). The melting point was unchanged on recrystallization from ethyl acetate.

Anal. Calcd. for $C_{26}H_{31}NO_8$: C, 64.31; H, 6.44; N, 2.89. Found: C, 64.26; H, 6.49; N, 2.89.

Benzyl 2-Acetamido-2-deoxy-3-*O*-[D-1-(methyl carboxylate) ethyl]-α-D-glucopyranoside (IV).—A mixture of 90 mg. of III and 1 ml. of 60% acetic acid was heated for 30 min. on a boiling water bath. Evaporation gave a glassy residue which was freed from benzaldehyde by codistillation with water. It was recrystallized from a mixture of acetone, ether, and pentane, giving needles, m.p. 120–122°, $[\alpha]^{23}D$ +137° (*c* 0.94, in chloroform).

Anal. Calcd. for $C_{19}H_{27}NO_8$: C, 57.42; H, 6.85; N, 3.52. Found: C, 57.40; H, 6.89; N, 3.52.

Compound IV also could be prepared conveniently directly from II: the benzylidene group was first removed with 60% acetic acid, then the crude product was esterified with diazomethane, and the resulting ester was recrystallized as described. In this way, 7.0 g. of II gave 3.0 g. of IV (50% over-all yield), m.p. 120–122°.

(8) P. M. Carroll, *Nature*, **197**, 694 (1963).

(9) W. T. J. Morgan and L. A. Elson, *Biochem. J.*, **28**, 988 (1934).

Benzyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-6-*O*-triphenylmethyl-α-D-glucopyranoside (V).—To a solution of 110 mg. of IV in 0.5 ml. of pyridine was added 100 mg. of triphenylchloromethane. The solution was heated to 100°, and 0.3 ml. of acetic anhydride was immediately added to the hot solution, which was allowed to cool to room temperature and left overnight. The solution was then poured into ice–water and the gummy precipitate obtained was separated, washed thoroughly with water and dried. It was dissolved in benzene and the solution was chromatographed on silica gel. Elution with a mixture of benzene and ether 4:1 gave 153 mg. (81%) of crystalline material. It was recrystallized from a mixture of ethyl acetate and hexane, to give colorless prisms, m.p. 149–151°, $[\alpha]^{25}D$ +101° (*c* 0.88, in chloroform).

Anal. Calcd. for $C_{40}H_{43}NO_9$: C, 70.47; H, 6.36. Found: C, 70.44; H, 6.40.

Benzyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (VI). From V.—Forty milligrams of V was detritylated by heating at 100° for 30 min. with 0.5 ml. of 60% acetic acid. The acetic acid was removed by evaporation, and the residue was dissolved in benzene and chromatographed on silica gel. A mixture of ether and ethyl acetate, 1:1, eluted 18.5 mg. (72%) of crystalline fractions, which were recrystallized from a mixture of acetone and ether, giving needles, m.p. 152–153° after sintering at 144° and resolidifying; $[\alpha]^{25}D$ +127° (*c* 1.49, in chloroform).

Anal. Calcd. for $C_{21}H_{29}NO_9$: C, 57.39; H, 6.65; N, 3.19. Found: C, 57.51; H, 6.79; N, 3.28.

From IV.—A solution of 2.0 g. of IV in 6 ml. of dry pyridine was allowed to react with 1.6 g. of triphenylchloromethane overnight at room temperature. The solution was then heated to 100°, 5 ml. of acetic anhydride was immediately added, and the reaction was allowed to proceed for an additional 7 hr. at room temperature. After pouring into water, the gummy precipitate was separated, then hydrolyzed with dilute acetic acid, and purified by chromatography as described in the previous section. Recrystallization from a mixture of acetone and ether gave 1.22 g. (55% over-all yield from IV), m.p. 152–153° (after sintering at 144°), identical with the product described previously.

Benzyl 2-Acetamido-4,6-di-*O*-acetyl-2-deoxy-3-*O*-[D-1-methyl carboxylate)ethyl]-α-D-glucopyranoside (VII).—Incomplete tritylation of the primary hydroxyl group occurred if insufficient time was allowed for the reaction between IV and triphenylchloromethane. A preparation of VI, obtained directly from IV, in which the addition of acetic anhydride to the mixture of IV and triphenylchloromethane in pyridine had been made without leaving the mixture overnight at room temperature, contained a second product. During the chromatography on silica gel this product was separated by elution with a mixture of ether and ethyl acetate, 9:1. Recrystallization from a mixture of acetone and ether gave needles, m.p. 128–129°, $[\alpha]^{27}D$ +118° (*c* 2.63, in chloroform). The product showed no hydroxyl group absorption in the infrared spectra. From 4.3 g. of IV, 0.6 g. (12%) of VII was thus obtained.

Anal. Calcd. for $C_{23}H_{31}NO_{10}$: C, 57.37; H, 6.49; N, 2.91. Found: C, 57.32; H, 6.50; N, 2.96.

An identical product was obtained by direct acetylation of IV in pyridine solution with acetic anhydride.

Benzyl 2-Acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (VIII).—To a solution of 300 mg. of IV in 9 ml. of methanol was added 1 ml. of 2 *N* sodium hydroxide, and the clear solution obtained was left overnight at room temperature. The solution was acidified with dilute acetic acid and evaporated. The residue was dissolved in a few milliliters of water and passed through a column of Dowex 50W-X8 (H^+ form). Evaporation of the solution gave a residue (275 mg.), which was recrystallized from a mixture of methanol and ethyl acetate, giving 250 mg. (86%) of needles, m.p. 160–161°, $[\alpha]^{20}D$ +168° (*c* 1.25, in methanol).

Anal. Calcd. for $C_{18}H_{25}NO_8$: C, 56.39; H, 6.57; N, 3.65. Found: C, 56 34; H, 6.70; N, 3.70.

2-Acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucose (*N*-acetylmuramic Acid) (IX).—A solution of 100 mg. of VIII in 10 ml. of 90% ethanol was hydrogenolyzed at room temperature and normal pressure in the presence of 10% palladium on charcoal as catalyst. The filtrate was concentrated by evaporation, and the residue was recrystallized from a mixture of ethyl acetate and methanol, giving 67 mg. (87%), m.p. 120–122°. A second crystallization gave 40 mg. of prisms, m.p. 122–124°. The product had a mutarotation from $[\alpha]^{22}D$ +59° (after 8 min.) to +39° (at equilibrium, after 6 hr., (*c* 1.58, in water).

Anal. Calcd. for $C_{11}H_{19}NO_8$: C, 45.04; H, 6.53; N, 4.77. Found: C, 44.77; H, 7.07; N, 4.71.

The substance was homogeneous in descending chromatography, using Whatman No. 1 paper. In a mixture of butanol, pyridine, and water, 6:4:3, the $R_{2\text{-amino-2-deoxyglucose}}$ was 1.0; and, in a mixture of butanol, acetic acid, and water, 4:1:5 (upper phase), the $R_{2\text{-acetamido-2-deoxyglucose}}$ was 2.0. The spot obtained with the silver nitrate reagent[10] was the pale-centered spot typical for muramic acid derivatives; a strong color was produced with a modified Morgan–Elson spray reagent.[11] Using the Reissig, *et al.*, modification[12] of the Morgan–Elson test, the molar extinction value, after a heating time of 3 min., was 17,300, very similar to that obtained for 2-acetamido-2-deoxyglucose under the same conditions; after 35 min., it was 14,500. In the Aminoff, *et al.*, modification[13] of this test, the molar extinction was 18,625 using filter no. 56 of the Klett–Sumerson spectrophotometer.

2-Acetamido-4,6-di-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucose (X).—A solution of 200 mg. of VII in 10 ml. of 90% ethanol was hydrogenated at room temperature and normal pressure for 18 hr. in the presence of 10% palladium on charcoal as catalyst. After filtration, the solution was evaporated and the residue was dissolved in ethylene dichloride and chromatographed on silica gel. Elution with ethyl acetate gave 142 mg. (87%) of material, which was crystallized from a mixture of acetone and ether into needles, m.p. 181–183°. A recrystallization from the same solvents gave m.p. 182–183°, $[\alpha]^{26}D$ +66° (*c* 1.44, in 90% ethanol). The product had no apparent mutarotation and the α-anomer was assumed on the basis of the positive rotation.

Anal. Calcd. for $C_{16}H_{25}NO_{10}$: C, 49.10; H, 6.44; N, 3.58. Found: C, 48.95; H, 6.47; N, 3.72.

Benzyl 6-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XII).—Ten milliliters of a dry chloroform solution containing 1.0 g. of 2-acetamido-3,4,6-tri-*O*-acetyl-deoxy-α-D-glucopyranosyl bromide (XI), that was prepared *in situ* according to Inouye, *et al.*,[14] was added in two equal portions to a stirred mixture of 0.55 g. of VI and 0.70 g. of mercuric cyanide in 10 ml. of nitromethane at room temperature. The second portion was added after 20 hr., and the reaction was allowed to proceed an additional 24 hr. The reaction mixture was then diluted with chloroform, and the organic layer was washed several times with a saturated sodium bicarbonate solution, then with water, and dried. After evaporation, the residue (1.2 g.) was dissolved in benzene and purified by chromatography on silica gel. A mixture of ether and ethyl acetate, 4:1, eluted a fraction which, on recrystallization from a mixture of acetone and ether, gave 0.42 g. of colorless needles, m.p. 152–153° (after previously sintering at 145°), identical with the starting material V. Ethyl acetate eluted a colorless product which crystallized from a mixture of acetone and ethanol in needles, weighing 0.035 g. (3.5%), m.p. 253–254°. A second crystallization from this solvent mixture gave m.p. 252–253° with resolidification on further standing and final melting at 260°; $[\alpha]^{26}D$ +58° (*c* 1.02, in chloroform).

Anal. Calcd. for $C_{35}H_{48}N_2O_{17}$: C, 54.68; H, 6.43; N, 3.67. Found: C, 54.60; H, 6.37; N, 3.73.

Benzyl 6-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-2-acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (XIII).—To a solution of 80 mg. of XII in 2 ml. of methanol was added 0.03 ml. of aqueous 2 *N* sodium hydroxide solution. The clear solution was left overnight at room temperature and then passed through a column of Dowex 50W-X8 (H^+ form). The column was washed with water and evaporation of the aqueous eluates gave 70 mg. of residue. Crystallization from methanol gave 35 mg. (60%) of needles, m.p. 227–228°, $[\alpha]D$ +87° (*c* 1.21, in methanol). The melting point was unchanged

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on further crystallization from methanol, and the infrared spectrum showed no ester band (potassium bromide disk).

Anal. Calcd. for $C_{26}H_{38}N_2O_{13}$: C, 53.23; H, 6.53; N, 4.77. Found: C, 53.07; H, 6.55; N, 4.70.

Acknowledgment.—The authors wish to thank Chas. Pfizer and Company for a kind gift of 2-acetamido-2-deoxy-D-glucose.

Tetra-*O*-acylglycosyl Chlorides from 1-Thioglycosides and Their Conversion to Penta-*O*-acyl Esters

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Received May 10, 1963

The ethyl tetra-*O*-acetyl-1-thioglycosides of α(or β)-D-glucopyranose, β-D-galactopyranose, and β-D-galactofuranose reacted with chlorine to produce the tetra-*O*-acetyl-β-D-glycosyl chloride. The corresponding derivative of D-mannose yielded an anomeric mixture of tetra-*O*-acetyl-D-mannopyranosyl chlorides. All of the tetra-*O*-acetyl-β-D-glycopyranosyl chlorides reacted with mercuric acetate in acetic acid to form the β-D-glycopyranose pentaacetate; tetra-*O*-acetyl-β-D-galactofuranosyl chloride reacted similarly to form β-D-galactofuranose pentaacetate. The latter reaction gives a new route to β-D-galactofuranose pentaacetate, since the halide was made through the 1-thiofuranoside. Ethyl 1-thio-α-D-glucofuranoside was benzoylated to the tetrabenzoate, m.p. 108–109°, $[\alpha]^{24}D$ +62.5° ($CHCl_3$), which was chlorinated to its sirupy tetra-*O*-benzoyl-D-glucofuranosyl chloride, and this with mercuric acetate yielded tetra-*O*-benzoyl-β-D-glucofuranosyl acetate, m.p. 130.5°, $[\alpha]^{23}D$ −34° ($CHCl_3$). This route likewise provides a new entry to the glucofuranose series. An interpretation of the course of these reactions is given.

The reaction of alkylthio compounds with bromine was established by Bonner.[2] The reaction takes the course shown below, wherein, in the sugar series, the alkylthio group is part of a dithioacetal function or is the thioacetal group of a 1-thioglycoside.

$$—SR' + Br_2 \longrightarrow —Br + BrSR'$$

In a fully acetylated aldose dithioacetal the reaction product is an *aldehydo*-acetate formed probably through the 1,1-dibromo derivative; in a 1-thioglycoside the product is a poly-*O*-acylglycosyl bromide. Weygand and associates[3] especially developed the application of this reaction in the sugar series. We have employed this reaction for the synthesis of acyclic analogs of nucleosides[4] and of nucleohexofuranosides.[5]

Herein we wish to report on the action of chlorine on 1-thioglycosides. In all cases studied save that of ethyl 1-thio-β-D-mannopyranoside (V) wherein an anomeric mixture (VII + VIII) was obtained, the ordinarily unstable tetra-*O*-acetyl-β-D-glycosyl chloride was formed regardless of the anomeric nature of the 1-thioglycoside. This statement is based upon isolated crystalline substances and does not necessarily establish these as the only reaction products. The mother liquors were investigated by thin-layer chromatographic techniques and were found to be rather complex. Chlorides of the β-D-form were produced from the acetylated ethyl 1-thioglycosides of α(or β)-D-glucopyranose (I and II), β-D-galactopyranose, and β-D-galactofuranose.

Following Bonner,[2] the chlorine reacts with the 1-ethylthio group to form the chlorosulfonium chloride I (illustrated in the D-glucose structure), which on heterolysis of the C-1 to S bond, could lead to two types of carbonium ions: III (D-glucose) or VI (illustrated for the D-mannose derivative). It would appear that the postulated bicyclic ion III, stabilized by resonance, is the favored form. Attack of chloride ion upon III would be hindered from the bottom side (as illustrated) and would lead exclusively to the β-D-glycosyl chloride. On the other hand, attack of a chloride ion upon VI could occur from either side and would lead to an approximately equal mixture of glycosyl chlorides, as was found for the D-mannose structure. With a few modern refinements, this explanation is essentially that given by Pacsu[6] in 1945 to explain the products formed in certain Koenigs–Knorr reactions and by Bonner[2] in 1948 to interpret the action of bromine on 1-thioglycosides.

It was then our endeavor to utilize the tetra-*O*-acylglycosyl chlorides so formed as an entry to the fully esterified sugar ester series. To this end the chlorides were replaced by acetoxy groups through reaction with mercuric acetate in acetic acid.[7] This reaction had been utilized for the formation of β-D-acetates from the acylated α-D-glycosyl halides. We were, therefore, surprised to find that all the tetra-*O*-acetyl-β-D-glycosyl chlorides employed likewise gave the β-D-form of the pentaacetate. This finding could be explained by the steric course of the reaction being completely dominated by the ortho ester effect, the 1,2-*trans*-acetates being formed regardless of the anomeric nature of the glycosyl halide. This reaction series provides another source for β-D-galactofuranose pentaacetate. When applied to the sirupy tetra-*O*-benzoyl-D-glucofuranosyl chloride (XI), herein formed from the known ethyl 1-thio-α-D-glucofuranoside (IX), a crystalline tetra-*O*-benzoyl-D-glucoforanosyl acetate (XII) was obtained which was likewise of the β-D-type. First crystals of

(1) Postdoctoral Fellow under Grant G14629 of the National Science Foundation (The Ohio State University Research Foundation Project 1178). Acknowledgment is made to a Fulbright travel grant.

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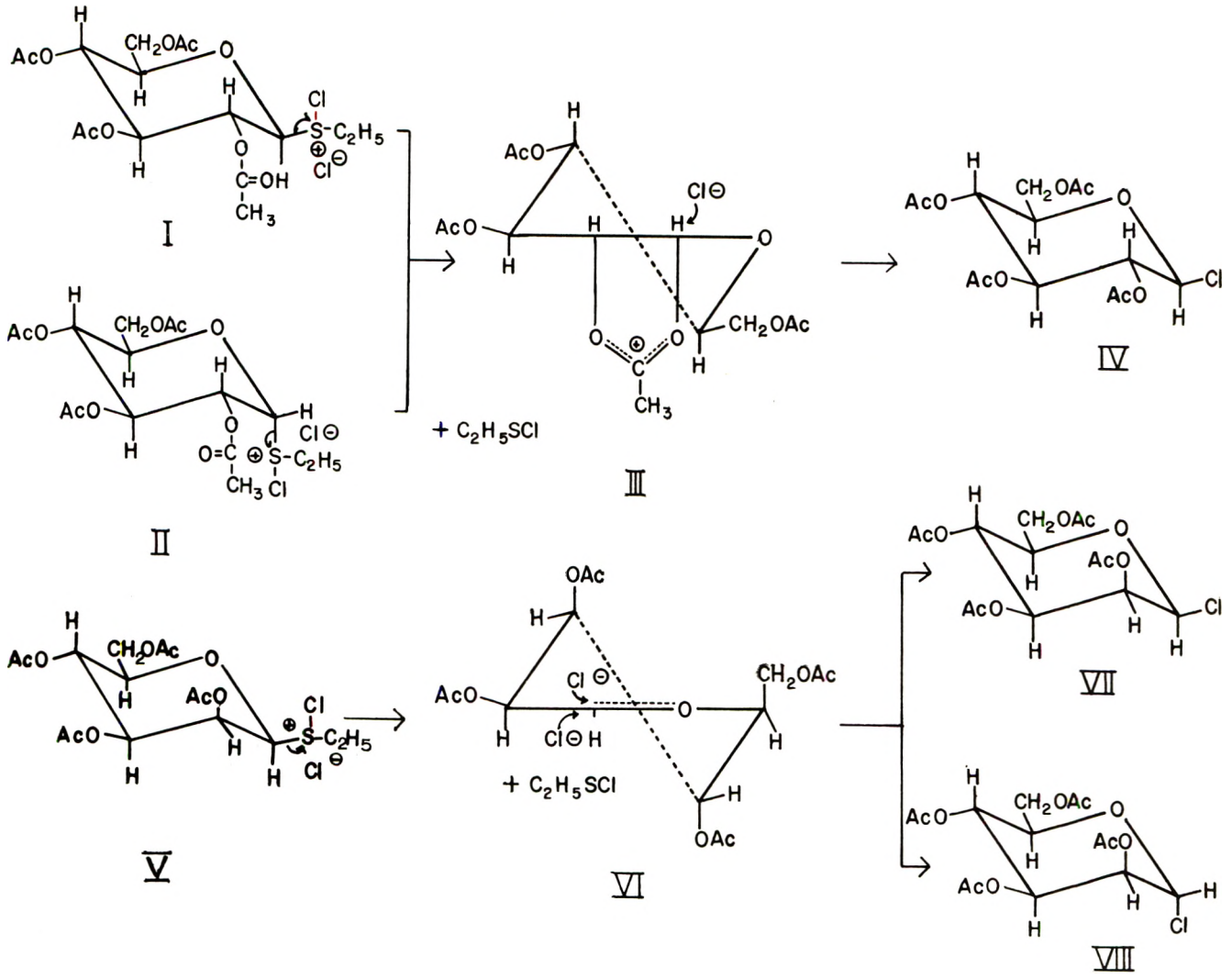
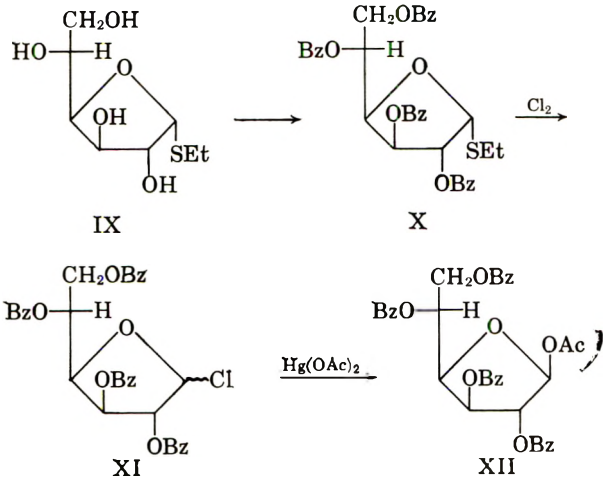


compound X were obtained by thin-layer chromatographic techniques, illustrating the further value of this method.



Experimental

Preparation of Tetra-*O*-acetyl-β-D-galactofuranosyl Chloride from Ethyl Tetra-*O*-acetyl-1-thio-α-D-galactofuranoside.—Ethyl tetra-*O*-acetyl-1-thio-α-D-galactofuranoside (4.0 g.) was dissolved in carbon tetrachloride (40 ml.) and to this was added 6 ml. of a solution of chlorine gas in dry chloroform (0.127 g. of chlorine per ml. of chloroform). After stirring for 0.5 hr., the solution was evaporated under reduced pressure to a colorless solid which, after removal of volatile by-products (repeated solution in ether and evaporation of solvent), was crystallized from absolute ether; yield, 3.1 g. (83%); m.p. 73°; $[\alpha]^{24}D$ −80° (c 0.9, chloroform). These constants identify the substance as tetra-*O*-acetyl-β-D-galactofuranosyl chloride.[8] The product was compared with that prepared by the method of Ness, Fletcher, and Hudson[8] and was found to be identical with it.

β-D-Galactofuranose Pentaacetate from Ethyl Tetra-*O*-acetyl-1-thio-β-D-galactofuranoside.—Tetra-*O*-acetyl-β-D-galactofuranosyl chloride (1.032 g., 2.82 mmoles), prepared from ethyl tetra-*O*-acetyl-1-thio-β-D-galactofuranoside as described in the preceding section, and 470 mg. (1.47 mmoles) of mercuric acetate were dissolved in 15 ml. of anhydrous acetic acid and allowed to stand overnight at room temperature. The residue obtained on solvent removal was taken up in chloroform, leaving a residue of mercuric chloride; yield of mercuric chloride, 360 mg. (93%). The chloroform solution was concentrated to a sirup which was crystallized by solution in 1 ml. of ethanol and nucleation. Recrystallization was effected from ethanol (2 ml.); yield, 645 mg. (58.5%); m.p. 98°, unchanged on admixture with authentic β-D-galactofuranose pentaacetate[8] of like melting point.

Tetra-*O*-acetyl-β-D-galactopyranosyl Chloride from Ethyl Tetra-*O*-acetyl-1-thio-β-D-galactopyranoside.—An amount of 1.00 g. (2.55 mmoles) of ethyl tetra-*O*-acetyl-1-thio-β-D-galactopyranoside[9,10] was dissolved in 8 ml. of carbon tetrachloride and to this was added 3 ml. of a solution of 0.45 g. of chlorine in carbon tetrachloride. The solution was maintained at room temperature for 30 min. after which the solvent was removed under reduced pressure. The residual sirup was obtained crystalline by solution in absolute ether and solvent removal (six times) and was recrystallized twice from 3 ml. of absolute ether; yield, 0.52 g. (55.5%); m.p. 93–95°; $[\alpha]^{20}D$ +12° (c 1, chloroform). For tetra-*O*-acetyl-

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β-D-galactopyranosyl chloride, Schlubach and Gilbert[11] report 93–94° and +6° while Korytnyk and Mills[12] report 93° and +15° for the constants.

The chlorination reaction also can be carried out in absolute chloroform solution. All solvents must be pure and dry. A slight excess of chlorine has no noticeable effect. For larger amounts of material, cooling with iced water is recommended. Codistillation with ether on the crude product is essential to remove the readily volatile secondary product ethanesulfenyl chloride. All of these mother liquors were investigated by thin-layer chromatography but no other crystalline products were isolated. The reaction mixtures were found to be rather complex with any anomeric forms, if present, being difficult to separate.

Penta-*O*-acetyl-β-D-galactopyranose from Tetra-*O*-acetyl-β-D-galactopyranosyl Chloride.—An amount of 247 mg. (0.67 mmole) of tetra-*O*-acetyl-β-D-galactopyranosyl chloride and 125 mg. (0.39 mmole) of mercuric acetate were dissolved in 3 ml. of acetic acid and maintained overnight at room temperature. To this solution was then added 30 ml. of chloroform and the whole was washed successively with water, 4% aqueous sodium bicarbonate, and again with water. The sirup obtained on solvent removal was crystallized from 95% ethanol and was recrystallized from this solvent; yield, 190 mg. (72%); m.p. 141°, undepressed on admixture with authentic β-D-galactopyranose pentaacetate[13] of like melting point.

Replacement of the acetic acid with dioxane, acetonitrile, or benzene led to much lower yields of product.

Tetra-*O*-acetyl-β-D-glucopyranosyl Chloride (IV) from Ethyl Tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (II).—An amount of 483 mg. (1.23 mmoles) of ethyl tetra-*O*-acetyl-1-thio-α-D-glucopyranoside[14] (II) was converted to tetra-*O*-acety -β-D-glucopyranosyl chloride (IV) as described for the conversion of ethyl tetra-*O*-acetyl-1-thio-β-D-galactopyranoside to tetra-*O*-acetyl-β-D-galactopyranosyl chloride with chlorine in carbon tetrachloride, and the crystalline product was purified in the same manner; yield, 330 mg. (73%); m.p. 99°; $[\alpha]^{20}D$ −14° (*c* 1, chloroform). Schlubach[15] records 99–100° and −13° for the corresponding constants.

Tetra-*O*-acetyl-β-D-glucopyranosyl chloride also was obtained by similar treatment of 520 mg. of ethyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[16] (I); yield, 295 mg. (61%); m.p. 97–98°, undepressed on admixture with authentic material.

Penta-*O*-acetyl-β-D-glucopyranose from Tetra-*O*-acetyl-β-D-glucopyranosyl Chloride.—Tetra-*O*-acetyl-β-D-glucopyranosyl chloride (290 mg., 0.79 mmole) was treated with mercuric acetate as described for the corresponding D-galactose compound, and the product was isolated in the same manner. Recrystallization from ethanol yielded pure penta-*O*-acetyl-β-D-glucopyranose; yield, 66 mg. (21%); m.p. 131°, undepressed on admixture with an authentic sample of like melting point.

Anomeric Mixture of Tetra-*O*-acetyl-D-mannopyranosyl Chlorides from Ethyl Tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (V).—An amount of 700 mg. (1.78 mmoles) of ethyl tetra-*O*-acetyl-1-thio-α-D-mannopyranoside[3b,9] (V) was treated with chlorine in carbon tetrachloride as described previously, and the product was isolated in the same manner and recrystallized from ether; yield, 330 mg. (50.5%); m.p. 95–96°; $[\alpha]^{20}D$ +7° (*c* 1, chloroform). The rotation indicated an approximately equal anomeric mixture. Separation was effected by slow evaporation from 10 ml. of ether. The first crop separated as stout, square crystals, m.p. 79°. The α-D anomer VIII is reported[17] to melt at 81°. The second crop consisted of long needles, m.p. 159°. The β-D-anomer VII is reported[12] to melt at 165°.

Ethyl Tetra-*O*-benzoyl-1-thio-α-D-glucofuranoside (X).—A solution of 7.5 ml. of chloroform and 5 ml. of dry pyridine and another of 4.6 ml. (40 mmoles) of benzoyl chloride in 7.5 ml. of dry pyridine were mixed after precooling to −5°. To the stirred solution was added 2.92 g. (10 mmoles) of ethyl 1-thio-α-D-glucofuranoside[5,18] (IX) at such a rate as to maintain the temperature below 0°. The solution was then maintained overnight at 0°, diluted with 30 ml. of chloroform, and washed successively with cold solutions of 5% sulfuric acid, 4% aqueous sodium carbonate, and finally cold water. A sirup was obtained on solvent removal from the dried (decolorizing carbon) solution. First seed of the desired product was obtained by thin-layer chromatography. An amount of 100 mg. of the sirup was applied to a 1-mm. layer of silica gel G (Stahl) on an 8 × 8 in. plate. Development was effected with ethyl acetate–chloroform (1:9 v./v.). The zone material at R_f 0.95 was removed and eluted with acetone. The sirup obtained on solvent removal crystallized after standing 3 weeks. The remaining sirup was dissolved in a few milliliters of ether and seeded. Crystalline material was obtained on standing overnight. Recrystallization was effected from 20 ml. of ethanol; yield, 3.02 g. (47.5%); m.p. 108–109°; $[\alpha]^{24}D$ +62.5° (*c* 1.5, chloroform).

Anal. Calcd. for $C_{36}H_{32}O_9S$: C, 67.49; H, 5.39; S, 5.30. Found: C, 67.61; H, 5.03; S, 5.00.

Tetra-*O*-benzoyl-β-D-glucofuranosyl Acetate (XII).—An amount of 1.28 g. (2 mmoles) of ethyl tetra-*O*-benzoyl-1-thio-α-D-glucofuranoside (X) was dissolved in 20 ml. of carbon tetrachloride to which was added 3.5 ml. of a solution of chlorine in carbon tetrachloride (0.15 g. per ml.). After stirring 30 min. the excess chlorine and solvent were removed under reduced pressure, and ether was added (several times) to the resultant sirup and removed by distillation. The resultant sirup resisted crystallization; $[\alpha]^{20}D$ −10.5° (*c* 1, chloroform). A similar value, indicating a probable anomeric mixture, was found by Schlubach and co-workers[19] for this sirupy substance prepared from D-glucofuranose pentabenzoate. An amount of 1.10 g. (1.79 mmoles) of the sirupy tetra-*O*-benzoyl-D-glucofuranosyl chloride was dissolved in 10 ml. of acetic acid to which was added 300 mg. (0.94 mmole) of mercuric acetate, and the whole was allowed to stand overnight at room temperature. The residue obtained on solvent removal was taken up in chloroform and filtered from mercury salts. The sirup obtained on chloroform removal was crystallized from ethanol and recrystallized from the same solvent; yield, 600 mg. (52.5%); m.p. 130°. Pure material XII was obtained on further recrystallization from ethanol; m.p. 130.5°; $[\alpha]^{23}D$ −34° (*c* 2, chloroform).

Anal. Calcd. for $C_{36}H_{30}O_{11}$: C, 67.71; H, 4.73. Found: C, 67.78; H, 4.61.

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(12) W. Korytnyk and J. A. Mills, *J. Chem. Soc.*, 636 (1959).
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(15) H. H. Schlubach, *Ber.*, **59**, 844 (1926).
(16) W. Schneider, J. Sepp, and O. Stiehler, *ibid.*, **51**, 220 (1918).
(17) E. Pacsu, *ibid.*, **61**, 1508 (1928).
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Glycosyl Halide Derivatives of 3-Amino-3-deoxy-D-mannose[1]

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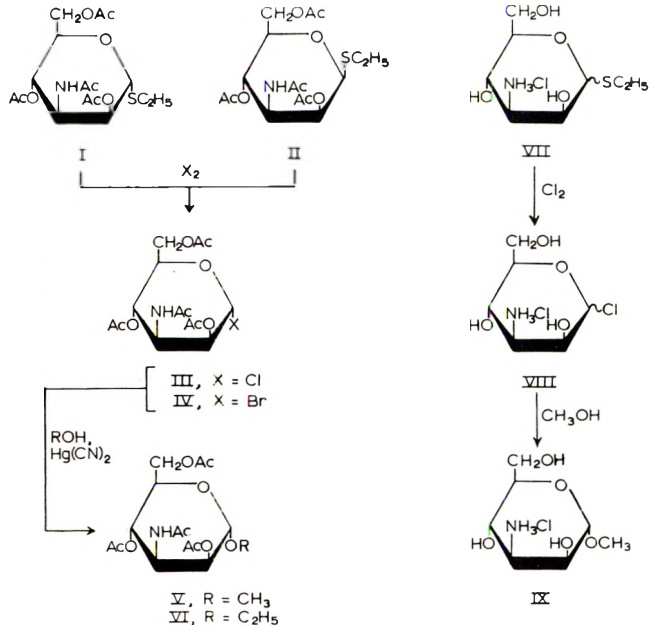
Received May 23, 1963

1-Thioglycoside derivatives of 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-D-mannopyranose react with chlorine or bromine to give 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl chloride or bromide, and the reaction provides a facile route to a versatile synthetic intermediate from readily available starting materials. Nonacetylated 1-thioglycoside derivatives of 3-amino-3-deoxy-D-mannose react with chlorine to give a novel glycosyl halide derivative in which the amino and hydroxyl groups are not acylated. This substance reacts with alcohols to give glycosides of the α-D configuration.

The work of Bonner[2] and of Weygand and associates[3] has opened a new route to the poly-*O*-acylglycosyl bromides, useful in the synthesis of nucleosides.[4] The method consists in the replacement of the ethylthio group of acylated 1-thioglycosides with bromine. In this laboratory we have been especially concerned with the extension of this reaction to the corresponding chlorides.[5] The glycosyl halide derivatives formed retain the ring form of their 1-thioglycoside precursor, and the anomeric disposition of the product is dependent on conformational, polar, steric hindrance, and neighboring group participation effects in the derivative considered.[2,3]

The present work describes the application of this procedure to amino sugar derivatives, for preparation of 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl bromide (IV) and the analogous chloride (III). Acetylated glycosyl halides are versatile synthetic intermediates and this work enables preparation of the stable crystalline III, with the rare 3-amino-3-deoxy-D-mannose structure,[6] in 15% yield from methyl α-D-glucopyranoside, with only two isolated intermediate stages.[7,8] The reaction of the nonacetylated 1-thioglycosides with chlorine also was found to give a chloride derivative, and some reactions of this novel nonacetylated glycosyl halide are discussed.

Mercaptolysis of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (IX) with ethanethiol and hydrochloric acid has been shown[8] to give ethyl 3-amino-3-deoxy-1-thio-α(and β)-D-mannopyranoside as a mixture which is readily resolved, after acetylation to the corresponding tetraacetyl derivatives I and II.[8] Either anomeric form I or II reacted readily with chlorine, under appropriate conditions, to yield the same crystalline 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl chloride (III) in nearly quantitative yield. The acetylated glycosyl chloride III is stable and suffers no apparent decomposition on storage over several weeks. With alcohols in the presence of mercuric cyanide[9] III gives glycosides with the α-D configuration, and no ortho ester type derivatives were observed in the products under these reaction conditions. In the case of the reaction with methanol, the structure of the product, methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside (V), was directly verified by comparison with a known sample prepared by acetylation of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride, the anomeric configuration of which is known with certainty since it is synthesized from methyl α-D-glucopyranoside.[6]



The positive specific rotation of the acetylated glycosyl chloride III would indicate that it possesses the α-D configuration, and this assignment is supported by the optical rotatory data listed in Table I for III and related derivatives.

The anomeric 1-thioglycosides I and II also underwent reaction with bromine under conditions similar to those used in the reaction with chlorine, to give a product formulated as 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl bromide (IV). This product was relatively stable and could be stored for several weeks, but, in contrast to the analogous chloride, it was difficult to purify, and acceptable analytical data were not obtained. However, it underwent conversion to the known acetylated methyl α-D-glycoside

(1) This work was supported by Grant No. CY-3232 (C5) (The Ohio State University Research Foundation Project 759E) from the Department of Health, Education, and Welfare, U. S. Public Health Service, National Institutes of Health, Bethesda, Md. Preliminary notices on portions of this work have appeared in *Science*, **140**, 386 (1963), and in Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963, p. 8D.

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(6) H. H. Baer and H. O. L. Fischer, *J. Am. Chem. Soc.*, **82**, 3709 (1960).

(7) A. C. Richardson, *J. Chem. Soc.*, 373 (1962).

(8) M. L. Wolfrom, D. Horton, and H. G. Garg, *J. Org. Chem.*, **28**, 1569 (1963).

(9) B. Helferich and K. F. Wedemeyer, *Ann.*, **563**, 139 (1949); R. Kuhn and W. Kirschenlohr, *Ber.*, **86**, 1331 (1953).

TABLE I

OPTICAL ROTATORY DATA

Compound	$[\alpha]_D$, deg. ($CHCl_3$)	$[M]_D$, deg.	Ref.
3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl chloride (III)	+55	+10,100	*a*
2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl chloride	+90	+32,850	*b*
Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside (V)	+40	+14,500	*a, c*
Methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside	+49	+17,800	*d, e*
Methyl 3-acetamido-3-deoxy-α-D-mannopyranoside	+44[f]	+10,350	*a, c*
Methyl α-D-mannopyranoside	+79[f]	+18,700	*g*
2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosyl chloride	−34	−12,500	*h*
Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside	−48	−17,300	*i, j*
Methyl β-D-mannopyranoside	−70[f,k]	−16,500	*j*

[a] See Experimental. [b] D. H. Brauns, *J. Am. Chem. Soc.*, **44**, 401 (1922); E. Pacsu, *Ber.*, **61**, 1508 (1928). [c] See ref. 6. [d] J. K. Dale, *J. Am. Chem. Soc.*, **46**, 1046 (1924). [e] T. L. Harris, E. L. Hirst, and C. E. Wood, *J. Chem. Soc.*, 2108 (1932). [f] In water. [g] E. Fischer and L. Beensch, *Ber.*, **29**, 2927 (1896); J. E. Cadotte, F. Smith, and D. Spriestersbach, *J. Am. Chem. Soc.*, **74**, 1501 (1952). [h] W. Korytnyk and J. A. Mills, *J. Chem. Soc.*, 636 (1959). [i] H. G. Bott, W. N. Haworth, and E. L. Hirst, *ibid.*, 2653 (1930). [j] H. S. Isbell and Harriet L. Frush, *J. Res. Natl. Bur. Std.*, **24**, 125 (1940). [k] Calculated for the unsolvated glycoside.

V under the same conditions as were used for the analogous reaction of the chloride III. This clearly establishes the structure of the glycosyl bromide precursor IV.

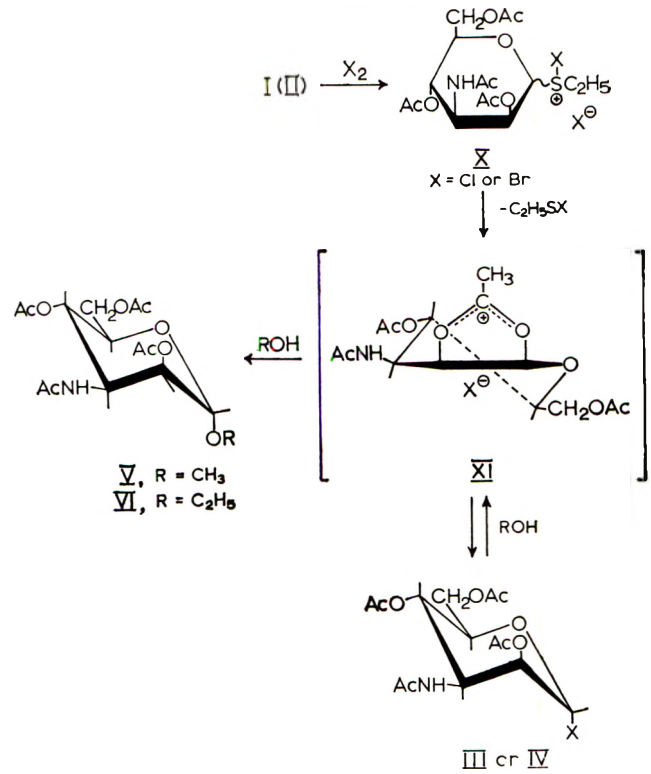
In contrast to the extensive investigations made on the poly-*O*-acetylglycosyl halides, the free glycosyl halides have received little study, and most of the reports have involved the glycosyl fluoride structure,[10] where the stability of the C–F bond permits saponification of the poly-*O*-acyl derivatives. Other glycosyl halides might be expected to be quite unstable in view of the reactivity of the halogen atom at the anomeric center toward hydroxyl groups. Ethyl 3-amino-3-deoxy-1-thio-α(and β)-D-mannopyranoside (VII), suspended in absolute chloroform, underwent reaction with chlorine heterogeneously, under the conditions that were described, to yield a crystalline product which was the unacetylated chloride VIII. A suitable recrystallizing solvent could not be found for this substance and its anomeric nature was not established. It was rapidly converted by water into 3-amino-3-deoxy-D-mannose, and chromatography indicated that this was essentially the sole reaction product. Methanol reacted readily with VIII, and the product, isolated in high yield, was identical with the known methyl 3-amino-3-deoxy-α-D-mannopyranoside (IX). Weygand and Ziemann[3] prepared methyl α-D-glucopyranoside by treating a methanolic solution of ethyl 1-thio-α-D-glucopyranoside with bromine; a nonacylated glycosyl halide is a probable intermediate in this reaction. Under similar conditions sugar diethyl dithioacetals also give glycosides.[11]

(10) F. Micheel and Almuth Klemer, *Advan. Carbohydrate Chem.*, **16**, 85 (1961).

(11) R. Kuhn, W. Baschang-Bister, and W. Dafeldecker, *Ann.*, **641**, 160 (1961).

An example of a crystalline, nonacylated highly reactive sugar derivative, 1-deoxy-1-diazo-D-*galacto*-heptulose has been reported.[12] Such derivatives can normally be isolated only as the acylated forms.

The steric course of the reactions leading to formation of the acetylated glycosyl halide derivatives III and IV, and their subsequent conversion into the glycosides V and VI with the α-D configuration, would suggest the involvement in each reaction of a common closed-ion intermediate XI, as proposed by Weygand and Ziemann[3] and mentioned by Wolfrom and Groebke.[5] The intermediate XI, probably distorted toward the half-chair form, would open by attack at C-1 from below the plane of the ring to give the observed products III, IV with the favored axial disposition of the halogen substituent. In this orientation, the interaction of the C-1–X dipole with the dipole formed from the unshared electron pairs of the ring oxygen is at a minimum,[13] and the halogen atom is *trans* to the C-5 substituent.[14] A reversal of the step III(IV) → XI may be regarded as the first step in the conversion of the glycosyl halide derivatives into α-D glycosides V, VI.



The formation of the α-D-glycosides is analogous to the reaction, with alcohols, of other 1,2-*trans* related poly-*O*-acetylglycosyl halides, first noted by Levene and Wolfrom[15] in the D-lyxose structure. In this case, as in others found later, the yield of the α-D-glycoside has been low owing to the operation of other pathways leading to ortho ester and β-D-glycoside formation.[16,17] In the present work, the use of mercuric cyanide[9] in a homogeneous medium afforded the α-D-gly-

(12) M. L. Wolfrom, R. L. Brown, and E. F. Evans, *J. Am. Chem. Soc.*, **65**, 1021 (1943).

(13) J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

(14) O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).

(15) P. A. Levene and M. L. Wolfrom, *J. Biol. Chem.*, **78**, 525 (1928).

(16) E. Pacsu, *Advan. Carbohydrate Chem.*, **1**, 77 (1945); R. U. Lemieux *ibid.*, **9**, 1 (1954); L. J. Haynes and F. H. Newth, *ibid.*, **10**, 207 (1955).

(17) H. S. Isbell and Harriet L. Frush, *J. Res. Natl. Bur. Std.*, **43**, 161 (1949).

cosides in high yield, and no other products were isolated.

The intermediate XI is pictured as being stabilized by acetate participation. It is not immediately apparent how this would apply to the unacetylated reaction series VII → VIII → IX wherein the α-D-glycoside was likewise obtained in high yield. As noted, the anomeric nature of VIII could not be established and indeed it may have been an anomeric mixture.

Experimental[18]

3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl Chloride (III). A. From Ethyl 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-β-D-mannopyranoside (II).—Dry chlorine was passed[5] for 5 min. through a chilled solution of II[8] (0.50 g.) in dichloromethane (20 ml.). After 10 min. at room temperature the solution was evaporated, and the residue twice evaporated from dry ether (30 ml.). The colorless sirup crystallized on trituration with petroleum ether; yield, 0.42 g. (90%). Recrystallization from anhydrous ether gave III as plates; m.p. 131–133°; $[\alpha]^{22}D$ +55 ± 2° (*c* 0.4, absolute chloroform[18]); λ_{max}^{KBr} 3.0 (NH), 5.70 (OAc), 6.05, 6.50 (NHAc), 13.40 μ (C–Cl[19]); X-ray powder diffraction data[20]: 11.87 w, 10.78 vw, 9.26 w, 8.51 w, 7.28 s (1), 5.45 m, 4.45 m (2), 4.07 m (3,3), 3.84 vw, 3.63 vw, 3.41 m (3), 3.17 w, 2.97 vw.

Anal. Calcd. for $C_{14}H_{20}ClNO_8$: C, 45.96; H, 5.47; Cl, 9.71, N, 3.83. Found: C, 45.80; H, 5.92; Cl, 10.05; N, 3.93.

B. From Ethyl 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-α-D-mannopyranoside (I).—A solution of I[8] (0.20 g.) in anhydrous ether (60 ml.) was treated with chlorine and processed as in A, to give crystalline III; yield, 0.18 g. (96%); X-ray powder diffraction data and other physical constants identical with those recorded for III prepared from II.

The product could be stored in a desiccator for several weeks without decomposition.

Methyl 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside (V). A. From 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl Chloride (III).—Five hundred milligrams of II was converted into III by treatment with chlorine, and to the product was added mercuric cyanide (0.50 g.), benzene (3 ml.), and anhydrous methanol (1 ml.). The mixture was stirred for 3 hr. at room temperature, diluted with chloroform (30 ml.), and washed with five 20-ml. portions of water until the washings gave no precipitate with silver nitrate solution. The solution was dried (magnesium sulfate) and evaporated, and the crystalline residue was recrystallized from ethanol–petroleum ether to give V; yield, 0.25 g. (46% on basis II); m.p. 151–152°, $[\alpha]^{20}D$ +40.2 ± 1.2° (*c* 0.4, water); λ_{max}^{KBr} 3.05 (NH), 5.70 (OAc), 6.02, 6.45 μ (NHAc); X-ray powder diffraction data[20] identical with that of an authentic specimen: 11.12 vw, 8.42 vw, 7.73 m, 6.73 s (1), 6.11 w, 5.85 s (2), 5.05 s (2,2), 4.81 vw, 4.56 vw, 4.43 m (3), 4.25 m (3,3), 4.06 w.

Anal. Calcd. for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.37; N, 3.87. Found: C, 50.29; H, 6.85; N, 3.87.

Richardson[7] quotes m.p. 153°, $[\alpha]D$ +41° (water), for this compound.

B. From 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl Bromide (IV).—To a chilled solution of ethyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-α-D-mannopyranoside[8] (I) (0.20 g.) in anhydrous ether (60 ml.), was added bromine (0.08 g.) dissolved in a small amount of ether. The well stirred mixture was evaporated after 10 min. at room temperature, the sirup re-evaporated with ether (twice), and the residue triturated with petroleum ether to give a pale yellow, amorphous product [yield, 0.18 g. (86%); m.p. 60°] to a viscous liquid which became mobile at 125°, $[\alpha]^{20}D$ +58.7 ± 0.8° (0.5 hr., *c* 0.63, pure chloroform); λ_{max}^{KBr} 2.95 (NH), 5.70 (OAc), 6.00, 6.45 μ (NHAc).

The same product was formed, in 81% yield, when ethyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-1-thio-β-D-mannopyranoside (II) was used as the starting material.

The compound could be stored in a desiccator for 2 weeks without apparent decomposition.

Treatment of IV (0.10 g.) with methanol in the presence of mercuric cyanide as in A gave V [yield, 0.05 g. (57%)] with physical constants identical to those of the product from A and to those of a sample prepared by acetylation of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (IX).

Methyl 3-Acetamido-3-deoxy-α-D-mannopyranoside.—Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside (V) was de-*O*-acetylated with methanolic ammonia at 0° to give the known methyl 3-acetamido-3-deoxy-α-D-mannopyranoside in 70% yield; m.p. 241–243°; $[\alpha]^{22}D$ +42.8 ± 0.8° (*c* 1.35, water). For this compound Richardson[7] records the corresponding constants 241–242° and +44°.

Ethyl 3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside (VI).—To 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranosyl chloride (III) prepared by the action of chlorine on I (1.00 g.) was added benzene (6 ml.), mercuric cyanide (1.0 g.), and anhydrous ethanol (2 ml.). The mixture was stirred for 3 hr. at room temperature, processed by the procedure used for V, and recrystallized from ethanol–petroleum ether as needles; yield, 0.65 g. (69% based on I); m.p. 162–163°; $[\alpha]^{20}D$ +32.7 ± 0.9° (*c* 0.6, methanol); λ_{max}^{KBr} 3.05 (NH), 5.70 (OAc), 6.05, 6.50 μ (NHAc); X-ray powder diffraction data[20]: 8.93 w, 7.83 m (3), 6.78 vw, 5.85 m (2), 4.62 vw, 4.45 m, 4.27 vw, 3.96 s (1), 3.70 vw, 3.56 vw, 3.44 vw, 3.36 vw.

Anal. Calcd. for $C_{16}H_{25}NO_9$: C, 51.20; H, 6.66; N, 3.73. Found: C, 51.14; H, 6.89; N, 3.78.

Ethyl 3-Acetamido-3-deoxy-α-D-mannopyranoside.—Dry ammonia was passed for 30 min. through a solution of ethyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-α-D-mannopyranoside (VI) (0.30 g.) in methanol (15 ml.) at 0°. After 1 hr. at room temperature the solution was evaporated and the residue was recrystallized from ethanol–ether; yield, 0.095 g. (52%); m.p. 209–210°, softening at 189°; $[\alpha]^{20}D$ +42.2 ± 1.2° (*c* 0.44, methanol); λ_{max}^{KBr} 2.95 (OH, NH), 6.02, 6.48 μ (NHAc); X-ray powder diffraction data[20]: 8.67 m (3), 7.94 m, 7.41 vw, 6.26 m (3,3), 5.97 s (1), 4.75 w, 4.15 vw, 3.93 s (2), 3.63 m, 3.41 vw, 3.24 vw, 3.12 w.

Anal. Calcd. for $C_{10}H_{19}NO_6$: C, 48.19; H, 7.63; N, 5.62 Found: C, 48.32; H, 7.69; N, 5.72.

3-Amino-3-deoxy-D-mannopyranosyl Chloride Hydrochloride (VIII).—A mixture (0.50 g.) containing approximately equal amounts of ethyl 3-amino-3-deoxy-1-thio-α- and β-D-mannopyranosides (VII), as isolated by mercaptolysis of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (IX),[8] was suspended in chloroform (50 ml.). Chlorine was passed for 10 min. through the chilled suspension, which was then stirred for 3 hr. and filtered. The crystalline solid was washed well with chloroform and dry ether; yield, 0.45 g. (100%). The crude product was insoluble in all nonhydroxylic solvents tried, and a suitable recrystallization solvent could not be found; m.p. 165–175° (preliminary browning at 160°); $[\alpha]^{21}D$ +34.8 ± 0.5° (*c* 0.9, *N*,*N*-dimethylformamide); λ_{max}^{KBr} (μ) 3.05 (OH), 6.25, 6.55 (NH_3^+), 13.65 (C–Cl[26]); X-ray powder diffraction data[20]: 10.59 w, 7.28 s (2), 5.17 vw, 4.86 vw, 4.32 vs (1), 4.08 vw, 3.28 w, 3.60 w, 3.39 m (3), 3.08 m (3,3), 2.98 w, 2.67 w.

Anal. Calcd. for $C_6H_{13}Cl_2NO_4$: C, 30.76; H, 5.55; Cl, 30.34; N, 5.98. Found: C, 30.65; H, 5.78; Cl, 30.30; N, 5.96.

Reaction of 3-Amino-3-deoxy-D-mannopyranosyl Chloride Hydrochloride (VIII) A. With Water.—A few milligrams of VIII was dissolved in water and the solution was examined by paper chromatography. A single major zone, R_m 1.0, indistinguishable from 3-amino-3-deoxy-D-mannose hydrochloride, was observed, together with a very weak zone, R_m 1.8.

B. Methanol.—A solution of VIII (0.20 g.) in anhydrous

(18) Melting points were taken with a Hershberg apparatus. Evaporations were performed under reduced pressure below 40°. Specific rotations were determined in a 2-dm. tube. Infrared spectra were obtained on a Perkin-Elmer Infracord infrared spectrophotometer. Paper chromatography was effected by the descending technique with the upper layer of a 4:1:5 1-butanol–ethanol–water system; R_m refers to mobility relative to that of 3-amino-3-deoxy-D-mannose hydrochloride. Zones were detected by the silver nitrate–sodium hydroxide procedure of W. E. Trevelyan, D. P. Proctor, and J. S. Harrison, *Nature*, **166**, 444 (1950). Ethanol-free chloroform was purified by washing successively with sulfuric acid, aqueous sodium bicarbonate, and water, and was dried with magnesium sulfate. Microanalyses were performed by W. N. Rond.

(19) W. A. Skinner, A. P. Martinez, H. F. Gram, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 148 (1961); A. P. Martinez, W. A. Skinner, W. W. Lee, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 6050 (1960).

(20) Interplanar spacing, Å., CuKα radiation. Relative intensity, estimated visually, s, strong; m, medium; w, weak; v, very. First few lines are numbered (1, strongest), doubled numbers indicate approximately equal intensities.

methanol (2 ml.) was refluxed for 1 min. and left 1 day at room temperature. Addition of ether to the solution gave crystalline methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (IX); yield, 0.16 g. (82%); physical constants identical to those of an authentic sample; X-ray powder diffraction data[20]: 10.98 m (3), 7.53 s (1), 6.03 vw, 5.45 vw, 5.23 vw, 4.46 s (2), 4.07 m, 3.79 m, 3.45 s (2,2), 3.14 w, 2.83 vw, 2.73 vw.

Examinations of the reaction mixture by paper chromatography revealed a major zone, R_m 1.66, corresponding to IX, with weak zones at R_m 1.0 and 2.7.

Conversion of 2-Amino-2-deoxy-1-thio-D-glucose Derivatives into Glycosyl Halide Derivatives. A Tetra-*O*-acetylglycosylsulfenyl Bromide[1]

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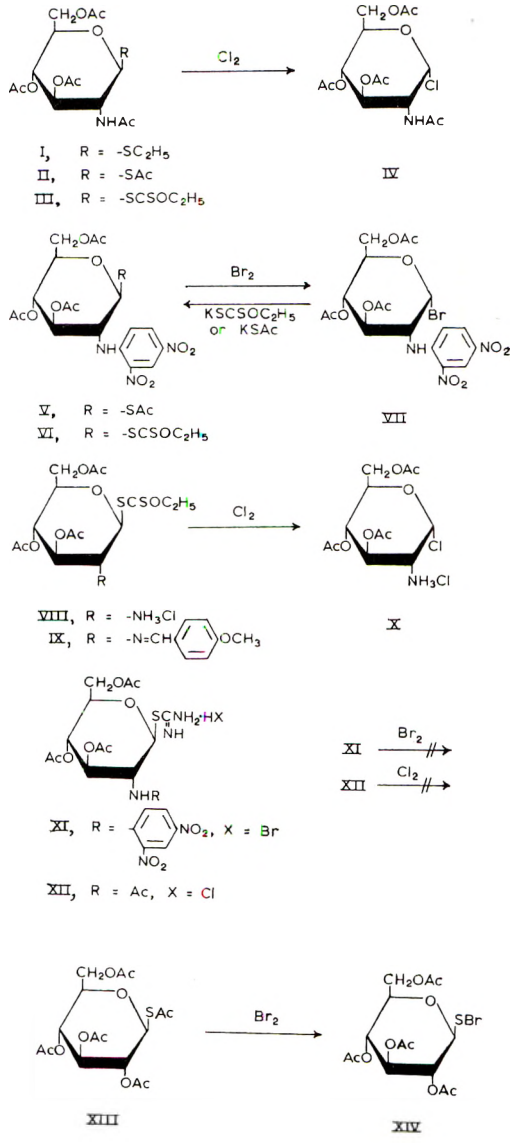
Received May 29, 1963

The *N*- and *S*-substituted derivatives I, II, III, V, VI, and VIII of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-1-thio-D-glucose react with chlorine or bromine to give the corresponding *N*-substituted 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chlorides (IV, X) or bromides (VII). 3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride hydrochloride (X) is also formed on chlorination of 3,4,6-tri-*O*-acetyl-2-anisylideneamino-2-deoxy-β-D-glucopyranosyl ethylxanthate (IX). Bromination of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (XIII) in carbon tetrachloride solution gives crystalline 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl bromide (XIV), a novel derivative in the carbohydrate field with potential value as a synthetic intermediate. The *N*-substituted 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea salt derivatives XI and XII were found to be unreactive under the halogenation conditions. The mechanism of these reactions is discussed from a common standpoint.

The conversion of acetylated phenyl 1-thioglycosides to poly-*O*-acetylglycosyl bromides by bromine treatment in an inert solvent was first described by Bonner,[2] and extended by Weygand and associates,[3] and others,[4] with the ethyl analogs. Chlorination to the corresponding glycosyl chlorides was described by Wolfrom and Groebke,[5] and the reaction was extended in this laboratory[6] to the synthesis of amino sugar glycosyl halides in the 3-amino-3-deoxy-D-mannose series.[6] The present work describes the conversion of a range of *N*- and *S*-substituted derivatives of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-1-thio-β-D-glucose into *N*-substituted 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromides or chlorides, and the behavior of related derivatives which do not react to give products of this type.

Most of the compounds utilized were prepared by the procedures described by Horton and Wolfrom.[7] 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranosyl ethylxanthate (VI) was prepared by treatment of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide (VII) with potassium ethylxanthate in acetone–ethanol solution, followed by chromatography of the product on silica gel.

Ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside[8] (I), 2-acetamido-3,4,6-tri-*O*-acetyl 1-*S*-acetyl-2-deoxy-1-thio-β-D-glucopyranose[7] (II), and



2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl ethylxanthate[7] (III), all reacted rapidly in

(1) This work was supported in part by Grant No. Cy-3232 (C5) (The Ohio State University Research Fund Project 759E) from the Department of Health, Education, and Welfare, U. S. Public Health Service, National Institutes of Health, Bethesda, Md., and in part by Contract No. DA-49-193-MD-2143 (The Ohio State University Research Fund Project 1187) from the Walter Reed Army Institute of Research, Washington, D. C. The opinions expressed in this article are those of the authors, and not necessarily those of either sponsoring agency. Preliminary report: Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963, p. 8D.

(2) W. A. Bonner, *J. Am. Chem. Soc.*, **70**, 3491 (1948).

(3) F. Weygand, H. Ziemann, and H. J. Bestmann, *Ber.*, **91**, 2534 (1958); F. Weygand and H. Ziemann, *Ann.*, **657**, 179 (1962).

(4) H. Zinner, A. Koine, and H. Nimz, *Ber.*, **93**, 2705 (1960).

(5) M. L. Wolfrom and W. Groebke, *J. Org. Chem.*, **28**, 2986 (1963).

(6) M. L. Wolfrom, H. G. Garg, and D. Horton, *ibid.*, **28**, 2989 (1963).

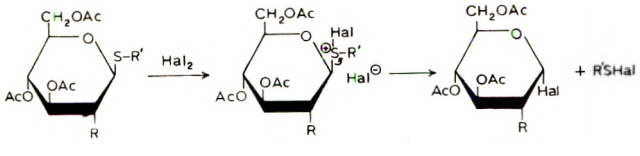
(7) D. Horton and M. L. Wolfrom, *ibid.*, **27**, 1794 (196.

(8) L. Hough and M. I. Taha, *J. Chem. Soc.*, 2042 (1952)6).

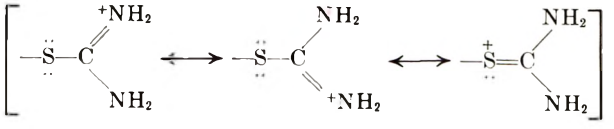
methylene chloride solution with chlorine at room temperature, to give crystalline 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[7,9] (IV) in high yield. Treatment of 3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-1-thio-β-D-glucopyranose[7] (V), or 3, 4, 6-tri-O-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranosyl ethylxanthate (VI), in methylene chloride solution, with bromine at room temperature gave in each case a high yield of crystalline 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide[7,10] (VII). Similarly, treatment of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl ethylxanthate hydrochloride[7] (VIII) in methylene chloride with chlorine gave a high yield of a crystalline product showing the correct analysis for the anticipated 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride hydrochloride (X). The latter compound has not to our knowledge been reported previously; it is the chlorine analog of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide, a compound first described by Irvine and co-workers[11] and widely used in synthetic work.[12] The infrared spectra of X and Irvine's compound[11] were closely similar. The same product X was produced, in practically quantitative yield, when an ethereal solution of 3,4,6-tri-*O*-acetyl-2-anisylideneamino-2-deoxy-β-D-glucopyranosyl ethylxanthate[13] (IX) was treated with chlorine at room temperature, indicating a rapid cleavage of the Schiff base substituent under these conditions. Generation of hydrogen chloride by hydrolysis of the sulfenyl chloride derivative formed from the C-1 substituent was not considered probable. Rapid chlorination of the (activated) aromatic nucleus, with cleavage of the (labilized) Schiff base by the hydrogen chloride thus formed, would logically explain the observed reaction.

The reaction at C-1 in each of the foregoing examples would appear to follow the mechanism proposed by Bonner[2] (Scheme A) for the bromination of phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside; *S*-halogenation by a halonium ion is followed by C-1 to *S*-heterolysis to yield a glycosyl carbonium ion, which is attacked, possibly synchronously, by halide ion, to give the α-D halide. The rapidity of the reaction suggests that initial formation of a β-D halide, and subsequent anomerization, is not involved.

SCHEME A



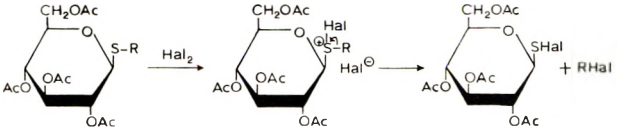
Attempted halogenation of the thiopseudourea derivatives 2-[3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranosyl]-2-thiopseudourea hydrobromide[7] (XI) (with bromine), and 2-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea hydrochloride[7] (XII) (with chlorine) under considerably more vigorous conditions than those used in the foregoing conversions, gave no detectable reaction, and in each case the starting material was recovered in high yield. It would appear probable that the inductive effect of the positively charged amidinium group and the contribution of resonance structures of the type



would so lower the electron density on the sulfur atom as to prevent electrophilic halogenation on the sulfur atom, the postulated first stage in the replacement reaction.

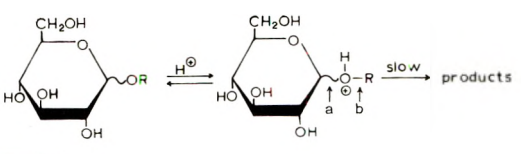
The reaction of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose[7,14] (XIII) follows a different course from the foregoing examples, and treatment of a carbon tetrachloride solution of XIII with bromine for five minutes at room temperature gives a high yield of a crystalline, strongly levorotatory product showing the correct analysis for tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl bromide (XIV). Formation of this product can be rationalized on the basis of an alternative cleavage pathway (Scheme B) of the initial halogenated

SCHEME B



derivative with, in this case, heterolysis of the sulfur to acetyl bond to give XIV and acetylium ion, which combines with the halide ion. It would appear that the course of the reaction will depend on the readiness with which the glycosyl carbonium ion (Scheme A) or the R^+ carbonium ion (Scheme B) are formed; clearly, in the case of ethyl 1-thioglycoside derivatives, Scheme A would be favored owing to the relative difficulty with which the $C_2H_5^+$ carbonium ion is formed, while in the case of XIII the more stable acetylium ion can form, to favor reaction by Scheme B. Further experiments will be necessary to provide proof of this hypothesis, but a relevant parallel case may be cited in the hydrolysis of alkyl and aryl D-glucopyranosides, which is believed to occur[15] (Scheme C) by initial reversible protonation to

SCHEME C



(9) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954); D. H. Leaback and P. G. Walker, *J. Chem. Soc.*, 4754 (1957); F. Micheel, F.-P. van de Kamp, and H. Petersen, *Ber.*, **90**, 521 (1957).

(10) P. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 116 (1960).

(11) J. C. Irvine, D. McNicoll, and A. Hynd, *J. Chem. Soc.*, **99**, 250 (1911); see also M. L. Wolfrom and T. M. Shen Han, *J. Org. Chem.*, **26**, 2145 (1961).

(12) D. Horton, "The Amino Sugars," R. W. Jeanloz and E. A. Balasz, Ed., Vol. 1, Academic Press, Inc., New York, N. Y., 1963, in press.

(13) W. Meyer zu Reckendorf and W. A. Bonner, *Ber.*, **94**, 2431 (1961).

(14) The authors wish to acknowledge an earlier synthesis of XIII by a route similar to that described in ref. 7 but not cited therein: J. F. Danielli, M. Danielli, J. B. Fraser, P. D. Mitchell, L. N. Owen, and G. Shaw, *Biochem. J.*, **41**, 325 (1947).

(15) C. Armour, C. A. Bunton, S. Patai, L. H. Selman, and C. A. Vernon, *J. Chem. Soc.*, 412 (1961).

the conjugate acid, which then undergoes rate-determining heterolysis, normally at point *a* with primary alkyl, or aryl groups, to give a glycopyranosyl carbonium ion intermediate. In the case of *t*-butyl β-D-glucopyranoside, however, the evidence[15] indicates cleavage at *b*, the *t*-butyl carbonium ion being generated more readily than the glycopyranosyl carbonium ion.

The sulfenyl bromide derivative XIV showed no change in rotation in chloroform or ether solution over an observation period of four hours. The relative stability of alkanesulfenyl halide in nonpolar solvents such as carbon tetrachloride has been noted.[16] Crystalline XIV could be stored in a desiccator at 25° for several days before it decomposed to an oil. By analogy with the general reactivity of alkyl and aryl sulfenyl halides,[17] carbohydrate sulfenyl halides should find wide application in syntheses, providing an electrophilic sulfur atom as an attacking group, in contrast to the nucleophilic character of known thio sugar derivatives.[18] The observed stability of XIV would indicate a reactivity intermediate between that of the very labile alkanesulfenyl halides and the more stable aryl analogs; it can be expected to undergo ionic addition to unsaturated functions, and to replace active hydrogen atoms as in ketones, diethyl malonate, ethyl acetoacetate, and phenols. With amines it should form sulfenamides; it should give disulfides with thiols, and sulfides with Grignard reagents or aromatic hydrocarbons (Friedel–Crafts conditions).

Experimental[19]

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl Chloride (IV). A. From Ethyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (I).—Chlorine was passed for 5 min. through a chilled solution of I[8] (100 mg.) in methylene chloride (10 ml.). Concentration of the solution after a 10-min. reaction time gave crystalline IV, yield, 90 mg. (96%); m.p. 130–132°; X-ray powder diffraction data identical with those of an authentic specimen.[7]

B. From 2-Acetamido-3,4,6-tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-1-thio-β-D-glucose (II).—Treatment of II[7] (0.50 g.) in methylene chloride (20 ml.), with chlorine, and processing as for A gave IV; yield, 0.38 g. (84%), with physical constants identical with those of authentic material.

C. From 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl Ethylxanthate (III).—Treatment of III[7] (0.50 g.) in methylene chloride (20 ml.) with chlorine, and processing as for A gave IV [yield (after two recrystallizations), 0.35 g. (73%)] with physical constants identical with those of authentic material.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranosyl Ethylxanthate (VI).—A solution of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide (VII)[7,10] (0.62 g.) in acetone (10 ml.) was mixed with a solution of potassium ethylxanthate (0.35 g.) in ethanol (10 ml.). After 1 hr. the product was poured into water (250 ml.), and after 24 hr. the yellow gum was washed by decantation, dried, dissolved in benzene (15 ml.), and placed at the top of a 17 × 150 mm. column of silica gel.[20] The colored zone was developed off the column with ether to give the product VI as a yellow glass; yield, nearly quantitative; $[\alpha]^{26}D$ +65 ± 0.6° (*c* 0.9, chloroform); λ_{max}^{KBr} 3.03 (NH), 5.73 (OAc), 6.17, 6.28, 6.56 (aryl C=C), 7.33 (C=S?), 7.48 (NO_2), 13.43, 13.84 μ (substituted benzene). Traces of colored side-products remained at the top of the column.

Anal. Calcd. for $C_{21}H_{25}N_3O_{12}S_2$: C, 43.82; H, 4.36; N, 7.30; S, 11.13. Found: C, 43.79; H, 4.57; N, 7.35; S, 11.53.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl Bromide (VII). A. From 3,4,6-Tri-*O*-acetyl-1-*S*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-1-thio-β-D-glucopyranose (V).—A solution of V[7] (100 mg.) in methylene chloride (5 ml.) at room temperature was treated dropwise with a slight excess of bromine in methylene chloride, and after 10 min. at room temperature the solution was concentrated and triturated with ether to give a crystalline product, which was filtered and washed well with ether; yield, 75 mg. (75%); m.p. 150–152° dec., undepressed on admixture with authentic VII[7]; infrared spectrum identical with that of authentic VII.

B. From 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranosyl Ethylxanthate (VI).—Under conditions similar to those used in A above, VI (100 mg.) gave 80 mg. (86%) of VII, m.p. 150–152°, with an infrared spectrum indistinguishable from that of authentic material.

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl Chloride Hydrochloride (X). A. From 3,4,6-Tri-*O*-acetyl-2-anisylideneamino-2-deoxy-β-D-glucopyranosyl Ethylxanthate (IX).—Chlorine was passed for 5 min. through a solution of IX[21] (1.0 g.) in anhydrous ether (30 ml.). A gummy product separated, and after 10 min. the ether was decanted and the residue triturated with anhydrous ether, whereupon it solidified, to give X in practically quantitative yield. Recrystallization from methylene chloride–ether was effected with little loss to give pure X; m.p. 155–157° dec., raised to 161–163° on further recrystallization; $[\alpha]^{20}D$ +146 ± 1° (*c* 0.5, chloroform); λ_{max}^{KBr} 2.90 (NH_3^+), 5.75 (OAc), 6.25 (NH_3^+), 13.55 μ (C–Cl); X-ray powder diffraction data[19]: 13.39 vw, 11.19 w, 10.28 s (1), 7.76 s (2), 5.47 m, 5.04 m, 4.77 m, 4.55 w, 4.33 m (3), 4.13 m (3,3), 3.93 vw, 3.87 vw.

Anal. Calcd. for $C_{12}H_{19}Cl_2NO_7$: C, 40.00; H, 5.27; Cl, 19.72; N, 3.88. Found: C, 40.26; H, 5.14; Cl, 19.50; N, 3.96.

B. From 3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl Ethylxanthate Hydrochloride (VIII).—Chlorine was passed for 5 min. through a suspension of VIII[7] (50 mg.) in methylene chloride (10 ml.) at 0°. The suspended material dissolved during this time, and concentration of the solution after an additional 10 min. at room temperature gave crystalline X; yield, 25 mg. (60%); m.p. 155–157° dec.; infrared spectrum identical with that of material isolated by procedure A above.

Attempted Reaction of 2-(Glycosyl)-2-thiopseudourea Derivatives with Chlorine and Bromine. A. Reaction of 2-[3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranosyl)-2-thiopseudourea Hydrobromide (XI) with Bromine.—A suspension of XI[7] (100 mg.) in methylene chloride was treated with a slight excess of bromine in methylene chloride at room temperature. After 1 hr. the undissolved solid was filtered and washed with methylene chloride, to give a quantitative return of material indistinguishable from the starting material by mixture melting point and infrared spectrum.

B. Reaction of 2-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea Hydrochloride (XII) with Chlorine.—Chlorine was passed for 10 min. through a suspension of XII[7] (500 mg.) in methylene chloride at 0°. After 1 hr. at room temperature the suspension was filtered to give a quantitative return of starting material.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylsulfenyl Bromide (XIV).—A slight excess of bromine in carbon tetrachloride was added to a solution of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (XIII)[7,14] (0.30 g.) in carbon tetrachloride (10 ml.). After 5 min. at room temperature the pale yellow solution was evaporated, reevaporated twice from small quantities of anhydrous ether to give a fully crystalline product; yield, 0.25 g. (75%); m.p. 102–104° (browning); $[\alpha]^{21}D$ −59 ± 1° (*c* 0.64, chloroform), $[\alpha]^{22}D$ −58 ± 1.5° (*c* 0.36, ether), both unchanged

(16) C. G. Moore and M. Porter, *J. Chem. Soc.*, 2890 (1958).

(17) I. B. Douglass, in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, London, 1961, p. 350.

(18) D. Horton and D. H. Hutson, *Advan. Carbohydrate Chem.*, **18**, 123 (1963).

(19) Melting points were taken with a Hershberg apparatus. Infrared spectra were measured with a Perkin-Elmer "Infracord" infrared spectrophotometer. Microanalytical determinations were made by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, Å., for CuKα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First few lines are numbered (1 strongest); double numbers indicate approximately equal intensities.

(20) Silica Gel Davison, Grade 950, 60–200 mesh, a product of the Davison Division of the W. R. Grace Chemical Co., Baltimore, Md.

(21) Prepared by Dr. D. H. Hutson of this laboratory by the method of Meyer zu Reckendorf and Bonner.[13]

after 4 hr.; λ_{max}^{KBr} 5.90 μ (OAc); $\lambda_{max}^{C_2H_5OH}$ 210 (1215), 256 mμ (ϵ 731); X-ray powder diffraction data[19]: 12.81 w, 11.19 s (2), 9.83 s (2,2), 8.93 s (2,2), 6.61 vw, 6.24 vw, 5.19 m (3), 4.85 s (1), 4.48 m, 4.11 s (1,1), 3.71 w, 3.56 w.

Anal. Calcd. for $C_{14}H_{19}BrO_9S$: C, 37.92; H, 4.28; Br, 18.05; S, 7.22. Found: C, 38.18; H, 4.74; Br, 18.00; S, 7.48.

The product could be stored unchanged in a desiccator for 2 days at 25°, but it changed to an oil during the third or fourth day.

Preparation of Some *trans*-Aminomercaptofuranose Sugars[1]

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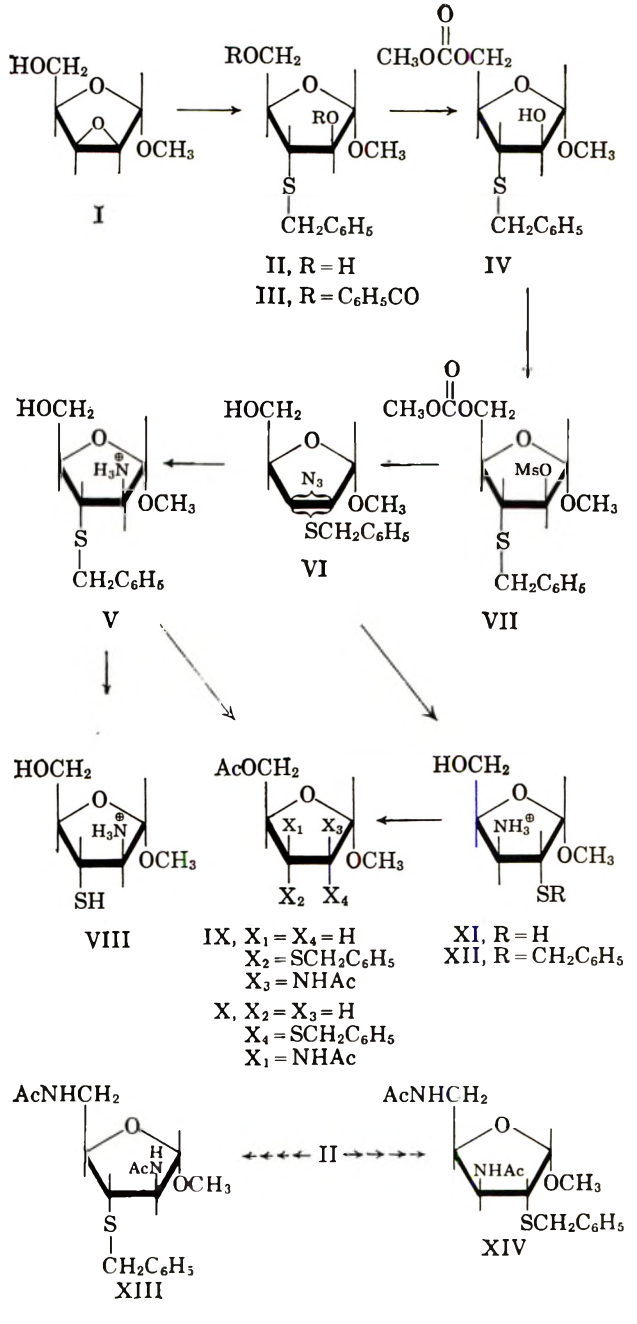
Received June 5, 1963

Two *trans*-aminomercapto glycosides, methyl 2-amino-2-deoxy-3-thio-α-D-arabinofuranoside hydrochloride (VIII) and methyl 3-amino-3-deoxy-2-thio-α-D-xylofuranoside hydrochloride (XI), have been prepared using the benzylthio neighboring group approach. Assignments of structure of the intermediates to the final products were made on the basis of n.m.r. interpretation. An estimate is made of the relative amount of ring-opening at the two carbons of an episulfonium ion intermediate.

Use of the benzylthio moiety as a neighboring group permitted the synthesis of two *trans*-aminomercaptopyranose glycosides.[2] The extension of these techniques to some furanosides has now led to the preparation of methyl 2-amino-2-deoxy-3-thio-α-D-arabinofuranoside hydrochloride (VIII) and the isomeric *trans*-aminomercaptan, methyl 3-amino-3-deoxy-2-thio-α-D-xylofuranoside hydrochloride (XI).

Both glycosides VIII and XI were derived from methyl 2,3-anhydro-α-D-lyxofuranoside (I).[3] Treatment of I with sodium benzyl mercaptide gave an excellent yield of a sirup that could be converted, in good yield, to a crystalline dibenzoate. Ring opening of 2,3-anhydrofuranosides has been generally observed to occur predominantly at C-3[4] and, on this basis, the diol II that formed the dibenzoate III was the expected major product. The structure assignment for III was verified by the nuclear magnetic resonance spectrum which showed the C-1 proton as a sharp singlet not visibly coupled to the *trans*-proton at C-2; the 2-benzylthio isomer of III would be expected to show its C-1 proton as a doublet with $J \cong 5$ c.p.s. according to its n.m.r. spectrum.[5b] The situation with the α-anhydrolyxoside (I) contrasts with that in the reaction of methyl 2,3-anhydro-β-D-lyxofuranoside and sodium benzyl mercaptide where the predominant product results from attack at C-2 of the epoxide.[5a] It seems probable that steric factors decide the position of attack in these two anomers; the bulky mercaptide ion's access to C-2 is seriously hindered by the C-1 methoxyl group in I but not in the β-anomer of I.

It was necessary to block the C-5 hydroxyl of II and this was done conveniently by reaction of II with slightly more than one equivalent of methyl chloroformate to give IV, which contained some II as shown by subsequent reactions. Use of the trityl blocking group for the C-5 hydroxyl gave poorer results. Treat-



(1) This work was carried out under the joint auspices of the Office of the Surgeon General, Medical Research and Development Command, under Contract No. DA 49-193-MD-2068 and of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service under Contract No. SA-43-ph-1892. The opinions expressed in this article are those of the authors and not necessarily those of either sponsoring agency.

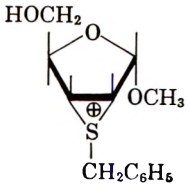
(2) (a) J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **83**, 3827 (1961); (b) L. Goodman and J. E. Christensen, *J. Org. Chem.*, **28**, 158 (1963).

(3) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 7 (1955).

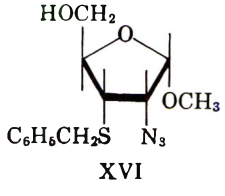
(4) For leading references, see C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **80**, 5247 (1958).

(5) (a) G. Casini and L. Goodman, *ibid.*, **85**, 235 (1963); (b) see K. L. Rinehart, Jr., W. S. Chilton, M. Hichens, and W. von Phillipsborn, *ibid.*, **84**, 3216 (1962), for a discussion of this point.

ment of IV with methanesulfonyl chloride afforded the methanesulfonate VII, again as a sirup, contaminated with some 2,5-di-*O*-methanesulfonate as a result of the presence of II in the starting material. When the crude methanesulfonate VII was treated with sodium azide in aqueous 2-methoxyethanol, the methoxycarbonyl group was cleaved and a mixture of azides (VI) was formed that also contained the 2(3),5-diazide mixture derived from the dimethanesulfonate of II. The azide mixture (VI) results from opening of a derived episulfonium ion intermediate (XV), at least predominantly. Although a direct S$_N$2 displacement of the methanesulfonate of VII by azide ion, a strong nucleophile, to give the azide XVI with a ribose configuration represents a



XV

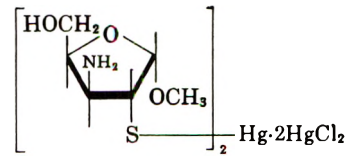


XVI

real possibility, no compounds derivable from XVI could be detected in the subsequent work. The n.m.r. spectra of the 3-benzylthiofuranosides isolated showed either a C-1 proton singlet or a C-1 proton doublet with $J \sim 1.5$ c.p.s., absorptions that are generally characteristic for *trans* C-1–C-2 proton couplings in a furanose sugar. Using these considerations as the basis, no evidence was found for the formation of XVI in the reaction of VII with azide ions since compounds derived from XVI should possess a *cis* relationship of the C-1–C-2 protons and would be expected to show coupling constants for these protons of about 4–5 c.p.s.[5b]

Reduction of the azide mixture (VI) with sodium borohydride in isopropyl alcohol[6] gave a mixture of amines (and diamines) that was acetylated yielding a mixture of IX, X, XIII, and XIV, the latter two compounds being derived from the dimethanesulfonate contaminant of VII. Chromatography using silicic acid served to separate the mixture of diamides XIII and XIV from the mixture of IX and X. Saponification of the mixture of monoamides IX and X yielded the amine mixture that was converted to a mixture of amine hydrochlorides, V and XII, easily separated into its components by recrystallization. The lower melting hydrochloride was converted to a crystalline N,O-diacetate whose n.m.r. spectrum identified it as the amide IX that was derived from the amine hydrochloride V. Thus, the C-1 proton of IX appeared at τ 5.18 as a singlet not detectably coupled to the *trans*-proton at C-2. The higher melting hydrochloride XII was converted to a crystalline N,O-diacetate X whose n.m.r. spectrum showed the C-1 proton as a doublet centered at τ 5.16 with $J = 5$ c.p.s. as a result of spin-coupling to the *cis*-proton at C-2.

Reduction of the free benzylthio amines derived from V and XII with sodium in liquid ammonia afforded the aminomercaptans, isolated as their mercaptides by precipitation with mercuric chloride. The mercaptide from XII gave an analysis consistent with structure XVII. Decomposition of the mercury salts derived from V and XII using hydrogen sulfide afforded the



XVII 2HCl

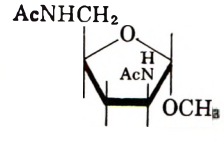
trans-aminomercaptans (VIII and XI, respectively) isolated as analytically pure, crystalline solids.

It was not apparent from the relative amounts of XII and V that were isolated whether the opening of the episulfonium ion XV had occurred predominantly at C-2 as would be predicted from purely steric considerations or at C-3, and the complexity of the reaction products prevented any reasonable estimation of the ratio of products derived from XV. In order to get a more quantitative idea of the position of ring opening of an ion such as XV, the diol II was converted to the 2,5-dimethanesulfonate which was then treated with sodium azide in 2-methoxyethanol by the reaction conditions used in preparing VI. The diazide mixture was converted by reduction and acetylation to a mixture of the diamides XIII and XIV which was not completely pure because of some elimination of benzyl mercaptan that took place in the sodium azide reaction. However, the purity of the mixture was such that a reasonably reliable estimate of the composition of the mixture could be made on the basis of rotation data, and this suggested that 78% of the arabinoside XIII, formed by attack on the ion intermediate at C-2, was present.

The n.m.r. spectrum of the mixture showed clearly the resonances associated with the C-1 proton of XIII and the C-1 proton of XIV, and from the relative areas of these absorptions it was estimated that the mixture contained 69% of XIII and 31% of XIV; this estimate was subject to greater error than that from the rotation data. If the assumption is reasonable that the ring opening of the ion derived from the dimethanesulfonate of II is comparable with that of XV, the ratio, V/XII, formed from VII *via* XV should be about 3.

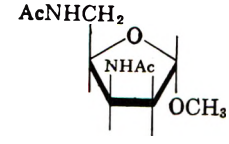
The pure diamides XIII and XIV required for reference rotations and n.m.r. spectra were easily obtained from the diamide mixture by fractional recrystallization. Again the n.m.r. spectra of the compounds served to assign their structures. Thus, the predominant diamide XIII showed the C-1 proton as a doublet at τ 5.12 with $J = 1.5$ c.p.s. as would be predicted for the poorly coupled C-1, C-2 *trans*-protons of a methyl furanoside. The xylose isomer XIV showed the C-1 proton as a doublet centered at τ 5.22 with $J = 4.5$ c.p.s. consistent with the *cis* arrangement of the C-1 and C-2 protons. These structure assignments for

XIII →



XVIII

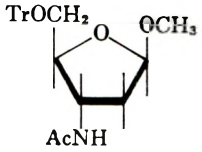
XIV →



XIX

(6) P. A. S. Smith, J. H. Hall, and R. O. Kan, *J. Am. Chem. Soc.*, **84**, 485 (1962).

XIII and XIV received further confirmation by a study of the n.m.r. spectra of the crystalline diamides XVIII and XIX, respectively, obtained by Raney nickel desulfurization of XIII and XIV. The C-1 proton of the 3-deoxyglycoside XVIII appeared as a singlet at τ 5.12 (in deuteriochloroform), and the C-1 proton of the 2-deoxyglycoside XIX appeared as a symmetrical triplet centered at τ 4.98 with J = 4 c.p.s. (in deuterated dimethyl sulfoxide) as a result of equal coupling of the C-1 proton to both C-2 protons. The appearance of a triplet for C-1 in XIX parallels the situation with 2′-deoxyadenosine,[7] but stands in contrast with that of the monoamide XX where the C-1 proton appears as a



XX

pair of doublets, one representing *cis* coupling with J = 5 c.p.s. and the other the result of *trans*-proton coupling with J = 1 c.p.s.[8]

Experimental[9]

Methyl 3-Benzyl-3-thio-α-D-arabinofuranoside (II) and Its Dibenzoate (III).—To a chilled (0°) solution containing 1.69 g. (13.6 mmoles) of benzyl mercaptan, 0.74 g. (13.7 mmoles) of sodium methoxide, and 30 ml. of methanol was added 1.00 g. (6.84 mmoles) of the epoxide I, and the resulting solution, under nitrogen, was heated at reflux for 18 hr. The mixture was adjusted to pH 7 with glacial acetic acid, then poured into 50 ml. of water and extracted with two 25-ml. portions of dichloromethane. The combined extracts were washed with two 25-ml. portions of water, then dried over magnesium sulfate. The solvent was evaporated, and the residue was washed by decantation with two 5-ml. portions of petroleum ether (b.p. 62–70°), then dried *in vacuo* to yield 1.73 g. (94%) of a pale yellow sirup that was suitable for further use.

The dibenzoate III was prepared from 34.8 g. (0.128 mole) of II, 250 ml. of pyridine, and 54.4 g. (0.387 mole) of benzoyl chloride to afford, after decomposition of the reaction mixture, 63.2 g. (102%) of cream-colored, crystalline product. Recrystallization from 1 l. of petroleum ether (b.p. 88–99°) gave 53.6 g. (87%) of product, m.p. 110–112°. The analytical sample, prepared in another experiment, had m.p. 110–111°; λ_{max}^{Nujol} 5.77, 5.81 (ester C=O), 7.79 (ester C–O–C), 14.05, and 14.26 μ (monosubstituted phenyl); $[\alpha]^{28}D$ +133°.

Anal. Calcd. for $C_{27}H_{26}O_6S$: C, 67.8; H, 5.48; S, 6.70. Found: C, 67.8; H, 5.90; S, 6.82.

A mixture of 25.9 g. of the dibenzoate III, 154 g. of potassium hydroxide, 400 ml. of methanol, and 75 ml. of water was heated at reflux for 4 hr., then cooled and evaporated *in vacuo*. The white residue was dissolved in 200 ml. of water, and the solution was extracted with one 200-ml. and one 100-ml. portion of dichloromethane. The combined extracts were washed with three 100-ml. portions of water, dried over potassium carbonate, and evaporated *in vacuo*, yielding 10.2 g. (70%) of pale yellow sirup II, $n^{23}D$ 1.5580. The analytical sample, $n^{23}D$ 1.5560, $[\alpha]^{26}D$ +145°, was obtained similarly from another run after decolorizing the sirup with Norit A in benzene. In the infrared it had λ_{max}^{film} 2.91 (OH), 14.20 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{13}H_{18}O_4S$: C, 57.8; H, 6.71; S, 11.9. Found: C, 58.0; H, 6.72; S, 11.7.

Methyl 3-Benzyl-5-*O*-methoxycarbonyl-3-thio-α-D-arabinofuranoside (IV).—To a chilled (0°) solution of 12.0 g. (44.4 mmoles) of II in 100 ml. of dry pyridine was added dropwise, with stirring, a solution of 4.94 g. (52.2 mmoles) of methyl chloroformate in 50 ml. of chloroform. The mixture was stirred for 1 hr. at 0° and at room temperature for 18 hr., then was poured, with stirring, into 400 ml. of cold saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with 100 ml. of chloroform. The combined solutions were washed with 100 ml. of water, dried over magnesium sulfate, and evaporated *in vacuo*. Pyridine was removed from the residue by the addition and evaporation of portions of toluene until the pyridine odor was gone. The residue, 14.5 g. (100% yield), was a sirup; λ_{max}^{film} 2.90 (OH), 5.70 (ester C=O), 7.82 (ester C–O–C), 14.19 μ (monosubstituted phenyl).

Methyl 3-Benzyl-5-*O*-methoxycarbonyl-2-*O*-methylsulfonyl-3-thio-α-D-arabinofuranoside (VII).—To a chilled (0°), stirred mixture of 14.5 g. (44.2 mmoles) of IV in 100 ml. of dry pyridine was added dropwise 13.4 g. (0.116 mole) of methanesulfonyl chloride. The solution was stirred at 0° for 1 hr. and at room temperature for 18 hr. and then was poured into 500 ml. of cold saturated aqueous sodium bicarbonate. The aqueous mixture was extracted with two 100-ml. portions of dichloromethane; the combined extracts were washed with two 100-ml. portions of water, then decolorized with Norit A, and dried over magnesium sulfate. After removal of the solvent *in vacuo*, toluene was added and evaporated to remove all the pyridine, leaving 17.4 g. (97%) of amber sirup; λ_{max}^{film} 5.70 (ester C=O), 7.33 and 8.50 (sulfonate ester), 7.83 (ester C–O–C), 14.15 μ (monosubstituted phenyl); there was no 3.0-μ –OH band.

Methyl 2(3)-Azido-3(2)-benzyl-3(2)-thio-α-D-arabino(xylo)furanoside (VI).—A mixture of 17.4 g. (42.8 mmoles) of VII, 28 g. (0.43 mole) of sodium azide, and 300 ml. of 95:5 2-methoxyethanol–water was heated with stirring under nitrogen at 110–120° for 18 hr., then cooled, and evaporated *in vacuo*. The residue was partitioned between 200 ml. of water and 200 ml. of dichloromethane. The aqueous layer was extracted with two 50-ml. portions of dichloromethane; the combined extracts were washed with two 100-ml. portions of water and then dried over magnesium sulfate. Evaporation *in vacuo* gave 11.9 g. (94%) of a dark oil; λ_{max}^{film} 2.90 (OH), 4.77 (N_3), 14.22 μ (monosubstituted phenyl); there was no ester C=O band at 5.70 μ.

Anal. Calcd. for $C_{13}H_{17}N_3O_3S$: N, 14.2. Found: N, 14.9.

Methyl 2-Amino-3-benzyl-2-deoxy-3-thio-α-D-arabinofuranoside Hydrochloride (V) and Methyl 3-Amino-2-benzyl-3-deoxy-2-thio-α-D-xylofuranoside (XII).—A mixture of 30.3 g. (0.102 mole) of VI, 9.0 g. (0.239 mole) of sodium borohydride, and 350 ml. of isopropyl alcohol was heated at reflux for 15 hr., then cooled, and evaporated *in vacuo*. The residue was partitioned between 400 ml. of dichloromethane and 350 ml. of water, the resulting emulsion being broken after filtration through Celite. The dichloromethane extract was washed with 250 ml. of water, dried over magnesium sulfate, and evaporated *in vacuo*, affording 27.5 g. (100%) of orange sirup; λ_{max}^{film} 2.99, 3.04 (OH, NH_2), 6.25 (NH_2 and aryl), 14.20 μ (monosubstituted phenyl). The sirup was dissolved in 130 ml. of cold (0°) pyridine containing 15 ml. (0.108 mole) of triethylamine, and this solution was treated with 67 ml. of acetic anhydride. The reaction mixture was kept at 5° for 18 hr., then stirred at room temperature for 1 hr., then added to 1 l. of ice–water. The mixture was neutralized with solid sodium carbonate and extracted with two 100-ml. portions of dichloromethane; the combined extracts were washed with two 100-ml. portions of water, then dried over magnesium sulfate. Evaporation *in vacuo* left 35.5 g. (98%) of a solid that was a mixture of the amides (IX and X) which contained some of the diamides (XIII and XIV).

This amide mixture was applied to a column of silica gel, 90–200 mesh (250 × 35 mm.). Elution with 200 ml. of ethyl acetate gave 1.26 g. (A) of orange liquid as a forerun which showed no amide bands in its infrared spectrum. A second portion of 800 ml. of ethyl acetate eluted 22.0 g. (B) of solid which was a mixture of the amides IX and X. Elution with 800 ml. of chloroform yielded no product, and finally 200 ml. of methanol eluted the crude diamide mixture (C).

Fraction B, 22.0 g., was dissolved in a mixture of 1 l. of methanol, 250 ml. of water, and 300 g. of potassium hydroxide,

(7) W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 1906 (1961).

(8) C. D. Anderson, W. W. Lee, L. Goodman, and B. R. Baker, *ibid.*, **83**, 1900 (1961).

(9) Melting points are uncorrected and were obtained with the Fisher-Johns apparatus. Optical rotations are given for 1% solutions in chloroform unless otherwise noted. Paper chromatography was run by the descending technique on Whatman No. 1 paper using solvent systems A, 1-butanol–acetic acid–water (5:2:3), and B, isopropyl alcohol–2 *N* hydrochloric acid (65:35). Spots were detected with the sodium azide–iodine[10] spray and were located relative to adenine (R_f adenine = 1.00). The n.m.r. spectra were obtained either with the Varian A-60 spectrometer or the Varian V-4311 spectrometer operated at 60 Mc.

(10) E. Chargaff, C. Levine, and C. Green, *J. Biol. Chem.*, **175**, 67 (1948).

and the solution was heated at reflux, under nitrogen, for 40 hr., then evaporated *in vacuo*. The residue was dissolved in 300 ml. of water and extracted with two 200-ml. portions of dichloromethane; the extracts were washed with water until neutral, then dried over magnesium sulfate and evaporated *in vacuo*, leaving 13.0 g. (77%) of yellow sirup which contained no N-acetate according to the infrared spectrum. Two grams (7.43 mmoles) of this residue was dissolved in 10 ml. of anhydrous ether, and a saturated solution of ethereal hydrogen chloride was added, dropwise, until precipitation was complete. The ether was decanted and the semisolid residue washed by decantation with several small portions of fresh ether leaving, after removal of the last traces of ether *in vacuo*, 2.04 g. (89%) of solid. This was dissolved in a minimum amount of methanol, and 25 ml. of ether was added. After chilling the solution, the white needles, 0.47 g. (21%), m.p. 211–213° dec., were collected and shown to be the 2-amine salt XII by infrared spectral comparison with the analytical sample. The filtrate from XII was evaporated *in vacuo* and the residue crystallized from 30 ml. of acetonitrile to give 0.68 g. (30%) of white needles, m.p. 159–162°, whose infrared spectrum showed it to be V, free from XII.

The analytical sample of XII, prepared in an earlier experiment, had m.p. 210–212° dec.; $[\alpha]^{25}D$ +59° (1% in methanol); λ_{max}^{Nujol} 2.99 (OH), 3.29, 3.66–3.82 (NH_3^+), 14.09 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{13}H_{20}ClNO_3S$: C, 51.1; H, 6.59; Cl, 11.6; N, 4.58; S, 10.5. Found: C, 51.2; H, 6.71; Cl, 11.4; N, 4.53; S, 10.4.

The analytical sample of V, prepared in an earlier experiment, had m.p. 159–162°; $[\alpha]^{25}D$ +104° (1% in methanol); λ_{max}^{Nujol} 2.99 (OH); 3.21, 3.7–4.2 (NH_3^+), 13.95 μ (monosubstituted phenyl).

Anal. Calcd. for $C_{13}H_{20}ClNO_3S$: C, 51.1; H, 6.59; Cl, 11.6; N, 4.58; S, 10.5. Found: C, 51.3; H, 6.54; Cl, 11.6; N, 4.55; S, 10.5.

Methyl 2,5-Diacetamido-3-benzyl-2,5-dideoxy-3-thio-α-D-arabinofuranoside (XIII) and Methyl 3,5-Diacetamido-2-benzyl-3,5-dideoxy-2-thio-α-D-xylofuranoside (XIV).—Fraction C was stirred with 30 ml. of ethyl acetate. The insoluble white solid, 2.14 g., m.p. 190–231°, was recrystallized from chloroform to give 1.08 g. of white crystals, m.p. 235–236°, which was shown to be XIV by comparison with the analytical sample. Petroleum ether (30–60°) was added to the ethyl acetate liquors which precipitated 2.54 g. of solid with m.p. 157–166°. Recrystallization from 50 ml. of ethyl acetate gave 1.01 g. of white crystals, m.p. 163–165°, which proved to be XII.

The analytical sample of XIV had m.p. 231–235°; $[\alpha]^{24}D$ −19.6°; λ_{max}^{Nujol} 3.01, 3.03, 6.40 (NH), 6.03 (amide C=O), 13.02, 14.27 μ (monosubstituted phenyl). The n.m.r. spectrum, in deuteriochloroform, showed resonances at τ 2.68 (aromatic), 4 (broad NH), 5.22 (C-1, doublet, J = 4.5 c.p.s.), 6.23 (benzyl CH_2), 6.65 (OCH_3), 7.98, and 8.10 (CH_3CO).

Anal. Calcd. for $C_{17}H_{24}N_2O_4S$: C, 57.9; H, 6.86; N, 7.95; S, 9.10. Found: C, 58.0; H, 6.98; N, 7.96; S, 9.01.

The analytical sample of XIII had m.p. 163–166°; $[\alpha]^{24}D$ +43.7°; λ_{max}^{Nujol} 3.02, 3.03, 6.40 (NH), 6.01, 6.03 (amide C=O); 13.07, 14.03 μ (monosubstituted phenyl). The n.m.r. spectrum, determined in deuteriochloroform, showed resonances at τ 2.70 (aromatic), 4 (broad, NH), 5.12 (C-1, doublet, J = 1.5 c.p.s.), 6.18 (benzyl CH_2), 6.66 (OCH_3), 7.99 and 8.12 (CH_3CO).

Anal. Calcd. for $C_{17}H_{24}N_2O_4S$: C, 57.9; H, 6.86; N, 7.95; S, 9.10. Found: C, 57.9; H, 6.82; N, 7.98; S, 9.09.

Methyl 2-Acetamido-5-*O*-acetyl-3-benzyl-2-deoxy-3-thio-α-D-arabinofuranoside (IX).—A mixture of 0.35 g. (1.14 mmoles) of V, 4 ml. of dry pyridine, 0.30 ml. of triethylamine, and 5 ml. of acetic anhydride was maintained at room temperature for 18 hr. then poured into ice–water. The solid was collected and dried yielding 0.28 g. (69%) of white crystals. Recrystallization from water afforded 0.26 g. (64%) of needles, m.p. 134–136°; $[\alpha]^{24}D$ +194°; λ_{max}^{Nujol} 3.11 and 6.40 (NH), 5.75 (ester C=O), 6.08 (amide C=O), 8.07 (ester C–O–C), 14.13 μ (monosubstituted phenyl). The n.m.r. spectrum, in deuteriochloroform, showed resonances at τ 2.70 (aromatic), 4–5 (broad, NH), 5.18 (C-1, singlet), 6.16 (benzyl CH_2), 6.64 (OCH_3), 7.96 and 8.06 (CH_3CO).

Anal. Calcd. for $C_{17}H_{23}NO_5S$: C, 57.8; H, 6.56; N, 3.96; S, 9.07. Found: C, 57.9; H, 6.62; N, 3.96; S, 9.21.

Methyl 3-Acetamido-5-*O*-acetyl-2-benzyl-3-deoxy-2-thio-α-D-xylofuranoside (X).—Acetylation of 0.35 g. (1.14 mmoles) of XII by the procedure described for the preparation of IX gave after recrystallization from water 0.37 g. (92%) of white crystals, m.p. 138–139°; m.m.p. 113–116° with IX; $[\alpha]^{24}D$ +133°; λ_{max}^{Nujol} 3.09 and 6.62 (NH), 5.74 (ester C=O), 6.05 (amide C=O), 8.14 (ester C–O–C), 14.40 μ (monosubstituted phenyl). The n.m.r. spectrum, in carbon tetrachloride, showed resonances at τ 2.66 (aromatic), 4–5 (broad, NH), 5.16 (C-1, doublet, J = 4.5 c.p.s.), 6.21 (benzyl CH_2), 6.63 (OCH_3), 7.98 and 8.11 (CH_3CO).

Anal. Calcd. for $C_{17}H_{23}NO_5S$: C, 57.8; H, 6.56; N, 3.96; S, 9.07. Found: C, 58.1; H, 6.61; N, 2.94; S, 9.26.

Methyl 2-Amino-2-deoxy-3-thio-α-D-arabinofuranoside Hydrochloride (VIII).—The free base of V was generated by dissolving 1.45 g. (4.73 mmoles) of V in 30 ml. of saturated aqueous sodium bicarbonate. The solution was extracted with three 15-ml. portions of dichloromethane; the extracts were washed with water, dried over magnesium sulfate, and evaporated *in vacuo*, giving 1.23 g. (96%) of the free amine. A solution of the amine in 8 ml. of dry 1,2-dimethoxyethane was added dropwise to a well stirred solution of 0.55 g. (24 mg.-atoms) of sodium in 25 ml. of liquid ammonia. The mixture was stirred for 30 min., then the excess sodium was decomposed by adding absolute ethanol to discharge the blue color. The ammonia was evaporated under nitrogen and the residue was dissolved in 8 ml. of water. The aqueous solution was adjusted to pH 7 with glacial acetic acid and was then treated with excess aqueous mercuric chloride solution. The white precipitate was washed with water and dried, then thoroughly triturated with dichloromethane to remove bibenzyl, affording finally 2.51 g. of white solid mercaptide.

The mercaptide was suspended in 25 ml. of methanol and hydrogen sulfide was bubbled through the well stirred suspension for 20 min. The reaction mixture was filtered through Celite and the filtrate was evaporated *in vacuo*, affording 0.86 g. (84%) of a tan, crystalline residue. The residue was dissolved in 15 ml. of methanol and precipitated with excess ether, giving a gummy product that solidified to a foam after being treated *in vacuo*. The nitroprusside-positive solid, 0.59 g. (58%), had $[\alpha]^{24}D$ +100.8° (1% in methanol); λ_{max}^{Nujol} 2.87, 2.96 (OH), 3.82 (SH), 5.0, 6.22 and 6.55 μ (NH_3^+); there was no phenyl absorption near 14 μ. It was homogeneous on paper chromatography in solvents A and B with R_{Ad} 0.96 and 1.38, respectively.[9]

Anal. Calcd. for $C_6H_{14}ClNO_3S$: C, 33.4; H, 6.54; Cl, 16.4; N, 6.49; S, 14.9. Found: C, 33.4; H, 6.63; Cl, 16.7; N, 6.31; S, 14.8.

A portion (0.50 g.) of amorphous, but analytically pure, solid from another run was crystallized from 15 ml. of acetonitrile to give 0.13 g. of a crystalline solid, m.p. 138–145°; $[\alpha]^{22}D$ +94.6 (1% in methanol).

Anal. Found: C, 33.6; H, 6.43; Cl, 16.5; N, 6.39; S, 15.0. Iodometric thiol titration indicated the material to contain 93% of the theoretical mercaptan.

Methyl 3-Amino-3-deoxy-2-thio-α-D-xylofuranoside Hydrochloride (XI).—The salt XII, 2.40 g. (7.83 mmoles), was converted to its free base and thence to its mercaptide using the procedure described for the similar conversion of V. The mercaptide was a brown solid, 4.81 g. In a previous run the mercaptide had been analyzed and appeared to be the bismercury compound XVII.

Anal. Calcd. for $C_{12}H_{26}Cl_4Hg_3N_2O_6S_2$: C, 13.1; H, 2.38, Cl, 12.9, N, 2.55. Found: C, 12.7; H, 1.84; Cl, 12.9; N, 2.51.

The mercaptan was generated from XVII with hydrogen sulfide and gave 1.00 g. (59%) of crystalline solid, which was reprecipitated from methanol with ether to give 0.73 g. (43%) of the nitroprusside-positive analytical sample, $[\alpha]^{24}D$ +73.5° (1% in methanol); λ_{max}^{Nujol} 3.02 3.17, (OH), 3.83 (SH), 6.22, 6.40, 6.60 μ (NH_3^+); there was weak and unexpected absorption at 14.3 μ. The product was homogeneous on paper chromatography in solvents A and B with R_{Ad} 0.98 and 1.36, respectively.

Anal. Calcd. for $C_6H_{14}ClNO_3S$: C, 33.4; H, 6.54; Cl, 16.4; N, 6.49; S, 14.9. Found: C, 33.5; H, 6.78; Cl, 16.7; N, 6.73; S, 14.6.

From another run the analytically pure solid showed 96% of the theoretical mercaptan content according to iodometric titration and gave a solid, m.p. 156–161°, after recrystallization from methanol–ether.

Conversion of the Diol II to the Mixture of Diamides XIII and XIV.—The diol II, 2.04 g. (7.53 mmoles) in 30 ml. of dry pyridine was treated conventionally with 2.96 g. (25.9 mmoles) of methanesulfonyl chloride yielding 3.39 g. (105%) of the dimethanesulfonate as a yellow oil whose infrared spectrum showed no

–OH absorption near 3.0 μ. The dimesylate, 3.2 g. (7.5 mmoles), was treated with excess sodium azide in 2-methoxyethanol as described for the preparation of VI, affording 2.09 g. (87%) of a yellow oil whose infrared spectrum showed little or no sulfonate ester absorption. The diazide, 2.0 g. (6.23 mmoles), was reduced with excess sodium borohydride in isopropyl alcohol to furnish 1.54 g. (92%) of a sirup whose infrared spectrum showed the absence of covalent azide absorption. Acetylation of 1.50 g. of the amine mixture in pyridine containing triethylamine afforded 1.57 g. (79%) of a yellow crystalline solid whose analysis showed it to be deficient in nitrogen and to contain excess sulfur as calculated for the diamide mixture. Chromatography of 1.50 g. of the solid over silicic acid gave 0.12 g. of a fraction eluted with ethyl acetate which appeared to be mostly dibenzyl disulfide and 1.27 g. of material eluted with methanol whose infrared spectrum indicated it to be a mixture of the diamides XIII and XIV, $[\alpha]^{24.5}D$ +29.8°.

Anal. Calcd. for $C_{17}H_{24}N_2O_4S$: C, 57.9; H, 6.86; N, 7.95; S, 9.10. Found: C, 57.5; H, 6.80; N, 7.24, 7.30, S, 8.63.

Methyl 2,5-Diacetamido-2,3,5-trideoxy-α-D-*threo*-pentofuranoside (XVIII).—A stirred mixture of 1.00 g. (2.83 mmoles) of XIII, approximately 12 g. of Raney nickel[11] (thoroughly washed with dioxane), and 50 ml. of dioxane was heated at reflux for 4.5 hr., then was cooled, and filtered through Celite with adequate washing. The filtrate and the washings were evaporated *in vacuo* leaving 0.75 g. (115%) of a sirup whose infrared spectrum showed the absence of benzyl absorption near 14.3 μ. Four recrystallizations of the residue using first benzene–petroleum ether (30–60°), then ethyl acetate afforded 0.23 g. (35%) of the analytical sample, m.p. 127–132°; $[\alpha]^{24.5}D$ +32°; λ_{max}^{Nujol} 3.03, 3.27 and 6.43 (NH), 6.09 μ (amide C=O).

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.2; H, 7.88; N, 12.2. Found: C, 52.1; H, 7.88; N, 12.4.

Methyl 3,5-Diacetamido-2,3,5-trideoxy-α-D-*threo*-pentofuranoside (XIX).—Desulfurization of 1.08 g. (3.06 mmoles) of XIV using the conditions described for preparation of XVIII gave, after four recrystallizations of the residue from ethyl acetate, 0.11 g. (15%) of the analytical sample, m.p. 200–206°; $[\alpha]^{26}D$ +172° (1% in dimethyl sulfoxide); λ_{max}^{Nujol} 3.04, 3.22, 6.39 (NH), 6.05 μ (amide C=O); there was no S-benzyl absorption at 14.3 μ.

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.2; H, 7.88; N, 12.2. Found: C, 52.5; H, 7.87; N, 12.0.

Acknowledgment.—The authors wish to thank Dr. Peter Lim and his group for the infrared spectral data, optical rotations, thiol titrations, n.m.r. spectra, and paper chromatography, and Mr. O. P. Crews and staff for the large-scale preparation of intermediates.

(11) Sponge nickel catalyst, Davison Chemical Co., Cincinnati 29, Ohio.

Syntheses with Partially Benzylated Sugars. II.[1] The Anomeric 1-*O*-Benzoyl-L-arabinopyranoses and 1-*O*-Benzoyl-L-arabinofuranoses and Their Tendencies to Undergo Acyl Migration

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Received July 1, 1963

The four 1-*O*-benzoyl-L-arabinoses have been prepared in pure form and their behavior in aqueous pyridine studied. Under the conditions chosen, both 1-*O*-benzoyl-α-L-arabinopyranose and 1-*O*-benzoyl-α-L-arabinofuranose are stable while the corresponding anomeric esters readily undergo acyl migration to yield 2-*O*-benzoyl-L-arabinopyranose. The rate of mutarotation of 1-*O*-benzoyl-β-L-arabinofuranose in aqueous pyridine is much faster than that of 1-*O*-benzoyl-β-L-arabinopyranose; since the rate of mutarotation of 2-*O*-benzoyl-β-L-arabinopyranose in aqueous pyridine is faster than either of the preceding mutarotations, it is concluded that the rates observed actually represent the acyl migration step in each of the two cases.

In 1956 Ness and Fletcher[3] observed that the 1-*O*-benzoyl group in 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose readily migrates under mildly alkaline conditions to the C-2 position, giving 2,3,5-tri-*O*-benzoyl-D-ribofuranose. The ease with which this rearrangement takes place stands in marked contrast to the stability of 1-*O*-benzoyl-β-D-glucopyranose[4] under such conditions and suggested that 1-*O*-acyl aldoses may fall into two classes, *viz.*, those with a hydroxyl group at C-2 *cis* to the 1-*O*-acyl group and a second, more stable class having a *trans* arrangement. Recent researches by various workers have tended to support this view. Lemieux and Brice[5] predicted that 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose ought to rearrange to 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose and Bonner[6] later showed that such a rearrangement did indeed take place.

While a variety of 1-*O*-acyl-β-D-glucopyranoses have been discovered in nature, it is significant that no α-anomers having the acyl group *cis* to the hydroxyl at C-2 have been found. The first attempt to make a representative of this class, 1-*O*-mesitoyl-α-D-glucose,[7] clearly showed that the ester of even a sterically hindered acid readily undergoes migration from the C-1 to the C-2 position in α-D-glucopyranose.[8] It was only through the reaction of ethyl 1-thio-β-D-glucopyranoside with silver mesitoate that Pedersen and Fletcher[9] finally succeeded in synthesizing 1-*O*-mesitoyl-α-D-glucopyranose, the first 1-*O*-acyl-α-D-glucopyranose. When silver benzoate was used in this reaction only 2-*O*-benzoyl-D-glucose was obtained, indicating the

(1) The paper by R. Barker and H. G. Fletcher, Jr., entitled "2,3,5-Tri-*O*-benzyl-D-ribosyl- and -L-arabinosyl bromides" [*J. Org. Chem.*, **26**, 4605 (1961)] is regarded as I of this series.

(2) Visiting Associate of the Public Health Service, 1961–1962; Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University, Sapporo, Japan.

(3) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 4710 (1956).

(4) L. Zervas, *Ber.*, **64**, 2289 (1931).

(5) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **33**, 109 (1955).

(6) W. A. Bonner, *J. Org. Chem.*, **24**, 1388 (1959), found that the methylation of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose with methyl iodide in the presence of silver oxide gives methyl β-D-glucopyranoside tetraacetate in 81.2% yield. It should be noted that the anomeric tetraacetate gave the same product under these conditions but in significantly lower yield (51%), demonstrating that migration between *trans* positions may indeed take place. However, the possibility of anomerization preceding acyl migration does not seem to be excluded here.

(7) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 2849 (1956).

(8) As far as we are aware, this represents the only known case of an O → O migration of a mesitoyl group.

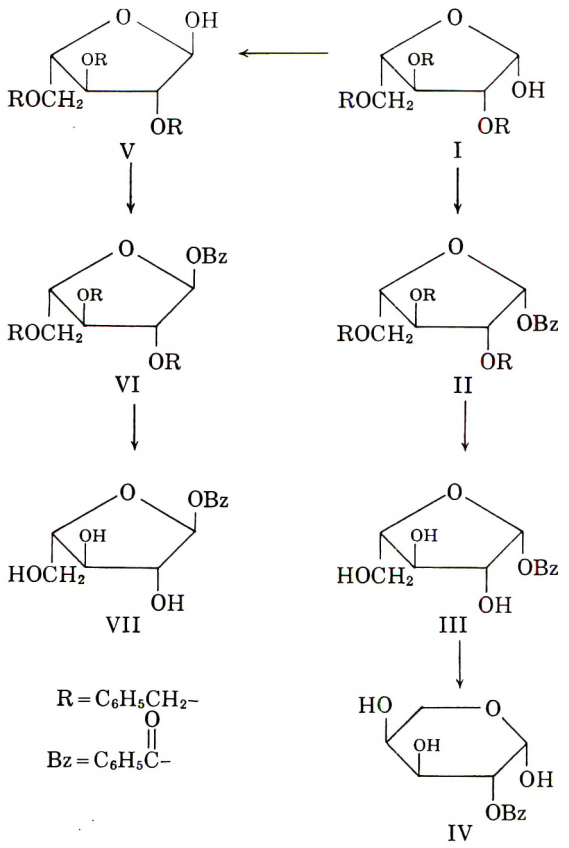
(9) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3215 (1960).

very considerable lability to be expected with 1-*O*-benzoyl-α-D-glucopyranose.

O. T. Schmidt and his coworkers[10-12] recently have shown that both the *p*-hydroxybenzoyl and galloyl groups readily migrate from C-1 to C-2 in α-D-glucopyranose. They were able to synthesize 1-*O*-galloyl-α-D-glucopyranose through condensation of tri-*O*-benzylgalloyl chloride with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[13] and subsequent hydrogenolysis of the benzyl groups.[14]

Inasmuch as the only anomeric pairs of 1-*O*-acylaldoses which have been studied were D-glucopyranose derivatives, it becomes of interest to examine the properties of a comparable pair of anomers in another sugar series and, particularly, of an aldofuranose. For this reason, we have undertaken the synthesis of the four possible 1-*O*-acyl-L-arabinoses.

Barker and Fletcher[1] described the synthesis of 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (I) *via* benzylation of crystalline methyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranoside, followed by hydrolysis of the glycoside, the over-all yield from L-arabinose being approximately 27%. We have now found that I may be prepared directly from L-arabinose in 48% yield by a simple sequence of steps without the isolation of intermediates,



making this potentially valuable intermediate[15] readily available. Careful purification of I indicated that the sample originally described[1] had been most probably a mixture of anomers, the β-anomer predominating.

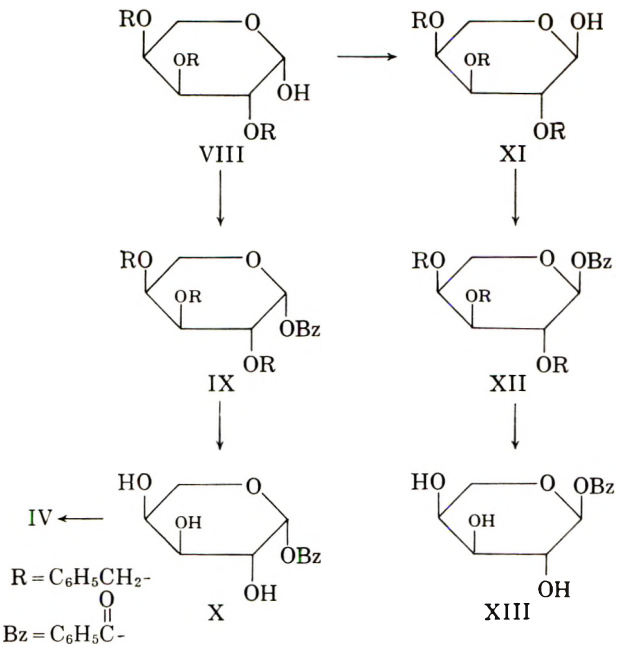
Under conditions chosen to minimize mutarotation, 2,3,5-tri-*O*-benzyl-β-L-arabinose (I) was benzoylated to give crystalline 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (II); catalytic hydrogenolysis of the benzyl groups of the latter afforded a mono-*O*-benzoylpentose which was stable in anhydrous pyridine and, on benzoylation in this solvent, was converted to the known β-L-arabinofuranose tetrabenzoate,[16] showing its structure to be 1-*O*-benzoyl-β-L-arabinofuranose (III). In 4:1 pyridine–water the *cis* ester III undergoes a rapid change which was followed polarimetrically; the rate was first order and the constant 0.026 (min., decimal logs), corresponding to a "half-life" of approximately 11.6 min. The product of the reaction was isolated in crystalline form and found to be identical with 2-*O*-benzoyl-β-L-arabinopyranose (IV), the enantiomorph of which was synthesized several years ago by Rammler and MacDonald.[17]

In anhydrous pyridine 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (I) undergoes mutarotation; subsequent removal of the pyridine, and crystallization of the residue from aqueous pyridine afforded 2,3,5-tri-*O*-benzyl-α-L-arabinose (V). Benzoylation of I after it had been allowed to mutarotate in pyridine solution gave the 1-*O*-benzoyl derivative (VI) which was hydrogenolyzed to 1-*O*-benzoyl-α-L-arabinofuranose (VII), the structure of which was confirmed by complete benzoylation to α-L-arabinofuranose tetrabenzoate.[16] As expected, the *trans* ester VII proved to be stable in both pyridine and 4:1 pyridine–water.

Successive benzylation and hydrolysis of methyl β-L-arabinopyranoside gave a crystalline tri-*O*-benzylpentose which showed a levomutarotation and is, therefore, 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose (VIII). When benzoylated under conditions chosen to minimize prior anomerization, VIII afforded a crystalline benzoate IX which was debenzylated in the usual fashion to yield 1-*O*-benzoyl-β-L-arabinopyranose (X); complete benzoylation converted X to β-L-arabinopyranose tetrabenzoate.[18] In 4:1 pyridine–water 1-*O*-benzoyl-β-L-arabinopyranose (X) mutarotated very slowly, the first-order rate averaging 0.00016 (min., decimal logs), corresponding to a "half-life" of 1881 min. The product was isolated and identified as 2-*O*-benzoyl-β-L-arabinopyranose (IV).

Attempts to obtain 2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (XI) in crystalline form were unsuccessful. However, benzoylation of an equilibrated 2,3,4-tri-*O*-benzyl-L-arabinopyranose (VIII + XI) readily gave 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (XII). Hydrogenolysis of the benzyl groups in XII afforded 1-*O*-benzoyl-α-L-arabinopyranose (XIII); the ester proved to be stable in 4:1 pyridine–water.

(10) O. T. Schmidt and H. Reuss, *Ann.*, **649**, 137 (1961).
(11) O. T. Schmidt and H. Schmadel, *ibid.*, **649**, 149 (1961).
(12) O. T. Schmidt and H. Schmadel, *ibid.*, **649**, 157 (1961).
(13) O. T. Schmidt, T. Auer, and H. Schmadel, *Ber.*, **93**, 556 (1960).
(14) In a recent paper [*Can. J. Chem.*, **40**, 2035 (1962)] J. J. Willard stated that "No reports have been found, in the literature, in which benzyl ether groups were removed by catalytic reduction from a carbohydrate also carrying ester groups. Since no other method is available for removal of benzyl ethers without loss of ester groups, the benzyl ether does not appear to be a useful blocking group in the synthesis of partial esters of the methyl glucosides." The work of Schmidt, Auer, and Schmadel (ref. 13) as well as that reported here clearly refutes this statement. Indeed, it is now obvious that *O*-benzyl groups may be cleaved in the presence of comparatively labile ester linkages.
(15) The utility of such compounds has been demonstrated by C. P. J. Glaudemans and H. G. Fletcher [*J. Org. Chem.*, **28**, 3004 (1963)] who employed the enantiomorph of I to synthesize 9-β-D-arabinofuranosyladenine, a type of substance which is difficultly accessible by other means.
(16) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **80**, 2007 (1958).
(17) D. H. Rammler and D. L. MacDonald, *Arch. Biochem. Biophys.*, **78**, 359 (1958).
(18) H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **69**, 1145 (1947).



In passing, it may be noted that each of the L-arabinofuranose derivatives described here is more levorotatory than the corresponding L-arabinopyranose derivative of the same anomeric configuration, in agreement with the generalization made recently by Bhattacharya, Ness, and Fletcher.[19]

Discussion

The conversions of 1-*O*-benzoyl-β-L-arabinopyranose (X) and of 1-*O*-benzoyl-β-L-arabinofuranose (III) to 2-*O*-benzoyl-L-arabinopyranose (IV) are obviously multi-step processes. In both cases the first step is acyl migration, C-1 to C-2. With the pyranose ester X, acyl migration is followed by anomerization of the form of 2-*O*-benzoyl-L-arabinose released (presumably β). With the furanose ester (III), the 2-*O*-benzoyl-L-arabinofuranose initially released (presumably β) may anomerize before ring expansion to 2-*O*-benzoyl-L-arabinopyranose (IV) which must then come to anomeric equilibrium. Since the over-all rate of mutarotation of the 1-*O*-benzoyl-β-L-arabinopyranose (X) is much slower than that of its furanose analog III, it seems reasonable to assume that the rate-controlling step is the acyl migration itself. However, with the faster reaction (III → IV) there is the possibility that the rate-controlling step is actually the anomerization of the 2-*O*-benzoyl-L-arabinopyranose (IV).[20] To settle this point, the rate of mutarotation of 2-*O*-benzoyl-L-arabinopyranose in aqueous pyridine was measured and found to be significantly faster (k = 0.064, $t_{1/2}$ = 4.7 min.) than the conversion of III to IV in the same solvent mixture.[21] It is, therefore, concluded that the acyl migration itself is most probably the rate-controlling step in the conversion of III to IV.

(19) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963).

(20) It is assumed that the anomerization of 2-*O*-benzoyl-L-arabinofuranose and the ring expansion are comparatively rapid reactions.

(21) It may be appropriate to remind the reader that the rate of the conversion of A to A + B is the same as the rate of conversion of B into A + B in a system A ⇌ B, irrespective of the proportions of A and B at equilibrium. Thus the (as yet unknown) 2-*O*-benzoyl-α-L-arabinopyranose would mutarotate at the same rate as its β-anomer described here. The argument put forward above is therefore valid irrespective of which anomer of 2-*O*-benzoyl-L-arabinopyranose is an intermediate in the rearrangement of either III or IX.

It seems possible that a study of the relative rates of migration of various types of acyl groups in a given sugar as well as a study of the relative rates of migration of a given acyl group in a variety of aldoses might lead to interesting generalizations.

Experimental[22]

2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose (I) from L-Arabinose.—Thirty grams of powdered L-arabinose was added to a mixture of 600 ml. of anhydrous methanol and 15 g. of Drierite and the suspension, after the addition of 4.5 ml. of concentrated sulfuric acid, was stirred at room temperature for 5 hr. The reaction mixture, then being devoid of reducing power, was filtered and the filtrate passed through a column containing 150 ml. of IR-45, the column being washed with 400 ml. of methanol. The combined solution and washings were concentrated *in vacuo* to a heavy sirup which was diluted with 50 ml. of freshly purified tetrahydrofuran and reconcentrated (35–40° bath). Freshly purified tetrahydrofuran (400 ml.) was added and the solution treated with 30 g. of Drierite, 156 g. of commercial powdered potassium hydroxide,[23] and 200 ml. of benzyl chloride. The mixture was stirred under gentle reflux overnight, cooled, filtered through a thin bed of Filter-Cel, and concentrated *in vacuo*, finally at *ca.* 1 mm. and 100° (bath). The crude sirupy methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside mixture was dissolved in 400 ml. of glacial acetic acid and the solution diluted with 60 ml. of 6 *N* hydrochloric acid. It was heated at 65° for 1.25 hr., concentrated *in vacuo* to one-third its volume and poured into 1500 ml. of a mixture of ice and water. After seeding, the mixture was left at 5° overnight, the aqueous layer then being decanted from the partially crystalline mass which was dissolved in 200 ml. of dichloromethane. The solution was washed with cold aqueous sodium bicarbonate solution, dried with magnesium sulfate, filtered through a thin bed of decolorizing carbon, and concentrated *in vacuo* to a thin sirup. This residue, dissolved in 200 ml. of cyclohexane, seeded and left 1 hr. at room temperature and then at 5° overnight, afforded 40.1 g. (48%) of 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose melting at 88–89°. In 9:1 (v./v.) dioxane–water (*c* 2.0) it gave $[\alpha]^{20}D$ +27.1° (2 min.) → −11.6° (20 hr., constant); in dichloromethane it showed $[\alpha]^{20}D$ +6.5° (*c* 4.25).

2,3,5-Tri-*O*-benzyl-α-L-arabinofuranose (V).—2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose (2.9939 g.) in a 1.5-dm. polarimeter tube was treated with 25 ml. of dry pyridine. Solution was almost instantaneous, the observed rotation going from $[\alpha]^{20}D$ +8.29° to −2.12° (constant) in 328 min. After 8 hr. the solvent was removed *in vacuo* (40° bath); on standing, the sirupy residue crystallized completely after 6 hr. It was redissolved in 3 ml. of pyridine, the solution diluted with 3 ml. of water and the mixture (two layers) kept at −5° for 1 week to give a microcrystalline powder, m.p. 78–80° and $[\alpha]^{20}D$ −4.52° in dichloromethane (*c* 3.49).

Anal. Calcd. for $C_{26}H_{28}O_5$ (420.48): C, 74.26; H, 6.71. Found: C, 74.53; H, 6.77.

The infrared spectrum of the compound appeared to be indistinguishable from that of its β-anomer.

1-*O*-Benzoyl-2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (II).—To a mixture of 45 ml. of dry pyridine and 2.5 ml. of benzoyl chloride which had been cooled to −15° was added (in small portions, with stirring) 5.6 g. of 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose. After the addition was complete, the mixture was stirred for 1 hr. at room temperature and left at room temperature overnight. The excess benzoyl chloride was destroyed by the dropwise addition of 5 ml. of water and, 30 min. later, the reaction mixture was diluted with dichloromethane. After washing successively with cold water, 3 *N* sulfuric acid and cold half-saturated aqueous sodium bicarbonate the solution was dried with sodium sulfate and concentrated *in vacuo*. The residue, dissolved in 30 ml. of warm isopropyl ether and seeded,[24] gave long, colorless needles (5.4 g., 77%). Recrystallized three times from methanol (10 parts) the pure product was obtained; m.p. 48°, $[\alpha]^{20}D$ +54.6° (*c* 2.98, CH_2Cl_2).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.75; H, 6.30.

(22) Melting points are corrected.

(23) Hooker Chemical Corp., Niagara Falls, N. Y.

(24) Seeds were obtained by adding pentane to a portion of the solution.

1-*O*-Benzoyl-2,3,5-tri-*O*-benzyl-α-L-arabinofuranose (VI).—2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose (40 g.) was dissolved in 350 ml. of dry pyridine and the solution kept at 20° until mutarotation had ceased. It was then cooled to −15° and, while stirred, treated dropwise with 15 ml. of benzoyl chloride. Stirring was continued at −15° for 1.25 hr. and the solution left at room temperature for 18 hr. Water (10 ml.) was added dropwise to the chilled solution to decompose the excess benzoyl chloride; the mixture was then diluted with dichloromethane and washed successively with cold 3 *N* sulfuric acid and aqueous sodium bicarbonate. Moisture was removed with sodium sulfate and the solution concentrated *in vacuo* (40° bath) to leave a residue (49 g., 98%) which crystallized completely. Recrystallized from 250 ml. of warm isopropyl ether the product (28 g., 56%) melted at 61–63° and showed $[\alpha]^{20}D$ −51.1° in dichloromethane (*c* 2.94).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.33; H, 6.38.

The same product was obtained in another experiment through the benzoylation of 2,3,5-tri-*O*-benzyl-α-L-arabinofuranose at a low temperature.

1-*O*-Benzoyl-α-L-arabinofuranose (VII).—A solution of 3.41 g. of 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-α-L-arabinofuranose in 200 ml. of ethyl acetate was treated with 0.4 g. of 10% palladium on charcoal[25] and the suspension was shaken with hydrogen at room temperature (25°) and pressure. The theoretical amount of hydrogen (476 ml.) was absorbed in 35 min. After removal of the catalyst, the solution was concentrated *in vacuo* to give a sirup which, dissolved in 20 ml. of dichloromethane, gave 1.5 g. (91%) of crystalline product. Recrystallized from 10 parts of boiling ethyl acetate, the ester melted at 130–131° and showed $[\alpha]^{20}D$ −93.2° in dry pyridine (*c* 2.31).

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.70; H, 5.55.

1-*O*-Benzoyl-α-L-arabinofuranose failed to mutarotate in anhydrous pyridine solution over the course of 4.5 hr.; when the pyridine solution was diluted with a quarter of its volume of water no mutarotation could be observed over the course of 24 hr. and, thereafter, unchanged 1-*O*-benzoyl-α-L-arabinofuranose was recovered.

A sample (0.5 g.) of 1-*O*-benzoyl-α-L-arabinofuranose was benzoylated in conventional fashion with benzoyl chloride in pyridine solution to give from ethanol 0.9 g. (81%) of **α-L-arabinofuranose tetrabenzoate** melting at 117–121° and showing $[\alpha]^{20}D$ −25.1° in chloroform (*c* 2.33). Ness and Fletcher[16] reported m.p. 117–121° and $[\alpha]^{20}D$ +27.9° (chloroform) for the enantiomorph of this compound.

1-*O*-Benzoyl-β-L-arabinofuranose (III).—A solution of 5.27 g. of 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-β-L-arabinofuranose in 300 ml. of ethyl acetate was reduced catalytically in the presence of 0.673 g. of 10% palladium-on-charcoal at room temperature (27°) and atmospheric pressure. The theoretical amount of hydrogen (735 ml.) was absorbed during 1.75 hr. The catalyst was removed by filtration and the solution concentrated *in vacuo* (40° bath) to 30 ml.; colorless needles formed spontaneously and, after storage at −5° overnight, were removed, 2 g. (78%). Recrystallized from boiling ethyl acetate, the 1-*O*-benzoyl-β-L-arabinofuranose melted at 140–143° and showed $[\alpha]^{20}D$ +59.8° in dry pyridine (*c* 1.98).

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.58; H, 5.99.

A sample (0.5 g.) of this ester was benzoylated in conventional fashion with benzoyl chloride in pyridine solution at −10° to give, from ethanol, 0.9 g. (81%) of **β-L-arabinofuranose tetrabenzoate** melting at 121–122° and showing $[\alpha]^{20}D$ +94.1° in chloroform (*c* 2.23). Ness and Fletcher[16] reported m.p. 120–122° and $[\alpha]^{20}D$ −94.0° (chloroform) for the D-form.

2-*O*-Benzoyl-β-L-arabinopyranose (IV) from 1-*O*-Benzoyl-β-L-arabinofuranose (III).—To 0.1065 g. of pure 1-*O*-benzoyl-β-L-arabinofuranose in a 1.5-dm. all glass polarimeter tube was added 10 ml. of anhydrous pyridine. As soon as solution was complete, the solution was diluted with 2.50 ml. of water and the resulting mutarotation observed. The changing specific rotation and first-order reaction constants calculated therefrom are given in Table I. Based on an average reaction rate of 0.026 the "half-life" of the reaction was approximately 11.6 min.

(25) In subsequent work the palladium black, made by the reduction (with hydrogen) of palladium chloride in methanol solution according to the method of O. T. Schmidt and W. Staab [*Ber.*, **87**, 393 (1954)], was found markedly superior to all other palladium catalysts for such debenzylations.

TABLE I

MUTAROTATION OF 1-*O*-BENZOYL-β-L-ARABINOFURANOSE IN AQUEOUS PYRIDINE

t, min.	$[\alpha]^{20}D$[a]	*k*, min., decimal logs
0	73 (extrapolated)	...
4	82	0.023
5	84	.023
5.5	85	.023
7	89	.026
9	93	.027
14	101	.028
15	103	.029
24	111	.030
44	117	.027
79	120	...
100	120	...

[a] Uncorrected for the small increase in volume caused by the solute.

In an experiment, essentially identical with the preceding rate measurement, using 0.393 g. of 1-*O*-benzoyl-β-L-arabinofuranose, the solution was concentrated *in vacuo* (40° bath) when mutarotation had ceased. The residual sirup was dissolved in a mixture of 5 ml. of ethyl acetate and 3 ml. of pentane and the solution kept at −5° overnight to give short needles. Recrystallized from 5 ml. of warm ethyl acetate, the product (0.3 g., 76%) melted at 133–135° and showed $[\alpha]^{20}D$ +145.4 → +102.5° in methanol (*c* 1.29). Rammler and MacDonald[17] reported m.p. 132–133° and $[\alpha]^{23}D$ −152 → −100° (methanol) for 2-*O*-benzoyl-β-D-arabinopyranose.

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.82; H, 5.77.

An authentic specimen of 2-*O*-benzoyl-β-L-arabinopyranose, prepared through the hydrogenolysis of benzyl 2-*O*-benzoyl-β-L-arabinopyranoside,[17] failed to depress the melting point of the product obtained through the rearrangement of 1-*O*-benzoyl-β-L-arabinofuranose.

The mutarotation of 2-*O*-benzoyl-β-L-arabinopyranose was measured as follows. A sample (33.6 mg.) of the crystalline ester in a 1-dm. polarimeter tube was dissolved in 3.00 ml. of anhydrous pyridine. Over the course of 4 min. the rotation (2.24°) was constant. Water (0.75 ml.) was then added and the mutarotation observed at 20°. The specific rotations and first-order rate constants are given in Table II.

TABLE II

MUTAROTATION OF 2-*O*-BENZOYL-β-L-ARABINOPYRANOSE IN AQUEOUS PYRIDINE

t, min.	$[\alpha]^{20}D$[a]	*k*, min., decimal logs
0	157 (extrapolated)	...
0.5	155	0.051
3	146	.059
5	142	.052
6	137	.068
7	134	.075
9	132	.068
11	129	.072
13	128	.070
31	124	...

[a] Uncorrected for the small increase in volume caused by the solute and assuming that the final volume was 3.75 ml. Based on an average rate of 0.064, $t_{1/2}$ was 4.7 min.

2,3,4-Tri-*O*-benzyl-β-L-arabinopyranose (VIII).—Pure methyl β-L-arabinopyranoside[26] (44.5 g.), powdered potassium hydroxide[23] (212 g.), and pure tetrahydrofuran (543 ml.) were combined and treated with 271 ml. of benzyl chloride. The mixture was stirred under reflux for 5.5 hr., cooled, and filtered through Filter-Cel which was thereafter washed with dichloromethane. The combined filtrate and washings were concentrated *in vacuo*, finally being held at 140° (bath) and 0.01-mm. pressure. The

(26) C. S. Hudson, *J. Am. Chem. Soc.*, **45**, 265 (1925).

crude, pale yellow methyl 2,3,4-tri-*O*-benzyl-β-L-arabinopyranoside (110 g., 94%) was dissolved in 2.2 l. of glacial acetic acid and the solution diluted with 880 ml. of 2 *N* hydrochloric acid. After being heated at 80° for 16 hr. the reaction mixture was cooled and poured into 18 l. of ice–water, seeded[27], and left at +5° until crystallization appeared to be complete (2 weeks). The 80.0 g. of tan solid was dissolved in 300 ml. of hot isopropyl ether, the solution filtered through a thin layer of Darco X, and left at room temperature, 54.2 g. (48%), m.p. 71–79°, $[\alpha]^{20}D$ +93.2° (*c* 0.84 in 9:1 dioxane–water, 3 min.). Recrystallized from 6.8 parts of warm cyclohexane, the 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose was obtained in pure form as long, fine needles, m.p. 83–86°. In 9:1 dioxane–water (v./v.), containing a trace of ammonia the substance showed $[\alpha]^{20}D$ +92.2° (3.5 min.) → +87.6° (3 hr.) (*c* 0.97); in dichloromethane (*c* 1.76) the substance showed $[\alpha]^{20}D$ +66.5° → +51.1° (2 days).

Anal. Calcd. for $C_{26}H_{28}O_5$ (420.48): C, 74.26; H, 6.71. Found: C, 74.45; H, 6.95.

1-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-β-L-arabinopyranose (IX).—To a mixture of 3.5 ml. of benzoyl chloride and 30 ml. of dry pyridine which was kept at 0° was added 10.0 g. of 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose. The mixture was allowed to warm to room temperature and, after 1 hr., was worked up in the usual way. When the purified sirupy product was dissolved in 50 ml. of warm methanol crystallization was spontaneous, 10.4 g. (83%), m.p. 81–83°, $[\alpha]^{20}D$ +129° (CH_2Cl_2, *c* 0.40). A second crop (1.67 g.) proved to be crude 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose. Recrystallization of the first crop from isopropyl ether, cyclohexane, isopropyl ether and, finally from methanol yielded pure 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-β-L-arabinopyranose as clear, stubby prisms, m.p. 82–83°, $[\alpha]^{20}D$ +127.2° (CH_2Cl_2, *c* 0.91).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.85; H, 6.33.

1-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (XII).—2,3,4-Tri-*O*-benzyl-β-L-arabinopyranose (15.5 g.) was dissolved in 80 ml. of dioxane, the solution treated with a little dilute aqueous ammonia and then diluted to 100 ml. with water. After 2 days at 20° the solution had ceased to mutarotate; it was then freeze-dried to give a sirup which was diluted with 15 ml. of pyridine. The solvent was removed *in vacuo* at less than room temperature and the amorphous residue diluted with 50 ml. of pyridine. The solution was cooled to below 0° and treated with 10 ml. of benzoyl chloride. After being allowed to warm slowly to room temperature the reaction mixture was worked up in the customary manner to give a stiff sirup which was dissolved in 300 ml. of boiling methanol. On standing at room temperature the solution deposited 7.2 g. of nearly pure 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose; a second crop (4.0 g.), obtained by evaporation of the mother liquor was less pure, while a third crop (6.9 g.) proved to be largely the β-anomer. In separating the two anomers advantage was taken of the fact that the α-anomer is comparatively insoluble in methanol while the β-anomer is comparatively insoluble in isopropyl ether. In this fashion 9.1 g. (47%) of nearly pure α-anomer was obtained. One further recrystallization from methanol afforded the pure product, m.p. 105°, $[\alpha]^{20}D$ −31.5° (CH_2Cl_2, *c* 0.82).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.49; H, 6.29.

1-*O*-Benzoyl-α-L-arabinopyranose (XIII).—Palladium chloride (0.6 g.) was suspended in ethyl acetate and reduced with hydrogen at room temperature. When the reduction was complete the catalyst was washed with ethyl acetate by decantation and a solution of 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (2.97 g.) in a mixture of 90 ml. of ethyl acetate and 10 ml. of methanol added. Stirred vigorously at room temperature, the mixture absorbed the theoretical amount of hydrogen in 4 hr. After removal of the catalyst, the solution was concentrated *in vacuo* at room temperature to a sirup. The sirup was diluted with 20 ml. of ethyl acetate and the solution reconcentrated in the same fashion. From 3 ml. of ethyl acetate the product slowly crystallized as very fine needles, 0.72 g. (48%), m.p. 122–125°. A second crop (0.3 g., m.p. 113–125°) raised the total yield to 68%. Recrystallization of the first crop from ethyl acetate afforded pure 1-*O*-benzoyl-α-L-arabinopyranose, m.p. 123–125°, $[\alpha]^{20}D$ +4.1° (methanol, *c* 0.86). In anhydrous pyridine (*c* 1.62) the pure ester showed $[\alpha]^{20}D$ −6.2°. When the solution was diluted with a quarter of its volume of water the rotation became $[\alpha]^{20}D$ +6.2°,[28] no mutarotation being observed over the course of 48 min.

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.79; H, 5.81.

A sample of the 1-*O*-benzoyl-α-L-arabinopyranose was benzoylated in conventional fashion to give α-L-arabinopyranose tetrabenzoate in 34% yield, m.p. 159°, $[\alpha]^{20}D$ +114.0° (chloroform, *c* 1.08). Fletcher and Hudson[18] reported m.p. 160–161° and $[\alpha]^{20}D$ +114.1° (chloroform) for this substance.

1-*O*-Benzoyl-β-L-arabinopyranose (X).—1-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-β-L-arabinopyranose (4.04 g.), dissolved in a mixture of 44 ml. of methanol and 44 ml. of ethyl acetate, was added to palladium which had been freshly made by the reduction of 0.43 g. of palladium chloride in the same solvent mixture. Stirred vigorously at room temperature, the mixture absorbed the theoretical amount of hydrogen in 3 hr. The catalyst was removed by filtration and the solution concentrated *in vacuo* at room temperature to a dry crystalline residue. Recrystallized at room temperature from a mixture of methanol and ethyl acetate, the product was obtained as elongated rectangular plates, 1.75 g. (89%), m.p. 136–143°, $[\alpha]^{20}D$ +173° (methanol, *c* 0.55). Recrystallized from warm acetone, the 1-*O*-benzoyl-β-L-arabinopyranose melted at 134–150° and showed $[\alpha]^{20}D$ +175° (methanol, *c* 0.82). Further recrystallization failed either to narrow the melting point range or alter the specific rotation.

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.43): C, 56.69; H, 5.55. Found: C, 56.82; H, 5.57.

Benzoylation of a sample of the 1-*O*-benzoyl-β-L-arabinopyranose in the usual fashion afforded β-L-arabinopyranose tetrabenzoate in 67% yield, m.p. 176°, $[\alpha]^{20}D$ +321.9° (chloroform, *c* 1.38). Wolfrom and Christman[29] reported m.p. 173–174° and $[\alpha]^{20}D$ +325° (chloroform) for β-L-arabinopyranose tetrabenzoate.

2-*O*-Benzoyl-β-L-arabinopyranose (IV) from 1-*O*-Benzoyl-β-L-arabinopyranose (X).—1-*O*-Benzoyl-β-L-arabinopyranose (0.3308 g.), dissolved in pyridine to a total volume of 10.0 ml., showed $[\alpha]^{20}D$ +164°, unchanged over the course of 11 min. Water (2.5

TABLE III

MUTAROTATION OF 1-*O*-BENZOYL-β-L-ARABINOPYRANOSE IN AQUEOUS PYRIDINE

t, min.	$[\alpha]^{20}D$[a]	*k*, min., decimal logs
0	158	.....
75	157	0.00017
120	156	.00013
183	155	.00018
285	154	.00018
475	152	.00017
640	150	.00018
1220	145	.00017
1611	142	.00017
2045	140	.00016
2697	137	.00015
4305	131	.00015
6000	128	.00014
7500	127	.00013
9985	125	.00014
11455	124	.....

[a] Assuming the volumes were additive.

(27) Seeds were initially obtained by chromatographing a sample of the sirupy material on neutralized Alcoa alumina, eluting with benzene–ether (1:1), and evaporating the eluate *in vacuo*. A sample of the crude hydrolysate was freed of acid at this point and found to give a negligible quantity of 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose. Since it showed ester carbonyl (as well as hydroxyl) absorption in the infrared region, the sample was treated briefly with sodium methoxide in methanol; a substantial quantity of 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose was then isolated. On the basis of this evidence, it seems likely that some 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-arabinopyranose is formed during the hydrolysis and that this ester is subsequently hydrolyzed during the extended period after the reaction mixture is diluted with the very large proportion of water.

(28) It is assumed that the volumes were additive. No satisfactory explanation of this reversal of the sign of rotation can be made at this juncture. Concentration of the aqueous pyridine solution led to the isolation of unchanged 1-*O*-benzoyl-α-L-arabinopyranose.

(29) M. L. Wolfrom and C. C. Christman, *J. Am. Chem. Soc.*, **58**, 39 (1936).

ml.) was then added and the mutarotation observed at 20°. The specific rotations and first-order rate constants are given in Table III. Based on an average rate of 0.00016, the "half-life" of the reaction was 1881 min.

When mutarotation had ceased, the solvent was removed *in vacuo* to give a sirup which was crystallized from ethyl acetate–pentane. The short, colorless needles thus obtained were recrystallized from the same solvent mixture 0.2 g. (66%), m.p. 133–135°, $[\alpha]^{20}D$ +145.4° → +102.5° (methanol, *c* 1.27). These values agree with those reported earlier in this paper for 2-*O*-benzoyl-β-L-arabinopyranose.

Acknowledgment.—We are indebted to Mr. Harry W. Diehl for the preparation of some starting materials. Analyses were performed by the Analytical Services Unit of this laboratory under the direction of Mr. H. G. McCann.

Syntheses with Partially Benzylated Sugars. III.[1] A Simple Pathway to a "*cis*-Nucleoside," 9-β-D-Arabinofuranosyladenine (Spongoadenosine)

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Received July 1, 1963

Condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride with methanol leads predominantly to methyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside. Condensation of the same halide with N-benzoyladenine and subsequent removal of the protecting groups readily gives 9-β-D-arabinofuranosyladenine, a type of glycoside which is difficultly accessible by other means.

The most generally applicable method for the synthesis of glycosides is that which Koenigs and Knorr[3] devised over sixty years ago. However, the condensation of a fully acylated glycosyl halide with a potential aglycon is normally a limited process in the sense that it leads to a product in which the aglycon is *trans* to the acyloxy group at C-2. With an acylated glycosyl halide bearing a halogen at C-1 *cis* to an acyloxy group at C-2, simple inversion predominates; with a *trans*-halide, participation of the acyloxy group at C-2 in the displacement of the halogen results either in no net inversion or formation of an ortho ester derivative.

A wide variety of special methods have been devised for the synthesis of 1,2-*cis*-glycosides. Two of these methods deserve particular attention. In the first, the configuration of C-2 in a *trans*-glycoside is inverted by one means or other. The ingenious synthesis of 9-β-D-arabinofuranosyladenine (V) from 9-β-D-xylofuranosyladenine, described by Reist, Benitez, Goodman, Baker, and Lee,[4] illustrates this approach. A second method involves the use of a glycosyl halide in which the hydroxyl group at C-2 is masked with a group which does not participate in the displacement of the halogen at C-1. The synthesis of the *cis*-linked disaccharide isomaltose (6-*O*-α-D-glucopyranosyl-D-glucose) through 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride by Wolfrom, Pittet, and Gillam[5] is of this type.

While the two aforementioned methods are eminently successful in some sugar series, their success depends, ultimately, on selective substitutions at C-2 of aldose derivatives; such selective substitution always involves a number of steps and is not practicable with some aldoses. The concept of using a glycosyl halide, *fully* substituted with the nonparticipating benzyl group has many attractive features inasmuch as hydroxyl groups are readily masked as benzyl ethers and the benzyl groups readily cleaved by catalytic hydrogenation. Exploratory work by Barker and Fletcher[6] recently showed that 2,3,5-tri-*O*-benzyl-D-ribofuranosyl and 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl bromides could be prepared, albeit only as highly reactive sirups. We wish now to describe the preparation of the more stable 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) and the studies of this substance which have led to the practicable synthesis of a 1,2-*cis*-nucleoside.

2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (I), readily preparable from D-arabinose by the improved procedure which Tejima and Fletcher[1] described for its enanthiomorph, was converted into 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) either directly with hydrogen chloride in the presence of a desiccant or indirectly through the action of hydrogen chloride on a mixture of anomers of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose (II).[7] The chloride III proved to be a nearly colorless sirup, markedly more stable than the corresponding bromide.[6] On condensation with methanol in the presence of sodium methoxide, it afforded a sirupy mixture of the anomeric methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides; vapor phase chromatography showed that the β-anomer (a 1,2-*cis*-glycoside) predominated.

In order to ascertain whether other β-D-arabinofuranosides could be made by this process, a purine[8] was used as an aglycon since there is considerable current interest in the biochemical properties of nucleosides containing the β-D-arabinofuranosyl moiety,[9] and adequate special

(1) Paper II of this series: S. Tejima and H. G. Fletcher, Jr., *J. Org. Chem.*, 2999 (1963).

(2) Visiting Associate of the Public Health Service, 1962–1963.

(3) W. Koenigs and E. Knorr, *Sitzber. Math. Naturw. Kl. Bayer. Akad. Wiss. Muenchen*, **30**, 108 (1900); *Ber.*, **34**, 957 (1901).

(4) E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **25**, 3274 (1962).

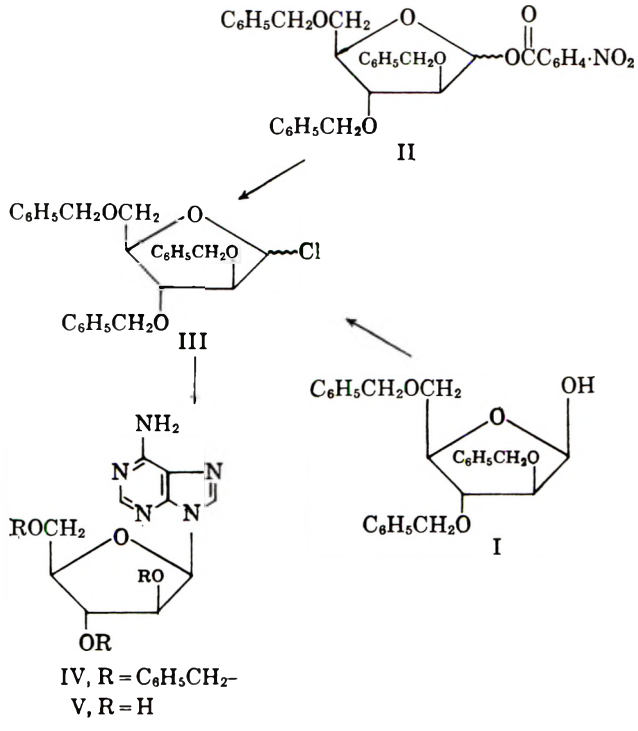
(5) M. L. Wolfrom, A. O. Pittet, and I. C. Gillam, *Proc. Natl. Acad. Sci. U. S.*, **45**, 700 (1961).

(6) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

(7) It should be noted, however, that the 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) differed in certain properties depending upon whether it was prepared from I or II. The available evidence appears to indicate that this difference arises from differing proportions of anomers in the two preparations of III; see the Experimental.

(8) The suggestion that adenine be used as first made to us by Professor B. R. Baker.

(9) M. Hubert-Habart and S. S. Cohen, *Biochim. Biophys. Acta*, **59**, 468 (1962); H. Tono, *J. Biol. Chem.*, **237**, 1271 (1962); M. G. Chu and G. A. Fischer, *Biochem. Pharmacol.*, **11**, 423 (1962); G. E. Underwood, *Proc. Soc. Exp. Biol. Med.*, **111**, 660 (1962); R. W. Talley and V. K. Vaitkevicius, *Blood*, **21**, 352 (1963); J. J. Brink and G. A. LePage, *Federation Proc.*, **22**, 184 (1963); G. A. LePage and I. G. Junga, *Cancer Res.*, **23**, 739 (1963); S. S. Cohen, *Perspectives Biol. Med.*, **6**, 215 (1963).



methods are available for the synthesis of pyrimidine β-D-arabinofuranosides.[10]

Condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) with a twofold excess of N-benzoyladenine, followed by alkaline N-debenzoylation, led to the isolation in 46% yield of a crystalline tri-*O*-benzylpentosyladenine which was further characterized as its crystalline picrate. Reductive hydrogenolysis of the tri-*O*-benzylpentosyladenine over palladium black afforded 9-β-D-arabinofuranosyladenine (V), identical with a sample kindly provided by Dr. Leon Goodman.[4] Investigation of the mother liquor afforded chromatographic evidence for the formation of the anomeric nucleoside, 9-α-D-arabinofuranosyladenine, in very low yield. The mother liquor also yielded a substantial quantity of methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranoside. Although the initial condensation had been conducted for one week at room temperature in the presence of a solid acid acceptor (molecular sieve) and of an excess of N-benzoyladenine, the isolation of the methyl glycoside may indicate that some 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride had survived to react with the barium methoxide used for the N-debenzoylation.

Discussion

While all benzylated glycosyl halides thus far prepared have been amorphous, it seems reasonable to assume that the proportions of anomeric forms in any one case are roughly those which are encountered with the corresponding acylated glycosyl halide. With both the 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromides[11] and 2,3,5-tri-*O*-benzoyl-L-arabinofuranosyl chlorides[12] the α-anomer greatly predominates. We might expect, therefore, that III is largely 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride and hence methyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside and IV are formed *via* Walden inversion at C-1. If this view were correct, one might predict that the synthetic pathway described here would be especially suitable for the synthesis of *cis*-glycosides from those sugars in which the dominant halide is *trans*. Furthermore, exploratory experiments appear to show that the proportion of anomeric products obtained from a given halide (lacking participating groups) may be modified through the use of appropriate reaction conditions,[13] suggesting the possibility that any desired anomer may be preparable from a given halide. A study of the mechanism of the displacement of halogens in glycosyl halides lacking participating groups is currently being pursued in this laboratory.

Experimental[14]

2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl Chloride (III). (A) From the 2,3,5-Tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (II).—A mixture of the anomeric forms of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses[6] ($[\alpha]^{20}D$ +6° in CH_2Cl_2, m.p. 70–79°, 0.3038 g.) which had been dried *in vacuo* at 50° was added to 7 ml. of a solution of hydrogen chloride in dichloromethane (0.31 *N*) which had been cooled to 0°. After standing at 0° for 2 hr., the reaction mixture was filtered, a nearly quantitative yield of *p*-nitrobenzoic acid being consistently recovered (the infrared spectrum being identical with authentic *p*-nitrobenzoic acid). On concentration *in vacuo* at room temperature, the filtrate gave a nearly colorless oil which was held in high vacuum over solid sodium hydroxide for 40 min.; the specific rotation of III, prepared in this fashion, varied from $[\alpha]^{20}D$ +91.1 to +96° (CH_2Cl_2, *c* 1.25). A portion (0.149 g.) of this chloride was dissolved in 5 ml. of benzene and the solution treated with a mixture of 3 ml. of benzene and 2 ml. of sodium methoxide in methanol (0.86 *N*). A white precipitate became visible after 15 sec.; after 5 hr. the reaction mixture was washed with four portions of water, dried over magnesium sulfate, filtered, and concentrated to a sirup which showed $[\alpha]^{20}D$ −52.6° (CH_2Cl_2, *c* 2.0).

Anal. Calcd. for $C_{27}H_{30}O_5$ (434.51): OCH_3, 7.14. Found: Found: OCH_3, 7.01.

Gas chromatography[15] showed the mixture to contain two components. The minor one cochromatographed with an authentic sample of methyl 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside[6]; it is assumed that the major peak is the β-anomer. Based on the heights of the peaks, the mixture consisted of 98.3% of the β-anomer of 1.7% of the α-anomer.

(B) From 2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (I).—2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (1.00 g.), prepared by the improved procedure for its enantiomorph described by Tejima and Fletcher,[1] was dissolved in 60 ml. of benzene which had been saturated with hydrogen chloride at room temperature. Anhydrous magnesium sulfate (5 g.) was added and the reaction mixture left at room temperature (with occasional shaking) for 2.5 hr., when the rotation had become constant. After filtration the solution was concentrated *in vacuo* and the residual sirup held briefly in high vacuum over solid sodium hydroxide; $[\alpha]^{20}D$ +72.5° (CH_2Cl_2, *c* 1.25).[16] The infrared spectrum of the sirup showed no hydroxyl absorption. A sample of the chloride (0.184 g.) was dissolved in 7.5 ml. of benzene and the solution treated with a mixture of 3 ml. of 1 *N* sodium methoxide in methanol and

(10) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 238 (1959).

(11) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **80**, 2007 (1958).

(12) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963).

(13) For instance, condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) with chloromercuri-N-benzoyladenine in dimethyl sulfoxide solution yields (after deblocking) a product which, on the basis of paper chromatographic behavior in acetone–water (95:5), appears to consist of the two anomeric 9-D-arabinofuranosyl–adenines in approximately equal quantities.

(14) Melting points are corrected.

(15) SE 30 (1.5%) on 100–400 Chromosorb W, silanized, was used at 260°, together with a flame ionization detector.

(16) When prepared by this method, III was uniformly found to have a lower specific rotation than when made from II. In another preparation dichloromethane was used in place of benzene, giving III with a rotation of $[\alpha]^{20}D$ +73° (CH_2Cl_2) and, thence, methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranoside with a methoxyl content of 7.18% and $[\alpha]^{20}D$ −41.3° (CH_2Cl_2). Use of III made from I gave poor yields of IV and the product thus obtained proved difficult to purify.

4 ml. of benzene. There was thus obtained a sirup which showed $[\alpha]^{20}D$ −39.3° (CH_2Cl_2, *c* 3.05).

Anal. Calcd. for $C_{27}H_{30}O_5$ (434.51): OCH_3, 7.14. Found: OCH_3, 7.36.

Gas chromatography[15] showed the sirup to consist of methyl 2,3,5-tri-*O*-benzyl-α-D-arabinofuranoside (15.6%) and its β-anomer (84.4%).[17] Using the previous numerical data and the specific rotation (with changed sign) which Barker and Fletcher[6] reported for methyl 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside ($[\alpha]^{20}D$ −44.6° in CH_2Cl_2), one may calculate the specific rotation of methyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside. Based on the mixture obtained in A, this value is $[\alpha]^{20}D$ −54.3°; the data obtained from B give a value of $[\alpha]^{20}D$ −54.9°.

9-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (IV).—Ten grams of a thoroughly dried mixture of the two anomeric forms of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose was added to 165 ml. of dichloromethane which had been saturated with anhydrous hydrogen chloride at 0°. After 2 hr. at 0°, the precipitate of *p*-nitrobenzoic acid (2.845 g., 97%) was removed by filtration and the solution concentrated *in vacuo* to a nearly colorless sirup which was held at 0.08 mm. and room temperature for 2 hr., $[\alpha]^{20}D$ +91.1° (CH_2Cl_2, *c* 2.27). The chloride was then dissolved in 100 ml. of dry dichloromethane and the solution added to a mixture of dried N-benzoyladenine (9 g., 2.14 moles/mole of II) and molecular sieve (29 g.).[18] The reaction mixture was stirred at room temperature in a glass-stoppered flask for 1 week, filtered through a layer of Celite, and concentrated *in vacuo* to a sirup (10.2 g.) which was dissolved in 100 ml. of methanol. Barium methoxide (0.9 *N*, 85 ml.) was added and the solution boiled under reflux for 5 hr. to give a dark solution which was neutralized with carbon dioxide and filtered. Solvent was removed from the filtrate and the semisolid mass was extracted with dichloromethane, the insoluble material being removed by centrifugation and then thoroughly washed. The combined extract and washings (350 ml.) were diluted with cyclohexane (450 ml.), filtered through Celite, and boiled in an open flask until the vapor temperature had risen to 70° when crystallization began spontaneously. The solution was allowed to cool slowly to give a mass of fine needles (5.20 g.). One recrystallization from 5.2 parts of warm isopropyl alcohol gave nearly pure 9-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-adenine, 4.38 g., 46%, m.p. 125–128°, $[\alpha]^{20}D$ +21.8° (CH_2Cl_2, *c* 2.0). Two further recrystallizations from isopropyl alcohol raised the melting point to 128–129° but did not change the specific rotation.

Anal. Calcd. for $C_{31}H_{31}N_5O_4$ (537.60): C, 69.25; H, 5.81; N, 13.03. Found: C, 69.40; H, 6.03; N, 12.85.

A sample of IV (50 mg.) was dissolved in 1 ml. of ethanol and to this solution was added 4 ml. of a 4% ethanolic solution of picric acid. The precipitate (73 mg.) was recrystallized from boiling ethanol–acetone (3:2, 30 ml.) to give flat yellow needles of IV picrate, 64.1 mg. (90%), m.p. 196–199°, $[\alpha]^{20}D$ +29.7° (CH_2Cl_2, *c* 0.45).

Anal. Calcd. for $C_{37}H_{34}N_8O_{11}$ (766.70): C, 57.95; H, 4.47; N, 14.61. Found: C, 58.06; H, 4.63; N, 14.89.

The original mother liquor from the preparation of IV was concentrated to a sirup which was chromatographed on 100 g. of Mallinckrodt 100-mesh silicic acid. Successive elution with benzene–ether (95:5), benzene–ether (70:30), ether, and acetone led to the recovery of a total of 2.06 g. of material. One fraction (eluted with benzene–ether, 95:5) (976 mg.) showed the infrared spectrum and gas chromatographic behavior[15] expected of a mixture of the anomeric methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides; the yield was 13%.

Anal. Calcd. for $C_{27}H_{30}O_5$ (434.51): OCH_3, 7.14. Found: OCH_3, 7.21.

A sample was hydrolyzed using the technique of Tejima and Fletcher[1] to give, from a mixture of isopropyl and ethyl ethers, needles, m.p. 75–79°, $[\alpha]^{26}D$ +12.7° (final, *c* 1.1, dioxane–water, 9:1, containing a trace of ammonia). An equilibrium value of $[\alpha]^{20}D$ −11.6° has been recorded[1] for 2,3,5-tri-*O*-benzyl-L-arabinofuranose under these conditions.

Another fraction (281 mg.), eluted from the silicic acid column with acetone, was hydrogenated over palladium black and then chromatographed on paper using acetone–water (95:5); two components were observed (under ultraviolet light), migrating at the same rates as authentic samples of the two anomeric 9-D-arabinofuranosyladenines.

9-β-D-Arabinofuranosyladenine (V).—Palladium chloride (300 mg.) was suspended in 150 ml. of methanol and reduced by shaking with hydrogen at room temperature. To the acidic suspension was then added a solution of 300 mg. of 9-(2,3,5-tri-*O*-benzyl β-D-arabinofuranosyl)adenine in 50 ml. of methanol. The reaction mixture was shaken with hydrogen until absorption of the gas was complete (100 min.). After the catalyst had been removed, the solution was passed through a column of Dowex 2-X8 (HCO_3^-) and concentrated *in vacuo* to a sirup (159 mg.) which crystallized on rubbing with water. Recrystallization from 12 ml. of hot water afforded the pure nucleoside, 148 mg. (93%, anhydrous basis), m.p. 258–260°, $[\alpha]^{20}D$ −1.7° (pyridine, *c* 0.54), λ_{max}^{EtOH} 258 mμ. The product did not depress the melting point of a sample of 9-β-D-arabinofuranosyladenine synthesized from 9-β-D-xylofuranosyladenine[4]; the infrared spectra and chromatographic behavior of the two samples were identical. The analytical sample was dried *in vacuo* at 100° overnight, losing 5.6% of its weight.

Anal. Calcd. for $C_{10}H_{13}N_5O_4$ (267.24): C, 44.94; H, 4.90; N, 26.21. Found: C, 45.06; H, 4.98; N, 26.09.

The nucleoside (26.1 mg., the analytical sample) was dissolved in hot water (2.50 ml.) and, after cooling (with partial crystallization), was treated with 0.60 ml. of 0.245 *M* sodium metaperiodate. It was left in the dark 4 days with intermittent shaking. Excess periodate was removed by the addition of barium chloride (24.5 mg.) followed by filtration. Ten milligrams of sodium borohydride was added to the filtrate, followed after 2 hr. by 3 drops of glacial acetic acid. The specific rotation of the solution of 2-*O*-[1-(9-adenyl)-2-(hydroxy)ethyl]glycerol (based on weight of the starting material) was $[\alpha]^{20}D$ +66°. When adenosine was oxidized and reduced in identical fashion, the resulting solution had $[\alpha]^{20}D$ +61°.

Oxidation and reduction of 9-α-D-ribofuranosyladenine, leading to a product with $[\alpha]^{20}D$ −66°, has been reported.[19]

Acknowledgment.—We are indebted to Dr. John A. Montgomery for the gift of a sample of authentic 9-α-D-arabinofuranosyladenine, to Mr. Harry W. Diehl for assistance in the preparation of 2,3,5-tri-O-benzyl-β-D-arabinofuranose, and to the Analytical Services Unit of this laboratory, under the direction of Mr. H. G. McCann, for analyses.

(17) The higher proportion of α-anomer found here suggests that III, prepared from I as described previously, contains a higher proportion of the β-anomer than is the case when it is prepared from II. This conclusion is supported by the fact that III is less dextrorotatory when prepared from I than when prepared from II.

(18) Type 4A, 1/16-in. pellets, Fisher Scientific Co.

(19) R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Am. Chem. Soc.* **80**, 2006 (1958).

On the Barrier to Inversion of Cyclooctatetraene. The Thermal Decomposition of Dibenzo[e,g][1,4]diazocine[1]

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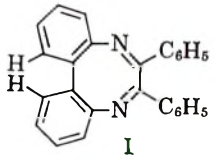
Received December 3, 1962

An attempt was made to measure the barrier to inversion of a cyclooctatetraene derivative by the thermal racemization of optically active dimethyl dibenzo[e,g][1,4]diazocine-3,10-dicarboxylate. At above 240° the compound fragmented to yield dimethyl 6-phenylphenanthridine-3,8-dicarboxylate and benzonitrile. The rate of the fragmentation reaction allowed estimation of the barrier to inversion of cyclooctatetraene as greater than 17 kcal./mole.

Cyclooctatetraene is known to possess a tub-like configuration (D_{2d}) with alternating long and short bonds,[2] while the most detailed quantum mechanical calculations published on the system (Pariser-Parr approximation)[3] indicate that the planar structure with alternating long and short bonds (D_{4h}) should be slightly more stable. More recently better approximations have indicated[4] that the D_{2d} structure should indeed be the more stable, but only by a few kcal./mole. An experimental determination of the difference in energy between these two forms was considered desirable, so that the accuracy of the theoretical calculations might be assessed. [The energy of the symmetrical (D_{8h}) structure of all equivalent bond lengths is calculated to be of such high energy that it is not being considered here although an experimental measurement of the $D_{2d} \rightarrow D_{8h}$ change has been reported.[5]]

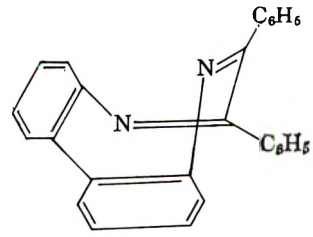
An experimental method was devised for setting a lower limit for the energy of the change from the D_{2d} form to the D_{4h} form. While in principle the energy could have been found, in fact the system underwent instead another reaction, which appears to be of a previously unknown type. While some modification of the system could probably have been made so as to give the desired results, an independent measurement of the desired quantity by another group[6] has made it unnecessary to pursue the problem further, and therefore only a lower limit to the energy for the change is reported here.

Instead of studying cyclooctatetraene itself, the system I was examined. This compound contains a (modified) cyclooctatetraene system which appeared



I

to be sufficient for our purposes. This particular system was chosen because an optically active derivative of it was already known.[7] While this molecule has an apparent plane of symmetry in a planar projection, it is really a cyclooctatetraene derivative and should have the three dimensional structure (A), and hence is



(A)

potentially optically active. If the eight-membered ring becomes planar as in I, any optical activity would be lost. Now (A) contains a derivative of the D_{2d} system of cyclooctatetraene, while the planar form contains a derivative of the D_{4h} system, and therefore measurement of the rate of racemization of an optically active derivative of I as a function of temperature would enable one to calculate the energy of activation (ΔH^*) for the racemization reaction, and the latter is a measure of the desired energy, with some minor complications. The only complication which appears to be of real significance is that caused by the van der Waals' interaction of the two hydrogens shown in the planar form. From the geometry of planar I, most of which can be rather accurately assumed, the distance between these hydrogens (assuming normal bond angles and lengths for the C–H bonds) was determined (see Appendix). Their van der Waals repulsion was calculated by the method of Hill[8] and found to be enormous (over 200 kcal./mole). Obviously the aromatic C–H bond angles would deform to move the hydrogens further apart and hence lower this energy. The energy required for such a deformation was calculated, and the deformation was allowed to proceed until the total energy (van der Waals plus bond deformation) was minimized.[9] The minimum total interaction energy of the hydrogens occurred when they were moved apart by distorting each C–C–H angle 23° from its normal value, and still amounted to 46 kcal./mole. Since this energy is still very large, further smaller effects were taken into account, specifically the bending of the angles in the eight-membered ring and the compression of the C–H bonds. These quantities, together with the angular distortion and van der Waals energies mentioned previously, were all simultaneously adjusted so as to minimize the total energy. The total interaction energy obtained in this way was 20 kcal./mole, and this value is used for subsequent calculations.

(1) This research was supported by a grant from the National Science Foundation.

(2) O. Bastiansen, L. Hedberg, and K. Hedberg, *J. Chem. Phys.*, **27**, 1311 (1957).

(3) N. L. Allinger, *J. Org. Chem.*, **27**, 443 (1962).

(4) M. A. Miller, unpublished results.

(5) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 671 (1962).

(6) K. Mislow and H. D. Perlmutter, *ibid.*, **84**, 3591 (1962).

(7) F. Bell, *J. Chem. Soc.*, 1527 (1952).

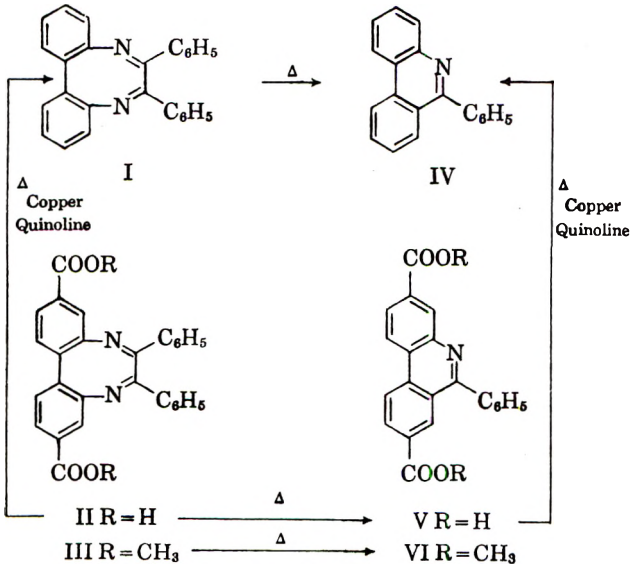
(8) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).

(9) F. H. Westheimer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, New York, N. Y., 1956, p. 523.

This total energy would be included in the experimental ΔH^*; so to find the energy change $D_{2d} \rightarrow D_{4h}$ it is necessary to subtract it from the observed ΔH^*. It was felt that this interaction was desirable from an experimental point of view in that it would raise the value of ΔH^* sufficiently to make the material reasonably stable with respect to racemization. Without this interaction the value of ΔH^* would be lower, and there was no guarantee that such a compound would even be resolvable.

An optically active derivative of I is II, the synthesis of which was reported some years ago.[7] For the present work, (−)-II was obtained with some small modifications of the published procedures. So as to avoid possible intermolecular reactions between the imine linkages and the carboxyl groups, which might present an alternative path for racemization, the ester III was first studied. When (−)-III was heated at 200° in mesitylene solvent for twenty-four hours, no racemization or reaction took place as judged by the lack of change in the optical rotation. At 242° the optical activity was lost at a conveniently measurable rate. The reaction was first order to 50% completion, and the first-order rate constant was found to be 1.56×10^{-6} sec.$^{-1}$.

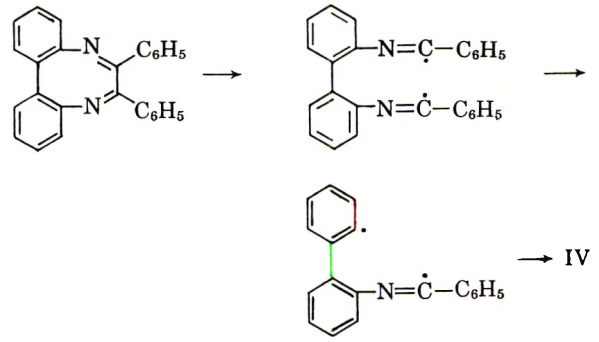
When (−)-III was heated in mesitylene at 278° for seventy-two hours on a preparative scale, an optically inactive compound, which was subsequently shown to be VI, was isolated in good yield. Under the same conditions racemic III also gave VI and in a similar manner II was converted to V. Under the same conditions it was then found that I was converted to IV. The latter is a known compound and the identification was by comparison with an authentic sample.



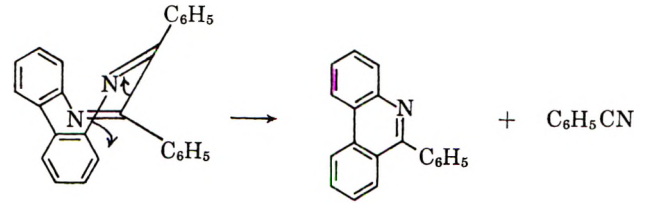
Compound VI was identified by analysis, molecular weight and infrared spectrum, and by hydrolysis to give V, which was also obtained by the thermal decomposition of II. Compound V was identified by analysis, infrared, and by decarboxylation to yield IV. These interconversions are summarized on the flow sheet.

The other product of the thermal fragmentation indicated by the stoichiometry was benzonitrile. This compound proved to be difficult to isolate under the reaction conditions, so a sample of III was placed in a small flask and heated until decomposition set in. A volatile material distilled which was identified as benzonitrile by the superimposability of its infrared spectrum with that of an authentic sample, and by hydrolysis to benzoic acid.

The mechanism of the thermal reaction is of interest, and since the reaction goes at high temperature in a hydrocarbon solvent, and since the rate of reaction is essentially the same in III when powerful electron-withdrawing groups are present, and in I, a reaction lacking in intermediates having a large charge separation is indicated. The reaction can be written as proceeding *via* a radical path.



Evidence that this mechanism is at least a reasonable possibility comes from the fact that biphenyl, benzaldehyde and polymeric material were isolated from the thermal decomposition of the dianil of benzil, as one would predict from a mechanism similar to that shown. This latter reaction occurred at a much slower rate than did the decomposition of I, however, and only traces of benzonitrile could be detected. The mechanism may also be written as a bond switching.



It has been shown that both the photolysis[10] and thermal decomposition[10] of cyclooctatetraene give benzene and acetylene, and the decomposition of I would seem to be a closely analogous reaction.

The thermal elimination reaction defeated the attempt to find the barrier to inversion, since it was shown that when the thermal decomposition of III was allowed to proceed to 50% completion, the starting material and product could be cleanly separated by chromatography. The recovered III was found to have the same optical rotation as the starting material. Since the racemic III is higher melting and less soluble than the pure enantiomer, very little racemic III was present. If the racemic compound were present in the recovered starting material to the extent of 1% or more it would easily have been detectable. The rate constant for the racemization must, therefore, be no larger than 1.56×10^{-8} sec.$^{-1}$ at 242°. From the

(10) (a) I. Tanaka and M. Okada, *J. Chem. Phys.*, **22**, 1780 (1954); (b) I. Tanaka, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **75**, 212 (1954).

Eyring equation then, ΔF^* is greater than 48 kcal./mole.

A summary of racemization data for hindered biphenyls[11] shows that these compounds have values of ΔS^* which range from +9 to −21 e.u. The very negative values are obtained when an *ortho* substituent is present which can rotate rather freely in the ground state but very slightly in the transition state. The restriction of the two phenyl substituents is less severe in this case and it would seem safe to say that the value for ΔS^* expected is no more negative than −21 e.u. At the observed temperature this corresponds to a value for $T\Delta S$ of −11 kcal./mole. The value for ΔF^* (greater than 48 kcal./mole), therefore, corresponds to a ΔH^* of greater than 37 kcal./mole.

The energy of the steric interaction between the interfering hydrogens in I, when minimized as previously indicated, amounted to 20 kcal./mole, and when this value was subtracted from the calculated value of ΔH^*, a difference was found which was greater than 17 kcal./mole, and this represents an estimate of a *minimum* value for the energy of the cyclooctatetraene $D_{2d} \rightarrow D_{4h}$ transition.[12] This minimum value is consistent with the other value (27 kcal./mole) reported[6] for the activation energy for this type of change. The theory indicates that this energy should be less than that for the $D_{2d} \rightarrow D_{8h}$ change (14 kcal./mole). The comparison of theory and experiment leaves something to be desired, however, and substantial improvements in the theoretical quantities are also possible. Our future efforts will be limited to improving the theory.

Experimental[13]

6,7-Diphenyldibenzo[*e,g*][1,4]diazocine (I).—This compound was prepared in 80% yield according to a published procedure,[14] yellow plates, m.p. 236–238° (lit.[14] m.p. 236–237°).

2,2′-Dinitro-4,4′-diphenyldicarboxylic Acid.—Twenty grams of 4,4′-diphenyldicarboxylic acid[15] was suspended in 200 ml. of concentrated sulfuric acid and 40 ml. of fuming (90%) nitric acid was added dropwise with stirring. The temperature was not allowed to rise above 60°. After stirring for 4 hr., the mixture was poured onto 2 kg. of crushed ice. The product was filtered and washed with water until the washings were neutral. After trituration with 50 ml. of hot methanol, 20 g. (73%) of a pale yellow powder was obtained, m.p. 341–343° (lit.[16] m.p. 335–337°).

The methyl ester was prepared by the Fischer esterification method and had m.p. 159–161° (lit.[17] m.p. 159–160°).

2,2′-Diamino-4,4′-diphenyldicarboxylic Acid.—The diamine was prepared according to the procedure of F. Bell.[7] The material was used without purification m.p. 306–309° (lit.[7] m.p. 307–309°).

Dibenzo[*e,g*][1,4]diazocine-3,10-dicarboxylic Acid (II).—A mixture of 10 g. of 2,2′-diamino-4,4′-diphenyldicarboxylic acid and 10 g. of benzil in 300 ml. of glacial acetic acid was heated under reflux for 24 hr. After cooling the solution, the resulting product was collected and washed with small portions of pentane. After recrystallization from ethanol, 12 g. (73%) of a pale yellow solid was obtained, m.p. 348–352° (lit.[7] m.p. 348°).[18]

The methyl and ethyl esters were prepared by the Fischer esterification method. The methyl ester (III) formed plates from methyl alcohol, m.p. 177–179°.

Anal. Calcd. for $C_{30}H_{22}N_2O_4$: C, 75.93; H, 4.67; N, 5.91. Found: C, 75.68; H, 4.70; N, 6.04.

The ethyl ester formed plates from ethyl alcohol, m.p. 177–179°.

Anal. Calcd. for $C_{32}H_{26}N_2O_4$: C, 76.47; H, 5.22; N, 5.58. Found: C, 76.54; H, 5.39; N, 5.66.

Resolution of Dibenzo[*e,g*][1,4]diazocine-3,10-dicarboxylic Acid (II).—Diacid II was resolved as the brucine salt as described by F. Bell.[7] From 10 g. of the brucine salt, 2.8 g. (56%) of optically active acid (II) was obtained. After several crystallizations from ethanol–water, yellow needles were obtained, m.p. 223–225°, $M^{19}D$ −1384° (diglyme, *c* 0.530).

Anal. Calcd. for $C_{28}H_{18}N_2O_4$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.03; H, 4.17; N, 6.26.

Fischer esterification of the resolved acid with methanol gave the optically active methyl ester (−III). Crystallization from methyl alcohol afforded plates m.p. 130–135°, $M^{20}D$ −1531° (*c* 0.420).

Anal. Calcd. for $C_{30}H_{22}N_2O_4$: C, 75.93; H, 4.67; N, 5.91. Found: C, 76.07; H, 4.86; N, 5.74.

Kinetics of Thermal Decomposition Methyl (−)-dibenzo[*e,g*.]-[1,4]diazocine-3,10-dicarboxylate, (−)-III.—Small pyrex glass tubes were filled three-quarters full (*ca.* 4 ml.) with a solution of (−)-III in mesitylene (4.2 mg./ml.) and sealed. The samples were placed in a constant temperature furnace at 242° ± 2°. Samples were removed at time intervals (zero time, 5 min. after placing samples in furnace) and the specific rotations were observed. First-order kinetics were observed for the first 50% of the reaction.

TABLE I

KINETIC DATA FOR THE REACTION III ⟶ VI AT 242° IN MESITYLENE SOLVENT

Time, hr.	$-\alpha_{obsd}$
0	6.625
25	5.750
49	5.047
73	4.400
167	2.576

Identification of Products from the Thermal Rearrangement of (−)-III.—A solution of 131 mg. of (−)-III in 20 ml. of mesitylene was sealed in a Pyrex tube and heated at 278° for 72 hr. The solvent was removed *in vacuo*. Chromatography of the residue on 5 g. of neutral alumina using benzene as eluent gave two products. The first product eluted, 60 mg. (69%), was optically inactive and had m.p. 240.5–242.5 and was identified as dimethyl 6-phenylphenanthridine-3,8-dicarboxylate (VI).

Anal. Calcd.: C, 74.38; H, 4.62; N, 3.77; O, 17.23; mol. wt., 371. Found: C, 74.33; H, 4.72; N, 3.80; O, 16.81; mol. wt., 362.

A similar experiment carried out with optically inactive III also gave VI, m.p. 240.5–242.5°, which did not depress when mixed with the product arising from (−)-III. The second product from the chromatography, 20 mg. (15%), proved to be starting material. After recrystallization from benzene it melted at 129–134° and it was not depressed upon admixture with authentic (−)-III. Its molecular rotation was unchanged, $M^{20}D$ −1528° (*c* 0.530). The benzene was evaporated from the filtrate and the rotation of the residue was measured, $M^{20}D$ −1518°. No racemization was detectable.

A further experiment was carried out to isolate the other organic fragment arising from the decomposition of III. In a small distillation apparatus was placed 1.5 g. of (±)-III. The compound when heated above its melting point gave as one product a clear liquid (0.5 g.) which had an infrared spectrum that was superimposable on that of phenylcyanide. Acid hydrolysis of this liquid gave an acid, m.p. 120–122°, after recrystallization from water, and which was undepressed when mixed with authentic benzoic acid.

Rearrangement of 6,7-diphenyldibenzo[*e,g*][1,4]diazocine (I) to 9-Phenylphenanthridine (IV).—A solution of 1.0 g. of I in 20 ml. of mesitylene was sealed in a Pyrex tube and heated at 278° for 7 days. The mesitylene was removed and the residue was crystallized from ethyl alcohol to give 0.5 g. (69%) of 9-phenyl-

(11) D. M. Hall and M. H. Harris, *J. Chem. Soc.*, 490 (1960).

(12) There are a good many uncertainties which enter into this calculation, some of which are difficult to estimate. Even if all of the errors the authors are able to imagine were to enter into the calculation in the same direction, it seems unlikely that the actual enthalpy for the inversion of 1,4-diazacyclooctatetraene could be less than 10 kcal./mole.

(13) All melting points are uncorrected.

(14) N. L. Allinger and G. A. Youngdale, *J. Org. Chem.*, **24**, 306 (1959).

(15) The authors are indebted to the Dow Chemical Company for furnishing a supply of this compound.

(16) Z. v. Jakubowski and St. v. Niemtowski, *Ber.*, **42**, 634 (1909).

(17) F. Ullmann and J. Bielecki, *ibid.*, **34**, 2174 (1901).

(18) This compound also was prepared by the method described by F. Bell, see ref. 7. Mixture melting point showed no depression.

phenanthridine, m.p. 103–104°. A mixture melting point with authentic material prepared as described[19] showed m.p. 103–105°. The infrared spectra of the two compounds were superimposable.

Decarboxylation of II to Give I.—A mixture of 1 g. of II and 1 g. of copper powder in 25 ml. of quinoline was heated under reflux for 3 hr. The mixture was filtered, 50 ml. of chloroform was added, and the organic phase was washed in turn with *N* hydrochloric acid and water. The organic phase was dried and the solvent was removed. The yellow solid was recrystallized from acetic acid to give 0.6 g. (75%) of I, m.p. 235–238°. A mixture melting point with I showed no depression.

Thermal Rearrangement of II.—When II was heated in mesitylene at 278° for 5 days an acid (V) which did not melt below 360° was obtained. The infrared spectrum of this acid was identical with that of the acid obtained by hydrolysis of VI.

Anal. Calcd. for $C_{21}H_{13}NO_4$: C, 73.46; H, 3.82; N, 4.08. Found: C, 73.09; H, 3.78; N, 3.98.

Decarboxylation of V to IV.—The acid V, 60 mg., and 100 mg. of copper powder in 2 ml. of quinoline were refluxed 3 hr. After filtration the quinoline was removed by heating *in vacuo* and the residue was recrystallized from ethanol to give 10 mg., of solid, m.p. 103–106°. The melting point was undepressed when mixed with authentic 9-phenylphenanthridine.[19]

Preparation and Thermal Rearrangement of Benzil Dianil.—A mixture of 4.2 g. of benzil, 4 g. of aniline, 0.5 g. of *p*-toluenesulfonic acid, and 60 ml. of toluene was heated under reflux for 2 days. The water which was formed from the reaction was removed with a water separator.

The cooled solution was filtered to remove the *p*-toluenesulfonic acid, and the solvent was removed *in vacuo*. The residues were recrystallized twice from an ether–pentane mixture, 5 g. (69%), m.p. 140–142° (lit.[20] m.p. 141–142°).

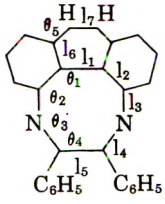
A solution of 100 mg. of benzil dianil in 20 ml. of mesitylene was heated in a sealed tube at 280° for 24 hr. Upon evaporation of the mesitylene only starting material (90 mg.) was isolated, m.p. 139–142°. A solution of 1 g. of benzil dianil and 20 ml. of benzene was heated in a sealed tube at 278° for 8 days. After the benzene was removed the residues were chromatographed on acid-washed alumina. The first product eluted with pentane was biphenyl (100 mg.), m.p. 68–76°, which was undepressed when mixed with an authentic sample. The second fraction contained about 50 mg. of benzaldehyde, characterized as its 2,4-dinitrophenylhydrazone, m.p. 236–237°. The third fraction (300 mg.), m.p. 139–142°, was eluted with a 50–50 pentane–ether mixture and was shown to be starting material by a mixture melting point determination. The largest fraction of material (500 mg.) was eluted with ether and appeared to be a noncrystalline polymer containing some starting material. The last product (about 5 mg.) was obtained by elution with methanol and was a deep purple water-soluble substance which was not characterized.

It was noted that, when the pure benzil dianil was heated above 400° in a small glass tube, traces of benzonitrile could be detected from the infrared spectrum of the distillate and by odor.

(19) A. Pictet and A. Hubert, *Ber.*, **29**, 1182 (1896).
(20) M. Siegfeld *Ber.* **25**, 2600 (1892).

Appendix

For the energy calculation, the initial geometry of the molecule in the planar form was assumed using normal bond lengths[21] and these minimally deformed angles.



l_1 1.520 Å.	θ_1 134°
l_2 1.390 Å.	θ_2 136°
l_3 1.475 Å.	θ_3 134°
l_4 1.350 Å.	θ_4 137°
l_5 1.450 Å	θ_5 120°
l_6 1.09 Å	
l_7 0.70 Å	

The stretching and bending constants used are those given by Westheimer[9] for the aromatic hydrogen and for ethylene. The ethylene bending constant was used in this calculation for all angles not involving the aromatic hydrogen. The energy of the system was minimized with respect to θ_1, θ_2, θ_3, θ_4, θ_5, l_6, and l_7, simultaneously and in the minimum energy form these quantities had the values: $\theta_1 = 129°$, $\theta_2 = 138°$, $\theta_3 = 141°$, $\theta_4 = 132°$, $\theta_5 = 111°$, $l_6 = 1.04$ Å., and $l_7 = 1.53$ Å.

(21) Tables of interatomic distances and configurations in molecules and ions, special publication no. 11, the Chemical Society, London (1958).

The Rearrangement of 2-Amino-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxides with Acetic Anhydride

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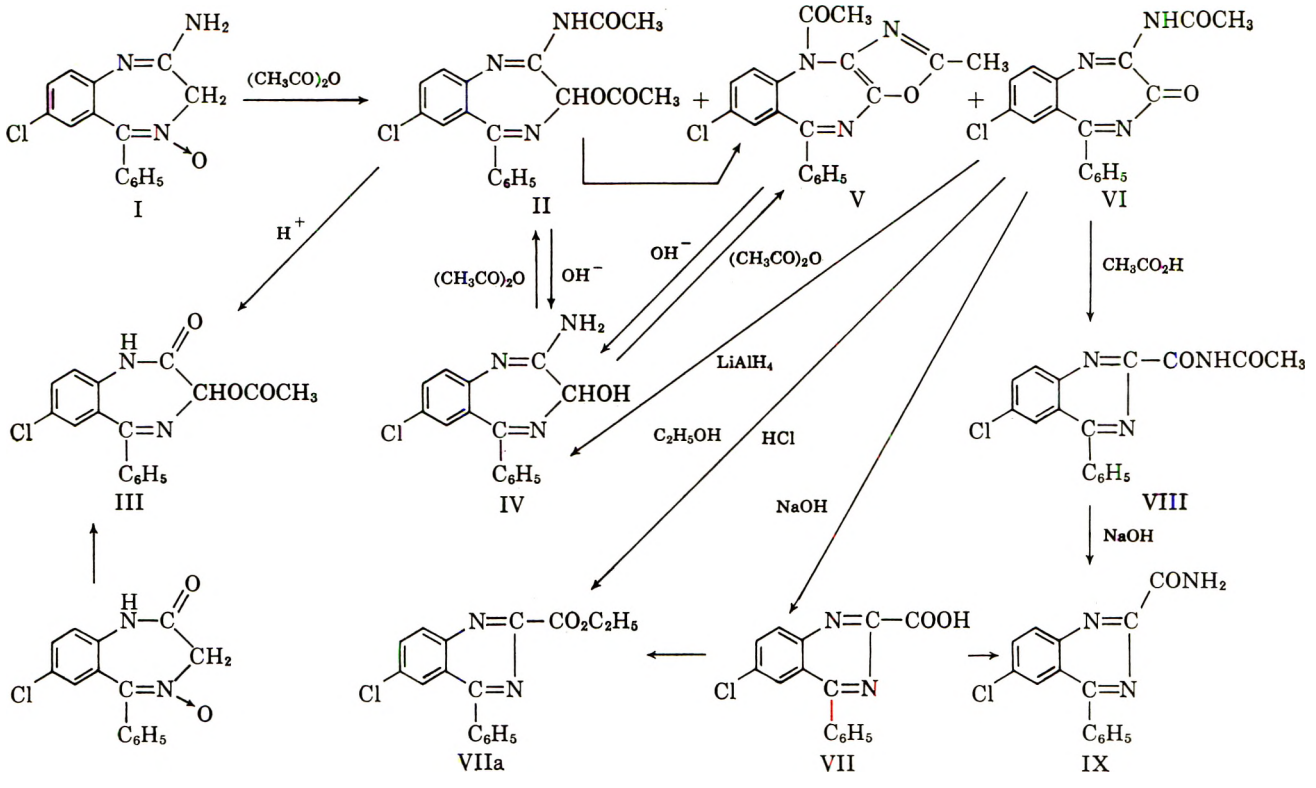
Received June 6, 1963

2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (I) gave 2-acetamido-3-acetoxy-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (II), 10-acetyl-7-chloro-2-methyl-5-phenyl-10*H*-oxazolo[4,5-*b*]-1,4-benzodiazepine (V), and 2-acetamido-7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-3-one (VI) upon treatment with acetic anhydride under varying conditions. The structures of the products were established by chemical and spectroscopic evidence. The 2-methylamino analog of I also was studied.

The rearrangement of 1,3-dihydro-5-aryl-2*H*-1,4-benzodiazepin-2-one 4-oxides[1] with acid anhydrides resulting in 3-acyloxy-1,3-dihydro-5-aryl-2*H*-1,4-benzodiazepin-2-ones recently has been reported from this laboratory.[2] In a similar manner, 2-amino-5-aryl-3*H*-1,4-benzodiazepine 4-oxides[3] have undergone rearrangements upon treatment with acid anhydrides. In some instances, however, several other products were isolated, the relative amounts often depending upon the conditions of the reactions.

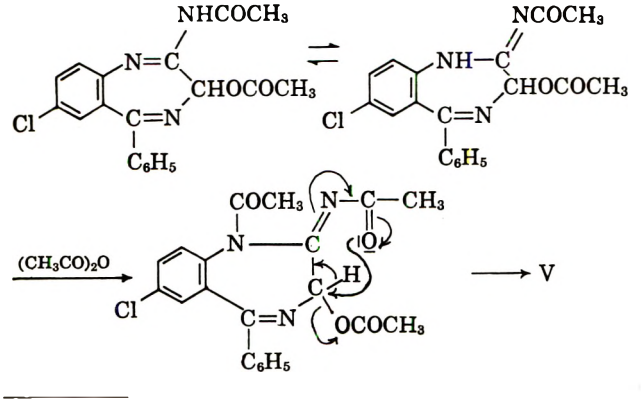
The reaction of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (I) with acetic anhydride gave three rearranged products (II, V, VI). 2-Acetamido-3-acetoxy-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (II), the expected compound, was hydrolyzed

(1)(a) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961); (b) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962).
(2) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962).
(3)(a) L. H. Sternbach, U. S. Patent 2,893,992 (1959); (b) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961); and (c) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).



with dilute acid to the known 3-acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[2] (III) and with alkali to 2-amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (IV).

The second product (V) of this reaction had an analysis corresponding to that of II minus the elements of water. Compound V also produced IV upon treatment with alkali. Compound IV, upon warming with acetic anhydride, was reacetylated to give II. The route (V → IV → II → III) proved the retention of the seven-membered ring in V and IV. Upon heating IV in acetic anhydride under reflux, V was formed. Compound V was stable to catalytic reduction and to acid. It absorbed in the infrared at 5.90 μ (C=O) and there were no bands corresponding to NH or OH. There were two methyl singlets in the n.m.r. spectrum (δ 2.25, 2.52).[4] Compound V was, therefore, assigned the structure 10 - acetyl - 7 - chloro - 2 - methyl - 5-phenyl - 10*H* - oxazolo[4,5 - *b*] - 1,4 - benzodiazepine. A plausible mechanism for its formation from II would be the acetylation of the tautomer of II followed by the elimination of acetic acid.



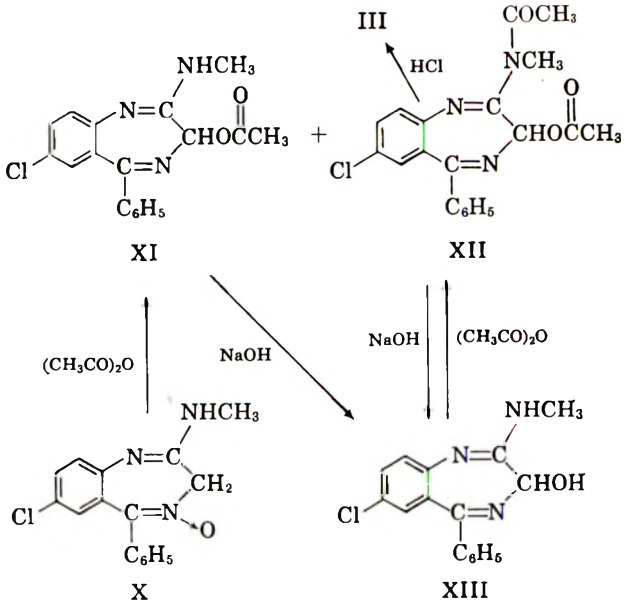
The third compound VI isolated from the original reaction had the empirical composition of the acetylated starting material (I) minus one mole of hydrogen. VI readily underwent a rearrangement and hydrolysis in cold dilute alkali to form 6-chloro-4-phenylquinazoline-2-carboxylic acid[2] (VII). In refluxing alcoholic hydrogen chloride, VI afforded the ethyl ester of VII. When heated with acetic acid, VI rearranged to the isomeric N-acetyl-6-chloro-4-phenylquinazoline-2-carboxamide (VIII). Compound VIII was further hydrolyzed to 6 - chloro - 4 - phenylquinazoline - 2-carboxamide (IX) with sodium hydroxide. IX was prepared unambiguously from VII for comparison. The conversion of VI to IV with lithium aluminum hydride confirmed the presence of the 1,4-benzodiazepine ring in VI. The infrared absorption spectrum of VI had two carbonyl bands (5.77, 5.88 μ), one of which was ascribed to the 2-acetamido group, and the second to a carbonyl group in the ring. From these transformations and infrared data as well as a consistent n.m.r. spectrum (methyl singlet, δ 2.14)[5] it was concluded that VI was 2-acetamido-7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-3-one.

7 - Chloro - 2 - methylamino - 5 - phenyl - 3*H*-1,4-benzodiazepine 4-oxide (X) was heated with acetic anhydride under varying conditions. When heated at 100° for a short time there was obtained a monoacylated, rearranged compound, 3-acetoxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XI). The infrared absorption at 5.72 μ suggested this structure instead of the possible alternative, 7-chloro-3-hydroxy - 2 - N - methylacetamido - 5 - phenyl - 3*H*-1,4-benzodiazepine. Heating either X or XI with acetic anhydride for an extended period of time produced the diacetylated compound, 3-acetoxy-2-N-methylacetamido - 7 - chloro - 5 - phenyl - 3*H* - 1,4-benzodiazepine (XII). Both XI and XII were con-

(4) The spectrum was determined in deuteriochloroform (tetramethylsilane standard) with a Varian A-60 spectrometer.

(5) Deuterio dimethyl sulfoxide.

verted into 7-chloro-3-hydroxy-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XIII) by treatment with alkali. Compound XII was hydrolyzed in dilute hydrochloric acid to the corresponding benzodiazepin-2-one (III).



Experimental[6]

Reactions between I and Acetic Anhydride. A.—A mixture of 15 g. of I and 300 ml. of acetic anhydride was heated on the steam bath for 1.25 hr. The reaction mixture turned red. After cooling 3.0 g. of white VI, m.p. 239–240° (turned dark green), was filtered off.

Anal. Calcd. for $C_{17}H_{12}ClN_3O_2$: C, 62.67; H, 3.71; N, 12.90; Cl, 10.88. Found: C, 62.37; H, 3.70; N, 13.27; Cl, 10.60.

The filtrate from the reaction mixture was concentrated *in vacuo*, and the residue was recrystallized twice from ethanol giving 11.2 g. of II, yellow, m.p. 181–182°.

Anal. Calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36; Cl, 9.59. Found: C, 61.94; H, 4.30; N, 11.45; Cl, 9.87.

B.—A mixture of 5.0 g. of I and 200 ml. of acetic anhydride was heated under reflux for 15 min. The reaction mixture became red. The solution was concentrated to one-third its volume *in vacuo*. After cooling there was obtained 1.75 g. of VI. The remainder of the acetic anhydride was removed *in vacuo*, and the residue was recrystallized twice from ethanol to afford V, yellow, m.p. 183–185°.

Anal. Calcd. for $C_{19}H_{14}ClN_3O_2$: C, 64.87; H, 4.01; N, 11.94; Cl, 10.08. Found: C, 64.66; H, 3.92; N, 11.86; Cl, 9.90.

C.—Compound II or IV was converted into V by heating in acetic anhydride under reflux for 0.5 hr., removing the solvent *in vacuo*, and recrystallizing the product from ethanol.

D.—Compound IV was converted to compound II by warming on a steam bath in acetic anhydride for a few minutes, cooling the solution, and filtering off the product.

2-Amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (IV). A.—To 3.0 g. of II suspended in 100 ml. of 50% alcohol was added with stirring 6 ml. of 4 *N* sodium hydroxide. When all of the solid had dissolved, the solution was acidified with acetic acid, diluted with water, and neutralized with sodium carbonate. The precipitated product was collected, washed with aqueous alcohol followed by acetonitrile, and recrystallized from isopropyl alcohol giving 1.5 g. of IV, m.p. 181–183°.

Anal. Calcd. for $C_{15}H_{12}ClN_3O$: C, 63.06; H, 4.24; N, 14.71; Cl, 12.41. Found: C, 63.45; H, 4.39; N, 15.00; Cl, 12.40.

(6) The melting points are uncorrected.

B.—To a suspension of 1.0 g. of lithium aluminum hydride in 75 ml. of ether was added with stirring 0.9 g. of VI. After 0.5 hr. the reaction mixture was cautiously treated with water to decompose the excess hydride, and the ether was filtered from the solids. Evaporation of the ether followed by several recrystallizations of the residue from cyclohexane and benzene gave IV, m.p. 181–183°.

7-Chloro-3-hydroxy-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XIII), m.p. 202–204°, was prepared according to procedure A for IV from either XI or XII.

Anal. Calcd. for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02; Cl, 11.83. Found: C, 64.26; H, 4.71; N, 14.26; Cl, 11.50.

3-Acetoxy-7-chloro-2-N-methylacetamido-5-phenyl-3*H*-1,4-benzodiazepine (XII).—Ten grams of X was heated in 250 ml. of acetic anhydride on the steam bath for 15 min., the solvent was removed *in vacuo*, and the residue was recrystallized from alcohol affording 3.1 g. of XII, m.p. 150–151°.

Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.72; N, 10.94; Cl, 9.23. Found: C, 62.21; H, 4.65; N, 10.67; Cl, 9.20.

3-Acetoxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XI).—One and nine-tenths grams of X was heated in 40 ml. of acetic anhydride on the steam bath for 5 min., the solvent was removed *in vacuo*, and the residue was recrystallized from ethanol yielding 0.7 g. of XI, m.p. 200–202°.

Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29; Cl, 10.37. Found: C, 63.17; H, 4.78; N, 12.22; Cl, 10.21.

3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2*H*-1-4-benzodiazepin-2-one (III).—A suspension of 2.0 g. of either II or XII in 50 ml. of alcohol containing 1 equivalent of hydrogen chloride was stirred until all of the solid dissolved. Upon dilution with an equal volume of water, a solid precipitated that was collected and recrystallized from ethanol to give white crystals of III, m.p. 241–243°.[2]

6-Chloro-4-phenylquinazoline-2-carboxylic acid (VII). A.—To a suspension of 2.0 g. of VI in 20 ml. of ethanol and 40 ml. of water was added with stirring 10 ml. of 4 *N* sodium hydroxide. The mixture was warmed to 40–50°. After 5 min. the mixture was filtered from undissolved matter, acidified with acetic acid, and the precipitated product was collected. Recrystallization from toluene gave 1.0 g. of VII, m.p. 215–216° (effervescent).

Anal. Calcd. for $C_{15}H_9ClN_2O_2$: C, 63.26; H, 3.19; N, 9.84; Cl, 12.46. Found: C, 63.28; H, 3.19; N, 9.84; Cl, 12.54.

B.—**6-Chloro-3,4-dihydro-4-phenylquinazoline-2-carboxylic acid**[2] (1 g.) was dissolved in 100 ml. of a dilute sodium hydroxide solution and a saturated solution of potassium permanganate was added until the color became permanent. The solution was filtered and acidified with acetic acid. Compound VII, m.p. 215–216° (effervescent), resulted.

2-Carbethoxy-6-chloro-4-phenylquinazoline (VIIa). A.—A mixture of 2.0 g. of VI in 25 ml. of ethanol and 25 ml. of 6 *N* hydrochloric acid was heated under reflux for 1 hr. The reaction mixture was concentrated to half volume and cooled, and the resultant precipitate was separated. The base was obtained by dissolving the precipitate in alcohol and adding an aqueous solution of triethylamine to give 1.0 g. of VIIa, m.p. 175–177°.

Anal. Calcd. for $C_{17}H_{12}ClN_2O_2$: C, 65.30; H, 4.19. Found: C, 65.39; H, 4.02.

B.—Compound VIIa also was prepared by esterification of VII, using thionyl chloride followed by ethanol.

6-Chloro-4-phenylquinazoline-2-carboxamide (IX). A.—A solution of 1.0 g. of VII in 10 ml. of thionyl chloride was heated under reflux for 1 hr. and then evaporated to dryness *in vacuo*. The residue was treated with alcoholic ammonia, and the product was collected and recrystallized from ethanol to give white crystals of IX, m.p. 264–266°.

Anal. Calcd. for $C_{15}H_{10}ClN_3O$: C, 63.49; H, 3.56; N, 14.85; Cl, 12.52. Found: C, 63.66; H, 3.65; N, 15.10; Cl, 12.60.

B.—A suspension of 1.0 g. of VIII in 30 ml. of 50% alcohol was treated with 1 equivalent of 1 *N* sodium hydroxide at room temperature. The resultant solution was acidified with acetic acid, and the precipitate was collected and recrystallized from alcohol to give IX, m.p. 264–266°.

Acknowledgment.—We wish to thank Dr. Gordon Ellis and his associates for the microanalyses and Mr. Bruce Hofmann for helpful discussions of the spectra.

Quinazolines and Benzodiazepines. XV.[1] 7-Nitro- and 7-Trifluoromethyl-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepines and Their Transformations

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Received May 15, 1963

Condensation of 2-chloro-5-nitro- or 2-chloro-5-trifluoromethylbenzophenones with ethylenediamine gave the 7-nitro- or 7-trifluoromethyl-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepines (Va,b), respectively. The trifluoromethyl derivative Vb was hydrolyzed to the corresponding carboxylic acid IX. The 1-methyl-7-nitro derivative VIa was converted into the 7-amino derivative which, *via* a Sandmeyer reaction, gave the 7-chloro, 7-bromo, and 7-cyano derivatives, respectively.

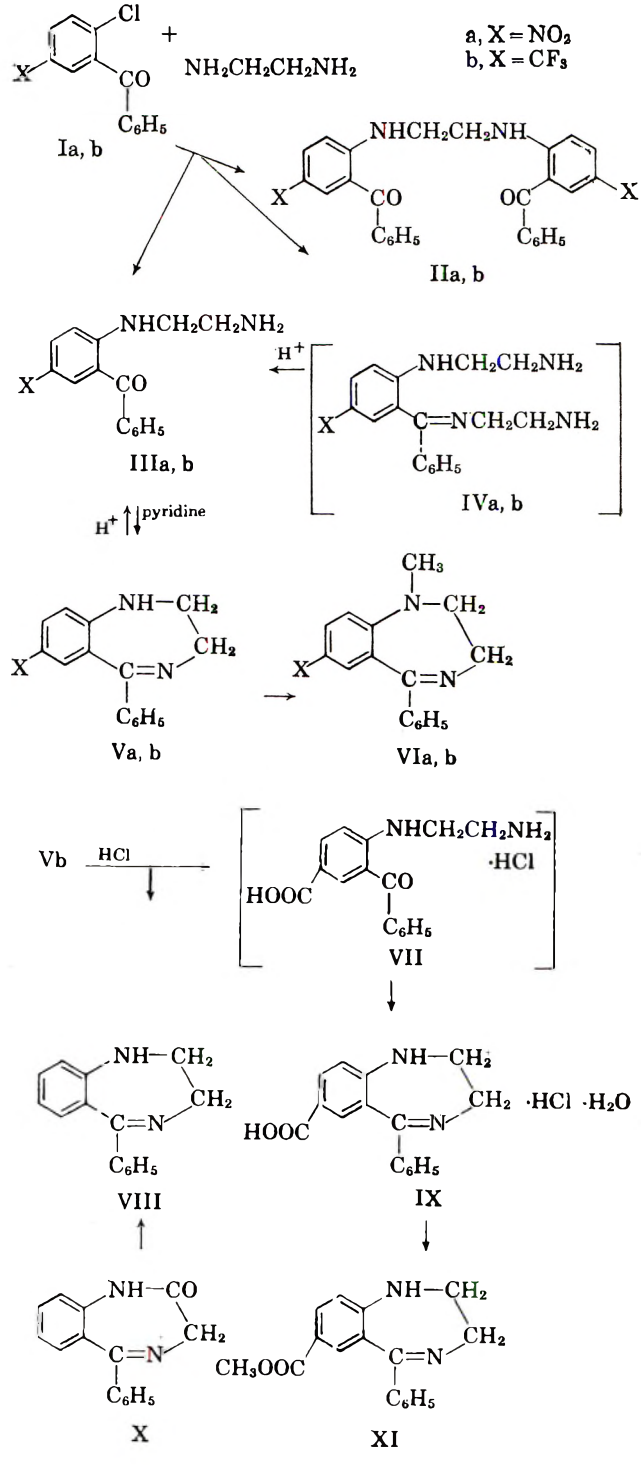
In continuation of our studies of 2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepines,[2] we sought synthetic methods leading to 7-nitro- and 7-trifluoromethyl derivatives. As starting materials, we chose the chlorobenzophenones Ia (X = NO_2)[3a] and Ib (X = F_3C),[3b] which on treatment with ethylenediamine, were expected to undergo nucleophilic displacement to form compounds of type III. In view of the marked tendency for formation of the benzodiazepine ring system,[2,4] we expected that these diamines would cyclize readily to form the desired benzodiazepines Va,b.

Heating compounds of type I with an excess of ethylenediamine in pyridine indeed resulted in replacement of the chlorine atom, and concomitant cyclization of the primary reaction products of type III, to the 2,3-dihydrobenzodiazepines Va[5] and Vb, respectively.[6,7]

The nitro compound Va was obtained in a 60% yield directly from the reaction mixture. Acid hydrolysis of the mother liquors followed by treatment with refluxing pyridine, yielded an additional amount of Va (30%). This seems to indicate that the reaction mixture contained, in addition to Va, an appreciable amount of the Schiff base IVa which was, however, not isolated in crystalline form.

In the case of Vb, the reaction mixture (Ib, ethylenediamine, and pyridine) was, after concentration, treated with cold acid to hydrolyze any Schiff base IVb which might be present. This yielded a small amount of crystalline IIIb and finally, after cyclization in pyridine, the desired Vb in 61% yield. Compound IIIa was best obtained by acid hydrolysis of Va. The "open" compounds III were relatively stable and did not show such a pronounced tendency to cyclize as the corresponding chloro derivatives discussed in our earlier paper.[2]

Vigorous treatment of Vb with hydrochloric acid resulted in hydrolysis of the trifluoromethyl to a carboxylic acid group, and also in partial decarboxylation. A compound which was most probably the hydrochloride VII crystallized from the reaction mixture; it could, however, not be purified due to its great tendency to cyclize. The crude hydrochloride



(1) Paper XIV: R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, in press.

(2) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

(3) (a) K. Fries, K. Eishold, and B. Vahlberg, *Ann.*, **454**, 287 (1927); (b) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 226 (1962).

(4) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

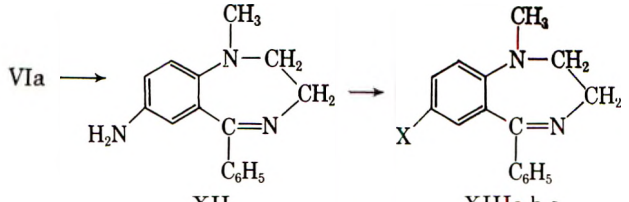
(5) While our work was in progress J. A. Hill, A. W. Johnson, and T. J. King [*J. Chem. Soc.*, 4430 (1961)] reported the isolation of Va as a by-product in the reaction of 6-(2-benzoyl-4-nitrophenoxy)podocarpan-6-ol with ethylenediamine, and proved its structure by synthesis from Ia and ethylenediamine.

(6) Small amounts of compounds of type II could also be isolated from the reaction mixture. Compound IIa was the major reaction product when a smaller excess of ethylenediamine was used.

(7) 2,5-Dichlorobenzophenone yielded, under similar conditions, the corresponding 7-chlorobenzodiazepine (V, X = Cl) in about 10% yield.

was, therefore, treated with boiling pyridine to cyclize it completely to the benzodiazepine. The product was isolated as the hydrochloride monohydrate IX,[8] and was characterized by conversion into the methyl ester XI. On treatment with alkali, the mother liquors from the acid hydrolysis yielded the decarboxylation product VIII. This compound was identified by direct comparison with a sample prepared from the benzodiazepinone X[4] by lithium aluminum hydride reduction.[2]

Compounds of type V were readily methylated,[2,9] *via* sodio derivatives, to yield the 1-methyl derivatives VIa and b. The nitro compounds Va and VIa were catalytically reduced to the corresponding 7-amino-2,3-dihydrobenzodiazepines.

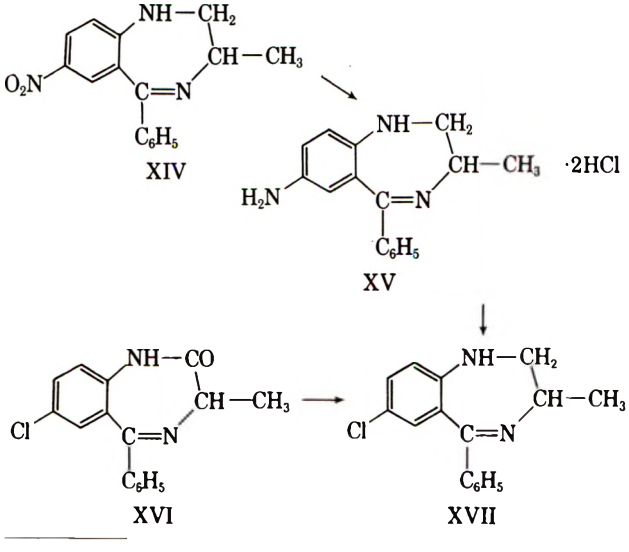


a, X = Cl
b, X = Br
c, X = CN

The 7-amino derivative XII was a useful intermediate for the preparation of compounds bearing a halogen or a cyano group in the 7-position. Benzodiazepines of this type were, as discussed previously,[2] not readily available by the lithium aluminum hydride reduction of the corresponding benzodiazepin-2-ones.

The Sandmeyer reactions leading to the 7-chloro or 7-bromo derivatives XIIIa,b proceeded in the normal way, but the 7-cyano derivative XIIIc could not be obtained by the conventional method; use of dimethylformamide as solvent, however, gave the desired product XIIIc, although in low yield (22%).

A homolog of Va was prepared by the reaction of Ia with propylenediamine. The structure of the product XIV was established by reduction to XV, followed by a Sandmeyer reaction, to give the chloro derivative XVII which, in turn, was prepared from the known benzodiazopinone XVI,[4] by lithium aluminum hydride reduction.[2]



The formation of compound XIV, in which the sterically less hindered amino group is attached to the aromatic nucleus, indicates that in the reaction sequence leading to 2,3-dihydrobenzodiazepines of type V or XIV, the first step is the nucleophilic exchange of the activated halogen atom, which is then followed by cyclization to the benzodiazepine.

Experimental

All melting points are corrected. The infrared absorption spectra of starting materials and products were compared whenever necessary, in order to establish structural changes. Identity of compounds was proved by mixture melting point determination and by comparison of infrared spectra. The spectra were determined in 1–5% chloroform solution, or in potassium bromide pellets.

2,3-Dihydro-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (Va).—A solution of 860 g. of 2-chloro-5-nitrobenzophenone (Ia) in a mixture of 2 l. of pyridine[10] and 800 ml. of ethylenediamine was refluxed for 5 hr., then the reaction mixture was concentrated *in vacuo* to dryness. The residue was crystallized by addition of methanol, to give almost pure reaction product in 60% yield (527 g.). The mother liquors were concentrated *in vacuo*, and the oily residue, consisting probably mostly of the Schiff base IVa was hydrolyzed by treatment for 2.5 hr. with an excess of boiling 1.5 *N* hydrochloric acid (2 l.). The mixture was then made alkaline and extracted with methylene chloride. The methylene chloride solution was dried, concentrated *in vacuo*, and the residue was cyclized by refluxing for 2.5 hr. in 1.1 l. of pyridine. Concentration *in vacuo* to a small volume, and addition of methanol yielded 266 g. of crystalline Va. This, together with 527 g. obtained from the original reaction mixture, resulted in a total yield of 90%.[11] After recrystallization from acetone, the product formed yellow needles melting at 211–212°.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.42; H, 4.90; Found: C, 67.36; H, 4.90.

2,2′′-Ethylenediiminobis(5-nitrobenzophenone) (IIa).—A solution of 26.1 g. (0.1 mole) of 2-chloro-5-nitrobenzophenone and 8 ml. (0.12 mole) of ethylenediamine in 75 ml. of pyridine was refluxed for 2 hr. and then concentrated *in vacuo*. The residue was dissolved in methylene chloride and the solution was washed with water and concentrated *in vacuo*. Methanol was added, and the crude crystalline reaction product (6.9 g.) was separated by filtration. It was dissolved in methylene chloride and washed with dilute hydrochloric acid and dilute sodium hydroxide. The organic layer was dried, concentrated *in vacuo*, and then diluted with ether. The precipitated crystalline reaction product (5.7 g.) was separated by filtration, and recrystallized from a mixture of methylene chloride and ether. It formed yellow needles melting at 217–218°; the melting point was depressed on admixture with Va.

Anal. Calcd. for $C_{28}H_{22}N_4O_6$: C, 65.87; H, 4.34; N, 10.98. Found: C, 65.88; H, 4.69; N, 11.30.

2-(2-Aminoethylamino)-5-nitrobenzophenone (IIIa) Hydrochloride.—A solution of 2 g. of Va in a mixture of 20 ml. of ethanol and 20 ml. of 3 *N* hydrochloric acid was refluxed for 18 hr. The solution was concentrated *in vacuo*, and the residue crystallized from methanol to yield 1.8 g. of the crude hydrochloride of IIIa. After recrystallization from a mixture of methanol and ether, yellow needles were obtained, melting at 225–227° dec.

Anal. Calcd. for $C_{15}H_{16}ClN_3O_3$: C, 55.99; H, 5.01. Found: C, 56.40; H, 4.96.

Base IIIa.—The hydrochloride was treated with aqueous alkali and the resulting free base was extracted with methylene chloride. Crystallization from ether gave yellow prisms melting at 118–119°. Treatment with boiling pyridine resulted in recyclization to Va.

(8) Heating *in vacuo* removed the mole of water of crystallization; exposure to moist air caused the reformation of the hydrate.

(9) The products VIa,b were obtained in much higher yields than in the case of the 7-chlorobenzodiazepine (VI, X = Cl), discussed in paper XI.[2] This is probably due to the effects of the strongly electron withdrawing groups (NO_2, CF_3) in the *para* position to the amino groups in Va and b, resulting in greater ease of formation of the corresponding sodio derivatives.

(10) See ref. 5. Hill and co-workers did not use pyridine in this reaction. We have found that the use of pyridine considerably increased the yield of Va.

(11) The mother liquors yielded small amounts (about 1%) of compound IIa.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30. Found: C, 63.40; H, 5.22.

2,3-Dihydro-1-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (VIa).—To a solution of 160 g. of Va in 1.6 l. of N,N-dimethylformamide was added 35.6 g. of sodium methoxide. The resulting mixture was stirred at room temperature for 1 hr., then 62.5 ml. of dimethyl sulfate was added, and the stirring continued for an additional 2 hr. The reaction mixture was then diluted with water and extracted with methylene chloride. The organic solution was concentrated *in vacuo*, and the residue crystallized from a mixture of methylene chloride and ether to give yellow prisms melting at 187–188°. The yield was 128.5 g. (76%).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38. Found: C, 68.32; H, 5.04.

2,3-Dihydro-5-phenyl-7-trifluoromethyl-1*H*-1,4-benzodiazepine (Vb) and 2-(2-Aminoethylamino)-5-trifluoromethylbenzophenone (IIIb).—A solution of 200 g. of Ib and 210 g. of ethylenediamine in 250 ml. of anhydrous pyridine was refluxed for 5 hr., and then concentrated *in vacuo*. The residue was dissolved in methylene chloride and the solution was washed with dilute sodium carbonate and concentrated. The residue was dissolved in 200 ml. of methanol and added, with stirring, to 4 l. of ice-cold aqueous 1 *N* hydrochloric acid. The mixture was stirred during an additional 5 hr. at room temperature, and the resulting yellow precipitate was filtered off and washed with ether. Evaporation of the ether extract gave 51 g., (25% recovery) of starting material Ib. The precipitate remaining on the funnel was combined with the acid aqueous layer. The mixture was made basic with 5 *N* sodium hydroxide and extracted with methylene chloride. Concentration of this extract gave a mixture of bases, from which, by repeated fractional crystallizations from hexane, a small amount of IIIb could be obtained. It formed yellow prisms, m.p. 71–73°.

Anal. Calcd. for $C_{16}H_{15}F_3N_2O$: C, 62.33; H, 4.91; N, 9.09. Found: C, 62.38; N, 5.06; N, 8.90.

The remainder of the crude mixture containing IIIb and Vb was evaporated, and the residue was dissolved in 600 ml. of pyridine, and refluxed for 3 hr. to achieve complete cyclization to Vb. The mixture was then concentrated, and the residue was dissolved in methylene chloride and purified by filtration through a bed of activated alumina. The product, obtained after concentration of the filtrate, crystallized from a mixture of benzene and hexane as yellow prisms melting at 116–118°, or from hexane as long yellow needles melting at 110–111°.[12] The yield was 61% based on unrecovered 2-chloro-5-trifluoromethylbenzophenone (Ib).

Anal. Calcd. for $C_{16}H_{13}F_3N_2$: C, 66.19; H, 4.51; N, 9.65. Found (prisms): C, 65.88; H, 4.63; N, 9.62. Found (needles): C, 66.10; H, 4.47; N, 9.71.

The hydrochloride was prepared in methanol–ether with the calculated amount of methanolic hydrochloric acid. It formed yellow prisms, m.p. 283–285°.

Anal. Calcd. for $C_{16}H_{14}ClF_3N_2$: C, 58.81; H, 4.32; N, 8.57. Found: C, 58.64; H, 4.72; N, 8.44.

2,2''-Ethylenediimimobis(5-trifluoromethylbenzophenone) (IIb).—The mother liquors from the crystallization of Vb yielded IIb, which was readily separated by means of its very low solubility in dilute hydrochloric acid. It formed yellow needles (from ethanol), m.p. 184–185°.

Anal. Calcd. for $C_{30}H_{22}F_6N_2O_2$: C, 64.75; H, 3.99; N, 5.04. Found: C, 64.69; H, 4.05; N, 5.13.

2,3-Dihydro-1-methyl-5-phenyl-7-trifluoromethyl-1*H*-1,4-benzodiazepine (VIb).—The product was prepared in the same way as VIa, using sodium hydride instead of sodium methoxide, to form the sodio derivative. After recrystallization from benzene–hexane and from hexane, pale yellow prisms (51% yield) were obtained melting at 151–152°.

Anal. Calcd. for $C_{17}H_{15}F_3N_2$: C, 67.09; H, 4.97; N, 9.21. Found: C, 67.16; H, 4.96; N, 9.46.

The hydrochloride was prepared in ether by addition of the calculated amount of methanolic hydrogen chloride. It formed orange prisms, melting at 261–262°.

Anal. Calcd. for $C_{17}H_{16}ClF_3N_2$: C, 59.91; H, 4.73; Cl, 10.41. Found: C, 59.88; H, 4.69; Cl, 10.38.

2,3-Dihydro-5-phenyl-*H*-1,4-benzodiazepine-7-carboxylic Acid Hydrochloride (IX) and 2,3-Dihydro-5-phenyl-1*H*-1,4-benzodiazepine (VIII) from Vb.—A solution of 60 g. of Vb in 600 ml. of 3 *N* hydrochloric acid was refluxed for 10 hr., and then cooled to 0°. The resulting yellow precipitate was filtered off, and washed successively with 3 *N* hydrochloric acid and ether, to give 48.3 g. of yellow crystals (probably VII), which melted at 185–187° with gas evolution, resolidified, and melted again at 315°. This crude hydrochloride was cyclized by heating in 500 ml. of refluxing pyridine for 3 hr. The solvent was evaporated, and the residue recrystallized from water to give IX as yellow prisms (41.3 g., 62% yield), m.p. 315–316° dec.[13]

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2 \cdot H_2O$: C, 59.89; H, 5.34; Cl, 11.06. Found: C, 59.88; H, 5.37; Cl, 11.28.

After drying at 118° *in vacuo*, the color changed to deep orange, and analysis of product agreed with that of anhydrous salt.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99. Found: C, 63.26; H, 5.42.

Short exposure to moist air reconverted the product to the yellow monohydrate.

The hydrochloric acid filtrate and washings obtained in the preparation were made basic with sodium hydroxide solution, and extracted with methylene chloride to give a 24% yield of VIII. It formed yellow plates (from dilute alcohol or petroleum ether), m.p. 145–147°.

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35. Found: C, 81.12; H, 6.39.

The product was identical with the compound prepared by lithium aluminum hydride reduction of the benzodiazepinone X.[4] This reduction was carried out in the same manner as described[2] for the 7-chloro derivative.

2,3-Dihydro-5-phenyl-1*H*-1,4-benzodiazepine-7-carboxylic Acid Methyl Ester (XI).—A solution of IX in methanol was treated in the customary way with an excess of diazomethane in ether. After crystallization from methylene chloride–petroleum ether (b.p. 40–60°) and dilute alcohol, pale yellow prisms were obtained, melting at 191–193°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75. Found: C, 72.75; H, 5.43.

The hydrochloride was prepared in methanol–ether, and formed yellow prisms, m.p. 251–252° dec.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.41; Cl, 11.20. Found: C, 64.74; H, 5.45; Cl, 11.25.

7-Amino-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XII) Dihydrochloride.—A suspension of 126.5 g. (0.45 mole) of VIa in 2.2 l. of methanol was hydrogenated at room temperature and atmospheric pressure in the presence of 130 g. (5 tablespoons) of Raney nickel. After the absorption of 1.35 moles of hydrogen (3 hr.) the catalyst was filtered off, and the filtrate acidified with an excess of methanolic hydrogen chloride. Part of the methanol was removed *in vacuo*, ether was added to the residual suspension, and the precipitated product (125 g.) was filtered. After recrystallization from a mixture of methanol and ether the product formed orange prisms melting at 267–268°.

Anal. Calcd. for $C_{16}H_{19}Cl_2N_3$: C, 59.26; H, 5.91. Found: C, 59.26; H, 6.22.

Base.—An ice-cold aqueous solution of the dihydrochloride of XII was made alkaline with potassium hydroxide. The base was extracted with methylene chloride and recrystallized from ether to form yellow prisms melting at 158–159°.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82. Found: C, 76.11; H, 7.03.

Acetyl Derivative.—A solution of 1.6 g. of the dihydrochloride of XII in a mixture of 20 ml. of pyridine and 10 ml. of acetic anhydride was left at room temperature for 60 hr. The precipitated crystalline hydrochloride of the reaction product (1 g.) was separated by filtration, and dissolved in ice–water. The base was liberated by treatment with dilute sodium hydroxide, and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo*, and the residue was crystallized from a mixture of methylene chloride and petroleum ether, to form yellow prisms melting at 176–177°.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53. Found: C, 73.51; H, 6.57.

7-Amino-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine dihydrochloride was prepared from Va, and crystallized in the same manner as the hydrochloride of XII. It formed yellow needles unmelted at 250°.

(12) The higher melting prisms were the more stable form. Both crystalline modifications had identical infrared spectra in chloroform solution, and yielded the same hydrochloride.

(13) The infrared spectrum, run as a 3% solution in piperidine–chloroform, showed a sharp band at 3630 cm.$^{-1}$ which is probably due to the O–H stretching frequency of the water of crystallization. Comparison with the spectrum of the anhydrous hydrochloride was impossible, owing to the extremely hygroscopic nature of the latter compound.

Anal. Calcd. for $C_{15}H_{17}Cl_2N_3$: C, 58.07; H, 5.52. Found: C, 58.23; N, 5.81.

The corresponding base was not obtained in crystalline form.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine Hydrochloride (XIIIa.)—To a cooled (−10°), stirred solution of 12.4 g. (0.038 mole) of 7-amino-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine dihydrochloride in 40 ml. of 1 *N* hydrochloric acid, was added 40 ml. of 1 *N* aqueous sodium nitrite. The temperature was allowed to rise to 10°. The resulting diazonium chloride solution was added over a period of 10 min. to a stirred solution of 7 g. of cuprous chloride in 40 ml. of concentrated hydrochloric acid, which had been diluted with 20 ml. of water. The mixture was diluted with 100 ml. of water and heated for 3 hr. to 35–40°. It was then cooled to 10°, and the precipitated orange-red copper complex (m.p. 168–169°) was separated by filtration and decomposed by treatment with 35 ml. of 10% aqueous ammonia at 40°. Compound XIIIa was extracted with methylene chloride, the extract was washed with water, dried, and concentrated *in vacuo*, and the residue was dissolved in acetone. The solution was filtered and treated with an excess of a solution of hydrogen chloride in isopropyl alcohol to give the hydrochloride of XIIIa (58%). The product was in every respect identical with the compound formerly described.[2]

7-Bromo-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XIIIb).—This compound was made in the same manner as XIIIa. It formed orange-yellow prisms (from hexane), m.p. 104–105°.

Anal. Calcd. for $C_{16}H_{15}BrN_2$: C, 60.96; H, 4.80; N, 8.89. Found: C, 60.94; H, 5.11; N, 8.78.

The **hydrochloride** was prepared in methanol–ether, and formed orange-yellow prisms, m.p. 257–258° dec.

Anal. Calcd. for $C_{16}H_{16}BrClN_2$: C, 54.64; H, 4.58; N, 7.97. Found: C, 54.60; H, 4.66; N, 7.75.

7-Cyano-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XIIIc).—To a cooled (0°–5°), stirred solution of 12.4 g. (0.038 mole) of the dihydrochloride of XII in 40 ml. of 1 *N* hydrochloric acid was added 40 ml. of 1 *N* sodium nitrite. The resulting diazonium chloride solution was added to a hot (80–90°), stirred suspension of 8 g. of cuprous cyanide in 300 ml. of N,N-dimethylformamide.[14] The reaction mixture was cooled to 60°, diluted with 200 ml. of 25% aqueous ammonia, and extracted with benzene. The organic layer was dried and concentrated *in vacuo*, and the residue was extracted with boiling ether. The ether extract was concentrated to 80 ml. and purified by chromatography on a column of 140 g. of Woelm grade I alumina. Elution with 750 ml. of ether yielded 5 g. of material which was crystallized from a mixture of ether and petroleum ether to give 2.2 g. of XIIIc (22%). Recrystallization from ether gave slightly yellow plates, melting at 149–150°.

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.19; H, 5.79; N, 16.36.

(14) Experiments using the conventional Sandmeyer method (addition of the diazonium chloride solution to a solution of cuprous cyanide in aqueous sodium cyanide) yielded only a red, crystalline, unidentified compound.

2,3-Dihydro-3-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (XIV) was prepared from Ia in the same manner as compound Va, using propylenediamine instead of ethylenediamine. The yield was 80%.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38. Found: C, 68.24; H, 5.71.

This compound was hydrolyzed to the aminoethylamino ketone as described for Va.

The base, **2-(2-aminopropylamino)-5-nitrobenzophenone**, after crystallization from a mixture of methylene chloride and ether, formed yellow needles melting at 98–99°.

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72. Found: C, 64.55; H, 5.79.

The **hydrochloride** formed yellow prisms from methanol–ether, melting at 204–205°.

Anal. Calcd. for $C_{16}H_{18}ClN_3O_3$: C, 57.40; H, 5.40. Found: C, 57.29; H, 5.78.

7-Chloro-2,3-dihydro-3-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XVII). A. From 2,3-Dihydro-3-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (XIV) *via* 7-Amino-2,3-dihydro-3-methyl-5-phenyl-1*H*-1,4-benzodiazepine Dihydrochloride (XV).—Compound XIV was hydrogenated in the same manner as VIa to yield XV as yellow prisms (from ethanol–ether), melting at 277–280° dec.

Anal. Calcd. for $C_{16}H_{19}Cl_2N_3$: C, 59.26; H, 5.91. Found: C, 59.39; H, 5.97.

This compound was converted *via* a Sandmeyer reaction into the 7-chloro compound. To a cooled stirred solution of 6.4 g. of XV in 30 ml. of 6 *N* hydrochloric acid was added 20 ml. of 1 *N* sodium nitrite solution, while the temperature was kept below 5°. The solution was then added at room temperature to a stirred solution of 4 g. of cuprous chloride in 40 ml. of concentrated hydrochloric acid. The mixture was heated to 40° for 30 min., then to 85–90° for 20 min., cooled, treated with an excess of aqueous ammonia, and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo;* the residue was dissolved in 40 ml. of ether, and adsorbed on to 60 g. of Woelm alumina grade I. Elution with 250 ml. of ether gave 0.7 g. of material, which on crystallization from a mixture of ether and petroleum ether, yielded 0.3 g. of XVII. Further recrystallization gave pale yellow prisms, melting at 127–128°.

Anal. Calcd. for $C_{16}H_{15}ClN_2$: C, 70.97; H, 5.58. Found: C, 71.25; H, 5.51.

B. From 7-Chloro-1,3-dihydro-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (XVI).—Reduction of XVI[4] with lithium aluminum hydride as described for the 3-demethyl derivative,[2] gave a 70% yield of XVII, which was in every respect identical with the product obtained by method A.

Acknowledgment.—We are indebted to Dr. A. Motchane and Mr. S. Traiman for determination of the infrared spectra, and to Dr. Al Steyermark and his staff for the microanalyses. Mr. L. A. Dolan was helpful in the preparation of larger quantities of starting materials and intermediates.

Reactions of Metal Chelates. VI.[1,2] The Synthesis and Reactions of a Stable Chelate Diazonium Salt[3]

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Received May 10, 1963

A monoamine derivative L of chromium(III) acetylacetonate has been prepared by reduction of a mononitro derivative I. The chelate amine L was transformed into a stable chelate diazonium fluoroborate N. The diazonium salt was converted into a monofluoro chelate O. Nitration of mono- and dichloro chromium acetylacetonates afforded a series of chloro-, nitro-substituted chelates. Apparent displacement of chloro by nitro was observed during nitration of the dichloro chelate C.

Recent reports from this and other laboratories have described the quasiaromatic properties of metal complexes of acetylacetone.[1,5-13] These chelates undergo a wide variety of electrophilic substitution reactions under relatively mild conditions. Stereochemical studies indicate that these substitutions are not attended by opening of the chelate rings.[14,15] The proton magnetic resonance spectra of unsymmetrically substituted metal acetylacetonates[7] and of certain acetylacetone–ethylene diamine complexes[16] suggest the presence of aromatic ring current in these substances. Classically, one of the most significant chemical indications of aromatic character is the stabilization of a diazonium ion. This paper reports a successful preparation of a chelate diazonium salt and its chemical properties.

Our first attempts to synthesize amino-substituted metal acetylacetonates A, the logical precursors of chelate diazonium salts, were unsuccessful. Attempts at direct amination of the chelate ring failed. Nitro-substituted chelates B, available from a previous study,[5] seemed to offer a route to the desired amino chelates A.

A B

M = Cr, Co, Rh

However, all attempts to reduce nitro groups on the nitrocobalt(III) or rhodium(III) chelates led to reduction of the metals and subsequent decomposition of the complexes.[5] On the other hand, chemical or catalytic reductions of the nitro chromium chelate B either afforded unchanged starting material or resulted in intractable mixtures of unidentified products. We had previously experienced difficulty in carrying out transformations on other trifunctional chelates.[11] It soon became apparent that the reduction of a trinitro chelate would be a formidable task. Our goal then became the synthesis of a chromium(III) chelate containing a single nitro group.

At this time we had prepared dichloro chromium acetylacetonate (C) for another study.[7] It appeared that this dichloro chelate C easily could be transformed into the dichloromononitro chelate D which could then be reduced to a monoamino chelate—avoiding the difficulties of reducing a trinitro derivative. Chloro groups on these chelate rings were known to be resistant to catalytic reduction.

Preliminary experiments revealed that the trichloro chelate E was inert under the conditions of nitration. This, of course, was to be expected. However, nitration of the dichloro compound C with copper nitrate trihydrate in acetic anhydride afforded a mixture of three chelates. These were separated by chromatography and eventually characterized as the expected dichloro mononitro chelate D and, unexpectedly, the dinitro monochloro chelate F, and the trichloro chelate E (Chart I). These surprising results may be interpreted in two ways: (a) disproportionation of the acetylacetonate rings during the reaction or (b) electrophilic cleavage of chlorine by the nitrating agent, followed by subsequent chlorination of the starting material in the presence of the released positive halogen.

The first of these alternative explanations is less likely in view of the retention of optical activity during electrophilic substitution of these chelate rings.[14,15] However, it is evident that this nitration should be carried out on the resolved dichloro chromium acetylacetonate C in order to reaffirm the validity of this assumption. The concept of electrophilic cleavage of halogen from these chelate rings by the nitrating reagent seems more plausible in view of our earlier experience with electrophilic substitutions[17] of groups other than hydrogen from metal acetylacetonate rings. Indeed, in all of the cases that we have examined,[11,17] disubstituted trisacetylacetonates undergo these cleavage reactions at a much greater rate than the mono- or the trisubstituted compounds. In order to investigate

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(4) On leave of absence from Sankyo Company, Ltd., Tokyo, Japan.

(5) J. P. Collman, R. L. Marshall, W. L. Young, III, and S. D. Goldby, *Inorg. Chem.*, **1**, 704 (1962).

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(17) J. P. Collman, W. L. Young, III, R. H. Barker, and M. Yamada, Abstracts, 142nd National Meeting of the American Chemical Society, Organic Division, Atlantic City, N. J., September, 1962, p. 40O.

CHART I

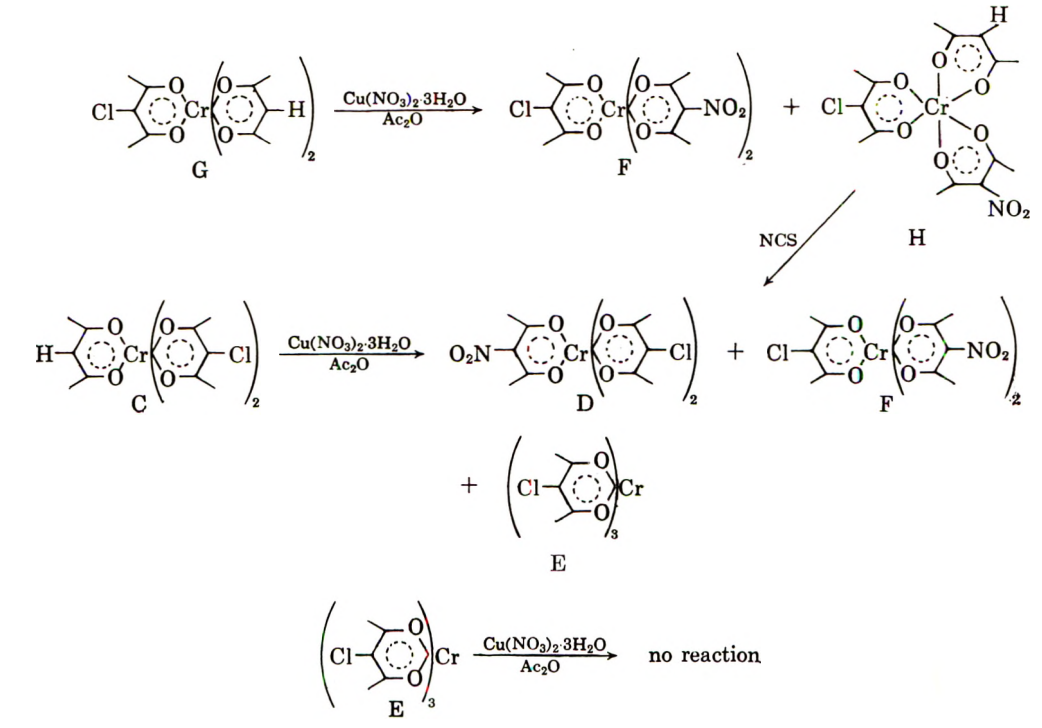
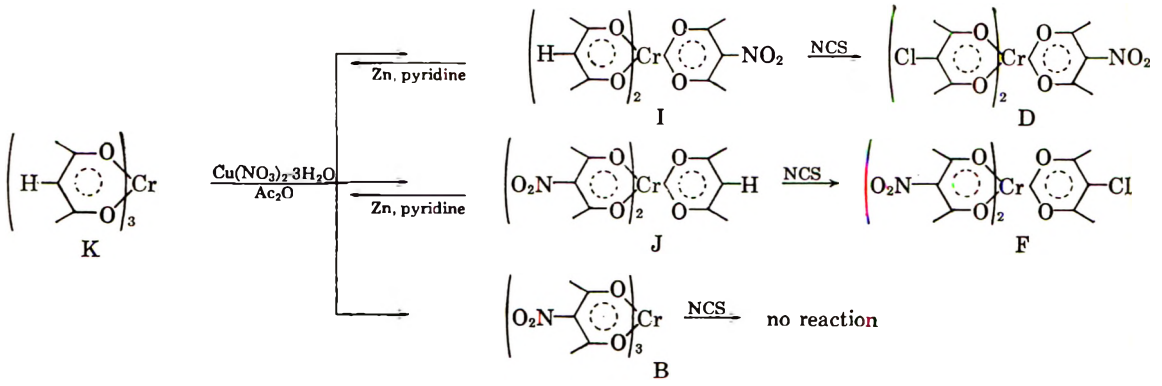


CHART II



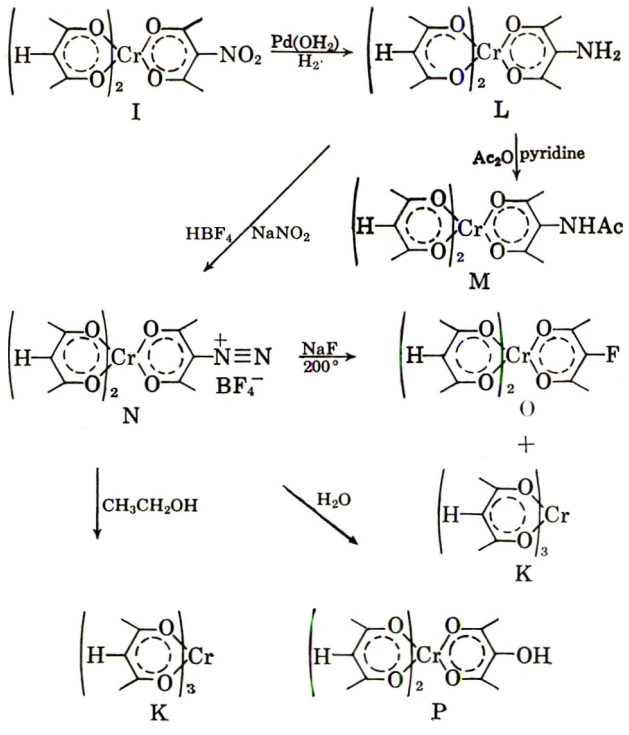
more fully this peculiar reaction, we carried out a nitration of the monochloro chromium chelate G under the same conditions. Two products, F and H, were separated and characterized from this reaction mixture, but neither of these compounds was derived from cleavage of chlorine atoms from the chelate ring. Treatment of the monchloro mononitro chromium chelate H with N-chlorosuccinimide (NCS) afforded the dichloro mononitro chelate identical with the product D isolated from nitrating the dichloro chromium chelate C (see Chart I), providing an extra check on the structures F, H, and D.

The structures of these mixed-ring chloro nitro chelates were further substantiated as the result of a series of experiments that were being conducted concurrently[5] with those described. Nitration of chromium acetylacetonate using limited amounts of the nitrating reagent afforded mixtures of the mononitro, dinitro, and trinitro chromium acetylacetonate. These partially nitrated chelates I, J, and B were easily separated by chromatography on Florisil. Chlorination of the dinitro chelate J afforded the dinitro monochloro chelate F in good yield. In the same way the mononitro dichloro chelate D was prepared from the mononitro chelate I. These reactions provided further support for the structures that were assigned to I, J, F, and D (see Chart II).

The ready accessibility of the mononitro chromium chelate I prompted us to use this substance as a precursor for the chelate amine and diazonium salt. Consequently, reductions of the chloronitro chelates were not attempted. Chemical reduction of the mononitro compound I with a wide variety of the usual reducing agents either failed to effect any transformation or gave rise to anomalous reactions. For example, treatment of the mononitro chelate I with zinc dust in pyridine at 60° afforded the unsubstituted acetylacetonate K. This surprising result involves reduction of the nitro group from an unsaturated carbon atom and replacement by hydrogen. A similar reaction was observed when the dinitro compound J was reduced with zinc dust in pyridine under the same conditions. However, under these conditions the trinitro chelate B afforded a very complex mixture which contained at least six components (as determined by thin layer chromatography experiments). This mixture did not contain the unsubstituted acetylacetonate K.

Catalytic hydrogenation of the nitro chelate I was more successful. Treatment of this nitro compound with hydrogen over palladium hydroxide afforded the

CHART III



monoamine L in good yield. The amino chelate L behaved as a normal aromatic amine forming stable salts with mineral acids, changing color upon salt formation, and reacting with acetic anhydride to afford an acetate derivative M. However, attempted hydrolysis of the N-acetyl group failed to yield the amine—probably because of the steric hindrance afforded by the flanking methyl groups on the chelate ring.

Treatment of an aqueous solution, the fluoroborate salt of the monamine L with a cold solution of sodium nitrite yielded a purple precipitate. This precipitate, which proved to be the pure chelate diazonium fluoroborate N was isolated by rapidly collecting the powder on a filter and washing repeatedly with anhydrous ether. The diazonium salt was decomposed by exposure to water or other nucleophilic solvents. However, aqueous solutions of the diazonium salt gave positive tests with β-naphthol. The structure of the chelate diazonium fluoroborate N is based on elemental analyses, a sharp infrared peak at 2200 cm.$^{-1}$ (diazonium ion), and reduction of the diazonium group to the unsubstituted chelate K by treatment with ethanol.

Attempted Sandmeyer reactions on the chelate diazonium salt were frustrated by the facile solvolysis of this ion. Hydrolysis of the chelate diazonium salt afforded a hydroxy-substituted chelate, which was isolated as a twelve hydrate. The water-soluble, hydroxy chelate behaved as a mild acid and was unstable in boiling solvents. All attempts to obtain this substance in its anhydrous form failed—although some of the waters of dehydration could be removed.

Initial attempts to effect a Schiemann reaction with the chelate diazonium salt by the usual procedures afforded tars and the unsubstituted acetylacetonate. However, sublimation of an intimate mixture of the powdered dry diazonium fluoroborate and anhydrous sodium fluoride at 200° under vacuum yielded a sublimate from which chromium acetylacetonate K and the monofluoro chromium chelate O could be separated by chromatography. The hitherto unknown fluoro-substituted chelate O was isolated in only 6% yield. The structure of this substance was assigned on the basis of elemental analyses and an infrared spectrum which exhibited carbon–fluorine stretching bands at 1490, 1320, and 1152 cm.$^{-1}$.

The chelate diazonium salt N exhibited good thermal stability, decomposing reproduceably from 165–167°. The salt was stored in a dry atmosphere for several months without any sign of decomposition.

Experiments in progress are designed to examine the mechanism of electrophilic cleavage of groups from unsymmetrically substituted chelate rings, and to carry out further transformations on the chelate diazonium salt.

Experimental

Nitration of Bis(2,4-pentanediono)(3-chloro-2,4-pentanediono)-chromium(III) (G).—A mixture of 1.0 g. (4.2 mmoles) of finely ground copper(II) nitrate trihydrate and 30 ml. of acetic anhydride was stirred for 45 min. at 0°. To this slurry was added 2.5 g. (6.5 mmoles) of monochlorochelate G, m.p. 197–198°. This reaction mixture was stirred for 4 hr. at 0°, allowed to come to room temperature, and then stirred for 1 more hr. This resulting mixture was poured into a mixture of 250 g. of ice, 150 ml. of water, and 20 g. of sodium acetate and stirred for 1 hr. The water layer was extracted three times with chloroform, and the combined chloroform extracts were washed with 5% aqueous sodium acetate solution and then water. After drying over sodium sulfate, the solvent was removed under vacuum. The resulting residue was purified by Florisil chromatography.

From the first band there was obtained 0.34 g. (10.7%) of bis(3 - nitro - 2,4 - pentanediono)(3 - chloro - 2,4 - pentanediono)-chromium(III) (F), m.p. 227°. The infrared spectrum was identical with that of a sample described later.

From the second band there was obtained 0.66 g. (23.6%) of (3 - nitro - 2,4 - pentanediono)(3 - chloro - 2,4 - pentanediono)-(2,4-pentanediono)chromium(III) (H), m.p. 205–208°. After recrystallization from ethanol, brown needles were obtained, m.p. 207–209°; infrared spectrum (KBr), 822 cm.$^{-1}$(NO_2) and 1200, 1270 cm.$^{-1}$ (unsubstituted C–H).

Anal. Calcd. for $C_{15}H_{19}O_8NClCr$: C, 42.01; H, 4.47; N, 3.27; Cl, 8.27. Found: C, 41.81; H, 4.38; N, 3.07; Cl, 8.12.

From the third band 0.52 g. (20.8%) of the starting material G was recovered.

Nitration of Bis(3-chloro-2,4-pentanediono)(2,4-pentanediono)chromium(III) (C).—A mixture of 0.95 g. (4.0 mmoles) of finely ground copper(II) nitrate trihydrate and 20 ml. of acetic anhydride was stirred for 45 min. at 0°. To this slurry was added 1.5 g. (3.6 mmoles) of dichloro chelate C, m.p. 199–200°. This reaction mixture was stirred for 4 hr. at 0°, allowed to come to room temperature, and then stirred for 1 more hr. The resulting slurry was poured into a mixture of 150 g. of ice, 70 ml. of water, and 12 g. of sodium acetate, and then stirred for 1 hr. to decompose the acetic anhydride. The water layer was extracted three times with chloroform and the combined chloroform extracts were washed with 5% aqueous sodium acetate solution and then with water. After drying over sodium sulfate, the solvent was evaporated under diminished pressure. The residue was purified by Florisil chromatography.

From the first band there was obtained 0.17 g. (19.5%) of tris(3 - chloro - 2,4 - pentanediono)chromium(III) (E), yellow needles, m.p. 207–208°. The infrared spectrum was identical with that of an authentic sample.[8]

The second fraction eluted with benzene afforded 0.20 g. (12.0%) of bis(3-chloro-2,4-pentanediono)(3-nitro-2,4-pentanediono)chromium(III) (D). After recrystallization from ethanol, yellow–brown hexagonal plates were obtained, m.p. 204–204.5°; infrared spectrum (KBr), 823, 1520 cm.$^{-1}$ (-NO_2).

Anal. Calcd. for $C_{15}H_{18}O_8NCl_2Cr$: C, 38.89; H, 3.93. Found: C, 39.03; H, 4.09.

From the third band 0.18 g. (10.6%) of bis(3-nitro-2,4-pentanediono)(3 - chloro - 2,4 - pentanediono)chromium(III) (F), m.p. 227° was obtained. The infrared spectrum was identical with that of an authentic sample.

From the fourth band 0.19 g. (12.7%) of the starting material C was recovered.

Nitration of Tris(3-chloro-2,4-pentanediono)chromium(III) (E).—A mixture of 0.88 g. (3.63 mmoles) of finely ground copper(II) nitrate trihydrate and 20 ml. of acetic anhydride was stirred for 45 min. at 0°. To this slurry was added 1.5 g. (3.3 mmoles) of chloro chelate E,[8] m.p. 207–208°. This reaction mixture was stirred for 4 hr. at 0°, allowed to come to room temperature, and then stirred for 1 more hr. The resulting mixture was poured into a slurry of 150 g. of ice, 70 ml. of water, and 12 g. of sodium acetate, and stirred for 1 hr. to decompose the acetic anhydride. The water layer was extracted three times with chloroform and the combined chloroform extracts were washed with 5% aqueous sodium acetate solution and then with water. After drying over sodium sulfate, the solvent was removed under vacuum. The resulting residue was purified by Florisil chromatography, and 1.02 g. of the starting material E, m.p. 209°, was recovered. The infrared spectrum was identical with that of an authentic sample.[8] The yield of recovered starting material was 68.0%.

Chlorination of (3-Nitro-2,4-pentanediono)(3-chloro-2,4-pentanediono)(2,4-pentanediono)chromium(III) (H).—To a boiling solution of the 100 mg. of nitrochloro chelate H in 5 ml. of chloroform was added 100 mg. of N-chlorosuccinimide in 2 ml. of chloroform with vigorous stirring. The reaction mixture was heated at reflux for 1 hr., cooled to room temperature, and washed with 5% aqueous sodium sulfite solution and then with water. After drying the organic layer over sodium sulfate, the solvent was removed under vacuum. The residue was recrystallized from ethanol, and 63 mg. (58.3%) of bis(3-chloro-2,4-pentanediono)(3-nitro-2,4-pentanediono)chromium(III) (D), m.p. 204.5°, was obtained.

Nitration of Tris(2,4-pentanediono)chromium(III) (K).—A mixture of 3.1 g. (12.9 mmoles) of finely ground copper(II) nitrate trihydrate and 200 ml. of acetic anhydride was stirred for 30 min. at 0°. To this slurry was added 7.5 g. (21.5 mmoles) of chelate K. The reaction mixture was stirred for 3 hr. at 0°, allowed to come to room temperature, and then stirred for 1 more hr. The resulting solution was poured into a slurry of 900 g. of ice, 900 ml. of water, and 22 g. of sodium acetate, and stirred for 1 hr. The water layer was extracted three times with chloroform and the combined chloroform extracts were washed four times with 5% aqueous sodium acetate solution and once with water. The organic layer was dried over sodium sulfate, and then removed under reduced pressure. The resulting residue was separated and purified by chromatography on Florisil (deactivated with 10% water) with benzene as the eluent.

From the first band 0.71 g. of bis(3-nitro-2,4-pentanediono)(2,4-pentanediono)chromium(III) (J), 7.5% yield, was obtained. After recrystallization from chloroform–ethanol, brown needles were obtained, m.p. 246–246.5°.

Anal. Calcd. for $C_{15}H_{19}O_{10}N_2Cr$: C, 41.01; H, 4.36; N, 6.38. Found: C, 41.30; H, 4.37; N, 6.44.

From the second band 5.46 g. of bis(2,4-pentanediono)(3-nitro-2,4-pentanediono)chromium(III) (I), 64.5% yield, was obtained. After recrystallization from ethanol, brown prisms were obtained, m.p. 178–180°.

Anal. Calcd. for $C_{15}H_{20}O_8NCr$: C, 45.69; H, 5.11; N, 3.55. Found: C, 46.14; H, 5.32; N, 3.89.

From the acetone eluent 0.88 g. (11.7%) of starting material K was recovered.

Chlorination of Bis(2,4-pentanediono)(3-nitro-2,4-pentanediono)chromium(III) (I).—To a boiling solution of 100 mg. of nitro chelate I in 5 ml. of chloroform was added a solution of 200 mg. of N-chlorosuccinimide in 3 ml. of chloroform. The slurry was heated at reflux for 1 hr. and then cooled to room temperature. The reaction mixture was washed with 5% aqueous sodium sulfite solution and then with water. After drying over sodium sulfate, the solvent was evaporated under vacuum. The resulting residue was purified by chromatography on deactivated Florisil (10% water).

From the benzene eluent 80 mg. (68.0%) of bis(3-chloro-2,4-pentanediono)(3-nitro-2,4-pentanediono)chromium(III) (D), m.p. 204–204.5°, was obtained. The infrared spectrum was identical with that of an authentic sample of D.

Chlorination of Bis(3-nitro-2,4-pentanediono)(2,4-pentanediono)chromium(III) (J).—To a boiling solution of 300 mg. of nitro chelate J in 15 ml. of chloroform was added 300 mg. of N-chlorosuccinimide in 15 ml. of chloroform. The slurry was heated under reflux for 1 hr. and then cooled to room temperature. The reaction mixture was washed with 5% aqueous sodium sulfite solution and then with water. After drying over sodium sulfate, the solvent was removed under vacuum. The resulting residue was separated and purified by chromatography on Florisil (deactivated with 10% water).

From the first benzene eluent 100 mg. of bis(3-nitro-2,4-pentanediono)(3-chloro-2,4-pentanediono)chromium(III) (F), m.p. 225–226° (30.9% yield), was obtained. The infrared spectrum was identical with that of an authentic sample.

From the second benzene eluent 140 mg. of starting material J (46.7% yield) was recovered.

Treatment of Bis(2,4-pentanediono)(3-nitro-2,4-pentanediono)chromium(III) (I) with Zinc Dust.—To a mixture of 1.5 g. of nitro chelate I, 1.5 g. of zinc dust, and 20 ml. of pyridine was added 3 ml. of glacial acetic acid, keeping the temperature at 60°. The mixture was stirred for 3 hr. at 60–70°. After cooling to room temperature, the reaction mixture was poured into a mixture of 150 g. of ice and 150 ml. of water. The water layer was extracted with chloroform. The organic layer was removed, dried over sodium sulfate, and then evaporated under reduced pressure. The resulting residue was purified by use of Florisil (deactivated with 10% water). From the benzene eluent 0.35 g. of tris(2,4-pentanediono)chromium(III) (K), m.p. 210–211° (25.7% yield), was obtained. The infrared spectrum was identical with that of an authentic sample.

Treatment of Bis(3-nitro-2,4-pentanediono)(2,4-pentanediono)chromium(III) (J) with Zinc Dust.—To a mixture of 0.8 g. of the nitro chelate J, 1.5 g. of zinc dust, and 10 ml. of pyridine was added 3 ml. of glacial acetic acid, keeping the temperature at 60°. The slurry was stirred for 3 hr. at 60–70°. The reaction mixture was cooled to room temperature and poured into 150 ml. of ice water. The water layer was extracted with chloroform. The organic layer was removed, dried over sodium sulfate, and then the solvent was evaporated under vacuum. The resulting residue was purified by chromatography on Florisil (deactivated with 10% water). From the benzene eluent was obtained 70 mg. of tris(2,4-pentanediono)chromium(III) (K), m.p. 210–211° (11.0% yield). The infrared spectrum was identical with that of an authentic sample.

Bis(2,4-pentanediono)(3-amino-2,4-pentanediono)chromium(III) (L).—A mixture of 6.0 g. of nitro chelate I, 2.0 g. of palladium hydroxide and 250 ml. of absolute ethanol (the chelate I was not completely dissolved in ethanol) was shaken in a Paar hydrogenator under 65 lb. pressure at room temperature for 24 hr. The catalyst was removed by filtration and washed with ethanol until the filtrate was colorless. The combined solvent was evaporated under vacuum. The residue was purified by chromatography on Florisil using benzene containing 5% methanol as the eluent. From the third band 3.83 g. of bis(2,4-pentanediono)(3-amino-2,4-pentanediono)chromium(III) (L) was obtained, m.p. 221–223° (69.1% yield). After recrystallization from benzene, brownish crystals were obtained, m.p. 221.5–223°.

Anal. Calcd. for $C_{15}H_{22}O_6NCr$: C, 49.44; H, 6.09; N, 3.85; mol. wt., 364.35. Found: C, 49.29; H, 6.13; N, 3.67; mol. wt., 412.

Acetylation of Bis(2,4-pentanediono)(3-amino-2,4-pentanediono)chromium(III) (L).—To a mixture of 100 mg. of amino chelate L and 2 ml. of acetic anhydride was added several drops of pyridine. This slurry was stirred at room temperature for 24 hr. and then poured into 100 g. of ice water containing 2 g. of sodium acetate. The water layer was extracted three times with chloroform. The combined solvent was washed with water and then dried over sodium sulfate. After the solvent was removed, a purple solid remained, m.p. 255–258°. The yield of acetylamino chelate M was 90 mg. (80.7%). After recrystallization from ethanol–petroleum ether, purple needles were obtained, m.p. 259.5–261°.

Anal. Calcd. for $C_{17}H_{24}O_7NCr$: C, 50.24; H, 5.95; N, 3.45. Found: C, 49.54; H, 5.92; N, 3.42.

Diazotization of Bis(2,4-pentanediono)(3-amino-2,4-pentanediono)chromium(III) (L).—Amino chelate L (0.73 g., 2.0 mmoles) was dissolved in a cold (0°) solution of 1.08 g. of 48% fluoroboric acid (6.0 mmoles) and 4.0 g. of water. To this solution was added 1.52 g. of a 10% aqueous sodium nitrite solution (2.2 mmoles of sodium nitrite) at 0° for 5 min. with vigorous stirring. A pale purple precipitate appeared. After stirring for 5 min., the purple solid was quickly collected by filtration and washed with cold absolute ethanol and then with cold ether. If this collection and washing steps were not accomplished quickly,

the precipitate became sticky and decomposed. The yield of chelate diazonium fluoroborate N was 0.51 g. (55.0%). The infrared spectrum exhibited a sharp peak at 2200 cm.$^{-1}$ (diazonium ion[18]) and a peak at 1050 cm.$^{-1}$ (fluoroborate anion[19]). The diazonium salt melted at 165° with decomposition.

Anal. Calcd. for $C_{15}H_{20}O_6N_2CrBF_4$: C, 38.90; H, 4.35; N, 6.05. Found: C, 38.67; H, 4.32; N, 6.17.

Reduction of the Chelate Diazonium Fluoroborate N with Ethanol.—A solution of 50 mg. of the chelate diazonium fluoroborate N in 2 ml. of absolute ethanol was heated at reflux on the steam bath for 2 hr. After the solvent was removed under vacuum, the resulting residue was purified by chromatography on Florisil using benzene. From the benzene eluent 15 mg. of tris(2,4-pentanediono)chromium(III) (K), m.p. 201–204° (40% yield), was obtained. After recrystallization from benzene–petroleum ether, the sample melted at 210–211°. The infrared spectrum was identical with that of an authentic sample.

Pyrolysis of the Chelate Diazonium Fluoroborate N.—A mixture of 1.0 g. of the chelate diazonium fluoroborate N and 4.0 g. of powdered sodium fluoride was heated at 180–200° (oil bath temperature) for 8 hr. under vacuum (0.5 mm.) in a sublimation apparatus. The sublimate weighed 240 mg. This solid was separated by chromatography on Florisil (deactivated with 10% water) using benzene. From the second benzene eluent was obtained 50 mg. of bis(2,4-pentanediono)(3-fluoro-2,4-pentanediono)chromium(III) (O), m.p. 208–210° (6.3% yield). After recrystallization from petroleum–ether, the melting point was 212.5–213.5°. The infrared spectrum exhibited selected maxima at 1490, 1320, and 1152 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{20}O_6FCr$: C, 49.04; H, 5.49; F, 5.17. Found: C, 48.76; H, 5.31; F, 4.72.

From the third benzene eluent 120 mg. of tris(2,4-pentanediono)chromium(III) (K), m.p. 209–211° (15.9% yield), was obtained. The infrared spectrum of this substance was identical with that of tris(2,4-pentanediono)chromium(III) (K).

Decomposition of the Chelate Diazonium Fluoroborate N in Water.—The chelate diazonium fluoroborate N (200 mg.) was dissolved in 2 ml. of water. This solution was warmed at 35–40° for 2 hr. and then extracted with a large amount of ether. The ether layer was separated and the solvent was removed under vacuum (at room temperature). The resulting residue weighed 130 mg., m.p. 121–123°. After recrystallization from ethanol–benzene, purple cubic crystals were obtained, m.p. 121–123.

Anal. Calcd. for $C_{15}H_{21}O_7Cr \cdot 12H_2O$: C, 30.97; H, 7.80. Found: C, 30.71; H, 7.60.

(18) (a) M. Aroney, R. J. W. LeFevre, and R. L. Werner, *J. Chem. Soc.*, 276 (1955); (b) K. B. Whetsel, G. F. Hawkins, and F. E. Johnson, *J. Am. Chem. Soc.*, **78**, 3360 (1956).

(19) G. A. Olah, S. J. Kuhn, and W. S. Tolgyesi, *ibid.*, **84**, 2733 (1962).

Direct Synthesis of Ternary Iminium Salts by Combination of Aldehydes or Ketones with Secondary Amine Salts[1,2]

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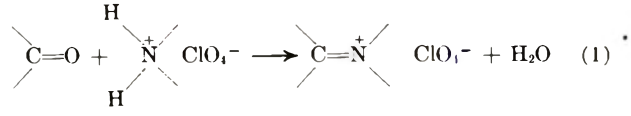
Received June 17, 1963

A general reaction for the preparation of ternary iminium perchlorates, $>C{=}\overset{+}{N}< ClO_4^-$, is found in the simple combination of an aldehyde or a ketone with a secondary amine perchlorate (Table I). The yields are excellent in the absence of serious steric interference. In the n.m.r. spectra of representative iminium salts, long-range coupling has been observed through three single bonds and the iminium bond and through four single bonds and the iminium bond. Mesityl oxide is converted to N-isopropylidenepyrrolidinium perchlorate (VI) by reaction with pyrrolidine perchlorate, thereby providing an efficient dealdolization process.

The importance of the $C{=}\overset{+}{N}\ X^-$ function in organic chemistry has been well documented by Hellmann and Opitz.[3] Immonium salts[4] or ternary iminium salts[5] (we prefer the latter name) occupy a key position in many organic reactions and are subject to rapid attack by a wide variety of nucleophilic reagents.[3,6] The salts are generally made by cleavage of a covalent C–Y bond in a $N{-}C{-}Y$ system,[4,7] by alkylation of aldimines or ketimines,[4] and by protonation of enamines.[4,8] It is also possible to obtain ternary iminium complex salts by direct combination of an aldehyde or ketone with a secondary amine complex salt, *e.g.*; hexahalostannates,[5,9-11] halobismuthates,[5,9-10] haloantimonates,[5,9-11] hexahaloplatinates,[9,10] or iodide–silver iodide complexes.[12]

We have now found an adaptation of this procedure, which is simple and generally useful, employing the perchlorate salts of the secondary amines. Our past experience directed us to the use of these salts since the products could be expected to be easily crystallizable and nonhygroscopic and since the monovalent perchlorate anion, being a poor nucleophile, would not interfere with reaction products sought beyond the ternary iminium stage.[8b] The general reaction which can be effected is that of a ketone or aldehyde with a secondary amine perchlorate to give a ternary iminium perchlorate.



(1)

As an example of the ease with which conversion occurs, the mixing of pyrrolidine perchlorate with a slight excess of acetone liberates heat and produces crystalline N-isopropylidenepyrrolidinium perchlorate

(1) Supported by a research grant (USPHS-GM-05829-05) from the National Institutes of Health, U. S. Public Health Service.

(2) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(3) H. Hellman and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, GMBH, Weinheim/Bergstr., Germany, 1960, p. 1, and throughout.

(4) J. Goerdeler in "Methoden der Organischen Chemie" (Houben-Weyl), Vol. XI/2, Georg Thieme Verlag, Stuttgart, Germany, 1958, pp. 616–618; see also C. R. Hauser and D. Lednicer, *J. Org. Chem.*, **24**, 46 (1959).

(5) M. Lamchen, W. Pugh, and A. M. Stephen, *J. Chem. Soc.*, 4418 (1954).

(6) N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956), and references therein.

(7) H. G. Reiber and T. D. Stewart, *ibid.*, **62**, 3026 (1940).

(8) The following references illustrate salt formation from enamines available from different representative sources: (a) N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954); (b) N. J. Leonard and K. Jann, *ibid.*, **84**, 4806 (1962); (c) N. J. Leonard, C. K. Steinhardt, and C. Lee, *J. Org. Chem.*, **27**, 4027 (1962).

(9) W. Pugh, *J. Chem. Soc.*, 2423 (1954).

(10) M. Lamchen, W. Pugh, and A. M. Stephen, *ibid.*, 2429 (1954).

(11) G. Opitz and W. Merz, *Ann.*, **652**, 139 (1962); see also G. Opitz, H. Hellmann, and H. W. Schubert, *ibid.*, **623**, 117 (1959).

(12) R. Kuhn and H. Schretzmann, *Ber.*, **90**, 557 (1957).

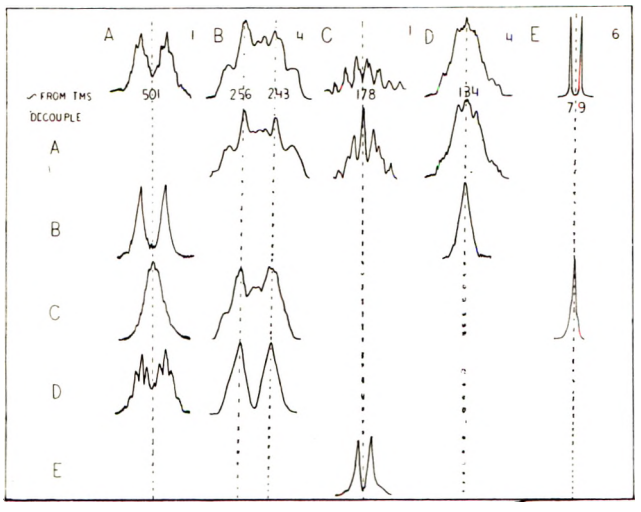
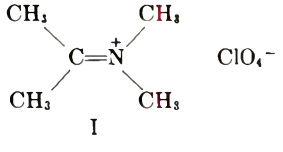


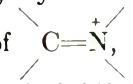
Fig. 1.—N.m.r. spin–spin decoupling with N-isobutylidenepyrrolidinium perchlorate (II).

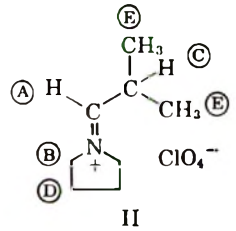
in a matter of seconds. The yield of pure product is 96% (see Experimental, procedure A). A solvent such as ethanol (1–2 vol.) also may be used. The yields are generally high for other representative ketones: ethyl methyl ketone, diethyl ketone, and cyclohexanone. Acetophenone gives the corresponding ternary iminium salt with pyrrolidine perchlorate in 70% yield, which is much greater than that obtainable by proceeding through the enamine from acetophenone and pyrrolidine followed by a separate protonation step. We expect the method to be applicable to substituted acetophenones. The perchlorate salts of other secondary amines perform in similar manner,[13] here exemplified with morpholine and dimethylamine. The product of acetone and dimethylamine perchlorate, N-isopropylidenedimethylaminium perchlorate (I), readily obtained in 92% yield, deserves special mention since it is the simplest symmetrically substituted iminium salt obtainable.



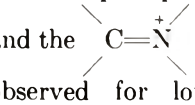
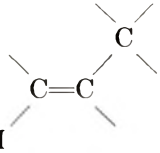
I

Illustrations of further scope of the reaction were obtained in the efficient condensation of cyclohexanone with morpholine perchlorate and of cyclohexanone with pyrrolidine fluoborate (see Table I). In general the fluoborate salts function less efficiently than the perchlorates but are probably handled with greater assurance of safety. Both perchlorates and fluoborates are far superior to any other secondary amine salts having representative simple anions, *e.g.*, chloride, bromide, nitrate, sulfate, which we have investigated. The condensation also can be effected in a solvent such as benzene, with azeotropic distillation of the water formed (see Experimental, procedure B). Aldehydes undergo reaction with pyrrolidine perchlorate efficiently with production of the corresponding ternary iminium salts (Table I), for which no route through an enamine—at least for the aromatic and α,β-unsaturated aldehydes—is possible. We have illustrated this facet of the reaction with benzaldehyde, isobutyraldehyde, 2-ethylbutyraldehyde, furfural, cinnamaldehyde, and pivalaldehyde. The general reaction (1) may be formulated as a nucleophilic carbonyl addition followed by the elimination of water.

All of the products have been characterized by elemental analyses, by the strong infrared absorption band indicative of  , and by the n.m.r. spectra, especially the chemical shifts for the methyl, methylene, or single protons attached to the carbon of the iminium grouping. We observed long-range coupling of these protons through the double bond with the α-methylene protons of the pyrrolidinium ring. While the n.m.r. spectra of the iminium compounds were suggestive of long-range coupling, the signals were sufficiently complex that the proton spin–spin coupling constants were not readily assignable except by double resonance experiments. The compound selected first for examination was N-isobutylidenepyrrolidinium perchlorate (II). As seen in compressed form at the top of Fig. 1, the spectrum consisted of signals, expressed in c.p.s. downfield from tetramethylsilane as 0.0, occurring at 501 (J = 9.0 c.p.s., doublet) (A), 249.5 (B), 178 (C), 134 (D), and 79 (J = 7.0 c.p.s., doublet) (E). The assignments were made as shown.



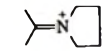
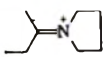
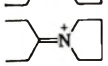
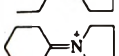
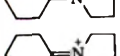
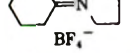
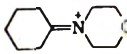
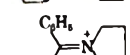
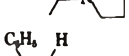
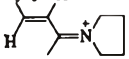
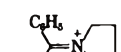
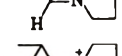
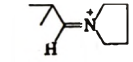
II

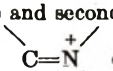
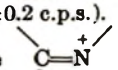
Where there were appreciable effects of spin–spin decoupling due to irradiation at applied frequencies corresponding to A through E, successively, the altered segments of the spectra are reproduced on the second through sixth lines in Fig. 1. The A proton was shown to be coupled to C (J_{AC} = 9.0 c.p.s.) (lines 2 and 4) and to B (J_{AB} = 2.0) (lines 2 and 3). The magnitude of J for spin–spin coupling through three single bonds and the  double bond is in the range previously observed for long-range coupling in the system  H.[14] The A proton also was possibly coupled to D, since decoupling from D by irradiation at 134 c.p.s. sharpened the spectrum of A (line 5 of Fig. 1). The B protons were shown to be coupled to A and D protons (line 3). When decoupled from C, the B spectrum became sharper. Irradiation at 134 c.p.s. simplified the B spectrum to two broad singlets (line 5, see also line 3) separated by about 13 c.p.s., showing that the two α-methylene groups were not identical. The coupling of the C proton to the E protons of the methyl groups was clearly observed when irradiation at 178 c.p.s. caused the signal for the E pro-

(13) Unpublished results in this laboratory by W. J. Musliner and P. C. Kelley.

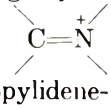
(14) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Ltd., Great Britain, 1959, p. 85.

TABLE I

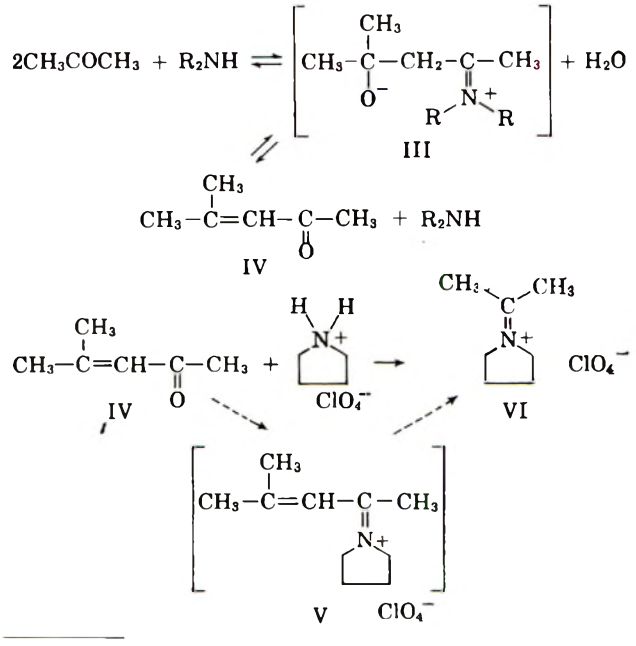
Perchlorate[a] Name	Structure	Procedure[b]	Yield, %	M.p., °C.	ν_{max}^{Nujol} (cm.$^{-1}$) C=N	N.m.r. τ[d]	N.m.r. J[e]	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
N-Isopropylidenedimethylaminium		A	92	298–300[c]	1687	7.53[f]	1.0	$C_5H_{12}ClNO_4$	32.35	32.42	6.52	6.54	7.55	7.55
N-Isopropylidenepyrrolidinium		A	96	232–233	1690	7.48[g]	1.4	$C_7H_{14}ClNO_4$	39.72	39.49	6.67	6.67	6.62	6.69
N-2-Butylidenepyrrolidinium		A	84	214–216	1680	7.53[h] 7.23	1.2 8.0	$C_8H_{16}ClNO_4$	42.57	42.56	7.15	7.22	6.21	6.28
N-3-Pentylidenepyrrolidinium		B	90	213–214	1665	7.22[h]	8.0	$C_9H_{18}ClNO_4$	45.10	44.93	7.57	7.58	5.85	6.11
N-Cyclohexylidenepyrrolidinium		A	90	239–240	1665	7.22[i]		$C_{10}H_{18}ClNO_4$[h]						
N-Cyclohexylidenepyrrolidinium fluoborate		B	63	220–222	1670	7.18[h]		$C_{10}H_{18}BF_4N$[h]						
N-Cyclohexylidenemorpholinium		B	94	239–241	1640	7.05[g]		$C_{10}H_{18}ClNO_5$	44.86	45.32	6.78	6.76	5.24	5.36
N-1-Methylbenzylidenepyrrolidinium		B	70	161–163	1658	7.22[g]		$C_{12}H_{16}ClNO_4$	52.65	52.40	5.90	6.04	5.12	5.13
N-1-Methylcinnamylidenepyrrolidinium		B	80	239–241	1622	7.42[f]		$C_{14}H_{18}ClNO_4$	56.10	56.38	6.05	6.11	4.67	4.67
N-Benzylidenepyrrolidinium		B	92	156–159	1658	1.01[h]	2.1	$C_{11}H_{14}ClNO_4$	50.87	50.86	5.44	5.43	5.40	5.46
N-Isobutylidenepyrrolidinium		A	92	238–240	1697	1.66[g,h]	2.0 9.0	$C_8H_{16}ClNO_4$	42.57	42.35	7.15	7.13	6.21	6.25
N-2-Ethylbutylidenepyrrolidinium		A	90	183–184	1690	1.58[h]	1.9 10.0	$C_{10}H_{20}ClNO_4$	47.33	47.12	7.95	7.83	5.52	5.61
N-Furfurylidenepyrrolidinium		A	83	99–100	1660	1.22[g] 7.04	1.8	$C_9H_{12}ClNO_5$	43.30	43.60	4.85	4.87	5.61	5.67
N-Cinnamylidenepyrrolidinium		A	87	156–157	1660	1.29[g]	1.8 10.0	$C_{13}H_{16}ClNO_4$	54.64	54.58	5.65	5.62	4.90	4.82
N-Neopentylidenepyrrolidinium		B	79[j]	307–308[c]	1682	1.73[g]	2.1	$C_9H_{18}ClNO_4$	45.10	45.21	7.57	7.66	5.85	5.68

[a] Perchlorate salt unless otherwise stated. [b] Made from the appropriate aldehyde or ketone and secondary amine salt by procedure A or B, or slight modification thereof, as indicated in the Experimental. [c] With decomposition. [d] τ values in p.p.m., for the proton on the carbon of  or for the protons on the carbon alpha to the iminium carbon, with reference to tetramethylsilane as 10.0 [see G. V. D. Tiers, "Table of τ Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul. Minn., 1958; G. V. D. Tiers, *J. Phys. Chem.*, 62, 1151 (1958)]. [e] Coupling constants in c.p.s. (±0.2 c.p.s.). The first value represents the long-range coupling through the iminium double bond. The second value is for the coupling between protons on adjacent carbons on the C-side of the  grouping. The major shape of the signal is that of a quintuplet. [f] Solvent: chloroacetonitrile. [g] Methylene chloride. [h] Deuteriochloroform. [i] Liquid SO_2. [j] Based on unrecovered pyrrolidine perchlorate. [k] See ref 8b.

tons to collapse from a doublet (J_{CE} = 7.0 c.p.s.) to a singlet (line 4 of Fig. 1). Similarly, irradiation at 79 c.p.s. changed the multiplet signal for the C proton to a broad doublet (bottom line), still coupled to A and perhaps B.

Another compound for which spin–spin decoupling revealed long-range splitting was N-isopropylidenedimethylaminium perchlorate (I). The n.m.r. spectrum consisted of two signals split into a quintuplet or septuplet. A decision between these possibilities was difficult because the line widths and the expected intensity ratio of 1:6:15:20:15:6:1 make the outside two peaks hard to find. Shoulders at the correct positions were observed. When the lowfield signal was followed and the highfield protons were decoupled, or *vice versa*, the remaining signal collapsed to a sharp singlet. The coupling constant, J = 1.0 c.p.s., observed was, therefore, assignable to long-range spin–spin coupling over four single bonds and one  bond. The results obtained with N-isopropylidenedimethylaminium perchlorate (I) support the observation that in N-isobutylidenepyrrolidinium perchlorate (II) the C and B protons are involved in long-range coupling. Long-range coupling was observed in the n.m.r. spectra of all the iminium salts derived from aldehydes and methyl ketones (Table I) except N-1-methylbenzylidenepyrrolidinium perchlorate, for which the signal for the methyl group was considerably broadened but the splitting was not resolved.

In further consideration of the chemistry of iminium salts, an interesting reversal of the aldol condensation has resulted from the treatment of mesityl oxide (IV) with pyrrolidine perchlorate. An intermediate dipolar ion containing the iminium group III has been postulated to explain the specific effect of a secondary amine in the aldolization–dealdolization of acetone.[15,16] We thought it should be possible to approach this type of intermediate by condensation of mesityl oxide with pyrrolidine perchlorate, thereby forming initially the α,β-unsaturated iminium salt V. The interrelation of III and V is obvious if the former is protonated and the latter hydrated. The reaction between IV and pyrrolidine perchlorate in ethanol (1:2 mole ratio) at room temperature gave *N-isopropylidenepyrrolidinium perchlorate (VI) in 96% yield.* The dealdolization could also be effected using benzene as a refluxing solvent with azeotropic removal of water.



Experimental[17]

General Method of Preparation of Amine Salts.—To 71.1 g. (1.0 mole) of pyrrolidine in 500 ml. of ether was added perchloric acid (70% 1:1 in ethanol) until just acid to congo red. A few drops of pyrrolidine were added and the solvent was removed under vacuum. The soft solid obtained was recrystallized from 2-propanol–ether giving pyrrolidine perchlorate, colorless needles, m.p. 240–242°.

General Method of Preparation of Ternary Iminium Salts. A.—To 17.2 g. (0.100 mole) of pyrrolidine perchlorate in an erlenmeyer flask was added 11.6 g. (0.200 mole) of anhydrous acetone. The pyrrolidine perchlorate dissolved immediately and, on swirling, crystals separated with the evolution of heat. After a few minutes the crystals were washed with ether and recrystallized from 2-propanol, yielding 20.3 g. (96%) of N-isopropylidenepyrrolidinium perchlorate, m.p. 232–233° (Table I). Minor variations in procedure A included heating the combination of secondary amine salt and carbonyl compound when necessary and using ethanol as a solvent to dissolve the secondary amine salt before adding the carbonyl compound. The reaction could be speeded, where necessary, by addition of a few drops of the secondary amine or of a tertiary amine such as triethylamine or pyridine.

B.—To 18.8 g. (0.100 mole) of morpholine perchlorate were added 19.2 g. (0.200 mole) of cyclohexanone and 2 or 3 drops of morpholine. When no reaction was observed, 200 ml. of benzene was added and the heterogeneous mixture was heated under reflux overnight, with stirring and while removing water continuously by means of a Dean–Stark trap. The separated solid was collected by filtration, washed with ethanol and ether and dried *in vacuo*. The product, N-cyclohexylidenemorpholinium perchlorate, 25.2 g. (94%), melted at 237–239°. Recrystallization from acetonitrile–ether raised the melting point to 239–241°. The use of a Soxhlet extractor containing molecular sieves and a solvent such as chloroform for azeotroping constituted a modification of procedure B, which was successful, for example, in the combination of pyrrolidine perchlorate and diethyl ketone, giving the iminium product in 86% yield.

Dealdolization of Mesityl Oxide.—A mixture of 17.2 g. (0.10 mole) of pyrrolidine perchlorate, 4.9 g. (0.05 mole) of mesityl oxide, 5 drops of pyrrolidine, and 200 ml. of benzene was heated under reflux overnight with stirring while water was removed continuously by means of a Dean–Stark trap. The solvent was removed *in vacuo*, and the solid remaining was recrystallized from ethanol; m.p. 232–233°; yield, 19.7 g. (93%). It was identified as N-isopropylidenepyrrolidinium perchlorate (VI) by melting point, mixture melting point, infrared, and n.m.r. spectra. When excess mesityl oxide was used, the yield of the same product, based on pyrrolidine perchlorate, was unchanged.

A simpler variation, using the same amounts of pyrrolidine perchlorate and mesityl oxide as listed, with five drops of pyrrolidine, in 20 ml. of ethanol, gave N-isopropylidenepyrrolidinium perchlorate in 96% yield after 36 hr. at 25°.

(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 345, 363.

(16) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 260.

(17) We wish to thank Mr. Josef Nemeth, Miss Mary Ann Weatherford, Mrs. Mary Rose Kung, and Mr. Gary D. Callahan for the microanalyses. The infrared absorption spectra were determined on a Perkin-Elmer Model 237 infrared spectrometer. The n.m.r. spectra were obtained at 60 Mc. with a Varian Associates Model A-60 spectrometer or with a Model V-4300B spectrometer equipped with a superstabilizer, using an audio sideband technique for the double resonance spectra. We are indebted to Mr. Oliver W. Norton for the n.m.r. double resonance experiments.

Cyclization of Aromatic Aldehyde and Ketone Phenylhydrazones with Carbon Monoxide to Yield Substituted Phthalimidines. Study of the Mechanism of the Reaction[1]

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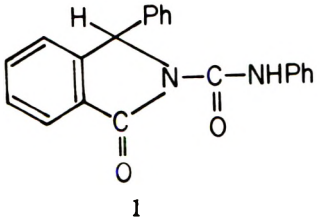
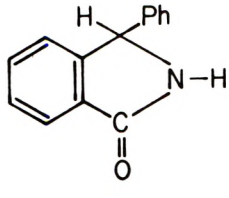
Received November 8, 1962

Benzaldehyde phenylhydrazone reacted with carbon monoxide in the presence of dicobalt octacarbonyl at 230° and 3540 p.s.i. to give mainly N-phenylphthalimidine. At 200° the yield of the major product was greatly decreased, whereas that of an organocobalt complex was increased. Tracer studies using benzaldehyde 1-phenylhydrazone-1-N^{15} established that the 2-N of the hydrazone was eliminated in the cyclization. Benzaldehyde *m*-tolylhydrazone at 230° gave the new compound, N-*m*-tolylphthalimidine. An independent synthesis of the latter compound is described. Under the same conditions, 1-naphthaldehyde phenylhydrazone afforded mainly 2-phenylbenz[*e*]isoindolin-1-one. Acetophenone phenylhydrazone yielded the new compounds N-phenyl-3-methylphthalimidine and 3-methylphthalimidine-N-carboxyanilide. In a crossed-over experiment using 1-naphthaldehyde phenylhydrazone and benzaldehyde *m*-tolylhydrazone, the fact that no crossed-over products were obtained showed that the rearrangement proceeded by an intramolecular mechanism. The infrared spectra of the N^{15} tracer compounds are described.

It recently has been shown[3] that benzophenone phenylhydrazone cyclized with carbon monoxide at 230° and 3800 p.s.i. to give 3-phenylphthalimidine-N-carboxyanilide (1), and at 190–220° to give a mixture of the same compound and 3-phenylphthalimidine (2). Because the number of carbon monoxide entities incorporated into the product was temperature dependent and scission of the N–N bond had occurred, we decided to study further the cyclization of aromatic phenylhydrazones in order to determine the generality and mechanism of this reaction.



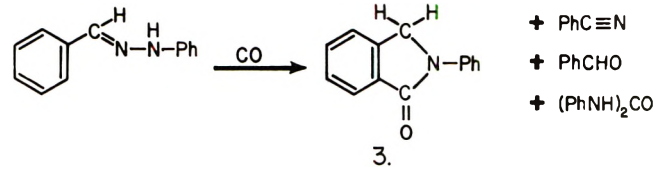
1



2

The aromatic aldehyde or ketone phenylhydrazone, dissolved in benzene as solvent, reacted with commercial high purity carbon monoxide in the presence of preformed dicobalt octacarbonyl as catalyst in a 300-ml. rocker bomb fitted with a glass liner. After the carbon monoxide was vented, only that portion of the reaction mixture which was still in the glass liner was freed of catalyst, either by chromatography or by heating it at 70°. The per cent yields of products reported in the experiments involving less than 1 g. of substrate were always less than those in which about 10 g. of starting material were used because of greater mechanical losses in the former than in the latter. Since about 10% of the substrate escaped through the hole of the liner (material outside of the liner was not recovered because of possible contamination), the reported yields of products are correspondingly lower than they actually were. In general, the aromatic aldehyde phenylhydrazones gave more complex product mixtures with lower yields of cyclic products (these were N-substituted phthalimidines) than did the aromatic ketone phenylhydrazones. In contrast to our findings, Murahashi and Horiie[4] reported recently that benzaldehyde phenylhydrazone did not give any definite result when treated with synthesis gas.

Benzaldehyde phenylhydrazone reacted with carbon monoxide at 230° and 3540 p.s.i. to give N-phenylphthalimidine (3) in 50% yield. It is interesting to note that one nitrogen has been eliminated from the phenylhydrazone in this reaction. The structure of compound 3 was confirmed by direct comparison (mixture melting point and infrared analysis) with an authentic sample of N-phenylphthalimidine, prepared by the reduction of phthalanil as described by Graebe.[5] In addition to the N-phenylphthalimidine, the reaction mixture also contained small amounts of benzonitrile, benzaldehyde, N,N′-diphenylurea, and a blue-black solid which appeared to be an organometallic complex. Treatment of the last substance with sodium hydroxide yielded ammonia and aniline.



3.

On lowering the carbonylation temperature to 200°, benzaldehyde phenylhydrazone gave only 5% of N-phenylphthalimidine in the product mixture. This reduction of the yield of cyclized product by lowering the reaction temperature is in accord with similar observations previously reported on the carbonylation of benzophenone phenylhydrazone.[3] In the 200° experiment a higher yield of the organocobalt complex was obtained as well as 3% of a yellow crystalline compound of empirical formula C_7H_6N. The remainder of the product mixture was again a complex mixture of oils.

In order to determine which nitrogen atom was eliminated from benzaldehyde phenylhydrazone during its conversion to N-phenylphthalimidine, labeled benzaldehyde 1-phenylhydrazone-1-N^{15} was treated with carbon monoxide under the same conditions as those used for the carbonylation of the normal phenylhydra-

(1) Presented before the XIX International Congress of Pure and Applied Chemistry, London, England, July, 1963.

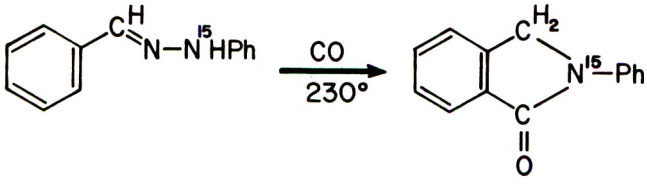
(2) Department of Chemistry, The University of Alberta, Calgary Branch, Calgary, Alberta, Canada.

(3) A. Rosenthal and Mary R. S. Weir, *Can. J. Chem.*, **40**, 610 (1962).

(4) S. Murahashi and S. Horiie, *Bull. Chem. Soc. Japan*, **33**, 78 (1959).

(5) C. Graebe, *Ann.*, **247**, 288 (1888).

zone. Alumina chromatography of the products from the labeled phenylhydrazone gave N-phenylphthalimidine-N^{15} (**4**). Infrared and mass spectrometric analyses showed conclusively that compound **4** was the

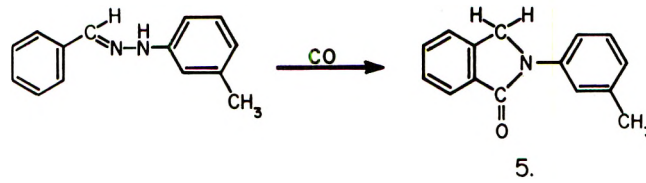


4.

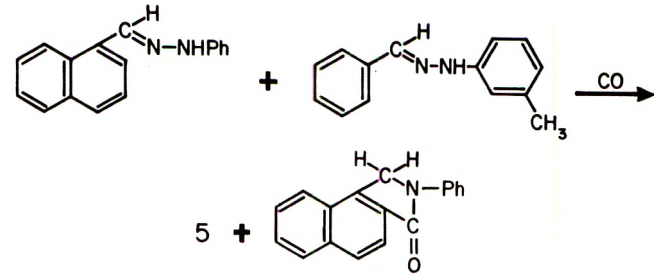
essentially pure N^{15} labeled compound. As shown in the Experimental section, the only peaks which were displaced (displacement of the N^{15} N-phenylphthalimidine shown in brackets) occurred at 1390 [10], 1372 [2], 1264 [4], 1149 [14], 1061 [6], and 877 cm.$^{-1}$ [4]. Since the labeled N-phenylphthalimidine did not exhibit any trace of peaks which would arise from N^{14}–C groups, it was tentatively surmised that the labeled compound was essentially pure. Unequivocal proof of the purity of the labeled N-phenylphthalimidine was provided by mass spectrometric analysis which showed that the labeled N-phenylphthalimidine contained 97.5% enriched nitrogen. Since the benzaldehyde 1-phenylhydrazone-1-N^{15} contained at least 95% enriched nitrogen (analysis supplied by Merck Sharp and Dohme of Canada), it was definitely concluded that the labeled N-phenylphthalimidine was essentially pure and that 2-N of the phenylhydrazone was completely eliminated during the reaction.

With reference to the infrared spectra (shown in the Experimental) of the normal and labeled benzaldehyde phenylhydrazones and N-phenylphthalimidines, the peaks at 1132 and 1149 cm.$^{-1}$ in the normal compounds were assigned to the N–Ph stretch of the hydrazone and the phthalimidine, respectively (or probably the C–N bond participated in ring vibration). Confirmation of this assignment is provided by the recent work of Kübler and co-workers.[6]

Although it appeared that the phenyl group attached to the nitrogen of the phthalimidine originated from the phenylhydrazone, it was conceivable that it also might have been produced by the solvent benzene. Since previous workers[7] have shown that the yield of ureas obtained from the carbonylation of azo compounds varied with the solvent used, it might be concluded that the solvent furnished the hydrogen which was necessary for the reduction of the azo compound to the hydrazo form and the latter was then carbonylated to yield the urea. On the basis of this assumption it might be expected that the solvent benzene could also supply phenyl groups in addition to hydrogen. In order to test this hypothesis a phenylhydrazone was chosen that contained a methyl "tagged" phenyl group on the nitrogen. Thus, when *m*-tolylhydrazone was carbonylated using benzene as solvent at 230°, N-*m*-tolylphthalimidine (**5**) was the sole cyclized product obtained. This "tagged" methyl group was shown to be in the *meta* position of the tagged substituted phthalimidine by comparing compound **5** with an authentic sample of N-*m*-tolylphthalimidine prepared by the condensation of phthalic anhydride with *m*-toluidine and subsequent reduction of the N-*m*-tolylphthalimide with tin and hydrochloric acid (each phthalimidine had the same melting point and infrared spectrum). Therefore, the group on the nitrogen of the N-phenylphthalimidine was a moiety of benzaldehyde phenylhydrazone and did not arise from the solvent. In addition, the *m*-tolyl group must not have come free during the rearrangement since the structural purity of the *m*-tolyl group had been retained. Further additional convincing proof that the reaction must have proceeded *via* an intramolecular mechanism was provided by carrying out a crossed-over carbonylation experiment involving two different phenylhydrazones having approximately the same rates of reaction. Thus, when an equimolar mixture of 1-naphthaldehyde phenylhydrazone and benzaldehyde *m*-tolylphenylhydrazone was carbonylated at 230°, the only cyclized products were N-*m*-tolylphthalimidine (**5**) and 2-phenylbenz[*e*]isoindolin-1-one (**6**).



5.



6.

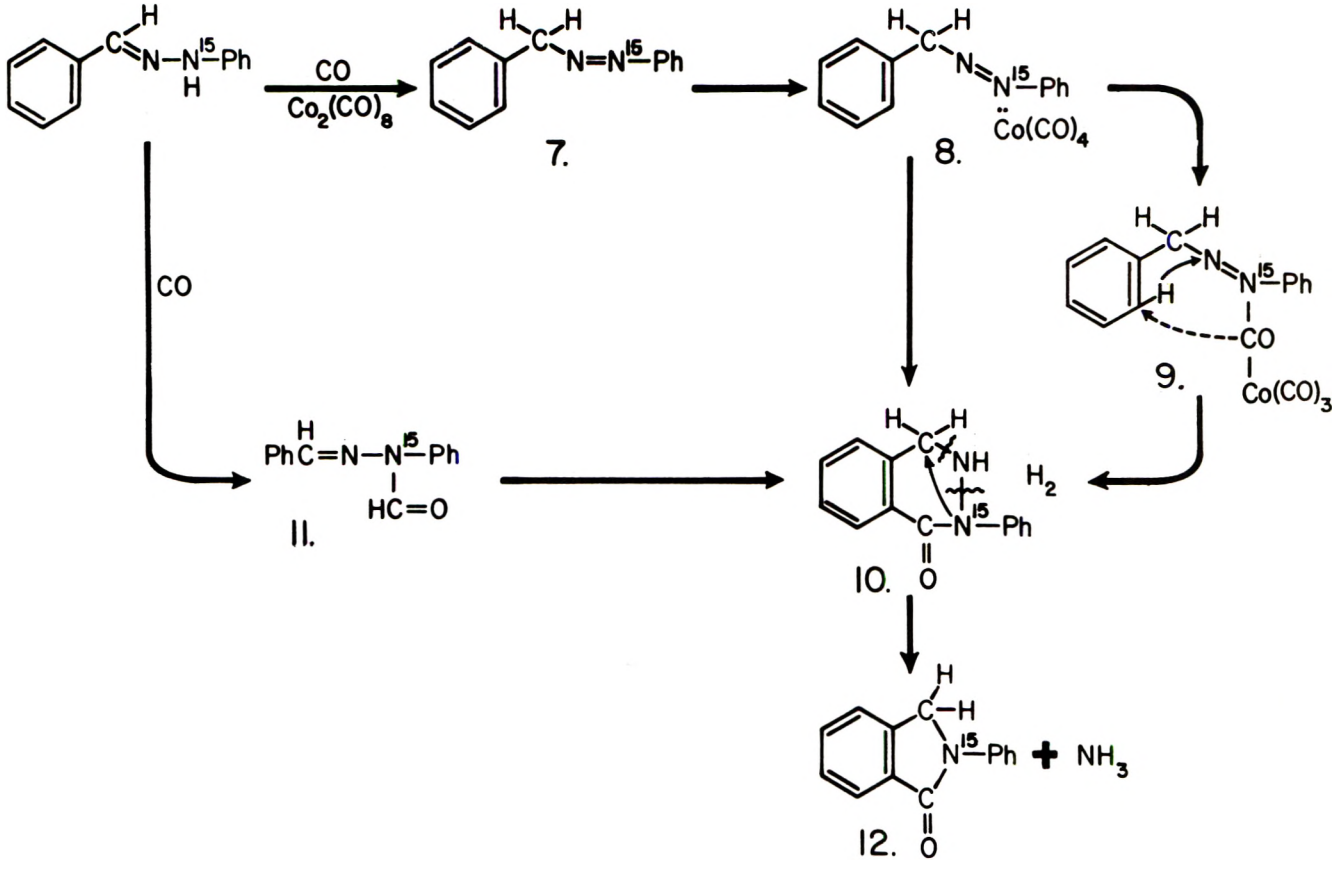
Because the aromatic aldehyde phenylhydrazones cyclized with carbon monoxide to yield a product in which one nitrogen was eliminated from the starting material whereas the diaryl ketone phenylhydrazones cyclized under similar conditions to give a product containing both nitrogens, it appeared of interest to carbonylate an alkyl aryl ketone phenylhydrazone. Carbonylation of acetophenone phenylhydrazone afforded 3-methylphthalimidine-N-carboxyanilide and 3-methyl-N-phenylphthalimidine. It would, therefore, appear that the substituents, other than hydrogen, attached to the carbon of the imino group have little effect on the cyclization. In this connection it is interesting to note that Murahashi and Horiie[8] recently reported that substituents on the carbon of C=N group of anils had no discernible steric effect on the velocity of the cyclization with carbon monoxide.

Although the complete mechanism for the unusual rearrangement of the aromatic aldehyde phenylhydrazones is unknown, the following postulations may be of interest since evidence for some of the proposed steps exist in the literature. Based on the fact that the phenylhydrazones of aldehydes and ketones rapidly tautomerize to benzene azoalkanes,[9] the assumption can be made that the azo tautomer **7** (Chart I) of benzaldehyde phenylhydrazone reacts with the metal carbonyl to give a nitrogen–metal Σ bond as shown in structure **8**.

(6) R. Kübler, W. Lüttke, and S. Weckberlin, *Z. Eleckt.*, **64**, 650 (1960).
(7) S. Horiie and S. Murahashi, *Bull. Chem. Soc. Japan*, **33**, 88 (1959).
(8) S. Horiie and S. Murahashi, *ibid.*, **33**, 247 (1960).
(9) R. O'Connor, *J. Org. Chem.*, **26**, 4375 (1961).

CHART I

MECHANISM OF CARBONYLATION OF BENZALDEHYDE 1-PHENYLHYDRAZONE-1-N^{15}



After CO from the metal carbonyl is inserted between the nitrogen and the cobalt atom[10] to give intermediate **9**, cyclization of the CO to the aromatic ring occurs to yield intermediate **10**. Alternatively, the assumption that the attack of dicobalt octacarbonyl on the phenylhydrazone gives the N-formyl compound **11** which undergoes cyclization to yield labeled N-phenylphthalimidine **12**, is based on the facts that amines gave formamides with dicobalt octacarbonyl,[11] and aniline yields formanilide, and N,N′-diphenylurea with nickel carbonyl.[12] Hydrogenolysis of the C–N bond might be expected to take place easily because of the activating effect of the benzylic group. The hydrogen must be furnished by the reactants in some type of transfer process, possibly *via* the formation and decomposition of cobalt hydrocarbonyl as envisaged by Natta, Pino, and Ercoli.[13] The apparent analogy between the rearrangement of benzaldehyde phenylhydrazone to yield N-phenylphthalimidine in the research described herein and the Fischer indole synthesis,[14] which also involves elimination of 2-N of the phenylhydrazone, is misleading, we believe, since the former reaction involves cyclization with carbon monoxide, whereas the latter does not.

Experimental

General Considerations.—The high pressure equipment has been described previously.[15] After each experiment, only the product inside the glass liner was utilized (part of the reaction mixture leaked through the hole of the glass liner into the metal reaction vessel). High purity carbon monoxide was obtained from the Matheson Co., East Rutherford, N. J. All melting points were obtained on a Leitz heating stage. The infrared analyses were done on a Perkin-Elmer Model 21 instrument using sodium chloride optics. The mass spectrometric analysis was done on an A. E. I. instrument with heated inlet.

Benzaldehyde 1-Phenylhydrazone-1-N^{15}.—To 0.75 g. of benzaldehyde was added with stirring 0.75 g. of 1-phenylhydrazine-1-N^{15},[16] and the hydrazone kept at 75° for 10 min. Anhydrous ethanol (50 ml.) was added and the hydrazone heated at reflux for 10 min. Removal of the solvent under reduced pressure was followed by recrystallization of the residue from 90% ethanol' m.p. 159–160°.

Infrared (KBr) (peaks given in brackets are for normal benzaldehyde phenylhydrazone): 3288 [3292] [w], 1588 (s), 1562 (m), 1509 [1516], 1488 (s), 1442 (m), 1356 (m), 1312 (m), 1298 (m), 1285 (m), 1255 (s), 1162 (w), 1122 [1132] (s), 1063 (s), 1025 (w), 926 (s), 900 (907) (w), 880 (m), 750 (s), 640 (s) cm.$^{-1}$.

Reaction of Benzaldehyde Phenylhydrazone with Carbon Monoxide to Yield N-Phenylphthalimidine. Procedure A (at 230–240°). Carbonylation of Normal Benzaldehyde Phenylhydrazone.—Benzaldehyde phenylhydrazone (8 g.) was carbonylated at 230–240° and at 3540 p.s.i. for 2.2 hr. as described previously.[3] The recorded pressure drop at 20° was 90 p.s.i. After the reaction mixture was filtered to remove the blue-black organocobalt complex (1.0 g.), the catalyst was destroyed by heating at 70°. The solution was again filtered, evaporated to dryness under vacuum, and the residue recrystallized twice from ethanol; yield, 4.2 g. (50%); m.p. 166.5–167.5°. Chromatography of this substance on alumina using benzene–chloroform (1:1) as developer showed one zone. The mixture melting point of the product with an authentic sample of N-phenylphthalimidine[5] was 166–167°.

(10) I. Wender, private communication.

(11) H. W. Sternberg, I. Wender, R. A. Friedel, and M. Orchin, *J. Am. Chem. Soc.*, **75**, 3148 (1953).

(12) W. Reppe, *Ann.*, **582**, 1 (1953).

(13) G. Natta, P. Pino, and R. Ercoli, *J. Am. Chem. Soc.*, **74**, 4496 (1952).

(14) C. F. H. Allen and C. V. Wilson, *ibid.*, **65**, 611 (1943).

(15) A. Rosenthal, R. F. Astbury, and A. Hubscher, *J. Org. Chem.*, **23**, 1037 (1958).

(16) Products of Merck Sharp and Dohme of Canada Limited, Montreal, Canada. The labeled phenylhydrazine contained at least 95% of N^{15}.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.37; H, 5.30; N, 6.70; O, 7.64; mol. wt., 209. Found: C, 80.15; H, 5.44; N, 6.69; O, 7.79; mol. wt. (Rast), 210.

Infrared spectrum of N-phenylphthalimidine in KBr ($cm.^{-1}$): 3030 (w), 1680 (s), 1590 (m), 1495 (s), 1468 (m), 1455 (w), 1439 (s), 1390 (s), 1327 (s), 1305 (s), 1264 (m), 1221 (m), 1200 (w), 1184 (w), 1149 (s), 1090 (m), 1061 (w), 945 (w), 894 (m), 877 (w), 751 (s), 732 (s), 681 (s) (s = strong; m = medium; w = weak).

Anal. of organocobalt complex. Found: C, 31.56; H, 4.13; N, 6.59.

The organocobalt complex was insoluble in ethanol and acetone. Treatment of the complex with hot concentrated sodium hydroxide yielded aniline (isolated and characterized as 2,4,6-tribromoaniline, m.p. 129–130°).

Since less than 1 g. of benzaldehyde 1-phenylhydrazone-1-N^{15} was available for carbonylation, it was decided to carry out an experiment on a like quantity of the normal phenylhydrazone using the same 300-ml. reaction vessel and to separate the products by chromatography. It was believed that the trace of moisture present in the carbon monoxide (the molar concentration remained essentially constant in all experiments) might have a greater hydrolytic effect on a 1-g. than on an 8-g. quantity of benzaldehyde phenylhydrazone.

An amount of 2 g. of the product obtained from the carbonylation of 2 g. of benzaldehyde phenylhydrazone was placed on a column of Florisil[17] and chromatographed with the following results. (i) Benzene eluted 0.35 g. of oil which contained benzaldehyde and benzonitrile (the former was isolated as the 2,4-dinitrophenylhydrazone derivative). A trace of an unstable red oil (no carbonyl) accompanied the first zone. (ii) N-Phenylphthalimidine (0.86 g., 42% yield) was eluted with benzene. (iii) Benzene–chloroform (4:1) eluted 0.05 g. of N,N′-diphenylurea which was recrystallized from chloroform; m.p. 251–252°; m.m.p. 251–252° with an authentic sample. (iv) Benzene–ethanol (9:1) eluted 0.2 g. of an oil (which contained no cyclic carbonyl group as evidenced by the fact that the material did not absorb in the region 1630 to 1750 $cm.^{-1}$).

Carbonylation of Benzaldehyde 1-Phenylhydrazone-1-N^{15} (1-Benzylidene-2-phenylhydrazine-2-N^{15}).—An amount of 0.80 g. of benzaldehyde 1-phenylhydrazone-1-N^{15} was carbonylated at 230–240° as described previously. The organocobalt complex (0.02 g.) was removed by filtration.

Anal. Found: N, 7.12.

The filtrate was then chromatographed as described in the preceding section with the following results. (i) Petroleum ether (b.p. 65–80°) eluted the catalyst. (ii) Benzene eluted a red zone which gave 0.32 g. of sirup. Rechromatography of this red material on alumina yielded 0.11 g. of benzaldehyde which was characterized as benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 239°, m.m.p. with an authentic sample of benzaldehyde 2,4-dinitrophenylhydrazone was 239–240°, the infrared spectra of both substances were identical. Benzonitrile (0.09 g.) was also isolated and characterized by comparison of its infrared spectrum with that of an authentic sample. The red oil, which was present in trace amount, contained no carbonyl group and was not characterized. (iii) After elution of the red zone, N-phenylphthalimidine-N^{15} was eluted with benzene and recrystallized from ethanol; yield, 0.20 g.; m.p. 166–167°; normal and labeled N-phenylphthalimidine had m.m.p. 166–168°; infrared (KBr) of labeled N-phenylphthalimidine was 1380 (s), 1325 (s), 1260 (m), 1135 (s), 1055 (w), 873 (w) $cm.^{-1}$. The remaining peaks of the normal and labeled N-phenylphthalimidine were identical. Analysis of N-phenylphthalimidine-N^{15} by mass spectrometric means showed 97.5% (± 1%) of N^{15} content. (iv) Further elution of the column with benzene–chloroform (4:1 v./v.) yielded 0.026 g. of a solid substance which on recrystallization from chloroform afforded N,N′-diphenylurea. (v) Benzene–ethanol (9:1 v./v.) gave 0.033 g. of an oil. As infrared analysis showed the absence of a cyclic carbonyl group, the material was not characterized.

Procedure B (at 200°.)—Benzaldehyde phenylhydrazone (8 g.) reacted with carbon monoxide at 200° to yield an organocobalt complex (2 g.), N-phenylphthalimidine (5% yield), and a yellow crystalline compound which crystallized from the original benzene solution (3%), m.p. 187–187.5°.

Anal. Calcd. for C_7H_6N: C, 80.76; H, 5.76; N, 13.46. Found: C, 80.49; H, 5.61; N, 13.59.

Infrared (KBr): 1595 (w), 1512 (s), 1492 (s), 1477 (s), 1455 (s), 1300 (m), 1262 (w), 1230 (w), 1185 (w), 1150 (s) $cm.^{-1}$. Ultraviolet: 4000 $cm.^{-1}$.

Anal. (of organocobalt complex). Found: C, 31.56; H, 4.13; N, 6.59.

Treatment of the complex with sodium hydroxide liberated ammonia and aniline (characterized as 2,4,6-tribromoaniline).

Infrared (KBr) of the complex: 3040 (w), 2920 (w), 2290 (w), 1712 (m), 1685 (w), 1600 (s), 1495 (s), 1400 (s), 1350 (m), 1185 (s) $cm.^{-1}$.

Carbonylation of Benzaldehyde *m*-Tolylhydrazone to Yield N-*m*-Tolylphthalimidine.—Benzaldehyde *m*-tolylhydrazone (8 g.) was carbonylated at 230° and the crude product recrystallized several times from ethanol; yield, 1.7 g.; m.p. 147–149°; m.m.p. 147–149° with an authentic sample of N-*m*-tolylphthalimidine. The infrared spectra of both substances were identical.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.70; H, 5.84, N, 6.28. Found: C, 80.52; H, 5.89; N, 6.42.

Infrared (KBr): 3080 (w), 2920 (w), 1685 (s), 1600 (s), 1495 (s), 1465 (m), 1448 (s), 1390 (s), 1338 (w), 1300 (s), 1222 (m), 1200 (s), 1182 (w), 1158 (s), 1105 (w), 1092 (m), 1075 (m) $cm.^{-1}$.

Synthesis of N-*m*-Tolylphthalimidine. A. N-*m*-Tolylphthalimide.—N-*m*-Tolylphthalimide was prepared according to a modification of the method used by Graebe.[5] A mixture of 3.2 g. (0.033 mole) of freshly distilled *m*-toluidine and 7.4 g. (0.050 mole) of phthalic anhydride in 60 ml. of acetic acid was heated at reflux for 1 hr. The solution was then poured into 450 ml. of water, boiled, and allowed to stand overnight. The resulting solid was filtered and air-dried, giving 7.3 g. of white powder which on crystallization from 95% ethanol had m.p. 175–178°.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.90; H, 4.64; N, 5.91. Found: C, 75.74; H, 4.65; N, 5.86.

B. **N-*m*-Tolylphthalimidine.**—N-*m*-Tolylphthalimide (4 g.) dissolved in ethanol was treated with 4.4 g. of granulated tin. The mixture was warmed on a water bath, and concentrated hydrochloric acid added gradually during the warming till all the tin had dissolved. The white solid, which precipitated on cooling overnight, was filtered, washed, and dried. On crystallization from 95% ethanol, it had m.p. 150–151°.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.70; H, 5.84; N, 6.28. Found: C, 80.61; H, 5.72; N, 6.28.

3-Methylphthalimidine-N-carboxyanilide and 3-Methyl-N-phenylphthalimidine from Acetophenone Phenylhydrazone.—Acetophenone phenylhydrazone (8 g.) was cyclized with carbon monoxide at 230° for 2.5 hr.

Chromatography of 2.9 g. of the crude product (first freed of catalyst) on alumina, using benzene as a developer, yielded 3-phenylphthalimidine-N-carboxyanilide, 0.9 g., which was recrystallized from ethanol, m.p. 97–99°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.25; H, 5.26; N, 10.52. Found: C, 71.98; H, 5.19; N, 10.48.

Infrared (KBr): 3205 (w), 1715 (s), 1685 (m), 1595 (s), 1505 (w), 1490 (w), 1470 (w), 1450 (m), 1355 (s) $cm.^{-1}$.

Further elution of the column with benzene–chloroform (9:1) afforded 3-methyl-N-phenylphthalimidine; yield, 0.52 g.; m.p. 76–78° (from ethanol).

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.70; H, 5.84; N, 6.28. Found: C, 80.76; H, 5.86; N, 6.05.

Infrared (KBr): 1685 (s), 1595 (s), 1500 (w), 1470 (w), 1455 (m), 1365 (m) $cm.^{-1}$.

Reaction of 1-Naphthaldehyde Phenylhydrazone with Carbon Monoxide to Yield 2-Phenylbenz[*e*]isoindolin-1-one, 1-Naphthonitrile, and Aniline.—Similarly, 1-naphthaldehyde phenylhydrazone (7 g.) was treated with carbon monoxide at 230–235° for 2.5 hr.

After removing the solid organocobalt complex (1.0 g.) from the reaction mixture, the filtrate was added to a column of Florisil. The catalyst was eluted using petroleum ether as developer. Organic material (6.7 g.) was then eluted with benzene–absolute ethanol (9:1). A 3.1-g. portion of the residue was chromatographed on B.D.H. Alumina (80 × 72 mm. diameter) column using benzene–absolute ethanol (99.4:0.6 v./v.) as developer. Four fractions, two of which fluoresced, were collected.

Fraction A (0.6 g.) was separated by vapor phase chromatography to yield aniline and 1-naphthonitrile, m.p. 31–33°. The latter compound was hydrolyzed with ethanolic potassium hydroxide according to the method of Rule and Barnett[18] to give 1-

(17) Product of Floridin Company, Tallahassee, Fla.

(18) H. G. Rule and A. J. G. Barnett, *J. Chem. Soc.*, **177** (1932).

naphthoic acid, m.p. 161°, m.m.p. 160–161° with an authentic sample. The infrared spectra of both compounds were identical.

Fraction B, which appeared as a brown zone (0.56 g.), was rechromatographed on alumina using benzene–chloroform (6:1 v./v.) as developer. Most of fraction B fluoresced and was identical to fraction C. The slow moving fraction called B (recrystallized from ethanol to yield 0.030 g., m.p. 225–226°) is possibly the N-carboxyanilide derivative of 2-phenylbenz[*e*] isoindolin-1-one.

Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.52; H, 4.64; N, 9.28. Found: C, 75.77; H, 5.14; N, 8.87.

Infrared spectrum of substance B (KBr): 3200 (w), 3030 (w), 2900 (w), 1700 (s), 1680 (m), 1645 (w), 1590 (s), 1548 (s), 1500 (m), 1447 (s), 1395 (w), 1359 (s), 1310 (w), 1275 (m), 1237 (s), 1178 (w), 1156 (m) cm.$^{-1}$.

Fraction C (0.33 g.) was rechromatographed on alumina according to the same procedure used for fraction B, yield 0.30 g. Recrystallization from ethanol gave pure material, m.p. 177°. The literature melting point of 2-phenylbenz[*e*]isoindolin-1-one[19] is 177°.

Anal. Calcd. for $C_{18}H_{13}NO$: C, 83.20; H, 5.02; N, 5.40. Found: C, 82.89; H, 5.32; N, 5.66.

Infrared spectrum of 2-phenylbenz[*e*] isoindolin-1-one in KBr: 3030 (w), 2900 (w), 1682 (s), 1643 (w), 1593 (m), 1550 (m), 1500 (m), 1444 (m), 1375 (s), 1294 (w), 1273 (w), 1245 (w), 1148 (m) cm.$^{-1}$.

Crossed Carbonylation Experiment of 1-Naphthaldehyde Phenylhydrazone and Benzaldehyde *m*-Tolylhydrazone to Yield 2-Phenylbenz[*e*]isoindolin-1-one and N-*m*-Tolylphthalimidine.—A mixture of 1-naphthaldehyde phenylhydrazone (0.32 g., 0.0013 mole) and benzaldehyde *m*-tolylphenylhydrazone (0.27 g., 0.0013 mole) was carbonylated as described previously in the Experimental section.

The product consisted of an organocobalt complex (0.066 g.) and a mixture of products which were separated by chromatography as described previously.

Benzaldehyde (0.032 g.), benzonitrile (about 0.020 g.), and 1-naphthonitrile were obtained from the first fraction. The second fraction was rechromatographed on alumina using benzene–petroleum ether (b.p. 30–65°) (6:1 v./v.) as developer. The product, 0.24 g., was recrystallized from ethanol, m.p. 177°, m.m.p. 177° with a sample of 2-phenylbenz[*e*]isoindolin-1-one prepared as described in the Experimental. The infrared spectra of both substances were identical.

The third fraction (0.14 g.), rechromatographed on alumina using benzene–chloroform (1:1 v./v.) as developer, was recrystallized from ethanol, m.p. 148–149°, m.m.p. 148–149° with an authentic sample of N-*m*-tolylphthalimidine. The infrared spectra of both compounds were identical.

(19) S. Murahashi, S. Horiie, and T. Jō, *Bull. Chem. Soc. Japan*, **33**, 81 (1959).

Acknowledgment.—Grateful acknowledgment is made to the National Research Council of Canada for financial support of this work.

This research also was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of this fund.

The authors also wish to express their gratitude to Dr. P. Kebarle of the University of Alberta, Edmonton, Canada, for the mass spectrometric analysis.

Aldehyde Hemihydrates

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Received May 23, 1963

A reinvestigation of the dry codistillation of barium *n*-dodecanoate and barium formate has shown that Krafft's *n*-dodecanal, which was first reported in 1880, is *n*-dodecanal hemihydrate. *n*-Dodecanal, *n*-decanal, and *n*-heptanal on treatment with water form isolable hemihydrates in which the carbonyl groups and water are chemically combined. Hemihydrate formation appears to be a general reaction for normal aliphatic aldehydes. The experimental evidence indicates that the structures of the addition products are α,α'-dihydroxy ether derivatives.

In 1880, Krafft reported the synthesis of *n*-dodecanal and other higher aldehydes by the dry codistillation of the barium salts of the corresponding acids and barium formate.[2] The C_{12} aldehyde was characterized as a solid, melting at 44.5°. Subsequent investigators, however, characterized *n*-dodecanal, obtained by numerous synthetic methods[3–8] and from natural products,[9,10] as a high boiling liquid with a melting point of about 11°.

Krafft's *n*-dodecanal has been the subject of periodic conjecture since its isolation. The product has been postulated to be *n*-dodecanal polymer,[11,12] a hydrogen bonded complex of *n*-dodecanal and *n*-dodecanol,[7] the hemiacetal of *n*-dodecanal and *n*-dodecanol,[13] and *n*-dodecanal enol.[5] The polymeric structure does not appear to be the correct structure of Krafft's *n*-dodecanal because polymers of *n*-dodecanal have been prepared, and they have properties inconsistent with the properties of Krafft's material.[8,12] The hydrogen bonded structure and the hemiacetal are not satisfactory because Krafft's *n*-dodecanal has been prepared from liquid *n*-dodecanal purified through the bisulfite addition product[5] and the semicarbazone derivative,[10] thereby precluding the presence of *n*-dodecanol. The enolic structure postulated by Zaar[5] seemed to be the correct structure even though enols of simple aldehydes generally cannot be isolated.[14] This investigation was undertaken to confirm the enolic structure of Krafft's *n*-dodecanal.

(1) To whom requests for reprints should be sent in care of The Pure Oil Company, Research Center, Crystal Lake, Ill.

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(9) E. S. Guenther and E. E. Langenau, *J. Am. Chem. Soc.*, **65**, 959 (1943).

(10) Yves. R. Naves. *Perfumery Essent. Oil Record*, **38**, 295 (1947).

(11) H. R. LeSueur, *J. Chem. Soc.*, **87**, 1888 (1905).

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(13) J. L. E. Erickson and C. R. Campbell, Jr., *J. Am. Chem. Soc.*, **76**, 4472 (1954).

(14) *Cf.* P. H. Hermans, "Theoretical Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1954, Chap. XII.

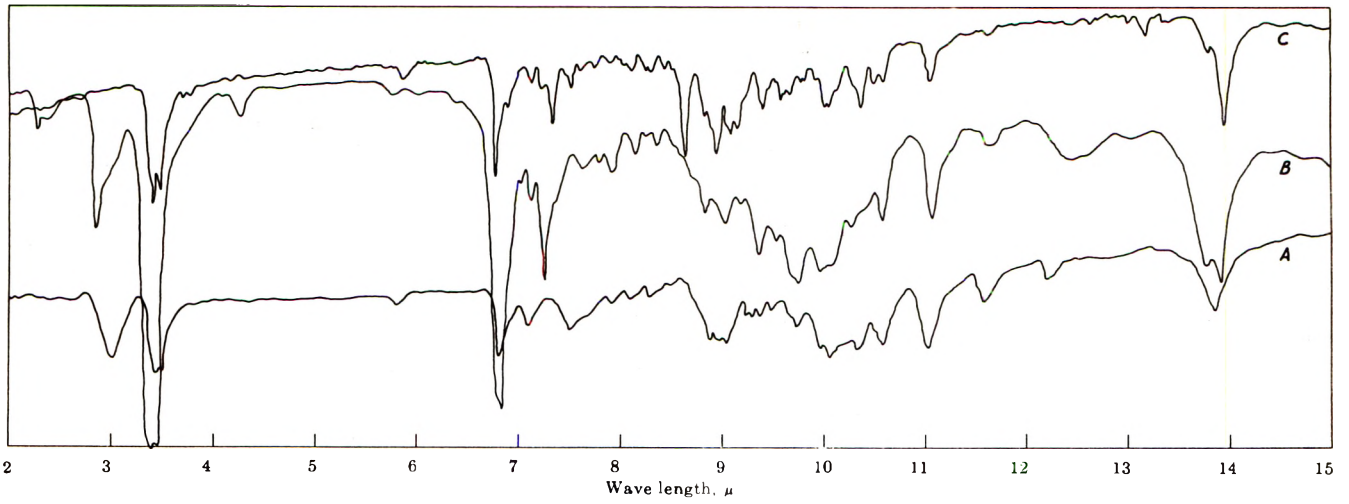


Fig. 1.—Infrared spectra of Krafft's *n*-dodecanal and *n*-dodecanal hemihydrate, solid (A); *n*-dodecanal-*n*-dodecanol hemiacetal, Nujol mull (B); and *n*-dodecanal trimer, Nujol mull (C).

Discussion

Krafft's procedure[2] was repeated to isolate his *n*-dodecanal for characterization by infrared analysis. Several experiments were carried out, but in each case, by-products were formed along with the desired product. Liquid *n*-dodecanal, *n*-dodecanal–*n*-dodecanol hemiacetal, and *n*-dodecanol were isolated by fractional distillation of the product mixture obtained from the dry co-distillation of barium *n*-dodecanoate and barium formate. A white, crystalline, odorless solid was isolated in low yields from the initial fractions and was characterized as Krafft's *n*-dodecanal by melting point and other properties. When the product was melted, decomposition occurred to yield liquid *n*-dodecanal. A direct comparison of the infrared spectra, shown in Fig. 1, of the solid product and the hemiacetal established the nonidentity of the compounds. These facts are in agreement with Zaar's earlier observations that Krafft's *n*-dodecanal affords liquid *n*-dodecanal on distillation, that the same carbonyl derivatives are formed from both products, and that Krafft's *n*-dodecanal and the hemiacetal are different.[4,5] The nonidentity of the solid and *n*-dodecanal trimer also was established in this work by direct comparison of the infrared spectra shown in Fig. 1.

Since several chemical reactions occurred when the mixture of the barium salts of *n*-dodecanoic and formic acids was thermally decomposed, attempts were made to develop a better preparative procedure to facilitate further characterization. Commercial stocks of liquid *n*-dodecanal purified through the bisulfite addition product and maintained under an inert atmosphere at a temperature slightly above the melting point of the aldehyde gave Krafft's *n*-dodecanal in low yields. Samples of liquid *n*-dodecanal that had been purified through the bisulfite addition product and also fractionally distilled formed the crystalline solid very slowly and in low yields on prolonged storage. Attempts to recrystallize the solid from most solvents resulted in decomposition to liquid aldehyde. On storage at room temperature, Krafft's *n*-dodecanal gradually reverted to liquid aldehyde as shown by infrared analysis and odor. Storage at lower temperatures reduced the rate of decomposition.

The properties of Krafft's *n*-dodecanal and the spectral evidence supported the enolic structure. The compound exhibits hydroxyl group absorption, and it has no carbonyl absorption as shown in Fig. 1. The absence of carbonyl absorption also tended to rule out the hydrogen bonded complex as a possible structure. However, additional evidence indicated that the enol could also be eliminated as a possible structure. Krafft's product did not give positive results in tests which are usually characteristic of enols, and it was found that liquid *n*-dodecanal from which Krafft's product had been removed did not form additional solid on storage. This latter observation was unexpected because the keto–enol equilibrium should of course be maintained.

The composition of Krafft's *n*-dodecanal was ultimately established as *n*-dodecanal hemihydrate by careful elemental analysis. Confirmatory evidence was obtained by the Karl Fischer and Zerewitinoff determinations, and by treatment of *n*-dodecanal, which had previously been separated from the hemihydrate, with trace amounts of water; the hemihydrate formed again on cool storage of the aldehyde. Conclusive evidence was obtained by treatment of liquid *n*-dodecanal with stoichiometric amounts of water; *n*-dodecanal hemihydrate identical with Krafft's *n*-dodecanal formed quantitatively. Pure anhydrous liquid *n*-dodecanal which cannot form the hemihydrate is thus difficult to prepare by the dry codistillation of the mixture of salts, by fractional distillation of the liquid aldehyde, or by use of conventional drying agents. The hemihydrate separates when samples of the liquid aldehyde containing trace amounts of water are stored.

To our knowledge, this investigation is the first characterization of a hemihydrate of a simple carbonyl compound, and it became of interest to examine the behavior of other aldehydes. It was found that both *n*-decanal and *n*-heptanal afford isolable hemihydrates. The infrared spectra of *n*-decanal hemihydrate and pure *n*-decanal reproduced in Fig. 2 show that the hemihydrate gradually decomposes to *n*-decanal in the infrared beam. The hemihydrate of *n*-heptanal was too unstable under ambient conditions to obtain the spectra in the usual manner. No further work was done with other aldehydes, but it seems probable that

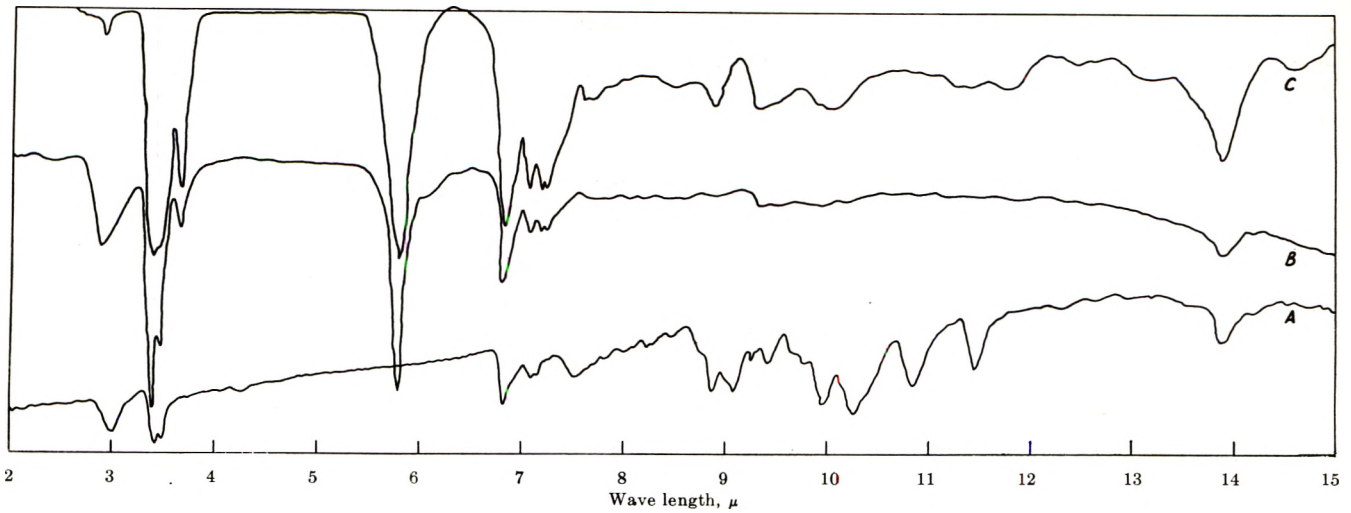


Fig. 2.—Infrared spectra of *n*-decanal hemihydrate, solid (A); *n*-decanal hemihydrate after 30 min. in infrared beam (B); and *n*-decanal, liquid (C).

hemihydrate formation is general for normal aliphatic aldehydes.

A few hydrates of simple aldehydes have been reported by other workers. In 1845, Bussy isolated a hydrate of *n*-heptanal,[15,16] and Noorduyn was later able to prepare a monohydrate and a dihydrate of the same aldehyde.[17] Colles reported several hydrates of acetaldehyde but the products were characterized only by analysis for acetaldehyde.[18] It is probable that one of Colles' hydrates which formed at −95° from a 2:1 molar mixture of acetaldehyde and water is acetaldehyde hemihydrate. Attempts were made in this investigation to prepare monohydrates by treatment of the aldehydes with equimolar quantities of water in both homogeneous and heterogeneous systems, but in each case, only the hemihydrate could be isolated. The melting points of each product prepared in this work are shown in Table I.

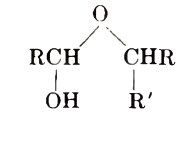
TABLE I

MELTING POINTS[a]

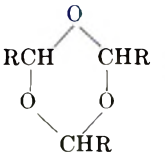
	n-Heptanal	*n*-Decanal	*n*-Dodecanal
Free aldehyde	−43.2 to −42.2	−5 to −3.2	11–12.5
Hemihydrate[b]	54–59 dec.[c]	58.5–63 dec.[c]	56–60 dec.[c]
		41–42 dec.	41–44 dec.
Hemiacetal	Not prepared	Not prepared	46–48
Trimer	Not prepared	Not prepared	55–57

[a] Unless stated otherwise, melting points were taken at atmospheric pressure and are reported without stem corrections. [b] Heating rate of 2°/min. [c] Evacuated capillary tubes.

The structures of the hemihydrates have not been rigorously established in this investigation, but it is probable that they are α,α'-dihydroxy ethers as shown in structure I. Compounds of structure I could form by simple addition of one molecule of the aldehyde monohydrate to the carbonyl group of another molecule of free aldehyde. Apparently, the equilibria are shifted to the hemihydrate, and its solubility characteristics



I, R = Alkyl
R′ = Hydroxyl
Ia, R = *n*-Undecyl
R′ = Hydroxyl
II, R = *n*-Undecyl
R′ = Hydrogen



III, R = *n*-Undecyl

and relatively high stability result in isolation of the hemihydrate and not the monohydrate. Some evidence in support of structure I has been collected during this work. The infrared data indicate that carbonyl groups are absent in the hemihydrates because carbonyl absorption[19a] is absent as shown in Fig. 1 and 2. It is possible that carbonyl absorption is obliterated in the spectra of the hemihydrates by strong hydrogen bonding of water of crystallization with the carbonyl groups. We consider this possibility to be unlikely however because infrared spectra of solutions of the hemihydrates in various solvents exhibit increasingly greater carbonyl group absorption with time, without the simultaneous appearance of the 6.0–6.2-μ peak characteristic of molecular water[19b] (see next paragraph). The absence of the 6.0–6.2-μ peak in the spectra of the pure hemihydrates is also partial support for structure I. Other tentative conclusions can be reached by comparing the spectrum of *n*-dodecanal hemihydrate (Ia) with spectra of *n*-dodecanal-*n*-dodecanol hemiacetal (II) and *n*-dodecanal trimer (III) shown in Fig. 1. The hemiacetal (Nujol mull) has a sharp peak at 2.85 μ which corresponds to an unassociated hydroxyl group while the hemihydrate (solid) has a broad band at 3.0 μ. This latter peak may be caused by associated hydroxyl groups, although the difference in the physical states of Ia and II during measurement of the spectra could result in frequency shifts of the hydroxyl absorption bands.[20] The hydroxyl groups of structure I would be expected to absorb at longer wave lengths because the positions of these groups favor intramolecular associa-

(15) M. Bussy, *J. Pharm. Chim.*, **8**, 321 (1845).

(16) In 1845, water was considered to be HO, and the atomic weights of C, H, and O were 6, 1, and 8, respectively. By modern atomic weights, the formula calculable from Bussy's analysis for *n*-heptanal is $C_7H_{14}O$, the correct empirical formula. Bussy's hydrate would then correspond to the hemihydrate.

(17) A. C. Noorduyn, *Rec. trav. chim.*, **38**, 344 (1919).

(18) W. M. Colles, Jr., *J. Chem. Soc.*, **89**, 1246 (1906).

(19) *Cf.* (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, Chap. 9; (b) H. M. Randall, *et al.*, "Infrared Determination of Organic Structures," D. Van Nostrand Company, Inc., New York, N. Y., 1949.

(20) See ref. 19a, Chap. 6.

tion.[21] Attempts to confirm experimentally the presence of two hydroxyl groups in the hemihydrates by the Zerewitinoff determination failed, presumably because the compounds decomposed in the solvent. The liberated water resulted in the detection of only one active hydrogen atom per mole of hemihydrate.[22] Dietherification with diazomethane also failed. Further examination of the spectra in Fig. 1 suggests the presence of ethereal oxygen atoms because of absorption in the 9-μ region. Absorption in this region arising from the C–O– stretching vibrations is characteristic of ethers.[19] The remainder of the "fingerprint" region is a complex series of bands which are similar in many respects. The peaks which occur at 10.6 μ and slightly greater than 11 μ appear to be characteristic of the ethereal oxygen atoms in structures Ia, II, and III.

Two inconsistencies remain. Zaar determined the molecular weight of Krafft's *n*-dodecanal in benzene by the freezing point technique, and he found that the molecular weight was about the same as that of *n*-dodecanal.[5] The origin of the water required to form *n*-dodecanal hemihydrate by Krafft's process also requires explanation. If Krafft's *n*-dodecanal decomposed in benzene to afford *n*-dodecanal and *n*-dodecanal monohydrate, the molecular weight determination would be very close to the molecular weight of *n*-dodecanal. Experimental evidence to support this hypothesis was obtained by infrared examination of benzene solutions of the hemihydrate. The hemihydrate was found to decompose in benzene solutions to yield *n*-dodecanal as shown by the appearance of the carbonyl peak immediately after solution occurred. Molecular water as measured by the 6.0–6.2-μ peak appeared only slowly in benzene solution. The pure hemihydrates also appear to decompose in a similar manner as illustrated by curves A and B in Fig. 2.

The formation of the necessary water during the dry co-distillation of the barium salts is difficult to explain because the salts were thoroughly dried before use. In later experiments, after Krafft's *n*-dodecanal had been characterized as the hemihydrate, it was established that water is evolved during the dry distillation when the temperature of the salt mixture is considerably above the boiling point of water. Water is apparently formed from the salts themselves during the high temperature decomposition. Krafft and Zaar probably did not observe product water because it combined with the aldehyde or because only small amounts of water were produced. Relatively small amounts of water are required to convert quantitatively the higher aldehydes to the hemihydrates.

Additional work is in progress on the mechanism of formation and decomposition of aldehyde hemihydrates.

Experimental[23]

Preparation of Acid Salts.—A solution of 100.2 g. *n*-dodecanoic acid, (0.50 mole), and 20.4 g. (0.51 mole) of sodium hydroxide in 1.1 l. of water was treated with 63.5 g. (0.26 mole) of barium chloride dihydrate in 150 ml. of hot water. The mixture was stirred vigorously during the addition and then cooled to 5°. Filtration, successive washing with water, Formula 30 alcohol (90.9 vol. % ethanol, 9.1 vol. % methanol), and ether, and drying at 60° (0.1 mm.) for 16 hr. gave barium *n*-dodecanoate.

Anal. Calcd. for $(C_{12}H_{23}O_2)_2Ba$ (535.97): Ba, 25.63. Found: Ba, 25.30.

A solution of 138.9 g. (3.02 moles) of formic acid, and 120.6 g. (3.01 moles) of sodium hydroxide in 500 ml. of water was treated with 366.5 g. (1.50 moles) of barium chloride dihydrate in 700 ml. of hot water. Formula 30 alcohol (4 l.) was then added with agitation to the cooled solution. Filtration, washing with Formula 30 alcohol, and drying at 105° for 5 days gave barium formate.

Anal. Calcd. for $(CHO_2)_2Ba$ (227.40): Ba, 60.44. Found: Ba, 59.60.

Similar procedures were used to prepare the calcium salts.

Krafft's *n*-Dodecanal.—Krafft's procedure was followed. A mixture of 75.0 g. of barium formate, 50.0 g. of barium *n*-dodecanoate, and 15.2 g. of barium carbonate (C.P. Baker's Analyzed) was thoroughly dispersed with a mortar and pestle. The mixture, 138 g., in a 500-ml. round-bottom flask equipped with a heating mantle, thermometer, and condensing apparatus was heated over 5.5 hr. (20 mm.). Distillation commenced when the pot temperature was about 248°. Slow distillation over a 2.5-hr. period at pot temperatures from 248 to 289° gave 14.0 g. of light yellow distillate which solidified to a semisolid mass in the cooled receiver. The product was fractionally distilled at 0.37 mm., and the distillation data are summarized in Table II.

TABLE II

Fraction	B.p., °C.	Wt., g.
1	60–62°	0.8
2	60–62°	2.0
3	60–75°	1.2
Trap	...	0.8
Not Distilled	...	8.9

Fraction 1 gave about 0.4 g. of a white crystalline, odorless solid after standing at 14° for a few hours. The product was collected by filtration, washed with cold anhydrous ether, and dried in the funnel. The product was characterized as Krafft's *n*-dodecanal by melting point, its reversion to liquid *n*-dodecanal on melting, and by infrared analysis.

After Krafft's *n*-dodecanal had been identified as *n*-dodecanal hemihydrate by comparison with hemihydrate prepared from liquid *n*-dodecanal, water was identified as a product of the dry distillation by infrared analysis and the anhydrous copper sulfate test. Water was found to distil from the reaction mixture at pot temperatures between 115 and 160° over the pressure range, 2–20 mm. Significant quantities of water, about 0.5–1.0 wt. % of the total salt mixture, were liberated from carefully dried salts; so water is probably a product of the reaction. Most of the water can be separated from the initial fractions of liquid *n*-dodecanal by use of reduced pressure and a cold trap.

Other experiments were carried out using modifications of this technique. Calcium salts and the barium and calcium salts together were also tried. In all experiments, liquid *n*-dodecanal, *n*-dodecanol, *n*-dodecanal-*n*-dodecanol hemiacetal, and water were isolated and identified by infrared analysis. In several experiments, it was difficult to obtain *n*-dodecanal hemihydrate uncontaminated with the hemiacetal by-product unless the aldehyde was further purified. Other products also formed during the dry distillation but they were not identified. An example of the fractional distillation at 0.11 mm. of 4.1 g. of product obtained from the dry distillation of 69.9 g. of barium formate, 27.1 g. of calcium *n*-dodecanoate, and 5.2 g. of calcium carbonate is shown in Table III.

Purification of Aldehydes.—*n*-Decanal[24] and *n*-dodecanal[25] were obtained from commercial stocks and converted to the bisulfite addition products which were stored under nitrogen in a desiccator. As needed, each aldehyde was recovered by steam distillation of the addition product from aqueous solutions of sodium bicarbonate, and the recovered aldehyde was fractionated,

(21) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

(22) D. L. Klass and W. N. Jensen, *J. Org. Chem.*, **26**, 2110 (1961).

(23) Elemental analyses were performed by the Analytical Research and Services Division of The Pure Oil Company, Crystal Lake, Ill., and Micro-Tech Laboratories, Skokie, Ill. Karl Fischer analyses were performed by Colburn Laboratories, Chicago, Ill., and by Prof. K. A. Connors of the School of Pharmacy, University of Wisconsin. All melting points are uncorrected.

(24) Aldrich Chemical Company, Inc., Milwaukee, Wis.

(25) Kindly supplied by the Research Division, Armour and Company, Chicago, Ill.

Table III

Fraction	B.p., °C.	Wt., g.	Product
1	62–65	0.52	*n*-Dodecanal
2	62–65	0.68	*n*-Dodecanal
3	57–65	0.48	Impure *n*-dodecanal
4	65–67	0.78	*n*-Dodecanal-*n*-dodecanol hemiacetal
5	65–75	0.11	*n*-Dodecanal-*n*-dodecanol hemiacetal
6	76–86	0.33	Impure *n*-dodecanol
Trap	...	0.84	Impure water
Residue	...	0.28	Not identified

stored under nitrogen, and used within 24 hr. A sample procedure was the following.

n-Decanal, 420 g., was added to a solution of 440 g. of sodium bisulfite in 950 ml. of water. The mixture was agitated overnight on a rolling mill and the addition product was collected by filtration, washed successively with water, alcohol, and ether, and dried. The addition product, 225 g., was added to 2 l. of preboiled water containing 225 g. of sodium bicarbonate, and the resulting mixture was steam-distilled. The distillate was washed with water and dried with sodium sulfate; yield, 65.9 g. Fractionation through a Vigreux column gave a major fraction or pure *n*-decanal; yield, 52.7 g.; b.p. 58–60° (1.5 mm.); $n^{19}D$ 1.4275.

Anal. Calcd. for $C_{10}H_{20}O$ (156.26): C, 76.71; H, 12.87. Found: C, 76.92; H, 12.78.

The oxime derivative was prepared in the usual manner and recrystallized from alcohol and benzene, m.p. 68–69°.

n-Dodecanal purified by this procedure exhibited b.p. 119–120° (10 mm.), $n^{25}D$ 1.4302.

Anal. Calcd. for $C_{12}H_{24}O$ (184.31): C, 78.19; H, 13.13. Found: C, 78.10, 78.00; H, 13.00, 13.03.

The oxime derivative was prepared in the usual manner and recrystallized three times from alcohol, m.p. 77–78°.

n-Heptanal was used as received.[26]

The purity of the aldehydes was determined by titration with hydroxylamine in the usual manner and from plots of the melting "plateaus." Four grams of the aldehyde was placed in a Pyrex test tube of 10-mm. i.d. carrying a calibrated thermometer, and the aldehyde was "quick frozen" to avoid polymerization; the C_{10} and C_{12} aldehydes were solidified at −29°, and *n*-heptanal was solidified at −49°. The tube containing the frozen aldehyde was then enclosed in a larger test tube of 20-mm. i.d. and the apparatus was transferred to a room maintained at a constant temperature, 22° for *n*-dodecanal and 7° for *n*-decanal and *n*-heptanal. The time and temperature variations were measured and plotted in the usual manner. The flatness of the "plateaus" was considered to be the best criterion of purity. The melting points are listed in Table I.

Hydration of *n*-Dodecanal.—The hemihydrate was prepared by treatment of 5.0 g. of *n*-dodecanal with 0.24 g. of water (1:0.5 molar ratio), and the resulting mixture was placed under nitrogen in a refrigerator at 15°. The entire reaction mixture solidified to yield the waxy hemihydrate quantitatively. The odorless, white crystalline product was transferred to a funnel, washed with cold anhydrous ether, and dried in an evacuated desiccator; all of these operations were carried out in a room maintained at 4–5°. The product was insoluble at room temperature in nitrobenzene, cyclohexanol, and diphenyl ether; partially soluble in dioxane, ether, benzene, and cyclohexane; and soluble in pyridine and tetrahydrofuran. An infrared examination of benzene, ether, and tetrahydrofuran solutions of the product showed that the hemihydrate slowly decomposes with the regeneration of *n*-dodecanal. Qualitative tests including the bromine and ferric chloride tests in different solvents were carried out for *n*-dodecanal enol under a variety of conditions and all tests were negative.[27] The hemihydrate was identical with Krafft's *n*-dodecanal. The hemihydrate was stored for about 1 hr. in a Dry Ice–acetone cooling bath before elemental analysis was performed.

Anal. Calcd. for $(C_{12}H_{24}O)_2H_2O$ (386.64): C, 74.55; H, 13.03. Found: C, 74.88; H, 13.01.

Numerous attempts were made to detect two active hydrogen atoms per molecule of *n*-dodecanal hemihydrate by the Zerewitinoff determination using a previously developed technique.[22] One active hydrogen atom was detected in pyridine solvent.

The Karl Fischer determinations for water were carried out with 0.25-g. samples of the product.

Anal. Calcd. for $(C_{12}H_{24}O)_2H_2O$ (386.64): H_2O, 4.66. Found: H_2O, 4.0, 3.9, 3.9.

Attempts were made to isolate *n*-dodecanal monohydrate by conducting a similar experiment with a 1:1 molar mixture of *n*-dodecanal and water. Only the hemihydrate could be isolated.

Anal. Calcd. for $(C_{12}H_{24}O)_2H_2O$ (386.64): C, 74.55; H, 13.03. Found: C, 74.57; H, 12.70.

Attempts also were made to prepare *n*-dodecanal monohydrate in homogeneous aqueous solutions of tetrahydrofuran and pyridine; the hemihydrate was isolated. On numerous occasions, small amounts of the hemihydrate formed on storage of "pure" aldehyde at temperatures slightly above 12°. Removal of the hemihydrate gave filtrates which did not yield additional product on storage until trace amounts of water were added.

n-Dodecanal hemihydrate decomposed slowly on storage under nitrogen at room temperature. Repurification was accomplished by washing the aged samples with chilled anhydrous ether followed by drying in an evacuated desiccator. Recrystallization from ether gave reduced yields of the hemihydrate. Low temperature recrystallization without excessive decomposition may be possible, but this technique was not tried.

Freshly prepared samples of the hemihydrate decomposed when heated in open capillary tubes to slightly turbid liquid aldehyde which appeared to contain minute droplets of suspended water, and the decomposition point varied with the rate of heating. The decomposition points listed in Table I were obtained at a heating rate of about 2°/min.

The instrument used for measurement of the infrared spectra was a Perkin-Elmer Model No. 21 recording spectrophotometer installed in a room maintained at 21°. The spectra of *n*-dodecanal hemihydrate shown in Fig. 1 were obtained by pressing a few crystals of the compound between the sodium chloride plates of the sample holder in a room maintained at 4–5°. The sample holder was then immediately transferred to the spectrophotometer and the spectra were recorded in the usual manner. This technique was found to be the best procedure for recording reproducible spectra of the hemihydrate.

Hydration of *n*-Decanal.—The hemihydrate was prepared by the procedure used for *n*-dodecanal hemihydrate. *n*-Decanal hemihydrate was isolated as odorless, white crystals when the mixture of aldehyde and water was stored at 0°.

Anal Calcd. for $(C_{10}H_{20}O)_2H_2O$ (330.54); C, 72.68; H, 12.81; H_2O, 5.45. Found: C, 72.74, 72.56; H, 13.00, 12.83; H_2O, 5.6, 5.3, 5.8.

Attempts to isolate *n*-decanal monohydrate from equimolar mixtures of water and *n*-decanal afforded only hemihydrate. At room temperature, the hemihydrate was insoluble in *sym*-tetrabromoethane, slightly soluble in ether, and soluble in acetic acid and pyridine. Methylation with diazomethane in ether failed. Small amounts of the hemihydrate deposited on several occasions when supposedly dry *n*-decanal was stored in the refrigerator. Removal of the precipitate gave filtrates which did not form hemihydrate until small amounts of water were added. The decomposition points listed in Table I were measured at a heating rate of about 2°/min. The infrared spectra of the hemihydrate shown in Fig. 2 were obtained by the technique used with *n*-dodecanal hemihydrate.

Hydration of *n*-Heptanal.—*n*-Heptanal hemihydrate was isolated by the procedure used for *n*-dodecanal hemihydrate when the mixture of aldehyde and water was stored at −40°. The white crystalline product was odorless.

Anal. Calcd. for $(C_7H_{14}O)_2H_2O$ (246.38): C, 68.24; H, 12.27; H_2O, 7.31. Found: C, 67.93; H, 12.12; H_2O, 8.0, 8.9, 8.9.

Attempts to prepare *n*-heptanal monohydrate using equimolar mixtures of aldehyde and water gave hemihydrate only. Attempts to obtain the infrared spectra of *n*-heptanal hemihydrate failed because the compound decomposed too rapidly under ambient conditions. The decomposition point shown in Table I was measured at a heating rate of about 2°/min.

***n*-Dodecanol-*n*-dodecanol Hemiacetal.**—The hemiacetal was prepared according to the procedure of Erickson and Campbell.[13] Recrystallization from acetone gave pure hemiacetal, m.p.

(26) Distillation Products Industries, Eastman Organic Chemicals, Rochester, N. Y.

(27) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 93, 98.

46–48°. The infrared spectrum of a Nujol mull of the hemiacetal is reproduced in Fig. 1.

n-Dodecanal Trimer.—Four grams of *n*-dodecanal was placed in a stoppered test tube under nitrogen. The test tube contained a side arm in which 1 drop of concentrated hydrochloric acid was placed to promote the polymerization. The aldehyde was frozen and kept in the refrigerator at 4–5° for 1 month. The product was then transferred to an erlenmeyer flask and 25 ml. of alcohol, 3.1 ml. of 0.5 *N* sodium hydroxide solution, and 40 ml. of 3.0 *N* hydroxylamine hydrochloride reagent were added. The mixture was stored at room temperature for 2 weeks to convert all unchanged aldehyde to the oxime, and the insoluble polymer was then filtered, washed with water, and air-dried; yield, 3.5 g. Recrystallization from alcohol afforded pure *n*-dodecanal trimer, m.p. 55–57° (lit.[8] m.p. 57°). Molecular weight determinations in benzene by the freezing point technique gave values of 526 and 529, calcd. 553. The infrared spectrum of a Nujol mull is reproduced in Fig. 1.

The Addition of Aromatic Nitroso Compounds to Conjugated Dienes

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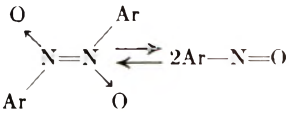
Received May 27, 1963

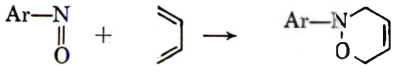
The addition of aromatic nitroso compounds to 2,3-dimethyl-1,3-butadiene was found to be a first-order reaction in respect to the nitroso compound and to the diene. The energies of activation of the reaction betweeen the conjugated diene and nitrosobenzene or *p*-bromonitrosobenzene were found to be, respectively, 14.23 and 12.46 kcal./mole. Nitrosobenzene failed to react with anthracene, but yielded an adduct with 1,3-cyclooctadiene.

Reactions involving the aromatic nitroso group lend themselves well to kinetic studies, since the nitroso group exhibits specific absorption bands in the visible, ultraviolet, and infrared spectra. Complications may arise from the fact that for many aromatic nitroso compounds in solution an equilibrium exists between the monomeric and dimeric forms. This complication may be avoided by the selection of aromatic nitroso



compounds known to be monomeric in solution, *e.g.*, nitrosobenzene, *p*-halonitrosobenzenes, and *p*-nitroso-N,N-dimethylaniline.[1]

The addition of aromatic nitroso compounds to conjugated dienes is commonly considered a Diels–Alder reaction of heteroatomic compounds.[2] The reaction generally proceeds smoothly at moderate temperatures. With few exceptions the sole reaction product has been found to be a substituted 3,6-dihydro-1,2-oxazine.[2–4] Kinetic studies of the addition of aromatic nitroso compounds to conjugated dienes have not been reported thus far.



The dissociation of a 3,6-dihydro-1,2-oxazine into conjugated diene and nitroso compound normally requires considerably higher temperatures than the addition. The formation of an aromatic nitroso compound by the dissociation of the Diels–Alder adduct of various aromatic nitroso compounds and 2,3-dimethyl-1,3-butadiene could not be detected at temperatures below 35°. The rate of this reverse reaction at temperatures below 35° is, therefore, negligible, facilitating the determination of the rate of the addition of aromatic nitroso compounds to 2,3-dimethyl-1,3-butadiene.

Nitrosobenzene when treated with 2,3-dimethyl-1,3-butadiene has been reported to yield small quantities of a side product of unknown structure in addition to the expected N-phenyl-3,6-dihydro-4,5-dimethyl-1,2-oxazine.[5] When a large excess of diene was employed the sole product of the reaction was the oxazine. The side product is believed to be derived from the reaction of nitrosobenzene and the oxazine derivative.[6] For *p*-bromonitrosobenzene, on the other hand, only one product, the expected oxazine, was observed in the addition reaction, employing various concentrations of 2,3-dimethyl-1,3-butadiene.

Results

In order to suppress the formation of a side product, the reaction of nitrosobenzene and 2,3-dimethyl-1,3-butadiene was studied in dichloromethane with a fifty-fold excess of diene. Several Guggenheim plots were constructed at 2° and 25°. The reaction was found to be a first-order reaction in respect to nitrosobenzene, with a specific rate constant at 2° and 25° of 2.84×10^{-4} and 2.10×10^{-3} l. moles^{-1} sec.$^{-1}$. The energy of activation was found to be 14.23 kcal./mole, and the frequency factor, 6.2×10^{6} l. moles^{-1} sec.$^{-1}$.

Nitrosobenzene did not form an adduct with anthracene, even after prolonged reflux in chloroform. An adduct between nitrosobenzene and 1,3-cyclooctadiene was obtained, but the yield was less than 5%, and the reaction was too slow to permit observation.

The reaction between *p*-bromonitrosobenzene and a fiftyfold excess of 2,3-dimethyl-1,3-butadiene also was found to be a first-order reaction (see Fig. 1). It was found to be first order in respect to *p*-bromonitrosobenzene and first order in respect to 2,3-dimethyl-1,3-butadiene when the concentrations of the reactants were of the same magnitude. The specific rate constants were found to be 1.10×10^{-3}, 3.84×10^{-3}, 7.60×10^{-3}, and 8.29×10^{-3} l. moles^{-1} sec.$^{-1}$ at 2,

(1) B. O. Gowenlock and W. Luettke, *Quart. Rev.* (London), **12**, 385 (1958); W. J. Mijs, "Structure and Properties of Some Monomeric and Dimeric Aromatic Nitroso Compounds," dissertation, University of Leyden, 1959.

(2) S. B. Needleman and M. C. Chang Kuo, *Chem. Rev.*, **62**, 407 (1962).

(3) J. Hamer and R. E. Bernard, *Rec. trav. chim.*, **81**, 734 (1962).

(4) J. Hamer and R. E. Bernard, *J. Org. Chem.*, **28**, 1405 (1963).

(5) Yu A. Arbuzov, N. L. Fedyukina, U. V. Shavyrina, and R. I. Shepeleva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 539 (1952); *Chem. Abstr.*, **47**, 4341 (1953).

(6) J. Hamer and A. Macaluso, *Tetrahedron Letters*, No. **6**, 381 (1963).

18, 25, and 30°, respectively. The energy of activation was found to be 12.46 kcal./mole, and the frequency factor, 9.3×10^6 l. moles^{-1} sec.$^{-1}$ (see Fig. 2).

The rate of the reaction between *p*-nitroso-N,N-dimethylaniline and 2,3-dimethyl-1,3-butadiene was too slow to permit observation.

Discussion

The positive value of Hammett's σ-constant for the bromo substituent, together with the higher rate constant and the lower energy of activation for the reaction of *p*-bromonitrosobenzene with 2,3-dimethyl-1,3-butadiene than for the corresponding reaction of nitrosobenzene, indicated that the reaction was accelerated by electron-withdrawing substituents on the phenyl ring.

A tentative ρ-constant may be found from the rate constants at 2 and 25° for the reactions of nitrosobenzene or *p*-bromonitrosobenzene and 2,3-dimethyl-1,3-butadiene. Employing +0.23 as the value of the σ-constant of the *para* bromo substituent, ρ was calculated to be 2.51 ± 0.04.

The sluggishness of the reaction between *p*-nitroso-N,N-dimethylaniline and 2,3-dimethyl-1,3-butadiene is then due to the electron donating effect of the dimethylamino group. The half-time of this reaction should be *ca.* forty-two hours at 25° if 0.1 *M* concentrations of nitroso compound and diene are used, assuming −0.60 as the value of the σ-constant of the *para* dimethylamino group.

It has been reported that *o*- or *p*-substituted nitrosobenzenes react considerably slower with dienes than nitrosobenzene, while the reverse was reported for *m*-substituted nitrosobenzenes.[7] Among the reported substituents were the nitro, methyl, and bromo groups.

Recently, however, we reported that the presence of a nitro group in either the *ortho*, *meta*, or *para* position in nitrosobenzene seemed to accelerate the reaction with dienes considerably.[3,4] It also is known that aliphatic nitroso compounds will undergo a Diels–Alder reaction only if a strong electron-withdrawing substituent is present on the carbon carrying the nitroso group.[2] Our results also indicate clearly that the electronic character of the substituent determines the acceleration or retardation of the addition reaction, and not, as reported by Kojima, the position of the substituent.

Our results fall in the general pattern of Diels–Alder reactions. The more electron-poor dienophiles commonly exhibit higher reactivities in these reactions. The frequency factor and energies of activation reported here are of the same order of magnitude as those reported for some conventional Diels–Alder reactions.[8] In view of this the failure of nitrosobenzene to add to anthracene is rather surprising. Maleic anhydride and other dienophiles add easily to anthracene.[9] The reason for the failure does not seem to lie with an excessively high energy of activation, the instability of the formed adduct, or the frequency factor. An attempted reaction of anthracene with *p*-nitronitrosobenzene also failed.

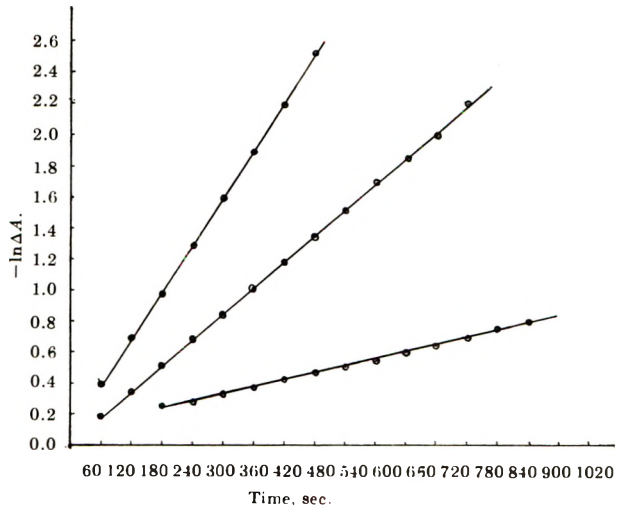


Fig. 1.—Guggenheim plot of the addition of nitrosobenzene or *p*-bromonitrosobenzene to 2,3-dimethyl-1,3-butadiene (fiftyfold excess), in dichloromethane: middle, *p*-bromonitrosobenzene at 2°; lower, nitrosobenzene at 2°; upper, nitrosobenzene at 25°.

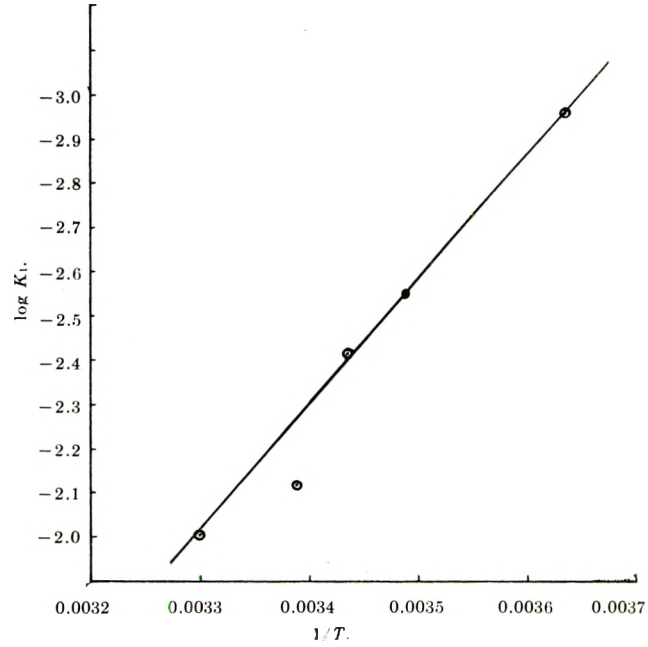


Fig. 2.—Log k *vs.* $1/T$ for the reaction between *p*-bromonitrosobenzene and 2,3-dimethyl-1,3-butadiene.

The Diels–Alder reaction fails with dienes having rings of eight to eleven members.[10] Nitrosobenzene, however, when treated with 1,3-cyclooctadiene at 5° for nearly one month yielded less than 5% of an adduct. The same adduct was obtained in approximately the same yield when nitrosobenzene was treated at room temperature for about five days with 1,3-cyclooctadiene. Attempts in this laboratory to effect a reaction between maleic anhydride and 1,3-cyclooctadiene failed.

Elemental analysis of the adduct of nitrosobenzene and 1,3-cyclooctadiene indicated a compound of the formula $C_{14}H_{17}NO$. The infrared spectrum of the adduct, determined in a potassium bromide pellet, showed the presence of a phenyl ring, and the absence

(7) S. Kojima, *Kogyo Kagak u Zasshi*, **58**, 540 (1958); **59**, 951 (1959) (cited from ref. 2).

(8) A. Wasserman, *J. Chem. Soc.*, 1028 (1936); G. B. Kistiakowsky and J. R. Lacher, *J. Am. Chem. Soc.*, **58**, 123 (1936).

(9) L. J. Andrews and R. M. Keefer, *ibid.* 6294 (1955).

(10) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 542 (1961).

of an NH or OH bond, excluding the possibility of an allylic addition such as that found with azodicarboxylate esters.[11] A weak band was found at 6.10 μ, indicating the presence of an isolated double bond, while the typical —N=O band had disappeared.

Experimental

Reagents.—Nitrosobenzene,[12] m.p. 68°, *p*-bromonitrosobenzene,[13] m.p. 94°, and *p*-nitroso-N,N-dimethylaniline,[14] m.p. 85°, were prepared by known procedures. Anthracene, 2,3-dimethyl-1,3-butadiene, and 1,3-cyclooctadiene were obtained from Columbia Organic Chemicals.

Kinetic Measurements.—The change of concentrations of the nitroso compounds were followed in the visible region (720–730 mμ) with a Beckman DB. Spectrograde dichloromethane was employed as the solvent. Solvent, dienes, and products did not absorb in the visible region. Solutions of the nitroso compounds were found to follow the Lambert–Beer law when the concentrations were between 0.025 and 0.002 mole/l.

In a typical run to obtain Guggenheim plots, the following concentrations were employed: diene, 2.5000 moles/l., and nitroso compound, 0.050 mole/l. Several Guggenheim plots were obtained for the reaction between nitrosobenzene and 2,3-dimethyl-1,3-butadiene at 2° and 25°, and for *p*-bromonitrosobenzene and the same diene at 2° (see Fig. 1).

p-Bromonitrosobenzene was treated with the same diene at 18°, 25°, and 30°, employing the following approximate concentrations: nitroso compound, 0.025 mole/l., and 2,3-dimethylbutadiene, 0.100 mole/l. A graph of time *vs.* log b/a $(a - x/b - x)$ yielded a straight line from which k was calculated.

Anthracene.—0.53 g. (3 mmoles) was treated with nitrosobenzene, 0.53 g. (5 mmoles) in chloroform, 75 ml., at room temperature. The optical density of the solution at 730 mμ remained unchanged after several hours standing, indicating that nitrosobenzene had not reacted. The solution was then refluxed under nitrogen for 2 hr. The optical density at 730 mμ was again unchanged.

Nitrosobenzene.—5.5 g. (51 mmoles) was mixed with 1,3-cyclooctadiene, 7.8 g. (72 mmoles) in ether, 50 ml. The optical density at 730 mμ was slightly reduced after 1 week of standing at 5°. After about 25 days of standing at 5°, the solution was concentrated to approximately 5 ml. by evaporation under reduced pressure. Ethyl alcohol, 5 ml., was added, and crystals precipitated after standing for 2 hr. at 5°. The yield of the isolated crude product was 0.5 g. (4.53%, based on nitrosobenzene), m.p. 80–83°. The crude product was purified by washing with ethanol, yielding 30 mg. of a white solid, m.p. 83.5–84.5°.

Anal.[15] Calcd. for $C_{14}H_{15}NO$: C, 77.73; H, 8.28; N, 6.48. Found: C, 77.78; H, 8.13; N, 6.40.

Infrared bands (determined in a potassium bromide pellet): 3.4 (m), 3.45 (s), 3.52 (s), 6.1 (w), 6.3 (s), 6.74 (s), 6.95 (s), 8.1 (s), 8.52 (s), 9.75 (s), 9.9 (m), 11.26 (m), 12.7 (s), 12.96 (m), 13.3 (s), 13.6 (m), and 14.48 (s) μ.

Acknowledgment.—Financial support of the Petroleum Research Fund enabled us to carry on this investigation.

(11) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **27**, 1947 (1962); B. Franzus and J. H. Surridge, *ibid.*, **27**, 1951 (1962).

(12) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 668.

(13) E. Bamberger, *Ber.*, **28**, 1222 (1895).

(14) A. I. Vogel, "Practical Organic Chemistry," Longmans Green and Co., New York, N. Y., 1957, p. 573.

(15) Microanalysis by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Free Radical Addition of Cyclic Ethers to Maleic Anhydride

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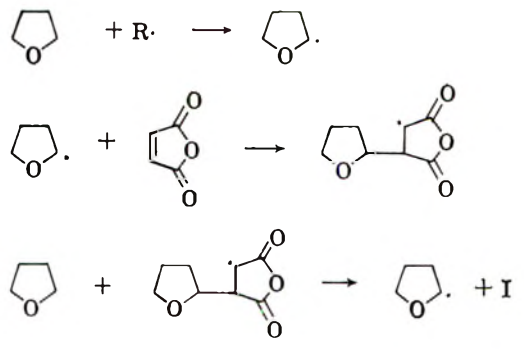
Contribution No. RP-62-36, Research Department of the Koppers Company, Inc., Monroeville, Pennsylvania

Received May 6, 1963

It has been found that free radicals initiate a reaction between tetrahydrofuran and maleic anhydride to form (tetrahydro-2-furyl)succinic anhydride in 70% yield. An analogous reaction using tetrahydro-2-methylfuran formed (tetrahydro-2-methyl-2-furyl)succinic anhydride in 70% yield. This reaction appears to be specific with respect to five-membered cyclic ethers since efforts to utilize other ethers either failed to yield a 1:1 adduct with maleic anhydride or gave only low conversions.

The free radical-promoted reactions of olefins with acetals and ortho esters have been studied extensively[2]; however, little is known relative to the behavior of simple ethers in this type of reaction. The formation of (α-alkoxybenzyl)succinic anhydrides by the addition of benzyl alkyl ethers to maleic anhydride in the presence of free radical initiators has been described.[3] More recently, the peroxide-induced reaction of various cyclic ethers with 1-octene was reported.[4] Ketonic products were obtained, and a chain mechanism involving α-hydrogen abstraction followed by decyclization of the ether was postulated.

The latter study prompts us to report the results of a similar investigation involving free radical-initiated reactions between cyclic ethers and maleic anhydride. Our results differ significantly from those reported by Wallace and Gritter[4] in that addition without ring opening has been observed as the major course of reaction. The reaction of tetrahydrofuran with maleic anhydride in the presence of free radical initiators was found to give a 70% yield of (tetrahydro-2-furyl)-succinic anhydride (I). The reaction probably proceeds by the following chain process.



The difference in the course of reaction of tetrahydrofuran with maleic anhydride and with 1-octene may arise from the double bond of maleic anhydride being more reactive than that of 1-octene. With the more reactive olefin, capture of the furyl radical might occur

(1) Maumee Chemical Co., Toledo, Ohio.

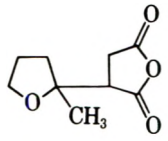
(2) For references see C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 287.

(3) T. Patrick, Jr., U. S. Patent 2,841,592 (1958).

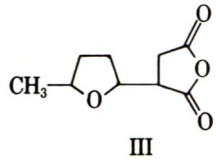
(4) T. J. Wallace and R. J. Gritter, *J. Org. Chem.*, **27**, 3067 (1962).

before rearrangement. Some support of such a hypothesis may be found in the effect of temperature upon the reactions. Whereas a 41% yield of 4-dodecanone was obtained from the reaction of tetrahydrofuran with 1-octene at 150° by Wallace and Gritter,[4] with these same reactants at 70° we found only a trace of carbonyl-containing product and recovered the bulk of the starting materials unreacted. Comparable experiments with tetrahydrofuran and maleic anhydride gave 54–60% yields of I at 70° and 42% yield at 150°. The failure to find the product of the ring fission reaction (butyrylsuccinic anhydride) in the products from the maleic anhydride–tetrahydrofuran reactions was not considered surprising. Such a compound would be the anhydride of a β-keto acid and as such might be unstable. It would be expected that rearrangement of the furyl radical would proceed more rapidly at elevated temperatures, and the decrease in yield of I in going from 70 to 150° may arise from the production of increased amounts of butyrylsuccinic anhydride, which condensed to produce the large amount of residue.[5]

The reaction of maleic anhydride with tetrahydro-2-methylfuran gave a 70% yield of adduct under conditions which resulted in a 60% yield of I in the case of tetrahydrofuran. Nuclear magnetic resonance spectra indicate that the product is a mixture of diastereomers of II rather than III.



II



III

An azobisisobutyronitrile-catalyzed reaction between maleic anhydride and tetrahydrothiophene gave a 31% conversion to a 1:1 adduct. Benzoyl peroxide was ineffective as an initiator for this reaction.

Although it is reported that tetrahydropyran adds about as readily as tetrahydrofuran to 1-octene,[4] we have found the reactions of tetrahydropyran and of 1,4-dioxane with maleic anhydride to lead only to nondistillable products. It thus appears that the five-membered ring cyclic ethers can differ appreciably from the corresponding six-membered ring compounds in free-radical reactions.

Attempts were made to effect reactions of tetrahydrofuran with chloromaleic anhydride, citraconic anhydride, dimethyl acetylenedicarboxylate, and diethyl maleate. Only in the case of diethyl maleate was more than a trace (27%) of 1:1 adduct obtained.

Experimental

Reaction of Maleic Anhydride with Tetrahydrofuran.—A 216-g. quantity of purified tetrahydrofuran[6] was heated to reflux under a nitrogen atmosphere, and a solution of 3.7 g. (0.015 mole) of benzoyl peroxide and 49.0 g. (0.5 mole) of maleic anhydride in 144 g. (2.0 moles) of tetrahydrofuran was added with stirring over an 8-hr. period. The temperature of the refluxing mixture rose from 65 to 68° during the addition. Excess tetrahydrofuran was then removed from the product by distillation at reduced pressure (25 mm.). After a 3.7 g. crude benzoic acid fraction distilled, there was obtained 59.2 g. (70%) of I, b.p. 129–142° (0.5–2 mm.), and a 19.5-g. residue. The distillation was stopped when the pot temperature reached 220° since some decomposition was occurring as evidenced by the appearance of color in the distillate and a rise in the pressure. The product was redistilled to obtain colorless distillate, b.p. 105–110° (0.1 mm.), $n^{25}D$ 1.4792.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92; neut. equiv., 85.1. Found: C, 56.84; H, 5.86; neut. equiv., 85.5.

The absence of aldehyde or ketone in the distillate was indicated by a negative result obtained with 2,4-dinitrophenylhydrazine test reagent.[7]

Experiments in which all of the reactants were present at the start of the reaction (10:1 ether–anhydride ratio) produced I in about 60% yield. The yield was further decreased to about 50% in going from a 10:1 to a 5:1 ratio of reactants. The decrease in the yield of I occurred largely with the production of larger quantities of nondistillable residue; essentially complete consumption of the maleic anhydride occurred.

In another experiment, a solution of tetrahydrofuran (5.0 moles) and maleic anhydride (0.5 mole) was heated at reflux in a Pyrex flask and illuminated by a sunlamp (General Electric, CG 401-E6) for 6 hr. There was obtained 52 g. (61%) of I and 28.6 g. of residue. A similar experiment using azobisisobutyronitrile (0.82 g., 0.005 mole) in place of light gave 54% of I.

The reaction was also carried out using *t*-butyl peroxide (3 mole % based on maleic anhydride) on twice the scale of the previous experiments. All the reactants were mixed before charging to a stainless steel autoclave and heating at 150–155° for 5 hr. There was obtained 71.1 g. (42%) of I and 76.3 g. of residue. The infrared spectrum and the refractive index of the product were identical with those of compound I obtained from reactions at lower temperatures and other initiators.

Preparation of the Dibutyl Ester of I.—This ester was prepared in order that the presence of the band of the tetrahydrofuran ring system (9.3 μ)[8] in the infrared spectrum might be observed without interference from the band of the cyclic anhydride system.

A solution of 43.0 g. (0.25 mole) of I, 200 ml. of *n*-butyl alcohol and 1.0 g. (0.006 mole) of *p*-toluenesulfonic acid was refluxed for 5 hr. while 2.7 ml. of water separated in a Dean–Stark trap. After removing the catalyst by washing with 5% sodium bicarbonate solution, the product was distilled under vacuum to yield 69.4 g. (93%) of the dibutyl ester, b.p. 149–153° (1 mm.), $n^{25}D$ 1.4515. The infrared spectrum showed the anticipated band at 9.4 μ.

Anal. Calcd. for $C_{16}H_{28}O_5$: C, 64.06; H, 9.4; sapon. equiv., 150. Found: C, 63.92; H, 9.35; sapon. equiv., 151.

Reaction of Maleic Anhydride with Tetrahydro-2-methylfuran.—A solution of 49 g. (0.5 mole) of maleic anhydride, 1.21 g. (0.005 mole) of benzoyl peroxide and 430 g. (5.0 moles) of purified[6] tetrahydro-2-methylfuran was refluxed (75–80°) under a nitrogen atmosphere for 5 hr. Distillation yielded 65.3 g. (70%) of II, b.p. 121–152° (1 mm.), and 22.6 g. of residue. Redistillation through a 2 × 24-cm. column packed with glass helices gave a heart cut, b.p. 150–151° (6 mm.), $n^{25}D$ 1.4752.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.67; H, 6.57; neut. equiv., 92.1. Found: C, 58.76; H, 6.69; neut. equiv., 92.3.

The n.m.r. spectrum of the product was compared with that of tetrahydro-2-methylfuran.[9] The spectrum of the product was in accord with structure II. The methyl proton line was observed to be split into a doublet (1.2-c.p.s. separation) probably because of the presence of two diastereomers. If the product had structure III, a much wider splitting, caused by spin coupling with the adjacent proton, would be expected. Such a splitting of the

(5) The data presented fit also the alternate mechanism suggested in the work of Wallace and Gritter.[4] In the present case, the decreased yield of (tetrahydro-2-furyl)succinic anhydride at 150° could be due to an increased rate of removal of this product, and butyrylsuccinic anhydride is not, therefore, necessarily involved.

(6) The ether was purified by distillation from sodium benzophenone ketyl. M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 25.

(7) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 97.

(8) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(9) The n.m.r. spectra were observed with a Varian Associates Model 4302 DP 60 high resolution spectrometer, field strength, 60 Mc. at 14 kilogauss. The spectra afford the first direct evidence that the initial site of hydrogen abstraction in free radical-catalyzed reactions of tetrahydrofurans with maleic anhydride is at position 2 of the tetrahydrofuran ring. If the initial free-radical attack were at any other position, the methyl would show spin–spin splitting as noted in the spectrum of tetrahydro-2-methylfuran.

methyl proton line (6 c.p.s.) was observed in the spectrum of tetrahydro-2-methylfuran.

The absence of aldehyde or ketone in the product was indicated by a negative test obtained with 2,4-dinitrophenylhydrazine test reagent.[7]

Reaction of Maleic Anhydride with Tetrahydrothiophene.—A solution of 5.0 g. (0.003 mole) of azobisisobutyronitrile, 24.5 g. (0.25 mole) of maleic anhydride and 220 g. (2.5 moles) of tetrahydrothiophene[10] was heated at 70–73° for 5 hr. under a nitrogen atmosphere. Distillation yielded 211 g. (96%) of tetrahydrothiophene, 10 g. (41%) of maleic anhydride, 14.2 g. (31%) of 1:1 adduct, b.p. 132–168° (1 mm.), and 7.2 g. of residue.

Anal. Calcd. for $C_8H_{10}O_3S$: S, 17.2; neut. equiv., 93.1. Found: S, 16.9; neut. equiv., 94.4.

A similar experiment using benzoyl peroxide in place of azobisisobutyronitrile yielded only recovered starting materials upon distillation.

Reaction of Maleic Anhydride with Tetrahydropyran.—A solution of 49 g. (0.5 mole) of maleic anhydride and 1.21 g. (0.005 mole) of benzoyl peroxide in 430 g. (5.0 moles) of purified[5] tetrahydropyran was heated at 69–71° for 6 hr. under a nitrogen atmosphere. Distillation of the product yielded 409 g. (95%) of tetrahydropyran, 19 g. (40%) of maleic anhydride, and 51.6 g. of residue. The residue solidified to an orange glass upon cooling.

A similar reaction was carried out in which no peroxide was used, but the reaction mixture was irradiated with a General Electric sunlamp while maintained at 85–90° for 6 hr. The product was identical with that of the previous experiment.

Reaction of Maleic Anhydride wth 1,4-Dioxane.—When a solution of 39.2 g. (0.4 mole) of maleic anhydride and 352 g. (4.0 moles) of purified[11] 1,4-dioxane was maintained at 96° and illuminated by a General Electric sunlamp for 8 hr., the product was found to consist of unreacted starting materials and 12.7 g. of residue. No trace of 1:1 adduct was detected.

Reaction of 1-Octene with Tetrahydrofuran.—A solution of 56.1 g. (0.5 mole) of 1-octene, 1.21 g. (0.005 mole) of benzoyl peroxide, and 360 g. (5.0 moles) of tetrahydrofuran was held at reflux (67–68°) for 8 hr. under a nitrogen atmosphere. After 3 hr. and after 5 hr., additional 1.21-g. portions of benzoyl peroxide were added. The product was distilled through a column packed with glass helices to yield 357 g. (99%) of tetrahydrofuran, 51.3 g. (91%) of 1-octene, and 8.6 g. of residue. A solid which separated from the residue was identified as benzoic acid by its infrared spectrum and its melting point. The residue gave a negative test with 2,4-dinitrophenylhydrazine reagent.[7] A trace of aldehyde or ketone was detected both by reagent and by infrared spectrum (5.8 μ) in a small intermediate fraction boiling between tetrahydrofuran and 1-octene.

A similar experiment employing 0.82 g. (0.005 mole) of azobisisobutyronitrile in place of benzoyl peroxide yielded a 1.2 g. fraction, b.p. 79–119° (4.5 mm.), $n^{20}D$ 1.4092, which showed a weak carbonyl band at 5.85 μ in its infrared spectrum. The bulk of the product was again unreacted starting materials.

Acknowledgment.—The authors wish to express their appreciation to Mr. W. E. Zitelli for assistance in the experimental work and to Mr. J. E. Graham for the determination and interpretation of infrared spectra. We are indebted to Dr. R. J. Kurland of Carnegie Institute of Technology for the n.m.r. spectra and their interpretation.

(10) The tetrahydrothiophene was dried by distilling and discarding a small portion. It was then used without additional treatment.

(11) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 285.

Pyrimido[5,4-*e*]-*as*-triazines. II. The Preparation and Reactions of Some Heteroaromatic 5-Aminopyrimido[5,4-*e*]-*as*-triazines[1]

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Received June 7, 1963

Syntheses are described for the preparation of 5-amino-3-methyl- and 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (VIIIa and VIIIb). These compounds are the first representatives of the pyrimido[5,4-*e*]-*as*-triazine ring system capable of resonance in both rings. Reaction of VIIIa and VIIIb with certain nucleophilic reagents under mild conditions produced other heteroaromatic pyrimido[5,4-*e*]-*as*-triazines.

In previous publications[3,4] from our laboratories we have reported the preparation of some dihydropyrimido[5,4-*e*]-*as*-triazines and the unsuccessful oxidization of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (XII) to 5-chloropyrimido[5,4-*e*]-*as*-triazine (XIII).[4] Although a few other partially saturated pyrimido[5,4-*e*]-*as*-triazines have been reported,[5] a heteroaromatic representative of this ring system capable of resonance in both rings has yet to be described. This paper is concerned with the synthesis of some aromatic 5-amino- and 5-hydroxypyrimido-[5,4-*e*]-*as*-triazines and is part of our program directed toward the preparation of pteridine analogs having potential antifolic acid activity.

Treatment of ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)formimidate (IIa) with hydrazine in an attempt to prepare 5-amino-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (Va) failed to provide an identifiable product. In contrast, reaction of ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)acetimidate (IIb)[6] with a methanolic solution of hydrazine in phosphate buffer gave directly 5-amino-3-methylpyrimido[5,4-*e*]-*as*-triazine (VIIIa)[7–10] in 23% yield. Undoubtedly, in this conversion 5-amino-1,2-dihydro-3-methylpyrimido[5,4-*e*]-*as*-triazine (Vb) is an intermediate which undergoes

(1) This work was supported by funds from the C. F. Kettering Foundation and from the Cancer Chemotherapy National Service Center, National Cancer Institutes, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) Affiliated with the Sloan–Kettering Institute.

(3) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **82**, 4592 (1960).

(4) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **28**, 923 (1963).

(5) (a) W. Pfleiderer and K. H. Schundehutte, *Ann.*, **615**, 42 (1958); (b) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, **84**, 1724 (1961); (c) E. C. Taylor, J. W. Barton, and W. W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961).

(6) J. A. Montgomery and C. Temple, Jr., *ibid.*, **25**, 395 (1960).

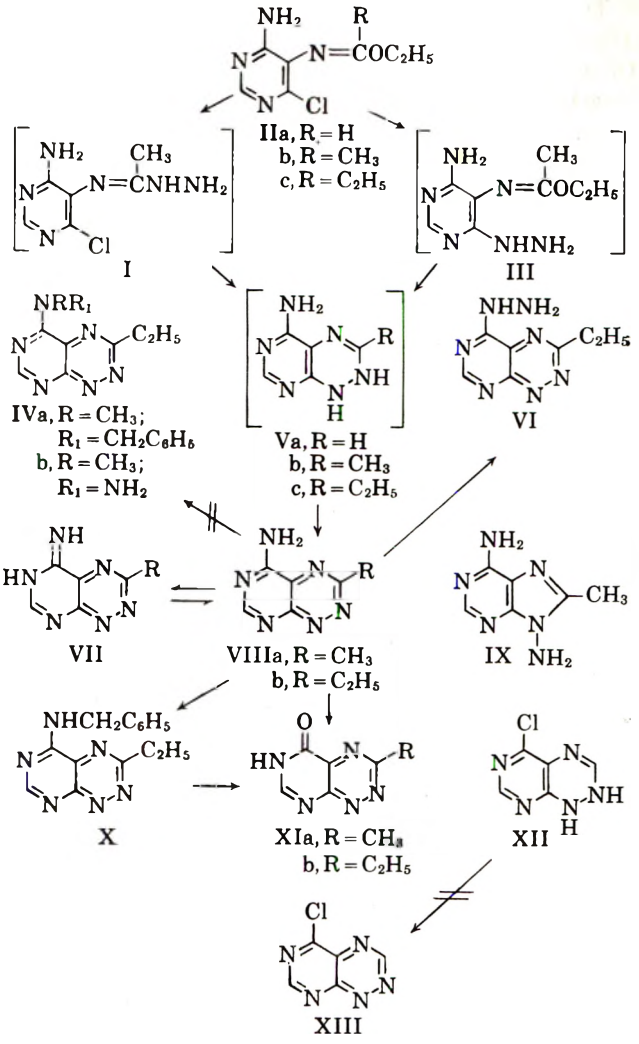
(7) The tautomerization of this compound to a structure like VII should be considered possible in view of the results obtained from studies conducted with certain 4-aminopteridines.[8] For another viewpoint see ref. 9.

(8) E. C. Taylor and C. K. Cain, *J. Am. Chem. Soc.*, **71**, 2538 (1949).

(9) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952).

(10) Two nonequivalent Kekulé forms for the *as*-triazine ring of pyrimido-[5,4-*e*]-*as*-triazines are possible. The Kekulé form used in this paper is reported[11] to be the more stable for *as*-triazine itself, based on quantum-mechanical computations.

(11) A. Maccoll, *J. Chem. Soc.*, 670 (1946).



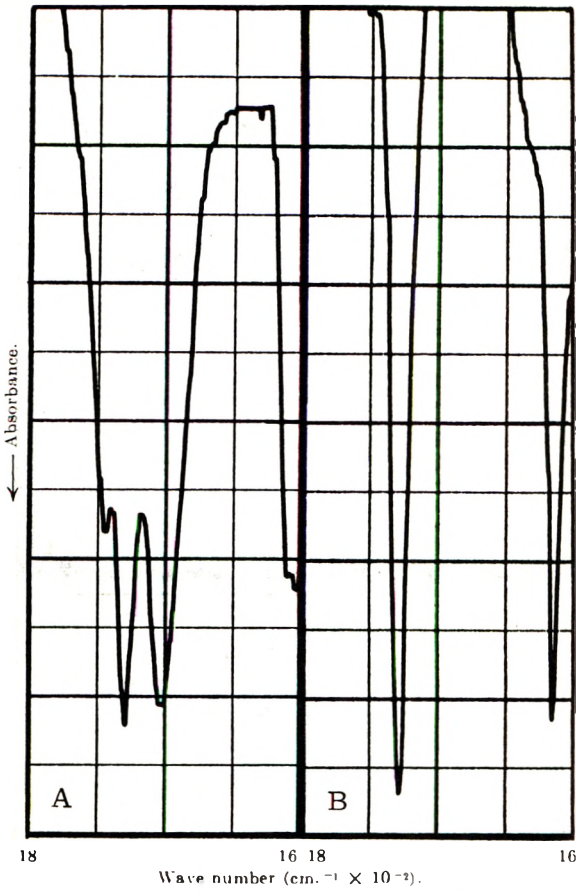


Fig. 1. Infrared spectra of XIa in the 1800–1600-cm.$^{-1}$ region for (A) solid state and (B) acetonitrile solution.

spontaneous air oxidization to provide VIIIa. The intermediate preceding Vb can be either ethyl *N*-(4-amino-6-hydrazino-5-pyrimidinyl)acetimidate (III) or *N*-amino-*N'*-(4-amino-6-chloro-5-pyrimidinyl)acetamidine (I). The mild conditions required for the conversion of imidates to amidrazones,[12] however, suggests that I is the precursor to Vb. The oxidization of Vb to VIIIa but not of XII to XIII is consistent with the observation that 2,4-diamino-5,6,7,8-tetrahydro- and 2,4-diaminodihydropteridine are readily oxidized to 2,4-diaminopteridine, but that neither 5,6,7,8-tetrahydro- nor 2,4-dichloro-5,6,7,8-tetrahydropteridine is dehydrogenated under a variety of conditions.[13]

The results obtained by Naylor, *et al.*,[14] indicated that the reaction of IIb with hydrazine could give 6,9-diamino-8-methylpurine (IX). This structure and the isomeric 6-hydrazino-8-methylpurine were eliminated from consideration by the hydrogen analysis and by comparison of the ultraviolet spectrum of VIIIa with those of 6,9-diaminopurine[15] and 6-hydrazinopurine.[16]

Under conditions that converted IIb to VIIIa, ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)propionimidate (IIc)[6] and hydrazine gave a 32% yield of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (VIIIb). When this reaction was attempted in methanol in the absence of phosphate salts, the major product isolated was $C_7H_9N_7$ rather than VIIIb ($C_7H_8N_6$). The same product was obtained in 74% yield by treatment of VIIIb with hot methanolic hydrazine. Apparently the amino group of VIIIb is replaced by hydrazine to give 3-ethyl-5-hydrazinopyrimido[5,4-*e*]-*as*-triazine (VI).[17] Similar type displacements of amino groups of other bicyclic pyrimidines have been reported.[18]

Additional support for the hydrazinolysis reaction was provided by reaction of VIIIb with benzylamine in boiling propanol to give 5-benzylamino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (X) in 82% yield.[17] Contrary to expectations, amination of VIIIb with benzylmethylamine or methylhydrazine under the usual conditions was unsuccessful. Under forcing conditions (Parr bomb), these reactions gave mixtures from which neither IVa nor IVb was isolated.

The replacement of the amino group of VIIIa and VIIIb with a hydroxy group took place under remarkably mild conditions. The action of one equivalent of aqueous sodium hydroxide at room temperature converted VIIIa and VIIIb, respectively, to 3-methyl- and 3-ethylpyrimido-[5,4-*e*]-*as*-triazine-5(6*H*)-

(12) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 200 (1961).

(13) E. C. Taylor and W. R. Sherman, *J. Am. Chem. Soc.*, **81**, 2464 (1959).

(14) R. N. Naylor, G. Shaw, D. V. Wilson, and (in part) D. N. Butler, *J. Chem. Soc.*, 4845 (1961).

(15) J. A. Montgomery and H. J. Thomas, unpublished data.

(16) J. A. Montgomery and L. B. Holum, *J. Am. Chem. Soc.*, **79**, 2185 (1957).

(17) The mechanism of this replacement reaction has not yet been determined but may involve opening of the pyrimidine ring by the basic reagent, followed by reclosure of the *as*-triazine intermediate to give the product. For similar type reactions of pteridines and purines, see ref. 18.

(18) (a) E. C. Taylor, Jr., *J. Am. Chem. Soc.*, **74**, 1651 (1952), and preceding papers; (b) C. W. Whitehead and J. J. Traverso, *ibid.*, **82**, 3971 (1960).

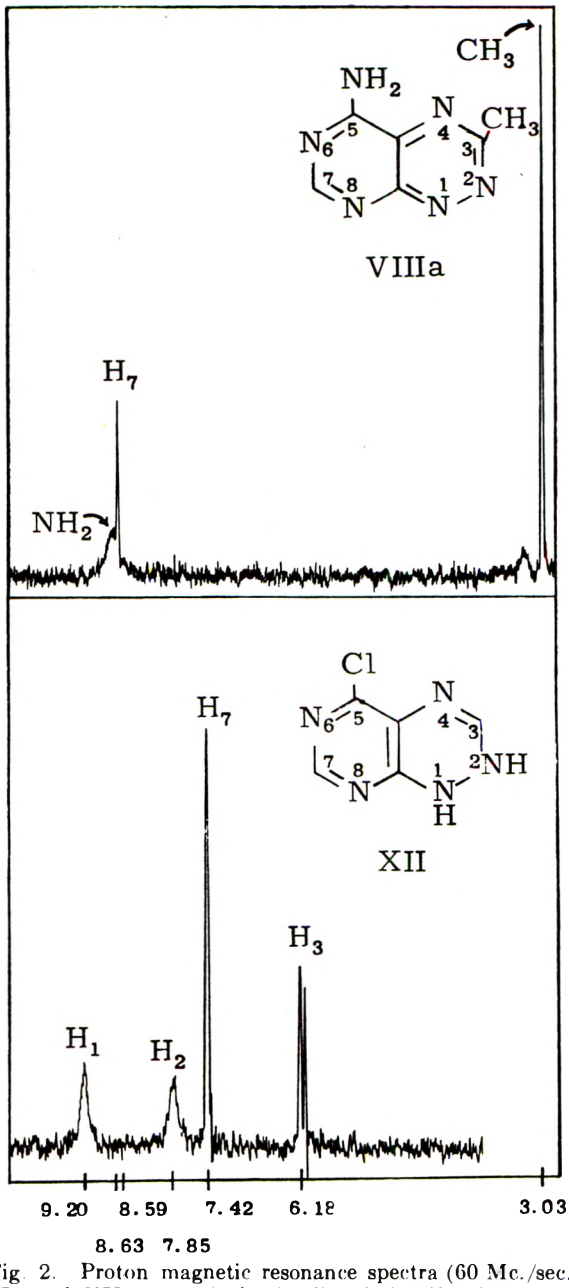


Fig. 2. Proton magnetic resonance spectra (60 Mc./sec.) of VIIIa and XII, respectively, in dimethyl sulfoxide-d_6 and dimethyl sulfoxide; field increases from left to right; chemical shifts in parts per million, relative to internal tetramethylsilane.

one (XIa and XIb) in 75 and 68% yield.[17,19] The detection of an intermediate, the structure of which is unknown, in the ultraviolet spectrum of a solution of VIIIa in 0.1 *N* sodium hydroxide implied that the conversion of VIIIa to XIa involved more than the bimolecular replacement of the amino group with the hydroxy group. The initial spectrum of this solution changed rapidly so that after about 25 minutes the maximum of the intermediate at 315 mμ had disappeared and the shoulder around 400 mμ had changed to the maximum of XIa at 372 mμ.[20] Furthermore, the ultraviolet spectrum and paper chromatograms showed that treatment of X with 0.1 *N* sodium hydroxide at room temperature caused hydrolysis of the benzylamino group to provide XIb, although the rate of conversion was slower than that of VIIIa to XIa.

(19) That other tautomers of XIa and XIb may exist is recognized.

(20) For comparison, the ultraviolet spectrum of 4-aminopteridine has been determined in 0.2 *N* sodium hydroxide.[21]

The ultraviolet spectra of XIa and 4-hydroxypteridine in an acidic medium are similar in that each shows three maxima, and dissimilar in that the long wavelength band of XIa is 26 mμ higher than the corresponding band in 4-hydroxypteridine.[21] Likewise, the long wave-length band of VIIIa occurs at a higher wave length than the corresponding band of 4-amino pteridine.[21] That the spectrum of XIa at pH 13 is practically identical with that of VIIIa at pH 7 is consistent with the observation that the spectrum of the anion of 4-hydroxypteridine closely resembles the spectrum of the neutral molecule of 4-aminopteridine.[21] In addition, replacement of the amino group of 4-aminopteridine with an alkylamino group produced a shift in the maxima to longer wave lengths,[9] and the same effect is observed by replacement of the amino group of VIIIb with a benzylamino group to give X.

The infrared spectrum of XIa in the solid state is unusual, not only in that it exhibits three carbonyl bands,[22] but that the bands occur at higher wave numbers than would be anticipated (Fig. 1). A solution of XIa in acetonitrile shows only one band in the carbonyl region (Fig. 1) and this suggests that the multiple bands in the solid state spectrum are due to crystal-orientation effects. No doubt the high frequency of this carbonyl absorption is associated with the electron-withdrawing effect of the triazine ring.

Comparison of the p.m.r. spectrum of XII with that of VIIIa at 60 Mc./sec. showed the expected differences (Fig. 2).[23] The spectrum of XII showed not only the C-3 and C-7 protons, but also the N-1 and N-2 protons, exchangeable with deuterium oxide. The doublet at 6.18 p.p.m., with a coupling constant of 3.0 c.p.s., is attributed to the spin–spin interaction of the proton at C-3 with the proton at N-2. The spectrum of VIIIa consisted of three bands with relative intensities 3:1:2, which are assigned to the 3-CH_3, the 7-ring proton, and the 5-NH_2, respectively.

Experimental

The melting points reported were determined on a Kofler Heizbank and are corrected. The ultraviolet and infrared spectra, respectively, were determined in aqueous solution with a Cary Model 14 recording spectrophotometer and in pressed potassium bromide disks with a Perkin-Elmer, Model 221, spectrophotometer.

Ethyl N-(4-amino-6-chloro-5-pyrimidinyl)formimidate (IIa).—A suspension of 6-chloro-4,5-diaminopyrimidine (1.27 g., 8.77 mmoles) in ethyl orthoformate (50 ml.) was heated with vigorous stirring at 83° (preheated oil bath) for 30 min., and then the temperature was raised to 95° within 10 min. After filtration the solution was evaporated to dryness, and the residue was washed with petroleum ether (85–105°) and dried *in vacuo* over phosphorus pentoxide; yield, 1.20 g. (68%); m.p. 109–110°. Recrystallization of this sample from benzene–petroleum ether (85–105°) did not raise the melting point. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 7: 250 (7.26), 282 (6.74). $\bar{\nu}_{max}$ cm.$^{-1}$: 3450 and 3280 (NH); 2980 and 2900 (aliphatic CH); 1640, 1630, and 1550 (NH, C=C, C=N).

Anal. Calcd. for $C_7H_9ClN_4O$: C, 41.85; H, 4.48; Cl, 17.70; N, 27.90. Found: C, 42.14; H, 4.76; Cl, 17.8; N, 28.23.

3-Ethyl-5-hydrazinopyrimido[5,4-*e*]-*as*-triazine (VI).—A suspension of 5-amino-3-ethylpyrimido[5,4-*e*]*as*-triazine (250 mg.,

(21) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(22) D. J. Brown and S. F. Mason [*J. Chem. Soc.*, 3447 (1956)] reported that the infrared spectrum of 4-hydroxypteridine in the solid state showed two carbonyl bands.

(23) The p.m.r. spectra were determined with a Varian Associates Model A-60 spectrometer. Probe temperature was 42 ± 1°.

1.42 mmoles) in methanol (5 ml.) containing anhydrous 95% hydrazine (0.05 ml.) was refluxed for 4 hr., and the mixture was allowed to stand at room temperature overnight. The pure solid was collected by filtration, washed with methanol (4 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 200 mg. (74%). This compound decomposed rapidly without melting above 200°. The sample was recrystallized from N,N-dimethylformamide–ethanol. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 270 (4.44), 372 (7.35). $\bar{\nu}_{max}$ cm.$^{-1}$: 3400 and 3260 (NH); 3080 (aromatic CH); 2980, 2945, 2860, and 2820 (aliphatic CH); 1625 (NH); 1555 and 1485 (C=C, C=N).

Anal. Calcd. for $C_7H_9N_7$: C, 43.95; H, 4.72; N, 51.25. Found: C, 43.90; H, 4.92; N, 51.32.

From the combined filtrate and wash, 50 mg. of VIIIb slightly contaminated with VI, was recovered.

5-Amino-3-methylpyrimido[5,4-*e*]-*as*-triazine (VIIIa).—Solid ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)acetimidate (2.0 g., 9.3 mmoles)[6] was added to a solution of sodium dihydrogen phosphate hydrate (1.35 g.) and disodium hydrogen phosphate (1.35 g.) in methanol (10 ml.) and water (25 ml.) containing 95% hydrazine (0.42 ml.). The mixture was heated at 80° for 2 hr. and the resulting solution was allowed to stand at room temperature overnight. The dark crystals that deposited were collected by filtration, washed with water (5 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 500 mg. This solid was recrystallized from ethanol (50 ml.) to yield 350 mg. (23%) of product in two crops, m.p. 277–280° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 245 (8.25), 350 (8.40), 358 (sh) (8.25); at pH 7: 252 (13.6), 280 (sh) (2.56), 372 (5.88). $\bar{\nu}_{max}$ cm.$^{-1}$: 3290 and 3100 (broad) (NH); 1655 (NH); 1575 and 1510 (C=C, C=N); 1445, 1350, and 1220 (strong unassigned bands).

Anal. Calcd. for $C_6H_6N_6$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.18; H, 3.95; N, 51.90.

5-Amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (VIIIb) was prepared by a similar process from 2.0 g. of ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)propionimidate[6]; yield, 500 mg. (32%); m.p. 223–225° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 246 (8.34), 350 (8.34), 359 (sh) (8.17); at pH 7: 253 (13.65), 371 (5.90). $\bar{\nu}_{max}$ cm.$^{-1}$: 3290 and 3100 (NH); 2975, 2940, and 2880 (aliphatic CH); 1650 (NH); 1570 and 1510 (C=C, C=N).

Anal. Calcd. for $C_7H_8N_6$: C, 47.72; H, 4.55; N, 47.72. Found: C, 47.60; H, 4.61; N, 47.98.

5-Benzylamino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (X).—A solution of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (1.0 g., 5.7 mmoles) in propanol (20 ml.) containing benzylamine (3.0 ml.) was refluxed for 5 hr. and evaporated to a small volume *in vacuo*. After this residue was washed on a funnel with water (60 ml.) to remove an insoluble dark oil, the remaining solid was dried *in vacuo* over phosphorus pentoxide to yield 1.28 g. (82%), m.p. 143–145° dec. For analysis a sample was recrystallized from petroleum ether (85–105°); m.p. 153–154° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 223 (15.6), 254 (5.85), 362 (sh) (12.1), 369 (12.3); at pH 7: 224 (17.9), 257 (9.75), 385 (8.35). $\bar{\nu}_{max}$ cm.$^{-1}$: 3190 (NH); 2950 and 2910 (aliphatic CH); 1600, 1585 (sh), 1560, and 1500 (C=C, C=N).

Anal. Calcd. for $C_{14}H_{14}N_6$: C, 63.18; H, 5.27; N, 31.55. Found: C, 63.22; H, 5.21; N, 31.68.

3-Methylpyrimido[5,4-*e*]-*as*-triazin-5(6H)-one (XIa).—A suspension of 5-amino-3-methylpyrimido[5,4-*e*]-*as*-triazine (250 mg., 1.54 mmoles) in 1.07 *N* sodium hydroxide (1.65 ml.) was stirred at room temperature for 3 hr. The resulting solution was neutralized with 1.03 *N* hydrochloric acid (1.71 ml.) and evaporated to dryness *in vacuo*. This residue was extracted with two 25-ml. portions of acetone, and the combined extracts were evaporated to yield 190 mg. (75%). Recrystallization of this solid from tetrahydrofuran–petroleum ether (85–105°) gave the analytical sample; m.p. 199–200° solidifies and remelts at 213–215 dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 236 (8.7), 264 (5.36), 336 (5.28). At pH 7: 249 (12.4), 355 (3.73); at pH 13: 251 (15.7), 278 (sh) (2.96), 372 (4.66). $\bar{\nu}_{max}$ cm.$^{-1}$: 3200 (NH); 2900–2500 (acidic H); 1750, 1735, and 1710 (C=O); 1610, 1595, 1540, and 1520 (C=C, C=N).

Anal. Calcd. for $C_6H_5N_5O$: C, 44.20; H, 3.07; N, 42.90. Found: C, 44.30; H, 3.03; N, 42.79.

3-Ethylpyrimido[5,4-*e*]-*as*-triazin-5(6H)-one (XIb) was prepared by a similar process from 500 mg. of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine: yield, 340 mg. (68%) m.p. 183–185° dec. A second recrystallization from tetrahydrofuran–petroleum ether gave the analytical sample; m.p., 185–188° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 237 (8.70), 265 (5.65), 338 (6.05); at pH 7: 250 (12.7), 360 (3.80); at pH 13: 250 (12.2), 280 (sh) (3.4), 373 (4.68). $\bar{\nu}_{max}$ cm.$^{-1}$: 3200 and 3150 (NH); 2980 (aliphatic CH); 2900–2500 (acidic H); 1730 and 1700 (C=O); 1610 (sh), 1600, 1540, and 1520 (C=C, C=N).

Anal. Calcd. for $C_7H_7N_5O$: C, 47.40; H, 3.95; N, 39.50. Found: C, 47.00; H, 3.78; N, 39.39.

Acknowledgment.—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical Section of Southern Research Institute who performed the spectral and most of the analytical determinations reported, and to Dr. W. C. Coburn and Mrs. M. C. Thorpe for their helpful discussion of the infrared and proton magnetic spectra. Some of the analyses were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

Aromaticity in Heterocyclic Systems. I. The Synthesis and Structure of Certain 4,6-Dihydroxyimidazo[4,5-c]pyridines[1]

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Received June 17, 1963

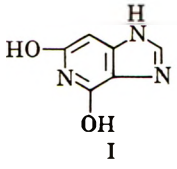
The synthesis of the imidazo[4,5-*c*]pyridine ring has been accomplished for the first time from imidazole intermediates. 4,6-Dihydroxyimidazo[4,5-*c*]pyridine and related 2-substituted derivatives have been prepared for the first time from the requisite 4-imidazoleacetamide-5-carboxylic acid ester. 4,6-Dihydroxyimidazo[4,5-*c*]-pyridine (I) has been shown by n.m.r. to exist as the diketo form Ia. This accounts for the ease of pyridine ring cleavage of the 4,6-dihydroxy compounds in the presence of hot acid or base. Evidence is considered which supports the existence of the more aromatic enol form Ic present as the anion in dilute base.

Although the synthesis of 4-aminoimidazo[4,5-*c*]-pyridine (3-deazaadenine) and 4-hydroxyimidazo[4,5-*c*]pyridine (3-deazahypoxanthine) previously has been reported,[3] other purine analogs such as 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I), the xanthine analog, and 2,4,6-trihydroxyimidazo[4,5-*c*]pyridine (II), the analog of uric acid, have not been recorded previously. Pre-

(1) Supported in part by Grant CH-28 from the American Cancer Society and in part by Grant NSF-G13291 from the National Science Foundation.

(2) In part from the Master's theses of Claude V. Greco and Calvin G. Beames, Jr., New Mexico Highlands University, 1953 and 1955.

(3) C. A. Salemink and G. M. Van der Want, *Rec. trav. chim.*, **68**, 1013 (1949).



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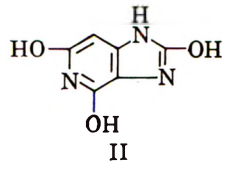


II

vious syntheses of the imidazo[4,5-*c*]pyridine ring[4-10] have all proceeded from the appropriate 3,4-diaminopyridine which was then ring closed by various means to give the requisite imidazo[4,5-*c*]pyridine.

It seemed of theoretical interest to investigate the possibility of an alternative synthesis which would involve a substituted imidazole that could then be ring closed to form the pyridine portion of the molecule.

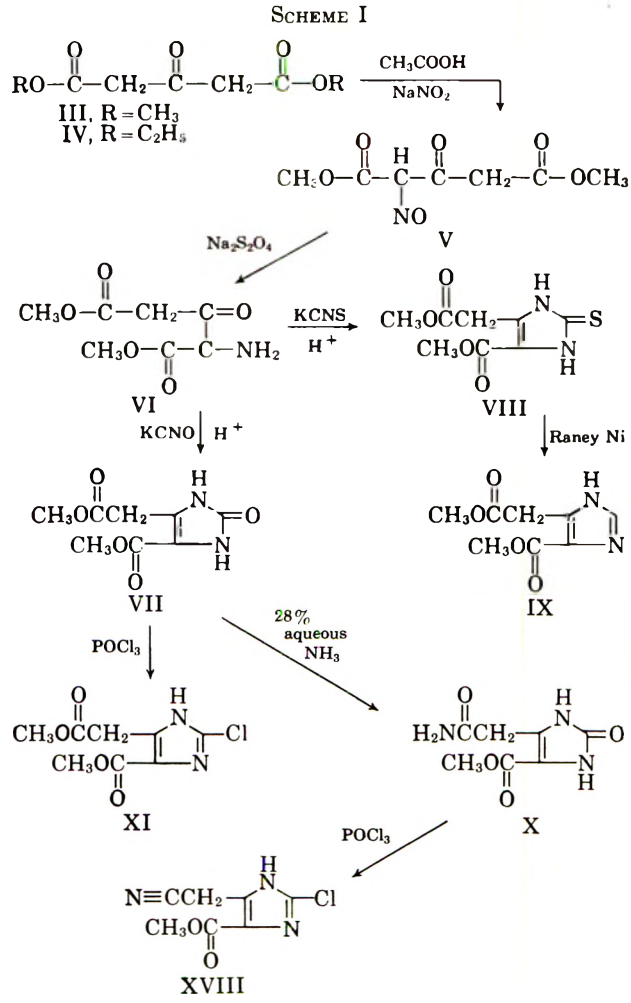
The synthesis of a number of previously unknown required derivatives of imidazole were accordingly investigated. The commercial availability of methyl acetonedicarboxylate (III)[11] and improvement in the synthesis of ethyl acetonedicarboxylate (IV)[12] provided a ready source of starting material for the present work. Methyl acetonedicarboxylate (III) was nitrosated with sodium nitrite in glacial acetic acid after a modified procedure of Pechmann[13] for the diethyl ester to yield dimethyl-2-nitroso-3-ketoglutarate (V) which was reduced with sodium hydrosulfite to the amino derivative VI. When VI was treated with potassium cyanate in the presence of sulfuric acid, 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) was readily obtained. Potassium thiocyanate in the presence of acid ring closed VI to 4-acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII). Treatment of 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) and phosphorus oxychloride provided 4-acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI).

When 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) was treated with aqueous ammonia heated on the steam bath, a monoamide, 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (X), was readily prepared. 4-Acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII) and hot aqueous ammonia provided 4-acetamide-2-imidazolethione-5-carboxylic acid methyl ester (XII). Treatment of XII with Raney nickel in refluxing ethanol gave 4-imidazoleacetamide-5-carboxylic acid methyl ester (XIII).

The assignment of structure for compounds X, XVI, and XIII as derivatives of 4-imidazoleacetamide-5-carboxylic acid methyl ester was made on the basis of n.m.r. studies.

Examination of Table I reveals that in trifluoroacetic acid, the methyl groups of imidazole-4,5-di-

SCHEME I



carboxylic acid dimethyl ester (XVII)[14] appear at 4.12 δ. Treatment of 4-acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII) with Raney nickel gave 4-acetic acid-2-imidazole-5-carboxylic acid dimethyl ester (IX). In compound IX the methyl group of the aliphatic ester appears at 3.94 δ, and the aromatic methyl ester shows a sharp singlet at 4.12 δ.

The n.m.r. spectrum of XIII reveals that the sharp singlet at 3.94 δ has disappeared, while the singlet at 4.12 ♀ remains. Thus, the structure of XIII must be 4-imidazoleacetamide-5-carboxylic acid methyl ester. Since XIII was prepared from XII, it follows that the structure of XII is 4-acetamide-2-imidazolethione-5-carboxylic acid methyl ester. Inspection of Table I shows that similar structural assignment can be made with the 2-chloroimidazole derivatives. Since XVI was prepared by the treatment of XI with ammonia, the structure of XVI must be 4-acetamide-2-chloroimidazole-5-carboxylic acid methyl ester. Treatment of X with phosphorus oxychloride gave 4-acetonitrile-2-chloroimidazole-5-carboxylic acid methyl ester (XVIII). Since the n.m.r. of XVIII shows the sharp singlet at 4.12 δ due to the methyl group of the aromatic ester, it follows that the structure of X is 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester. Thus, in all cases the aliphatic ester reacted to give the corresponding amide. This might be expected, due to the known greater reactivity of aliphatic esters over aromatic esters.

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(11) The authors wish to thank Chas. Pfizer and Co., Inc., Brooklyn, N. Y., for a generous gift of this compound used in this study.
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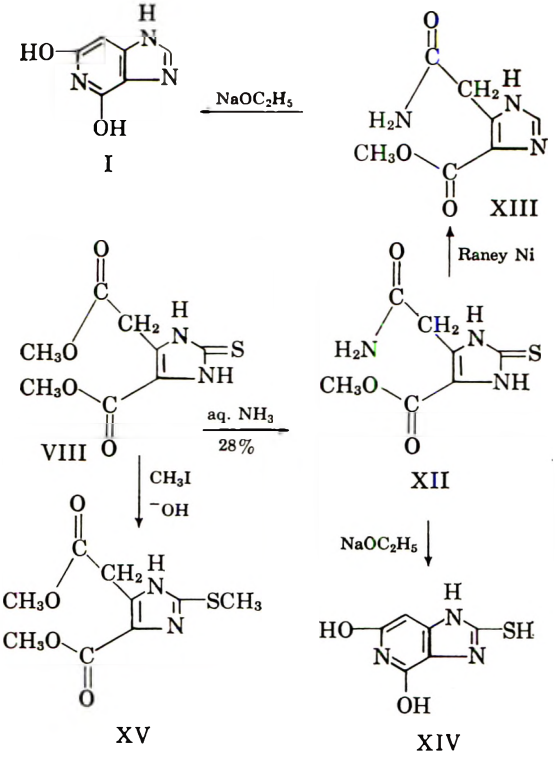
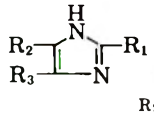
SCHEME II



Strong supporting evidence for this structural assignment of XIII is found in the infrared spectra. Compound IX exhibits two sharp bands in the carbonyl region, 1740 cm.$^{-1}$ (alkyl ester) and 1710 cm.$^{-1}$ (aryl ester). The corresponding monoamide XIII exhibits the same sharp band at 1710 cm.$^{-1}$ (aryl ester), but the band at 1740 cm.$^{-1}$ has been replaced by amide carbonyl absorption at 1680 cm.$^{-1}$.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF CERTAIN IMIDAZOLE DERIVATIVES[a]

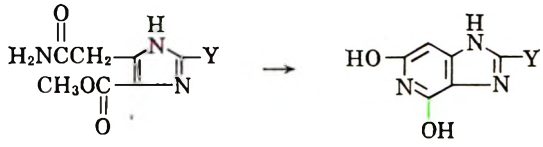


Compound	R_1	R_2	R_3
IX	H (8.85)	CH_2—C(=O)—OCH_3 (4.39) (3.94)	C(=O)—OCH_3 (4.12)
XI	Cl	CH_2—C(=O)—OCH_3 (4.38) (3.94)	C(=O)—OCH_3 (4.12)
XIII	H (8.80)	CH_2—C(=O)—NH_2 (4.38)	C(=O)—OCH_3 (4.12)
XV	SCH_3 (2.85)	CH_2—C(=O)—OCH_3 (4.30) (3.90)	C(=O)—OCH_3 (4.10)
XVI	Cl	CH_2—C(=O)—NH_2 (4.36)	C(=O)—OCH_3 (4.11)
XVII	H (8.97)	C(=O)—OCH_3 (4.12)	C(=O)—OCH_3 (4.12)
XVIII	Cl	CH_2—C≡N (4.43)	C(=O)—OCH_3 (4.12)

[a] N.m.r. spectra run in trifluoroacetic acid with tetramethylsilane as an external standard. Values expressed as p.p.m. δ. All spectra appeared as sharp singlets.

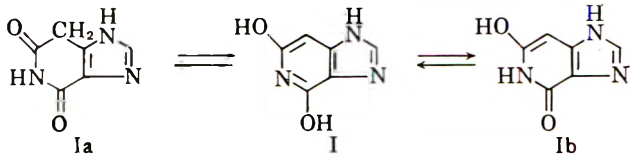
Attempts to cyclize X, XII, XIII, XVI, and XVIII to a derivative of imidazo[4,5-*c*]pyridine were made using refluxing methanolic hydrogen chloride, concentrated sulfuric acid, refluxing 2 *N* sodium hydroxide, concentrated hydrochloric acid, and refluxing formamide. No cyclized product could be isolated from these reactions. It is now known that, due to the general instability of the 4,6-dihydroxyimidazo[4,5-*c*]pyridine ring, the desired compounds, if formed, would have had little chance of surviving under these conditions. In an effort to vary this approach, 4-acetamide-2-chloroimidazole-5-carboxamide (XIX) was prepared from 4-acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI) and ethanolic ammonia at 150°. Attempts to ring close XIX by various means were likewise unrewarding.

The synthesis of 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I) was finally accomplished from XIII by employing sodium ethoxide in refluxing absolute ethanol. The preparation of 4-acetamide-2-chloroimidazole-5-carboxylic acid methyl ester (XVI) was accomplished from XI and aqueous ammonia. Ring closure of XVI with sodium ethoxide in absolute ethanol gave 2-chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX). 4,6-Dihydroxyimidazo[4,5-*c*]pyridine-2-thiol (XIV) was similarly prepared from the amide ester XII. The uric acid analog, 2,4,6-trihydroxyimidazo[4,5-*c*]pyridine (II), was obtained from X by boiling aqueous sodium carbonate which was found to be a superior reagent for this specific ring closure.



A general study of the action of refluxing *N* sulfuric acid on the various 4,6-dihydroxyimidazo[4,5-*c*]pyridines revealed that 50% decomposition occurred in 90 minutes with the 2-chloro derivative (XX), in 135 minutes with 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I). Refluxing 0.01 *N* sodium hydroxide hydrolyzed XX and I 50% in 10 minutes as judged by the loss of ultraviolet absorption at 316 and 310 mμ, respectively. The compounds 2,4,6-trihydroxyimidazo[4,5-*c*]pyridine (II) and 4,6-dihydroxyimidazo[4,5-*c*]pyridine-2-thiol (XIV) also decomposed under similar conditions at a slightly slower rate. Although detailed studies were not made to identify the degradation products, in most instances general absorption in the 250-mμ region, typical of imidazole derivatives, was noted. With 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I) the ultraviolet absorption spectra of the acidic and basic degradation products were identical to that of 4-imidazoleacetamide-5-carboxylic acid, prepared by the action of refluxing 2 *N* sodium hydroxide on the ester XIII. Since the corresponding purines, xanthine and uric acid, are essentially unchanged by these conditions, further structural studies of these imidazo[4,5-*c*]pyridines were initiated.

Inspection of I reveals that 4,6-dihydroxyimidazo-[4,5-*c*]pyridine could well exist in the diketo form Ia or the monoketo form Ib. Examination of the n.m.r. spectrum of 4,6-dihydroxyimidazo[4,5-*c*]pyridine in trifluoroacetic acid revealed a sharp singlet at 9.1 δ (proton at position 2), another singlet at 4.5 δ which integrated for two protons, and finally a broad absorp-

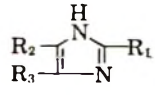


Ia I Ib

tion at 10.1 δ attributed to NH at position 5 since the proton in the imidazole ring is known to exchange in trifluoroacetic acid. Such a spectrum is consistent only with structure Ia where the singlet at 4.5 δ is due to the CH_2 grouping in position 7. Similarly, 2-chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX) in trifluoroacetic acid showed one proton (NH) at 10.15 δ and a singlet (2 protons) at 4.5 δ. Inspection of the ultraviolet absorption spectra of I and XX revealed that the trifluoroacetic acid, employed as a solvent, had not altered the compounds by hydrolysis. 2-Chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX) was also examined in deuterated dimethyl sulfoxide in the n.m.r. Absorption appeared at 10.8 δ (1 proton, NH) and a singlet at 3.9 δ (2 protons), which again is strong support for the diketo structure. The structure Ia explains the ready hydrolysis of the pyridine ring since this system is simply a cyclic imide. It is of interest that no evidence of the structure Ib could be detected by n.m.r. Structure Ib might be expected since this tautomer would give the system stability due to increased aromaticity. Inspection of the ultraviolet absorption of the 4,6-dihydroxyimidazo[4,5-*c*]pyridines (Table III) reveals some interesting facts. The absorption maxima of these compounds at pH 1, as compared to the uncyclized imidazoles (Table II), are approximately in the range one might expect for a conjugated cyclic imide. However, at pH 11 in each case the absorption maxima of the 4,6-dihydroxyimidazo-[4,5-*c*]pyridines undergo a bathochromic shift of approximately 20–45 mμ. It would thus appear that in a basic solution the anion which is formed has more aromatic character than the unionized species. Thus, it is quite possible that the proton is removed from

TABLE II

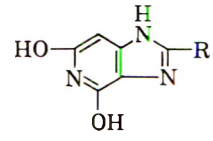
ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN IMIDAZOLES IN AQUEOUS SOLUTION AT PH 1



Compound	R_1	R_2	R_3	λ_{max}, mμ	ε	λ_{min}, mμ	ε
VII	OH	$CH_2CO_2CH_3$	CO_2CH_3	269	10,280	229	1720
VIII	SH	$CH_2CO_2CH_3$	CO_2CH_3	257	12,180	275	9200
				284	9,940	223	3910
X	OH	CH_2CONH_2	CO_2CH_3	270	10,540	227	1392
XI	Cl	$CH_2CO_2CH_3$	CO_2CH_3	244	7,670		
XII	SH	CH_2CONH_2	CO_2CH_3	257	13,800	223	3880
				285	10,750		
XIII	H	CH_2CONH_2	CO_2CH_3	226	10,200		
XV	SCH_3	$CH_2CO_2CH_3$	CO_2CH_3	263	12,450		
XVI	Cl	CH_2CONH_2	CO_2CH_3	244	9,800		
XVIII	Cl	$CH_2C{\equiv}N$	CO_2CH_3	247	12,550		

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 4,6-DIHYDROXYIMIDAZO[4,5-*c*]PYRIDINES



		pH 1		pH 11	
Compound	R	λ_{max}, mμ	ε	λ_{max}, mμ	ε
I	H	242	5,440	262	8,300
		290	6,030	308	7,860
II	OH	302	7,700	278	10,700
				321	7,540
XIV	SH	259	12,800	242	19,400
		309	8,760	320	7,330
XX	Cl	271	7,060	265	5,380
				316	8,170

position 7 to give an anion of type Ic or Id, which would afford greater aromaticity to the system and better conjugation with the imidazole ring. An n.m.r. study of 2-chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX) in deuterium oxide in the presence of sodium peroxide revealed no strong absorption. Thus, there is rapid exchange with the hydrogens at position 7, which is additional evidence for the existence of an anion such as Ic.

Ic Id

Experimental[15]

4-Acetic Acid-2-imidazolone-5-carboxylic Acid Dimethyl Ester (VII).—To 128 g. of methyl acetonedicarboxylate[11] and 160 ml. of glacial acetic acid was added, with stirring, a solution of 43.2 g. of sodium nitrite dissolved in 64 ml. of water. The sodium nitrite solution was added at such a rate that the temperature remained between 25–35°. After addition of all the sodium nitrite solution, the mixture was stirred an additional 30 min.; then 600 ml. of water was added, and the solution was stirred for an additional hour. The mixture was transferred to a 4-l. beaker, and 800 ml. of water was added. To this solution was added 384 g. of sodium hydrosulfite, and the solution was stirred until all the solid had dissolved. The mixture was then adjusted to pH 4 by the addition of dilute sulfuric acid, and to this solution was added, in small portions, 200 g. of potassium cyanate. During this process the solution was stirred and cooled in an ice bath. After addition was complete, the solution was allowed to stand for 20 min. and then was heated to 70° on a steam bath. The solution was cooled overnight, and the light yellow crystals were filtered to yield 31.25 g. of crude material, m.p. 208–218°. The yellow solid was recrystallized from methanol and melted at 228–230°.

Anal. Calcd. for $C_8H_{10}N_2O_5$: C, 44.9; H, 4.7; N, 13.2. Found: C, 44.5; H, 4.9; N, 13.5.

4-Acetic Acid-2-imidazolone-5-carboxylic Acid Diethyl Ester.—This compound was similarly prepared from ethyl acetonedicarboxylate[12] in an over-all yield of 38%. The product was recrystallized from hot water to give white needles, m.p. 186–187°.

Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.6; H, 5.8; N, 11.6. Found: C, 49.6; H, 5.9; N, 11.6.

4-Acetic Acid-2-imidazolethione-5-carboxylic Acid Dimethyl Ester (VIII).—This compound was prepared by the same procedure employed for the synthesis of 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) except that 184 g. of potas-

(15) All melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus.

sium thiocyanate was used instead of 200 g. of potassium cyanate. No cooling in an ice bath was necessary for this addition. After the yellow solution was heated to 70°, charcoal was added, and the solution was filtered and cooled to yield 32.0 g. of a yellow solid, m.p. 220–222°, which was recrystallized from water to raise the melting point to 222°.

Anal. Calcd. for $C_9H_{11}N_2O_4S$: C, 44.3; H, 4.9; N, 11.5. Found: C, 44.1; H, 5.2; N, 11.6.

4-Acetic Acid-2-imidazolethione-5-carboxylic Acid Diethyl Ester.—This compound was similarly prepared from ethyl acetonedicarboxylate[12] to give a product, m.p. 163–164°, after recrystallization from water.

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$: C, 46.5; H, 5.4. Found: C, 46.7; H, 5.8.

4-Acetic Acid-2-imidazole-5-carboxylic Acid Dimethyl Ester (IX).—To 500 ml. of absolute methanol was added 30 g. of 4-acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII) and 60 g. of wet Raney nickel. The mixture was heated to vigorous reflux for 12 hr. The solution was then filtered, the nickel was washed with hot methanol, and the washings were added to the filtrate. The methanol was then removed under reduced pressure, and the yellow residue was recrystallized from water to yield 13.0 g., m.p. 163–178°. A second recrystallization from water raised the melting point to 178–180°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.5; H, 5.0; N, 14.2. Found: C, 48.8; H, 5.2; N, 14.4.

4-Acetic Acid-2-imidazole-5-carboxylic Acid Diethyl Ester.—This compound was prepared in a similar fashion. Recrystallization of the product from hot water gave white needles, m.p. 130–131°.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.1; H, 6.2; N, 12.8. Found: C, 52.7; H, 6.6; N, 12.8.

4-Acetamide-2-imidazolone-5-carboxylic Acid Methyl Ester (X).—To 100 ml. of boiling 28% ammonium hydroxide was added 6.0 g. of the diester (VII) in small portions. After addition was complete, the solution was boiled for 10 min. on the steam bath, filtered, and cooled in an ice bath. The dark solution was then acidified with dilute sulfuric acid and cooled overnight. The crystals were filtered to yield 4.0 g. (73%) of crude product, m.p. 290–295° dec., which was recrystallized from water to give a pure product, m.p. 299–301° dec.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.8; H, 4.6; N, 21.4. Found: C, 42.3; H, 4.6; N, 21.2.

4-Acetamide-2-imidazolone-5-carboxylic Acid Ethyl Ester.—This compound was similarly prepared. The product was recrystallized from water and melted at 278–279°.

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.1; H, 5.2. Found: C, 45.1; H, 5.4.

4-Acetic Acid-2-chloroimidazole-5-carboxylic Acid Dimethyl Ester (XI).—Dry 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII, 5 g.) was added to 75 ml. of phosphorus oxychloride. The solution was refluxed for 3.5 hr., and the excess phosphorus oxychloride was removed under reduced pressure using a water bath as the source of heat. The residue was poured, with vigorous stirring, onto crushed ice, and the mixture, while still cold, was adjusted to pH 5 with 28% ammonium hydroxide. The solution was allowed to stand 30 min. at room temperature and then was extracted with ether in a continuous extractor for 30 hr. Distillation of the ethereal solution left 3.9 g. (72%) of yellow solid, which was recrystallized from benzene to yield white crystals, m.p. 137°.

Anal. Calcd. for $C_8H_9ClN_2O_4$: C, 41.3; H, 3.9; N, 12.0. Found: C, 41.9; H, 4.0; N, 12.2.

4-Acetamide-2-chloroimidazole-5-carboxamide (XIX).—4-Acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI, 2 g.) was added to 150 ml. of ethanol which had been saturated with ammonia at 0°. The reaction mixture was heated in a steel vessel at 150° for 6 hr. The alcoholic solution was cooled and evaporated to dryness on the steam bath, and a small amount of cold water was added to dissolve the inorganic salts. The aqueous solution was filtered, and the product was recrystallized from water to yield 0.424 g. The solid was recrystallized twice from water using decolorizing charcoal and gave a product melting at 275° dec.

Anal. Calcd. for $C_6H_7ClN_4O_2$: C, 35.6; H, 3.4; N, 27.7. Found: C, 35.6; H, 3.6; N, 27.9.

4-Acetic Acid-2-methylthioimidazole-5-carboxylic Acid Dimethyl Ester (XV).—To 100 ml. of water was added 3 g. of VIII and just enough potassium hydroxide to effect solution. Methyl iodide (1.0 g.) was added, and the solution was stirred vigorously at 20° for 1 hr. The pH of the solution at the end of this period was 8. The solution was cooled overnight and filtered to yield 2.6 g. of white solid, m.p. 102–105°, which was recrystallized from water to give needles, m.p. 107°.

Anal. Calcd. for $C_9H_{12}N_2O_4S$: C, 44.3; H, 4.9; N, 11.5. Found: C, 44.1; H, 5.2; N, 11.6.

4-Acetamide-2-imidazolethione-5-carboxylic Acid Methyl Ester (XII).—4-Acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII, 20 g.) was added in small portions to 300 ml. of boiling 28% ammonium hydroxide on a steam bath. After each addition the flask and contents were shaken to effect solution. After addition was complete, the dark solution was boiled an additional 5 min. and then filtered and cooled. The solution was acidified to pH 3 with dilute sulfuric acid and cooled overnight, and the light tan crystals were filtered and washed with water to yield 15.7 g. (84%). The compound was recrystallized from water to give a melting point of 233° dec.

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.1; H, 4.2; N, 19.5. Found: C, 39.1; H, 4.1; N, 19.5.

4-Acetamide-2-imidazolethione-5-carboxylic Acid Ethyl Ester.—This compound was similarly prepared from 4-acetic acid-2-imidazolethione-5-carboxylic acid diethyl ester and was recrystallized from water to give a melting point of 235–236°.

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.9; H, 4.8; N, 18.3. Found: C, 42.3; H, 5.2; N, 18.4.

4-Acetonitrile-2-chloroimidazole-5-carboxylic Acid Methyl Ester (XVIII).—To 4.0 g. of 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (X) was added 75 ml. of phosphorus oxychloride. This mixture was refluxed for 2.5 hr., and then the volume of the solution was reduced to 35 ml. under reduced pressure. The dark liquid was poured slowly with stirring onto crushed ice, and the cold, aqueous solution was adjusted to pH 5 with 28% aqueous ammonia and extracted with ether. The ethereal solution was then washed with a small amount of water and dried over sodium sulfate, and the ether was distilled to leave a yellow viscous residue. The crude product was recrystallized from benzene to yield 1.6 g. (40%) of pure white crystals, m.p. 137°.

Anal. Calcd. for $C_7H_6ClN_3O_2$: C, 42.0; H, 3.0; N, 21.0. Found: C, 42.3; H, 2.7; N, 20.6.

4-Imidazoleacetamide-5-carboxylic Acid Methyl Ester[(XIII).—4-Acetamide-2-imidazolethione-5-carboxylic acid methyl ester (XII, 4 g.) and 15 g. of Raney nickel catalyst were added to 100 ml. of absolute ethanol. The mixture was refluxed for 2 hr.; then the Raney nickel was filtered, and the alcoholic filtrate was evaporated to dryness on a steam bath. The light grey residue was easily recrystallized from water to yield 1.48 g. of pure white solid (44%), m.p. 242–244°.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.9; H, 5.0; N, 22.9. Found: C, 46.2; H, 5.0; N, 22.9.

4-Imidazoleacetamide-5-carboxylic Acid Ethyl Ester.—This compound was similarly prepared from 4-acetamide-2-imidazolethione-5-carboxylic acid ethyl ester to give white crystals (75% yield), m.p. 206° dec.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.7; H, 5.6; N, 21.4. Found: C, 48.5; H, 5.3; N, 20.8.

2,4,6-Trihydroxyimidazo[4,5-c]pyridine (II). Method 1.—To 35 ml. of boiling 10% sodium carbonate solution was added 3.5 g. of 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (m.p. 278–279°). The solution was refluxed for 5 min., and the reaction mixture was treated with charcoal and filtered. The hot filtrate was neutralized (pH 3) with concentrated hydrochloric acid, which precipitated the desired product. The solution was filtered while hot, and the product was suspended in boiling distilled water and filtered. The product was washed three times with distilled water and dried in a vessel open to the atmosphere. The yield of cyclized material was 0.592 g. (22.2%), m.p. > 300°.

Anal. Calcd. for $C_6H_5N_3O_3 \cdot H_2O$: C, 38.9; H, 3.8; N, 22.7. Found: C, 39.5; H, 3.9; N, 23.0.

A sample was dried in an oven at 130°.

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.1; H, 3.0; N, 25.2. Found: C, 42.9; H, 3.5; N, 24.8.

Method 2.—When 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (X, 4.0 g.) was employed as in method 1, a white solid (1.6 g., 47%), m.p. > 300°, was obtained. This product was washed with ethanol and recrystallized from glacial acetic acid. The compound thus obtained was shown by ultraviolet absorption spectra to be identical to that prepared by method 1.

4,6-Dihydroxyimidazo[4,5-c]pyridine-2-thiol (XIV).—Sodium (4.5 g.) was dissolved in 180 ml. of absolute ethanol, and then 6.0 g. of 4-acetamide-2-imidazolethione-5-carboxylic acid methyl ester (XII) was added. The solution was refluxed for 15 min. on a steam bath, and then the pH was adjusted to 6 with glacial acetic acid. The mixture was stirred for 30 min. and cooled. The light green solid was filtered, suspended in 75 ml. of distilled water, and stirred an additional 30 min. The crude material was filtered and washed well first with distilled water and then with ethanol. The light green solid was dried at 60° to yield 5.3 g., m.p. > 300°.

Anal. Calcd. for $C_6H_5N_3O_2S \cdot H_2O$: C, 35.8; H, 3.5; N, 20.9. Found: C, 36.0; H, 4.6; N, 20.5.

A sample was dried at 130°.

Anal. Calcd. for $C_6H_5N_3O_2S$: C, 39.3; H, 2.7; N, 22.9. Found: C, 39.3; H, 3.0; N, 22.7.

4,6-Dihydroxyimidazo[4,5-c]pyridine (I).—4-Imidazoleacetamide-5-carboxylic acid methyl ester (XIII, 10.0 g.) was added to 7.5 g. of sodium dissolved in 300 ml. of absolute ethanol. The solution was refluxed on a steam bath for 30 min. and then acidified with glacial acetic acid. The mixture was stirred for 30 min., cooled, and filtered, and the light tan material was suspended in 100 ml. of water, stirred for 30 min., and again filtered. The cyclized product was dried to yield 7.5 g. (91%), m.p. > 300°, and a small sample was recrystallized from glacial acetic acid and dried at 130° for analysis.

Anal. Calcd. for $C_6H_4N_3O_2$: C, 47.7; H, 3.3; N, 27.8. Found: C, 47.6; H, 3.4; N, 28.0.

4-Acetamide-2-chloroimidazole-5-carboxylic Acid Methyl Ester (XVI).—4-Acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI, 10 g.) was treated with aqueous ammonia as for the synthesis of XII and X. The solid was recrystallized from methanol–water to give 8.0 g. of product, m.p. 235–237° dec.

Anal. Calcd. for $C_7H_8ClN_3O_3$: C, 38.7; H, 3.7; N, 19.3. Found: C, 38.6; H, 3.3; N, 19.0.

2-Chloro-4,6-dihydroxyimidazo[4,5-c]pyridine (XX).—4-Acetamide-2-chloroimidazole-5-carboxylic acid methyl ester (XVI, 10.0 g.) was added to 7.5 g. of sodium dissolved in 300 ml. of absolute ethanol. This solution was refluxed on a steam bath for 30 min. and then transferred to an erlenmeyer flask. The pH of the solution was adjusted to 6 with glacial acetic acid, and the mixture was stirred for 30 min. and cooled. The light yellow material was filtered, suspended in 100 ml. of distilled water, and stirred for 30 min. The cyclized product was filtered and dried to yield 5.5 g. of light pink solid (65%), m.p. > 300°. A small sample was recrystallized from glacial acetic acid for analysis.

Anal. Calcd. for $C_6H_4ClN_3O_2$: H, 2.2; N, 22.6. Found: H, 2.5; N, 22.7.

4-Imidazoleacetamide-5-carboxylic Acid.—To 50 ml. of 2 *N* sodium hydroxide was added 2 g. of 4-imidazoleacetamide-5-carboxylic acid methyl ester (XIII). The solution was gently refluxed for 45 min. and then acidified with glacial acetic acid and placed in the refrigerator for 12 hr. The crude brown crystals which were filtered weighed 1.2 g. (70.6%). The crude product was reprecipitated from hot dilute sodium hydroxide (30 ml.) with acetic acid, and the white crystals obtained melted at 240° dec. The compound was dried over phosphorus pentoxide at 110° for analysis.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 42.6; H, 4.1; N, 24.8; neut. equiv., 169. Found: C, 42.4; H, 3.9; N, 24.9; neut. equiv., 168.

The Conversion of 3-Aminoalkylidene-2,4-pyrandiones into 4-Pyridones

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Received April 29, 1963

Dehydroacetic acid reacts rapidly with primary amines in warm aqueous dimethylformamide to give aminoethylidenepyrandiones. These compounds can be converted into N-substituted 4-pyridones. Proof of structure of the intermediate compounds and the mechanistic pathway of the dehydroacetic acid–pyridone conversion are discussed.

The conversion of dehydroacetic acid (I) into 2,6-dimethyl-4-pyridinol by the action of aqueous ammonia was first described by Haitinger in 1885.[1] When methylamine was used, 1,2,6-trimethyl-4-pyridone was formed in 94% yield.[2]

Two mechanisms have been proposed for the reaction of ammonia with I. The simpler route, as suggested by Brody and Ruby,[3] involves attack by ammonia at the 6-position followed by opening of the pyrone ring and recyclization with the loss of water and carbon dioxide. A more complicated mechanism was proposed earlier by Feist.[4] He postulated that ammonia condensed first with the carbonyl group in the side chain with elimination of water. This step is analogous to the reaction of ammonia with ethyl acetoacetate.[5] The pyrone ring would then be opened (presumably by attack of water) and subsequently closed to the pyridone system. The isolation of 3-(1-iminoethyl)-4-hydroxy-6-methyl-2-pyrone and its conversion into 2,6-dimethyl-4-pyridinol[6a,b] would lend support to the latter theory.

We have synthesized several N-substituted 4-pyridones (Table III) using dehydro acids and primary amines as starting materials. The rearrangement of the intermediate compounds (Table II) was studied in detail. Phenethylamine and dehydroacetic acid were heated in 50% aqueous dimethylformamide for 30 minutes. A nonbasic compound, whose analysis indicated condensation with loss of one molecule of water, was obtained in 70% yield. A minor product, isolated in 5% yield, was shown to be 1-phenethyl-2,6-dimethyl-4-pyridone (IV) by an unequivocal synthesis in which 2,6-dimethyl-4-pyrone (V) was used as starting material.[7,8]

The ultraviolet spectrum of the major product shows maxima at 237 and 314 mμ while the pyridone IV has a single maximum at 266 mμ. The course of the

(1) L. Haitinger, *Ber.*, **18**, 452 (1885).

(2) S. Hünig and G. Kobrich *Ann.*, **617**, 181 (1958).

(3) F. Brody and P. R. Ruby, "Pyridine and Derivatives," Part 1, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 186.

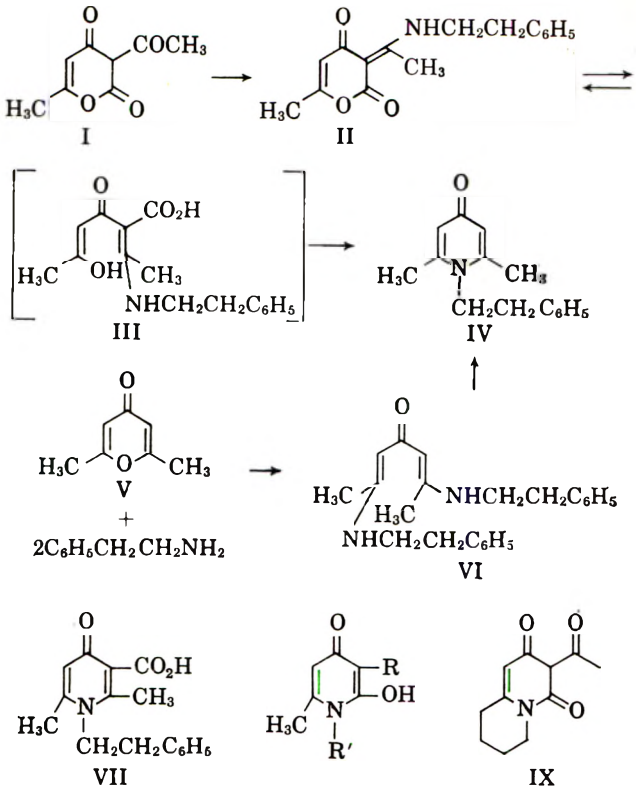
(4) F. Feist, *Ann.*, **257**, 253 (1890).

(5) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 106.

(6) (a) S. Iguchi, K. Hisatsune, M. Himeno, and S. Muraoka, *Chem. Pharm. Bull.* (Tokyo), **7**, 323 (1959). (b) NOTE ADDED AUGUST 7, 1963: S. Garratt, *J. Org. Chem.*, **28**, 1886 (1963), reported the conversion of 3-(α-methylamino)ethylidene-6-methylpyran-2,4-dione into N-methyllutidone by the action of methylamine. In this case, bis-2,7-methylaminohepta-2,5-dien-4-one was isolated as an intermediate.

(7) R. T. Conley, E. Nowoswiat, and W. G. Reid, *Chem. Ind.* (London), 1157 (1959).

(8) R. T. Conley, E. Nowoswiat, and E. Kosak, Abstract of Papers, 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960, p. 13-O. We wish to thank Dr. Conley for a private communication in which he described the experimental conditions for ring closure of bis(aminovinyl) ketones.



VIIIa, R = alkyl or acetyl; R′ = H
b, R = acetyl; R′ = $CH_2CH_2C_6H_5$

reaction was followed by measuring the ultraviolet spectrum of the solid material isolated periodically from an aliquot of reaction solution (Table I). The results show that the intermediate compound is formed rapidly and is converted slowly into IV.

TABLE I

REACTION OF DEHYDROACETIC ACID WITH PHENETHYLAMINE IN DIMETHYLFORMAMIDE–WATER (1:1) AT 105°

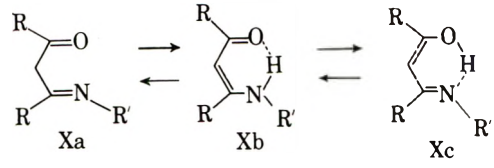
Time	λ_{max}^{MeOH}, mμ			ϵ_{max}		
30 min.	237		314	21,300		22,700
90 min.	237	266	314	18,400	8,900	18,900
3 hr.	237	266	314	11,300	9,600	11,300
6 hr.		266	314		19,800	8,600
12 hr.		266			20,900	

Structures II, VII, and VIIIb were regarded as possibilities for the intermediate compound. The insolubility of the intermediate in sodium bicarbonate and hydroxide solution definitely excludes structure VII. Although 2,6-dimethyl-4-hydroxy-3-pyridinecarboxylic acid was the major product formed in the reaction of ammonia with dehydroacetic acid at temperatures below 100°,[9] we have never been able to isolate pyridonecarboxylic acids in our work with primary amines. In one attempt to synthesize this type of compound, 2,6-dimethyl-4-oxo-3-pyrancarboxylic acid[10] was treated with a solution of phenethylamine in aqueous dimethylformamide at steam bath temperature. Rapid decarboxylation took place under these conditions; compound IV was the only product isolated.

Ketene reacts with pyridine to give a compound of rather complex structure. One of the degradation products (IX) as well as simpler models (VIIIa) were studied by Berson and co-workers.[11,12] A hypsochromic shift of the highest absorption band occurs when the ultraviolet spectra of these compounds are measured in basic solution. The compounds are soluble in sodium hydroxide solution, give positive ferric chloride tests and form 2,4-dinitrophenylhydrazone derivatives. Since none of these properties were shown by the intermediate we isolated, structure VIIIb also may be rejected.

Evidence for structure II was obtained by degradation of the intermediate to sodium dehydroacetate and phenethylamine in the presence of hot alcoholic sodium carbonate solution. The infrared spectrum (chloroform) of II showed strong bands at 1700 (lactone C=O), 1660, 1610, and 1580 $cm.^{-1}$. There was no OH or NH absorption in the normal frequency range in either the infrared or near infrared spectrum; however, strong hydrogen bonding or chelation effects would be expected in this type of compound.[13]

The nuclear magnetic resonance spectra of a number of compounds obtained from the condensation of β-diketones with primary amines have been studied.[14] Of the three tautomeric possibilities (Xa, Xb, or Xc), the compounds were shown to exist predominantly in the ketamine form Xb. Confirmatory evidence for the ketamine structure in the case of the intermediates reported in this paper was provided by the n.m.r. spectrum (deuteriochloroform) of compound XI. The data obtained was quite similar to that reported by Dudek and Holm. The significant feature of the spectrum was a doublet centered at 5.37 τ (J = 6.0 c.p.s.). This indicates splitting of the $N-CH_2$ signal by a hydrogen attached to the nitrogen atom.



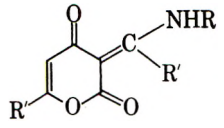
The pathway from compound II to the pyridone ring system most likely involves the open chain intermediate III; however, this part of the mechanism has not been proved conclusively. The dependence upon water for the conversion of II to IV was demonstrated by heating a solution of the ketamine in purified dimethylformamide. At the end of four hours, the ultraviolet spectrum of the recovered solid product did not show the typical 4-pyridone absorption at 266 mμ.

Subtle steric factors apparently play a part in the transformation of the ketamine intermediates into 4-pyridones. This was evident from the fact that α-methylphenethylamine and dehydroacetic acid gave XII as the sole product after twelve hours under the usual reaction conditions (see Table I). Formation of the pyridone XVI in this case required treatment with warm mineral acid. Analogy for this rearrangement is found in the acid-catalyzed conversion of α-anilinomethylene δ-lactones into cyclic enamines.[15] We sug-

(9) J. N. Collie, *J. Chem. Soc.*, **77**, 971 (1900).
(10) J. N. Collie and T. P. Hilditch, *ibid.*, **787** (1907).
(11) J. A. Berson, W. M. Jones, and L. F. O'Callaghan, *J. Am. Chem. Soc.*, **78**, 622 (1956).
(12) J. A. Berson and W. M. Jones, *ibid.*, **78**, 1625 (1956).
(13) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *ibid.*, **71**, 3337 (1949).
(14) G. O. Dudek and R. H. Holm, *ibid.*, **84**, 2691 (1962).
(15) F. Korte, *Angew. Chem. Intern. Ed. Engl.*, **1**, 61 (1962).

TABLE II

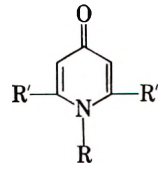
AMINOALKYLIDENEPYRANDIONES

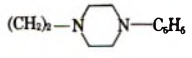
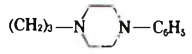


Compd.	R	R′	Yield, %	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
II	$CH_2CH_2C_6H_5$	CH_3	70	90–91	$C_{16}H_{17}NO_3$	70.85	6.28	5.17	71.06	6.19	5.27
XI	$CH_2C_6H_5$	CH_3	69	80–81	$C_{15}H_{15}NO_3$	70.04	5.84	5.45	70.11	5.99	5.37
XII	$CHCH_3CH_2C_6H_5$	CH_3	70	84–85	$C_{17}H_{19}NO_3$	71.58	6.66	4.91	71.52	6.37	4.91
XIII	$(CH_2)_3N(CH_3)_2$	C_6H_5	27	120–121	$C_{23}H_{24}N_2O_3$	73.40	6.39	7.45	73.69	6.53	7.47
XIV	$CH_2CH_2C_6H_5$	C_6H_5	34	146–147	$C_{26}H_{21}NO_3$	78.99	5.32	3.54	78.99	5.31	3.60
XV	β-(3-Indolyl)ethyl	CH_3	80	196–198	$C_{18}H_{18}N_2O_3$	69.68	5.81	9.03	69.29	6.17	9.12

TABLE III

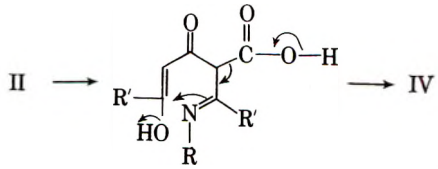
4-PYRIDONES



Compd.	R	R′	Method[a]	Yield, %	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IV	$CH_2CH_2C_6H_5$	CH_3	A	25	164–166	$C_{15}H_{17}NO$	79.30	7.50	6.17	79.20	7.76	6.23
XVI	$CHCH_3CH_2C_6H_5$	CH_3	A	31	235–236	$C_{16}H_{19}NO\cdot HCl$	69.06	7.20	12.77[b]	69.04	7.57	12.71[b]
XVII	$CH_2CH_2C_6H_5$	C_6H_5	A	48	247–252[c]	$C_{25}H_{21}NO$	85.47	5.98	3.99	85.50	6.05	3.77
XVIII	β-(3-Indolyl)ethyl	CH_3	A	79	281–282	$C_{17}H_{18}N_2O$	76.69	6.77	10.53	75.87	6.66	10.60
XIX	$(CH_2)_3$-$N(CH_3)_2$	CH_3	B	70	123–125	$C_{12}H_{20}N_2O$	69.3	9.62	13.46	69.8	9.66	13.38
XX	$(CH_2)_3OH$	CH_3	B	74	188–189	$C_{10}H_{15}NO_2$			7.73			7.88
XXI		CH_3	B	48	157–158	$C_{19}H_{25}N_3O$			13.50			13.42
XXII		CH_3	B	50	144–145	$C_{20}H_{27}N_3O$			12.92			12.67

[a] Method A is the rearrangement of the corresponding pyrandione by heating in dilute sulfuric acid–methanol. Method B is heating a mixture of dehydroacid and amine in water or aqueous dimethylformamide for 6 hr. [b] Chloride ion by titration. [c] Lit. m.p. 258°, M. J. Chauvelier, *Bull. soc. chim. France*, 734 (1954).

gest structure XXIII as an intermediate for the conversion of aminoalkylidene pyrandiones into 4-pyridones in acidic media. In such a species, there should be less crowding in the transition state for ring closure than in structure III; decarboxylation and ring closure would probably occur in concerted fashion.



XXIII

Some hydrolytic cleavage of the aminoalkylidenepyrandione to dehydro acid and primary amine took place during rearrangement in acid. This side reaction was especially serious when R′ = phenyl. At first it was thought that this cleavage represented an alternative pathway for pyridone formation from the intermediate compounds. To test this idea, an equimolar mixture of dehydroacetic acid and phenethylamine was subjected to the conditions of the acid-catalyzed rearrangement. No 4-pyridone was formed; the only solid product isolated was 2,6-dimethyl-4-pyrone, a product of rearrangement of dehydroacetic acid. Therefore, the 4-pyridones formed in the acid-catalyzed rearrangement of aminoalkylidenepyrandiones must be derived from an open-chain species such as XXIII.

Experimental[16]

General Procedure for Synthesis of Aminoalkylidenepyrandiones.—Equimolar quantities of the dehydro acid and primary amine are dissolved in 50% aqueous dimethylformamide. The solution is heated under reflux *ca.* 30 min. in the case of the simpler amines. When higher molecular weight amines or dehydrobenzoylacetic acid are used, a dimethylformamide solution is heated under reflux for 6 hr. The solvents are distilled *in vacuo* and the residual oil is stirred with ether to cause solidification. The crude product may be purified by recrystallization from benzene–hexane or ether–benzene.

3-(1-Phenethylamino)ethylidene-6-methyl-3*H*-pyran-2,4-dione (II).—A solution of 16.8 g. (0.10 mole) of dehydroacetic acid and 12.1 g. (0.10 mole) of phenethylamine in 60 ml. of 50% dimethylformamide was heated under reflux for 30 min. The solvent was distilled *in vacuo* and the residue was treated with ether to produce a solid material. The crude product was stirred for 15 min. in 100 ml. of cold 10% hydrochloric acid, then filtered to give 19.0 g. (70%) of ivory-colored crystals, m.p. 88–89°. An analytical sample of 3-(1-phenethylamino)ethylidene-6-methyl-3*H*-pyran-2,4-dione (II) was prepared by recrystallization from benzene–ether, m.p. 90–91°; λ_{max}^{MeOH} 237, 314 mμ (ε 20,600; 22,200). The infrared spectrum (chloroform) showed strong bands at 1700 (lactone C=O), 1660, 1610, and 1580 cm.$^{-1}$.

(16) Melting points were taken in open capillaries and are corrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 spectrophotometer; ultraviolet spectra were measured with a Warren Spectracord. The n.m.r. spectrum was determined at 60 Mc. with a Varian, Model HR-60, spectrometer.

The compound was insoluble in dilute sodium hydroxide solution, and the ferric chloride test was negative. The iodoform test was also negative and no dinitrophenylhydrazone formed.

The acid filtrate from the previous experiment described was made basic and extracted with chloroform. Drying and concentration *in vacuo* gave 1.05 g. (4.6%) of 1-phenethyl-2,6-dimethyl-4-pyridone, m.p. 164–167°.

2,6-Diphenethylamino-2,5-heptadien-4-one (VI).—A solution of 6.0 g. (0.049 mole) of 2,6-dimethyl-4-pyrone in 50 ml. of water was treated with 11.7 g. (0.097 mole) of phenethylamine. The solution was heated at 90° for 30 min. and cooled. The solid material which formed was collected and recrystallized from benzene–ether to give 4.8 g. (29%) of light yellow crystals, m.p. 114–115°; λ_{max}^{MeOH} 380 mμ (ε 47,400); $\nu_{max}^{CHCl_3}$ 1695, 1590, 1540 (sh), and 1315 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.31; H, 8.05; N, 8.05. Found: C, 79.46; H, 7.96; N, 8.18.

1-Phenethyl-2,6-dimethyl-4-pyridone (IV).—A mixture of 3.80 g. (0.011 mole) of the bis(aminovinyl) ketone (VI) and 50 ml. of water was steam distilled over a 6-hr. period. The distillate was concentrated *in vacuo*, the residue was dissolved in methanol–ether and converted to the hydrochloride (1.26 g., m.p. 257–259°). The free base was regenerated and extracted into chloroform. Drying and concentration *in vacuo* gave a white solid which was stirred in ether and collected; yield, 0.78 g.; m.p. 168–170°. A mixture melting point with 1-phenethyl-2,6-dimethyl-4-pyridone prepared by acid-catalyzed rearrangement of compound II was not depressed.

Conversion of 3-(1-Phenethylamino)ethylidene-6-methyl-3*H*-pyran-2,4-dione (II) into 1-Phenethyl-2,6-dimethyl-4-pyridone (IV).—A solution of 24.0 g. (0.089 mole) of the pyrandione in 200 ml. of methanol and 100 ml. of 30% sulfuric acid was heated under reflux for 1 day. The solution was diluted with 100 ml. of water, and the methanol was distilled. The aqueous solution was made alkaline and extracted with chloroform. Drying and concentration *in vacuo* gave 13.5 g. of yellow solid. Recrystallization from aqueous methanol gave 5.0 g. of white crystalline product, m.p. 168–169°. A further recrystallization gave the analytical sample, m.p. 164–166°; λ_{max}^{MeOH} 266 mμ (ε 20,000); $\nu_{max}^{CHCl_3}$ 1640 and 1560 cm.$^{-1}$.

The identity of the compound with that obtained from dehydroacetic acid and phenethylamine after 12-hr. heating in 50% dimethylformamide was established by spectroscopic and mixture melting point determinations.

2,6-Dimethyl-4-oxo-3-pyrancarboxylic Acid.—A modified procedure of Collie and Hilditch[10] was used. A 10-g. sample of dehydroacetic acid was heated in the presence of 35 ml. of 85% sulfuric acid at 95–100° for 30 min. The orange-colored solution was poured onto 200 g. of ice. The solid which formed was filtered and washed with water to give 1.7 g. of the desired pyrancarboxylic acid, m.p. 97–99° (lit.[10] m.p. 98.5–99°); mixture melting point with dehydroacetic acid was depressed to 80–90°.

Reaction of 2,6-Dimethyl-4-oxo-3-pyrancarboxylic Acid with Phenethylamine.—A solution of 0.70 g. (5.7 mmoles) of phenethylamine and 0.96 g. (5.7 mmoles) of 2,6-dimethyl-4-oxo-3-pyrancarboxylic acid in 25 ml. of 50% dimethylformamide was heated on the steam bath for 90 min. During the first few minutes a brisk evolution of gas was noticed. The solvents were concentrated *in vacuo* and the residue was triturated with ether. The light yellow solid obtained (0.47 g.) had m.p. 150–160°. Recrystallization from benzene–ether gave material with m.p. 159–163°; mixture melting point with 1-phenethyl-2,6-dimethyl-4-pyridone was not depressed.

Basic Cleavage of 3-(1-Phenethylamino)ethylidene-6-methyl-3*H*-pyran-2,4-dione.—A mixture of 0.56 g. (2.1 mmoles) of compound II, 10 ml. of 10% sodium carbonate solution, and enough methanol to give a clear solution was heated under reflux for 2 hr. The methanol was distilled *in vacuo* and cold dilute hydrochloric acid was added to the aqueous solution until pH 4 was attained. The precipitated material was collected and washed with cold water; yield, 0.18 g.; m.p. 108–110°; a mixture melting point with dehydroacetic acid showed no depression.

Behavior of Compound II when Heated under Anhydrous Conditions.—A solution of 1.88 g. of 3-(1-phenethylamino)-ethylidene-6-methyl-3*H*-pyran-2,4-dione (II) in 25 ml. of dried and distilled dimethylformamide was heated at 103° for 4 hr. The absence of the 266-mμ band in the ultraviolet spectrum of the recovered solid indicated that no 4-pyridione formed. There was recovered 1.51 g. (80%) of starting material, m.p. 89–90°.

Hydrolysis of 3-(1-Phenethylamino)ethylidene-6-methyl-3*H*-pyran-2,4-dione in Acidic Medium.—A solution of 6.78 g. (0.025 mole) of compound II in 40 ml. of methanol, 20 ml. of water, and 7 ml. of concentrated sulfuric acid was heated under reflux for 2 hr. The solution was concentrated to a small volume; the solid material which formed at this point was collected and treated with cold dilute sodium hydroxide solution. A chloroform extract yielded 1.69 g. of 1-phenethyl-2,6-dimethyl-4-pyridone (IV). The basic aqueous extract was acidified with hydrochloric acid to give 1.01 g. of dehydroacetic acid.

Attempted Formation of 1-Phenethyl-2,6-dimethyl-4-pyridone from Dehydroacetic Acid and Phenethylamine in Acidic Medium.—To a solution of 16.8 g. (0.10 mole) of dehydroacetic acid in 200 ml. of methanol and 100 ml. of 30% sulfuric acid (by volume) was added 12.1 g. (0.10 mole) of phenethylamine. The solution was heated under reflux for 1 day. The methanol was removed by distillation and the acidic aqueous solution was extracted with benzene. The organic extract was concentrated to produce 1.7 g. of dehydroacetic acid, m.p. 109–111°. The aqueous layer was made alkaline and extracted with chloroform. Concentration of the dried extract gave 7.7 g. of acid-soluble material, m.p. 130–140°. Recrystallization from benzene–ether gave 3.6 g. of white crystalline compound, m.p. 134–135°; mixture melting point with 2,6-dimethyl-4-pyrone showed no depression.

Acknowledgment.—The authors wish to thank Dr. Charles D. Hurd of Northwestern University for helpful discussions during the course of this work, Dr. Elva Kurchacova and Mr. Floyd R. Bunn for analytical services, and the Department of Chemistry, University of Notre Dame, for measurement of the n.m.r. spectrum.

Concerning the Position of Thiocyanation in Pyrrole[1]

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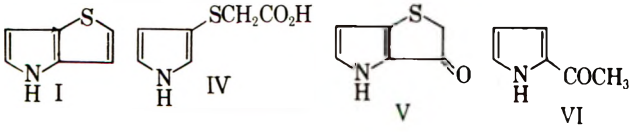
Received June 17, 1963

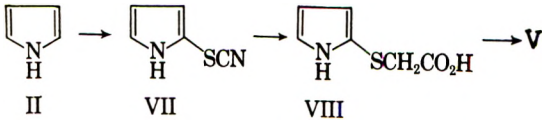
Chemical evidence is presented which confirms the assignment of the structure of 2-thiocyanopyrrole to the product of the thiocyanation of pyrrole. The thiocyanopyrrole obtained from pyrrole is converted to 2-methylsulfonylpyrrole, the structure of which is established by its identity with 2-methylsulfonylpyrrole synthesized from diethyl 3,4-pyrroledicarboxylate by thiocyanation, methylation, oxidation, and decarboxylation.

The position of thiocyanation in pyrrole has been of recent interest.[3,4] In the synthesis of thieno[3,2-*b*]-pyrrole (I), the initial step was thiocyanation of pyrrole (II) with thiocyanogen to give a compound whose structure was assigned as 3-thiocyanopyrrole (III).[5] The evidence for this assignment was that the ketone V, obtained by treating III with bromoacetic acid in basic aqueous methanol and subsequent ring closure of the resulting acid IV with polyphosphoric acid, yielded 2-acetylpyrrole (VI) upon desulfurization with Raney nickel.[5]



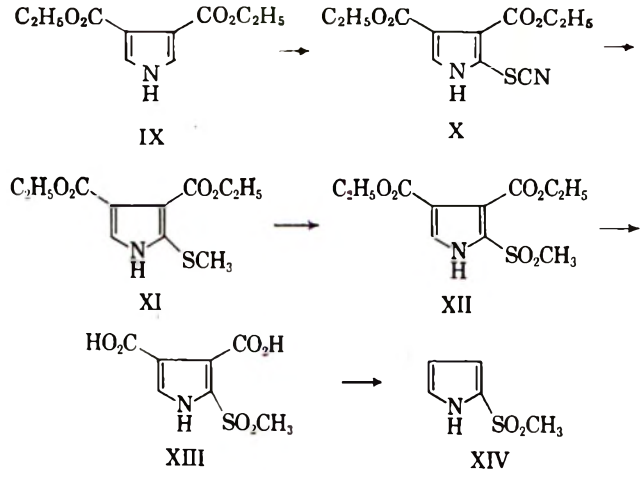
I IV V VI

In studies of the nuclear magnetic resonance spectra of various substituted thiophenes[6] and pyrroles,[7] it developed[3] that the n.m.r. spectra of monothiocyanopyrrole and its simple derivatives are consistent with those of 2-substituted pyrroles and not of the 3-isomers. Gronowitz, Hörnfeldt, Gestblom, and Hoffman, therefore, reassigned the structure of the thiocyanation product as 2-thiocyanopyrrole and recognized the occurrence of rearrangement in the ring closure of 2-pyrrolylthioacetic acid (VIII) in polyphosphoric acid.[3] This paper reports new chemical evidence concerning the position of thiocyanation in pyrrole.



II VII VIII

The initial goal was the thiocyanation of a pyrrole having the 3 and 4 positions blocked by groups that could be removed subsequently. Diethyl 3,4-pyrroledicarboxylate[8] (IX) appeared to be a suitable starting material, provided that the combined effect of the two electron-withdrawing groups would not entirely inhibit the thiocyanation. Although attempts at the thiocyanation with thiocyanogen under a variety of conditions failed, the desired monothiocyano derivative X could be obtained in good yield with the aid of the more reactive reagent thiocyanogen chloride.[9] The infrared spectrum of X has a band at 2155 cm.$^{-1}$ due to the thiocyano group, plus bands for the N–H and ester groups. Compound X was converted to the methylthiopyrrole XI by the reaction with methyl iodide and base in aqueous methanol.[5] Oxidation of XI with hydrogen peroxide in acetic acid[10] occurred to yield the sulfone XII, the infrared spectrum of which has bands at 1300 and 1133 cm.$^{-1}$ due to the sulfonyl group. The sulfone XII underwent basic hydrolysis to the diacid XIII which was decarboxylated upon heating under reflux in 2-aminoethanol[11] to yield 2-methylsulfonylpyrrole (XIV). The reactions all occurred in yields of better than 70% except for the decarboxylation, which occurred in a yield of 53%.



IX X XI XII XIII XIV

The infrared spectrum of 2-methylsulfonylpyrrole (XIV) shows absorption due to the N–H group at 3420 and the sulfonyl group at 1300 and 1135 cm.$^{-1}$, and has no bands due to carbonyl absorption. The n.m.r. spectrum consists of three multiplets assigned to the three ring protons as follows: $\tau_5 = 2.95$, $\tau_3 = 3.06$, and $\tau_4 = 3.67$ p.p.m., and a singlet at $\tau = 6.86$ p.p.m. due to the side-chain methyl hydrogens. The coupling constants, calculated from a spectrum in which coupling with the proton on nitrogen has been eliminated by addition of a few per cent of pyrrolidine,[3] are $J_{34} = 3.6$, $J_{45} = 2.5$, and $J_{35} = 1.4$ c.p.s. These values are in the range expected for a pyrrole substituted in the α-position, the reported values being $J_{34} = 3.40$–3.80, $J_{45} = 2.40$–3.10, and $J_{35} = 1.35$–1.50 c.p.s.[7]

The second objective was to transform the monothiocyanopyrrole obtained from pyrrole to the corresponding sulfone and to compare this with 2-methylsulfonylpyrrole (XIV). Pyrrole was treated with thio-

(1) Supported in part by a research grant (C 3969-Bio) from the National Cancer Institute, Public Health Service.

(2) National Science Foundation Fellow, 1962–1963.

(3) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv. Kemi*, **18**, 151 (1961); see also S. Gronowitz, U. Rudén, and B. Gestblom, *ibid.*, **20**, 297 (1963).

(4) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *J. Org. Chem.*, **26**, 2615 (1961).

(5) D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

(6) S. Gronowitz and R. A. Hoffman, *Arkiv. Kemi*, **16**, 563 (1960).

(7) S. Gronowitz, A. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *ibid.*, **18**, 133 (1961).

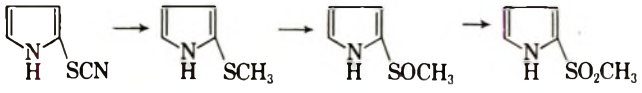
(8) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

(9) R. G. R. Bacon and R. G. Guy, *J. Chem. Soc.*, 318 (1960).

(10) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 801.

(11) E. J. Chu and T. O. Chu, *J. Org. Chem.*, **19**, 266 (1954).

cyanogen at −70° in methanol[6] and the thiocyano compound VII was converted to the methylthiopyrrole XV by treatment with methyl iodide and alkali in aqueous methanol.[5] The infrared spectrum of the methylthiopyrrole XV was superimposable on a previously published spectrum[3] of a sample prepared in the same way.



VII XV XVI XVII

The oxidation of the methylthiopyrrole XV to the sulfone proved to be the critical step. The best results were obtained in a stepwise conversion, first to the sulfoxide and then to the sulfone. Attempts to prepare the sulfone directly from XV gave, in poor yields, a mixture of the sulfoxide and sulfone which proved to be difficult to separate. The sulfoxide XVI was prepared either by oxidation with hydrogen peroxide in acetone (73% yield) or with hydrogen peroxide in aqueous acetic acid (81% yield).[10] The infrared spectrum of the sulfoxide XVI shows strong absorption at 1015–1040 cm.$^{-1}$ in the region for sulfoxide absorption. The decoupled n.m.r. spectrum shows the ring protons as three quartets assigned as follows: τ_5 = 3.05, τ_3 = 3.33, and τ_4 = 3.83 p.p.m., and a singlet due to the methyl protons at τ = 7.05 p.p.m. The coupling constants calculated are J_{34} = 3.60, J_{45} = 2.55, and J_{35} = 1.40 c.p.s., in good agreement with those expected for the 2-isomer but not for the 3-isomer.[7] The sulfoxide XVI was reduced to XV with lithium aluminum hydride,[12] thus establishing that no rearrangement had occurred in the oxidation to the sulfoxide.

The sulfone XVII was formed in a 52% yield from the sulfoxide by oxidation with hydrogen peroxide in acetic acid. The sulfone XVII obtained from thiocyanopyrrole proved to be identical with 2-methylsulfonylpyrrole (XIV) (melting point, mixture melting point, infrared, and n.m.r. spectra).

These results provide chemical evidence that thiocyanation of pyrrole does occur in the α-position and that the previously reported monothiocyanopyrrole[3,5] is, indeed, 2-thiocyanopyrrole (VII).

Experimental[13]

Diethyl 2-Thiocyanopyrrole-3,4-dicarboxylate (X).—A solution of thiocyanogen chloride[9] was prepared by adding potassium thiocyanate (2.95 g., 30.4 mmoles) in one portion to a solution of chlorine (2.13 g., 30.0 mmoles) in 170 ml. of acetic acid which had previously been dried by refluxing with a few milliliters of acetic anhydride. The resulting solution was stirred for 0.5 hr. at room temperature. Diethyl 3,4-pyrroledicarboxylate, prepared according to Kornfeld and Jones,[8] was added in one portion to the solution of thiocyanogen chloride and the reaction mixture was stirred at room temperature for 16 hr.

The yellow solution containing dispersed potassium chloride was poured into 600 ml. of cold water, whereupon a yellow solid formed. The mixture was allowed to stand in the refrigerator for 45 min., after which it was filtered, washed with cold water, and the yellow solid allowed to air dry. The crude product weighed 6.1 g. (82%), m.p. 140.5–142.5°. An analytical sample was prepared by three recrystallizations from 95% ethanol, m.p. 144–145°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44. Found: C, 49.25; H, 4.34; N, 10.53.

Diethyl 2-Methylthiopyrrole-3,4-dicarboxylate (XI).—A solution of diethyl 2-thiocyanopyrrole-3,4-dicarboxylate (X) (3.0 g., 11.2 mmoles) and methyl iodide (2.0 g., 14.0 mmoles) in 35 ml. of methanol was cooled in an ice bath. To the stirred solution was added in one portion a solution of potassium hydroxide (0.7 g., 12.5 mmoles) in 20 ml. of water and 10 ml. of methanol. The reaction mixture was stirred for 4 hr. during which time it was allowed to warm to room temperature. Most of the methanol was removed under vacuum on the steam bath. The yellow oil, which formed in the aqueous phase, was extracted with four portions of methylene chloride and the combined extracts were dried over magnesium sulfate. After filtration, the solvent was evaporated on the steam bath to yield a yellow oil. This oil solidified upon cooling 1 hr. in the refrigerator; 2.6 g. (90%), m.p. 86–92°. Recrystallization from benzene–low boiling petroleum ether (b.p. 30–60°) yielded crystals melting at 94–96°.

Anal. Calcd. for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.23; H, 5.80; N, 5.27.

Diethyl 2-Methylsulfonylpyrrole-3,4-dicarboxylate (XII).—Diethyl 2-methylthiopyrrole-3,4-dicarboxylate (XI) (1.2 g., 4.67 mmoles) was dissolved in 8 ml. of glacial acetic acid. To this solution was added 6 ml. of 30% hydrogen peroxide. The resulting solution was refluxed for 1 hr. and then allowed to cool and stand at room temperature for 16 hr. The reaction mixture was partially neutralized with 7 *N* ammonium hydroxide until crystals formed, after which it was cooled for 1 hr. in an ice bath. The crystals were filtered, washed with water, and dried overnight in a vacuum desiccator over phosphorus pentoxide to yield 1.0 g. of white needles (74%), m.p. 122–125°. An analytical sample was prepared by recrystallizing three times from ethanol–water, m.p. 125–127°.

Anal. Calcd. for $C_{11}H_{15}NO_6S$: C, 45.65; H, 5.22; N, 4.84. Found: C, 45.71; H, 5.24; N, 4.73.

2-Methylsulfonylpyrrole-3,4-dicarboxylic Acid (XIII).—A solution of diethyl 2-methylsulfonylpyrrole-3,4-dicarboxylate (0.8 g., 2.8 mmoles) and potassium hydroxide (0.6 g., 15 mmoles) in 9 ml. of water and 9 ml. of ethanol was refluxed for 2 hr. The reaction mixture was cooled to room temperature and concentrated to about half under vacuum. The reaction mixture was made slightly acidic with concentrated hydrochloric acid, and a white solid formed. The reaction mixture was cooled in an ice bath, filtered, washed with water, and the solid air-dried. The crude product (0.5 g., 78%) was recrystallized from water, m.p. 282–284° dec.

Anal. Calcd. for $C_7H_7NO_6S$: C, 36.04; H, 3.03; N, 6.01. Found: C, 36.29; H, 3.08; N, 5.94.

2-Methylsulfonylpyrrole (XIV).—2-Methylsulfonylpyrrole-3,4-dicarboxylic acid (0.137 g., 0.59 mmole) in 1 ml. of 2-aminoethanol was heated at reflux for 15 min. The yellow reaction mixture was cooled and poured into 10 ml. of water. The clear aqueous solution was acidified with concentrated hydrochloric acid and extracted with four portions of methylene chloride. The combined methylene chloride extracts were washed once with 10% sodium bicarbonate, twice with water, and dried over magnesium sulfate. After filtration, the solvent was removed on a steam bath. There was obtained 45 mg. (53%) of light yellow needles, m.p. 121–123°. An analytical sample was prepared by recrystallizing twice from a methylene chloride–low boiling petroleum ether (b.p. 30–60°) solvent pair, m.p. 122–123°.

Anal. Calcd. for $C_5H_7NO_2S$: C, 41.36; H, 4.86; N, 9.65. Found: C, 41.19; H, 4.80; N, 9.76.

2-Methylsulfinylpyrrole (XVI). Method A.—Freshly distilled 2-methylthiopyrrole (1.5 g., 13.3 mmoles), prepared from pyrrole according to the method of Matteson and Snyder,[5] was dissolved in 3 ml. of acetone. To this solution was added dropwise a solution of 2 ml. of 30% hydrogen peroxide and 3 ml. of acetone. The temperature rose and the reaction mixture turned a rose color within minutes after addition of the hydrogen peroxide solution. The reaction mixture was allowed to stand at room temperature for 72 hr. Most of the acetone was removed under vacuum. The brown liquid that remained was taken up in methylene chloride; water was added and the layers were separated. The aqueous phase was extracted again with methylene

(12) F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **73**, 2251 (1951).

(13) Melting points are uncorrected. The spectra were determined by Mr. D. H. Johnson and his associates. The microanalyses were performed by Mr. Josef Nemeth and his associates.

chloride. The combined extracts were dried over magnesium sulfate. After filtration and removal of the solvent on the steam bath, there was obtained 1.26 g. (73%) of an orange liquid which crystallized upon standing in the refrigerator for 2 hr., m.p. 83–88°. Infrared and n.m.r. spectra showed the product to contain less than 5% of the sulfone. An analytical sample was prepared by chromatography on a short column of neutral alumina, eluting with methylene chloride. The clear liquid obtained crystallized upon standing in the refrigerator and the solid was recrystallized three times by dissolving in methylene chloride and adding low boiling petroleum ether (b.p. 30–60°) almost to the cloud point, m.p. 88.5–90°.

Anal. Calcd. for C_5H_7NOS: C, 46.47; H, 5.46; B, 10.84. Found: C, 46.78; H, 5.47; N, 10.67.

Method B.—Freshly distilled 2-methylthiopyrrole[4] (3.0 g., 26.6 mmoles) was dissolved in 3 ml. of acetic acid. Water was added until the solution became cloudy. The mixture was stirred magnetically and cooled in an ice bath, whereupon more solid formed. To this heterogeneous mixture was added 4 ml. of 30% hydrogen peroxide at such a rate as to maintain the temperature between 10–14°. The reaction mixture became homogeneous shortly after addition of the hydrogen peroxide; it was then allowed to warm to room temperature and was stirred for 13 hr. The reaction mixture was made slightly basic with 50% potassium hydroxide, extracted with four portions of methylene chloride, and the combined extracts were dried over magnesium sulfate. After removal of the drying agent and solvent, there was obtained 3.14 g. (81%) of tan colored crystals, m.p. 73–83°. Two recrystallizations as described in method A gave product melting at 87–89°.

Reduction of 2-Methylsulfinylpyrrole (XVI) with Lithium Aluminum Hydride.[11]—To a suspension of lithium aluminum hydride (0.19 g., 5 mmoles) in 12 ml. of dry ether was added in portions a solution of 2-methylsulfinylpyrrole (XVI) (0.488 g., 3.78 mmoles) in 20 ml. of ether. After the addition, the reaction mixture was refluxed for 6 hr. The excess lithium aluminum hydride was destroyed with water and the aluminum salts were dissolved by the addition of 10% hydrochloric acid. The two layers were separated and the aqueous phase was extracted with three more portions of ether. The combined ether extracts were dried over magnesium sulfate. Filtration and evaporation of the solvent yielded a yellow liquid. Distillation of the liquid through a 24-cm. heated column gave a 50% yield of 2-methylthiopyrrole (XV), identified by comparison of the infrared spectrum with that of an authentic sample.

2-Methylsulfonylpyrrole (XVII).—A solution of 2-methylsulfinylpyrrole (0.122 g., 0.94 mmoles) and 30% hydrogen peroxide (0.4 ml., 4.0 mmoles) in 2 ml. of glacial acetic acid was allowed to stand at room temperature for 43 hr. Ten milliliters of water was added and the reaction mixture was extracted with three portions of methylene chloride. The combined methylene chloride extracts were washed once with 10% sodium bicarbonate solution and once with water, followed by drying over magnesium sulfate. The drying agent was filtered off and the solvent removed on a steam bath to yield 71 mg. (52%) of a light yellow solid, m.p. 115–119°. The solid recrystallized from benzene–low boiling petroleum ether (b.p. 30–60°), m.p. 121.5–123°. This compound proved to be identical with 2-methylsulfonylpyrrole (XIV) as shown by melting point, mixture melting point, and comparison of the infrared and n.m.r. spectra.

The Methylpyrroles. Synthesis and Characterization

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Received July 3, 1963

Convenient syntheses have been devised for all the C-methylpyrroles with the exception of 3-methylpyrrole. Lithium aluminum hydride reduction of a C-acyl to a C-alkyl group was the key step in most of the syntheses. Attempts to use this method for the preparation of N-methylpyrroles were unsuccessful because reduction of C-acyl-N-methylpyrroles stopped at the hydroxymethyl stage, regardless of whether the acyl group was at the 2- or the 3-position. 1,2-Dimethylpyrrole and 1,2,3,5-tetramethylpyrrole were prepared, however, by methylation of the potassium salts of the required C-methyl derivatives. Infrared, ultraviolet, and proton magnetic resonance spectra are tabulated for pyrrole and fourteen N- and C-methylpyrroles.

In the course of a general study of the behavior of indoles and pyrroles in acidic media,[1] an extensive series of methylpyrroles was required. Although these compounds have been known for many years, most of the reported synthetic routes are tedious to carry out and the compounds themselves have not been well characterized.[2] Exceptions are 2,5-dimethylpyrrole and its N-substituted derivatives which can be prepared with ease from 1,4-diketones and the appropriate amines.[1b]

The pyrroles studied in the course of this work are listed in Table II. Pyrrole, 1-methylpyrrole, 2,4-dimethylpyrrole, and pentamethylpyrrole were purchased. Ring closure of the appropriate 1,4-diketone, the method used to prepare 2,5-dimethyl- and 1,2,5-trimethylpyrrole,[1b] was used for the synthesis of 2,3,-4,5-tetramethylpyrrole. 1,2-Dimethyl- and 1,2,3,5-tetramethylpyrroles were prepared by N-methylation of the appropriate precursor. The other pyrroles were synthesized as described subsequently.

Profiting by the observations that carbonyl groups attached to positions 2 or 3 of the pyrrole ring can be reduced to hydrocarbon residues by lithium aluminum hydride,[3] we have devised relatively simple syntheses of only two or three steps for the remaining C-methylpyrroles, with the exception of 3-methylpyrrole. The methods are summarized in equations 1–6 and yields of products are given in Table I. Starting materials for the hydride reductions were prepared by methods in the literature as shown in the equations and cited in Table I. It should be noted that the conversion of a carbonyl group to an alkyl group is not new in the pyrrole series, Wolff–Kishner reductions having been used for many years for this purpose.[2,4] However, the present methods offer much greater freedom in the choice of starting materials.

(1) For leading references see: (a) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962); (b) E. B. Whipple, Y. Chiang, and R. L. Hinman, *ibid.*, **85**, 26 (1963); (c) Y. Chiang and E. B. Whipple, *ibid.*, **85**, 2763 (1963).

(2) For further discussion of this point and characterization of some of the higher alkylpyrroles, see P. S. Skell and G. P. Bean, *ibid.*, **84**, 4655 (1962).

(3) (a) A. Treibs and H. Scherer, *Ann.*, **577**, 139 (1952); (b) A. Treibs and H. Derra-Scherer, *ibid.*, **589**, 188 (1954); (c) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954); (d) acyl groups at the 3-position of the indole nucleus also are reduced to the hydrocarbon residue [E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953)], but acyl groups at the 2-position are reduced only to the carbinol [E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959)].

(4) (a) H. Fischer and B. Walach, *Ann.*, **450**, 109 (1926); (b) J. W. Cornforth and M. E. Firth, *J. Chem. Soc.*, 1091 (1958); (c) F. P. Doyle, M. D. Mahta, G. S. Sach, and J. L. Pearson, *ibid.*, 4458 (1958).

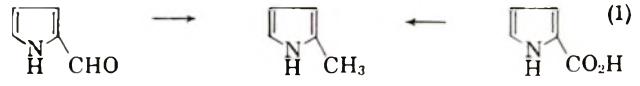
TABLE I

SUMMARY OF $LiAlH_4$ REDUCTIONS

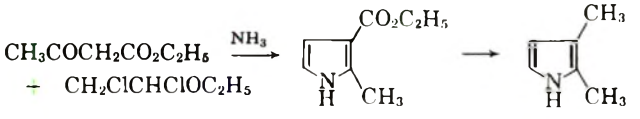
Pyrrole derivative reduced	Ref. to preparation of starting material	Yield of starting material	Moles of pyrrole deriv. reduced	Moles of $LiAlH_4$	Vol. of[a] solvent, ml.	Product (as derivative of pyrrole)	Yield, %	Overall yield, %
2-Formyl	*b*	80	0.2	0.4	700[c]	2-Methyl	63	48
2-Carboxylic acid		20	0.1	0.2	300	2-Methyl	54	10
2-Methyl-3-carbethoxy[d]	*e*	53	0.045	0.09	100	2,3-Dimethyl[a]	61[a]	30
1,3,4-Triscarbomethoxy	*f*	40	0.02	0.08	150	3,4-Dimethyl	50	20
3-Carbethoxy-4-methyl-2-carboxylic acid	*g*	50	0.025	0.17	150	2,3,4-Trimethyl	47	25
2,5-Dimethyl-3-formyl		62	0.04	0.08	100	2,3,5-Trimethyl[h]	81	50
3-Carbethoxy-2,5-dimethyl	*i*	60	0.15	0.30	200	2,3,5-Trimethyl[h]	80	48
1-Methyl-2-formyl[j]	*k*	62	0.05	0.10	250[l]	2-Hydroxymethyl-1-methyl[l]	76[j]	
1,2,5-Trimethyl-3-formyl		99	0.05	0.10	125[m]	3-Hydroxymethyl-1,2,5-trimethyl[n]	44	

[a] Tetrahydrofuran except where noted otherwise. Reaction mixture refluxed overnight except where noted otherwise. [b] See ref. 6. [c] Ether, reflux time 4 hr. [d] Reduction of 2-methylpyrrole-3-carboxylic acid was effected in 40% yield. [e] E. Benary, *Ber.*, **44**, 493 (1911). [f] See ref. 11. [g] See ref. 10. [h] Picrate (from methanol), m.p. 83°. *Anal.* Calcd. for $C_7H_{11}N \cdot C_6H_3N_3O_7$: C, 46.15; H, 4.14; N, 16.75. Found: C, 46.15; H, 4.17; N, 16.56. [i] H. Fischer and B. Heyse, *Ann.*, **439**, 254 (1924), and G. Korschun, *Ber.*, **37**, 2196 (1904). [j] Reduction of 1-methylpyrrole-2-carboxylic acid was effected in tetrahydrofuran in 82% yield. [k] See ref. 8. [l] Ether. [m] Reflux time, 4 hr. [n] *Anal.* Calcd. for $C_8H_{13}NO$: C, 69.02; H, 9.41; N, 10.06. Found: C, 69.10; H, 9.32; N, 9.84.

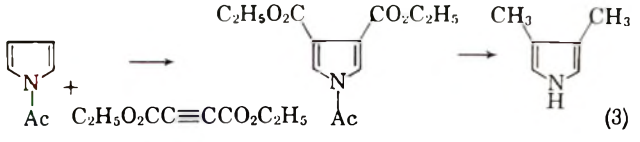
2-Methylpyrrole



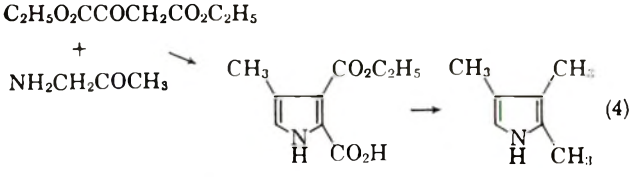
2,3-Dimethylpyrrole



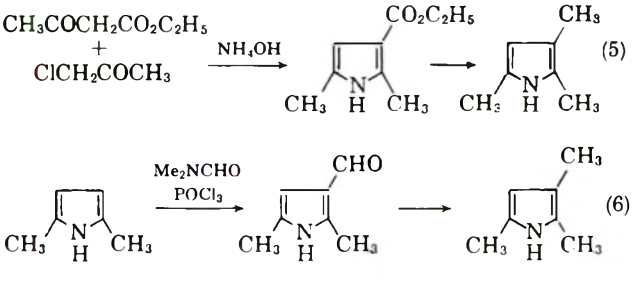
3,4-Dimethylpyrrole



2,3,4-Trimethylpyrrole



2,3,5-Trimethylpyrrole



A few points about the syntheses deserve special comment. Although in our hands the reduction of 3-carbethoxy-2-methylpyrrole gave 2,3-dimethylpyrrole in 61% yield, essentially the same procedure was reported by Treibs to give only tar.[3a] We have no simple explanation for this difference. However, Treibs proposed that the carbinols, which are presumed to be intermediate in the formation of the alkylpyrroles, would readily undergo polymerization, and polymerization of 1-methylpyrrole-2-carbinol has been reported to occur with explosive violence.[4c] In most of our experiments lithium aluminum hydride was present in 300% excess of that required to reduce the carbonyl group to the alkyl group. Since the previous workers[3a] appear to have used in general only small excesses of hydride, substantial quantities of carbinol may have been present at the time of work-up during which polymerization was observed. The success of our technique would then be due simply to the use of more drastic conditions for reduction. Treibs also reported[3b] that carboxyl groups are reduced more readily than are carbethoxy groups. Although our conditions were too severe to permit this distinction to be observed, in all cases studied higher yields of methylpyrroles were obtained from reduction of the esters than from the corresponding acids (Table I).

The loss of the *N*-acetyl group from 1-acetyl-3,4-dicarbethoxypyrrole has a number of precedents of which the closest is found in the hydride reduction of 1-acylindoles.[5]

An attempt was made to prepare 2,3-dimethylpyrrole by formylation of 3-methylpyrrole with dimethylformamide,[6] followed by hydride reduction. The products of formylation consisted of a mixture of 2-formyl-3-methyl- and 2-formyl-4-methylpyrrole in a 4:1 ratio, as measured by n.m.r. Reduction of this mixture produced a mixture of 2,3- and 2,4-dimethylpyrroles, also in a 4:1 ratio. The ratio of products from the formylation reaction was foreshadowed by the 15:1 ratio[7] of conjugate acids of 3-methylpyrrole observed by n.m.r. in 12–18 *M* sulfuric acid,[1c] and foretells in turn the general pattern to be expected of electrophilic substitution of 3-methylpyrrole.

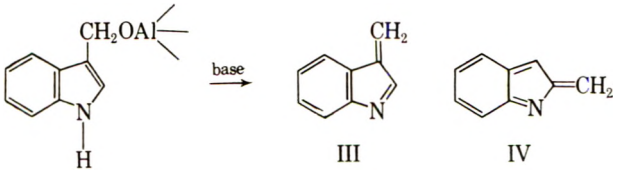
(5) (a) V. M. Mićović and M. Lj. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953); (b) see also N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 575–590.

(6) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Syn.*, **36**, 74 (1956).

(7) Steric hindrance by the 3-methyl group to substitution at the 2-position by the bulky complex of dimethylformamide and phosphorus oxychloride [see, for example, G. F. Smith, *J. Chem. Soc.*, 3842 (1954)] would account for the decreased ratio of 2- to 5-substitution in formylation as compared to that for protonation.

An attempt to extend the general method to the reduction of acylpyrroles bearing an N-methyl group was not successful. It has been observed that N-methylpyrrole-2-carboxaldehyde (I) is similar to pyrrole-2-carboxaldehyde (II) in its failure to undergo many typical reactions of aldehydes,[8a] and earlier work[8b] had shown that inverse addition in the hydride reduction of 2-acylpyrroles leads to carbinols. However, even massive excesses of hydride (6 moles of hydride/mole of aldehyde) in the normal mode of addition did not carry the reduction of I beyond the carbinol stage. The reduction of N-methylpyrrole-2-carboxylic acid also stopped at the carbinol stage, as expected. This effect of an N-methyl group is, interestingly, conveyed also to the 3-position, as shown by the formation of 1,2,5-trimethylpyrrole-3-carbinol from the corresponding formyl compound in contrast to the clean reduction of the formyl to the C-methyl group in the des-N-methyl case (Table I).

These results bear on the mechanism proposed by Leete to explain a similar effect of an N-methyl group in the indole series.[3d] It was assumed in the earlier work[3d] that abstraction of hydrogen from the N–H of an indole-3-carbinol would be accompanied by loss of hydroxyl (in reality —O—Al—) from the carbinol to form a 3-methyleneindolenine III, which would in turn be reduced to the 3-alkylindole. An N-methyl

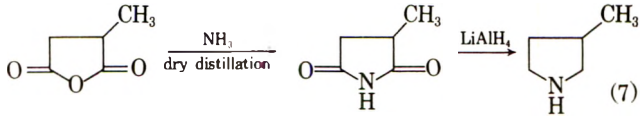


group would prevent this 1,4-elimination. Significantly, 2-hydroxymethylindole did not undergo hydrogenolysis by lithium aluminum hydride, and the lack of reactivity was attributed to the difficulty of forming structure IV, which would be of higher energy than structure III. The clear preference for structures of type III as compared to type IV can be deduced from protonation studies.[1a] In the pyrrole series, structures of type IV are preferred in protonation, but the preference for IV over III is not as marked as is the inverse relationship in the indole series.[1b,c] With the protonation work as background the hydrogenolysis of carbinol groups at the 2- or 3-positions of pyrrole and the inhibition by N-methyl in both cases appears to be entirely consistent with the Leete mechanism.

The preceding methods provide routes to all the C-methylpyrroles except 3-methyl, for which a simple synthesis has yet to be found. Of the more recent methods[4b,9,10] devised for the preparation of 3-methylpyrrole that of Lancaster and VanderWerf[10] is the most straightforward, leading to the desired product in 35% overall yield for the four steps. If 2,3,4-trimethyl- and 3,4-dimethylpyrrole are desired in addition to 3-methylpyrrole, this method becomes very attractive because the two additional pyrroles can be obtained by reduction of intermediates prepared *en route* to 3-methylpyrrole. The economy of effort more than makes up for the number of steps.

In attempting to devise a simpler route to 3-methylpyrrole, the reaction of 1-carbomethoxypyrrole with ethyl propiolate was carried out in a manner similar to that used for the reaction with dimethyl acetylenedicarboxylate. However, instead of the desired 1-carbomethoxy-3-carbethoxypyrrole, a product was obtained which contained ester and vinyl groups, and appeared to be a β-pyrrylacrylic acid ester, formed by conjugate addition of the pyrrole ring to the acetylenic ester. The preference of pyrroles to add to dienophiles in the conjugate manner rather than in Diels–Alder fashion is well known.[11]

A fairly extensive study of the dehydrogenation of 3-methylpyrrolidine also was made. The pyrrolidine is readily obtained by the sequence shown in equation 7.



(7)

The rhodium–alumina catalyst which has been used for the conversion of pyrrolidine to pyrrole[12] was effective, but at 600° where no pyrrolidine was recovered the product was a mixture of about 20% 3-methylpyrrole and 75% of what appeared from n.m.r. and v.p.c. data to be 2-methylpyrrole.[13] At 400° no 2-methylpyrrole was isolated, but 30–40% of the product mixture was unchanged 3-methylpyrrolidine. Despite the quite different boiling points of the two materials, separation by fractional distillation was difficult, probably because of association. Some higher boiling material, probably of the pyrrolidylpyrrole type found in the dehydrogenation of pyrrolidine,[12] and in the hydrogenation of pyrrole,[14] was obtained in each case, and an attempt to effect complete conversion by continuous recyclization of the product mixture at the lower temperatures led to increased quantities of the higher boiling materials. Attempts to carry out the reaction in a static system[15] under pressure at lower temperatures (<300°) were also unsuccessful.

In the course of preparing 3-methylpyrrolidine it was found that the base forms a hydrate from which water cannot be removed by ordinary dessicants such as calcium sulfate. The water, which was identified by v.p.c. and n.m.r., could be removed by calcium hydride. In the v.p.c. the hydrate gives rise to two peaks, one for water and one for the pyrrolidine, from which the composition of the hydrate is estimated as 3-methylpyrrolidine $\cdot 2H_2O$. In the usual method of isolation of the pyrrolidine the hydrate distils first at 92–94°, and the free base comes over at 103–104° after all of the hydrate has been removed. When the crude mixture was treated with calcium hydride before distilla-

(8) (a) W. Herz and J. Brasch, *J. Org. Chem.*, **23**, 1513 (1958); (b) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954); R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, *ibid.*, **76**, 4485 (1954).

(9) H. Plieninger and W. Bühler, *Angew. Chem.*, **71**, 163 (1959).

(10) R. E. Lancaster, Jr., and C. A. VanderWerf, *J. Org. Chem.*, **23**, 1208 (1958).

(11) N. W. Gabel, *ibid.*, **27**, 101 (1962); *cf.* R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 457 (1961).

(12) J. M. Patterson and P. Drenchko, *J. Org. Chem.*, **24**, 878 (1959).

(13) Isomerization of alkylpyrroles at high temperatures has been noted previously. For leading references see I. A. Jacobson, H. H. Heady, and G. V. Dineen, *J. Phys. Chem.*, **62**, 1563 (1958); I. A. Jacobson and H. B. Jensen, *ibid.*, **66**, 1245 (1962); also ref. 2.

(14) D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249 (1958).

(15) H. Adkins and L. G. Lundsted, *ibid.*, **71**, 2964 (1949).

TABLE II

SPECTRAL PROPERTIES OF PYRROLES

Pyrrole	B.p. [m.p.] (mm.), °C.	Lit. B.p. [m.p.] (mm.), °C.	n_D (°C.)	Infrared bands, μ[p] NH[q]	>C=C< (?)[r]	Ultraviolet bands[s] Free base (in H_2O) λ_{max} mμ	ϵ_{max}	λ_{max} mμ	Conjugate acid[w] ϵ_{max}	
Pyrrole[a]	132	130–131 (761)[b]		2.96[t]	6.38 (w), 6.46 (w), 6.53 (m)[v]	205[z]	6700[z]	241	3900	(7.6)
1-Methyl[a]	116	112–114[c]			6.50 (sh), 6.56 (sh), 6.66 (s)	210	5800	247	4100	(7.2)
2-Methyl	146–149	148 (755)[d]	1.5017 (23)[n]	2.93	6.35 (m), 6.43 (w)	208	7100	233	4500	(4.3)
3-Methyl	143–143.5	80 (70)[e]	1.4961 (25)[o]	2.92	6.40 (m)	208	5900	258	4800	(4.8)
1,2-Dimethyl	139–141 (760)	139–140[c]	1.4910 (25)[f]		6.26 (w), 6.48 (m), 6.70 (s)	210	7200	240	4500	(5.1)
2,3-Dimethyl	97 (65)	65 (14)[g]	1.4978 (25)	2.95	6.30 (m), 6.51 (w)	208	5600	246	3800	(5.7)
2,4-Dimethyl[a]	166	160–165 (760)[h]		2.96	6.30 (m), 6.64 (w)	209	5800	249	5200	(4.0)
2,5-Dimethyl	[i]			2.90	6.25 (w), 6.55 (w)	209	7700	237, 275[y]	2900, 740[y]	(2.5)
3,4-Dimethyl	66–67 (16)	65–66 (14)[j]		2.92[s]	6.36 (w), 6.70 (w)[x]	205[z]	4400	271	5800	(4.0)
1,2,5-Trimethyl	[i]				6.24 (w), 6.38 (m), 6.62 (s)	211	8300	243[aa]	3100[aa]	(3.0)
2,3,4-Trimethyl	79 (15) [39.5–40]	[39][j]		2.90	6.25 (w)	208	5100[bb]	262	5000[bb]	(6.8)
2,3,5-Trimethyl	78–80 (15–16)	75–76 (14–15)[k]	1.5045 (24)	2.99	6.22 (s), 6.46 (w), 6.60 (w)	212	6600	252	5700	(4.0)
1,2,3,5-Tetramethyl	80–81 (16)	62–64 (5)[l]	1.4950 (25)		6.30 (m), 6.60 (m)	216	7500	259	5600	(5.1)
2,3,4,5-Tetramethyl	[110]	[112][l]		2.90	6.20 (m), 6.42 (w)	216	5800[cc]	265	5200[cc]	(2.0)
1,2,3,4,5-Pentamethyl[a]	[70]	[69–70][m]			6.28 (w), 6.54 (w)	216	7000	269	5600	(5.1)

[a] Indicates pyrroles which were purchased; all others were prepared in this laboratory. [b] G. L. Ciamician and M. Dennstedt, *Ber.*, **16**, 1536 (1883). [c] H. Rapaport and E. Jorgensen, *J. Org. Chem.*, **14**, 664 (1949). [d] Ref. 4b. [e] Ref. 2. [f] Reported $n^{25}D$ 1.4913 (footnote *c*). [g] O. Piloty, *Ber.*, **45**, 2586 (1912). [h] Ref. 22. [i] Ref. 1b. [j] Ref. 4a. [k] G. Korschun, *Ber.*, **38**, 1125 (1905). [l] F. Ya Perveev and E. M. Kuznetsova, *Zh. Obshch. Khim.*, **28**, 2360 (1958). [m] Private communication from supplier, Aldrich Chemical Co. [n] Reported $n^{25}D$ 1.5002 (ref. 2). [o] Reported $n^{25}D$ 1.4955 (ref. 2). [p] Measurements made on pure liquid. [q] All bands very strong. [r] Reported for CCl_4 solution: 2.8 μ (ref. 21b). [s] Values reported for 3,4-diethylpyrrole (pure liquid): 2.97, 6.39, 6.60 μ (ref. 21b). [t] Assignment on basis of ref. 21a. [u] Reported: 6.34, 6.40, 6.53 μ (ref. 21a). [v] Measurements made on 10^{-4}–10^{-5} *M* solutions of pyrroles. [w] Figures in parentheses are molarities of sulfuric acid solutions on which measurements were made. [x] λ_{max} (95% EtOH) 208 mμ (ϵ_{max} 7300) λ_{max} (*n*-hexane) 217 mμ (ϵ_{max} 7900). Each value is the average of two determinations on freshly distilled material. [y] Values assigned to β-protonated isomer (ref. 1b). [z] Broad. [aa] Long tail absorption to 300 mμ due to β-protonated isomer (ref. 1c). [bb] Uncertain because of impurities observed in n.m.r. [cc] Uncertain because absorption intensity of free base decreases very rapidly with time. Spectrum of conjugate acid undergoes little change.

tion only material of b.p. 103–104° was obtained. Recognition of the existence of the hydrate explains a discrepancy in boiling points for 3-methylpyrrolidine reported some sixty years apart in the literature.[16]

For the syntheses of the N-methylpyrroles methylation of the potassium salt proved the best procedure for 1,2-dimethyl- and 1,2,3,5-tetramethylpyrrole. Synthesis of 1,2-dimethylpyrrole by way of the appropriate 2,5-dimethoxytetrahydrofuran[17] also was carried out, but the last step, conversion of the tetrahydrofuran to the pyrrole by the action of methylamine in acetic acid gave only low yields of product.

Finally it should be noted that the synthesis of 2,3,4,-5-tetramethylpyrrole from commercially available 3,4-dimethylhexane-2,5-dione[18a] is much more convenient than that reported recently in *Organic Syntheses*,[18b] and has the added advantage of being simply extended to the synthesis of N-alkyl derivatives by the substitution of the appropriate amine for ammonia.

As mentioned at the beginning of this report, characterization of the methylpyrroles (and of the alkylpyrroles generally[2]) has in the past been minimal. We report here the infrared, ultraviolet, and proton magnetic resonance spectra at 60 Mc. of all the simple C-methylpyrroles that have been synthesized or purchased, as well as data for some of their N-methyl derivatives (Tables II and III).

(16) F. F. Blicke and C. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952), reported 92–94°, whereas H. Oldach, *Ber.*, **20**, 1657 (1887), gave 103–105°.

(17) N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 867 (1952).

(18) (a) This reaction previously had been carried out with liquid ammonia under pressure; see L. A. Brooks and M. Markarian, U. S. Patent 2,417,046; *Chem. Abstr.*, **41**, 3821c (1947). (b) A. W. Johnson and R. Price, *Org. Syn.*, **42**, 92 (1962).

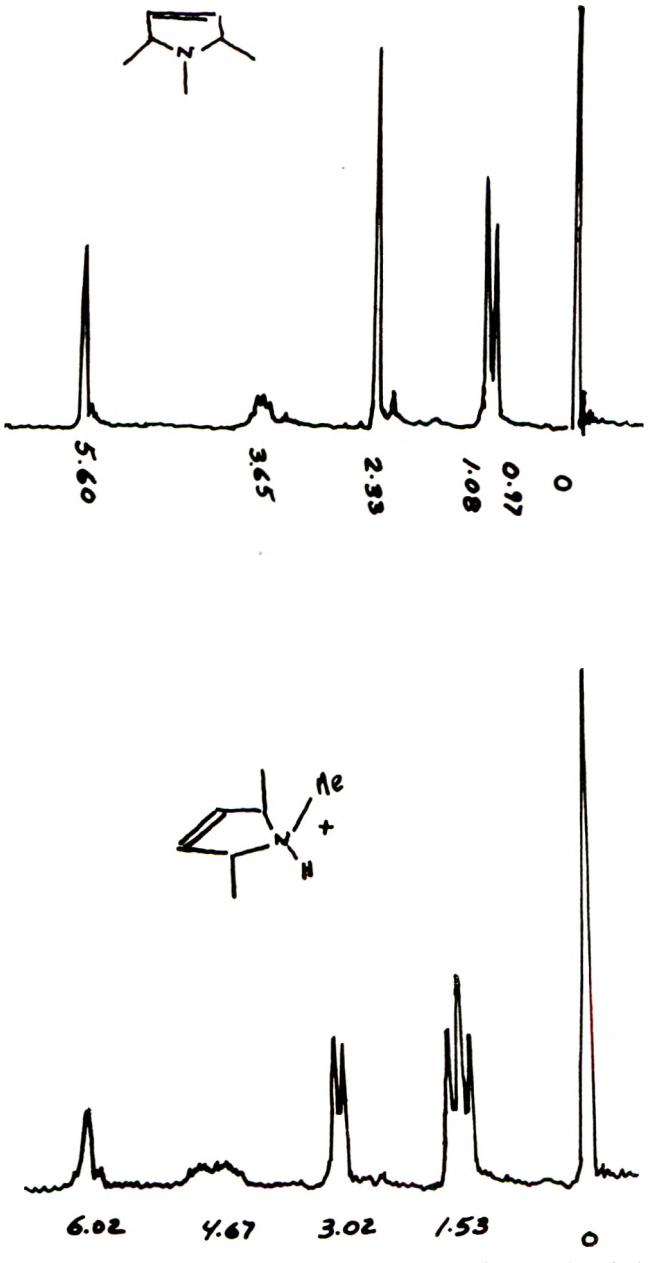


Fig. 1.—Proton magnetic resonance spectra of 1,2,5-trimethyl-Δ^3-pyrroline; values in p.p.m. relative to internal tetramethylsilane; upper, in carbon tetrachloride, lower, in trifluoroacetic acid.

From the ultraviolet data it is apparent that the introduction of methyl groups generally causes small bathochromic shifts in the 205-mμ band of pyrrole. Increases in intensity accompany 2-substitution, whereas introduction of a 3-methyl group has the reverse effect. In this connection it should be noted that an erroneous early report of the ultraviolet spectrum of pyrrole in hexane (λ_{max} 210, 240 mμ; ϵ_{max} 15000, 300)[19a] has been quoted by a number of authors without verification[19b,20] and has led to incorrect conclusions about the perturbing effect of methyl substituents,[20] in particular that alkyl substitution generally causes a decrease in intensity of absorption.[20a] Redetermination of the spectrum of purified pyrrole revealed successive bathochromic shifts and increases in ϵ_{max} in changing from solutions in water to 95% ethanol to *n*-hexane, but even in the last case ϵ_{max} was only about half the value reported earlier and in the concentration range of our experiments there was no evidence of a a peak at 240 mμ (Table II). Bathochromic shifts accompanying methyl substitution in the pyrrole conjugate acids are much larger than those observed for the free bases. The additivity of substituent effects on the 241 mμ band of pyrrole conjugate acid[1c] and the fact that the absorption maximum of a 3-protonated conjugated acid appears at longer wave lengths than its 2-protonated isomer[1b] have been pointed out in other work from this laboratory.

In the infrared spectra, weak bands assigned to the vinyl C–H appear in the customary place from 3.18 to 3.26 μ and methyl CH appears as a strong band in the region from 3.37–3.46 μ. Neither band is shifted much by ring substitution. In the region of 6.25–6.70 μ appear bands that have been previously assigned to carbon–carbon double bonds of pyrrole.[21] This assignment should be accepted with caution, however, since pyrrolidine and 3-methylpyrrolidine both have bands of medium intensity at 6.38 and 6.44 μ. Almost all the pyrroles studied had bands of weak intensity between 5.9 and 6.0 μ. On the assumption that these were due to carbonyl groups formed by autoxidation, a sample of 2,4-dimethylpyrrole, in which this absorption was particularly strong, was distilled from sodium under a nitrogen atmosphere. The intensity of this band in the distillate was greatly reduced, although it was still visible. As the distillate stood open to the atmosphere during fifteen minutes, the intensity of the band increased greatly. By the next day crystals

TABLE III

PROTON MAGNETIC RESONANCE SPECTRA OF PYRROLES IN CARBON TETRACHLORIDE

	Chemical shifts at ring positions indicated[a]				
	1	2	3	4	5
Pyrrole[d,e]	7.7	6.62	6.05	6.05	6.62
1-Methyl	(3.60)	6.37	5.92	5.92	6.37
2-Methyl[d,e]	7.2	(2.16)	5.72	5.89	6.36
3-Methyl	[b]	6.28	(2.05)	5.85	6.42
1,2-Dimethyl	(3.48)	(2.16)	5.67	5.77	6.30
2,3-Dimethyl[e]	7.1	(2.02)	(1.96)	5.82	6.28
2,4-Dimethyl[c,e]	7.0	(2.07)	5.57	(2.00)	6.08
3,4-Dimethyl[c]	[b]	6.27	(1.95)	(1.95)	6.27
2,5-Dimethyl[e]	7.1	(2.13)	5.57	5.57	(2.13)
1,2,5-Trimethyl	(3.27)	(2.10)	5.52	5.52	(2.10)
2,3,5-Trimethyl[c]	[b]	(2.02)	(1.87)	5.42	(2.08)
2,3,4-Trimethyl[c]	[b]	(2.08)	(1.84)	(1.92)	6.15
1,2,3,5-Tetramethyl	(3.28)	(2.05)	(1.89)	5.41	(2.10)
2,3,4,5-Tetramethyl[c]	6.8	(1.98)	(1.80)	(1.80)	(1.98)
Pentamethyl	(3.27)	(2.02)	(1.82)	(1.82)	(2.02)

[a] Referred in p.p.m. to internal tetramethylsilane with positive sense in direction of decreasing magnetic field. Figures in parentheses denote shifts of methyl group protons. [b] Not measured (all NH peaks are very broad). [c] For reported values at 60 Mc. relative to an internal dioxane reference, see R. J. Abraham, E. Bullock, and S. S. Mitra, *Can. J. Chem.*, **37**, 1859 (1959). [d] For values at 40 Mc., see G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.*, **83**, 5020 (1961); R. Abraham and H. Bernstein, *Can. J. Chem.*, **39**, 905 (1961); also ref. 2. [e] For measurements on pure liquids, see *ibid.*, **37**, 1057 (1959).

(19) (a) C. Menczel, *Z. Physik. Chem.* (Leipzig), **126**, 161 (1927); (b) K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(20) (a) G. H. Cookson, *ibid.*, 2789 (1953); (b) V. Eisner and P. H. Gore, *ibid.*, 922 (1958).

(21) (a) P. Mirone, *Gazz. chim. ital.*, **86**, 165 (1956); (b) V. Eisner and R. L. Erskine, *J. Chem. Soc.*, 971 (1958).

had formed in the red oil.[22] To minimize autoxidation all distillations were carried out under nitrogen and spectral measurements were made as soon as possible on freshly distilled material.

For characterization of pyrroles picrates would be useful solid derivatives, were it not for the tendency of pyrroles to dimerize under acidic conditions.[1] The more highly substituted pyrroles such as the 2,3,4-[4a] and 2,3,5-trimethyl- (this work, Table I) and 2,3,4,5-tetramethyl-[4a] pyrroles form picrates of the parent monomers. 2,3-Dimethylpyrrole[23] yields a picrate of its dimer, which is nevertheless useful as a derivative. 3-Methylpyrrole also formed a product melting sharply at 103–103.5°, but a satisfactory analysis for the picrate of either the monomer or the dimer could not be obtained. No products were obtained from attempts to prepare trinitrobenzene derivatives of the pyrroles in methanol.

In the course of this work we had occasion to carry out reductions of 1,2,5-trimethyl- and 2,3,4,5-tetramethylpyrrole with zinc and hydrochloric acid by the procedure reported for the former.[24] The Δ^3-pyrrolines were the principal products in both cases. The *trans* configuration was assigned to the methyls of 1,2,5-trimethyl-Δ^3-pyrroline on the basis of the n.m.r. spectrum taken in trifluoroacetic acid (Fig. 1). In carbon tetrachloride the C-methyls appear as a doublet centered at 1.03 p.p.m. (tetramethylsilane reference), with a coupling constant of 7 c.p.s., but in the conjugate acid the methyl resonance is a triplet centered at 1.53 p.p.m., indicating that the two methyls are in different environments. The remainder of the spectrum is assigned as follows: doublet at 3.02 p.p.m. ($N-CH_3$); broad multiplet at 4.67 p.p.m. (ring protons at 2- and 5-position); singlet at 6.01 p.p.m. (vinyl protons). The technique of assigning stereochemistry by the use of the n.m.r. spectrum of the conjugate acid of an N-alkylamine may be useful in other cases.[25]

Experimental[26]

2,5-Dimethyl-3-formylpyrrole.—The procedure was similar to that used for the synthesis of pyrrole-2-carboxaldehyde.[6] While holding the temperature at 20–25°, 16.9 g. (0.11 mole) of phosphosur oxychloride was added dropwise with stirring to 10 g. of dimethylformamide in a flask protected from atmospheric moisture. A solution of 2,5-dimethylpyrrole (9.5 g., 0.1 mole) in 2 g. of dimethylformamide was added slowly to the stirred mixture while the temperature was maintained at 20–25°. The mixture was stirred at 50° for 30 min., then poured onto 100 g. of ice. The mixture was made alkaline with 125 ml. of 20% sodium hydroxide and heated to boiling for 1 min. After cooling a brown solid separated and was removed by filtration. The filtrate was extracted with ether, the ether was evaporated, and the residual solid was combined with the brown solid isolated by filtration. Crystallization of the combined solids from acetone yielded 7.6 g. (62%) of pale yellow solid, m.p. 144–144.5° (lit.[27] m.p. 144°).

3-Formyl-1,2,5-trimethylpyrrole.—The procedure was similar to and on the same scale as that described previously, but 20 ml. of ethylene dichloride was added to the phosphorus oxychloride–dimethylformamide mixture, followed by 1,2,5-trimethylpyrrole in 5 ml. of ethylene dichloride. The reaction mixture was then heated to 50–60° for 15 min. and finally for 2–3 min. at 85°. After the reaction mixture had cooled to room temperature, 200 ml. of water was added and the mixture was then made alkaline with a solution of 25 g. of sodium hydroxide in 100 ml. of water. The mixture was heated at 85° for 10 min., cooled, and the dichloroethylene layer was separated. The aqueous phase was extracted with two 25-ml. portions of chloroform. The combined chloroform and dichloroethylene solutions were dried over sodium sulfate and the solvents were removed *in vacuo*. The solid residue was crystallized from an acetone–ether mixture, yielding 13 g. (99%) of 3-formyl-1,2,5-trimethylpyrrole, m.p. 96.5–97° (lit.[27] m.p. 96°).

2,3,4,5-Tetramethylpyrrole.—This compound was prepared in 74% yield from 3,4-dimethylhexane-2,5-dione[28] and ammonia by the method reported previously for 2,5-dimethylpyrrole.[1b] The product was a white solid, m.p. 110° (lit.[4a] m.p. 112°).

Reductions with Lithium Aluminum Hydride.—These reactions were all carried out by essentially the same procedure, the compound to be reduced being added to the stirred slurry of the hydride. The conditions are summarized in Table I. Decomposition of excess hydride was effected by the addition in succession of *n* ml. of water, *n* ml. of 15% sodium hydroxide solution, and 3 *n* ml. of water,[5a] where *n* is the number of grams of hydride originally used. The inorganic solids were removed by filtration, the organic layer was dried over magnesium or sodium sulfate, and the solvents were then removed *in vacuo* and the residue was distilled through a 12-in. spinning-band column.

V.p.c. Analysis of Methylpyrroles.—The purity of all methylpyrroles was established by n.m.r. and v.p.c. analysis. With a Perkin-Elmer Model 154-B chromatograph, equipped with an O column, and using helium as the carrier gas at a flow rate of about 80 ml./min., all purified pyrroles showed a single peak of retention time greater than 6 min. at a temperature 15–20° below their boiling points. Under these conditions 2-methyl- and 3-methylpyrrole were easily separated (see section on dehydrogenation of 3-methylpyrrolidine). These isomers could also be identified in their mixtures by infrared spectra,[2] but we found the v.p.c. method more sensitive.

Dehydrogenation of 3-methylpyrrolidine.—The procedure was adapted from that used for the dehydrogenation of pyrrolidine.[12] The reaction chamber was a Pyrex tube 34 × 1.3 cm., preceded by a preheater 22 × 1.3 cm. The preheater contained 15 ml. of Berl saddles, while the reaction tube contained 25 ml. of rhodium–alumina catalyst[12] with a 3-ml. layer of Berl saddles above it and a 7-ml. layer beneath it. Charges of 5–10 g. of 3-methylpyrrolidine were dropped slowly into the reaction tube under dry nitrogen at a flow rate of 150 ml./min. Under these conditions the product mixture obtained as analyzed by v.p.c. is given in Table IV.

TABLE IV

PRODUCT MIXTURE OBTAINED AS ANALYZED BY V.P.C.

	Yields of products[a]		
Compound	600°	500°	400°
3-Methylpyrrolidine	none	10%	30–40%
3-Methylpyrrole	20%	40%	60–70%
2-Methylpyrrole	75%	40%	None
Higher boiling materials	5%	Some	Some

[a] Temperatures are of catalyst bed.

On a Perkin-Elmer O column, column temperature 70°, and flow rate of helium about 80 ml./min., 2-methyl and 3-methylpyrrole had retention times of 12 and 13 min., respectively.

2,3,4,5-Tetramethyl-Δ^3-pyrroline.—The procedure was a modification of that described for the reduction of 1,2,5-trimethylpyrrole.[24] Ten grams of tetramethylpyrrole was dissolved in 50 ml. of methanol and 50 g. of zinc powder was added. Then 300 ml. of 10% hydrochloric acid in methanol was added dropwise to the stirred mixture while the temperature was held at 15–20°. Finally, 50 ml. of concentrated hydrochloric acid was added and

(22) H. Fischer, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 217.

(23) O. Piloty and S. J. Thannhauser, *Ann.*, **390**, 201 (1912).

(24) G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

(25) The authors are indebted to Dr. E. B. Whipple for suggesting and carrying out this experiment.

(26) Boiling points and melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model-21 recording spectrophotometer, equipped with sodium chloride optics. Ultraviolet spectra were determined with a Beckman DK-2 recording spectrophotometer using quartz cuvettes of 1-cm. light path.

(27) E. Ghizi and A. Drusiani, *Atti. accad. sci. ist. Bologna, Classe sci. fis.*, **11**, 14 (1957); *Chem. Abstr.*, **52**, 11818a (1958).

(28) Aldrich Chemical Co., Milwaukee, Wis.

the mixture was stirred for four more hours. Residual zinc was removed by filtration, and the methanol was removed under reduced pressure. The residue was diluted with water, brought to pH 10 with 10% sodium hydroxide solution, and extracted with ether. The combined extracts were dried over potassium carbonate and distilled. The first fraction, b.p. 140–144°, weighed 2 g. and appeared to be the pyrrolidine. A second fraction of 4.5 g. (45%), distilling at 149°, was the Δ^3-pyrroline. The infrared spectrum (pure liquid) had a band at 6.10 μ. The 60-Mc. n.m.r. spectrum in carbon tetrachloride (tetramethylsilane reference) showed a doublet centered at 8.92 p.p.m. with coupling constant of 7 c.p.s., assigned to the 2- and 5-methyls (*cf.* 1,2,5-trimethylpyrrole). A singlet at 8.48 p.p.m. is assigned to the 3- and 4-methyls, and a broad peak at 6.40 p.p.m. is due to the ring protons at the 2- and 5-positions.

The **perchlorate**, recrystallized from methanol and ether, melted at 172°.

Anal. Calcd. for $C_8H_{10}ClNO_4$: C, 42.58; H, 7.14; N, 6.20. Found: C, 42.60; H, 7.13; N, 6.46.

1-Methylpyrrole-2-carboxylic Acid.—Fifteen grams of 1-methylpyrrole-2-carboxaldehyde was dissolved in a solution of 10 g. of sodium hydroxide in 300 ml. of water, and 20 g. of potassium permanganate was added in three portions to the stirred mixture. The temperature rose to 60–70° and was maintained there for 3–4 hr. The filtrate obtained by removal of the manganese dioxide was cooled to 5° and acidified to pH 2 with 5% hydrochloric acid. The product separated in white needles which were recrystallized from water, yielding 3.4 g. (20%) of pure material, m.p. 134–135° (lit.[29] m.p. 135°).

1,2-Dimethylpyrrole.—2-Methylpyrrole (8.19, 0.1 mole) was added dropwise to a stirred mixture of 4.7 g. (0.12 g.-atom) of potassium metal in 200 ml. of anhydrous ether, contained in a flask which was under a positive pressure of nitrogen and which had been previously dried over an open flame while purging with nitrogen. The mixture was refluxed overnight, cooled, and then 30 g. of methyl iodide was added. The resulting solution was refluxed for 4 hr., cooled, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in ether, about 1 g. of potassium metal was added, and the mixture was refluxed for 4 hr. A chaser of 5 ml. of phenyl ether was added and the pyrrole was distilled. The colorless liquid, weighing 6.2 g. (65%), distilled at 74° (65 mm.), and its vapor chromatogram showed a single peak.

1,2,3,5-Tetramethylpyrrole.—The procedure was similar to that presented previously for the preparation of 1,2-dimethylpyrrole, but 1,2-dimethoxyethane was used as the solvent, and the second treatment with potassium was not needed. The product, which weighed 17 g. (67% based on 22 g. of 2,3,5-trimethylpyrrole), was a colorless liquid that distilled at 80–81° (16 mm.).

Anal. Calcd. for $C_8H_{11}N$: C, 77.99; H, 10.63; N, 11.37. Found: C, 78.11; H, 10.75; N, 11.57.

When more than a 20% excess of potassium was used, the product was contaminated by what appeared from n.m.r. data to be pentamethylpyrrole.

(29) E. Fischer, *Ber.*, **46**, 2510 (1913).

Arrested Deamination in the Fischer Indole Synthesis. The Synthesis of 1,2,3,3a,4,8b-Hexahydropyrrolo[3,4-*b*]indoles with Angular Substitution[1]

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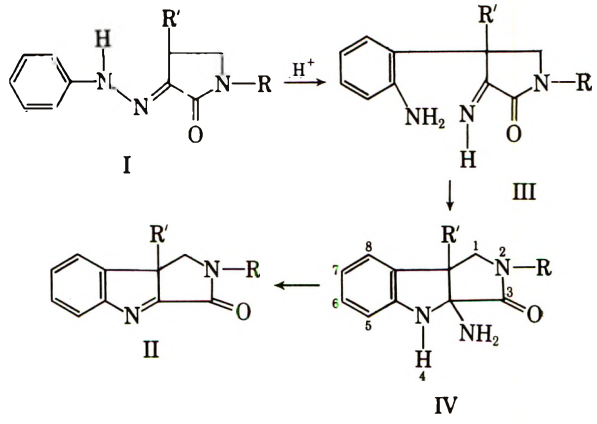
Received June 6, 1963

Phenylhydrazones of 1-substituted 4-benzyl-2,3-dioxopyrrolidines (I) rearrange in methanol–hydrochloric acid mixtures to yield 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (IV). This type of transformation represents a normal Fischer indole synthesis arrested at the point at which ammonia is usually eliminated. The compounds IV were converted into a variety of other products containing the hexahydropyrrolo[3,4-*b*]indole ring system. Thus, it was possible to reduce the lactam carbonyl to a methylene group, to replace the angular 3a-amino function by hydrogen or hydroxyl, to acylate the 4-nitrogen, and to obtain products embodying two or more of such changes. It was shown that compounds of this series resemble alkaloids of the indoline type with respect to ultraviolet spectra and certain color tests.

Compounds in the pyrrolo[3,4-*b*]indole series have recently been made available by application of the Fischer indole synthesis to phenylhydrazones of 2,3-dioxopyrrolidines.[4] In order to make possible a more complete assessment of the potential biological activity of compounds containing this new heterocyclic ring system it was considered of interest to prepare members of the series of the type II, in which an angular substituent and an indolenine rather than an indole nucleus is present. Reduction of such compounds was expected to lead to structures of the type IX, related to the heterocyclic ring system of eserine, but with the position of the nitrogen changed in the outer pyrrolidine ring.

It was anticipated that the compounds II would result from the Fischer indole reaction of phenylhydrazones of 4-substituted 2,3-dioxopyrrolidines (I). When four phenylhydrazones of a series of recently obtained 1-substituted 4-benzyl-2,3-dioxopyrrolidines[5] (I, R′ = benzyl; R = methyl, isopropyl, cyclohexyl, or benzyl) were heated for a short time with methanolic hydrochloric acid, however, rearrangement products which



(1) Supported by a research grant (RG-4371) from the National Institutes of Health, U. S. Public Health Service.

(2) National Science Foundation Undergraduate Research Participant, 1961–1962.

(3) National Science Foundation Cooperative Predoctoral Fellow, 1959–1960. This paper is based principally on a thesis submitted by Richard J. Owellen in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology, September, 1960.

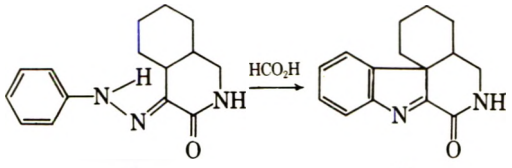
(4) P. L. Southwick and R. J. Owellen, *J. Org. Chem.*, **25**, 1133 (1960).

(5) P. L. Southwick and E. F. Barnas, *ibid.*, **27**, 98 (1962).

retained all three nitrogens of the starting materials were produced in yields of 40–90%. Thus indolenine derivatives II were not formed, but a family of compounds of more novel structure became available for chemical and biological investigation.

It was evident that the first phases of the mechanism of the Fischer indole synthesis had proceeded, since the rearrangement products readily underwent loss of ammonia when heated for thirty minutes with aqueous acetic acid or when heated for longer periods of time with sodium ethoxide. The easy removal of one nitrogen from these products by mild hydrolysis indicated that the N–N bond of the phenylhydrazones had been cleaved in the rearrangement itself, as expected in the Fischer reaction. This result suggested that the products might have the imine structure III, analogous to a product reported by Plieninger[6] to result from acid treatment of the phenylhydrazone of α-ketobutyrolactone. However, the spectroscopic data and the chemical behavior discussed below have led us to conclude that the compounds have the structure of 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (IV, R′ = benzyl). It should be noted that somewhat analogous 1-acyl-2-aminoindolines have been described by Leuchs and his associates,[7] who obtained them by the action of ammonia on suitable 1-acyl-2-halo- or 1-acyl-2-acyloxyindolines.

The failure of the compounds IV to undergo conversion to the indolenines II can apparently be attributed to ring strain which would be associated with a structure such as II. An analogous Fischer indole reaction was carried out by Abramovitch and Muchowski[8a] on the phenylhydrazone A to yield a product tentatively



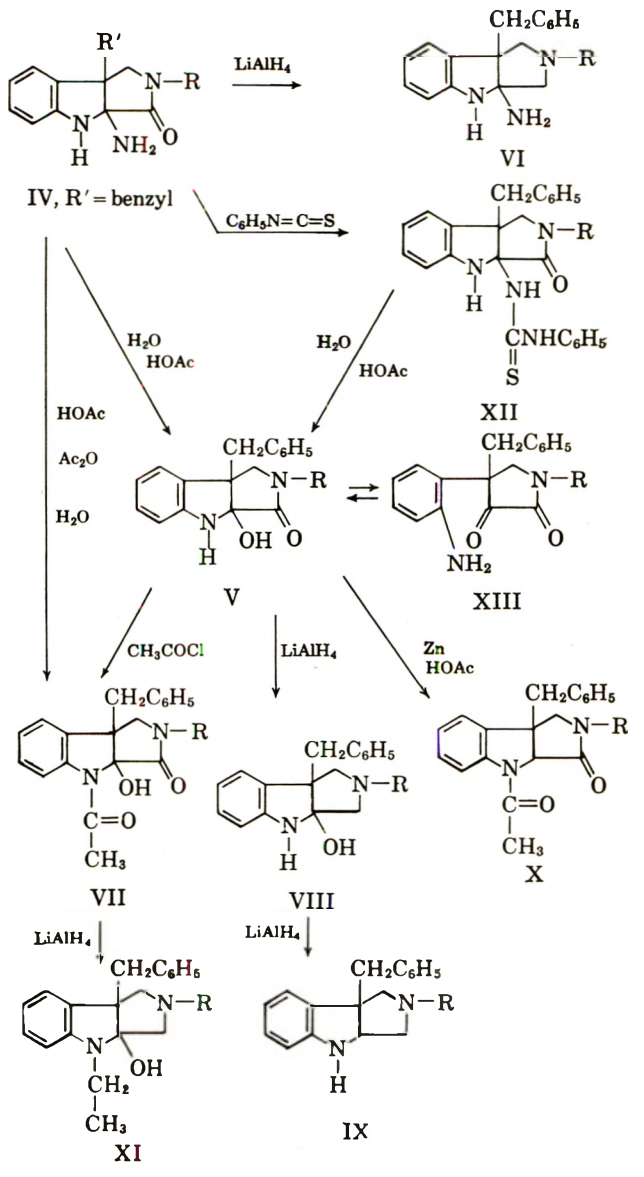
identified as the indolenine B. The difference between this result and our observations with phenylhydrazones of the type I would appear to reflect the difference in the size of the lactam ring. Our results suggest that the indolenine double bond is not readily accommodated in a fused ring system of the type II, in which two rings are five-numbered and rather rigid; whereas if the indolenine B has been obtained as indicated, it is clear that no comparable difficulty exists when the more flexible six-membered lactam (piperidone) ring is present.[8b,c]

(6) (a) H. Plieninger, *Ber.*, **83**, 273 (1950); (b) H. Plieninger and I. Nogradi, *ibid.*, **88**, 1965 (1955).

(7) (a) H. Leuchs, D. Philpott, P. Sander, A. Heller, and H. Köhler, *Ann.*, **461**, 27 (1928); (b) H. Leuchs, A. Heller, and A. Hoffmann, *Ber.*, **62**, 871 (1929).

(8) (a) R. A. Abramovitch and J. M. Muchowski, *Can. J. Chem.*, **38**, 557 (1960). (b) Other interesting effects which can be attributed to the strain which would accompany the presence of a tetrahedral and a trigonal carbon at the junction of two fused five-membered rings have been reported recently by Zaugg and his associates, who have discussed the literature pertaining to the strain energy of such a system. See H. E. Zaugg and R. W. DeNet, *J. Am. Chem. Soc.*, **84**, 4574 (1962), and references cited therein. (c) A referee has pointed out that the rapid ring opening of the presumed indolenine hydroperoxide from autoxidation of cyclopentanoindole [B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1951)] also may illustrate the effects of strain in such systems.

CHART I



Starting from compounds of type IV, a variety of related structures were obtained, as indicated in Chart I. The numbered formulas in the chart designate structural types; individual compounds under discussion will be identified by appending to the number for the structural type a letter indicating the nature of the group R: b for benzyl, c for cyclohexyl, i for isopropyl, and m for methyl. Most of the reactions were first examined with the cyclohexyl derivative IVc, and then applied to one or more of the other compounds. In all compounds which were studied the group R′ was benzyl.

It will become apparent from the ensuing discussion that the interrelationships and properties of the varied reaction products support the assigned structure IV for the initial rearrangement products. It should be noted at the outset, however, that the uncyclized imine structure III for these compounds does not appear to be consistent with their failure to yield diazonium salts (IVc appeared to be converted largely to an N-nitroso compound), to give condensation products with salicylaldehyde, or to undergo hydrogenation in the presence of platinum or Raney nickel catalysts. Moreover, the ultraviolet data to be dis-

cussed and the lack of an infrared band assignable to an imino group[9] favor the choice of structure IV over structure III.

Also pertinent to the question of whether structure III or structure IV should represent the initial rearrangement products was the behavior of a phenylthiourea derivative obtained from one of the rearrangement products (IVc) with excess phenyl isothiocyanate. The hydrolysis of this substance, which occurred when it was merely heated for a short time in aqueous acetic acid, resulted in the loss of the entire phenylthioureido group; the hydrolysis products were phenylthiourea and the same compound (Vc) produced by mild hydrolysis of IVc itself. A product formed by reaction of the aromatic amino group of IIIc with phenyl isothiocyanate could yield phenylthiourea only by cleavage of the bond between nitrogen and the aromatic ring. Since such cleavage is not reasonable, the phenyl isothiocyanate must have reacted with a different nitrogen atom, and in the case of structure III, this would be the nitrogen of the imino group. Such a result would require that the imino group be reactive and the amino group be relatively inert toward phenyl isothiocyanate. No reason for such unexpected behavior is evident. Structure IV, on the other hand, would seem to accommodate the observations plausibly through direct conversion to a derivative of structure XIIc.

It would not have been surprising to find the products Vc, Vi, and Vm, obtained by hydrolysis of compounds of the types IV or XII with aqueous acetic acid, existing at least in part in an open form XIII. However, although some samples of Vc showed a barely discernible absorption at 5.68 μ, the infrared spectra of these compounds in chloroform never displayed the strong absorption at that wave length which is characteristic of the ketonic carbonyl of 2,3-dioxopyrrolidines.[10,11] The open form XIII can therefore have been present only in a very small concentration in these solutions, and the tricyclic fused ring formula V with the angular hydroxyl probably correctly represents the structure of the compounds. The infrared spectra in chloroform solution showed a shoulder at *ca.* 2.8 μ and a broad absorption at *ca.* 3.0 μ consistent with the O–H and N–H bonds of formula V.[12]

Lithium aluminum hydride reduction of the angular amino compounds IVc, IVi, and IVm removed the lactam (pyrrolidone) carbonyl group, but all of the nitrogen atoms were retained. The yields were in the range 47 to 61%. The infrared spectra revealed no evidence of a carbon–nitrogen double bond or other unsaturation. The composition and the additional spectroscopic evidence to be discussed subsequently favor formula VI for these basic compounds, with the fused ring system and angular amino group left undisturbed during the reductions.

Lithium aluminum hydride reduction also removed the pyrrolidone carbonyl group from the compounds Vc and Vm, but two reduction products were obtained in each case, one in which the angular hydroxyl group was retained (structure VIII) and a second in which that group had been removed (structure IX). Combined yields of both products were typically around 70%, but the relative amounts of VIII and IX obtained varied considerably between different runs. It was found that treatment of VIIIc with lithium aluminum hydride under the conditions of the original reduction converted a part of it into the desoxy compound IXc, but the conversion was never found to be complete. The infrared spectra of compounds VIIIc and VIIIm showed bands at 2.80 and 2.95 μ, indicating the presence of both O–H and N–H bonds, whereas IXc and IXm showed only the N–H absorption at 2.95 μ. The successful synthesis of the 1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles IXc and IXm represented the fulfillment of one of the original objectives of the investigation.

Compound Vc was also reduced with zinc and acetic acid, a procedure which has been applied to 2-hydroxyindolines by Volz and Wieland.[13] As in the case of the latter compounds, the hydroxyl group was removed. In the present instance, acetylation accompanied the reduction to yield a product of structure X. The compound showed no infrared bands corresponding to N–H or O–H absorption, and had very intense absorption at 5.94 μ,[14a] evidently representing both amide and pyrrolidone carbonyl groups. The same procedure also gave Xc from IVc.

Acetylation of either the angular amino compound IVc or the angular hydroxy compound Vc yielded a product of structure VIIc with an angular hydroxyl group and an acetylated indoline nitrogen. (The processing of the reaction mixtures would have allowed for hydrolytic removal of the angular nitrogen.) It was found that compound VIIc could be made directly from the phenylhydrazone Ic in 50% yield by adding acetic anhydride to acetic acid–hydrochloric acid solutions in which rearrangement of the phenylhydrazone was being carried out. The acetylated angular hydroxy compound VIIc showed broad hydroxyl absorption (3.04–3.13 μ) indicative of hydrogen bonding. Two well separated carbonyl bands were present (5.92 and 6.13 μ). The 6.13-μ band can no doubt be assigned to the N-acetyl group, and the shift to longer wave length as compared to the band for the N-acetyl group in compound X probably reflects hydrogen bonding with the angular hydroxyl.[14b]

Lithium aluminum hydride reduction of VIIc reduced both amide carbonyls to yield the N-ethyl derivative XIc, with the angular hydroxyl retained as in compounds VIIIc or VIIIm. The infrared spectrum of com-

(9) The phenylhydrazones all displayed very strong infrared bands at 6.20–6.24 μ which were much diminished in intensity in their rearrangement products. The remaining weaker absorption at 6.18–6.24 μ persisted in all members of the series of compounds, including the fully reduced structures IX. A band at this position is characteristic of indolines. See W. V. Philipsborn, H. Meyer, H. Schmid and P. Karrer, *Helv. Chim. Acta.*, **41**, 1257 (1958).

(10) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(11) *Cf.* (a) W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 98, 1554, 1560 (1957); (b) W. R. Vaughan and I. S. Covey, *J. Am. Chem. Soc.*, **80**, 2197 (1958); (c) H. H. Wasserman and R. C. Koch, *Chem. Ind.* (London), 128 (1957); *J. Org. Chem.*, **27**, 35 (1962).

(12) In the case of compound Vm, crystallization from different solvents (95% ethanol or an *n*-hexane–benzene mixture) produced different crystalline forms which exhibited the same infrared spectrum in chloroform, but gave potassium bromide pellet spectra which differed slightly in the carbonyl region.

(13) H. Volz and T. Wieland, *Ann.*, **604**, 1 (1957).

(14) (a) This carbonyl absorption is at a wave length intermediate between that observed for N-acetylindoles (5.90 μ) and for some acetylated indoline alkaloids (6.01 μ). See B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **76**, 5603 (1954). (b) Witkop and Patrick found the carbonyl absorption of an N-acetylindoline derivative (demethylaspidospermine) shifted to 6.12 μ by hydrogen bonding with a hydroxyl group.

TABLE I

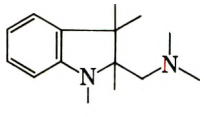
COLOR TESTS AND ULTRAVIOLET MAXIMA

Compound	H_2SO_4–$Ce(SO_4)_2$ colors[a]		HNO_3 colors[b]		Ultraviolet maxima			
					Neutral solution[c]		Acid solution[d]	
	Immediate	After 20 min.	Immediate	After 15 min.	λ, mμ	log ε	λ, mμ	log ε
Ic	...	...	Blue	Orange				
IVc	Pale crimson	Crimson	Pale yellow	Red-brown	241	3.78	235	3.79
					295	3.37	286	3.58
Vc	Crimson	Deep crimson	Pale crimson	Pale red-orange				
VIc	Bright orange	Orange-red	Pale yellow	Pale orange-brown	246	3.86	238	3.87
					301	3.43	294	3.40
VIIc	Pale wine-red	Pale red-brown	None	Pale yellow	252	4.11		
					277 i	3.42		
					287	3.30		
VIIIc	Bright orange	Orange-red	Pale yellow	Orange	246	3.89	241	3.90
					300	3.43	301	3.45
IXc	Orange-red	Orange-red	Yellow	Orange	246	3.85	246	3.86
					301	3.40	302	3.42
Xc	Pale pink	Pale yellow-brown	None	None	252	4.09		
					279	3.41		
					288	3.33		
XIc	Pale crimson	Pale crimson	Deep scarlet	Deep scarlet	258	4.08	252	4.08
					311	3.58	302	3.35

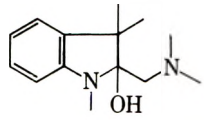
[a] The reagent[21] was a 1:1 mixture, by volume, of concentrated sulfuric acid and 1% ceric sulfate in 2 *N* sulfuric acid. [b] The reagent was concentrated nitric acid. [c] Ultraviolet spectra in 95% ethanol; i indicates inflection. [d] Solvent was 0.1 to 0.25 *N* hydrochloric acid in aqueous ethanol.

pound XIc showed only a single sharp band at 2.80 μ in the O–H or N–H region.

The members of this series of hexahydropyrrolo[3,4-*b*]indoles resemble such alkaloids as ajmaline,[15] tetraphyllicine,[16] and C-alkloid-Y[17] in that they incorporate the partial structures C or D. As a result, there were noted among these compounds some similarities to the properties of the alkaloids or their



C



D

derivatives which cannot be attributed just to the presence of the indoline structure alone. All of the members of the series show typical indoline ultraviolet spectra (Table I), with principal maxima near 250 mμ and secondary maxima near 300 mμ, but it is particularly significant that when the spectrum of a compound of the type IX (IXc) was measured in dilute acid solution there was almost no change, although the spectra of aromatic amines or simple indolines[18] are completely altered in appearance and greatly reduced in intensity in such acid solutions. In this respect, the behavior of IXc parallels that of deoxydihydroajmaline,[18] and it is evident that the indoline nitrogen is not being protonated in either case, probably, as pointed out by Hodson and Smith[18] with respect to deoxydihydroajmaline, because a more basic nonindoline nitrogen, only two carbons removed, has been protonated first. The compounds VIIIc and XIc also retained spectra of the indoline type in acid solution, although a small hypsochromic shift was observed.[19]

Compounds of the types IV and VI, like eserine, contain a basic nitrogen atom attached at the 2-position of the indoline portion of the structure. The ultraviolet spectra of these compounds are very similar to that of eserine,[18] both in neutral solution and in dilute acid solution, in which all of the spectra undergo a hypsochromic shift of 6 to 10 mμ. This spectroscopic resemblance to eserine constitutes additional substantial evidence that these compounds incorporate a 2-aminoindoline structure. The compounds VIIc and Xc showed ultraviolet spectra typical of N-acylindolines.[20]

Certain color tests which have proved useful in the classification of curare alkaloids,[17b,21] were found applicable to the synthetic hexahydropyrrolo[3,4-*b*]indoles obtained in the present investigation (see Table I). With ceric sulfate in sulfuric acid[21] all of the compounds tested developed characteristic colors, but the colors were rather pale in the case of the compounds VIIc, Xc, and XIc in which the indoline nitrogen was substituted. A stable orange color was obtained from compound IXc, as is true of indoline alkaloids having an unsubstituted indoline nitrogen.[17b] The test with concentrated nitric acid served to distinguish compounds with an acylated indoline nitrogen (VIIc and Xc gave little or no color) from the other members of the series. The most striking result with nitric acid was the deep scarlet color obtained from XIc which recalls the similar characteristic color reportedly obtained from C-alkaloid-Y.[17a] Like XIc, the alkaloid is believed to

(15) See (a) R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956); (b) M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Peak, N. V. Bringi, and E. Wenkert, *J. Am. Chem. Soc.*, **84**, 622 (1962), and references cited therein.

(16) (a) C. Djerassi, M. Gorman, S. C. Pakraski, and R. B. Woodward, *ibid.*, **78**, 1259 (1956); (b) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakraski, *ibid.*, **79**, 1217 (1957).

(17) (a) H. Fritz, T. Wieland, and E. Besch, *Ann.*, **611**, 268 (1958); (b) A. R. Battersby and H. F. Hodson, *Quart. Rev.* (London), **14**, 77 (1960).

(18) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 1877 (1957).

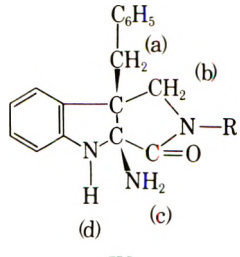
(19) Addition of sodium hydroxide did not further extend the bathochromic shift represented by the change in spectra upon changing the hydrochlorides of VIII and IX into the corresponding free bases, although certain alkaloids containing the 2-hydroxyindoline structure show a bathochromic shift in sodium hydroxide.[17] The reason for this difference is not clear, but it may be associated with such structural dissimilarities as the more rigid ring systems or the additional basic nitrogen in VIII and XI as compared to the alkaloids.

(20) *Cf.* J. Kebrle, H. Schmid, P. Waser, and P. Karrer, *Helv. Chim. Acta*, **36**, 102 (1953).

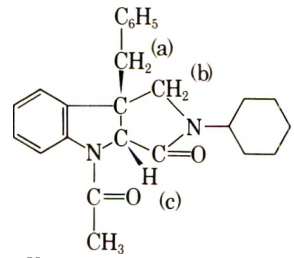
(21) H. Schmid, J. Kebrle, and P. Karrer, *ibid.*, **35**, 1864 (1952).

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA



IV



Xc

Compound	Proton position	Line pattern	Line positions (c.p.s.) separation from TMS[a]	Chemical shift, τ-scale[b] Individual proton	Av.
IVb[c]	a	AB quartet	1 −161, 2 −174	7.17	7.00
			3 −186[d], 4 −199	6.82	
	b	AB quartet	1 −186[d], 2 −195	6.81	6.56
			3 −217, 4 −226	6.32	
	c	Broad peak (2 protons)	−122	...	7.97
	d	Broad peak (1 proton)	−303		4.95
IVc[e]	a	AB quartet	1 −162, 2 −175	7.17	6.97
			3 −189, 4 −202[d]	6.77	
	b	AB quartet	1 −193, 2 −202[d]	6.69	6.50
			3 −218, 4 −227	6.31	
	c	Broad peak[f]	*ca.* −119		*ca.* 8.02
	d	Broad peak (1 proton)	*ca.* −298		*ca.* 5.03
Xc[e,g]	a	Singlet (2 protons)	−180		7.00
	b	Singlet (2 protons)	−221		6.31
	c	Singlet (1 proton)	−281		5.31[h]
	d	Singlet (3 protons)	−141		7.65

[a] Determinations were made at 60 Mc. with a Varian high-resolution dual purpose instrument, Model V-4302. The solvent used was deuteriochloroform, with tetramethylsilane (TMS) as the internal reference. [b] Calculated chemical shifts for individual protons in pairs which give AB quartets (see Jackman, ref. 22a, pp. 89–90) are recorded in the left-hand column. In the right-hand (Av.) column absorptions appearing as singlets are given, as well as midpoints of AB quartets and approximate centers of broad unresolved absorptions. [c] In compound IVb the N-benzyl group gave rise to a barely resolved AB quartet with lines at −247, −262, −266, and −282 c.p.s.; midpoint 5.60 τ. [d] Strongest signal of the overlapping AB patterns; coincidence of lines indicated. [e] In the spectra of IVc and Xc the lines at *ca.* 6.30 τ were apparently superimposed over a broad unresolved absorption which is presumed, on the basis of its appearance and chemical shift, to be due to the proton on C-1 of the cyclohexyl group. [f] The absorption overlapped that arising from a portion of the spectrum of the cyclohexyl group. [g] A multiplet corresponding approximately to one proton was observed at *ca.* 1.88 τ on the downfield side of the main aromatic absorption of Xc. These signals may arise from the proton at position 5 of the ring system, which might be subjected to a long-range shielding effect by the acetyl carbonyl group at position 4 (*cf.* Jackman, ref. 22a, pp. 121–125). [h] The chemical shift of this proton is intermediate between those of similarly situated protons at the 2-position of the N-acetylindoline structures in spegazzinidine (doublet at 5.95 τ) and 3-dehydrospegazzinidine dimethyl ether (singlet at 4.89 τ). See C. Djerassi, *et al.*, *J. Am. Chem. Soc.* **84**, 3480 (1962). The downfield shift of this absorption in the spectra of compound Xc and 3-dehydrospegazzinidine dimethyl ether relative to its position in the spectrum of spegazzinidine reflects the effect of an α-carbonyl group, which in compound Xc may be partly offset by long-range shielding from the aromatic ring in the benzyl group (*cf.* Jackman, ref. 22a, pp. 18–19 and 51–52).

contain the partial structure D with an angular hydroxyl group and a substituted indoline nitrogen.

Nuclear magnetic resonance (n.m.r.) spectra of several numbers of this series were measured, and in the case of two types of compounds (IV and X) the signals from the various hydrogens were sufficiently well separated to permit an analysis of the significant part of the data (see Table II). In structures IV and X the angular benzyl methylene group and the only hydrogen-bearing carbons of the pyrrolidine rings are all separated from each other by a quaternary carbon, the atom at position 8b of the ring system. Hence there should be no vicinal spin–spin coupling affecting these hydrogens, and relatively simple line patterns might be anticipated. In the case of compound Xc, the spectrum from these portions of the structure was in fact, as simple as possible; there were single unresolved lines with appropriate intensity relationships for the benzyl methylene hydrogens at position a (see formulas given with Table II), for the pyrrolidine methylene hydrogens at position b, for the single pyrrolidine hydrogen at position c, and for the acetyl methyl hydrogens at position d. Evidently the individual hydrogens constituting the geminal pairs at positions a and b do not differ sufficiently from each other in chemical shift to give rise to resolved patterns of the AB type,[22a] despite the fact that these hydrogens are configurationally nonequivalent in this asymmetric structure.

On the other hand, the data indicate that each of the two pairs of geminal hydrogens at positions a and b in compounds IVb and IVc give rise to an AB quartet. These two quartets overlap to a slightly different extent in the spectra of the two compounds; as indicated in Table II, line 3 of the pattern from position a coincides with line 1 from position b in the spectrum of IVb, whereas line 4 of the pattern from position a coincides

(22) (a) See L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp. 89, 90. (b) private communication from Dr. Bernard L. Shapiro; the compound in question is that labeled VII in the communication by F. A. Hochstein, H. Els, W. D. Celmer, B. L. Shapiro, and R. B. Woodward, *J. Am. Chem. Soc.*, **82**, 3225 (1960); the geminal coupling constant was 9.8 ± 0.2 c.p.s.. (c) See L. M. Jackman, ref. 22a, Chap. 4.

with line 2 from position b in the spectrum of IVc. The amino proton at position d evidently gave rise to the broad and somewhat variable absorption seen at *ca.* 5.0 τ in the spectra of IVb and IVc, and the two protons of the angular amino group at position c appeared as a rather broad but well defined absorption at *ca.* 8.0 τ in the spectrum of IVb. The latter absorption was evident in the spectrum of IVc, also, but overlapped the absorption of the cyclohexane ring. The geminal coupling constants for the hydrogens at b in IVb and IVc were in the range of 9 to 10 c.p.s., close to a value observed for analogously situated geminal hydrogens in the γ-lactone portion of an oleandomycin degradation product[22b]; the spectra of five-membered lactams and lactones are apparently similar in this respect.

The indicated assignments of the lines of the n.m.r. spectra are supported by chemical shift data on related pyrrolidones which have been examined in this laboratory, and by similar data in the literature.[22c] That the spectra of compounds IVb and IVc are more complex than that of Xc may in part reflect the fact that with molecules in the relatively unstrained *cis* configuration at the junction of the two five-membered rings the angular benzyl group would be *cis* to the angular amino group in compounds IVb and IVc, so that the two protons of the geminal pair at position a, as well as those at position b, could be unequally influenced by the amino group.

One of the compounds in the pyrrolo[3,4-*b*]indole series prepared previously,[4] 2-cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole, has shown some indications of weak activity in tests for central nervous system effects.[23] Several compounds obtained in the present investigation are undergoing biological screening, but no significant activity has been demonstrated as yet.

Experimental[24]

1-Isopropyl-4-benzyl-2,3-dioxopyrrolidine.—A suspension of 20 g. of 1-isopropyl-4-benzal-2,3-dioxopyrrolidine[5] in 250 ml. of 95% ethanol and 1 ml. of concentrated hydrochloric acid was hydrogenated over 120 mg. of Adams' platinum oxide catalyst in a Parr apparatus for 30 min. at *ca.* 5-atm. initial pressure while the pressure bottle was heated with an infrared lamp. (Recent experiments with other similar compounds indicate that a 10% palladium-on-calcium carbonate catalyst used in neutral ethanol at room temperature may give superior results in this type of hydrogenation.) The solution was filtered while still hot to remove the catalyst and an insoluble, white by-product, and evaporated to dryness under reduced pressure. The residual oil was crystallized from aqueous ethanol to give 10 g. (50%) of white needles. For analysis the compound was recrystallized three times from cyclohexane to give long colorless needles, m.p. 171–172.5°.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.38; H, 7.17; N, 6.06.

Infrared spectrum (μ): 2.80 w, 3.14 s, 3.32 s, 3.40 m, 3.48 m, 5.62 w, 5.98 s, 6.19 m, 6.66 m, 6.82 s, 6.97 m, 7.16 s, 7.21 s, 7.28 s, 7.45 m, 7.53 m, 7.83 s.

1-Substituted 4-Benzyl-2,3-dioxopyrrolidine Phenylhydrazones (I, R′ = Benzyl).—These compounds were prepared by suspending the 1-substituted 4-benzyl-2,3-dioxopyrrolidines[5] in 95% ethanol (5 ml./g.), adding phenylhydrazine (150 mole %) and glacial acetic acid (2 ml.), then heating the mixture at the boiling point for 10 to 20 min. Most of the starting material gradually dissolved and the solution turned yellow before the product began to precipitate. At the end of the heating period the mixture was cooled in an ice bath to complete precipitation of the product, which was collected by filtration, washed with cold 95% ethanol, and air-dried. Yields quoted are of the crystalline products as obtained in this way directly from the reaction mixtures. In a number of cases the products were pure enough to be used in the subsequent reaction without further purification. For analysis the compounds were recrystallized three times from 95% ethanol. Results with individual compounds are described in subsequent sections.

1-Methyl-4-benzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 10 g. (95%) of pale yellow cubic crystals m.p. 163–165°, from 8 g. of 1-methyl-4-benzyl-2,3-dioxopyrrolidine. The analytical sample melted at 168–170° dec.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.96; H, 6.63; N, 14.44.

Infrared spectrum: 2.97 m, 3.31 m, 3.39 m, 3.44 m, 5.88 s, 6.20 s, 6.68 s, 6.85 m, 6.96 s, 7.09 m, 7.62 m, 7.74 m, 7.94 s.

1-Isopropyl-4-benzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 4 g. (48%) of long white needles, m.p. 205–206°, from 6 g. of 1-isopropyl-4-benzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.32; H, 7.06; N, 12.92.

Infrared spectrum: 2.97 w, 3.32 m, 3.37 w, 3.42 w, 5.91 m, 5.97 m, 6.22 s, 6.60 m, 6.65 m, 6.70 m, 6.90 m, 6.97 s, 7.28 w, 7.74 m.

1,4-Dibenzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 10 g. (75%) of fluffy white needles, m.p. 189–191°, from 10 g. of 1,4-dibenzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.28; N, 11.37. Found: C, 77.38, 77.13; H, 6.24, 6.10; N, 11.50. (No reason for the low carbon value is apparent.)

Infrared spectrum: 2.98 w, 3.33 w, 3.43 w, 5.90 s, 6.20 s, 6.61 w, 6.68 m, 6.71 m, 6.92 m, 6.98 m, 7.36 w, 7.54 w, 7.76 w, 7.98 s.

1-Cyclohexyl-4-benzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 24 g. (86%) of pale yellow or colorless prisms, m.p. 194–196° dec., from 20 g. of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.00; H, 7.72; N, 11.80.

Infrared spectrum: 2.99 w, 3.33 m, 3.41 m, 3.49 m, 5.95 s, 6.24 s, 6.62 m, 6.68 m, 6.73 m, 7.01 s, 7.77 m, 7.99 s.

The normal white phenylhydrazone melting at 194–196° dec. (1 g.) was isomerized to what may be a *syn–anti* isomer when it was refluxed for 2 hr. on the steam cone in a chloroform–benzene mixture (1:1 by volume), and the solution was evaporated to dryness. The residual oil crystallized slowly from a benzene–*n*-hexane mixture. There resulted 0.6 g. (60%) of bright orange needles that melted at 119–120° after three more recrystallizations from 95% ethanol. This material remained unchanged during 36-hr. refluxing in 95% ethanol.[25]

Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.32; H, 7.44; N, 11.55.

Infrared spectrum: 3.09 w, 3.42 s, 3.51 m, 6.04 s, 6.28 s, 6.64 s, 6.74 m (sh), 6.91 s (sh), 7.02 s, 7.66 m, 7.78 m, 8.01 s.

2-Substituted 3a-Amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (IV).—The 1-substituted 4-benzyl-2,3-dioxopyrrolidine phenylhydrazone (I) was suspended in a solution prepared from methanol (10 ml./g. of phenylhydrazone) and concentrated hydrochloric acid (1 ml./g. of phenylhydrazone). The mixture was heated on a steam cone until complete solution had occurred. After the solution had been cooled to room temperature rapidly in an ice bath, 10 to 20% aqueous sodium hydroxide was added slowly with cooling until the solution was strongly basic. ("Alkacid" test paper, Fisher Scientific Co.,

(23) The authors are indebted to Smith Kline and French Laboratories for biological screening. 2-Cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-indole produced some behavioral effects indicative of central nervous stimulation in rats at high dose levels, and was found partially effective in preventing one of the central effects of reserpine in the rat, the reserpine-induced ptosis. *Cf.* J. R. Gillette, J. V. Dingell, F. Sulser, R. Kuntzman, and B. B. Brodie, *Experientia*, **17**, 417 (1961), and references cited therein.

(24) Melting points are uncorrected. Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Geller Microanalytical Laboratories, Bardonia, N. Y. Ultraviolet spectra were determined with a Cary recording spectrophotometer; infrared spectra with a Perkin-Elmer Model 21 spectrophotometer. Intensities of infrared bands are recorded as strong, s (0–30% transmittance), medium, m (30–60% transmittance), and weak, w (60–90% transmittance); wave lengths (μ) are given for the 2.5- to 8.0-μ range in chloroform. Shoulders are indicated by (sh).

(25) R. A. Abramovitch, *Can. J. Chem.*, **36**, 354 (1958), reports the occurrence of *syn–anti* isomerization of the phenylhydrazone of 4-methyl-2,3-dioxopiperidine in the presence of zinc chloride or boron trifluoride, and the failure of the substance, unlike the isomer described here, to undergo the Fischer indole synthesis.

indicated a pH >12.) The product was extracted into chloroform and the solution was dried over magnesium sulfate. After filtration the chloroform solution was evaporated to dryness under reduced pressure, the residual oil was taken up in hot benzene or chloroform, and *n*-hexane was added to induce crystallization. Yields quoted are of the crystalline products as obtained in this way. (Alternatively, initial crystallization of IVc was induced by adding anhydrous ether to the residual oil.) The compounds were recrystallized from benzene–*n*-hexane mixtures with the exception of the 2-benzyl and 2-isopropyl compounds (IVb and IVi), with which chloroform–*n*-hexane mixtures were used. Benzene was avoided altogether in work with these compounds because it formed solvated crystals. Compound IVc crystallized well from mixtures of benzene and anhydrous ether. Results with individual compounds are listed.

3a-Amino-8b-benzyl-2-methyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]-indol-3(2*H*)-one (IVm).—The yield was 1.4 g. (70%) of colorless needles, m.p. 176–177°, from 2 g. of 1-methyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.76; H, 6.37; N, 14.60.

Infrared spectrum: 2.97 w, 3.36 m, 3.43 w, 3.50 w, 5.92 s, 6.22 m, 6.70 m, 6.75 s, 6.83 s, 6.90 m, 6.96 m, 7.12 m, 7.17 m, 7.66 m, 8.02 m.

3a-Amino-8b-benzyl-2-isopropyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (IVi).—The yield was 1.5 g. (75%) of short white needles, m.p. 148.5–149°, from 2.0 g. of 1-isopropyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone.

Anal. Calcd. for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.62; H, 7.05; N, 13.19.

Infrared spectrum: 2.95 m, 3.33 m, 3.44 w, 5.91 s, 6.17 m, 6.71 s, 6.80 s, 7.18 m, 7.28 m, 7.62 m.

3a-Amino-2,8b-dibenzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (IVb).—The yield was 2 g. (57%) of crude product, m.p. 90–100°, from 3.5 g. of 1,4-dibenzyl-2,3-dioxopyrrolidine phenylhydrazone. After two recrystallizations from acetic acid–water, two from benzene–*n*-hexane, and four more from benzene, white needles were obtained, m.p. 132–133°.

Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.28; N, 11.63. Found: C, 78.30; H, 6.48; N, 11.25.

Infrared spectrum: 2.98 w, 3.33 w, 3.43 w, 5.90 s, 6.23 s, 6.61 w, 6.68 m, 6.71 m, 6.92 m, 6.98 m, 7.36 w, 7.54 w, 7.76 w, 7.98 s.

3a-Amino-8b-benzyl-2-cyclohexyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (IVc).—The yield was 18 g. (90%) of colorless prisms, m.p. 163–164°, from 20 g. of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone.

Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.48; H, 7.31; N, 11.87.

Infrared spectrum: 3.01 w, 3.38 w, 3.43 m, 3.51 w, 5.97 s, 6.24 m, 6.76 m, 6.84 m, 6.91 m, 7.20 w, 7.79 w.

Starting with 1.0 g. of the orange isomer (m.p. 119–120°) of the normal phenylhydrazone, the same product was obtained in a yield of 0.4 g. (40%). The identity of the two products was shown by a mixture melting point determination.

2-Substituted 3a-Amino-8b-benzyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles (VI).—To a stirred solution of lithium aluminum hydride dissolved in ether (0.04 g./ml.) the solid 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]-indol-3(2*H*)-one (IV) was added in small portions. The lithium aluminum hydride was present in excess; 1 g. was used per gram of compound reduced. The mixture was refluxed for 2 hr. with stirring after the addition was complete. The excess hydride was destroyed by slow addition of a 20% aqueous solution of sodium potassium tartrate with continued stirring. The mixture was allowed to stir for 20 min. and was then filtered. The ether layer was separated and evaporated to dryness. The residual oily product was crystallized from *n*-hexane. Results with individual compounds are described.

3a-Amino-8b-benzyl-2-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIm).—The yield was 0.35 g. (61%) of white needles, m.p. 144–145°, from 0.6 g. of compound IVm. Three recrystallizations from cyclohexane failed to raise the melting point.

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.29; H, 7.98; N, 14.55.

Infrared spectrum: 2.95 w, 3.42 m, 3.53 w, 3.62 m, 6.22 m, 6.73 s, 6.83 s, 7.18 m, 7.58 w, 7.98 m.

3a-Amino-8b-benzyl-2-isopropyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIi).—The yield was 0.45 g. (47%) of white needles, m.p. 118–119°, from 1.0 g. of compound IVi. Three more recrystallizations from *n*-hexane failed to raise the melting point.

Anal. Calcd. for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20; N, 13.67. Found: C, 77.77; H, 8.46; N, 13.61.

Infrared spectrum: 2.91 w, 3.34 s, 3.56 m, 6.18 m, 6.70 s, 6.80 s, 7.10 m, 7.17 m, 7.32 m, 8.00 m.

3a-Amino-8b-benzyl-2-cyclohexyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIc).—The yield was 6.0 g. (62%) of colorless prisms from 10 g. of compound IVc. Three recrystallizations from *n*-hexane yielded a product of m.p. 107–108°. (Another crystalline form, m.p. 115–117°, was also encountered.)

Anal. Calcd. for $C_{23}H_{29}N_3$: C, 79.49; H, 8.41; N, 12.09. Found: C, 79.61; H, 8.44; N, 12.13.

Infrared spectrum: 2.96 w, 3.43 m, 3.51 m, 3.60 w, 6.24 m, 6.74 m, 6.84 m, 6.90 m, 7.18 w, 7.36–7.48 w.

2-Substituted 3a-Hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (V).—A mixture of the 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]-indol-3(2*H*)-one (IV) and 60% aqueous acetic acid (*ca.* 6 ml./g. of compound) was heated on a steam cone. Compounds Vc and Vm precipitated during a heating period of 30 to 90 min. The mixture was then cooled (to room temperature for Vc and Vm, to 0° for Vi) and the product was collected by filtration, washed with water, and air-dried. Yields quoted are of the initial crystalline product unless otherwise indicated.

2-Methyl-3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (Vm).—The yield was 1.2 g. (48%) of orange plates from 2.5 g. of compound IVc. After three recrystallizations from benzene–*n*-hexane or aqueous acetic acid, white plates were obtained, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 72.91; H, 6.17; N, 9.39.

Infrared spectrum: 3.00 w, 3.35 w, 3.43 w, 3.50 w, 5.91 s, 6.20 w, 6.69 w, 6.74 m, 6.82 m, 6.88 w, 7.12 w, 7.68 w.

A second form of the compound, m.p. 215–217°, was obtained by crystallization from 95% ethanol.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.36; H, 6.28; N, 9.29.

The 217° form melted at 207° when crystallized from benzene–*n*-hexane. The infrared spectra of the two forms were identical in chloroform, although the potassium bromide pellet spectrum of the 207° form showed a closely spaced splitting of the carbonyl band (5.83, 5.88, 5.94 μ) not found in the 217° form.

2-Isopropyl-3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (Vi).—The yield after two recrystallizations from absolute ethanol was 0.8 g. (53%) of white needles, m.p. 197°, from 1.5 g. of compound IV heated for 2.5 hr.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 8.69; H, 6.88. Found: C, 74.71; H, 8.55; N, 7.01.

2-Cyclohexyl-3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (Vc).—The yield was 3.5 g. (70%) of pale yellow prisms, m.p. 163–166°, from 5.0 g. of compound IV. After three recrystallizations from aqueous acetic acid, colorless plates were obtained, m.p. 164–165°.

Anal. Calcd. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.69; H, 7.32; N, 7.79.

Infrared spectrum: 2.80 w, 3.00 m, 3.34 m, 3.41 s, 3.49 m, 5.96 s, 6.19 m, 6.78 s, 6.81 s, 6.87 s, 7.30 w, 7.70 m, 7.95 m.

When IVc was refluxed with ethanolic sodium ethoxide, ammonia was evolved. The reaction mixture yielded Vc (29% yield) as the only crystalline product.

2-Substituted 8b-Benzyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles (IX) and 2-Substituted 8b-Benzyl-3a-hydroxy-1,2,3,-3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles (VIII).—To a solution of lithium aluminum hydride (1 g./g. of compound to be reduced) in anhydrous ether (*ca.* 100 ml./g. of hydride) the 2-substituted 3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3-(2*H*)-one (V) to be reduced was added in solid form. The mixture was stirred and refluxed for 1–8 hr. then the excess hydride was destroyed by cautious addition of a 20% aqueous sodium potassium tartrate solution. The mixture was stirred for an additional 30 min., and the ether solution filtered and evaporated to dryness under reduced pressure. Results in the preparation of individual compounds are given.

8b-Benzyl-2-cyclohexyl-3a-hydroxy-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIIIc).—The reduction of 4 g. of compound Vc using a 1-hr. reaction period yielded an oil which was dissolved in hot *n*-hexane. When the solution was cooled to *ca.* 30° and allowed to stand, white needles, m.p. 126–130°, were deposited first. Recrystallization from cyclohexane afforded 0.95

g. (32%) of fluffy white needles, m.p. 129°. (Yields in different runs varied from 20 to 32%, and IXc once separated before VIIIc.) An analytical sample, m.p. 129–130°, was prepared by successive crystallizations from *n*-hexane and cyclohexane.

Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.29; H, 7.75; N, 7.13, 8.16.

Infrared spectrum: 2.80 w, 2.95 w, 3.43 s, 3.51 m, 3.60 m, 6.21 m, 6.72 m, 6.82 m, 6.89 m, 7.15 m, 7.27 m, 7.46 m, 7.60 w.

8b-Benzyl-2-cyclohexyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (IXc). A. From Vc Directly.—The *n*-hexane solution from which the crystals of compound VIIIc had been deposited initially in the procedure described previously was concentrated by evaporation. A 1.15-g. quantity (40%) of compound IXc was deposited as colorless prisms, m.p. 96–99°. Yields of this product varied from 37 to 49% in different runs. Repeated recrystallization from *n*-hexane raised the m.p. to 98–100°.

Anal. Calcd. for $C_{23}H_{28}N_2$: C, 83.08; H, 8.49; N, 8.43. Found: C, 83.04; H, 8.23; N, 8.51.

Infrared spectrum: 2.95 w, 3.42 s, 3.51 m, 3.60 w, 6.22 m, 6.70 w, 6.76 m, 6.83 m, 6.90 m, 7.29 w, 7.57–7.68 w, 8.02 w.

B. From VIIIc.—Reduction of 0.65 g. of compound VIIIc by the same procedure used with Vc yielded, as the first crop of crystals from *n*-hexane, 0.15 g. (23%) of recovered starting material, and, as the second crop, 0.35 g. (56%) of compound IXc, m.p. 93–98°. Recrystallization from *n*-hexane gave colorless prisms, m.p. 98–110°. In another run 32% of VIIIc was recovered and 41% of IXc was obtained.

8b-Benzyl-3a-hydroxy-2-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIIIm).—An 8-hr. reaction period was used for the reduction of 5.5 g. of Vm. The crude product was dissolved in a boiling benzene–*n*-hexane mixture and the solution allowed to cool slowly to room temperature. Crystals of compound VIIIm separated over a period of several hours. After removal of the mother liquor by decantation the product (1.1 g., 22%, m.p. 128–129°) was recrystallized three times from benzene–*n*-hexane mixtures to give colorless prisms, m.p. 129–130°.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.14; H, 7.17; N, 10.00. Found: C, 76.55, 77.15; H, 7.05, 7.18; N, 10.35.

Infrared spectrum: 2.79 w, 2.92 w, 3.38 m, 3.48 m, 3.56 m, 6.18 m, 6.70 m, 6.80 m, 7.12 m, 7.42 w, 7.55 m, 7.96 m.

8b-Benzyl-2-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (IXm).—The mother liquor from which the crystals of compound VIIIm had separated, as described previously, was cooled for 36 hr. in a refrigerator. A second product (IXm) (2.3 g., 48%, m.p. 84–85°) separated and was recrystallized twice from benzene–*n*-hexane mixtures to yield long, colorless needles, m.p. 84.5–85.5°.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.55; H, 7.58; N, 10.78.

Infrared spectrum: 2.90 w, 3.38 m, 3.49 m, 3.58 m, 6.21 m, 6.71 s, 6.81 s, 7.14 w, 7.38 w, 7.59 w, 7.97 m.

4-Acetyl-8b-benzyl-2-cyclohexyl-3a-hydroxy-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (VIIc). A.—To 5 g. of compound Vc was added 10 ml. of freshly distilled acetyl chloride, and the mixture was warmed on a steam cone until all of the excess acetyl chloride had evaporated. The flask was then cooled to room temperature and 25 ml. of cold water was added. The gummy product was stirred until it had completely solidified. The water layer was then decanted and the solid recrystallized from aqueous ethanol to give 3.2 g. (57%) of white needles, m.p. 195–198°. Two recrystallizations from a benzene–*n*-hexane mixture raised the m.p. to 199–200°.

Anal. Calcd. for $C_{25}H_{28}N_2O_2$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.67; H, 7.01; N, 6.90.

Infrared spectrum: 3.04–3.13 w, 3.42 m, 3.51 m, 5.92 s, 6.13 s, 6.27 m, 6.76 s, 6.84 m, 7.10 m, 7.30 s, 7.43 s, 7.56 m, 7.74 m.

B.—To a solution of 35 ml. of glacial acetic acid and 8 ml. of acetic anhydride saturated with dry hydrogen chloride was rapidly added 3.5 g. of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone. The mixture was swirled until the solution was complete, allowed to stand for 90 min. at room temperature, and then made strongly basic by addition of 20% aqueous sodium hydroxide with cooling. The product was extracted into benzene, and the benzene solution was dried over magnesium sulfate, then chromatographed on alumina. The product was eluted with acetone after the column had been washed with benzene, and was crystallized from an acetic acid–water mixture. Two grams (50%) of white needles was obtained, m.p. 197–198°. A mixture melting point with the product obtained by procedure A was not depressed.

8b-Benzyl-2-cyclohexyl-4-ethyl-3a-hydroxy-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (XIc).—To a solution of 2 g. of lithium aluminum hydride in 50 ml. of anhydrous ether, 1.9 g. of compound VIIc was added in small portions. The mixture was stirred and refluxed for 1 hr., then 20% aqueous sodium potassium tartrate solution was added dropwise until the excess hydride was destroyed. The mixture was then stirred for 30 min. and filtered. The ether solution was evaporated to dryness under reduced pressure and the residual oil was crystallized from *n*-hexane. There resulted 0.7 g. (40%) of colorless prisms which, after two more recrystallizations from *n*-hexane, melted at 91.5–93°.

Anal. Calcd. for $C_{25}H_{32}N_2O$: C, 79.74; H, 8.57; N, 7.44. Found: C, 79.67; H, 8.63; N, 7.91.

Infrared spectrum: 2.80 m, 3.44 s, 3.51 s, 3.60 m, 6.23 s, 6.73 s, 6.84 s (sh), 6.90 s, 7.29 s, 7.42 s, 7.74 s.

4-Acetyl-8b-benzyl-2-cyclohexyl-1,3a,4,8b-tetrahydropyrrolo-[3,4-*b*]indol-3(2*H*)-one (Xc).—A solution of 1.0 g. of compound IVc in 50 ml. of 80% aqueous acetic acid was refluxed with 2 g. of zinc dust for 24 hr.[13] The solution was filtered to remove unchanged zinc, and diluted to 250 ml. with water. After standing 3 hr. the mixture was filtered to give 0.2 g. (19%) of product. Following three recrystallizations from cyclohexane or a benzene–*n*-pentane mixture white needles were obtained, m.p. 188–189°.

Anal. Calcd. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21; N-acetyl, 9.79. Found: C, 77.07; H, 7.24; N, 7.35; N-Acetyl, 9.04.

Infrared spectrum: 3.43 m, 3.51 w, 5.94 s, 6.26 w, 6.77 m, 6.85 m, 6.89 m, 6.98 m, 7.18 s, 7.41 w, 7.72 m, 7.82 w.

8b-Benzyl-2-cyclohexyl-3a-N-phenylthioureido-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (XIIc).—To 3 g. of compound IVc was added 4.5 ml. of phenyl isothiocyanate, and the mixture was heated on a steam cone for *ca.* 7 min. The resulting oil became viscous when cooled and then crystallized. The crystals were collected on a filter and washed successively with *n*-pentane and 50% aqueous ethanol. Recrystallization from 70% aqueous ethanol yielded 3.5 g. (86%) of white crystals, m.p. 173–174°. Further recrystallizations from 70% aqueous ethanol raised the m.p. to 181–182°.

Anal. Calcd. for $C_{30}H_{32}N_4OS$: C, 72.55; H, 6.50; N, 11.28. Found: C, 72.25; H, 6.36; N, 11.25.

Infrared spectrum: 3.02 w, 3.35 w, 3.42 m, 3.51 w, 5.98 s, 6.15 m, 6.61–6.68 s, 6.73 s, 6.82 s, 6.89 m, 7.10 w, 7.19 w, 7.42 m, 7.68 m, 7.95 m.

Compound Vc was recovered unchanged when treated with phenyl isothiocyanate by the same procedure used with IVc.

Acetic Acid Hydrolysis of the Phenylthiourea Derivative XIIc.—Compound XIIc (1.5 g.) was heated on a steam cone for 1 hr. in 300 ml. of 75% (by volume) aqueous acetic acid. The solution was allowed to cool to room temperature slowly and then was evaporated under reduced pressure to remove the solvents. The last traces of acetic acid were removed from the residue by adding and evaporating three 100-ml. portions of benzene. During the third evaporation a white solid, m.p. 148–150°, precipitated. Recrystallization from hot water produced fine white needles, m.p. 152–153°. The infrared spectrum (Nujol mull) was identical with that of authentic phenylthiourea, and there was no mixture melting point depression.

The mother liquor from which the phenylthiourea had separated was concentrated to yield a brown oil. A white crystalline compound, m.p. 140–145°, precipitated when the oil was dissolved in *n*-heptane with a few drops of absolute ethanol added. Recrystallization from the same solvent mixture afforded white needles, m.p. 165–167°, which were shown to be compound Vc.

Reaction of Compound IVc with Nitrous Acid.—A solution containing 1 g. of compound IVc and 1.5 ml. of concentrated hydrochloric acid in 8 ml. of 95% ethanol was cooled to 5° and treated with 10 ml. of a cold 10% aqueous sodium nitrate solution. The mixture was allowed to stand in an ice bath for 5 min. and was then extracted with ether. The ether extract was washed with ice–water, dried over magnesium sulfate, and evaporated under reduced pressure without heating. The residue was recrystallized three times from a benzene–*n*-hexane mixture to yield 0.35 g. (32%) of a product which melted at 155–156° with extensive decomposition, corresponded in composition approximately to a mononitroso derivative of IVc, and gave a Liebermann's test.

Anal. Calcd. for $C_{23}H_{26}N_4O_2$: C, 70.74; H, 6.71; N, 14.35. Found: C, 71.34; H, 6.91; N, 14.32.

Infrared spectrum: 295–3.02 w, 3.43 m, 3.51 m, 5.90 s, 6.18 m, 6.23 m (sh), 6.70 w (sh), 6.80 (sh), 6.90–7.00 s, 7.50–7.57 s, 7.74 m, 7.84 s, 7.98 s.

Synthetic Experiments Related to the Indole Alkaloids. III. The Reductive Cyclization of 1-[2-(3-Indolyl)-2-oxoethyl]pyridinium Salts to Quinolizine Derivatives Related to the Indole Alkaloids[1]

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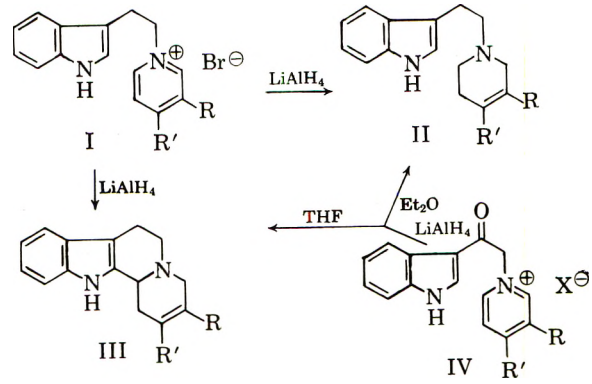
Received December 18, 1962

Reduction of 1-[2-(3-indolyl)-2-oxoethyl]pyridinium salts IV with lithium aluminum hydride in tetrahydrofuran solution gave indolo[2,3-*a*]quinolizine derivatives III, whereas in diethyl ether solution 1-[2-(3-indolyl)-ethyl]-1,2,5,6-tetrahydropyridines II were obtained. This method presents a convenient route to these quinolizines and has been utilized in a synthesis of *dl*-$\Delta^{15(20)}$-yohimbene, which has previously been converted into sempervirine and *dl*-alloyohimbane, and also in a synthesis of flavopereirine.

In previous papers in this series,[4] the reduction of a 2-[2-(3-indolyl)ethyl]- or 2-[2-(3-indolyl)-2-oxoethyl]-isoquinolinium salt with lithium aluminum hydride was shown to be a ready means of obtaining in good yield the basic ring skeleton of the yohimbine alkaloids. We now wish to report the extension of our original investigations to the use of pyridinium salts and the utilization of the reaction as a means of obtaining simple quinolizine derivatives related to the indole alkaloids.[5] This same "reductive cyclization" approach to the α-indole alkaloids also has been described recently by Wenkert.[6] The main difference in the two reaction sequences is our choice of 1-[2-(3-indolyl)-2-oxoethyl]-pyridinium salts as starting materials and an interesting solvent effect upon the course of the reduction. Since the final products from several of the examples chosen to illustrate the two methods are the same, we report those of our results not anticipated by Professor Wenkert's publication, or results that are necessary for structural proof.

Early attempts at the reductive cyclization of indolylethylpyridinium salts with lithium aluminum hydride were unsuccessful. Elderfield,[7] as well as K.T.P.,[8] found several years ago that the reduction of 1-[2-(3-indolyl)ethyl]pyridinium bromide (I, R = R′ = H) with lithium aluminum hydride or sodium borohydride gave only the tetrahydropyridine derivative II; no cyclization to the indolo[2,3-*a*]quinolizine system III was observed. The conditions under which the cyclization of salts of type I can be effected have been determined recently by Wenkert.[6]

The intermediate pyridinium salts IV used in our reaction sequence were obtained by condensation of 3-acetylindole with the appropriate pyridine in the presence of iodine or from the reaction of ω-bromoacetylindole, itself easily prepared from 3-acetylindole and bromine,[9] and the pyridine.



In initial experiments the parent salt (IV, R = R′ = H) was subjected to lithium aluminum hydride reduction in ether and in tetrahydrofuran solutions. The general procedure for the work-up of the reaction mixture involved decomposition of the excess hydride and treatment of the solutions with dilute hydrochloric acid, followed by basification, and chromatography of the mixtures of the crude bases. Rather surprisingly, different products were obtained when the reduction of 1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide (IV, R = R′ = H) was carried out in ether and in tetrahydrofuran solutions. When ether was the solvent employed, 1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = R′ = H) was isolated in 33% yield. Verification of this structure was obtained by absorption of one mole of hydrogen in the presence of Adams' catalyst with the formation of 1-[2-(3-indolyl)-ethyl]piperidine, the identity of the latter being established by comparison with authentic material obtained by lithium aluminum hydride reduction of 1-[1,2-dioxo-2-(3-indolyl)ethyl]piperidine prepared from indole-3-glyoxyloyl chloride and piperidine.[10] However, when the reduction of IV (R = R′ = H) was carried out in tetrahydrofuran solution the tetracyclic product, 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (III, R = R′ = H), was formed in 56% yield. Hydrogenation of this material gave 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine, a compound well characterized in the literature. The yields of both products were found to vary with length of reaction time (see Table I). The position of the double bond in III (R = R′ = H) was not established directly, but rather the structure (instead of the alternative 3,4,6,7,12,12b-hexahydro product) was formulated by analogy with products formed in

(1) Presented at the 2nd International Symposium on the Chemistry of Natural Products, Prague, Czechoslovakia, August 1962.

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TABLE I

PRODUCTS ISOLATED FROM THE LITHIUM ALUMINUM HYDRIDE REDUCTIONS OF SALTS OF STRUCTURE IV

Parent pyridine	Solvent	Reaction time, hr.	% II	% III
Pyridine	Ether	6	33	
Pyridine	Ether	3	42	
Pyridine	THF[a]	4.5		44
Pyridine	THF	2		56
3-Ethylpyridine	Ether	4	35	5
3-Ethylpyridine	THF	4.5		48
3-Ethylpyridine	THF	2		52
3-Ethyl-4-methylpyridine	THF	3.5		62
5,6-Tetramethylenepyridine	THF	3		67

[a] THF = tetrahydrofuran.

similar reductions of substituted pyridinium salts where definite assignments could be made on the basis of n.m.r. spectral data (see Experimental[11]).

A similar solvent effect on the course of the lithium aluminum hydride reduction was observed with 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide (IV, R = Et; R′ = H) in ether and in tetrahydrofuran solutions. When the former solvent was employed, 3-ethyl-1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = Et; R′ = H) was isolated together with a small amount of 3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (IV, R = Et; R′ = H). The latter compound was the sole product when tetrahydrofuran was the solvent for the reaction, and the small variations in yield with reaction time are summarized in Table I.

Both the tetrahydropyridine (II, R = Et; R′ = H) and the quinolizine (III, R = Et; R′ = H) absorbed one mole of hydrogen on catalytic reduction, demonstrating the presence of the isolated double bond. Definitive proof of the structures assigned to these compounds was obtained from their nuclear magnetic resonance spectral data which are reported in the Experimental. The quinolizine III was converted into the alkaloid flavopereirine,[12] from *Geissospermum laeve* or *vellosi*, by a reaction sequence reported in the literature[13] involving reduction of III (R = Et; R′ = H) to octahydroflavopereirine, oxidation with mercuric acetate to 3-ethyl-1,2,3,4,6,7-hexahydro-12*H*-indolo[2,3-*a*]quinolizinium perchlorate, followed by dehydrogenation of this salt with palladium–carbon. The flavopereirine, isolated as the perchlorate, was identical with the natural product.

Further extensions of this reaction sequence in the pyridinium series were next investigated with the aim of ultimately obtaining pentacyclic compounds possessing rings D and E in the fully reduced state. We first chose a disubstituted pyridine, β-collidine, as a model. This readily gave the intermediate pyridinium salt (IV, R = Et; R′ = CH_3) which was reduced in the usual manner with lithium aluminum hydride in tetrahydrofuran solution and gave a base with properties similar to those of the products described by formula III previously.

The assignment of structure III (R = Et; R′ = CH_3), 2-methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine, was on the basis of analytical data, as well as the absence of absorption due to olefinic protons and also the α-proton of the indole nucleus in its n.m.r. spectrum. It is interesting that the reduction and cyclization of the pyridine nucleus occurs predominantly in the way shown, a fact which was also noted by Wenkert.[6] By using 3,4-diethylpyridine one would have an easy method of obtaining a product related to dihydrocorynantheane and flavocoryline.

The use of 5,6,7,8-tetrahydroisoquinoline in this reaction offered an interesting route to the alloyohimbanes. The intermediate salt (IV, R = R′ = $-(CH_2)_4-$) was obtained in poor yield from the reaction of 3-acetylindole, iodine, and the tetrahydroisoquinoline. The low yield was due to mechanical loss in the isolation procedure. An excellent yield of the salt was obtained, however, from the reaction of ω-bromoacetylindole and the isoquinoline. Reduction of this salt with lithium aluminum hydride in tetrahydrofuran solution gave 1,2,3,4,5,7,8,13,13b,14-decahydrobenz-[*g*]indolo[2,3-*a*]quinolizine (III, R = R′ = $-(CH_2)_4-$) [$\Delta^{15(20)}$-yohimbene]. The physical characteristics of this product agreed with those described in the literature[14] and the structure was supported by the absence of olefinic proton and α-indole proton absorption in the n.m.r. spectrum. Attempts to reduce the isolated double bond in $\Delta^{15(20)}$-yohimbine by the usual methods were unsuccessful[14]; even the highly active platinum catalyst recently described by Brown[15] did not effect reduction, nor did the conditions used by Janot and coworkers[16] in the preparation of alloyohimbane from sempervirine prove effective. $\Delta^{15(20)}$-Yohimbene has been converted into sempervirine and also *dl*-alloyohimbane and *dl*-epialloyohimbane, and its synthesis thus constitutes syntheses of these products.[17]

$\Delta^{15(20)}$-Yohimbene was a satisfactory intermediate for resolving an interesting point in sempervirine chemistry reported in the literature. Sodium borohydride reduction of N-methylsempervirinium salts V gave a hexahydro base formulated as VI, though the alternative position for the double bond (C-3–C-14) was also considered.[18] Methylation of $\Delta^{15(20)}$-yohimbene should give a base identical with that obtained from the sodium borohydride reduction, and on treatment with sodamide and methyl iodide in liquid ammonia solution $\Delta^{15(20)}$-yohimbene gave such a product.[19] This directly confirmed the correctness of structure VI.

The instability of members of this series of compounds is worthy of mention. Without exception those quinolizines or 1,2,5,6-tetrahydropyridines containing an isolated double bond in ring D or at the junction of rings D and E rapidly decomposed in air and light. During recrystallizations, solutions obtained colorless

(11) The spectra were recorded from a Varian V-4302 dual purpose, 60-Mc., n.m.r. spectrometer, and chemical shift values are reported in τ units, using tetramethylsilane as internal standard. We are indebted to Dr. T. H. Crawford for his assistance in the determination of these spectra.

(12) Numerous syntheses of flavopereirine have been effected: see ref. 6, 24, and among others, A. Le Hir, M.-M. Janot, and D. van Stolk, *Bull. soc. chim. France*, 551 (1958); K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2024 (1958); H. Kaneko, *J. Pharm. Soc. Japan*, **80**, 1374 (1960); Y. Ban and M. Seo, *Tetrahedron*, **16**, 5 (1961).

(13) A. Le Hir, M.-M. Janot, and D. van Stolk, *Bull. soc. chim. France*, 551 (1958). We are indebted to Professor H. Rapoport for authentic samples of flavopereirine and its perchlorate.

(14) E. Wenkert and R. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

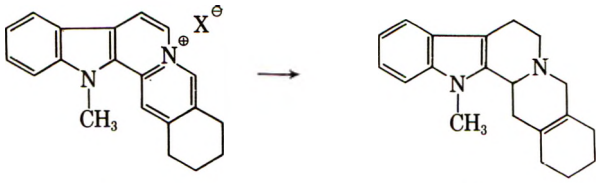
(15) H. C. Brown and C. A. Brown, *ibid.*, **84**, 1494 (1962).

(16) A. Le Hir, R. Goutarel, and M.-M. Janot, *Compt. rend.*, **235**, 63 (1952).

(17) See reference quoted in ref. 14.

(18) B. Witkop, *J. Am. Chem. Soc.*, **75**, 3361 (1953).

(19) We are indebted to Dr. B. Witkop for his gift of 1-methyl-$\Delta^{15(20)}$-yohimbene picrate to carry out direct comparisons.



V VI

after treatment with charcoal became yellow within a few minutes, and this effect was most noticeable in hydrocarbon solvents. This phenomenon is undoubtedly connected with an oxidative process involving the double bond, for when this was removed by reduction the bases were found to be stable and more easily purified.

Experimental[20]

3-Ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium Iodide (IV, R = Et; R′ = H; X = I).—3-Ethylpyridine (2.8 g., 0.03 mole) and 3-acetylindole (1.6 g., 0.01 mole) were warmed together on a water bath. Iodine (2.54 g., 0.01 mole) was added and the mixture heated at 95–100°. The product began to crystallize after several minutes, and heating was continued for 1 hr. The solid product was triturated with ethanol (*ca.* 20 ml.) and the cream powder collected. The iodide (3.1 g., 80%) crystallized from water as a mixture of fawn plates and needles, m.p. 257° dec., with darkening from 248°. Both of these crystalline forms of the iodide separated from ethanol as fine colorless needles, m.p. 260–262° dec. with darkening from 255°.

Anal. Calcd. for $C_{17}H_{17}N_2OI$: C, 52.1; H, 4.4; N, 7.1. Found: C, 52.0; H, 4.5; N, 7.2.

Solutions of the iodide in ethanol gradually became deep yellow on standing at room temperature for several hours.

3-Ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium Bromide (IV, R = Et; R′ = H; X = Br).—A mixture of 3-bromoacetylindole[9] (0.48 g., 0.002 mole) and 3-ethylpyridine (0.28 g., 0.003 mole) was gently warmed on a water bath for a few minutes. The solid product was rubbed with a little ethanol and the colorless powder that precipitated was collected and washed with ether. The bromide separated from water as colorless needles, m.p. 268–271° dec.

Anal. Calcd. for $C_{17}H_{17}N_2OBr$: C, 59.1; H, 5.0; N, 8.2. Found: C, 58.7; H, 4.7; N, 8.2.

Conversion into the Iodide.—The addition of an aqueous solution of potassium iodide to an aqueous solution of the bromide in hot water produced an immediate precipitate of 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide that crystallized from water as colorless needles, m.p. and m.m.p. 259–261° dec. with a sample prepared using the same procedure.

2-[2-(3-Indolyl)-2-oxoethyl]-5,6,7,8-tetrahydroisoquinolinium Chloride (IV, R, R′ = $-(CH_2)_4-$; X = Cl).—5,6,7,8-Tetrahydroisoquinoline[21] (2.7 g., 0.02 mole) and 3-chloroacetylindole[22] (1.7 g., 0.009 mole) were mixed together in a flask protected by a drying tube, and then warmed on a water bath. A pink solution formed and after 1–2 min. the reaction mixture solidified to a cream mass. Titration with ethanol (6–7 ml.) yielded a colorless powder, m.p. 269–270°. The chloride (2.9 g., quant.) crystallized from methanol as colorless plates, m.p. 270–272° dec.

Anal. Calcd. for $C_{19}H_{19}N_2OCl$: C, 69.8; H, 5.9; N, 8.6. Found: C, 69.3; H, 6.1; N, 8.7.

Conversion into the Iodide.—This was carried out as described previously, the iodide crystallizing from water as cream needles, m.p. 249–251° dec. The melting point was not depressed on admixture with a sample of the iodide prepared by the following method.

2-[2-(3-Indolyl)-2-oxoethyl]-5,6,7,8-tetrahydroisoquinolinium Iodide (IV, R,R′ = $-(CH_2)_4-$; X = I).—3-Acetylindole (0.8 g., 0.005 mole) and 5,6,7,8-tetrahydroisoquinoline (2.0 g., 0.015 mole) were heated together on a steam bath with iodine (1.25 g., 0.005 mole) for 40 min. The cooled melt was extracted with boiling water (charcoal) and on cooling a yellow oil was deposited. The mother liquor was decanted and when the oil was rubbed with a little ethanol a pale yellow powder precipitated. The iodide (84 mg., 4%) crystallized from water as fine cream needles, m.p. 251–252° dec.

Anal. Calcd. for $C_{19}H_{19}N_2OI$: C, 54.6; H, 4.6; N, 6.7. Found: C, 54.7; H, 4.6; N, 6.8.

1-[2-(3-Indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = R′ = H).—1-[2-(3-Indolyl)-2-oxoethyl]pyridinium iodide[4] (2.7 g., 0.0075 mole) was added portionwise over a period of 30 min. to a stirred solution of lithium aluminum hydride (1.0 g., 0.025 mole) in anhydrous ether (*ca.* 200 ml.) while a stream of dry nitrogen was passed into the reaction vessel. The mixture was heated under gentle reflux for 6 hr. and as the reaction progressed the yellow starting material dissolved and a flocculant white substance precipitated. At the end of the reaction period the excess hydride was decomposed by the addition of hydrated sodium sulfate and the precipitated inorganic material removed by filtration under nitrogen. The etheral filtrate was pale green with a blue fluorescence. Dilute hydrochloric acid was added with the immediate precipitation of a yellow gum. After removal of the ether on a water bath, the acidic solution was allowed to stand for 2 hr. Making basic with aqueous potassium hydroxide solution precipitated the bases, which were extracted into ether and dried (sodium sulfate). The yellow oil obtained on removal of the solvent was absorbed onto 8 g. of neutral alumina which was then added to a column of alumina (65 g.). Elution with a 1:1 mixture of benzene–petroleum ether yielded a pale yellow crystalline material. 1-[2-(3-Indolyl)ethyl]-1,2,5,6-tetrahydropyridine (0.52 g., 33%) crystallized from hexane as colorless needles, m.p. 152–153° (lit.[7] m.p. 152–153°).

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 79.6; H, 8.0; N, 12.4. Found: C, 79.5; H, 8.1; N, 12.4.

The mixture melting point of this sample with 1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine was 114–116°. Further development of the column with benzene and a mixture of benzene–ether (4:1) yielded a few milligrams of yellow oily material that could not be characterized.

The picrate, prepared in ethanol, crystallized from ethanol as orange needles, m.p. 174–175°.

Anal. Calcd. for $C_{21}H_{21}N_5O_7$: C, 55.4; H, 4.7; N, 15.4. Found: C, 54.9; H, 4.7; N, 15.1.

Platinum oxide (15.4 mg.), suspended in absolute alcohol (10 ml.), was reduced and saturated with hydrogen. 1-[2-(3-Indolyl)ethyl]-1,2,5,6-tetrahydropyridine (30.0 mg.) was added and hydrogen (3.12 ml., theoretical 3.21 ml.) was absorbed over a period of 20 min. The colorless, crystalline residue of 1-[2-(3-indolyl)ethyl]piperidine separated from hexane as small, colorless needles, m.p. 149–150° (lit.[7], m.p. 151–152°), not depressed on admixture with an authentic specimen prepared by reduction of 1-[1,2-dioxo-2-(3-indolyl)ethyl]piperidine.[10] The infrared spectra of the samples were identical.

1,2,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine (III, R = R′ = H).—1-[2-(3-Indolyl)-2-oxoethyl]pyridinium iodide (1.7 g., 0.0047 mole) was added portionwise over a period of 15 min. to a stirred solution of lithium aluminum hydride (0.6 g., 0.015 mole) in tetrahydrofuran (120 ml.). Marked effervescence occurred, and the solution developed a pale green color with a green fluorescence. After 2 hr. heating in a stream of dry nitrogen, the reaction mixture was worked up as described previously. The residual brown gum from the ether extract was absorbed onto neutral alumina (8 g.) and transferred to the top of a column of alumina (50 g.). Elution with a 1:1 mixture of benzene–petroleum ether yielded 1,4,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine (0.58 g., 56%) m.p. 144–146°. It crystallized from hexane or petroleum ether as clusters of thick, colorless plates, m.p. 147–148° (lit.[6] m.p. 144–144.5°).

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.3; H, 7.2; N, 12.5. Found: C, 79.7; H, 7.2; N, 12.6.

Ultraviolet absorption: λ_{max} 2260, 2830, 2910 Å.; log ϵ 4.61, 3.92, 3.84; λ_{min} 2470, 2890 Å.; log ϵ 3.30, 3.81.

The crystalline base or its solutions in hydrocarbon or alcoholic solvents rapidly changed from colorless to pale yellow-green in the presence of air and light.

(20) Petroleum ether refers to the fraction b.p. 60–80° unless otherwise stated. Evaporations were under reduced pressure on a water bath and melting points were determined in capillaries. Ultraviolet spectra were recorded in 95% ethanol solution, using an Optica CF4 spectrophotometer, and analyses were performed by the C.S.I.R.O. Microanalytical Service, Melbourne. Woelm neutral alumina, activity 4, was found most successful in the chromatography experiments.

(21) R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948).

(22) R. Majima and M. Kotake, *ibid.*, **55B**, 3865 (1922).

The picrate formed in ethanol, crystallized from aqueous methanol as clusters of orange needles, m.p. 119–121°.

Anal. Calcd. for $C_{21}H_{19}N_5O_7 \cdot H_2O$: C, 53.5; H, 4.5; N, 14.9. Found: C, 53.7; H, 4.5; N, 15.1.

Further development of the column with benzene and a 4:1 mixture of benzene–ether gave 55 mg. of a yellow oil that could not be induced to crystallize or form a crystalline derivative.

Adams' catalyst (20 mg.) was suspended in ethanol (10 ml.) and saturated with hydrogen. The preceding base (40 mg.) was added, and hydrogen (4.6 ml., theoretical 4.4 ml.) was absorbed over a period of 10 min. 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine separated from hexane as small colorless prisms, m.p. 152–153° (lit.[23] m.p. 147–147.5°).

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0. Found: C, 79.3; H, 8.1.

The mixture melting point of the product with 1-[2-(3-indolyl)-ethyl]piperidine was 119–121°.

3-Ethyl-1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (II, R = Et; R′ = H).—Dried, powdered 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium iodide (IV, R = Et; R′ = H) (3.44 g. 0.0087 mole) was added to a stirred solution of lithium aluminum hydride (1.2 g., 0.03 mole) in ether (300 ml.) under an atmosphere of dry nitrogen and the pale green mixture was heated under reflux for 3 hr.

Using the previous general work-up procedure, the final oily product obtained was absorbed onto alumina (10 g.) and transferred to the top of a column of alumina (100 g.) and eluted with a 1:4 mixture of benzene–petroleum ether. The first two fractions (800 ml.) contained 3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (0.111 g., 5%), m.p. 143–145°. (The characterization of this product is described fully subsequently.) Further development of the column with a 1:1 mixture of benzene–petroleum ether gave pale yellow, crystalline material, m.p. 117–120°. The 3-ethyl-1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine (0.879 g., 40%) crystallized from a colorless solution in hexane as very pale yellow, irregular prisms, m.p. 121–123° (lit.[6] m.p. 119–122°).

Anal. Calcd. for $C_{17}H_{22}N_2$: N, 11.0. Found: N, 10.9.

N.m.r. spectrum (deuteriochloroform): ind-α-H, 3.22; olefinic CH, 4.62; ethyl CH_3, 9.00 τ (triplet, J = 7.0 c.p.s.).

The picrate, prepared in alcohol, separated as orange-red needles, m.p. 155–157°, and successive crystallizations from methanol raised this value to 165–167° (lit.[6] m.p. 161–163°).

Anal. Calcd. for $C_{23}H_{25}N_5O_7$: C, 57.1; H, 5.2; N, 14.5. Found: C, 57.0; H, 5.3; N, 14.1.

Palladium on carbon (20 mg., 20% catalyst) was suspended in ethanol (10 ml.) and saturated with hydrogen. The unsaturated base prepared previously (37.4 mg.) was added, and hydrogen (3.84 ml., theor. 3.63 ml.) was absorbed over a period of 4 hr. The oily base was very soluble in hexane and petroleum ether (b.p. 40–60°) and could not be obtained crystalline.

Ultraviolet absorption: λ_{max} 2230,2830, 2920 Å.; λ_{min} 2440, 2890 Å. It was characterized as the picrate which was formed in ethanol and crystallized from methanol–water in the form of fine, orange needles, m.p. 127–128°.

Anal. Calcd. for $C_{23}H_{27}N_5O_7$: C, 56.9; H, 5.6; N, 14.4. Found: C, 56.8; H, 5.6; N, 14.2.

3-Ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (III, R = Et; R′ = H).—The finely powdered iodide (5.88 g., 0.015 mole) was added in small portions over a period of 15 min. to a stirred solution of lithium aluminum hydride (2.0 g., 0.05 mole) in tetrahydrofuran (300 ml.). Marked effervescence occurred, and the solution became pale green with a green fluorescence. After 2 hr. heating in a nitrogen atmosphere, the reaction mixture was worked up as before. The residual yellow fluorescent glass was absorbed onto alumina (10 g.) and transferred to the top of a column of alumina (100 g.). Elution with a 1:1 mixture of benzene–petroleum ether gave a crystalline product, m.p. 143–145°. The 3-ethyl-1,4,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizine (1.32 g., 52%) crystallized from hexane as colorless plates, m.p. 146–148° (lit.[6] m.p. 143–145°).

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.9; H, 8.0; N, 11.1. Found: C, 80.2; H, 7.9; N, 11.4.

Ultraviolet absorption: λ_{max} 2260, 2830, 2910 (sh.) Å.; log ε 4.52, 3.83, 3.75; λ_{min} 2450 Å.; log ε 3.17. N.m.r. spectrum (deuteriochloroform): olefinic CH, 4.62; ethyl CH_3, 8.97 τ (triplet, J = 7.3 c.p.s.).

The crystalline base or its solutions very rapidly became yellow on exposure to air and light.

The picrate was formed in ethanol and crystallized from an ethanol–petroleum ether mixture as small, yellow needles, m.p. 184–186° dec.

Anal. Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.4; H, 4.8; N, 14.6. Found: C, 56.9; H, 4.4; N, 14.5.

Adams' catalyst (10 mg.), suspended in ethanol (10 ml.), was reduced and saturated with hydrogen. The previous unsaturated base (25.2 mg.) was added and hydrogen (2.42 ml., theoretical 2.36 ml.) was absorbed over a period of 80 min. The colorless 3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (octahydroflavopereirine) could not be obtained crystalline (Thesing and Festag[24] report an oil; Hughes and Rapoport[25] and Wenkert[6] report m.p. 163–164°). The picrate was prepared in ethanol and crystallized from methanol as small, irregular orange prisms, m.p. 208–210° dec., alone and when mixed with authentic octahydroflavopereirine picrate, kindly supplied by Dr. J. Thesing. The infrared spectra of the two samples were superimposable.

2-Methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (III, R = Et; R′ = CH_3). A.—Finely powdered 3-ethyl-1-[2-(3-indolyl)-2-oxoethyl]-4-methylpyridinium iodide (IV, R = Et; R′ = CH_3; X = I) (1.2 g., 0.003 mole) was added to a solution of lithium aluminum hydride (0.7 g., 0.018 mole) in dry tetrahydrofuran (100 ml.) and the mixture heated under reflux for 3.5 hr. in a nitrogen atmosphere. After cooling the reaction mixture, water was cautiously added to decompose the excess hydride. Treatment with dilute hydrochloric acid gave a yellow solution containing suspended grey inorganic matter. This was removed as described previously and tetrahydrofuran evaporated from the filtrate at 30–40° under reduced pressure. As the solution concentrated a yellow product separated and was collected by filtration. Further concentration of the mother liquor precipitated a yellow oil that solidified on standing. This was identified as the quinolizinium hydroiodide (0.7 g., 61%) which crystallized from methanol as colorless needles, m.p. 296–298° dec.

Anal. Calcd. for $C_{18}H_{23}N_2I$: C, 54.8; H, 5.8; N, 7.1. Found: C, 54.8; H, 5.8; N, 7.1.

No coloration was obtained with Ehrlich's reagent. The free base was obtained by the addition of ammonia to an aqueous solution of the hydroiodide. It separated from aqueous methanol as colorless needles, m.p. 171–173°.

Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.2; H, 8.3; N, 10.5. Found: C, 80.7; H, 8.3; N, 10.5.

Ultraviolet absorption: λ_{max} 2260, 2820, 2900 Å.; log ε 4.39, 3.92, 3.83; λ_{min} 2470, 2880, Å.; log ε 3.34, 3.82. N.m.r. spectrum (deuteriochloroform): methyl of $(CH_3)C{=}C$, 8.33; ethyl methyl, 9.00 τ; (triplet, J = 7.0 c.p.s.); no olefinic proton.

B.—In another reduction it was possible to isolate the quinolizine as its crystalline hydrochloride. After decomposition of the reaction mixture with hydrated sodium sulfate and removal of the inorganic salts, the filtrate was acidified with dilute hydrochloric acid and the volume of the solution reduced by heating on the water bath. On cooling, colorless crystals of 2-methyl-3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizinium hydrochloride (0.85 g., 43%) separated. It crystallized from methanol as long, colorless needles, m.p. 281–282° with frothing.

Anal. Calcd. for $C_{18}H_{23}N_2Cl$: N, 9.3. Found: N, 9.0.

From the acidic mother liquors, by a process involving basification, ether extraction, and chromatography as described in the previous experiments, a further 325 mg. (18%) of the free base was obtained, m.p. 171–172°. Further development of the chromatography column with a 4:1 mixture of benzene–ether gave 170 mg. of a brown oil that could not be induced to crystallize or to form a crystalline picrate or hydrochloride.

1,2,3,4,5,7,8,13,13b,14-Decahydrobenz[*g*]indolo[2,3-*a*]quinolizine (III, R,R′ = $-(CH_2)_4-$).—2-[2-(3-Indoiyl)-2-oxoethyl]-5,6,7,8-tetrahydroisoquinolinium chloride (IV, R, R′ = $-(CH_2)_4-$; X = Cl) (2.4 g., 0.0076 mole) was added in small portions to lithium aluminum hydride (1.0 g., 0.025 mole) suspended in dry tetrahydrofuran (150 ml.). Vigorous effervescence occurred and a yellow-green solution with an intense pale green fluorescence was formed. After 3 hr. reflux with stirring in a nitrogen atmosphere, hydrated sodium sulfate was added and the reaction mixture worked up as previously described. The final brown oil was

(23) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).

(24) J. Thesing and W. Festag, *Experientia*, **17**, 127 (1959).

(25) N. A. Hughes and H. Rapoport, *J. Am. Chem. Soc.*, **80**, 1604 (1958).

absorbed onto alumina (10 g.) and transferred to the top of a column of alumina (80 g.). The column was eluted with a 1:1 mixture of benzene–petroleum ether and 200-ml. fractions taken. Fractions 2,3 and 4 were combined and on removal of the solvent a pale yellow crystalline residue was obtained. 1,2,3,4,5,7,8,-13,13b,14-Decahydrobenz[*g*]indolo[2,3-*a*]quinolizine, $\Delta^{15(20)}$-yohimbene, (1.42 g., 67%) separated from benzene as colorless needles, m.p. 196–197° with darkening (lit.[14] m.p. 196–197°). N.m.r. spectrum (deuteriochloroform): methylene, 6.99–8.34 τ; no olefinic proton.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 82.0; H, 8.0; N, 10.1. Found: C, 81.6; H, 7.9; N, 10.2.

The base, or its solutions, rapidly became yellow on exposure to air and light.

The picrate, formed in ethanol, separated from aqueous methanol as fine yellow needles, m.p. 178–180° dec., with previous darkening.

Anal. Calcd. for $C_{25}H_{25}N_5O_7$: C, 59.2; H, 5.0; N, 13.8. Found: C, 59.5; H, 5.1; N, 13.6.

Further development of the column with a 4:1 mixture of benzene–ether gave a small amount of a brown oily material which could not be characterized.

1,2,3,4,5,7,8,13,13b,14-Decahydro-1′-methylbenz[*g*]indolo-[2,3-*a*]quinolizine (N-Methyl-$\Delta^{15(20)}$-yohimbene) (VI).—Liquid ammonia (*ca.* 15 ml.) was distilled from sodium and collected in a small flask immersed in a Dry Ice–ethanol bath. A crystal of ferric nitrate was added, followed by sodium (22 mg.). The mixture was stirred for several minutes, $\Delta^{15(20)}$-yohimbine (225 mg.) was added, and after a further 10 min. methyl iodide (150 mg.) was introduced. Stirring was continued at room temperature until all the ammonia had evaporated, and then water was added and the product collected (230 mg., m.p. 112–115°). N-Methyl-$\Delta^{15(20)}$-yohimbene crystallized from aqueous methanol as fine, colorless needles, m.p. 137–138° (lit.[18] m.p. 137–139°). N.m.r. spectrum (deuteriochloroform): ind-N methyl, 6.37; methylene, 6.85–8.15 τ.

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.1; H, 8.3; N, 9.6. Found: C, 81.9; H, 7.9; N, 9.7.

The picrate, prepared in alcohol solution, crystallized from methanol as yellow needles, m.p. 182–185° (lit.[18] m.p. 188–192°).

Anal. Calcd. for $C_{26}H_{27}N_5O_7 \cdot CH_3OH$: C, 58.6; H, 5.6; N, 12.7. Found: C, 58.5; H, 5.4; N, 13.0.

The melting point of the picrate was not depressed on admixture with an authentic sample kindly provided by Dr. B. Witkop, and the infrared spectra of the two samples were identical.

Acknowledgment.—The authors wish to thank Professor G. M. Badger for his constant interest and encouragement throughout this work.

Aromatic Cyclodehydration. LIV.[1] Indolo[2,3-*a*]acridizinium Salts

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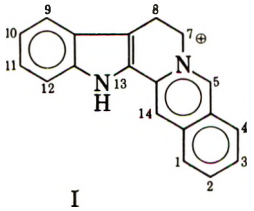
Received April 29, 1963

9*H*-[3,4-*b*]Pyridoindole-1-carboxaldehyde has been synthesized and quaternized with benzyl halides. Cyclization of the crude quaternary salts in acidic media has afforded indolo[2,3-*a*]acridizinium salts.

The indolo[2,3-*a*]acridizinium[2] (VI) nucleus may be considered as the parent system of the yohimbine, reserpine, and alstoniline[3] alkaloids. A near approach to the synthesis of VI has been made by four different research groups,[4a–d] each of which prepared 7,8-dihydroindolo[2,3-*a*]acridizinium salts (I). Two of these groups[4c,4d] have recorded their attempts to dehydrogenate the 7,8-dihydro system (I) to the fully aromatic



I

nucleus (VI). Glover and Jones[4c] report that their experiments were unsuccessful. Swan,[4d] using tetrachloro-*o*-benzoquinone as the dehydrogenating agent, isolated (as the iodide) a chocolate brown powder. This substance "was probably not obtained pure" and no analysis was reported. The reported absorption spectrum was simpler (only two maxima) than that of any known acridizinium compound, and the ultimate absorption maximum was at 345 mμ as against 399 mμ for the acridizinium ion.[5]

It appeared probable that the methods of aromatic cyclodehydration[6] might provide a direct route to the aromatic system without recourse to dehydrogenation of a quaternary salt. The preparation of 1-methoxymethyl-9*H*-[3,4-*b*]pyridoindole (methoxyharman, II) from methoxyacetaldehyde and tryptophan[7] was followed by cleavage of the ether linkage by hydrobromic acid, affording the carbinol III. The carbinol was oxidized to the aldehyde IV[8] using activated manganese dioxide.

Quaternization of the pyridoindolecarboxaldehyde with benzyl bromide was carried out in dimethylformamide at room temperature, and the crude salt (V, X = Br) was used directly in the cyclization. Cyclodehydration was brought about by heating the quaternary salt V for 24 hr. in polyphosphoric acid at 120°, and the orange-yellow product had the properties which would be expected of an indoloacridizinium system.

Quaternary salts derived from 3-methoxybenzyl bromide and 2,3-dimethoxybenzyl bromide were cyclized to the expected indoloacridizinium salts VII and

(1) For the preceding communication of this series, see *J. Org. Chem.*, **28**, 1669 (1963). This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health, presented before the XIXth Meeting of the International Union for Pure and Applied Chemistry, London, England, July, 1963.

(2) The name acridizinium has been proposed for the benzo[*b*]quinolizinium system: *J. Am. Chem. Soc.*, **77**, 4812 (1955). The *Chemical Abstracts* name for VI is 13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium.

(3) R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, **19**, 683 (1954).

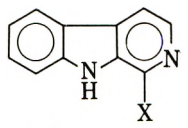
(4) (a) R. M. Jacob and J. Fouché, 16th Congress, Union of Pure and Applied Chemistry, Paris, 1957; Resumés des Comm., Vol. II, p. 316. (b) R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.*, **23**, 435 (1958). (c) E. E. Glover and G. Jones, *J. Chem. Soc.*, 1750 (1958). (d) G. A. Swan, *ibid.*, 2038 (1958).

(5) An additional complication is that, in the text of Swan's paper, (ref 4d) the dehydrogenation of 7,8-dihydroindolo[2,3-*a*]acridizinium (I) is discussed, while, in the experimental part, only the dehydrogenation of the 13-methyl derivative of I is described.

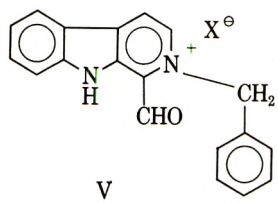
(6) C. K. Bradsher, *Chem. Rev.*, **38**, 447 (1946).

(7) *Cf.* H. R. Snyder, S. M. Parmenterer, and L. Katz, *J. Am. Chem. Soc.*, **70**, 222 (1948).

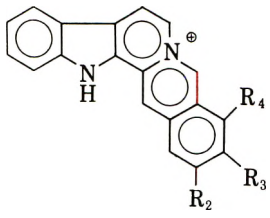
(8) We are indebted to Dr. Hans Berger who developed this procedure for the synthesis of 9*H*-[3,4-*b*]pyridoindole-1-carboxaldehyde in this laboratory.

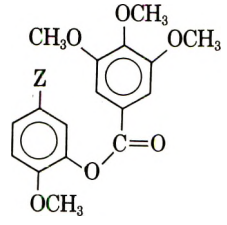


II, X = CH_2OCH_3
III, X = CH_2OH
IV, X = CHO



V





VIII. Since the methoxyl groups facilitate cyclization, heating in concentrated hydrochloric acid for 15 min. on the steam bath was sufficient.[9] The quaternary salt from 3-(3,4,5-trimethoxybenzoxy)-4-methoxybenzyl bromide (XII) proved more difficult to cyclize, but did afford a product IX having the expected composition, and some of the features of the gross reserpine skeleton.

Experimental

All analyses were by Dr. I. A. Schoeller, Mikroanalytisches Laboratorium, Kronach, West Germany. Unless otherwise indicated all infrared absorption spectra were determined by use of potassium bromide pellets. Unless otherwise indicated ultraviolet absorption spectra were made with the Cary Model 14 PM spectrophotometer using acetonitrile as the solvent. Wave lengths marked with an asterisk (*) represent shoulders rather than clearly defined peaks.

1-Methoxymethyl-9*H*-[3,4-*b*]pyridoindole (II).[7]—A mixture containing 2 g. of *dl*-tryptophan, 1.5 g. of methoxyacetaldehyde[10] in 80 ml. of water, and 1 ml. of ethanol was heated at 60° for 22 hr. The solution was then diluted to 500 ml. and boiled for a few minutes, and then 96 ml. of 10% potassium dichromate solution and 20 ml. of acetic acid were added. Heating was continued for only 2–3 min. and then the brown suspension was cooled under the water tap. After the addition of sodium sulfite to destroy excess oxidant, the mixture was made alkaline with solid sodium carbonate, and extracted repeatedly with ether. Evaporation of the ether left 1.57 g. of crude methoxyharman suitable for the next step. An analytical sample was prepared by recrystallization from dilute ethanol, m.p. 129–130°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.55; H, 5.70; N, 13.22. Found: C, 73.21; H, 5.92; N, 13.51.

1-Hydroxymethyl-9*H*-[3,4-*b*]pyridoindole (III).—Two grams of crude methoxyharman was dissolved in 60 ml. of 48% hydrobromic acid and the mixture refluxed for 1.5 hr. The red solution was evaporated to near dryness, 60 ml. of water was added, and refluxing was continued for two additional hours. The hot solution was filtered to remove a small amount of tar, cooled, and made alkaline with sodium carbonate. The crude grayish precipitate, m.p. 218–220°, yield 1.9 g. (93%), was pure enough for further reactions. Recrystallization was difficult because the substance was nearly insoluble in most of the common organic solvents. Further purification could be effected if the carbinol was dissolved in hot 10% hydrochloric acid (Norite) and precipitated by addition of solid potassium carbonate to the cooled solution. The grayish white precipitate, when collected, washed with water, and dried, melted at 220–223°. The analytical sample was obtained as colorless needles by crystallizing 325 mg. from 700 ml. of water, m.p. 228–229°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found[11]: C, 72.92; H, 5.27; N, 14.19.

The ultraviolet absorption spectrum of this compound, as well as that of the related methoxymethylpyridoindole II closely resembles the spectrum of harman.

9*H*-[3,4-*b*]Pyridoindole-1-carboxyaldehyde (IV).—One gram of the hydroxyharman III and 10 g. of specially prepared manganese dioxide[12] were suspended in 350 ml. of tetrachloroethane and were stirred for 16 hr. by means of a magnetic stirrer. The temperature went as high as 39° because of the heat from the stirrer motor. The reaction mixture was filtered through filter-aid, the residue washed with chloroform, and the combined solutions evaporated to dryness. The product was recrystallized from ethanol affording 0.51 g. (52%) of yellow aldehyde as a microcrystalline powder, m.p. 198–200°. The analytical sample was recrystallized from benzene, m.p. 202–202.5°.

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.46; H, 4.08; N, 14.28. Found: C, 73.68; H, 3.66; N, 13.95.

The oxime crystallized from ethanol as almost colorless needles, m.p. 264–266° dec.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29. Found: C, 68.14; H, 4.47.

1-Formyl-2-benzyl-9*H*-[3,4-*b*]pyridoindolium Perchlorate (V).—The pyridoindolecarboxaldehyde IV was usually dissolved in the minimum quantity of dimethylformamide and an excess of benzyl bromide added and the mixture was allowed to stand for 7 days. The crude bromide salt precipitated by the addition of ether was satisfactory for further reactions, but a small sample was converted to the perchlorate by the addition of 20% perchloric acid to an ethanol solution. The orange product precipitated from acetonitrile–ethyl acetate as a powder, m.p. 223–224° dec. The alcohol solution had a blue fluorescence.

Anal. Calcd. for $C_{19}H_{15}N_2O_5Cl$: C, 58.99; H, 3.91; N, 7.24. Found: C, 58.86; H, 3.93; N, 7.32.

Indolo[2,3-*a*]acridizinium Perchlorate (VI).—The crude pyridoindolium V bromide (1.0 g.) was mixed with polyphosphoric acid (20 g.) and heated for about 24 hr. at 120°. The mixture was next cooled and stirred and water was added, causing the precipitation of the product as a phosphate salt. The grayish brown solid was collected, washed with water, and dried. The dry salt was dissolved in methanol acidified with a small quantity of hydrochloric acid, and ion exchanged through an Amberlite IRA-401 chloride column. The alcoholic solution was concentrated and 20% perchloric acid added to the hot solution. The precipitate was collected, washed with cold water–ethanol, and dried. The brownish product which decomposed starting at 275°, (0.72 g., 72%) was recrystallized from acetonitrile–ether, affording an analytical sample as yellow-orange crystals, m.p. 307–310° dec., which showed a strong yellow-green fluorescence in solution. The infrared absorption spectrum showed a peak at 2.96 μ (assigned to indole NH) but no significant absorption in the carbonyl region; λ_{max}[13] (log ϵ) 209 (4.29), 255 (4.44), 280 (4.19), 288* (4.17), 346 (4.24), 401 (3.83), and 443 mμ (3.71).

Anal. Calcd. for $C_{19}H_{13}N_2O_4Cl$: C, 61.88; H, 3.55; N, 7.60. Found: C, 62.14; H, 3.90; N, 7.57.

3-Methoxyindolo[2,3-*a*]acridizinium (VII) Perchlorate.—The pyridoindole carboxaldehyde (0.5 g.) was quaternized with *m*-methoxybenzyl bromide in the usual way. The quaternary salt which formed was precipitated from solution as an oil or impure solid by the addition of ether. The solvent was decanted and the residue was taken up in a small quantity of methanol. Ten milliliters of concentrated hydrochloric acid was added and the mixture heated on the steam bath for 15 min. A yellowish precipitate formed, and after cooling the mixture, it was collected and washed with cold water. To a hot alcoholic solution of the salt, 20% perchloric acid was added dropwise, and after cooling the mixture, the precipitated perchlorate salt was collected, washed with water, and dried. The yellowish product (0.81 g., 80%) decomposed slowly when heated above 280°. The analytical sample, obtained by recrystallization from aceto-

(9) Spectrographic evidence indicates that the activated (methoxy)-benzyl salts may undergo some cyclization at room temperature during the quaternization period.

(10) C. D. Hurd and J. L. Abernethy, *J. Am. Chem. Soc.*, **63**, 1966 (1941); the initial distillate obtained by the Hurd and Abernethy procedure was usually used *without* fractionation.

(11) Analysis by D. C. Daessle, Montreal, Quebec, Canada.

(12) *Cf.* R. J. Highet and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 4399 (1955); J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952). In later experiments it was found more convenient to use 350–700 ml. of acetone or chloroform as the solvent since subsequent concentration of the solution was made easier.

(13) This measurement made in 95% ethanol solution using the Perkin-Elmer Model 202 spectrophotometer.

nitrile or acetonitrile–ether, decomposed at temperatures above 300°, but did not melt below 400°.

Anal. Calcd. for $C_{20}H_{13}N_3O_5Cl$: C, 60.23; H, 3.79; N, 7.02. Found: C, 60.51; H, 3.92; N, 6.96.

The infrared absorption spectrum showed the absence of any significant absorption in the carbonyl region and a definite absorption at 2.94 μ assigned to the indole NH; λ_{max} (log ϵ) 258 (4.36), 268* (4.33), 330 (4.29), 405 (3.82), and 440* mμ (3.49).

3,4-Dimethoxyindolo[2,3-*a*]acridizinium (VIII) Perchlorate.—Starting with 0.8 g. of the pyridoindolecarboxaldehyde and using 2,3-dimethoxybenzyl bromide[14] instead of 3-methoxybenzyl bromide, but otherwise following the procedure used for making the 3-methoxy derivative VII, the desired 3,4-dimethoxyindoloacridizinium perchlorate VIII was obtained as a red-brown product, m.p. about 290° dec.; yield, 1.41 g. (81%). An analytical sample, prepared by recrystallization from acetonitrile or acetonitrile–ether, was orange, m.p. 313–314°; λ_{max} (log ϵ) 260 (4.53), 290 (4.37), 359 (4.50), 385* (4.17) and 480 mμ (3.90).

Anal. Calcd. for $C_{21}H_{17}N_2ClO_6$: C, 58.82; H, 4.00; N, 6.53. Found: C, 58.93; H, 4.05; N, 6.53.

The infrared absorption spectrum showed no significant absorption in the carbonyl region but a strong absorption at 2.96 μ, assigned to indole NH.

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzaldehyde (X).—Isovanillin[15] (3.0 g.) was dissolved in freshly distilled pyridine and the solution cooled and stirred vigorously while a slight excess of 3,4,5-trimethoxybenzoyl chloride[16] was added slowly in small portions. After the solution had been kept for several hours at room temperature, the pasty mixture was poured into 2 l. of 3 *N* hydrochloric acid containing some ice. The precipitate was collected, washed with water, and dried, giving 5.5 g. (81%) of a slightly yellow colored solid, m.p. 145–150°, that was pure enough for the next step. The analytical sample formed irregular crystals, m.p. 158–160°, from benzene–petroleum ether (60–90°).

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.88; H, 5.17.

(14) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **127**, 1434 (1925).

(15) A. Lovecy, R. Robinson, and S. Sugasawa, *ibid.*, 817 (1930).

(16) W. H. Perkin, Jr., and C. Weizmann, *ibid.*, **89**, 1649 (1906).

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzyl Alcohol (XI).—A pasty suspension of 3.0 g. of the aldehyde in methanol was added in small portions to a cooled solution (5%) containing 1 g. of sodium borohydride in methanol. After the reaction was complete the excess hydride was destroyed by dropwise addition of dilute sulfuric acid. The precipitated alcohol was collected, washed with water, and dried; yield, 2.5 g. (82%); m.p. 120–125°. The colorless alcohol formed irregular crystals from benzene–petroleum ether, m.p. 128–129°.

Anal. Calcd. for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.46; H, 5.70.

3-(3,4,5-Trimethoxybenzoxy)-4-methoxybenzyl Bromide (XII). A well stirred suspension of the alcohol XI (2.0 g.) in dry ether (100 ml.) was maintained at 0° and treated dropwise with 1.0 g. of phosphorus tribromide. The mixture was allowed to stand overnight at room temperature, and then shaken repeatedly with cold water until free from acid. The ethereal solution was dried, the ether evaporated, and the residue crystallized from benzene–petroleum ether as colorless nodules; m.p. 112–113°; yield, 1.7 g. (74%).

Anal. Calcd. for $C_{18}H_{19}O_6Br$: C, 52.57; H, 4.66. Found: C, 52.56; H, 4.71.

2-Methoxy-3-(3,4,5-trimethoxybenzoxy)indolo[2-3-*a*]acridizinium (IX) Perchlorate.—One gram of the pyridoindole carboxaldehyde IV was quaternized with XII in the usual way. To the crude quaternary salt in 25 ml. of methanol, 10 ml. of concentrated hydrochloric acid was added, and cyclization carried out as usual, except that heating was continued for 1 hr. instead of the usual 15 min. The acid was evaporated, the resulting oil taken up in methanol and precipitated as the perchlorate by the addition of 20% perchloric acid. The oily perchlorate was washed with water and recrystallized from acetonitrile–ether. The product which showed some signs of decomposition during recrystallization consisted of a red-brown powder; m.p. 203–209° dec.; yield, 2.26 g. (73%). Alcoholic solutions of the product showed a very strong yellow-green fluorescence, and the infrared spectrum showed an absorption in the carbonyl region at 5.75 μ and another absorption in the 2.90-μ region attributed to the NH peak.

Anal. Calcd. for $C_{30}H_{25}N_2ClO_{10}\cdot H_2O$: C, 57.47; H, 4.34; N, 4.47; OCH_3, 19.80. Found: C, 57.41; H, 4.30; N, 4.49; OCH_3, 20.43.

The Solvolysis of 4α- and 4β-Methylcholesteryl *p*-Toluenesulfonate[1a]

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Received April 25, 1963

The hydrolysis of 4α-methylcholesteryl *p*-toluenesulfonate (IX) in 60% aqueous acetone in the presence of potassium acetate yields 55% of 3α,5α-cyclo-4α-methylcholestan-6β-ol (XVIII) together with minor amounts of diene and unrearranged parent alcohol X. The type and distribution of products obtained indicate that this solvolytic reaction is completely analogous to that of cholesteryl *p*-toluenesulfonate. In contrast, under the same conditions, 4β-methylcholesteryl *p*-toluenesulfonate (XVI) yields 80% of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), 5–7% of the ring-contracted alcohol 3β-(1β-hydroxyethyl)-Δ^5-A-norcholestene (XIX) and a trace of unrearranged parent alcohol (XVII); no 3α,5α-cyclosterol is obtained. Elucidation of the structures of these products and a discussion of factors which may account for the striking difference in solvolytic behavior of IX and XVI are presented.

The 3β-hydroxy-Δ^5 system of steroids represents a useful substrate for the study of homoallylic participation in solvolytic reactions. Under nonacidic conditions, the solvolysis of ester derivatives of this system yields the corresponding homoallylic rearrangement product, namely, a 3α,5α-cyclo-6β substituted steroid.[2] Substantial rate enhancement also is observed[3]; for example, the relative rates of acetolysis at 100° of cholestanyl and cholesteryl *p*-toluenesulfonates are 1:100. Rate acceleration and stereospecific formation of products in the cholesteryl system may be explained in terms of an activation process involving ionization at C-3 facilitated by participation of the C-5–C-6 double bond. The extent of participation in the transition state for ionization depends upon how effectively the p-orbital at C-5 of the double bond can overlap with the developing p-orbital at C-3. Simonetta and Winstein[4] have applied semiempirical molecular orbital calculations to the cholesteryl cation with the important results that (a) at a normal C-3–C-5

(1)(a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this project under Grant 1347-A4; (b) taken in part from the doctoral dissertation of R. M. de Sousa, The Catholic University of America, 1963.

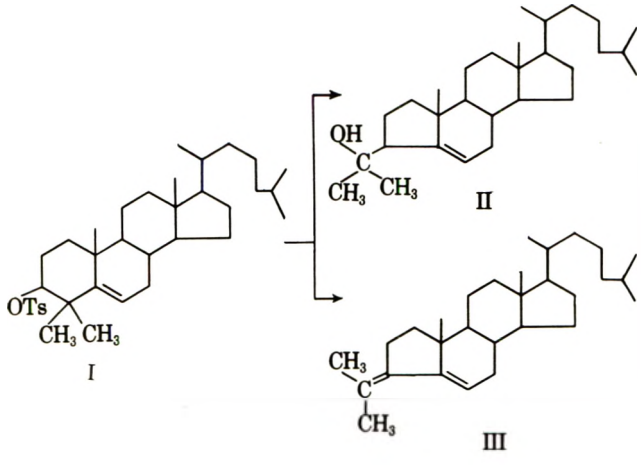
(2) E. S. Wallis, E. Fernholtz, and F. T. Gephardt, *J. Am. Chem. Soc.*, **59**, 137 (1937).

(3) S. Winstein and R. Adams, *ibid.*, **70**, 838 (1948).

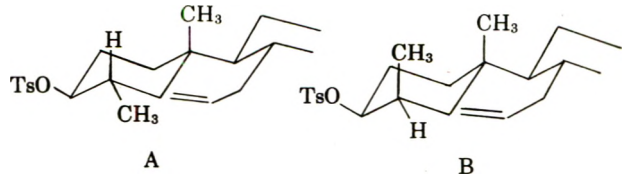
(4) M. Simonetta and S. Winstein, *ibid.*, **76**, 18 (1954).

distance of 2.5 Å. electron delocalization may lead to appreciable stabilization, and (b) with moderate compression of the C-3–C-5 distance, the 1,3-overlap integral increases significantly.

With a view toward learning the effect of substituents at C-4 upon the 1,3-electron delocalization in this system, a study of the products[5a] and kinetics[5b] of solvolysis of 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) was undertaken. The rate of solvolysis of this compound was found to be about four times faster than that of cholesteryl *p*-toluenesulfonate, while the saturated analog, 4,4-dimethylcholestanyl *p*-toluenesulfonate, solvolysed at a rate only one-third greater than cholestanyl *p*-toluenesulfonate. These results clearly indicate participation of the double bond in I in the rate-limiting ionization step. Two further inferences may also be drawn. Firstly, contrary to a "flattened A-ring" which has been proposed by Allinger[6] as a means of relieving the 1,3-diaxial methyl interaction between the methyl groups at C-4 and C-10 in 4,4-dimethyl-3-keto steroids no substantial flattening can exist in I. If such flattening did occur, participation would be precluded due to the increased C-3–C-5 distance, and the rate of solvolysis of I would, therefore, resemble that of cholestanyl *p*-toluenesulfonate. Secondly, the rate enhancement observed for I over cholesteryl *p*-toluenesulfonate may be considered to arise from either a steric effect of the geminal dimethyl group at C-4, involving a Thorpe–Ingold[7] type compression of the C-3–C-5 distance and thus allowing better overlap, or the methyl groups may stabilize the homoallylic ion by an inductive mechanism. A further point of interest in the solvolysis of 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) is the observation that no *i*-steroid is formed but only ring-contracted diene III (70%) and ring-contracted alcohol 3-(2-hydroxypropyl)-Δ⁵-A-norcholestene (II) (20%).[5a]

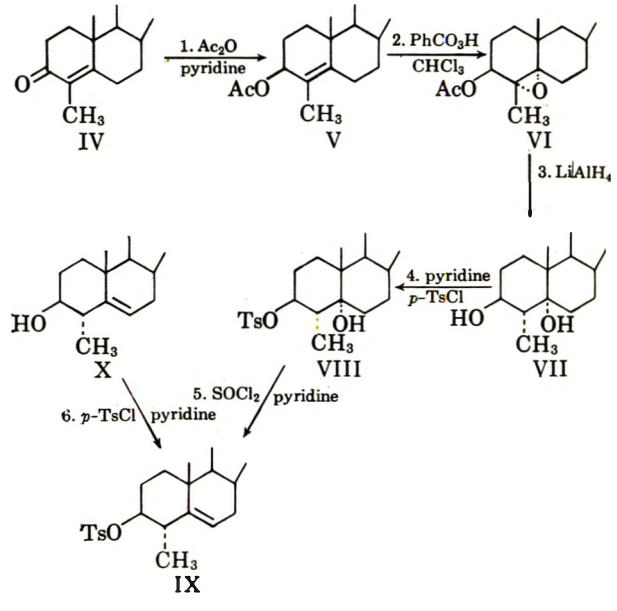


An obviously pertinent extension of this study is the investigation of the solvolytic behavior of the isomeric 4α- and 4β-methylcholesteryl *p*-toluenesulfonate esters, IX and XVI, respectively, which is reported in this paper. 4β-Methylcholesteryl *p*-toluenesulfonate (XVI) resembles 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) in that the 1,3-diaxial interaction between the C-4 and C-10 methyl groups is present. 4α-Methylcholesteryl *p*-toluenesulfonate (IX) does not possess this interaction, and, in this sense, resembles cholesteryl *p*-toluenesulfonate. These stereochemical relationships are depicted by structures A and B.



Preparation of Compounds.—4α-Methylcholesteryl *p*-toluenesulfonate (IX) was prepared *via* the steps outlined in Chart I. Dehydration of the 4α-methylcholestane-3β,5α-diol 3-*p*-toluenesulfonate (VIII) with thionyl chloride in pyridine was found to be the best method of preparation for compound IX. The direct tosylation of the parent alcohol, 4α-methylcholesterol (X), gave low yields of IX. 4α-Methylcholesterol (X) has been prepared by Julia and Lavaux[8] by dehydration of the 3-monoacetate of VII followed by saponification. An alternative method for the preparation of X is *via* sodium borohydride reduction of 4-methyl-Δ³,⁵-cholestadien-3-ol acetate.[9] A maximum yield of 12% of X was achieved by this method. The

CHART I



position of the double bond in IX was established to be at C-5–C-6 rather than the *a priori* more likely C-4–C-5 position (the hydrogen at C-4 and the hydroxyl group at C-5 are *trans* coplanar in VIII) by the following data. Firstly, the n.m.r. spectrum[10] showed the absence of CH_3–C=C in the 8.3-τ region and the presence of one vinyl proton 4.70 τ. Secondly, the material was levorotatory which is characteristic of

(5)(a) R. M. Moriarty and E. S. Wallis, *J. Org. Chem.*, **24**, 1274, 1987, (1959); (b) W. J. A. Vanden Heuvel, R. M. Moriarty, and E. S. Wallis, *ibid.*, **27**, 725 (1962).

(6) N. L. Allinger and M. A. Da Rooge, *J. Am. Chem. Soc.*, **84**, 4561 (1962).

(7) For a recent discussion of the Thorpe–Ingold effect see: P. von R. Schleyer, *ibid.*, **83**, 1368 (1961).

(8) S. Julia and J. P. Lavaux, *Compt. rend.*, **254**, 3702 (1962).

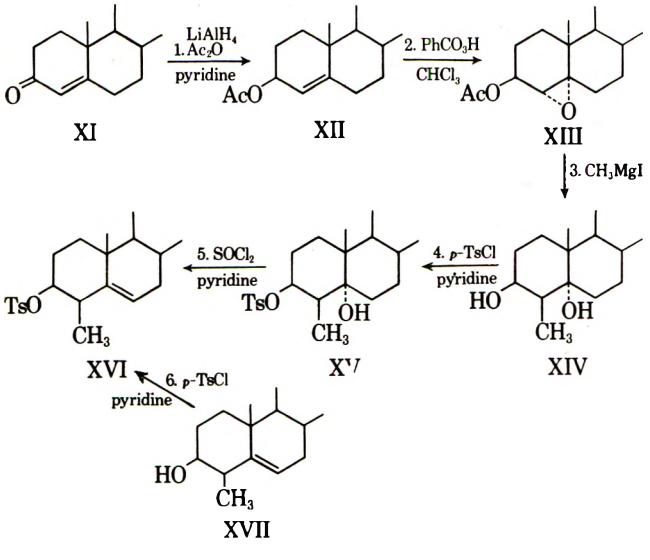
(9) Unpublished experiment of J. A. Feeley. This synthesis will be reported in a future paper dealing with the mechanism of sodium borohydride reduction of dienol acetates.

(10) All peak positions are reported in τ-values relative to tetramethylsilane as internal reference. Carbon tetrachloride is used as solvent unless otherwise stated.

Δ^5 steroids.[11] Thirdly, the same compound was obtained by tosylation of the parent alcohol X prepared by the borohydride reduction of the enol acetate mentioned before[9] or *via* the method of Julia and Lavaux.[8] The direction of dehydration in this case is probably determined by the relative stabilities of the products. In the cholesteryl series, infrared olefinic stretching frequencies indicate that the Δ^5 double bond (1690 cm.$^{-1}$) is more stable than the Δ^4 double bond (1657 cm.$^{-1}$).[12]

The synthesis of 4β-methylcholesteryl *p*-toluenesulfonate (XVI) is outlined in Chart II. Again the final step in this synthesis is the thionyl chloride–pyridine dehydration of the hydroxy tosylate precursor. 4β-Methylcholestane-3β,5α-diol (XIV) has been previously prepared by Julia and Lavaux,[13] who also transformed the 3-monoacetate derivative *via* dehydration and saponification into 4β-methylcholesterol (XVII). Δ^4-Cholesten-3β-ol-acetate (XII) (allocholesteryl acetate) was prepared in 60% yield by lithium aluminum hydride reduction of cholestenone (XI) followed by acetylation and separation from epiallocholesteryl acetate by chromatography. The highly stereoselective α-epoxidation of XII has been discussed by Henbest and Wilson.[14] The stereochemistry of the Grignard reaction product XIV is reasonable in terms of analogy with the course of lithium aluminum hydride reduction of epoxide XIV to yield only cholestane-3β,5α-diol.[14] Tosylate XVI also could be obtained from 4β-methylcholesterol (XVII) by direct treatment with *p*-toluenesulfonyl chloride in pyridine, although in much inferior yields compared with the previously described method.

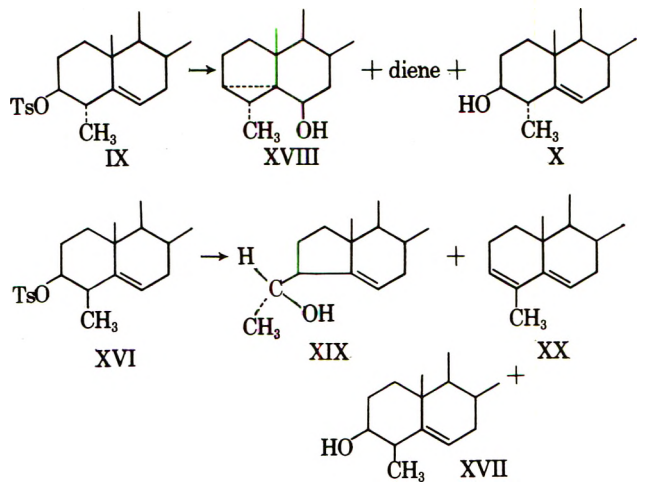
CHART II



Experimental Results

The products resulting from the buffered hydrolysis of 4α-methylcholesteryl *p*-toluenesulfonate (IX) and 4β-methylcholesteryl *p*-toluenesulfonate (XVI) are outlined in Chart III.

CHART III



The crude product from the hydrolysis of XVI was readily separable by chromatography into an olefinic part and alcoholic part. The crystalline olefinic fraction accounted for 80% of the product and was identified as 4-methyl-$\Delta^{3,5}$-cholestadiene (XX); m.p. 73–74°; $[\alpha]_D$ −100°; λ_{max}^{EtOH} 231 sh (ϵ 15,800), 239 (20,000), 247 mμ sh (11,000).[13] The alcohol part, upon rechromatography, yielded 4–7% of rearranged alcohol XIX, $C_{28}H_{48}O$, m.p. 113–14°, $[\alpha]_D$ −40°. A trace of a second alcohol was also obtained which proved to be 4β-methylcholesterol (XVII). Alcohol XIX was immediately recognized as not being an *i*-steroid due to the presence of unsaturation (tetranitromethane[15] and bromine in carbon tetrachloride) and also due to the negative sign of its rotation (the 3β-ol-Δ^5 → 3α,5α-cyclo-6β-ol transformation is invariably accompanied by a change in the sign of optical rotation from a negative value to a positive value).[16] The n.m.r. spectrum of XIX showed absence of cyclopropyl protons in the 9.5–9.9-τ region. The vinyl proton at C-5 was observed at 4.30 τ and the (CH_3)–CH–OH methyl appeared as a doublet at 8.76 τ. Oxidation of XIX with chromium trioxide in pyridine yielded a crude product which possessed infrared absorption (CCl_4) at 5.83 and 5.93 μ. This result corresponds to oxidation of the ethanol side chain at C-3 to a mixture of the unconjugated and conjugated carbonyl derivative. Chromatographic separation yielded the pure latter compound, λ_{max}^{EtOH} 257 mμ (ϵ 13,600). The properties of this material are in agreement with those reported for 3-acetyl-Δ^4-A-norcholestene.[17] Mild acid-catalyzed rearrangement of XIX (filtration over acidic alumina) afforded 4-methyl-$\Delta^{3,5}$-cholestadiene (XX). These data are taken to establish the structure of XIX as 3β-(1β-hydroxyethyl)-Δ^5-A-norcholestene. The stereochemistry of the hydroxyl group of the ethanol side chain is tentatively assigned the β-configuration (using the C-20 pregnane convention). This assignment is based upon the presumed stereochemistry of attack of solvent on the intermediary homoallylic ion (see discussion section).

(11) S. Bernstein, E. M. Hicks, Jr., D. M. Clark, and E. S. Wallis, *J. Org. Chem.*, **11**, 646 (1946).

(12) R. N. Jones and F. Herling, *ibid.*, **19**, 1252 (1954).

(13) S. Julia and J. P. Lavaux, *Compt. rend.*, **251**, 733 (1960).

(14) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(15) Although it has been reported[18b] that cyclopropyl containing compounds give a faint yellow color with tetranitromethane, the conditions for use of the reagent in the present study were standardized based upon the production of no color with 3α,5α-cyclocholestan-6β-ol.

(16) This conclusion is based upon an examination of the optical rotations of numerous 3α,5α-cyclo-6β substituted steroids.

(17) S. Julia, J-P Lavaux, S. R. Pathak, and G. H. Whitham, *Compt. rend.*, **256**, 1537 (1963).

Julia, *et al.*,[17] have also reported, in preliminary form, results on the hydrolysis of 4β-methylcholesteryl *p*-toluenesulfonate (XVI). They have found the same products and amounts of products as obtained in the present investigation. They assign, without explanation, the β-configuration to the hydroxyl group of the hydroxyethyl side chain of XIX. Stereoselective synthesis is required to establish this point of stereochemistry.

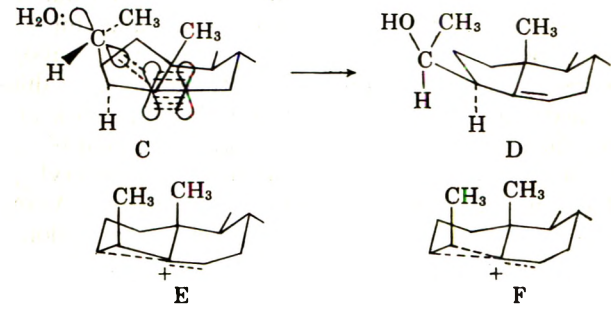
The products from the solvolysis of IX were separated into the olefinic component (20%) and the alcohol part (75%) by means of chromatography. The ultraviolet spectrum of the dienic fraction was similar to that of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), although this material failed to crystallize. Rechromatography of the alcoholic fraction yielded two alcohols. The first of the alcohols XVIII, $C_{28}H_{48}O$, m.p. 101–102°, $[\alpha]D$ +18°, gave no indication of being unsaturated in the tetranitromethane test[15] and bromine in carbon tetrachloride test, and showed no olefinic absorption in the infrared. The saturated nature of XVIII, together with its positive sign of rotation and mode of formation indicated an *i*-steroidal structure for this substance. Further, chemical evidence supporting this conclusion came from the oxidation of XVIII with chromium trioxide–pyridine to a ketone with infrared carbonyl absorption (CCl_4) at 5.91 μ and no ultraviolet absorption above 225 mμ. These properties are consonant with the properties expected for the corresponding *i*-ketone. The structure of XVIII is therefore assigned as 3α,5α-cyclo-4α-methylcholestane-6-β-ol. The second alcohol was identified as the unrearranged parent compound, namely, 4α-methylcholesterol (X), by comparison with a known sample.

Discussion of Results

It is clear from the identity and distribution of the products formed in the solvolysis of 4α- and 4β-methylcholesteryl *p*-toluenesulfonate (IX and XVI) that the configuration of the C-4 methyl group plays a key role in the product forming step. A reasonable description of the influence of the methyl group may be achieved by considering (a) steric strain present in the ground states of IX and XVI, (b) steric and electronic factors contributing to the stability of the corresponding homoallylic ions derived from IX and XVI, and, (c) the steric factors present in the observed and possible products.

The solvolysis of 4α-methylcholesteryl *p*-toluenesulfonate (IX) is completely analogous to that of cholesteryl *p*-toluenesulfonate. This is not unexpected due to the neutral steric influence of the equatorial methyl group at C-4. The corresponding homoallylic ion in this case should possess enhanced stability due to the inductive effect of the methyl group. The *i*-steroid XVIII which is obtained is no more strained than *i*-cholesterol itself. No conceivable alternative path of decomposition for the intermediary ion is open; ring contraction to a five-membered A-ring structure is energetically unrewarding both in terms of strain energy and electronic stability; *i.e.*, transformation of the homoallylic ion to an open secondary carbonium ion is accompanied by a considerable decrease in electronic stability with no compensating gain in steric stability.

The solvolytic behavior of XVI is comparatively more complex. The ground state of XVI is strained to the extent of about 3.7 kcal./mole due to the 1,3-diaxial C-4–C-10 dimethyl interaction.[6] Both the transition state for ionization and the intermediary homoallylic ion retain this steric interaction. Formation of the ring-contracted alcohol is clearly accompanied by a favorable free energy change due to removal of this steric destabilization. Furthermore, obtention of one alcohol is in agreement with stereospecific attack upon the unsymmetrical homoallylic ion C as indicated (C → D).



Also contributors E and F must be considered in describing the homoallylic intermediate. Formation of unrearranged parent alcohol may derive from an unsymmetrical contributor such as E.

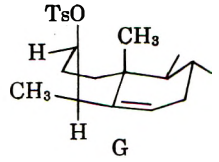
The formation of 80% of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), to a first approximation, may be considered as a simple loss of a proton from the intermediary homoallylic ion. Two further modes of formation which cannot be excluded by the present data are (a) the corresponding *i*-steroid forms but undergoes dehydration under the reaction conditions, and (b) the diene originates by partial dehydration *in situ* of XIX.

The *i*-steroid, 3α, 5α-cyclo-4β-methylcholestan-6β-ol, would be expected to possess high reactivity. A 3α, 5α-cyclosterol is estimated to be about 6 kcal./mole less stable than the corresponding Δ^5-sterol.[18] In addition, 3α, 5α-cyclo-4β-methylcholestan-6β-ol would be further destabilized to the extent of 3.7 kcal./mole[6] due to the 1,3-diaxial methyl interaction and to at least 4 kcal./mole due to the additional interactions of the axial hydroxyl group with the two methyl groups. If equilibration could take place under the reaction conditions employed for the solvolysis, rearrangement of the i-steroid to diene XX would be possible. At present, this possibility cannot be experimentally tested due to the unavailability of 3α,5α-cyclo-4β-methylcholestan-6β-ol. The second conceivable origin of diene XX may be from dehydration of initially formed XIX *via* Wagner-Meerwein rearrangement followed by proton loss. This path is considered due to the facts that (a) such a reaction has been carried out, albeit under acidic condition, (b) XIX undergoes mutarotation at room temperature in chloroform solution, and (c) the ultraviolet spectrum of XIX upon standing develops absorption typical of diene XX. These results point to a facile dehydration of XIX to XX. Such a dehydration could also occur under the solvolytic conditions used for its formation. This reaction is currently under investigation.

A basically different explanation for predominant diene formation is that the ground state conformation of the A-ring of 4β-methylcholesteryl *p*-toluenesulfonate (XVI) may exist in a boat form (G). Such a confor-

(18)(a) C. W. Shoppee and D. F. Williams, *J. Chem. Soc.*, 2488 (1956); (b) C. W. Shoppee and G. H. R. Summers, *ibid.*, 3361 (1952).

mational change replaces the 1,3-dimethyl interaction by a 1,4-diaxial tosyloxy-methyl interaction and two sets of eclipsed hydrogen interactions at C-1 and C-2. Assuming that A-values[19] may be applied in this system, we may compare the A-value for tosyloxy, variously estimated at 0.6, 0.7, and less likely 1.7 kcal/mole, with the corresponding A-value[19] for methyl of 1.5–1.9 kcal./mole. Furthermore, the conformational equilibria involving 1,3-diaxial dimethyl have an interaction energy of 3.7 kcal./mole[6] while the corresponding value for methyl hydroxyl is 2.2–2.4 kcal./mole (the A-value for hydroxyl is 0.4–0.9 kcal./mole). The value for the two eclipsed sets of hydrogens at C-1 and C-2 is about 1.8 kcal./mole. Consideration of these energy values 3.7 kcal./mole for a chair A-ring and about 4.0 kcal./mole for a boat A-ring indicate that discussion of the mechanism of solvolysis of 4β-methylcholesteryl *p*-toluenesulfonate (XVI) in terms of a boat form A-ring is not unwarranted. The value of such a formulation is



that the *trans* coplanar relationship of the C-3 tosyloxy group and C-4 hydrogen presents the requisite stereochemistry for elimination. Furthermore, hydrogen participation may occur in the activation step for ionization. That such participation occurs and provides substantial anchimeric assistance is indicated by the relative rates of methanolysis at 35° for cholestanyl, epicholesteryl, and cholesteryl *p*-toluenesulfonates, 1:15:100.[20] The proposal of a boat form A-ring for XVI and the rejection of a boat form A-ring for 4,4-dimethylcholesteryl *p*-toluenesulfonate (I) (see introduction) is not inconsistent in that one methyl group at C-4 in the geminal dimethyl case is always axially oriented and thus destabilized by interactions with protons on the α-side of the A-ring.

Experimental[11]

4-Methylcholestenone (IV) was prepared by the method of Ringold and Malhotra[22] in 25% yield and had m.p. 102–103°, $[\alpha]_D$ +108° (*c* 1), λ_{max}^{EtOH} 251 mμ (ε 15,200).

4-Methyl-Δ⁴-cholesten-3β-ol Acetate (V).—To a stirred slurry of 5.0 g. of lithium aluminum hydride in 300 ml. of 1:1 ether–tetrahydrofuran at reflux, 10 g. of 4-methylcholestenone, dissolved in 150 ml. of ether, was added dropwise over 0.5 hr. The reaction mixture was kept at reflux for 2 hr. Excess reducing agent was decomposed by addition of acetone followed by water. Extraction with ether, drying, and concentration under reduced pressure yielded 10 g., m.p. 132–134°; recrystallization from acetone yielded 8.0 g., m.p. 151–152° (lit.[8] 152°).

Acetylation of this material with acetic anhydride–pyridine yielded 7.0 g. of acetate, m.p. 108–111° (from acetone), $[\alpha]_D$ +40° (c 1) (lit.[8] 111°, $[\alpha]_D$ +45°).

4α,5α-Oxido-4β-methylcholestan-3β-ol Acetate (VI).—To a solution of 4.4 g. (10 mmoles) of compound V in 60 ml. of benzene was added a solution of 13 mmoles of perbenzoic acid in chloroform at room temperature. After 8 hr. at room temperature, an additional 100 ml. of benzene was added, and the resulting solution was washed with a solution of 25% aqueous sodium carbonate followed by washing with water. The dried benzene solution was concentrated to dryness *in vacuo*. The resulting oil, 4.3 g., showed no tendency to crystallize. Chromatography on unactivated Merck neutral alumina, 140 g., yielded two crystalline products. Elution with pentane–benzene (8:2) yielded 600 mg., of m.p. 80–81°, which may be the corresponding 4β,5β-oxide, but this material was not further investigated. Elution with pentane–benzene (1:1, 1.3 l.) yielded product which after recrystallization from acetone afforded 1.05 g. of the desired oxide VI, m.p. 132–34°, $[\alpha]_D$ +78° (*c* 1) (lit.[9] 131°, $[\alpha]_D$ +80°).

4α-Methylcholestane-3β,5α-diol (VII).—To a stirred slurry of 0.6 g. of lithium aluminum hydride in 100 ml. of ether at reflux was added 1.2 g. of compound VI in 50 ml. of ether. After 2 hr. at reflux, 50 ml. of tetrahydrofuran was added, and the reaction was kept at reflux for an additional 2 hr. At the end of this period, aqueous acetone was added and the solution was extracted with ether–benzene (1:1). Concentration of the dried combined extracts yielded 1.2 g. of crystalline solid. Recrystallization from ethanol yielded 0.90 g., m.p. 172–173° (lit.[9] 171°).

4α-Methylcholesteryl *p*-Toluenesulfonate (IX).—Compound VII (0.90 g.) was dissolved in 4 ml. of purified pyridine by warming. After cooling to 20°, 0.90 g. of *p*-toluenesulfonyl chloride was added, and the solution was swirled for about 2 min., whereupon the reaction mixture solidified. It was kept at room temperature for 12 hr. Then an additional 10 ml. of pyridine was added, the solution was cooled to 0°, and 2.3 ml. of thionyl chloride was added dropwise with stirring. The reaction mixture was kept at 0° for 15 min. and then diluted with 100 ml. of ether. The ether solution was cautiously treated with ice to decompose the excess thionyl chloride, washed with saturated sodium bicarbonate and water, dried, and concentrated to dryness *in vacuo*. The crude crystalline product was kept at 45° and 0.001 mm. for 15 min. The product was recrystallized from rigorously dried acetone and yielded 750 mg. of the *p*-toluenesulfonate ester IX, m.p. 121–122° dec., $[\alpha]_D$ −3° (*c* 0.4). The infrared spectrum (CCl_4) possessed absorption bands at 8.40 and 8.46 μ which are characteristic of the *p*-toluenesulfonate ester group. The analytical sample was prepared by recrystallization from acetone.

Anal. Calcd. for $C_{35}H_{54}O_3S$: C, 75.73; H, 9.79. Found: C, 75.71; H, 9.70.

Δ⁴-Cholesten-3β-ol Acetate (XII).—A solution of 2.5 g. of cholestenone in 30 ml. of ether and 30 ml. of tetrahydrofuran was added dropwise to a stirred slurry of 0.8 g. of lithium aluminum hydride in 80 ml. of ether. The reaction mixture was heated to reflux and kept at reflux for 1 hr. The product was isolated in the usual way and acetylated directly with 4 ml. of acetic anhydride in 10 ml. of pyridine. A gum resulted which was chromatographed on 60 g. of neutral alumina. Elution with hexane–benzene yielded 1.0 g., m.p. 78–79°. Recrystallization from acetone yielded 0.74 g., m.p. 81–82° (lit.[23] 85°).

4α,5α-Oxidocholestan-3β-ol Acetate (XIII).—This material was prepared in 60% yield by the epoxidation of XIII according to the method of Henbest and Wilson[14] and had m.p. 115–117°.

4β-Methylcholestane-3β,5α-diol (XIV).—To a stirred solution of 4α,5α-oxidocholestan-3β-ol acetate (XIII) (11 g.) in 130 ml. of anisole at 60°, a ninefold molar excess of methylmagnesium iodide in ether was added dropwise. The reaction was stirred overnight at 60°. At the end of this period it was cautiously added to 0.5 l. of acetic acid–water solution (1:1). This mixture was heated on the steam bath for 10 min. and then thoroughly extracted with ether. The ether solution was washed with saturated sodium bicarbonate solution and water. The dried ether solution was concentrated to dryness *in vacuo* and then heated at 50° and 0.001 mm. to remove the residual anisole. The crude crystalline product weighing 10 g. was chromatographed on 400 g. of Merck neutral alumina. Elution with chloroform yielded 6 g. of material of m.p. 179–182°. Recrystallization yielded 4.56 g., m.p. 181–183°, $[\alpha]_D$ +18° (*c* 1) (lit.[13] 181.5–182.5°, $[\alpha]_D$ +17°).

4β-Methylcholestane-3β,5α-diol 3-*p*-Toluenesulfonate (XV).—A solution of 2.0 g. of compound XIV in 3 ml. of dry pyridine was

(19) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc. New York, N. Y., 1962, pp. 236–237.

(20) L. C. King and M. J. Bigelow, *J. Am. Chem. Soc.*, **74**, 6238 (1952).

(21) Melting points are uncorrected and were determined on a Fisher-Jones melting point block. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were determined on a Bausch and Lomb Model 505 recording spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrophotometer operating at 60.0 Mc. Optical rotations were taken in chloroform solution. Anhydrous magnesium sulfate was used as drying agent. Microanalysis were carried out by George I. Robertson, Florham Park, New Jersey.

(22) H. J. Ringold and S. K. Malhotra, *ibid.*, **84**, 3402 (1962).

(23) H. McKennis and G. Gaffney, *J. Biol. Chem.*, **175**, 218 (1948).

cooled to 20°, and 2.0 g. of *p*-toluenesulfonyl chloride was added in one portion. The reaction was allowed to stand at room temperature overnight. An additional 7 ml. of dry pyridine was added, and a 1-ml. aliquot was removed for isolation of the hydroxy tosylate XV. Treatment of this aliquot with ice yielded solid which was collected and dried under high vacuum. Recrystallization from dry acetone yielded material, m.p. 97–98° dec., $[\alpha]_D$ −1.2° (c 0.4).

Anal. Calcd. for $C_{35}H_{56}SO_4$: C, 73.38; H, 9.85. Found: C, 73.43; H, 9.71.

4β-Methylcholesteryl *p*-Toluenesulfonate (XVI).—The pyridine solution of hydroxy tosylate XV was cooled to 0°, and 4 ml. of thionyl chloride was added dropwise with stirring. After 10 min. at 0°, 100 ml. of ether was added. The ether solution was cautiously treated with water. The ether was washed with a saturated solution of sodium bicarbonate followed by water. The ether solution was dried and concentrated to dryness *in vacuo* yielding a crystalline solid. Recrystallization from dry acetone yielded 1.4 g., m.p. 98–100° dec., $[\alpha]_D$ −77.8° (*c* 1).

Anal. Calcd. for $C_{35}H_{54}SO_3$: C, 75.73; H, 9.79. Found: C, 75.36; H, 9.53.

Hydrolysis of 4α-Methylcholesteryl *p*-Toluenesulfonate (IX).—A solution of 400 mg. of IX in 60 ml. of acetone and 10 ml. of water containing 400 mg. of potassium acetate was kept at reflux for 12 hr. Then most of the acetone was removed under reduced pressure. The remainder was extracted with ether; the ether solution was dried and concentrated to dryness *in vacuo* yielding 300 mg. of crystalline product. This material was chromatographed upon 5 g. of Merck neutral alumina. Elution with pentane yielded 60 mg. of oil which failed to crystallize. The ultraviolet spectrum of this oil was similar to that of XX. Further elution with benzene–ether (1:1) yielded 180 mg. of XVIII, m.p. 99–101°, $[\alpha]_D$ +18° (*c* 1). The analytical sample prepared by recrystallization from acetone had m.p. 101–102°.

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 83.90; H, 12.01.

Elution with chloroform afforded 60 mg. of crystalline material. Upon recrystallization from acetone, this material had m.p. 164–165°, $[\alpha]_D$ −16°, identical with a sample of 4α-methylcholesterol (X).

Hydrolysis of 4β-Methylcholesteryl *p*-Toluenesulfonate (XVI).—A solution of 2.0 g. of tosylate XVI was dissolved in 300 ml. of acetone and 50 ml. of water containing 2.1 g. of potassium acetate. This reaction mixture was kept at reflux overnight. The acetone was removed under vacuum, and the residue was thoroughly extracted with ether. The ether solution was dried and concentrated *in vacuo* to a gum, 1.4 g. Chromatography upon 60 g. of Merck alumina yielded 1.20 g. of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX), identified by comparison with a known sample. Further elution with benzene–ether (1:1, 3:7) gave 110 mg. of crystalline material which upon recrystallization from acetone yielded 90 mg. of XIX, m.p. 113–114°, $[\alpha]_D$ −40° (*c* 0.4).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 84.00; H, 12.30.

Further elution with chloroform gave 6 mg. of material identified as 4β-methylcholesterol (XVII) by comparison with a known sample prepared by the method of Julia.[13]

Chromium Trioxide–Pyridine Oxidation of IX.—To a chromium trioxide–pyridine complex, prepared by portionwise addition of 24 mg. of chromium trioxide to 0.25 ml. of pyridine, was added a solution of 24 mg. of IX in 0.25 ml. of pyridine. The reaction mixture was stored at room temperature overnight. Ice was added followed by water, and the final mixture was extracted with six portions of chloroform. The combined extracts were washed with dilute hydrochloric acid, a saturated solution of sodium bicarbonate, and finally with water. The organic layer was dried and concentrated to dryness under reduced pressure. The resulting gum, 27 mg., possessed infrared absorption (CCl_4) at 5.91 μ, and no ultraviolet absorption above 225 mμ. Chromatography upon neutral alumina (Merck) yielded 17 mg., m.p. 100–106°.

Anal. Calcd. for $C_{28}H_{48}O$: C, 84.35; H, 11.63. Found: C, 84.00; H, 11.82.

Chromium Trioxide–Pyridine Oxidation of XIX.—The required oxidizing complex was prepared by portionwise addition of 43 mg. of chromium trioxide to 0.50 ml. of pyridine. A solution of 43 mg. of XIX in 0.50 ml. of pyridine was added, and the reaction mixture was allowed to stand at room temperature overnight. Isolation of the product by the method used yielded a gum weighing 47 mg. This material possessed infrared absorption (CCl_4) at 5.83 and 5.93 μ (C=O in ratio of 2:5, respectively). Chromatography upon Merck basic alumina yielded 21 mg., m.p. 97–99°, λ_{max}^{EtOH} 257 mμ (ε 13,700).

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.10. H, 11.40.

Dehydration of XIX.—A 9-mg. sample of XVIII in benzene was charged to a Woelm acid-washed alumina column. After 0.5 hr., elution with pentane yielded 5 mg., m.p. 71–72°, undepressed upon admixture with an authentic sample of 4-methyl-$\Delta^{3,5}$-cholestadiene (XX).

Acknowledgment.—The authors wish to thank Prof. J. Rocek of this department for several illuminating discussions. Also, the invaluable assistance of Prof. P. von R. Schleyer of Princeton University is acknowledged for determining the n.m.r. spectra.

Electrophilic Substitution of the Benzenethiols. II. Acylbenzene- and Acyltoluenethiols[1,2]

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Received May 3, 1963

Acylarylthiols are prepared from arylthiol precursors. The new procedure comprises protection of the sulfur atom with a carboxymethyl group, acylation of the aromatic ring, and, finally, removal of the protective group.

An earlier paper[4] described a new method of obtaining monohaloarylthiols from arylthiols. A summary of the steps involved is provided by equation 1.

This scheme suggested an attractive means of obtaining acylarylthiols, compounds previously preparable only by tedious, classical methods, or by the use of a more complex approach.[5] A survey of the literature revealed no examples of the Friedel–Crafts acylation of arylmercaptoacetic acids, though Dann and Kokorudz[6] report formation of *p*-acetylphenylmercaptoacetic acid in very low yield by the action of hydrogen fluoride on phenylmercaptoacetic acid. In view of the ease with

$$C_6H_5SH \longrightarrow C_6H_5SCH_2CO_2H \xrightarrow[-H^+]{X^+} XC_6H_4SCH_2CO_2H \xrightarrow[H_2O_2]{H^+} XC_6H_4SH \quad (1)$$

(1) This work is the subject of Canadian, United States, and other patent applications.

(2) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(3) Arapahoe Chemicals, Inc., Boulder, Colo.

(4) D. Walker and J. Leib, *J. Org. Chem.*, **27**, 4455 (1962).

(5) D. S. Tarbell and A. H. Herz, *J. Am. Chem. Soc.*, **75**, 4657 (1953).

(6) O. Dann and M. Kokorudz, *Chem. Ber.*, **86**, 1449 (1953).

TABLE I

ACETYLATION OF ARYLMERCAPTOACETIC ACIDS

Starting material	Solvent	Product	Yield, %	M.p., °C.	Analyses[a] Found C	H	S
$C_6H_5SCH_2CO_2H$	$C_6H_5NO_2$	4-$CH_3COC_6H_4SCH_2CO_2H$[b]	62	156–158	...	...	...
	CS_2–$C_6H_5NO_2$		96				
2-$CH_3C_6H_4SCH_2CO_2H$	$C_6H_5NO_2$	4-CH_3CO-2-$CH_3C_6H_3SCH_2CO_2H$	57	118–119	58.69	4.98	14.35
	CS_2–$C_6H_5NO_2$		90				
3-$CH_3C_6H_4SCH_2CO_2H$	$C_6H_5NO_2$	2-CH_3CO-3(5)-$CH_3C_6H_3SCH_2CO_2H$[c]	2	161–162[d]	58.69	5.42	14.52
		4-CH_3CO-3-$CH_3C_6H_3SCH_2CO_2H$	77				
	CS_2–$C_6H_5NO_2$	4-CH_3CO-3-$CH_3C_6H_3SCH_2CO_2H$	94	121–122	58.75	5.58	14.41
4-$CH_3C_6H_4SCH_2CO_2H$	$C_6H_5NO_2$	5-Methylbenzo[*b*]thiophen-3-ol	25	98–100	...	...	...
	CS_2–$C_6H_5NO_2$	2-CH_3CO-4-$CH_3C_6H_3SCH_2CO_2H$	70	161–162	58.59	5.27	14.54

[a] Calcd. for $C_{11}H_{12}O_3S$: C, 58.93; H, 5.4; S, 14.28. [b] Methyl ester, b.p. 175° (1 mm.), m.p. 42–43° (petroleum ether, b.p. 30–60°). *Anal.* Calcd. for $C_{11}H_{12}O_3S$: C, 58.93; H, 5.4; S, 14.28. Found: C, 58.47; H, 5.21; S, 13.82. [c] Gives a yellow color on warming with mineral acids.

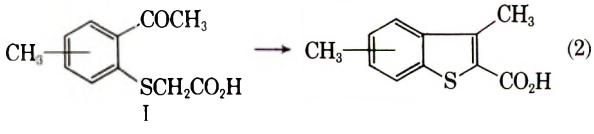
which arylmercaptoacetic acids are known to cyclize to thioindigoid dye intermediates,[6,7] acylation of these acids under Friedel–Crafts catalysis might be expected to lead, at least in part, to the formation of benzo[*b*]-thiophen-3-ols. However, absence of any confirmatory data led us to study the acylation of arylmercaptoacetic acids in the hope of obtaining acylarylmercaptoacetic acids. We expected that these latter acids would be cleaved to acylarylthiols by the action of hydrogen peroxide in the presence of mineral acids (equation 1).

This paper describes the acetylation and benzoylation of phenylmercaptoacetic acid and of all three tolylmercaptoacetic acids, as well as the preparation of acylarylthiols, and their disulfides, from the acylarylmercaptoacetic acids thus obtained.

Results and Discussion

Acylarylmercaptoacetic Acids. A. Acetylations in Nitrobenzene.—Phenylmercaptoacetic acid and *o*-tolyl- and *m*-tolylmercaptoacetic acids were acetylated in nitrobenzene to give good yields of *p*-acetylarylmercaptoacetic acids (see Table I).

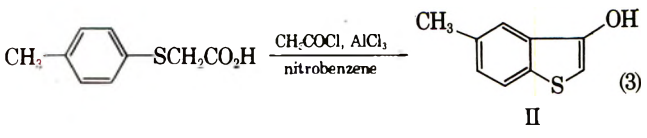
In the case of the acetylation of *m*-tolylmercaptoacetic acid a very small amount of 2-acetyl-3(or 5)-methylphenylmercaptoacetic acid (I) was also obtained. The *ortho* orientation of the acetyl group with respect to the sulfur atom was established by cyclization to a benzo[*b*]thiophene (equation 2).



I (2)

The position of the methyl group in the benzene ring was not established although the compound I isolated by us appeared to possess properties similar to those previously described[8] for 2-acetyl-3-methylphenylmercaptoacetic acid.

Friedel–Crafts acetylation of *p*-tolylmercaptoacetic acid could not be carried out in nitrobenzene, possibly owing to steric hindrance of the bulky nitrobenzene–aluminum chloride–acetyl chloride complex; instead, cyclization to 5-methylbenzo[*b*]thiophen-3-ol (II) appeared to be the predominant reaction (equation 3).



(3)
II

The structure of 5-methylbenzo[*b*]thiophen-3-ol (II) was established by converting this material to 5-methylbenzo[*b*]thiophene-2,3-dione.[9]

B. Acetylations and Benzoylations in Carbon Disulfide–Nitrobenzene.—In the preferred method of acylating arylmercaptoacetic acids carbon disulfide containing a small amount of nitrobenzene was employed as the reaction medium. The final reaction mixture was decomposed in the usual way and the desired acylarylmercaptoacetic acid simply filtered. Very high yields of substantially pure product were thus obtained.

Phenylmercaptoacetic acid and all three tolylmercaptoacetic acids were acetylated by this method (see Table I). The acetyl group entered the position *para* to the sulfur atom except in the case of *p*-tolylmercaptoacetic acid where substitution occurred *ortho* to the sulfur atom. In the latter case the *ortho* orientation of the acetyl group was established by cyclizing 2-acetyl-4-methylphenylmercaptoacetic acid to 3,5-dimethylbenzo[*b*]thiophene-2-carboxylic acid.

Under the conditions used for preparing 2,4-dinitrophenylhydrazones of 2-acetyl-4-methylphenylmercaptoacetic acid and 4-acetyl-2-methylphenylmercaptoacetic acid esterification of the carboxylic acid group also took place.

Benzoylation of phenylmercaptoacetic acid and *o*-tolyl- and *m*-tolylmercaptoacetic acids proceeded in the same facile manner as did acetylation (see Table II). On the other hand *p*-tolylmercaptoacetic acid could not be benzoylated by any of the methods described. This failure may again be largely due to steric hindrance (compare the acetylation of *p*-tolylmercaptoacetic acid in nitrobenzene).

Acylarylthiols and Their Disulfides.—The acylarylmercaptoacetic acids were readily converted to acylarylthiols by the oxidative acid-catalyzed cleavage reaction described in the preceding paper.[4] However, since the acylarylthiols were only slightly volatile in steam, and could not be removed as formed, the thiol produced in the scission competed with unchanged

(7) K. Holzle, *Experientia*, **3**, 149 (1947).

(8) F. Krollpfeifer, K. L. Schneider, and A. Wissner, *Ann.*, **566**, 139 (1950).

(9) The method used was the same as that employed by P. Friedlander, A. Bezdrik, and P. Koeniger, *Ber.*, **41**, 235 (1908), for converting benzo[*b*]-thiophen-3-ol to benzo[*b*]thiophene-2,3-dione.

TABLE II

BENZOYLATION OF ARYLMERCAPTOACETIC ACIDS

Starting material	Product	Yield, %	M.p., °C.	Analyses—Calculated C	Calculated H	Calculated S	Found C	Found H	Found S
$C_6H_5SCH_2CO_2H$	4-$C_6H_5COC_6H_4SCH_2CO_2H$	90	134–135	66.16	4.44	11.73	66.09	4.46	11.71
2-$CH_3C_6H_4SCH_2CO_2H$	4-C_6H_5CO-2-$CH_3C_6H_3SCH_2CO_2H$	86	124–125	67.11	4.93	11.2	67.73	5.07	10.88
3-$CH_3C_6H_4SCH_2CO_2H$	4-C_6H_5CO-3-$CH_3C_6H_3SCH_2CO_2H$	50	102–103	67.11	4.93	11.2	67.40	5.26	11.05

TABLE III

CLEAVAGE OF ACYLARYLMERCAPTOACETIC ACIDS (1.25 *M* H_2O_2)

Acylarylmercaptoacetic acid	Products	Yield,[c] %	M.p. or b.p., (mm.) °C.	Analyses—Calculated C	Calculated H	Calculated S	Found C	Found H	Found S
	Unchanged acid	28	156–158						
4-$CH_3COC_6H_4SCH_2CO_2H$	4-$CH_3COC_6H_4SH$	26	135–136 (7)						
	$(4\text{-}CH_3COC_6H_4S\text{-})_2$	27	97–98						
	Unchanged acid	19							
4-CH_3CO-2-$CH_3C_6H_3SCH_2CO_2H$	4-CH_3CO-2-$CH_3C_6H_3SH$	17	146–147 (6)[a]	65.02	6.06	19.29	65.20	6.11	18.94
	$(4\text{-}CH_3CO\text{-}2\text{-}CH_3C_6H_3S\text{-})_2$	53	112.5–113.5	65.42	5.49	19.40	65.83	5.68	19.05
	Unchanged acid	27							
4-CH_3CO-3-$CH_3C_6H_3SCH_2CO_2H$	4-CH_3CO-3-$CH_3C_6H_3SH$	18	139–140 (7)	65.02	6.06	19.29	64.76	6.21	19.60
	$(4\text{-}CH_3CO\text{-}3\text{-}CH_3C_6H_3S\text{-})_2$	40	60–61	65.42	5.49	19.40	65.29	5.32	19.50
	Unchanged acid	33							
4-$C_6H_5COC_6H_4SCH_2CO_2H$	4-$C_6H_5COC_6H_4SH$[b]	27	71–72	72.86	4.71	14.96	72.72	4.48	14.50
	$(4\text{-}C_6H_5COC_6H_4S)_2$	35	126–127	73.21	4.25	15.03	73.12	4.21	14.80

[a] M.p. 30–31°. [b] *p*-Nitrobenzoyl ester, m.p. 157–158°. Calcd. for $C_{20}H_{13}O_4NS$: C, 66.10; H, 3.61; N, 3.86; S, 8.82. Found: C, 65.97; H, 3.63; N, 3.66; S, 8.65. [c] Based on starting acid.

TABLE IV

CLEAVAGE OF ACYLARYLMERCAPTOACETIC ACIDS (2.0–2.5 *M* H_2O_2)

Acylarylmercaptoacetic acid	Moles of H_2O_2 per mole of mercapto acid	Disulfide	M.p., °C.	Yield, %
4-$CH_3COC_6H_4SCH_2CO_2H$	2.0	$(4\text{-}CH_3COC_6H_4S)_2$	96–97[a]	84
4-CH_3CO-2-$CH_3C_6H_3SCH_2CO_2H$	2.0	$(4\text{-}CH_3CO\text{-}2\text{-}CH_3C_6H_3S)_2$	112.5–113.5[a]	80
4-CH_3CO-3-$CH_3C_6H_3SCH_2CO_2H$	2.0	$(4\text{-}CH_3CO\text{-}3\text{-}CH_3C_6H_3S)_2$	60–61[a]	82
4-$C_6H_5COC_6H_4SCH_2CO_2H$	2.0	$(4\text{-}C_6H_5COC_6H_4S)_2$	126–127[a]	86
4-C_6H_5CO-2-$CH_3C_6H_3SCH_2CO_2H$	2.5[c]	$(4\text{-}C_6H_5CO\text{-}2\text{-}CH_3C_6H_3S)_2$	Viscous oil[b]	21
4-C_6H_5CO-3-$CH_3C_6H_3SCH_2CO_2H$	2.2	$(4\text{-}C_6H_5CO\text{-}3\text{-}CH_3C_6H_3S)_2$	Viscous oil[b]	84

[a] These materials were identical with those prepared as described in Table III. [b] These materials could not be isolated as solids. No elemental analyses were obtained. [c] This experiment gave 56% acidic product (not identified), 21% disulfide, and 23% thiol, b.p. 172–175 (1 mm.), m.p. 81–82 (petroleum ether, b.p. 88–98°). *Anal.* Calcd. for $C_{14}H_{12}OS$: C, 73.65; H, 5.3; S, 14.04. Found: C, 73.44; H, 5.31; S, 14.08.

sulfide for the oxidizing agent. Thus, the products of the interaction of one mole of acylarylmercaptoacetic acid and one and a quarter moles of hydrogen peroxide were unchanged acid and acylarylthiol mixed with the corresponding disulfide. Yields of thiol and disulfide, based on conversion of acylarylmercaptoacetic acid, were consistently better than 70% (see Table III). By using two moles of hydrogen peroxide per mole of acylarylmercaptoacetic acid disulfides were produced directly usually in over 80% yield (see Table IV). In some cases the crude disulfides were oily; however, trituration with aqueous sodium hydroxide frequently converted oily to granular products. The oiliness was probably due, in major part, to the presence of thiols.

Most of the hydrogen peroxide cleavage reactions were carried out at 100°. In one cleavage reaction carried out at 60°, using two and a half moles of hydrogen peroxide, substantial amounts of acylarylsulfonylacetic acid accompanied a low yield of di(acylaryl) disulfide.

Reduction of di(acylaryl) disulfides to the corresponding thiols generally did not prove satisfactory[10] (see Table V). Reduction of di(4-benzoyl-3-methylphenyl) disulfide with zinc and acetic acid led to the formation of 4-benzyl-3-methylbenzenethiol in fair yield. Considerable resin formation was apparent in almost all of the reductions carried out, perhaps because of formation of styrene derivatives and/or condensation of thiol and keto groups.

Another approach to the preparation of acylarylthiols was to oxidize the acylarylmercaptoacetic acids to acylarylsulfinylacetic acids and hydrolyze the latter in boiling dilute mineral acid. Moderate yields of acylarylthiols were obtained in this way though some di-

(10) Since the work described in this paper was completed a new method of preparing arylthiols from disulfides has been published: J. R. Campbell, *J. Org. Chem.*, **27**, 2207 (1962). This method may offer a promising approach to the preparation of acylarylthiols from di(acylaryl) disulfides.

TABLE V

REDUCTION OF DI(ACYLARYL) DISULFIDES

Disulfide	Thiol	Yield, %	M.p. or b.p. (mm.), °C.
$(4\text{-}CH_3COC_6H_4S\text{-})_2$	$4\text{-}CH_3COC_6H_4SH$[a]	29	133–136 (7)
$(4\text{-}CH_3CO\text{-}2\text{-}CH_3C_6H_3S\text{-})_2$	$4\text{-}CH_3CO\text{-}2\text{-}CH_3C_6H_3SH$[a]	15	150–154 (7)[b]
$(4\text{-}C_6H_5CO\text{-}3\text{-}CH_3C_6H_3S\text{-})_2$	$4\text{-}C_6H_5CH_2\text{-}3\text{-}CH_3C_6H_3SH$[c]	42	128 (0.2)

[a] These materials were identical with those prepared as described in Table III. [b] M.p. 30–31° (petroleum ether, b.p. 30–60°). [c] *Anal.* Calcd. for $C_{14}H_{14}S$: C, 78.45; H, 6.58; S, 14.96. Found: C, 78.42; H, 6.81; S, 15.40. S-Benzoyl derivative, m.p. 65–66° (aqueous methanol). *Anal.* Calcd. for $C_{21}H_{18}OS$: C, 79.21; H, 5.7; S, 10.06. Found: C, 79.48; H, 5.76; S, 10.04.

TABLE VI

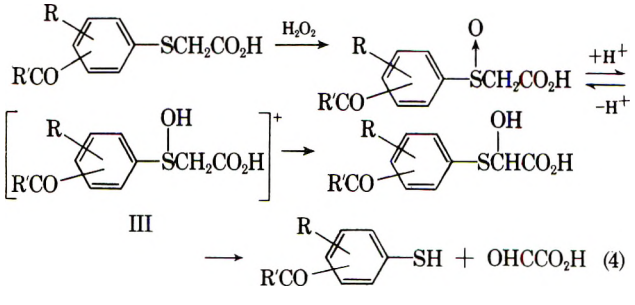
ACYLARYLSULFINYLACETIC ACIDS

Acylarylsulfinylacetic acid	Yield, %	M.p., °C.	Analyses—Calculated C	H	S	Found C	H	S
$4\text{-}CH_3COC_6H_4SOCH_2CO_2H$	47	136–137	53.09	4.45	14.13	53.58	4.68	13.89
$4\text{-}CH_3CO\text{-}2\text{-}CH_3C_6H_3SOCH_2CO_2H$	100[a]	Syrup	...	...	...	...	...	...
$2\text{-}CH_3CO\text{-}4\text{-}CH_3C_6H_3SOCH_2CO_2H$	90	181–182 dec.	54.98	5.03	13.34	55.32	5.12	12.91
$4\text{-}C_6H_5CO\text{-}3\text{-}CH_3C_6H_3SOCH_2CO_2H$	100[a]	Syrup	...	...	...	...	...	...

[a] Crude yield.

sulfide was frequently found among the reaction products (see Table VI).

It was noticed from qualitative observations, that the acid-catalyzed hydrolytic cleavage of acylarylsulfinylacetic acids occurred at a slower rate than was the case with the haloarylsulfinylacetic acids.[4] While this may be due in part to the lower solubility of the acylarylsulfinylacetic acids alternative reasoning is possible. The sulfinyl group in acylarylsulfinylacetic acids would, on account of the deactivating acyl group, be expected to be less "basic" than the same group in the halo- or alkylarylsulfinylacetic acids. The less "basic" arylsulfinylacetic acid would not be expected to form easily the conjugate acid III necessary for the rearrangement (equation 4).[11]



In regard to the necessity of formation of a conjugate acid it is interesting to note that hydrogen peroxide oxidation of *p*-nitrophenylmercaptoacetic acid to *p*-nitrobenzenethiol and di(*p*-nitrophenyl) disulfide also proceeded with some difficulty. In this case, even at 100°, the oxidizing agent quite successfully competed with proton at the *p*-nitrophenylsulfinylacetic acid stage with the result that *p*-nitrophenylsulfonylacetic acid was also formed. The importance of the formation of conjugate acids to the rearrangement of arylsulfinyl acetic acids (ref. 4 and equation 4) is further emphasized by the inability of arylsulfonylacetic acids to form conjugate acids and hence rearrangement products.

(11) A referee has suggested that protonation of the carbonyl group may also be a factor in the difference between the halo- and acyl-substituted compounds.

Summary

The scheme outlined in equation 1 has been successfully applied to the preparation of acylarylthiols from arylthiol precursors. Yields of acylarylthiols obtainable directly according to equation 1 are only moderate; the process lends itself very well, however, to the direct preparation of high yields of di(acylaryl) disulfides. Although the present study of the new process has been limited to the acylation of benzenethiol and the three toluenethiols there seems no reason why it could not be extended to heterocyclic and condensed homocyclic aromatic ring systems. The new process is limited in its generality inasmuch as the position taken up by the entering acyl group depends on the substituents already in the ring.

Experimental[12]

Acetylations. A. In Nitrobenzene.—Aluminum chloride (3.3–4.0 moles) was added slowly to nitrobenzene (11 moles). Two-thirds of this solution was treated, at 0–5°, with acetyl chloride (1.1 moles); the remaining one-third was treated, at 0–5°, with the arylmercaptoacetic acid (1 mole). The acetyl chloride–aluminum chloride mixture was then added, over 1.5 hr., to the arylmercaptoacetic acid–aluminum chloride mixture. Throughout the addition the temperature was maintained at 8–10° with an ice–water bath. After completion of the addition the mixture was stirred at 7–10° for 1 hr. and then allowed to warm to room temperature during an additional 4 hr. The deeply colored nitrobenzene solution was decomposed by pouring it into a large excess of ice and hydrochloric acid; removal of the nitrobenzene by steam distillation left a crude acylarylmercaptoacetic acid.

The crude acetylation products from phenyl-, *o*-tolyl-, and *m*-tolylmercaptoacetic acids were solids at room temperature and were not steam volatile. These solids were partially purified by solution in aqueous sodium bicarbonate followed by filtration and acidification. Pure samples were obtained by crystallization first from water or aqueous methanol, and then from carbon tetrachloride containing a little methanol.

Only in the case of the acetylation of *m*-tolylmercaptoacetic acid were two acidic products isolated. Acidification of the sodium bicarbonate solution at 35° precipitated 4-acetyl-3-methylphenylmercaptoacetic acid, which was immediately filtered. A small amount of the second acid deposited when the filtrate was cooled. Further work (see subsequent reaction) showed that the second acid was 2-acetyl-3(or 5)-methylphenylmercaptoacetic acid.

(12) Temperatures are uncorrected. Microanalyses were by Drs. G. Weiler and F. B. Strauss, Oxford, England.

The product from the attempted acetylation of *p*-tolylmercaptoacetic acid was steam volatile. It was partially separated from the nitrobenzene during the steam distillation of the latter. Further work showed that this steam volatile solid was 5-methylbenzo[*b*]thiophen-3-ol (see subsequent reaction).

B. In Carbon Disulfide–Nitrobenzene.—Acetyl chloride (1.1 moles) was added gradually to a suspension of aluminum chloride (3.3–4.1 moles) in carbon disulfide (16.5 moles) at 0–5° under ice-bath cooling. Arylmercaptoacetic acid (1 mole) was then sprinkled in gradually while the temperature was held below 10°. Small quantities of nitrobenzene were added periodically to ease stirring. The amount of nitrobenzene used varied from 0.5 to 2.5 moles. After all the acid had been added the suspension was stirred until evolution of hydrogen chloride had ceased. The mixture was decomposed by pouring it into a large excess of ice and hydrochloric acid. Carbon disulfide was removed by distillation and the acetylarylmercaptoacetic acid was filtered, washed with petroleum ether (b.p. 88–98°), and dried. The product thus obtained was essentially pure. Analytical specimens were obtained by crystallization from water or a mixture of carbon tetrachloride and methanol.

The structure of 2-acetyl-4-methylphenylmercaptoacetic acid was established by converting it to 3,5-dimethylbenzo[*b*]thiophene-2-carboxylic acid (which see). Table I summarizes results of the acetylation experiments.

Partial Proof of Structure of 2-Acetyl-3(or 5)-methylphenylmercaptoacetic Acid.—The acidic by-product from the preparation of 4-acetyl-3-methylphenylmercaptoacetic acid was shown to contain an acetyl group in an *ortho* position to the sulfur atom by the following experiment.

The acid (0.01 mole), m.p. 161–162° dec., was boiled in 20% hydrochloric acid (20 ml.) for 5 hr. The solid product was filtered and crystallized twice from aqueous acetic acid. The yield of pure 3,4(or 3,6)-dimethylbenzo[*b*]thiophene-2-carboxylic acid, m.p. 261–262° dec., was 90%.

Anal. Calcd. for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.54. Found: C, 63.71; H, 5.07; S, 15.65.

Proof of Structure of 5-Methylbenzo[*b*]thiophen-3-ol.—Steam distillation of the decomposed reaction mixture from the attempted acetylation of *p*-tolylmercaptoacetic acid in nitrobenzene gave a steam volatile solid, m.p. 96–98°. A single crystallization from petroleum ether (b.p. 88–98°) gave colorless needles, m.p. 98–100°. The literature[6] reports a melting point of 101–102° for 5-methylbenzo[*b*]thiophen-3-ol.

The compound, m.p. 98–100°, was converted to 5-methylbenzo[*b*]thiophene-2,3-dione by a known method.[9] 5-Methylbenzo[*b*]thiophene-2,3-dione was obtained as red prismatic needles, m.p. 146–147° (aqueous methanol) (lit.[13] m.p. 144–145°).

Anal. Calcd. for $C_9H_6O_2S$: S, 17.99. Found: S, 17.76.

Proof of Structure of 2-Acetyl-4-methylphenylmercaptoacetic Acid.—The acid (2 g.) was heated in 30% aqueous sodium hydroxide (20 ml.) for 5 hr. Dilution of the suspension with water followed by acidification gave a quantitative yield of 3,5-dimethylbenzo[*b*]thiophene-2-carboxylic acid, m.p. 262–264° dec. Recrystallization from acetic acid gave an analytically pure sample, m.p. 263–264° dec. (lit.[8] m.p. 262°).

Anal. Calcd. for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.54. Found: C, 63.91; H, 5.13; S, 15.65.

Preparation of 2,4-Dinitrophenylhydrazones.—Derivatives of 2-acetyl-4-methylphenylmercaptoacetic acid and 4-acetyl-2-methylphenylmercaptoacetic acid were prepared in the following way. A suspension of 2,4-dinitrophenylhydrazine (0.25 g.) in boiling ethanol (20 ml.) was treated with concentrated hydrochloric acid (2 ml.) and the mixture heated until a clear solution resulted. The acetyl compound (0.25 g.) was added to this solution. The mixture was boiled for 10 min., allowed to stand for 30 min., cooled, and filtered. The crystals thus obtained were purified by recrystallization from ethanol. Analysis showed that the carboxy group had been esterified during this process. 2,4-Dinitrophenylhydrazone of ethyl 2-acetyl-4-methylphenylmercaptoacetate had m.p. 142°.

Anal. Calcd. for $C_{19}H_{20}N_4O_6S$: C, 52.77; H, 4.66; N, 12.96; S, 7.41. Found: C, 52.41; H, 4.22; N, 13.24; S, 7.39.

2,4-Dinitrophenylhydrazone of ethyl 4-acetyl-2-methylphenylmercaptoacetate had m.p. 122–123°.

Anal. Calcd. for $C_{19}H_{20}N_4O_6S$: N, 12.96; S, 7.41. Found: N, 12.89; S, 7.25.

Benzoylations.—Aluminum chloride (4 moles) was suspended in carbon disulfide (80 moles), and benzoyl chloride (1.1 moles) was added over 15 min. The temperature was held below 15° with an ice–water bath. Arylmercaptoacetic acid (1 mole) was sprinkled in over 20 min. while the temperature was held at about 15°. Nitrobenzene (about 2 moles in all) was added periodically to ease stirring. After the arylmercaptoacetic acid had been added, the mixture was held at 15° for 1.5 hr., and then allowed to warm to room temperature in 4 hr. The reaction mixture was decomposed in the usual way, carbon disulfide was removed by distillation, and the benzoylmercaptoacetic acid was collected by filtration. The crude product was partially purified by dissolving it in aqueous sodium bicarbonate, filtering, and acidifying. Further purification was effected by crystallization from carbon tetrachloride containing a very small amount of petroleum ether (b.p. 88–98°). Table II summarizes results of the benzoylation experiments.

Acylarylthiols and Disulfides from Acylarylmercaptoacetic Acids. A. 1.25 Moles of Hydrogen Peroxide at 100°.—Acylarylmercaptoacetic acid (0.1 mole) was refluxed in water (200 ml.) containing sulfuric acid (11 g.). Hydrogen peroxide (0.1 mole as a 30% aqueous solution) was added dropwise to the refluxing mixture over a period of about 15 min. After addition of the hydrogen peroxide was completed the mixture was refluxed for 20 min. and a further 0.025 mole of hydrogen peroxide added over 10 min. The suspension was refluxed an additional 2 hr. and cooled. The oily product was extracted with ether and the ether layer extracted first with aqueous sodium bicarbonate and then with sodium hydroxide. Acidification of the sodium hydroxide extract gave acylarylthiol. Evaporation of the ether layer generally gave an oily disulfide which became granular on trituration with aqueous sodium hydroxide. Aqueous methanol was used to crystallize the disulfides. Petroleum ether (b.p. 63–69°) was used to crystallize the solid thiols. Table III summarizes the results obtained.

B. 2.0–2.5 Moles of Hydrogen Peroxide at 100°.—Acylarylmercaptoacetic acid (0.1 mole) was refluxed in water (200 ml.) containing sulfuric acid (4 g.). Hydrogen peroxide (0.1 mole as a 30% aqueous solution) was added dropwise to the refluxing mixture over a period of about 20 min. Some 20 min. after addition of the first 0.1 mole of hydrogen peroxide, another 0.05 mole was added over 10 min. About 15 min. later an additional 0.05 mole of hydrogen peroxide was added and the mixture refluxed an additional 90 min. In those cases where the product was oily, trituration with aqueous sodium hydroxide frequently gave a manageable solid product. Aqueous methanol proved a useful solvent for crystallization. Table IV summarizes the results obtained.

C. 2.5 Moles of Hydrogen Peroxide at 60°.—A suspension of finely powdered 4-acetyl-3-methylphenylmercaptoacetic acid (0.15 mole) in 10% hydrochloric acid (150 ml.) was heated to 60°. Hydrogen peroxide (0.15 mole as a 30% aqueous solution) was added dropwise over 15 min. After stirring for 30 min. an additional 0.15 mole of hydrogen peroxide was added over 10 min. One hour later a further 0.075 mole of hydrogen peroxide was added and the mixture stirred an additional 2 hr. The temperature was maintained at 60° throughout the reaction. After cooling to 10° the solid product was filtered and extracted with aqueous sodium bicarbonate. The sodium bicarbonate solution on acidification gave 4-acetyl-3-methylphenylsulfonylacetic acid (14%), m.p. 146–148°. A single crystallization from water yielded needles, m.p. 150–151°.

Anal. Calcd. for $C_{11}H_{12}O_5S$: C, 51.54; H, 4.72; S, 12.51; equiv. wt., 256.3. Found: C, 51.91; H, 4.54; S, 12.04; equiv. wt., 255.5.

The solid insoluble in aqueous sodium bicarbonate was oily in appearance. Treatment with aqueous sodium hydroxide gave a granular product, m.p. 57–59°. Crystallization from aqueous methanol yielded di(4-acetyl-3-methylphenyl) disulfide (26%) as plates, m.p. 60–61°. The sodium hydroxide on acidification gave a small amount of an unidentified resinous product.

Acylarylsulfonylacetic acids are undoubtedly formed in most oxidation reactions which use excess hydrogen peroxide. In addition to the cited preparation of 4-acetyl-3-methylphenylsulfonylacetic acid, we isolated 4-acetylphenylsulfonylacetic acid, m.p. ~170° dec., and 4-acetylphenylmethyl sulfone from the aqueous liquors from the acid-catalyzed oxidation cleavage of 4-acetylphenylmercaptoacetic acid. The crude acid, m.p. ~170° dec., was converted to 4-acetylphenylmethyl sulfone by heating at 160–180° for 3 hr. A specimen of this sulfone, when crystallized from water, melted at 127–128°.

(13) C. E. Dalgliesh and F. G. Mann, *J. Chem. Soc.*, 893 (1945).

TABLE VII

ACID-CATALYZED CLEAVAGE OF ACYLARYLSULFINYLACETIC ACIDS

Acylarylsulfinylacetic acid	Thiol	Yield, %	B.p. (mm.), °C.
$4\text{-}CH_3CO\text{-}2\text{-}CH_3C_6H_3SOCH_2CO_2H$	$4\text{-}CH_3CO\text{-}2\text{-}CH_3C_6H_3SH$	43	143–144 (5)
$2\text{-}CH_3CO\text{-}4\text{-}CH_3C_6H_3SOCH_2CO_2H$	$2\text{-}CH_3CO\text{-}4\text{-}CH_3C_6H_3SH$[a]	45	139–140 (5.5)
$4\text{-}C_6H_5CO\text{-}3\text{-}CH_3C_6H_3SOCH_2CO_2H$	$4\text{-}C_6H_5CO\text{-}3\text{-}CH_3C_6H_3SH$[b]	39	152 (2)

[a] M.p. 32–33°. *Anal.* Calcd. for $C_9H_{10}OS$: C, 65.02; H, 6.06; S, 19.29. Found: C, 65.20; H, 6.19; S, 19.01. Disulfide, m.p. 178° (aqueous methanol). *Anal.* Calcd. for $C_{18}H_{18}O_2S_2$: C, 65.42; H. 5.49; S, 19.40. Found: C, 65.84; H, 5.47; S, 19.01. [b] *Anal.* Calcd. for $C_{14}H_{12}OS$: C, 73.65; H, 5.3; S, 14.04. Found: C, 74.15; H, 5.69; S, 13.24. S-Benzoyl derivative, m.p. 97.5–98.5 (methanol). *Anal.* Calcd. for $C_{21}H_{16}O_2S$: C, 76.18; H, 4.85; S, 9.64. Found: C, 76.72; H, 4.95; S, 9.68.

Anal. Calcd. for $C_9H_{10}O_3S$: C, 54.53; H, 5.08; S, 16.17. Found: C, 54.32; H, 4.91; S, 15.95.

This material gave no depression of melting point with an authentic sample prepared from 4-acetylphenylmethyl sulfide[14] by hydrogen peroxide oxidation.[15]

Thiols from Di(acylaryl) Disulfides.—The disulfide (0.05 mole) was refluxed in acetic acid (1 mole) and water (2 moles) and the mixture treated, over a period of 40 min., with zinc dust (0.3 to 0.4 mole). After refluxing for an additional 3 hr. the mixture was poured into water. Excess zinc was removed by adding a little concentrated hydrochloric acid. The oil was taken up in ether and crude thiol extracted from this with aqueous sodium hydroxide. Acidification of the sodium hydroxide solution gave crude thiol which was redissolved in ether; the ether was washed with water and dried. The ether was distilled and the thiol purified by vacuum distillation.

The reduction of di(4-benzoyl-3-methylphenyl) disulfide using zinc and acetic acid gave 4-benzyl-3-methylbenzenethiol as the major product. Table V summarizes the results obtained.

Acylarylthiols from Acylarylsulfinylacetic Acids. A. Preparation of Acylarylsulfinylacetic Acids.—Acylarylmercaptoacetic acid (0.1 mole) was suspended in 75% acetic acid (250 ml.) and the mixture stirred and heated to about 60°. Hydrogen peroxide (0.1 mole as a 30% aqueous solution) was added over 50 min. at this temperature. The mixture was kept at 60° for 5 hr. and allowed to stand overnight. Half of the solvent mixture was removed under vacuum at 50–60° (rotary evaporator). Cooling of the acetic acid solution sometimes led to crystallization of the acylarylsulfinylacetic acid. In a few cases the acylarylsulfinyl acetic acid was obtained as a sirup by complete evaporation of the aqueous acetic acid. Table VI summarizes the results obtained.

(14) G. B. Bachman and C. L. Carlson, *J. Am. Chem. Soc.*, **73**, 2857 (1951).

(15) U. S. Patent 2,802,033 (1957) to E. I. du Pont de Nemours and Co.

B. **Cleavage of Acylarylsulfinylacetic Acids.**—Acylarylsulfinylacetic acid (0.05 mole) was refluxed in 6% sulfuric acid (200 ml.) for 5 to 6 hr. The oily suspension was extracted with ether and the ether extracted first with aqueous sodium bicarbonate and then with aqueous sodium hydroxide. Acidification of the sodium bicarbonate extracts usually gave some acidic material (2-acetyl-4-methylphenylsulfinylacetic acid gave some high melting acid, probably 3,5-dimethylbenzo[*b*]thiophene-2-carboxylic acid or its sulfoxide). Acidification of the sodium hydroxide extracts gave the crude thiols which were purified by distillation. The neutral ether layer on evaporation usually yielded a small quantity of the disulfide (the neutral product from 2-acetyl-4-methylphenylsulfinylacetic acid was complex). Table VII summarizes the results obtained.

Hydrogen Peroxide Oxidation of 4-Nitrophenylmercaptoacetic Acid.—4-Nitrophenylmercaptoacetic acid (0.05 mole) was finely ground and suspended in water (55 ml.) containing 80% phosphoric acid (3 ml.). The suspension was boiled and hydrogen peroxide (0.055 mole as a 30% aqueous solution) added over about 30 min. Steam was passed in during the peroxide addition and for 1 hr. after that. The solid in the reaction flask turned first to a yellow oil and finally to a solid. About 0.5 g. of product steam distilled; this proved to be a mixture of about equal weights of 4-nitrobenzenethiol, m.p. 76–77°, and di(4-nitrophenyl) disulfide, m.p. 179–180°. The contents of the reaction flask were filtered and the solid extracted with aqueous sodium bicarbonate. Acidification of this extract gave 3.9 g. of acidic material, m.p. 155–160°. Several crystallizations of the latter from methanol afforded 4-nitrophenylsulfonylacetic acid, m.p. 168° dec.

Anal. Calcd. for $C_8H_7NO_6S$: N, 5.71; S, 13.06. Found: N, 5.76; S, 13.40.

The solid insoluble in aqueous sodium bicarbonate was di(4-nitrophenyl) disulfide, m.p. 175–177°. Crystallization from acetic acid gave a pure product, m.p. 180–181°

The Reaction between Acenaphthenequinone and Phenyllithium

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Received March 4, 1963

The reaction between acenaphthenequinone and phenyllithium gave the expected *trans*-1,2-diphenyl-1,2-acenaphthenediol in low yields as well as four other solid products. Two of these were known compounds. The structures of one of the other products (II) and of several new compounds related to it have been established. II is the result of the unusual 1,4-addition of phenyllithium to an aryl ketone.

The reaction between acenaphthenequinone and phenylmagnesium bromide gave *trans*-1,2-diphenyl-1,2-acenaphthenediol in 81% yield.[1] In the reactions of other quinones with organometallic reagents,[2] better yields of 1,2-addition products were obtained by the use of phenyllithium rather than phenylmagnesium bromide. The present study shows that acenaphthenequinone behaved more like phenanthrenequinone[3] and gave the *trans*-1,2-diphenyl-1,2-acenaphthenediol in poor yields, 10–28%, as well as several other solid products and a dark oil from which no more solid could be isolated either by crystallization or by chromatography. Naphthalic anhydride (1–6%) was isolated from five of the twenty-five reactions which were carried out. Fourteen of the reactions gave the lactone of 1-(diphenylhydroxymethyl)-8-naphthoic acid (I, 7–22%). These compounds were identified by comparison with known samples.[4] Four of the reactions gave small amounts of a lactone melting at 176°, which has not

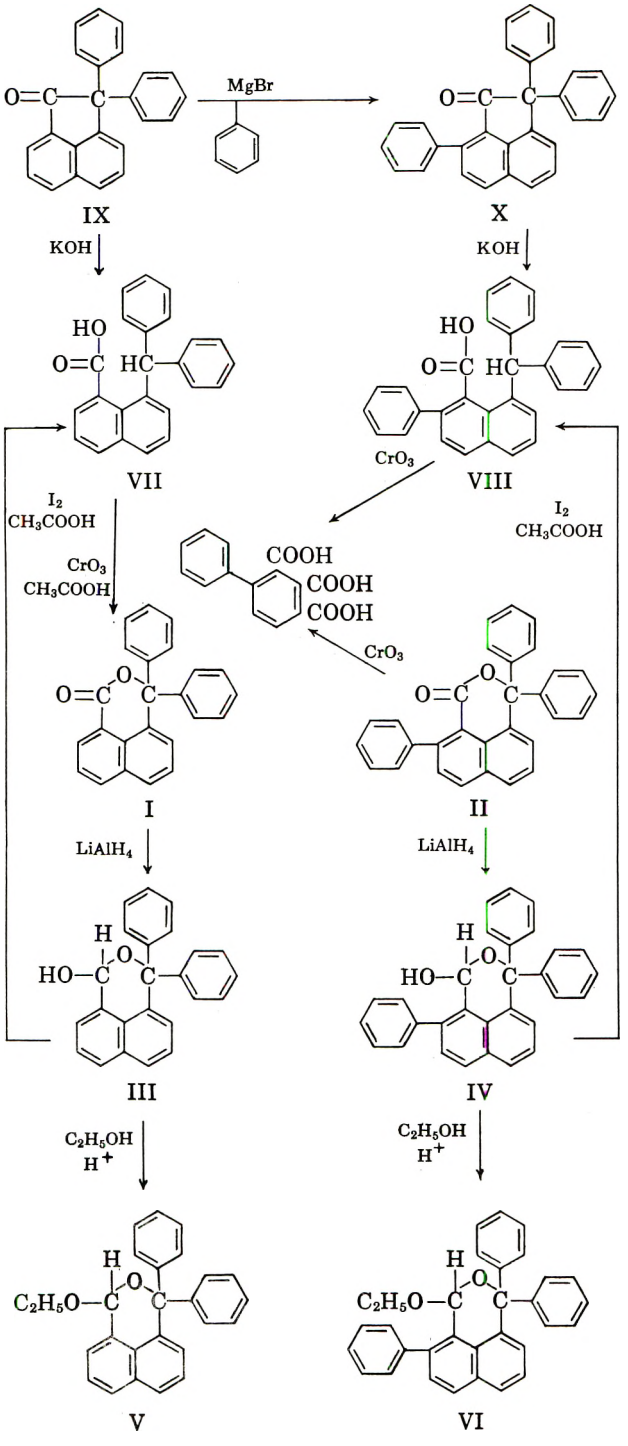
(1) P. D. Bartlett and R. F. Brown, *J. Am. Chem. Soc.*, **62**, 2927 (1940).

(2) H. M. Crawford, *ibid.*, **61**, 3310 (1939); **70**, 1081 (1948); H. M. Crawford and M. McDonald, *ibid.*, **71**, 2681 (1949).

(3) H. M. Crawford, M. Lumpkin, and M. McDonald, *ibid.*, **74**, 4087 (1952).

(4) G. Wittig, M. Leo, and W. Wiemer, *Ber.*, **64**, 2405 (1931).

CHART I

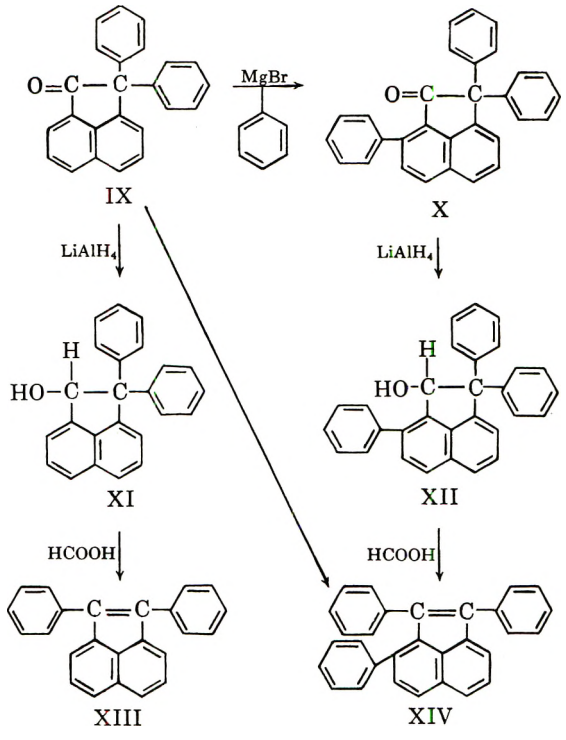


been completely identified. Ten of the reactions gave 1–30% of a compound which has been identified as the lactone of 1-(diphenylhydroxymethyl)-7-phenyl-8-naphthoic acid (II). The lactone II was identified by infrared and nuclear magnetic resonance spectra and by the similarity of a series of compounds related to it and another series of known compounds related to the lactone I.

In Chart I, all of the compounds with odd numbers were already known and were made by the methods which have been described. All of the compounds with even numbers, except X, are described for the first time.

The infrared spectra of corresponding compounds were compared and in every case they showed marked similarities.

In one attempt to make X from IX, the only product (48%) was a bright orange-red compound XIV, which was made later from IX, isolating and identifying the intermediates X and XII.



Again the infrared spectra of the corresponding compounds were very similar.

Experimental

Melting points are uncorrected.

Acenaphthenequinone was prepared in 50% yields by the oxidation of acenaphthene.[5]

The Reaction between Acenaphthenequinone and Phenyllithium.—As in other studies of this type[2,3] the quantities of reactants and the method of procedure were varied. The best yields of solid products were obtained by adding 0.05 mole of quinone suspended in ether, to 0.125 mole of phenyllithium in ether. After standing overnight, the organometallic product was decomposed with cold ammonium chloride solution. The ether layer was allowed to evaporate slowly, and successive crops of solid were removed and recrystallized. After no more solid could be separated from the heavy, dark oils, a benzene solution of the oil was poured onto a column of alumina. Successive portions of petroleum ether (b.p. 60–70°), ethyl acetate, and methanol were used to elute material from the column. In some cases the first ether solution was chromatographed immediately with no difference in the results. Any solids resulting from the evaporation of the various fractions were crystallized and identified. *trans*-1,2-Diphenyl-1,2-acenaphthenediol was obtained in yields varying from 10 to 28%. No *cis* diol was isolated from any of the twenty-five reactions. In five of the reactions 1–6% of naphthalic anhydride was obtained. Fourteen of the reactions gave the known lactone of 1-(diphenylhydroxymethyl)-8-naphthoic acid (I). Its identity was established by mixture melting point with a known sample of the lactone, prepared from naphthalic anhydride and phenyllithium.[4]

Two other solids were isolated, but never from the same reaction; the 176° lactone was obtained four times in yields of 3–15%, and 179° lactone II, was obtained ten times in yields of 1–30%.

The 176° Lactone.—This compound crystallized from methanol in small, colorless needles. It gave no 2,4-dinitrophenylhydrazone or oxime. It gave no color and was recovered unchanged after heating with hydrogen chloride in glacial acetic acid. It was recovered unchanged after heating with Lucas' reagent or

(5) C. S. Maxwell and C. F. H. Allen, *Org. Syn.*, **24**, 1 (1944).

with iodine in glacial acetic acid. It depressed the melting point of known samples of the *cis* diol melting at 174–176°; of IX melting at 173–174°; of the monoethyl ether of the *cis* diol melting at 176.5–177.5° (kindly supplied by R. F. Brown[6]); and of 1,2,2-triphenyl-1-acenaphthenol melting at 167–169°. The 176° compound is soluble in aqueous potassium hydroxide from which it was recovered by treatment with hydrochloric acid. This indicates a lactone structure. Treatment with phenyllithium gave biphenyl as the only identifiable product. The infrared spectrum shows absorption at 3.4, 3.5, 5.8, and 8.6 μ in addition to the bands due to monosubstituted benzenes. The nuclear magnetic resonance spectrum indicates a $-CH_2-$ group, a large number (19–27) of aromatic protons, and three others not on a naphthalene or benzene ring.

Anal. C, 87.2; H, 5.4; mol. wt., 373 (in benzene).

Lactone of 1-(Diphenylhydroxymethyl)-7-phenyl-8-naphthoic Acid (II).—This lactone is much less soluble than the 176° lactone. It can be crystallized from ethanol, benzene, or ethyl acetate as colorless prisms melting at 179–180°. It gave no carbonyl derivatives, gave no color with hydrogen chloride in acetic acid, and was recovered unchanged after heating with sulfuric acid in acetic acid. It was not soluble in alcoholic potassium hydroxide. This agrees with the behavior of the known lactone I to which it corresponds. (It reacted with phenyllithium to give a very small amount of a compound which melted at 255° and contained 86.93% C and 5.53% H.) The infrared spectra of I and II were run on the same paper. Both showed no absorption in the hydroxyl region; carbonyl absorption at 5.7, 8.2, and 9.1 μ, and the rest of the spectra were very similar. The n.m.r. spectrum of II is consistent with the structure assigned.

Anal. Calcd. for $C_{30}H_{20}O_2$: C, 87.35; H, 4.9; mol. wt., 412. Found: C, 86.62; H, 5.2; mol. wt., 415 (in camphor).

Oxidation of II with chromium trioxide in glacial acetic acid gave benzoic acid, benzophenone (identified as the 2,4-dinitrophenylhydrazone), and biphenyl-2,3,4-tricarboxylic acid melting at 208–209° (lit.[7] 210°). The same acid was obtained by the oxidation of VIII. The infrared spectrum of the acid, in carbon disulfide, showed absorption at 13.4 and 14.3 μ for a monosubstituted benzene, as well as the absorption for the carboxyl groups.

1-Hydroxy-3,3-diphenyl-1*H*,3*H*-9-phenylnaphtho[1,8-*c*,*d*]pyran (IV).—Compound II (2 g.) was refluxed for 4 hr. with 1.5 g. of lithium aluminum hydride in 50 ml. of ether. The excess lithium aluminum hydride was decomposed with water and the ether extract allowed to evaporate. Treatment of the resulting glass with methanol and diisopropyl ether gave 1.9 g. (90%) of white solid. Recrystallization from ethanol gave IV, m.p. 198.5–199.5°. For comparison, the lactone I was reduced by a similar procedure and product III was obtained. It melted at 164–165° (lit.[8] 166–167.5°). Both III and IV showed infrared absorption at 2.8 μ and none in the carbonyl region.

Anal. Calcd. for $C_{30}H_{22}O_2$: C, 86.93; H, 5.35. Found: C, 87.28, H, 5.7.

1-Ethoxy-3,3-diphenyl-1*H*,3*H*-9-phenylnaphtho[1,8-*c*,*d*]pyran (VI).—This acetal was prepared very easily by treating the hydroxy compound IV in ethanol with a trace of acid. In fact, if the excess lithium aluminum hydride (after the reduction of II) was decomposed with ethyl acetate, or the aluminum hydroxide sludge was dissolved in hydrochloric acid, the first crop of crystals separating was the hydroxy compound IV, and later the acetal VI was obtained. Crystallization from ethanol gave small colorless prisms melting 150–151°. The corresponding acetal V[8] was prepared in the same way and melted at 197–198°. Both acetals showed infrared absorption in the ether region, 8.5–10.0 μ, and none in the hydroxyl or carbonyl regions.

Anal. Calcd. for $C_{32}H_{26}O_2$: C, 86.84; H, 5.92. Found: C, 86.6; H, 6.0.

1-(Diphenylmethyl)-7-phenyl-8-naphthoic Acid (VIII).—The hemiacetal IV (0.3 g.) was refluxed for 35 min. with 0.2 g. of iodine in 25 ml. of acetic acid as described for the preparation of VII from III. The solution was poured into water containing a small amount of sodium bisulfite. The solid (0.26 g., 87%) crystallized from ethanol as shiny, colorless plates and melted at 259–260°. This same acid was obtained by opening the ketone ring of X by refluxing it with potassium hydroxide in diethylene glycol. Refluxing with potassium hydroxide in ethanol did not open this ring.[9] The corresponding acid VII was prepared according to the method of Zsuffa[9] by refluxing 2.0 g. of IX with 10 g. of potassium hydroxide, 10 ml. of water, and 100 ml. of ethanol for 4 hr. Dilution of the solution with water gave a quantitative yield of the acid VII. One crystallization from ethanol and ethyl acetate gave a white solid, m.p. 228–229°. Both acids (VII and VIII) showed infrared absorption at 3–3.5, 5.85, and 8.2 μ. Letsinger and Lansbury[8] made the lactone I by oxidation of the acid VII. A similar oxidation of the acid VIII by chromium trioxide gave biphenyl-2,3,4-tricarboxylic acid, identical with the acid obtained by the oxidation of the lactone II.

Anal. Calcd. for $C_{30}H_{22}O_2$: C, 86.93; H, 5.35. Found: C, 86.8; H, 5.5.

1,1,3-Triphenyl-2-acenaphthenone (X).—This ketone was described by Fuson and Griffin[10] as resulting from a forced reaction of phenylmagnesium bromide on 2,2-diphenyl-1-acenaphthenone (IX). Their product melted at 160–161° and its color was not mentioned. The ketone IX was made by the usual pinacol rearrangement of *trans*-1,2-diphenyl-1,2-acenaphthendiol. In the first attempt to make the ketone X (using 9.6 g., 0.03 mole, of the ketone IX and 0.17 mole of phenylmagnesium bromide and chromatographing on alumina) the only product obtained was 5.5 g. (48%) of a bright orange-red solid XIV which is described later. The melting point was 145–146°. Another attempt, using 3.9 g. of IX, gave 1.02 g. of a pale yellow solid, m.p. 145–146°, which showed infrared absorption at 5.7 and 5.8 μ. A later crop of crystals melted at 157–158°. A third attempt, using 3.8 g. of IX, was chromatographed at once and gave 2.1 g. (45%) of material first melting at 157–158°, identical with the material from the second attempt. After several recrystallizations from ethanol and ethyl acetate, the shiny lemon yellow plates melted at 168.5–169°. The infrared absorption spectra of IX and X are very similar, showing carbonyl absorption at 5.85 μ. A mixture melting point of ketone X with a sample supplied by Dr. Griffin[10] was 161–169°.

Anal. Calcd. for $C_{30}H_{20}O$: C, 90.88; H, 5.09. Found: C, 90.6; H, 5.2.

2-Hydroxy-1,1,3-triphenylacenaphthene (XII).—The yellow ketone X (0.3 g.) was refluxed for 1 hr. with 0.2 g. of lithium aluminum hydride in 30 ml. of ether. Excess lithium aluminum hydride was decomposed with ethyl acetate. The ether extract gave a quantitative yield of colorless needles of the alcohol XII melting 172–173°. The infrared spectra of this alcohol and the corresponding alcohol XI showed identical absorption at 2.8 μ and none in the carbonyl region.

Anal. Calcd. for $C_{30}H_{22}O$: C, 90.42; H, 5.57. Found: C, 90.4; H, 5.6.

1,2,3-Triphenylacenaphthylene (XIV).—This hydrocarbon was prepared by heating the alcohol XII with formic acid for 15 min. on the steam bath. The solution was colorless at first but quickly became yellow, then orange. The solution was diluted with water, and the resulting solid was separated and crystallized from ethanol and ethyl acetate. It separated as bright orange-red needles and melted at 143–145°. The mixture melting point was 144–145° with the orange-red hydrocarbon described earlier. The infrared spectra of this hydrocarbon and of the red hydrocarbon XIII (made according to the directions of Letsinger and Lansbury[8] from XI) were practically identical.

Anal. Calcd. for $C_{30}H_{20}$: C, 94.70; H, 5.30; mol. wt., 380. Found: C, 94.8; H, 5.3; mol. wt., 385.

Acknowledgment.—The author wishes to thank Mr. Jerry P. Heeschen of the Dow Chemical Company for the n.m.r. spectra, and Mr. F. M. Roberts of Texaco, Inc., for most of the carbon–hydrogen analyses.

(6) R. F. Brown, *J. Am. Chem. Soc.*, **74**, 428 (1952).

(7) G. Charrier and E. Ghigi, *Ber.*, **69**, 2223 (1936).

(8) R. L. Letsinger and P. T. Lansbury, *J. Am. Chem. Soc.*, **81**, 938 (1959).

(9) M. Zsuffa, *Ber.*, **43**, 2918 (1910).

(10) R. C. Fuson and G. W. Griffin, *J. Am. Chem. Soc.*, **79**, 1941 (1957).

The Synthesis and Properties of n-Octane-d_{18} and 2,2,4-Trimethylpentane-d_{18}[1]

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Received July 9, 1963

A relatively simple apparatus and procedure for preparing a variety of perdeuterated aliphatic compounds are applied to the synthesis of n-octane-d_{18} and 2,2,4-trimethylpentane-d_{18}. The properties of these compounds are reported.

As part of a continuing study of the relationship of physical properties to hydrocarbon structure, the changes in the properties when deuterium is substituted for hydrogen in hydrocarbons have been under study in this laboratory. Earlier, benzene-d_6 and cyclohexane-d_{12} were prepared[4] and the properties determined.[5-7] The changes in the properties upon deuteration observed with these two hydrocarbons and the recent corresponding states treatments of classically, isotopically substituted liquids[8] suggested that the preparation and study of additional perdeuterated hydrocarbons having significantly different spatial and symmetry characteristics might be worthwhile.

Although the literature[9-12] records the preparation of a number of perdeuterated hydrocarbons, none of the procedures appeared to be satisfactory for the synthesis of molar quantities in the C_6 to C_{12} molecular weight range. The reported syntheses may be divided into two broad classes.

(1) Syntheses starting from available chemical intermediates and utilizing classical chemical reactions to construct the desired perdeuterated molecule. An example of this procedure is the synthesis of spiropentane-d_8 starting from calcium carbide by House, Lord, and Rao.[11]

(2) Syntheses starting from a hydrocarbon possessing the same carbon skeleton as that desired in the final product and involving exchange of the hydrogens of the hydrocarbon with the deuterium atoms in a deuterium-containing molecule, *e.g.*, D_2O, D_2SO_4. The synthesis of benzene-d_6 by Ingold and co-workers[12] is a classic example of this approach.

Group 1 syntheses suffer from the fundamental disadvantage that each hydrocarbon structural-type requires a different synthetic route. Further, as the carbon skeleton of the molecule becomes more complex, the number of synthetic steps frequently increases rapidly. Since group 2 routes do not have these disadvantages, the present effort was confined to developing a procedure of this type but avoiding the problems noted below.

The exchange of deuterium between deuteriosulfuric acid and aromatic hydrocarbons proceeds readily at temperatures where no skeletal changes or other side reactions occur to any significant extent. Unfortunately, with aliphatic hydrocarbons Setkina and co-workers[13] have found that under mild conditions only the tertiary hydrogens are exchanged. Under forcing conditions the expected carbonium ion rearrangements accompany the exchange.[14] Similarly, Dixon and Schiessler[15] found that the vapor phase exchange between deuterium oxide and hydrocarbons is attended by significant cracking and/or isomerization.

In contrast, Burwell and co-workers[16-19] in their study of the mechanism of hydrogen exchange observed that the exchange of deuterium gas with aliphatic hydrocarbons proceeded rapidly in the vapor phase over metal catalysts and was accompanied by little or no carbon skeletal rearrangement. This procedure suffers only from the disadvantage that for the synthesis of molar quantities of a C_6 to C_{12} paraffin hydrocarbon extremely large volumes (of the order of thousands of liters at STP) of deuterium must be used. To avoid this a scheme involving the direct deuterium–hydrocarbon exchange but avoiding the handling of large amounts of deuterium was developed.

The Apparatus and Procedure.—Figure 1 is a flow diagram of the apparatus. A complete description of the apparatus and full experimental details may be found in ref. 20. The principal operations occurring in the system are the following.

(1) Hydrogen–deuterium gas is continuously circulated through the entire apparatus.

(2) In the "deuterator" section this gas mixed with hydrocarbon vapor passes over a pelleted nickel on kieselguhr[21] catalyst. A statistical distribution of deuterium and hydrogen atoms between the gas and the hydrocarbon results, *e.g.*

(1) Presented before the Division of Fuel Chemistry, 141st National Meeting of the American Chemical Society, Washington, D. C., March 20–24, 1962.

(2) American Petroleum Institute Fellow, 1957–1959.

(3) Abstracted from a thesis submitted in partial fulfillment of the requirements for the Ph.D. degree, 1959.

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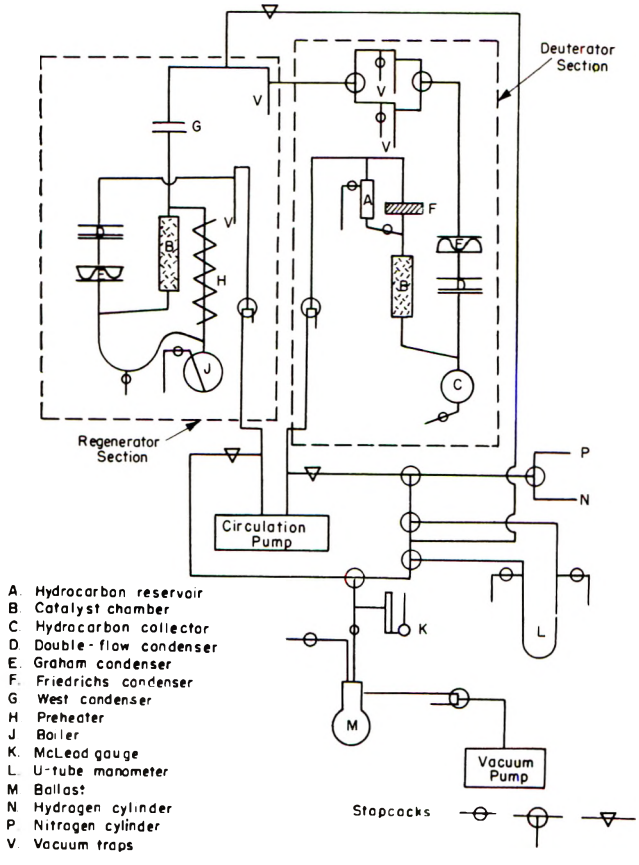

Fig. 1.—Deuteration apparatus.

$$D_2 + C_8H_{18} \rightleftharpoons C_8H_{17}D + HD$$

The partially deuterated hydrocarbon is then separated by condensation and the hydrogen–deuterium gas passes to the "regenerator" section.

(3) Here, the hydrogen–deuterium gas, mixed with superheated deuterium oxide vapor, is passed over the nickel on kieselguhr catalyst at 300°. The gas is reenriched in deuterium from the heavy water and as

$$HD + D_2O \rightleftharpoons HDO + D_2$$

the gases leave the "regenerator" the water is separated by condensation while the hydrogen–deuterium gas returns to the "deuterator" section.

By this technique, the advantages of both the deuterium–hydrocarbon and deuterium oxide–hydrocarbon exchange processes are realized without the disadvantages of either. Although the hydrocarbon was in contact with approximately 1000 liters of deuterium gas during each twenty-four-hour period of operation, there were only twelve liters of gas in the apparatus at any given time.

The apparatus was all glass except for the circulation pump which consisted of two counteracting brass Sylphon[22] bellows. Neither the deuterium oxide nor the hydrocarbon came in contact with the pump.

The maximum transfer of deuterium from heavy water to hydrocarbon is obtained by passing the hydrocarbon through the deuterator only once per charge of heavy water to the boiler. A method of operation for accomplishing this and an equation for calculating the number of equilibrations (or cycles) to obtain a given amount of a hydrocarbon of a given deuterium content are discussed in detail in ref. 20.

Catalysts.—An extensive investigation of catalysts was not made. However, it was observed that nickel supported on kieselguhr produced rapid deuterium exchange with less cracking and isomerization than platinum on carbon or platinum on glass beads.

Preparation of *n*-Octane-d_{18} and 2,2,4-Trimethylpentane-d_{18}.—*n*-Octane-d_{18} and 2,2,4-trimethylpentane-d_{18} were chosen for synthesis because: complete physical property and thermodynamic data are available on the hydrocarbons; they have appreciably different (for isomers) viscosities, viscosity–temperature characteristics and boiling points; in many approaches to the correlation of molecular structure and physical properties the normal paraffins are used as base-line or reference compounds[23]; they are liquid over a relatively extensive temperature range; and the corresponding deuteriocarbons should be separable by efficient fractional distillation from any impurities resulting from isomerization or cracking. *n*-Octane is the highest-boiling octane and 2,2,4-trimethylpentane is the lowest-boiling octane.

n-Octane-d_{18} was prepared from Phillips Research grade *n*-octane by the exchange procedure described previously. At 115–130° the mixture of hydrocarbon vapor and deuterium gas reached isotopic equilibrium very rapidly, and there was almost no cracking or isomerization as shown by efficient fractional distillation and gas–liquid chromatography.[24] The product of the exchange reaction contained approximately 0.2% of lower-boiling impurities. These were removed by fractional distillation to yield an *n*-octane-d_{18} containing less than 0.1% of hydrocarbons having a different carbon skeleton and of isotopic composition 99.1% D, 0.9% H. Isotope per cents were estimated from density and quantitative infrared measurements.

Unfortunately, the rate of attainment of isotopic equilibrium between 2,2,4-trimethylpentane vapor and deuterium was extremely slow at the temperature used for the deuteration of *n*-octane. It is believed that this was due to the phenomenon described by Burwell[16–19]; *i.e.*, a single adsorption–desorption of the hydrocarbon on the catalyst surface will not result in complete isotopic equilibration if the hydrocarbon possesses a quaternary carbon atom. The quaternary carbon atom in 2,2,4-trimethylpentane has attached to it a 2-methylpropyl group and three methyl groups. Should the 2-methylpropyl group be chemisorbed on the catalyst surface one-half of the hydrogen atoms in the hydrocarbon molecule will equilibrate with deuterium and the deuterium content will be half that produced by an equivalent chemisorption of *n*-octane and deuterium. However, chemisorption of the hydrocarbon molecule *via* a methyl group (the probability of this event is 0.5, on the basis of the hydrogen atoms accessible to the catalyst) will yield a deuterium con-

(22) Manufactured by the Fulton Sylphon Co., Knoxville, Tenn.

(23) (a) H. Wiener, *J. Am. Chem. Soc.*, **69**, 17, 2636 (1947); *J. Chem. Phys.*, **15**, 766 (1947); *J. Phys. Chem.*, **52**, 425, 1082 (1948); (b) J. R. Platt, *ibid.*, **56**, 328 (1952); (c) J. B. Greenshields and F. D. Rossini, *ibid.*, **62**, 271 (1958).

(24) A 10-ft column of Apiezon L on firebrick was used at 85°. The retention times of seventeen of the eighteen possible octanes were individually determined with this column and it was established that as little as 0.1% of any of the isomers could be detected in either *n*-octane or 2,2,4-trimethylpentane. The missing isomer was 2,2,3,3-tetramethylbutane. See ref. 20 for details including the retention times of the various isomers.

TABLE I

DENSITIES AND VISCOSITIES OF n-OCTANE-d_{18} AND 2,2,4-TRIMETHYLPENTANE-d_{18}

Hydrocarbon	% D	Density (g./cc.) 0°	20°	37.8°	60°	Viscosity (cp.) 0°	20°	37.8°	60°
n-Octane	0.0	0.7185	0.7027	0.6884	0.6703	0.7091	0.5428	0.4437	0.3524
	99.1	0.8337	0.8152	0.7984	0.7765	0.7668	0.5895	0.4852	0.3794
	100.0[a]	0.8347	0.8162	0.7794	0.7774	0.7673	0.5899	0.4856	0.3796
2,2,4-Trimethylpentane	0.0	0.7081	0.6919	0.6774	0.6587	0.6495	0.5042	0.4146	0.3323
	97.4	0.8197	0.8007	0.7835	0.7612	0.6989	0.5406	0.4424	0.3536
	100.0[a]	0.8226	0.8036	0.7863	0.7639	0.7001	0.5415	0.4430	0.3541

[a] Obtained by linear extrapolation of the property of the most highly deuterium-substituted product.

TABLE II

REFRACTIVE INDICES, MOLAR REFRACTIONS, AND MOLAR VOLUMES OF n-OCTANE-d_{18} AND 2,2,4-TRIMETHYLPENTANE-d_{18}

Hydrocarbon	% D	n^tD 20°	30°	40°	Molar refraction 20°	Molar volume 20°
n-Octane	0.0	1.39756_0	1.39270	1.38789	39.193	162.55
	99.1	1.39311	1.38831	1.38348		
	100.0[a]	1.39307	1.38827	1.38344	38.706	162.15
2,2,4-Trimethylpentane	0.0	1.39137	1.38657	1.38152	39.256	165.09
	97.4	1.38715	1.38235	1.27736		
	100.0[a]	1.38704	1.38224	1.37725	38.776	164.69

[a] Obtained by linear extrapolation of the property of the most highly deuterium-substituted product.

TABLE III

TEMPERATURE COEFFICIENTS

Compound	$-d\eta/dT \times 10^3$ (cp. deg.$^{-1}$, 20°)[a]	$-1/\eta\ d\eta/dT \times 10^2$ (deg.$^{-1}$, 20°)[a]	(g./cc.$^{-1}$ deg.$^{-1}$, 20°)	$d\eta/dT \times 10^4$ 30°
n-Octane	5.328	0.982	7.96	4.84
n-Octane-d_{18}	7.629	1.293	9.34	4.82
2,2,4-Trimethylpentane	6.076	1.205	8.12	4.93
2,2,4-Trimethylpentane-d_{18}	6.511	1.202	9.60	4.90

[a] Calculated from the differential form of the equation $\log \eta = A - B/(C + T)$.

tent one-eighteenth that produced by the equivalent chemisorption of n-octane and deuterium.

An attempt was made to produce equilibration by raising the temperature of the catalyst chamber. Not only should complete equilibration be favored by more frequent adsorption–desorption of the hydrocarbon on the catalyst surface, but the temperature increase should also increase the probability of a methylene-type adsorption suggested by both Burwell[9] and Kemball.[25] Such adsorption would by its nature increase the deuterium content of the molecule.

Equilibrium between deuterium and the hydrocarbon was approached rapidly in the 181–195° range but was accompanied by extensive cracking and isomerization. A temperature of 154–164° was used as a compromise between a rapid reaction with extensive production of impurities and a very slow reaction without production of detectable impurities.

The 2,2,4-trimethylpentane-d_{18} obtained under these conditions had approximately 1.8% of impurities due to cracking and isomerization. Upon efficient fractional distillation a material was obtained with the isotopic composition 97.4% D, 2.6% H, and containing less than 0.1% of any material with a different carbon skeleton.

It was shown by g.l.c. and fractional distillation that of the 1.8% impurities in the crude product approximately 1.6% were lower molecular weight compounds. These were not further identified, but the 0.2% of isomeric octanes were concentrated by fractional distillation and analyzed by g.l.c. Three peaks were observed. However, under the conditions used, 2,5-dimethylhexane had the same retention time as 2,4-dimethylhexane and 2,2,3-trimethylpentane had the same retention time as 3,3-dimethylhexane. Thus there may have been as many as five isomeric octanes present. The major isomeric impurity (~0.1%) was 2,4-dimethylhexane and/or 2,5-dimethylhexane; the other impurities were 2,2-dimethylhexane and 3,3-dimethylhexane and/or 2,2,3-trimethylpentane.

Properties.—The physical properties of the hydrocarbons and corresponding deuteriocarbons are shown in Tables I, II, and III. The procedures for obtaining the properties have been described previously.[4,5]

Acknowledgment.—Financial support of this research by the American Petroleum Institute and the National Science Foundation is gratefully acknowledged.

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Syntheses of α-Keto Amides and Acids from Ethyl Alkylidenecyanoacetates[1]

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Received December 31, 1962

Ethyl alkylidenecyanoacetates (I) have been used as starting materials for the synthesis of α-keto acids. The key intermediates in this synthesis are epoxy amides (II) prepared from I and hydrogen peroxide. The epoxy amides were converted into the corresponding acids (III) by alkaline hydrolysis. Decarboxylation gave α-keto amides (IV); further, the amides (IV) were hydrolyzed to α-keto acids in good yield.

Ethyl alkylidenecyanoacetates were readily prepared from many carbonyl compounds by the Knoevenagel-Cope[2] reaction with ethyl cyanoacetate. It is well known that oxidation of the double bond adjacent to a cyano group with hydrogen peroxide results in the formation of an epoxy amide rather than an epoxy nitrile.[3,4] In the present study, the ethyl alkylidenecyanoacetate (I) was converted into the epoxy amide (II) by oxidation with hydrogen peroxide in the presence of an alkali such as sodium tungstate[5] or trisodium phosphate. The use of potassium carbonate as a catalyst gave a poor yield of II from I except in the case of ethyl cyclohexylidenecyanoacetate. The oxidations were carried out in ethanolic solution at an optimum temperature of 70–80°. After the peroxide had been consumed, the solvent was removed by distillation. In many cases the epoxy amides were isolated as viscous oils which solidified after standing overnight. Yields were from 50–80%.

The epoxy compounds (II) could be hydrolyzed in excellent yield to the corresponding acids (III) with alcoholic potassium hydroxide.

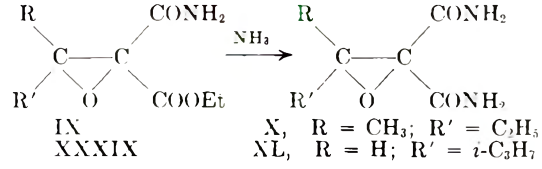
Decarboxylation of a glycidic acid is a well known synthetic method for the preparation of an aliphatic aldehyde.[6] In the present work, the epoxy acids were generally converted into resinous products by heating to the decomposition point. However, in the presence of a small amount of water, III smoothly gave α-keto amides (IV) on decarboxylation. Keto amides were hydrolyzed to α-keto acids in good yield.

The synthetic steps are shown in Chart I.

Payne[7] obtained 3-methyl-2,3-epoxy-2-ethoxycarbonylbutyramide (VI) in 37% yield by oxidation of ethyl isopropylidenecyanoacetate with 50% hydrogen peroxide under controlled pH conditions. In the present work, treatment of the same unsaturated nitrile with an excess of 30% hydrogen peroxide in the presence of sodium tungstate at 70–80° for one hour gave a 61% yield of VI. It could be hydrolyzed in 85% yield to 3-methyl-2,3-epoxy-2-carboxybutyramide (VII). Purification of VII by recrystallization from water was unsuitable since the resulting crystals always contained a small amount of decarboxylation product. It was best recrystallized from absolute ethanol. The compound gave mainly a resinous product when it was heated at 140–150°; in addition, a very small amount of colorless plates sublimed. The latter was assigned the keto amide structure (VIII) by infrared absorption and elementary analysis. The most efficient conversion of VII to 3-methyl-2-oxobutyramide (VIII) was achieved by decarboxylation in a warm aqueous solution. The yield was 50%.

The reaction of ethyl 1-methylpropylidenecyanoacetate with hydrogen peroxide was carried out under similar conditions to give 3-methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (IX) in 80% yield. By the use of potassium carbonate as a catalyst, the yield was 40%. With sodium or potassium hydroxide as catalyst, the yield was only 30%.

This epoxy ester reacted with dry ammonia in ethanol to form 3-methyl-2,3-epoxy-2-carbamoylvaleramide (X).



IX XXXIX

X, R = CH_3; R' = C_2H_5
XL, R = H; R' = i-C_3H_7

The conversion of the ester IX to 3-methyl-2,3-epoxy-2-carboxyvaleramide (XI) was effected by the usual alkaline hydrolysis. The yield was 86%. A 50% yield of 3-methyl-2-oxovaleramide (XII) was secured when the decarboxylation was carried out in water, acetic acid, or xylene solution. (See Table IV.) The hydrolysis of XII gave 3-methyl-2 oxovaleric acid (XIII) in good yield. XIII could also be prepared from XI by reaction with dilute hydrochloric acid. XII and XIII formed the corresponding oximes.

The epoxidation of ethyl cyclopentylidenecyanoacetate proceeded to the epoxy amide XXVII in 75% yield. Alkaline hydrolysis of the ethoxycarbonyl group and successive acidification with dilute hydrochloric acid at room temperature gave cyclopentaneglyoxylamide (XXVIII) directly without isolation of the corresponding epoxy acid. XXVIII was also hydrolyzed easily to the corresponding α-keto acid by dilute hydrochloric acid in excellent yield. Without isolating XXVIII, the over-all yield of cyclopentaneglyoxylic acid (XXIX) from XXVII was 60%.

Trisodium phosphate was used as catalyst in the epoxidation of ethyl benzylidenecyanoacetate. Sodium tungstate and potassium carbonate were unsuitable in this case. Other conditions and results in the formation of the α-keto acid (XLVIII) were similar to the preceding cases.

2,3-Epoxy-2-carboxypelargonamide (XLIV) gave no keto amide by the usual process. By heating the aqueous solution for a length of time, about 95% of the starting material was recovered. Meanwhile the epoxy amide (XLIV) was converted into 2-oxopelargon-

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(3) J. V. Murray and J. B. Cloke, *ibid.*, **56**, 2749 (1934).

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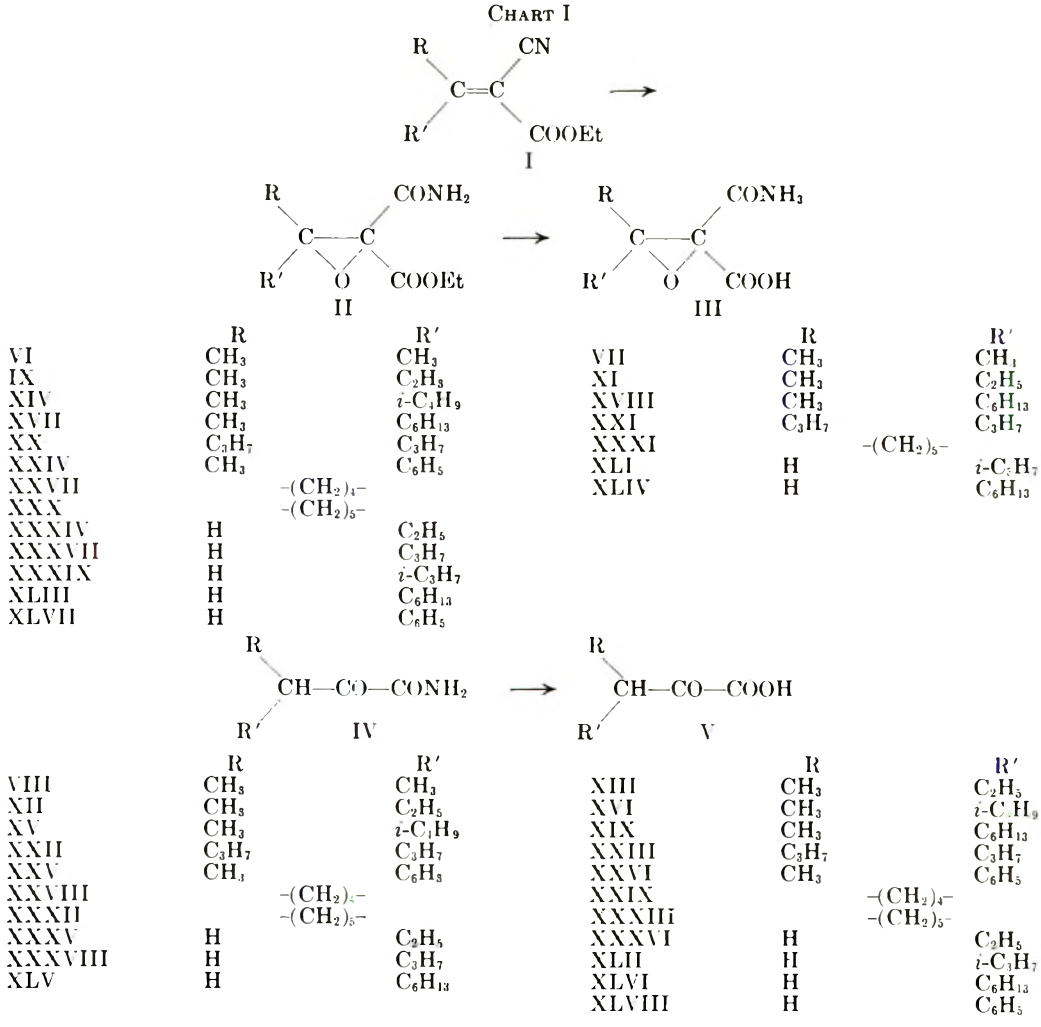
CHART I



	R	R′
VI	CH_3	CH_3
IX	CH_3	C_2H_5
XIV	CH_3	i-C_3H_9
XVII	CH_3	C_6H_{13}
XX	C_3H_7	C_3H_7
XXIV	CH_3	C_6H_5
XXVII	$-(CH_2)_4-$	
XXX	$-(CH_2)_5-$	
XXXIV	H	C_2H_5
XXXVII	H	C_3H_7
XXXIX	H	i-C_3H_7
XLIII	H	C_6H_{13}
XLVII	H	C_6H_5

	R	R′
VII	CH_3	CH_3
XI	CH_3	C_2H_5
XVIII	CH_3	C_6H_{13}
XXI	C_3H_7	C_3H_7
XXXI	$-(CH_2)_5-$	
XLI	H	i-C_5H_7
XLIV	H	C_6H_{13}

	R	R′
VIII	CH_3	CH_3
XII	CH_3	C_2H_5
XV	CH_3	i-C_4H_9
XXII	C_3H_7	C_3H_7
XXV	CH_3	C_6H_5
XXVIII	$-(CH_2)_5-$	
XXXII	$-(CH_2)_5-$	
XXXV	H	C_2H_5
XXXVIII	H	C_3H_7
XLV	H	C_6H_{13}

	R	R′
XIII	CH_3	C_2H_5
XVI	CH_3	i-C_4H_9
XIX	CH_3	C_6H_{13}
XXIII	C_3H_7	C_3H_7
XXVI	CH_3	C_6H_5
XXIX	$-(CH_2)_4-$	
XXXIII	$-(CH_2)_5-$	
XXXVI	H	C_2H_5
XLII	H	i-C_3H_7
XLVI	H	C_6H_{13}
XLVIII	H	C_6H_5

TABLE I

EPOXIDATION OF ETHYL ALKYLIDENECYANOACETATES

Epoxy compound	Ethyl alkylidenecyanoacetate	Yield, %[a]	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VI	Isopropylidene[b]	61 (A)	101[c]	$C_8H_{13}NO_4$	51.33	7.00	7.48	50.89	6.53	7.45
IX	1-Methylpropylidene[d]	80 (A), 40 (C), 30 (D)	77	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.28	7.45	7.01
XIV	1,3-Dimethylbutylidene[d]	71 (A)	69 (b.p. 178–182°, 5 mm.)	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.37	8.01	6.15
XVII	1-Methylheptylidene[d]	64 (A)	88	$C_{13}H_{23}NO_4$	60.68	9.01	5.44	60.62	8.78	5.42
XX	1-Propylbutylidene[d]	50 (A)	99	$C_{12}H_{21}NO_4$	59.24	8.70	5.75	58.85	8.40	5.84
XXIV	1-Phenylethylidene[d]	70 (A)	91	$C_{13}H_{15}NO_4$	62.64	6.07	5.62	62.40	6.11	5.58
XXVII	Cyclopentylidene[e]	75 (A)	123	$C_{11}H_{15}NO_4$	56.32	7.09	6.57	55.99	6.83	6.53
XXX	Cyclohexylidene[d]	65 (A), 69 (C), 20 (D)	111	$C_{11}H_{17}NO_4$	58.13	7.54	6.16	58.23	7.45	6.07
XXXIV	Propylidene[f]	48 (A)	130–131	$C_8H_{13}NO_4$	51.33	7.00	7.48	51.45	6.93	7.48
XXXVII	n-Butylidene[g]	55 (A)	110–111	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.20	7.09	7.07
XXXIX	Isobutylidene[g]	52 (A) 64 (B), 28 (C)	122	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.35	7.38	7.16
XLIII	Heptylidene[h]	47 (A)	81–82	$C_{12}H_{21}NO_4$	59.24	8.70	5.76	59.13	8.40	5.75
XLVII	Benzilidene[i]	46 (B)	152–154	$C_{12}H_{13}NO_4$	61.27	5.57	5.96	61.27	5.40	5.91

[a] Capital letters refer to epoxidation methods designated by these letters in the Experimental section. [b] F. S. Prout, *J. Org. Chem.*, 18, 928 (1953). [c] Lit.[7] 102–103°. [d] See ref. 2. [e] V. J. Harding and W. N. Haworth, *J. Chem. Soc.*, 97, 486 (1910). [f] K. V. Anwers, *Ber.*, 56, 1172 (1923). [g] F. D. Popp and A. Catala, *J. Org. Chem.*, 26, 2738 (1961). [h] A. Lapworth and J. A. McRae, *J. Chem. Soc.*, 121, 2741 (1922). [i] W. Baker and A. Lapworth, *ibid.*, 127, 560 (1925).

amide (XLV) by heating at 130–140° in an oil bath. The crude keto amide turned a violet color with ferric chloride in an alcoholic solution, but it gave no discoloration after purification. Therefore, it is assumed that the decarboxylation of the epoxy amide is accompanied with the formation of a very small amount of β-keto amide as a by-product. The yield of XLV was 88%.

4-Methyl-2,3-epoxy-2-carboxyvaleramide (XLI) gave no 4-methyl-2-oxovaleramide, either by heating at the decomposition point (159°) or by warming it in the aqueous solution. By the former treatment a

TABLE II

HYDROLYSIS OF ETHYL 2,3-EPOXY-2-CARBAMOYLCARBOXYLATES

Epoxy acid	Yield, %[a]	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VII	85 (A)	133–134 dec.	$C_6H_9NO_4$	45.28	5.70	8.80	44.96	5.61	8.77
XI	86 (A), 70 (B)	140–141 dec.	$C_7H_{11}NO_4$	48.55	6.40	8.09	48.37	5.88	8.16
XVIII	84 (A)	108 dec.	$C_{11}H_{19}NO_4$	57.62	8.53		56.97	8.30	
XXI	57 (C)	117 dec.	$C_{10}H_{17}NO_4$	55.80	7.96		56.01	7.84	
XXXI	80 (A)	145 dec.	$C_9H_{13}NO_4$	54.26	6.58	7.03	54.31	6.50	7.02
XLI	92 (A)	159–160 dec.	$C_7H_{11}NO_4$	48.55	6.40	8.09	48.52	6.41	8.11
XLIV	85 (A)	118 dec.	$C_{10}H_{17}NO_4$	55.80	7.96	6.51	55.52	7.60	6.44

[a] Capital letters refer to hydrolysis methods designated by these letters in the Experimental section.

TABLE III

PREPARATION OF 2-OXOCARBOXYAMIDES FROM 2,3-EPOXY-2-CARBAMOYLCARBOXYLIC ACIDS

Keto amide	Yield, %[a]	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIII	50 (A)	112[b]	$C_5H_9NO_2$	52.16	7.88	12.17	51.89	7.77	11.99
Oxime		130–132	$C_5H_{10}N_2O_2$			21.53			21.54
XII	52 (A)	71	$C_6H_{11}NO_2$	55.79	8.58	10.85	55.81	8.59	10.85
Oxime		115–116	$C_6H_{12}N_2O_2$	49.98	8.39	19.43	50.18	7.82	19.39
XV	42[c]	143–145	$C_5H_{15}NO_2$	61.12	9.62	8.91	61.26	9.37	8.84
Oxime		103	$C_8H_{16}N_2O_2$			16.27			16.22
XXII	80 (A)	63	$C_9H_{17}NO_2$	63.13	10.00	8.18	62.84	9.49	8.20
XXV	64 (A)	116	$C_{10}H_{11}NO_2$	67.78	6.26	7.91	67.53	6.11	7.84
XXVIII	40[d]	134	$C_7H_{11}NO_2$	59.55	7.85	9.92	59.37	7.62	9.91
XXXII	48 (A)	120	$C_8H_{13}NO_2$	61.91	8.44	9.03	62.07	8.18	9.02
Oxime		177 dec.	$C_8H_{14}N_2O_2$			16.46			16.41
XXXV	53 (A), 82 (B)	105–106	$C_5H_9NO_2$	52.16	7.88	12.17	52.48	7.71	12.24
XXXVIII	47 (A)	87–88	$C_6H_{11}NO_2$	55.79	8.58	10.85	55.27	8.10	10.50
XLV	88 (B)	112[e]	$C_9H_{17}NO_2$	63.13	10.00	8.18	63.11	9.90	8.14
Oxime		134	$C_9H_{18}N_2O_2$			15.04			14.96

[a] Capital letters refer to decarboxylation methods designated by these letters in the Experimental section. [b] Lit. m.p. 109° [G. Barger and A. J. Ewins, *J. Chem. Soc.*, **97**, 284 (1910)]. [c] From 3,5-dimethyl-2,3-epoxy-2-carboxycaproamide hydrate (see Experimental). [d] From 2-ethoxycarbonyl-1-oxaspiro[2.4]heptane-2-carboxyamide (see Experimental). [e] Lit. m.p. 111° [J. Schreiber, *Compt. rend.*, **242**, 139 (1956)].

TABLE IV

DECARBOXYLATION OF 3-METHYL-2,3-EPOXY-2-CARBOXYVALERAMIDE (XI) IN VARIOUS SOLVENTS

No.	Solvent	Heating time	Yield of XII, %
1	Water	2–3 min.	52
2	Acetic acid	2–3 min.	50
3	Ethanol	2–3 min.	Recovered
4	Benzene[a]	1 hr.	Trace
5	Toluene	10 min.	Trace
6	Toluene	5 hr.	47
7	Xylene	10 min.	48

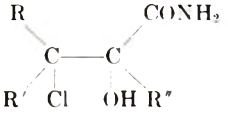
[a] In suspension.

resinous product was obtained. On the other hand, the direct conversion of the epoxy amide XLI to 4-methyl-2-oxovaleric acid (XLII) in the presence of hydrochloric acid gave good results.

The epoxidation of ethyl butylidenecyanoacetate was also carried out by use of trisodium phosphate as a catalyst. The use of sodium tungstate as a catalyst lowered the yield from 55 to 40%.

In a few cases, oxirane ring-openings of epoxy amides were tried by treatment with concentrated hydrochloric acid. Chlorohydrins were formed but it was not confirmed which isomers were obtained.

These results are shown in Tables I–V.



XLIX, R = H; R′ = *i*-C_3H_7; R″ = COOH
L, R, R′ = $-(CH_2)_5-$; R″ = COOEt

Experimental

Epoxidation of Ethyl Alkylidenecyanoacetates. A.—Into a round-bottom flask equipped with thermometer and condenser was charged a solution of 0.05 mole of ethyl alkylidenecyanoacetate in 30–50 cc. of ethanol. To this was added 1.5 g. of sodium tungstate dihydrate and then 50 cc. of 30% hydrogen peroxide. A moderate exothermic reaction was held at 70–80° by warming on a water bath for 1–3 hr. After removal of the solvent, the residue was extracted by the use of chloroform or ether and the solvent evaporated. The oily residue solidified when it was allowed to stand at room temperature. The semi-solid was washed with petroleum ether (b.p. 30–70°) to give colorless crystals of 2,3-epoxy-2-ethoxycarbonylcarboxyamide. The product was recrystallized prior to analysis.

The epoxidation of ethyl 1,3-dimethylbutylidenecyanoacetate was carried out according to the procedure already described. The ethereal extract was concentrated and distilled under reduced pressure. The fraction distilling at 178–182° (5 mm.) was collected. The distillate was dissolved in chloroform and then petroleum ether was added. When the solution was allowed to stand overnight in an icebox, a precipitate was formed. The precipitate was collected by suction filtration, and washed with petroleum ether. Recrystallization from chloroform–petroleum ether gave colorless microcrystals.

B.—The epoxidation was carried out as in A using 70 cc. of ethanol as solvent, 3.5 g. of trisodium phosphate dodecahydrate as catalyst, and 70 cc. of 30% hydrogen peroxide as oxidant. The separation of the product was carried out according to the procedure A.

TABLE V

SYNTHESIS OF 2-OXOCARBOXYLIC ACIDS

Keto acid	Yield, %[a]	B.p. (mm.), m.p., °C.	Formula	Analyses, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
XIII	75 (A)	82–84 (18)[b] (m.p. 40)	$C_6H_{10}O_3$	55.37	7.75		55.01	7.59	
Oxime		164 dec.[c]	$C_6H_{11}NO_3$			9.65			9.51
XVI	80 (B)	104–110 (7)	$C_8H_{14}O_3$	60.74	8.92		60.04	8.69	
Oxime		132 dec.	$C_8H_{15}NO_3$			8.09			8.03
XIX	92 (A)	126–129 (8)[d]	$C_{10}H_{18}O_3$	64.49	9.74		63.97	9.41	
Oxime		90 dec.[e]	$C_{10}H_{19}NO_3$			6.96			6.71
XXIII	80 (B)	118–124 (7)	$C_9H_{16}O_3$	62.76	9.36		62.00	9.21	
Oxime		144 dec.	$C_9H_{17}NO_3$			7.48			7.33
XXVI	90 (B)	53	$C_{10}H_{10}O_3$	67.40	5.66		66.86	5.56	
Oxime		120 dec.	$C_{10}H_{11}NO_3$			7.25			7.02
XXIX	60 (A)[f]	54[g]	$C_7H_{10}O_3$	59.14	7.09		58.77	7.11	
Oxime		131 dec.	$C_7H_{11}NO_3$			8.91			8.92
XXXIII	98 (B)	50[h]	$C_8H_{12}O_3$	61.52	7.75		60.98	7.62	
Oxime		170	$C_8H_{13}NO_3$			8.18			8.18
XXXVI	83 (B)	61–63 (6)[i]	$C_5H_8O_3$						
Oxime		145 dec.[j]	$C_5H_9NO_3$			10.68			10.52
XLII	82 (A)	90–94 (20), (m.p. 10)[k]	$C_6H_{10}O_3$						
Oxime		148 dec.[l]	$C_6H_{11}NO_3$			9.65			9.42
XLVI	95 (B)	42[m]	$C_9H_{16}O_3$						
Oxime		97[n]	$C_9H_{17}NO_3$			7.48			7.20
XLVIII	47 (A)[o]	154–156 dec.[p]	$C_9H_8O_3$	65.85	4.91		65.48	4.91	
Oxime		173 dec.[q]	$C_9H_9NO_3$			7.82			7.51

[a] Capital letters refer to synthetic methods designated by these letters in the Experimental section. [b] Lit. b.p. 73° (10 mm.), m.p. 38–40°: A. Meister, *J. Biol. Chem.*, 190, 269 (1951). [c] Lit. m.p. 164° dec.: L. Bouveault and R. Locquin, *Compt. rend.*, 141, 115, (1905). [d] Lit. b.p. 124–125° (9 mm.): R. Locquin, *Bull. soc. chim. France*, [3] 31, 1153 (1904). [e] Lit. m.p. 89–90° dec.: R. Locquin *ibid.*, [3] 31, 1075 (1904). [f] Potassium salt of 2-carboxy-1-oxaspiro[2.4]heptane-2-carboxyamide (see Experimental) was treated by method A. [g] J. D. Fissekis, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, 81, 2715 (1959), report m.p. 25–30° for this derivative. [h] Lit. m.p. 45–49°: D. D. E. Newman and L. N. Owen, *J. Chem. Soc.*, 4713 (1952). [i] Lit. b.p. 66° (6 mm.): F. Adickes and G. Andresen, *Ann.*, 555, 41 (1944). [j] Lit. m.p. 145° dec.: K. E. Hamlin and W. H. Hartung, *J. Biol. Chem.*, 145, 351 (1942). [k] Lit. b.p. 84° (15 mm.): J. Schreiber, *Ann. Chim.* (Paris), [12] 2, 98 (1947). [l] Lit. m.p. 147° dec.: T. Uyemura, *Bull. Agr. Chem. Soc. Japan*, 15, 353 (1939). [m] Lit.[i] m.p. 43–44°. [n] Lit.[i] m.p. 98–98.5°. [o] 3-Phenyl-2,3-epoxy-2-ethoxycarbonylpropionamide (XLVII) was treated with ethanolic potassium hydroxide, and then the potassium salt was treated by method A. [p] Lit. m.p. 156° dec.: M. Bergmann and A. Miekeley, *Ann.*, 458, 40 (1927). [q] Lit. m.p. 173–174° dec.: Ch. Gränacher, *Helv. Chim. Acta.*, 5, 610 (1922).

C.—To a flask equipped with stirrer, thermometer, and dropping funnel were charged 0.05 mole of ethyl alkylidenecyanoacetate, 10 cc. of 30% hydrogen peroxide, and 50–60 cc. of ethanol. Ten cubic centimeters of 4 *N* potassium carbonate was added dropwise to the mixture with stirring and cooling at 40–45°. After an additional 3 hr., the solvent was removed under reduced pressure. The reaction mixture, containing a precipitate, was diluted with water, chilled, and filtered to give the corresponding epoxy amide II.

D.—The process was carried out as in the foregoing method using 20 cc. of 15% hydrogen peroxide and 10 cc. of 4 *N* sodium hydroxide (or potassium hydroxide) at 30–35°. The reaction mixture was allowed to stand for 1 day at room temperature and then concentrated under vacuum. The residue was digested with ethanol to be separated into ethanol-soluble and insoluble parts. From the ethanol-soluble part, the corresponding epoxy amide II was obtained.

The ethanol-insoluble part was dissolved in water and acidified with dilute hydrochloric acid. The resulting precipitate was collected by filtration. Recrystallization from ethanol gave colorless microcrystals. This compound was identified as the corresponding 2,3-epoxy-2-carbamoylcarboxylic acid (III) by infrared spectrum and by the melting point.

By this method, 2-carboxy-1-oxaspiro[2.5]octane-2-carboxyamide (XXXI) was obtained in 12% yield from ethyl cyclohexylidenecyanoacetate. From ethyl 1-methylpropylidenecyanoacetate, XI was also obtained in a few per cent yield.

Hydrolysis of 2,3-Epoxy-2-ethoxycarbonylcarboxyamides. A.—To a three-necked flask equipped with a stirrer, dropping funnel, and thermometer was charged a solution of 2,3-epoxy-2-ethoxycarbonylcarboxyamide in ethanol, and ethanol containing an excess of potassium hydroxide was added dropwise under stirring at room temperature. After the mixture was allowed to stand overnight, the resulting white precipitate was separated by filtration, washed with ethanol, and dried. The potassium salt was again dissolved in a small amount of water, cooled in an ice bath, and neutralized with dilute hydrochloric acid. The resulting precipitate was collected by filtration, washed with a small amount of cold water, and dried. A sample was recrystallized from absolute ethanol or methanol prior to analysis.

B.—A mixture of 2,3-epoxy-2-ethoxycarbonylcarboxyamide and water containing an excess of sodium hydroxide was warmed on a water bath for about 1 hr. and allowed to cool to room temperature. The mixture was then treated with dilute hydrochloric acid and the resulting precipitate was collected by filtration.

C.—Hydrolysis of 3-propyl-2,3-epoxy-2-ethoxycarbonylcaproamide (XX) with ethanolic potassium hydroxide was carried out as before. (Treatment of the potassium salt with dilute hydrochloric acid gave only 3-propyl-2,3-epoxy-2-carboxycaproamide hydrate.) The barium salt was prepared from the potassium salt by the addition of barium chloride dissolved in hot water. A suspension of 3 g. of the barium salt and 1 g. of anhydrous magnesium sulfate in 30 cc. of ether was stirred at 0–5° and treated by adding the solution containing 0.6 g. of sulfuric acid in 3 cc. of ether in dropping form. The mixture was automatically stirred overnight at room temperature. After removal of barium sulfate by filtration, the filtrate was dried over magnesium sulfate and concentrated under vacuum to give 1.3 g. of 3-propyl-2,3-epoxy-2-carboxycaproamide (XXI), m.p. 117° dec.

Recrystallization of XXI from chloroform gave 3-propyl-2,3-epoxy-2-carboxycaproamide hydrate, m.p. 102° dec., which was dehydrated by heating at 70–80°.

Anal. Calcd. for $C_{10}H_{17}NO_4 \cdot H_2O$: C, 51.49; H, 8.21; N, 6.01. Found: C, 51.41; H, 7.81; N, 5.96.

3,5-Dimethyl-2,3-epoxy-2-carboxycaproamide Hydrate.—3,5-Dimethyl-2,3-epoxy-2-ethoxycarbonylcaproamide (XIV) was treated with alcoholic potassium hydroxide. The resulting potassium salt was dissolved in water and neutralized with dilute hydrochloric acid to give 3,5-dimethyl-2,3-epoxy-2-carboxycapro-

amide hydrate. The yield was 87%. Recrystallization from ether gave colorless microcrystals, m.p. 105° dec.

Anal. Calcd. for $C_9H_{15}NO_4 \cdot H_2O$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.49; H, 7.52; N, 6.41.

This compound was used for the following reaction without further dehydration.

3-Phenyl-2,3-epoxy-2-carboxybutyramide Hydrate.—Hydrolysis of 3-phenyl-2,3-epoxy-2-ethoxycarbonylbutyramide (XXIV) was carried out by method A. 3-Phenyl-2,3-epoxy-2-carboxybutyramide hydrate was obtained in 60% yield; m.p. 104° dec. (colorless needles from ether).

Anal. Calcd. for $C_{11}H_{11}NO_4 \cdot H_2O$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.01; H, 6.11; N, 5.58.

This was used without further treatment for the following preparation.

Decarboxylation of 2,3-Epoxy-2-carbamoylcarboxylic Acids. A.—The epoxy acid III was heated with a small amount of water for a short time and allowed to cool to room temperature. The reaction mixture containing precipitated product was filtered to give colorless plates of essentially pure 2-oxocarboxyamide (IV). A sample was recrystallized from water prior to analysis. The oxime was obtained by the usual way.

B.—2,3-Epoxy-2-carbamoylcarboxylic acid (III) was heated at 130–140° in an oil bath for 5–10 min. Here, carbon dioxide evolved. The product solidified after cooling. Recrystallization from ethanol or water afforded colorless plates of 2-oxocarboxyamide.

In the case of 2,3-epoxy-2-carboxypelargonamide (XLIV), the crude product gave a violet color with ferric chloride in ethanol whereas the pure substance gave no discoloration.

3,5-Dimethyl-2-oxocaproamide (XV).—3,5-Dimethyl-2,3-epoxy-2-carboxycaproamide hydrate was heated with water for 1.5 hr. The mixture was cooled and extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate, and then the ether was removed by distillation. Fractional distillation of the residue gave 3,5-dimethyl-2-oxocaproamide (XV), b.p. 122–130° (8 mm.), which solidified on standing in an ice bath, m.p. 138–143°. Recrystallization from ethanol gave colorless microcrystals, m.p. 143–145°.

Cyclopentaneglyoxylamide (XXVIII).—To a solution of 3 g. of 2-ethoxycarbonyl-1-oxaspiro[2.4]heptane-2-carboxyamide (XXVII) in ethanol, ethanolic potassium hydroxide was added at room temperature. A white crystalline precipitate formed during the addition. After the mixture had stood overnight, it was separated by filtration, washed with ethanol, and dried. The yield of the potassium salt was 2.8 g. (89%). The potassium salt was dissolved in water and neutralized with dilute hydrochloric acid. After standing overnight at room temperature, the resulting precipitate was collected by filtration. An additional amount of the product was obtained from the mother liquor by allowing it to stand for 2–3 days. The total yield was 0.8 g. (40% based on XXVII). Recrystallization from water gave colorless plates of cyclopentaneglyoxylamide.

Decarboxylation of 3-Methyl-2,3-epoxy-2-carboxyvaleramide (XI) in Various Solvents.—The decarboxylation of XI was carried out according to procedure A using water, acetic acid, ethanol, benzene, toluene, and xylene as solvent. The results are shown in Table IV.

Synthesis of 2-Oxocarboxylic Acids. A. From 2,3-Epoxy-2-carbamoylcarboxylic Acids.—The epoxy acid III was heated with an excess of dilute hydrochloric acid (1:1) for 1 hr. The solution was cooled and extracted by using three portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate, and then the solvent was removed by distillation. The fractional distillation under reduced pressure gave colorless liquid of 2-oxocarboxylic acid (V).

XLVIII was recrystallized from chloroform to give colorless plates, m.p. 154–156° dec.

B. **From 2-Oxocarboxyamides.**—The keto amide IV was treated with a slight excess of dilute hydrochloric acid and then extracted with ether. From the ethereal extract, 2-oxocarboxylic acid (V) was obtained by fractional distillation (or by recrystallization of the residue).

3-Methyl-2,3-epoxy-2-carbamoylvaleramide (X).—Reaction of a sample of 3-methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (IX) with ammonia in alcohol at room temperature gave X, m.p. 237° dec.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03. Found: C, 48.79; H, 6.72.

4-Methyl-2,3-epoxy-2-carbamoylvaleramide (XL).—4-Methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (XXXIX) was shaken 15 min. with concentrated aqueous ammonia. The solid dissolved, followed shortly thereafter by precipitation of the product XL, m.p. 181–182°.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.83; H, 6.48; N, 16.28.

Reaction of Epoxy Amide II with Concentrated Hydrochloric Acid.—A sample of 4-methyl-2,3-epoxy-2-ethoxycarbonylvaleramide (XXXIX) was dissolved in concentrated hydrochloric acid and allowed to stand at room temperature for 2 days. Recrystallization of the resulting precipitate gave prisms, m.p. 113–114° dec., having an analysis in substantial agreement for 4-methyl-3-hydroxy-2-chloro-2-carbamoylvaleric acid or its isomer, 4-methyl-3-chloro-2-hydroxy-2-carbamoylveric acid (XLIX, R = C_2H_5, R′ = H).

Anal. Calcd. for $C_7H_{12}NO_4Cl$: C, 40.10; H, 5.76; N, 6.67; Cl, 16.91. Found: C, 40.57; H, 5.94; N, 6.48; Cl, 16.29.

A sample of 3-phenyl-2,3-epoxy-2-ethoxycarbonylpropionamide (XLVII) was shaken with concentrated hydrochloric acid at room temperature for a few minutes. The product, m.p. 169–172°, had an empirical formula in agreement with 3-phenyl-3-chloro-2-hydroxy-2-ethoxycarbonylpropionamid (L) or its isomer, 3-phenyl-3-hydroxy-2-chloro-2-ethoxycarbonylpropionamide.

Anal. Calcd. for $C_{12}H_{14}NO_4Cl$: C, 53.04; H, 5.19; Cl, 13.04. Found: C, 52.96; H, 4.94; Cl, 12.75.

Acknowledgment.—The authors wish to express their sincere thanks to Dr. Taro Hayashi and Dr. Tatsuo Takeshima for their kind advice. Our study was aided by a grant from the Scientific Research Fund of the Ministry of Education.

1-Iodo-2-(perfluoroalkyl)cycloalkanes by the Free Radical Addition of Iodoperfluoroalkanes to Cyclohexane and Cyclopentene

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Received May 2, 1963

Iodoperfluoroalkanes and cyclohexene or cyclopentene gave adducts in up to 50% conversion (80–90% yield) by a short chain free radical process initiated by peroxides, azonitriles, or radiant energy. The *trans–cis* ratio of the nonplanar 1-iodo-2-(perfluoroalkyl)-cyclohexanes varied with the iodoperfluoroalkane being added, and with the initiation method. 1-Iodoperfluorobutane and cyclopentene gave only a *trans* adduct; cyclopentadiene gave no adduct at all. Trifluoriodomethane, 1-iodoperfluoropropane, and 2-iodoperfluoropropane gave adducts with cyclohexene in relative amounts of 0.05:1:2; the ratio of R_fI addition to abstraction (giving R_fH) was 6.56 for $CF_3CF_2CF_2I$ and only 1.73 for $(CF_3)_2CFI$. No CF_3H could be detected from CF_3I. Though formed at a greater rate, the adducts from 2-iodoperfluoropropane were unusually labile and were isolated in lower yield. This behavior was not typical for $(CF_3)_2CFI$; it reacted faster and more efficiently than $CF_3CF_2CF_2I$ with 1-heptene and norbornene.

Free radical addition of 1-iodoperfluoropropane to strained bicyclic olefins like norbornene or norbornadiene occurred with great facility when an azonitrile initiator was used.[1,2] In analogous reaction of cyclohexene or cyclopentene with tetrahalomethanes, however, there is also a serious competing process by which an allylic hydrogen is abstracted.[3] The ratio of addition to abstraction for cyclohexene and $BrCCl_3$ was found[4] to be only 1.2, while for 1-octene it was 43. Consequently, a chain of reasonable length, which depends on efficient propagation and transfer steps for its success, has been difficult to achieve with cyclic olefins.[3,4] Indeed, preliminary experiments showed that cyclohexene and 1-iodoperfluoropropane in *equimolar* amount gave only a 2 to 5% conversion to adducts[5] using the procedure[1] which gave excellent addition to β-pinene, norbornene, or vinyl acetate. Serious wastage of initiator must have occurred, since essentially all the olefin and 1-iodoperfluoropropane were recovered.

A more careful examination of the reaction system was therefore made in order to discover the reasons for the inefficient chain reaction with cyclohexene. We also wished to learn if this behavior was typical for iodoperfluoroalkanes (R_fI) having shorter or longer R_f groups and for both primary and secondary iodides. In order to ascertain optimum conditions, the effect of reaction variables—temperature, extent of reaction, reactant ratios, and initiator concentration—on yield and conversion to adducts was explored. The mode of generating the initiating radicals was also varied, since photochemical or X-ray initiation would not introduce extraneous initiator fragments unavoidably associated with peroxide or azonitrile catalysts. The relative rate of addition and the ratio of addition to abstraction as a function of the structure of the R_fI was determined for cyclohexene and for norbornene (which has no abstractable allylic hydrogen) and 1-heptene. The stereochemistry of the addition reaction was examined in detail, and evidence was obtained which provided a rational basis for discussion of this radical chain reaction. The reaction of R_fI with cyclopentene and with cyclopentadiene was also carried out, taking advantage of the techniques first developed for cyclohexene.

The n.m.r. spectra,[5] dipole moments, conformation equilibria, and some of the novel aspects of the chemistry of the adducts are being reported separately.

Results and Discussion

Synthesis of Adducts Using Azonitrile or Peroxide Initiators.—Iodoperfluoroalkanes having R_f groups varying from CF_3– to $CF_3(CF_2)n$– (n = 1, 2, 3, 6) and $(CF_3)_2CF$– gave widely differing amounts of *cis* and *trans* isomers of the family of 1-iodo-2-(perfluoroalkyl)-cyclohexanes. Results for azonitrile and peroxide-induced reactions are given in Table I. The lowest conversion and efficiency was shown by CF_3I and the highest by $CF_3(CF_2)_2I$, or higher homologs. The secondary iodide, $(CF_3)_2CFI$, gave a lower yield than did $CF_3(CF_2)_2I$. *In order to attain a 50% conversion at 90% yield of adducts, a severalfold excess of cyclohexene, 3–5 mole % (on R_fI) of initiator, and a sufficient length of time for the decomposition of the initiator must be employed.*

Gas–liquid chromatography (g.l.c.) was used to establish the amounts of the various products. The rate of reaction at 65° and isomer ratios are shown graphically for $CF_3(CF_2)_2I$ in Fig. 1 and for $(CF_3)_2$-CFI in Fig. 2. It is apparent that the *trans–cis* adduct ratio is dependent upon the structure of R_fI.

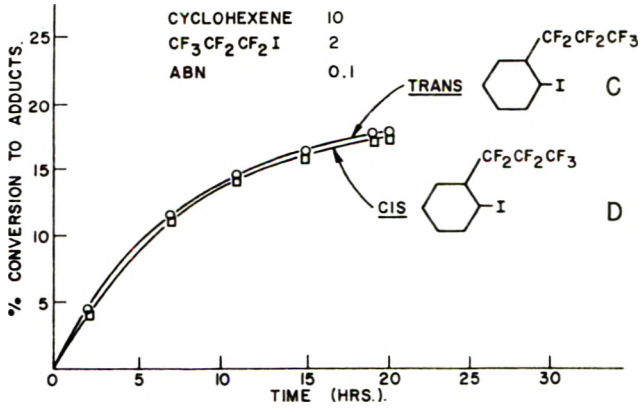

Fig. 1.—Rate of conversion to adducts from $CF_3CF_2CF_2I$ and cyclohexene at 65°.

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(2) N. O. Brace, Abstracts of the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., 1962, p. 95Q.

(3) For a review of the subject see C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 247.

(4) E. S. Huyser, *J. Org. Chem.*, **26**, 3261 (1961).

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(6) N. O. Brace, to be published.

TABLE I

AZONITRILE OR PEROXIDE-INDUCED ADDITION OF R_fI TO CYCLOHEXENE

Expt. no.	R_fI	Mole	Cyclohexene,[a] R_fI, moles	Initiator, mole %	Temp., °C.	Time, hr.	Conversion, %[b]	Yield,[b] %	*trans*/*cis*	Reaction efficiency[c]
1	CF_3I[d]	0.25	5	ABN 4	80	20	7.0	90	1.81	1.7
2	CF_3I[d]	.25	8	ABN 4	80	15	8.0	90	1.95	2.0
3	CF_3CF_2I[d]	.40	8[e]	DTBP 10	130	15	40.0	..	1.14	4.0
4	$(CF_3)_2CFI$	.5	4	ABN 6	68	22	16	70	2.5	2.7
5	$(CF_3)_2CFI$	.17	4	ABN 6	50	30	19	80	2.5	3.3
6	$(CF_3)_2CFI$	.15	4[e]	ABN 6.7	68	15	25	80	...	3.8
7	$(CF_3)_2CFI$	.25	8	ABN 12	68	21	50	80	2.7	4.2
8	$CF_3(CF_2)_2I$	.2	1	ABN[f] 1.2	53	11	*ca.* 7	95	...	4.2
9	$CF_3(CF_2)_2I$[d]	.1	1	DTBP 3.4	140	10	*ca.* 7	95	...	2.0
10	$CF_3(CF_2)_2I$	.15	4[e]	ABN 6.7	71	16	35	90	1.01	5.0
11	$CF_3(CF_2)_2I$	.4	5	ABN 6[g]	68	46	50[g]	87	1.01	7.9
12	$CF_3(CF_2)_2I$	.2	5[e]	ABN 3	50	22	50	90	1.01	16.1
13	$CF_3(CF_2)_3I$	.2	1[e]	ABN 5	72	13	21.5	90	...	4.2
14	$CF_3(CF_2)_3I$	.1	2[e]	ABN 5	75	10	27	90	1.07	5.2
15	$CF_3(CF_2)_6I$	.1	2[e]	ABN 5	75	12	31	88	1.05	6.1
16	$CF_3(CF_2)_6I$	.1	3[e]	ABN 5	75	22	35	88	1.1	7.0

[a] Treated with activated alumina under nitrogen to remove peroxide unless otherwise noted. [b] Conversion is mole of adducts per mole of R_fI charged times 100; yield is per cent of distilled adducts on R_fI used up. [c] Moles of adducts per mole of α,α-azobisisobutyronitrile[9] (ABN) or per mole of di-*t*-butyl peroxide (DTBP) charged. [d] Reaction in a 400-ml. sealed shaker tube. [e] Cyclohexene *not* treated to remove peroxide. [f] Either ABN or azobis-2,4-dimethylvaleronitrile[9] (AVN) were used. [g] One-half of the ABN was added after 23 hr. The conversion (by g.l.c.) was 23% after 23 hr.

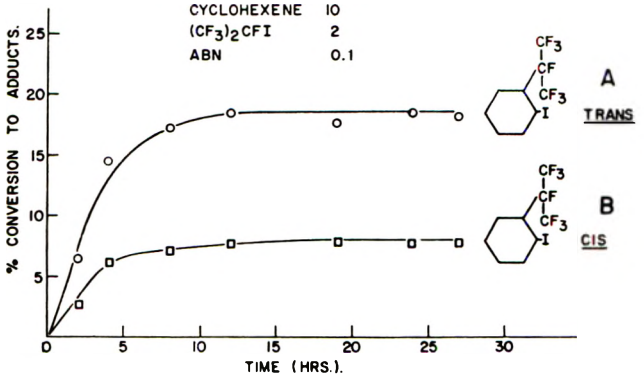


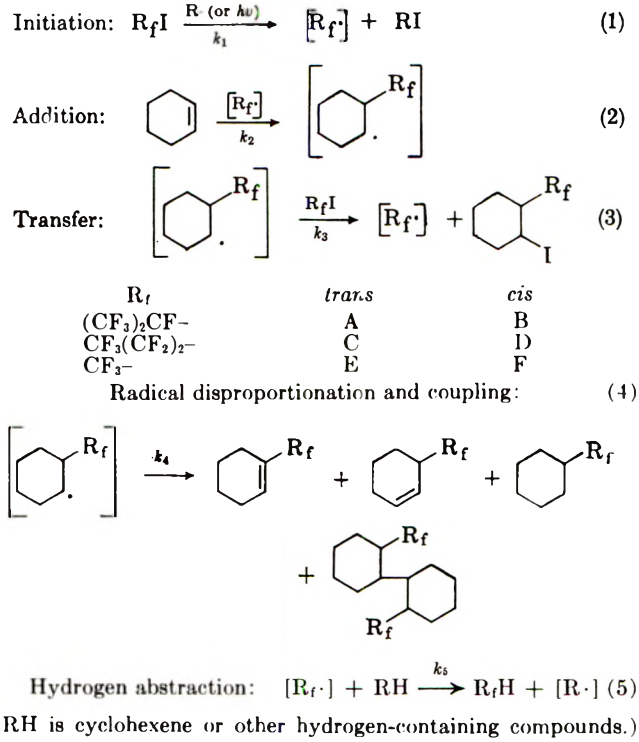
Fig. 2.—Rate of conversion to adducts from $(CF_3)_2CFI$ and cyclohexene at 65°.

Ratios for other R_fI are listed in Table I. Less efficient reaction resulted from replacing part of the excess cyclohexene with cyclohexane[7] or benzene. The conversion to adducts was cut in half. Evidently, the over-all rate of reaction is affected by the concentration of cyclohexene.[8] Peroxide-free cyclohexene gave a *slower* rate of addition and lower conversion to product than did untreated cyclohexene. In fact, $(CF_3)_2CFI$ and cyclohexene in sealed cylinders which contained some oxygen were found to react on standing at 25°. Reaction was apparently induced by peroxide formed *in situ*.

Side Reactions Which Caused Poor Efficiency.—In Chart I are summarized the successive steps (1 to 3) in the normal chain reaction sequence.[3] Steps 4 and 5 are side reactions which remove some of the adduct radicals or R_f radicals from the system and reduce the length of the repetitive chain process. A third cause of poor efficiency was decomposition of the adducts themselves. This resulted ultimately in hydrogen iodide being formed which itself is an efficient radical chain inhibitor. In some unknown manner small amounts of iodocyclohexane and cyclohexenyl iodide were also formed, probably through cyclohexenyl radical (from equation 5) abstraction and disproportionation reactions.

The reason for the poor efficiency observed with CF_3I was the slow rate of transfer (equation 3) rather

CHART I



(RH is cyclohexene or other hydrogen-containing compounds.)

(7) W. J. Kirkham and J. C. Robb, *Trans. Faraday Soc.*, **57** [10], 1757 (1961), observed a sevenfold reduction in the rate of $BrCCl_3$ telomerization of styrene when cyclohexane was used as solvent.

(8) In the case of $(CF_3)_2CFI$ and cyclohexene in cyclohexane solution a significant side reaction gave as much iodocyclohexane as *cis* and *trans* adducts, whereas only a trace of iodocyclohexane was obtained from $CF_3CF_2CF_2I$ and cyclohexene in cyclohexane. Hydrogen abstraction from cyclohexane by $(CF_3)_2CF\cdot$, or $(CH_3)_2\dot{C}CN$ occurred, since a mixture of ABN and $(CF_3)_2CFI$ in cyclohexane (no cyclohexene) gave iodocyclohexane in a facile, but short chain process. Kirkham and Robb[7] noted that no reaction occurred between $BrCCl_3$ and cyclohexane when photolyzed at 3650 Å.

than hydrogen abstraction. Some of the intermediate adduct radical was used up in coupling and disproportionation reactions. The amount of CF_3H obtained was too small to detect by mass spectrum analysis, in contrast to the large amount[4] of $HCCl_3$ given by CCl_3Br or CCl_4.[3,4]

With CF_3CF_2I, using di-*t*-butyl peroxide initiator, CF_3CF_2H again was a minor side product, but a significant amount of high-boiling residue was found. However, hydrogen abstraction was a major side reaction of $(CF_3)_2CF\cdot$, giving $(CF_3)_2CFH$ which was quantitatively determined by g.l.c. analysis. The ratio of adducts A and B to $(CF_3)_2CFH$ was about 2.0; for C and D to $CF_3CF_2CF_2H$, the ratio was 6.56. These results will be discussed later.

Inhibition of addition to cyclohexene by decomposition of the labile adducts A and B was demonstrated in three parallel experiments. As seen in Fig. 1, *cis* and *trans* adducts from $CF_3CF_2CF_2I$ continued to be formed up to 20 hours, whereas with $(CF_3)_2CFI$ (Fig. 2) adduct concentration leveled off after 12 hours of reaction. Initiator [azobisisobutyronitrile (ABN), half-life,[9] 4.6 hours. at 68°] is not completely decomposed during this time. *In a mixture of $(CF_3)_2CFI$ and $CF_3CF_2CF_2I$ with cyclohexene, formation of both sets of adducts ceased after 15 hours* (Fig. 3). Therefore, cyanoisopropyl radicals were being consumed by side reactions not giving addition. This is true in spite of the fact that twice as much of the adducts from $(CF_3)_2CFI$ as from $CF_3CF_2CF_2I$ was obtained. The total rate of conversion to products in separate experiments is compared directly in Fig. 4. At first a slower rate of reaction of $CF_3CF_2CF_2I$ was observed compared with $(CF_3)_2CFI$; after 8 hours the rate of C and D formation was faster and after 12 to 20 hours, the total amount of addition exceeded that obtained from $(CF_3)_2CFI$. Note also that chain initiation by azobisisobutyronitrile was still occurring after 20 hours in the presence of $CF_3CF_2CF_2I$ and its adducts.

Under these conditions $(CF_3)_2CFI$ and 1-heptene gave complete conversion to the adduct $(CF_3)_2CFCH_2CHI(CH_2)_4CH_3$ (G) in only one hour. Therefore, *$(CF_3)_2CFI$ itself is not responsible for inhibition of addition to cyclohexene.* The $(CF_3)_2CFI$ adduct A was unaffected by heating in cyclohexene at 71° for one hour, but with azobisisobutyronitrile present about 35% of A was converted to disproportionation and coupling products of equation 4. Hence, cyanoisopropyl radicals readily induce decomposition of this labile adduct, and hydrogen iodide and iodine are in some manner released. Proof for this was easily secured.

In preparative experiments with $(CF_3)_2CFI$ a solid hydroiodide salt precipitated during reaction; at the same time, adduct radical disproportionation and coupling products were obtained. The water-soluble salt was identified as tetramethyl-5-imino-2-pyrrolidone hydroiodide formed by cyclization[10,11] and partial hydrolysis[11] of the hydrogen iodide adduct of tetramethylsuccinonitrile, the coupling product from cyanoisopropyl radicals. In reactions of $CF_3CF_2CF_2I$ no precipitate of salt was observed; however, the adduct radical disproportionation and coupling product mixture was obtained, though in smaller amount.

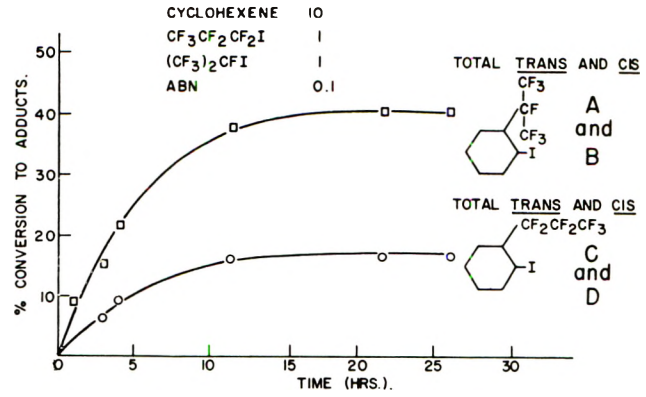


Fig. 3.—Relative rates of reaction of $CF_3CF_2CF_2I$ and $(CF_3)_2CFI$ with cyclohexene at 65°.

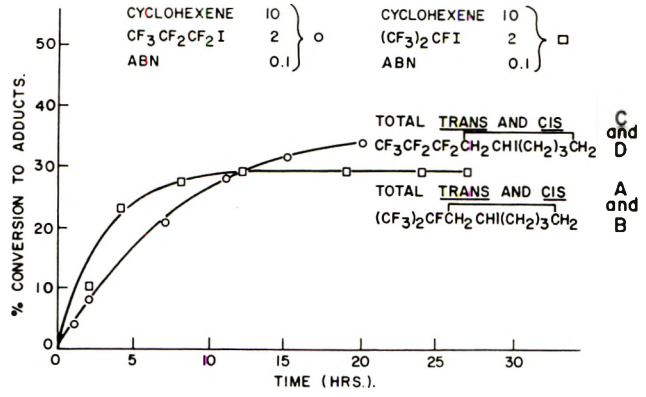
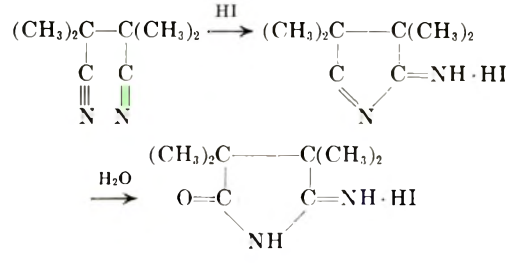


Fig. 4.—Rate of conversion to adducts at 65°; —O— of $CF_3CF_2CF_2I$ and cyclohexene; —□— of $(CF_3)_2CFI$ and cyclohexene.



In peroxide-induced reactions a significant amount of 1-cyclohexen-3-one was invariably obtained, which was also present in cyclohexene exposed to the air. It was, therefore, probably derived from the hydroperoxide.

Reaction Induced by Radiant Energy.—For the experiments listed in Table II, reaction was induced by sunlight passing through Pyrex glass, by ultraviolet light from mercury vapor in an internal quartz coil[12] or by X-rays from a gold target. It was anticipated that cleaner product could be obtained at the lower temperatures possible with irradiation, and, of course, initiator decomposition products would be absent. Unfortunately, photolysis[13] of the adducts also usually occurred,

(9) C. G. Overberger, M. T. O'Shaughnessy, and H. Shalit, *J. Am. Chem. Soc.*, **71**, 2661 (1949). The half-life of AVN (see footnote *f* of Table I) is one hour at 68°.

(10) T. J. Dougherty, *ibid.*, **83**, 4849 (1961).

(11) A. F. Bickel and W. A. Waters, *Rec. trav. chim.*, **69**, 1493 (1950); *cf.* M. C. Ford and W. A. Waters, *J. Chem. Soc.*, 1857 (1951). Bickel and Waters previously observed the cyclization of TMSN to tetramethyl succinimide during alkaline hydrolysis. Acid hydrolysis, however, gave an intractable mixture.

(12) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.*, **14**, 239 (1949).

(13) G. V. D. Tiers, *ibid.*, **27**, 2261 (1962).

TABLE II

RADIATION-INDUCED ADDITION OF R_fI TO CYCLOHEXENE

Expt. no.	R_fI	Mole	Cyclohexene/R_fI, moles	Temp., °C.	Time, hr.	Conversion,[a] %	Yield,[a] %	*trans*/*cis*
1[b]	CF_3I	0.05	35.2	20–40	11.7	35.4	*ca.* 50	1.4
2[c]	$(CF_3)_2CFI$	.1	4.0	25–30	168	26	46	1.5
3[b]	$(CF_3)_2CFI$	.08	5.0	2	10.5	9.3	...	2.54
				2	22	14.0		2.16
				2	50	18.6		2.1
4[b]	$CF_3(CF_2)_2I$	.22	4.55	−20 to 2	19.5	41[b]	72	0.82–0.92
5[c]	$CF_3(CF_2)_2I$	.20	5.0	25–35	96	39	77	0.87
6[d]	$CF_3(CF_2)_3I$	.10	5.0	47	35	32	70	1.0
7[d]	$CF_3(CF_2)_3I$	.14	4.5	48–60	126	49	68	1.04
8[e]	$CF_3(CF_2)_6I$	.1	3.0	25	3.5[f]	20	90	1.07
9[e]	$CF_3(CF_2)_6I$	.1	3.0	25	5.75[g]	41	75	1.10

[a] Conversion is moles of adducts per mole of R_fI charged times 100; yield is per cent of distilled adducts based on R_fI used up. [b] A cell having an internal quartz coil described by Kharasch and Friedlander[12] was used, mounted under a −70° condenser. Shielding of the portion of the coil not immersed in liquid gave cleaner reaction. [c] Pyrex heavy-walled tube sealed *in vacuo*, was placed outside in the sun in August. [d] A General Electric 275-watt sunlamp placed eight inches from the liquid in a Pyrex flask was used. [e] See Experimental. [f] 30,000 rads/min. calculated by Dr. F. W. Stacey from standard dosimetry methods. [g] 45,000 rads/min. calculated by Dr. F. W. Stacey.

TABLE III

PHYSICAL PROPERTIES OF 1-IODO-2(PERFLUOROALKYL)CYCLOHEXANES

$R_fCH_2CHI(CH_2)_3CH_2$ R_f	Isomer	B.p., °C. (mm.)	Retention time, min.		$n^{25}D$	d^{25}_4	ϵ	Ultraviolet, $\lambda_{max}^{CH_3OH}$ mμ	Analyses: Calcd. C	H	F	I	Found C	H	F	I
CF_3—	*trans*-	76 (17)	13.9[a]		1.4803	...	...	...	30.23	3.62	20.5	45.64	30.3	3.6	20.0	45.8
	cis-	48 (2.5)	22.9[a]		1.4811	...	...	...					30.3	3.6	20.3	45.1
CF_3CF_2—	*trans*-	60 (6.0)	7.0[a]	18.0[b]	1.4512	1.766	517	265	29.29	3.07	28.96	38.69	29.3	3.0	29.1	38.9
	cis-	70 (6.0)	14.0[a]	28.2[b]	1.4527	1.780	512	260					29.4	3.0	29.1	39.0
$(CF_3)_2CF$—	*trans*-	48 (1.3)	9.2[a]	20.8[b]	1.4392	1.792	525	266	28.7	2.64	35.3	33.6	28.7	2.9	35.8	33.0
	cis-	50 (1.3)	12.5[a]	26.4[b]	1.4387	1.804	498	261					28.9	2.8	35.7	33.3
$CF_3(CF_2)_2$—	*trans*-	76 (8.0)	7.5[a]	19.0[b]	1.4311	1.772	516	265	28.7	2.64	35.3	33.6	28.8	2.7	35.3	33.8
	cis-	80 (8.0)	15.5[a]	28.6[b]	1.4331	1.784	533	261					28.8	2.7	35.2	33.8
$CF_3(CF_2)_3$—	*trans*-	80 (5)[e]	9.05[c]	8.8[d]	1.4170[e]	1.792[e]	...	...	28.05	2.59	39.94	29.64	28.3	2.4	39.1	29.8
	cis-	78 (3.3)[e]	13.1[c]	10.2[d]	1.4188[e]	1.801[e]	...	...					28.2	2.4	39.4	29.4
$CF_3(CF_2)_6$—	*trans*-	74 (0.7)[e]	15.0[c]	15.3[d]	1.3933[e]	...	...	...	27.0	1.74	49.3	21.95	27.2	1.8	49.0	22.1
	cis-	m.p. 45–46[e]	20.7[c]	20.1[d]	Solid	...	...	...					27.0	1.8	49.0	22.0

[a] One-meter tricresyl phosphate (20%) on firebrick column at 124° using helium carrier gas (1.5-p.s.i. applied pressure) at about 53 ml./min. [b] Two-meter polypropylene glycol (Perkin-Elmer "R") column at 150° using helium carrier gas (15-p.s.i. applied pressure) at about 46 ml./min. [c] Same column at 173°; helium at about 27 ml./min. [d] Three-meter "Apiezon" M on alkaline washed "Chromosorb" W (60–80 mesh) at 150° using helium (15-p.s.i. applied pressure) at about 65 ml./min. [e] Approximately 95% pure indicated isomer; remainder is the other isomer.

which limited the usefulness of this technique. Much iodine and decomposition products were obtained. As with azonitrile initiator, CF_3I and $(CF_3)_2CFI$ gave lower yields than did $CF_3CF_2CF_2I$. Free radical addition of $CF_3(CF_2)_6I$, induced by X-ray irradiation at room temperature, gave a moderate conversion in a few hours, and no free iodine. No advantage in yield or rate of reaction over azonitrile initiation could be realized. The *trans*–*cis* isomer ratios were lower for $(CF_3)_2CFI$ or $CF_3CF_2CF_2I$ addition than the values obtained with analogous azonitrile-initiated reactions. The ratio of C to D was quite close to the equilibrium ratio,[6] which indicated equilibration was occurring during reaction. This observation is consistent with the dependence of isomer ratio upon irradiation time and temperature.

Physical Properties and Separation of *cis* and *trans* Isomers.—The physical constants and analyses of the various adducts, including the retention times for g.l.c. columns and conditions we have used, are listed in Table III. For each pair of isomers the *trans* adduct had the lower boiling point (or retention time), refractive index (except for A and B), and density. The ultraviolet absorption maximum of the *trans* isomers having C_2F_5– or isomeric perfluoropropyl groups occurred at a slightly longer wave length (265 mμ) than the *cis* isomers (261 mμ). The absorption maximum of iodocyclohexane in ethanol was reported[14] to be 259 mμ while that of $CF_3CH_2CH_2I$[14] was 261 mμ. For comparison, the maximum for $(CF_3)_2CFI$ in methanol is 252 mμ (ε 189) and in isooctane, 278 mμ (ε 237). Preparative g.l.c. was required to separate cleanly *cis* and *trans* isomers, except for *cis*-1-iodo-2-(perfluoroheptyl)cyclohexane which was obtained as a crystalline solid. Not only were the isomers similar in volatility, but the thermal stability of A and B was not sufficient to permit fractional distillation under conditions adequate for their separation. Decomposition to iodine, HI, and tars occurred when the distillation flask was heated above 75°. By careful fractionation in an efficient spinning-band column the adducts from $CF_3(CF_2)_nI$ (n = 1, 2, 3) were separated to a great extent (95–99%).

Relative Reactivity of R_fI with Olefins.—By allowing an equimolar mixture of two R_fI to compete for an equivalent amount of cyclohexene, the relative reactivity was determined (see Fig. 3). In similar fashion 1-heptene and norbornene were employed as the olefin substrate. The data are in Table IV. *$(CF_3)_2CFI$ was invariably twice as reactive as $CF_3CF_2CF_2I$ even though the over-all rate of reaction varied considerably*

(14) R. N. Haszeldine, *J. Chem. Soc.*, 1764 (1953).

TABLE IV

RELATIVE REACTIVITY OF R_fI WITH OLEFINS

Olefin	Ratio of addition (k_2) $CF_3CF_2CF_2I$ / CF_3I	Ratio of addition (k_2) $(CF_3)_2CFI$ / $CF_3CF_2CF_2I$	Ratio of addition to abstraction (k_2/k_5) $CF_3CF_2CF_2I$	Ratio of addition to abstraction (k_2/k_5) $(CF_3)_2CFI$
1-Heptene	4[a,b]	2[b,c]	104	192
Norbornene	5[a,b]	2[b,d]	46[b,d]	33[b,d]
Cyclohexene	18	2	6.56[e]	1.73[e,f]

[a] A mixture of 0.05 mole each of olefin, the two R_fI, 0.35 mole of cyclohexane, and 0.0025 mole of ABN was kept at 78° for ten hours. Total conversion was 83 to 89%. [b] Analysis was by g.l.c. using the "R" column at 150°, with 15 p.s.i. of helium pressure. [c] A mixture of 0.01 mole each of olefin, the two R_fI, 0.07 mole of cyclohexane, and 0.00025 mole of ABN was kept at 78° for 4 hours. Total conversion was 87%. [d] Amount of compound (0.01 mole) heated for 3 hr. at 65° using 0.0001 mole of ABN. Conversion was 96%. [e] After 21 hours of reaction at 65°. [f] k_2/k_5 was 2.05 after 4.5 hours.

with each olefin. However, with CF_3I and $CF_3CF_2CF_2I$ the same set of olefins gave quite different results; with cyclohexene $CF_3CF_2CF_2I$ gave eighteen times as much adduct as CF_3I, but with 1-heptene and with norbornene the discrimination was not so great (rate factor = 4 to 5). These ratios are consistent with results from a different series of reactions in which 1-heptene and norbornene or 1-heptene and cyclohexene were allowed to compete for $CF_3CF_2CF_2I$ (Table V).

TABLE V

RELATIVE REACTIVITY OF OLEFINS WITH $CF_3CF_2CF_2I$

Olefin mixture	Ratio of adducts	Total conversion, %
1-Heptene–norbornene	1/1	100
1-Heptene–cyclohexene	14/1	*ca.* 30

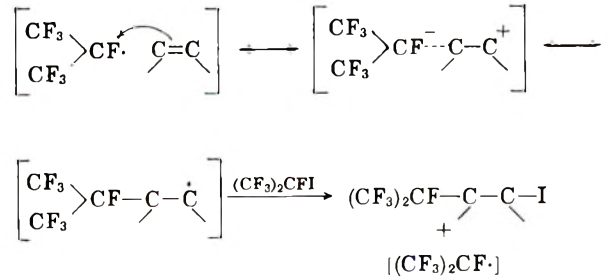
Norbornene and 1-heptene reacted at comparable rates, but cyclohexene was only 1/14 as reactive as 1-heptene. A strong retardation of addition to 1-heptene also was observed when cyclohexene was present. This we would now ascribe to chain-breaking reactions involving cyclohexene and its adducts. It is significant also that telomers of 1-heptene and norbornene were obtained only with CF_3I. The rate of transfer (k_3) was sufficiently low to permit addition of the adduct radical to another molecule of olefin before transfer occurred. Ordinarily, telomers of such reactive nonpolymerizable olefins with R_fI were not observed.

Ratio of Addition to Hydrogen Abstraction.—The much smaller ratio of addition to abstraction for $(CF_3)_2CF\cdot$ and cyclohexene (k_2/k_5 = 1.73) as compared with $CF_3CF_2CF_2\cdot$ (k_2/k_5 = 6.56) is especially striking when compared with the ratios observed for reaction with 1-heptene or norbornene (Table IV). For $(CF_3)_2CF\cdot$, k_2/k_5 = 192 after 7 hours of reaction with two moles of 1-heptene; for $CF_3CF_2CF_2\cdot$ it was 104, according to g.l.c. analysis of sealed reaction mixtures. *Thus, addition of $(CF_3)_2CFI$ to the open chain olefin was twice as efficient and rapid as the addition of $CF_3CF_2CF_2I$.* It is significant that with two moles of $(CF_3)_2CFI$ and only one mole of 1-heptene k_2/k_5 fell to 33.5. In the first case all of the R_fI was gone in less than an hour and the yield of adduct was 99%; in the second instance hydrogen abstraction by $(CF_3)_2CF\cdot$ continued on after all the olefin was used up, since the yield of adduct was still 99%. These results provide strong presumptive evidence for ascribing the lower k_2/k_5 value of $(CF_3)_2CF\cdot$ with cyclohexene to a greater steric retardation of k_2 with the bulkier R_fI. From the decrease in k_2/k_5 with time it appears that with cyclohexene also, hydrogen abstraction continues unabated after adduct concentration has reached a maximum (see Fig. 4). The much smaller difference in k_2/k_5 values of the two isomeric R_fI with norbornene is consistent with a considerably smaller steric retardation of k_2.

Theoretical Considerations.—It is interesting to consider the basis for the marked differences in addition and transfer rates of the various R_fI with cyclohexene and other olefins. A decrease in bond dissociation energy in the series $CF_3I > CF_3CF_2I > CF_3CF_2CF_2I > (CF_3)_2CFI$ may be postulated in accord with the known[3] variation of RX dissociation energies with alkyl structure. An increase in the resonance energy of $R_f\cdot$ with increasing size has been suggested[15,16] as the reason for the greater reactivity of $CF_3CF_2CF_2I$ over CF_3I in addition to ethylene or propargyl alcohol. Presumably this comes about because of a lower activation energy for addition, since the reaonance energy of $R_f\cdot$ can be contributed to the adduct radical in the addition step (equation 2, Chart I). In this connection it may be appropriate to reiterate the principle cited by Walling[17]: "... as one goes down a table of bond dissociation energies and radical stabilization, the radicals are formed with increasing ease. But they become progressively less reactive. This balance is often very important in determining the scope of a given type of chain reaction." Not only may R_f radicals differ in energy, but the adduct radicals with various olefins may have quite different stabilization energies. The competition between transfer and hydrogen abstraction or coupling reactions can be profoundly affected.

The greater reactivity of $(CF_3)_2CFI$ over $CF_3CF_2CF_2I$ may be attributed to a smaller bond dissociation energy, principally as a result of steric pressure on the I–C– bond by the flanking CF_3 groups, and partly because of resonance stabilization. The twofold difference in reactivity between $(CF_3)_2CFI$ and $CF_3CF_2CF_2I$ may be thus explained, but a further consideration may also be significant.

In addition of a radical to an olefin, polar structures involving a dipole interaction between the radical and the π-electrons of the double bond can reduce the energy required to bring the two species together.[17,18]



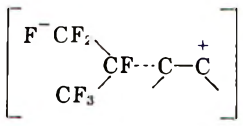
(15) F. E. Lawlor, Abstracts, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., 1955.

(16) J. D. Park, F. E. Rogers, and J. R. Lacher, *J. Org. Chem.*, **26**, 2089 (1961).

(17) C. Walling, *Chem. Eng. News*, **39**, 102 (1961).

(18) A. P. Stefani and M. Szwarc, *J. Am. Chem. Soc.*, **84**, 3661 (1962); (b) J. Gresser, A. Rajbenbach, and M. Szwarc, *ibid.*, **83**, 3005 (1961); (c) A. P. Stefani, L. Herk, and M. Szwarc, *ibid.*, **83**, 4732 (1961).

One would certainly expect that $(CF_3)_2CF\cdot$ would be better able to participate in a polar addition complex of the sort pictured than would $CF_3CF_2CF_2\cdot$ which has only two β-fluorines. The addition complex may actually involve additional resonance structures such as

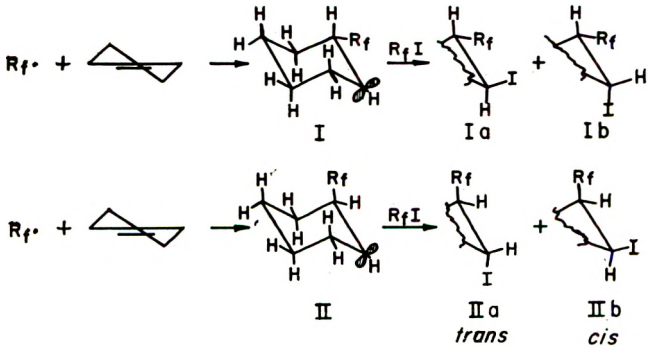


which can contribute to the over-all structure. In other words $(CF_3)_2CF\cdot$ is the more electrophilic radical. A similar argument may be given for $CF_3CF_2\cdot$ or $CF_3\cdot$ when compared with $CH_3\cdot$ or alkyl as has been done by Stefani and Szwarc.[18]

It is evident that selectivity of the olefin towards addition or hydrogen abstraction of $R_f\cdot$ is strongly influenced by the over-all reaction process. The marked difference in reactivity of cyclohexene and 1-heptene is a manifestation of the generally observed preference for addition of a radical to a more accessible terminal olefinic linkage.[3] In this respect the unusually low "methyl affinity" of cyclohexene in comparison with other olefins[18b] is quite consistent, as is the unusually high reactivity of norbornene which involves, of course, relief ring strain. The reduced selectivity of $CF_3\cdot$ (0.8) as compared with $CH_3\cdot$ (1.0 by definition)[18] is another indication that $R_f\cdot$ will be less discriminating in its reactions. In further studies this discrimination of addition of R_fI *vs.* abstraction by $R_f\cdot$ with various olefins will be explored.

Stereochemistry of the Addition Reaction.—The discovery[5] that the isomeric adducts A, B, C, and D assume different preferred conformations makes the stereochemical course of the reaction of great interest. There are evidently two contradictory steric considerations: (1) the bulky and electronegative iodine and perfluoroalkyl groups would prefer to be separated as far from each other as possible[1]; (2) in cyclohexane chair structures, axial hydrogens exert a crowding force on large axial substituents on the same side of the ring.[19]

One possible representation of the steric relationships which are involved during reaction is as follows.



It has been possible from a study of the n.m.r. spectra and dipole moments of the adducts to ascertain the preferred conformation of the 1,2-substituted cyclohexane rings.[5] These data are being reported in detail separately,[6] but the conclusions are summarized here.[20]

The *cis* isomers in the chair conformation have the R_f group (rather than the smaller iodo group) exclusively in the more open equatorial position. The *trans* isomers are faced with a disagreeable decision; either the two groups must be both equatorial and uncomfortably close to each other or they must both be subjected to repulsions by the four axial protons. For those *trans* isomers in which R_f is larger than CF_3– and linear, the preferred choice is to go into the diaxial conformation, with considerable bending away from the axial protons. This option appears to be closed to the adducts with $(CF_3)_2CF$– (which is branched at the bonding carbon) because of space limitations in the axial position. In both cases some distortion of the ring from a true chair structure is probable.[6]

The *trans* (a,a) conformers IIa from $CF_3(CF_2)_nI$ (n = 1, 2, 3, 6) have a higher energy content at 70° than the *cis* (a,e) conformers Ib, according to thermal equilibration studies.[6] Therefore, the slight preference for *trans* over *cis* in the preparative experiments must arise from kinetic control. The rate of transfer of adduct radical II with R_fI, giving *trans* isomer IIa, may be slightly faster than in the case of radical I, which gives *cis* isomer Ib, for steric reasons. The bulky R_f group of I is in a gauche position with respect to the incipient bond with R_fI; for II the groups are in an *anti* or *trans* position. In the transition state complex in radical transfer reactions of this type, a high degree of rigidity (because of low entropy value) has been postulated.[3,4,18]

The 3:1 preference for *trans* over *cis* isomer from $(CF_3)_2CFI$ is a more striking illustration of kinetic control, since *trans* (e,e) adduct is also slightly less stable[6] than the *cis* (e,a) conformer at 70°. Observe that the n.m.r. data indicate there is no detectable interconversion of *cis* conformers Ib and IIb or of *trans* conformers Ia and IIa (when R_f is greater than CF_3). Transfer of radical I from the more open equatorial side of the ring with $(CF_3)_2CFI$ might be expected to occur at a faster rate than from the axial side which may suffer from *axial* hydrogen opposition limiting the rate of transfer. A more sophisticated treatment must be deterred for the present.

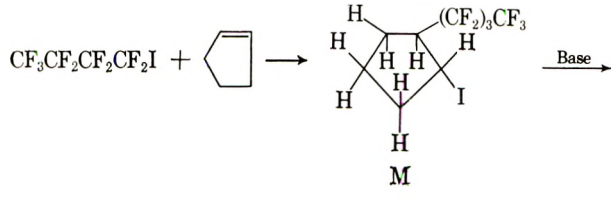
In the case of CF_3I adducts, the fact that equilibration between conformations Ia and IIa (but not between Ib and IIb) is taking place above −90° may be decisive in giving a *trans*–*cis* ratio of 2.0. Transfer with CF_3I in the *anti* sense can occur with either radical I or II. The *cis* adduct exists to a detectable degree only in the (e,a) conformation Ib, derived from radical I. Therefore, Ib has only half the probability of being formed as Ia and IIa, other factors being equal.

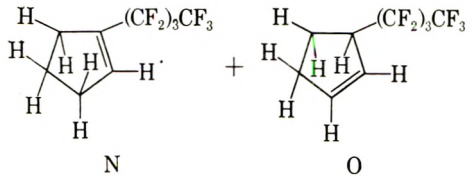
Iodoperfluoroalkane Addition to Cyclopentane.—Free radical addition of 1-iodoperfluorobutane to cyclopentene by either light- or azonitrile-induced reaction gave *trans*-1-iodo-2-(perfluorobutyl)cyclopentane (M) in 40% conversion (80% yield). No evidence for an

(19) For a recent excellent discussion see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York, N. Y., 1962, p. 204.

(20) Adduct A prefers conformation Ia, and adduct B, conformation Ib according to n.m.r. spectra.[5] The *trans* adducts from $CF_3(CF_2)_nI$ (n = 1, 2, 3, 6), however, assume the diaxial conformation IIa even though the *cis* adducts prefer conformation Ib. Temperatures from 90° to −100° did not significantly affect the n.m.r. spectra of the *cis* or *trans* adducts from $CF_3(CF_2)_nI$ (n = 1, 2, 3) or from $(CF_3)_2CFI$, and the *cis* adduct from CF_3I. Just as found for iodocyclohexane, however, the mobile equilibrium of the two *trans* conformers of E (Ia ⇌ IIa) was arrested at −90° to −105°.[6]

isomeric adduct was obtained. The *trans* structure is consistent with the n.m.r. spectrum which has a low-field multiplet of four lines spaced 5 to 6 c.p.s. apart at −267 c.p.s. (relative to tetramethylsilane at 60 Mc.). The splitting is attributed to the proton on C-1 coupled with two protons (J = *ca.* 6 c.p.s.) on C-5 and with a proton on C-2 (J = *ca.* 5 c.p.s.). These are reasonable values for coupling constants of *trans*-oriented protons of cyclopentane rings.[21]





From an examination of models it is clear that a *cis* adduct would have considerable crowding of the R_f and iodo groups.

Elimination of HI by heating *M* with tri-*n*-butylamine gave an olefin mixture (94%) which consisted of the Δ^1-isomer N (18%) and the Δ^2-isomer O (82%) according to g.l.c. analysis and n.m.r. spectra. The relative amounts of N and O are reasonable for preferential *trans* elimination of hydrogen iodide, taking into consideration the dihedral angle of about 123° rather than the preferred 180° known to obtain for *trans* elimination in this system.[22,23] The corresponding *cis* adduct would be expected to give a preponderance of N by elimination of the more acidic *trans* proton attached to the carbon atom bearing the R_f group.[6]

The dipole moment of M (2.99 D.) was quite close to the value (3.09 D.) obtained for *endo*-2-iodo-3-*exo*-(perfluoropropyl)norbornane.[1,6] This further supports the *trans* structure, since the bond angles are quite similar to those found in the five-membered ring of the *trans*-norbornane derivative.

Radical addition to cyclopentadiene of 1-iodoperfluoropropane could not be effected, nor would the azonitrile-induced addition to 1-heptene occur in the presence of this reactive diene. It is probable that the perfluoropropyl radicals, therefore, add readily to the conjugated diene, but that transfer of the resonance-stabilized adduct radical with R_fI does not occur at a rate sufficient to maintain a chain reaction. Such a situation was observed for styrene[1] which gives a stable benzyl-type adduct radical.

Experimental

All experiments were carried out in an atmosphere of nitrogen. Gas–liquid chromatography of all compounds was done with a Perkin-Elmer vapor fractometer, Model 154-C. The columns and conditions used are listed in Table III. Except where specified, a reagent grade of cyclohexene was used (99.82 mole % minimum, Phillips Petroleum Co., treated with Woelm activated alumina, activity grade I, to remove peroxide). Iodotrifluoromethane, 1-iodoperfluoroethane, 1-iodoperfluoropropane, and 1-iodoperfluoroheptane were obtained from Columbia Organic Chemical Co. 1-Iodoperfluoroethane (b.p. 13°, 99.9% pure), 1-iodoperfluoropropane (colorless, b.p. 41°, $n^{25}D$ 1.3250, 99.9% pure), and 1-iodoperfluoroheptane [b.p. 70° (70 mm.), $n^{25}D$ 1.3270, containing about 10% of an isomeric impurity as shown by g.l.c.] were redistilled. 1-Iodoperfluorobutane was prepared from iodoperfluoroethane and tetrafluoroethylene[24] and redistilled, b.p. 67.8°; $n^{25}D$ 1.3258 (98% pure). 2-Iodoperfluoropropane was prepared from perfluoropropylene and iodine pentafluoride,[25] b.p. 39.5°; $n^{25}D$ 1.3263 (99.9% pure). 1-Heptene was obtained from the Humphrey-Wilkinson Co., and redistilled, b.p. 93°; $n^{25}D$ 1.3975. Cyclopentene, from the Aldrich Chemical Co., was redistilled, b.p. 44°; $n^{25}D$ 1.4190 (100% pure). Norbornene was redistilled, b.p. 94–95°, sublimable solid (99% pure). 1-Hydroperfluoropropane[26] (b.p. −17°) and 2-hydroperfluoropropane[26] (b.p. −18°) were a gift from S. Andreades. Experiments with CF_3I and CF_3CF_2I were carried out in Hastelloy C-lined steel 400-ml. shaker tubes.

trans-1-Iodo-2-(perfluoroisopropyl)cyclohexane (A) and *cis* Isomer B. (a) From Azobisisobutyronitrile-Initiated Reaction.—Cyclohexene (54.7 g., 0.67 mole, 99.8 mole %), 2-iodoperfluoropropane (50.0 g., 0.17 mole), and azobisisobutyronitrile (1.6 g., 0.01 mole) were heated at 50° in an oil bath at constant temperature for 30 hr. in a flask fitted with a syringe port and having a −70° condenser. Samples removed showed by g.l.c. analysis a steady increase in product concentration up to 25 hr., and then a decrease; the ratio of A to B fell from 3.3 after 9 hr. to 2.7 after 17 hr. The conversion to A and B from g.l.c. analysis was 21%; the yield was 82%. The orange solution (101.2 g.) was cooled to 5° and filtered. 2-Hydroperfluoropropane and 2-iodoperfluoropropane were lost during filtration. The filtrate (96.2 g.) was fractionated in a 3-ft. platinum spinning band column (column A). 2-Iodoperfluoropropane (30.4 g.) cyclohexene (50 g.), and a mixture of A and B (with small amount of impurities), b.p. 36–43° (0.8 mm.) (12.5 g., 19.5% conversion), distilled, leaving a dark residue of 1.2 g. (10%). The adducts were kept dark and cold. Preparative g.l.c. was used for purification.

The solid obtained at 5° was rinsed with 25 ml. each of cyclohexene and dichloromethane. Azobisisobutyronitrile (ABN) (0.215 g.), m.p. 100–101° (undepressed by mixture with ABN), was obtained. Other substances were present in the filtrate.

(b) Isolation and Identification of Tetramethyl-5-imino-2-pyrrolidone Hydroiodide.—2-Iodoperfluoropropane (150.0 g., 0.5 mole), cyclohexene (164 g., 2.0 moles), and ABN (5.0 g., 0.03 mole) were heated for 22 hr. at 52–70°. Solid (0.335 g.) remained in the flask when the product mixture was decanted at 5°. The light sensitive solid was placed in a subliming tube and volatile material removed at 125° at 0.1 mm., leaving 0.23 g. of nonvolatile salt. It decomposed when heated in an open melting point tube. In a sealed capillary tube, however, the salt melted at 315° without evident decomposition. It was soluble in water, giving a precipitate of silver iodide by reaction with silver nitrate solution, and was recrystallized from acetone in the dark at 5°. A solution gradually darkened and formed tar. An infrared spectrum[27] (potassium bromide disk) showed a strong bonded NH band at 3.0 μ, carbonyl group bands at 5.60 and 6.15 μ, and several longer wave-length bands. These bands are analogous to those reported[28] for creatinine hydrochloride which also has an HX·HN=C–NHCO– grouping.

Anal. Calcd. for $C_8H_{14}N_2OI$: C, 34.18; H, 5.02; N, 9.97; I, 45.15. Found: C, 34.4; H, 5.7; N (Dumas), 9.5; I, 44.8.

(c) Relative Rates of Allylic Hydrogen Abstraction and of Addition of 2-Iodoperfluoropropane or 1-Iodoperfluoropropane to Cyclohexene.—Cyclohexene (4.2 g., 0.05 mole), 2-iodoperfluoro-

(21) C. D. Jardestzky, *J. Am. Chem. Soc.*, **84**, 62 (1962).

(22) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, Inc., New York, N. Y., 1959, p. 472.

(23) (a) P. I. Abell and C. Chiao, *J. Am. Chem. Soc.*, **82**, 3610 (1960); (b) C. H. De Puy, R. D. Thurn, and G. F. Morris, *ibid.*, **84**, 1314 (1962).

(24) R. N. Haszeldine, *J. Chem. Soc.*, 2856 (1949); *ibid.*, 3761 (1953).

(25) M. Hauptschein and M. Braid, *J. Am. Chem. Soc.*, **83**, 2383 (1961).

(26) A. M. Lovelace, D. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Corp., New York, N. Y., 1958, p. 60.

(27) I am indebted to Dr. R. K. Miller for assistance in obtaining and interpreting the infrared spectrum.

(28) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand and Company, Inc., Princeton, N. J., 1949, p. 229.

propane (3.0 g., 0.10 mole), and ABN (0.081 g., 0.0005 mole) were sealed in a 10-ml. stainless steel cylinder, filled with nitrogen, and heated at 73° for 20.5 hr. While inverted, the cylinder was sampled at 7.5 mm. allowing the liquid to expand at 25° into a 1-l. volume chamber which had been previously evacuated to 0.5 mm. A 25-ml. portion of the gas mixture was passed into the vapor fractometer. Relative areas of $(CF_3)_2CFH$, $(CF_3)_2CFI$ and of cyclohexene were determined for the original mixture, for samples taken at 4.5 and 20.5 hr., and two known weighed mixtures of these compounds. The amount of $(CF_3)_2CFH$ increased from about 12.2 to 16% conversion during this time, but the amount of $(CF_3)_2CFI$ converted to adducts could not be accurately determined by this technique, because of changes in weight/area factors with change in composition and low volatility of the adducts. However, the total product mixture at −50° was sampled with a cold syringe and the composition determined by g.l.c. analysis. The conversion to $(CF_3)_2CFH$ was 15.9%, to A, 19.3%, and to B, 8.2%; the amount of $(CF_3)_2CFI$ used up was 50%, and the ratio of addition to abstraction was, therefore, 1.73. The radical coupling products less volatile than B were not observed by this technique.

An identical procedure using 1-iodoperfluoropropane gave $CF_3CF_2CF_2H$ (8.2%), recovered $CF_3CF_2CF_2I$ (42%), and C and D (26 and 27.8%, respectively). The ratio of addition to abstraction was 6.56. The yield of adducts was 93% based on 1-iodoperfluoropropane used up. To determine product composition the g.l.c. weight/area factors were determined at two levels of conversion: $CF_3CF_2CF_2H$ (weight %, 1.66; weight/area, 0.70); $CF_3CF_2CF_2I$ (32.0; 2.16); cyclohexene (52.3; 0.78); C and D (13.48; 1.25); and $CF_3CF_2CF_2H$ (9.50; 0.79); $CF_3CF_2CF_2I$ (29.0; 1.98); cyclohexene (54.6; 0.85); and C and D adducts (6.82; 1.31). The 1-m. tricresyl phosphate column operated at 124° was used (see Table III). Similar results were obtained using $(CF_3)_2CFI$ and its products.

trans-1-Iodo-2-(perfluoropropyl)cyclohexane (C) and the *cis* isomer D. (a) ABN-Initiated Reaction.—1-Iodoperfluoropropane (62.0 g., 0.20 mole), cyclohexene (Phillips, 99.8%, *not* treated with activated alumina; 82 g., 1.0 mole) and ABN (1.00 g., 0.008 mole) were heated at 50° for 22 hr. G.l.c. analysis showed a steady increase in conversion with time. The ratio of *trans* C to D *cis* isomers was constant at 1.01. Distillation of the slightly colored liquid in a 16-in. platinum spinning band column (column B) gave cuts: (1) 1-iodoperfluorpropane, b.p. 41°, $n^{25}D$ 1.3335 (21.5 g.); (2) cyclohexene, b.p. 50° (200 mm.), $n^{25}D$ 1.4418 (65 g.); (3) contained tetramethylsuccinonitrile (TMSN), C, and D, b.p. 40–42° (2.2 mm.) (2.2 g.); (4) a second impure fraction, b.p. 47–50° (2.0 mm.), $n^{25}D$ 1.4620, 7.3 g., which contained 79.4% of C, 10.5% of D, 1-cyclohexen-3-one (*ca.* 0.4 g.), and iodocyclohexane and/or 3-iodo-1-cyclohexene (*ca.* 0.1 g.); (5) C and D, b.p. 51–53° (2.0 mm.), $n^{25}D$ 1.4340, 28.9 g.; and hold-up in the column, $n^{25}D$ 1.4475, 1.5 g. There was no tarry residue. The hold-up contained C, D, and "dimeric" coupled products[6] with retention times of 27.4 (*ca.* 0.15 g.) and 39.3 min. (*ca.* 0.6 g.). The trap contained 2.5 g. of 1-iodoperfluoropropane and 1-hydroperfluoropropane mixture. The total conversion of C and D was 50% on 1-iodoperfluoropropane (90% yield). The conversion under other conditions is given in Table I; analytical data and physical properties are in Table III. C and D were separated by g.l.c. on a preparative scale. Fractionation in column A gave partial separation; cuts containing 80% of C and 20% of D, and 5% of C and 95% of D were obtained.

(b) Ultraviolet Light-Reduced Reaction at −20 to 0°.—A reaction vessel identical to that described by Kharasch and Friedlander[12] was used. 1-Iodoperfluoropropane (63.7 g., 0.215 mole) and cyclohexene (82.3 g., 1.0 mole, 99.82% not treated with alumina) was irradiated at −20°. In a few minutes, a dark deposit formed in the reactor and the liquid darkened. After 1 hr., a 23% conversion to C and D was attained; the ratio of C to D was 0.86. After 4 hr. at −15° to −13°, the conversion was 38%, and after 6 hr. at −13°, 51.0%. Further irradiation at 0° for 8 hr., (14 hr. total) gave no further increase of C and D, and, after 5.5 hr. at 0 to 2° (19.5 hr. total), a small decrease in C and D. The ratio of C/D also rose to 0.92. The total amount of (perfluoropropyl) cyclohexane and of 1- and 3-(perfluoropropyl)-1-cyclohexene was: after 1 hr., 1.5%, 4 hr., 2.0%; 6 hr., 2.7%; 14 hr., 3.4%; and 19.5 hr., 3.5%.

Distillation gave C and D (41% conversion, 72% yield on recovered 1-iodoperfluoropropane), the (perfluoropropyl)cyclohexane–cyclohexene mixture (which see) (1.2 g.), and iodocyclohexane and 3-iodo-1-cyclohexene as above not separated from C and D (1.55 g., 3.4% conversion, g.l.c. analysis). The residue was 1.3 g. of black tar. The darkly colored distilled C and D was treated with activated alumina and carbon to remove iodine.

trans-1-Iodo-2-(trifluoromethyl)cyclohexane (E) and *cis* Isomer F by ABN-Initiated Reaction.—CF_3I (49.0 g., 0.25 mole), cyclohexene (162.0 g., 2.0 mmoles), and ABN (1.64 g., 0.01 mole) were shaken at 80° for 15 hr., and vented at 50° into a cold trap. The CF_3I which was collected (5.0 g., 95.3%) contained no CF_3H by mass spectra analysis. The liquid (211 g.) was cooled to −20°, sampled for g.l.c. analysis, filtered from 0.2 g. of tetramethylsuccinonitrile (TMSN) (m.p. 155–160°, crude), and distilled in column A using a liquid nitrogen cooled trap to collect CF_3I (39.5 g.). Cyclohexene, b.p. 50° (200 mm.) (156.0 g.) and a mixture of E and F and coupled products [b.p. 49–52° (2.5 mm.), $n^{25}D$ 1.4814 to 1.4828 (7.53 g.)] were obtained. The residue (1.4 g.) was a light-sensitive gum, soluble in dichloromethane. Analyses showed 24.0% iodine and mol wt. (ebulloscopic in acetone) of 280. The volatile products were redistilled, b.p. 66–75° (17 mm.), without effecting a separation. The sample contained (weight %) 20% of CF_3I, 74% of cyclohexene, 0.8% of isomeric trifluorocyclohexenes, 1.8% (3.8 g.) of *trans* adduct E, 0.9% (1.9 g.) of *cis* adduct F, and 0.31% of TMSN (8% conversion to E and F).

Time-of-flight mass spectra analysis[29] of g.l.c. separated cuts showed the main components (80 to 90%) were E and F. The presence of cyclohexenyl iodide in one cut was confirmed, but it was only about 0.008% of the total material distilled. Preparative g.l.c. was used to separate the materials, which then were better than 99% pure isomer. The addition of CF_3I to cyclohexene, by reaction with a large amount of magnesium amalgam, has been recently reported.[30] The physical properties of the isomer mixture obtained in 43% yield agree well with the values for the pure isomers given in Table III.

cis- and *trans*-1-Iodo-2-(perfluoroethyl)cyclohexanes by Peroxide-Initiated Reaction.—Cyclohexene (184 g., 2.0 moles) di-*t*-butyl peroxide (6.0 g., 0.04 mole) and iodopentafluoroethane (98.4 g., 0.4 mole) were shaken for 15 hr. at 130°. The product mixture was transferred while cold to a distilling flask and fractionated in column A. Low boiling liquid (26 g.) collected in the −70° trap and was analyzed by g.l.c. [2.5-m. "R" polypropylene glycol column, helium at 14 p.s.i., temperature programmed at the rate of 40°/min. from 25 to 100°], and time-of-flight mass spectrum analysis.[29] Compounds were eluted in the order: hydropentafluoroethane (2.8%), isobutylene (9.4), iodopentafluoroethane (85%), acetone (0.07), iodomethane (0.09), cyclohexane (0.02), *t*-butyl alcohol (0.18), cyclohexene (2.3), and benzene (0.16). There was less benzene and cyclohexane in the original cyclohexene than this.

The first fraction, b.p. 43° (160 mm.), 162.0 g., contained cyclohexene, acetone, *t*-butyl alcohol, and other substances. Fraction 2, b.p. 49–52° (5.0 mm.) (6.0 g.), contained about 1% of 1- (and 3)-(perfluoroethyl)cyclohexene, 55% of *trans*-1-iodo-2-(perfluoroethyl)cyclohexane, 22% of 1-cyclohexen-3-one, 5.5% of iodocyclohexane and 3-iodo-1-cyclohexene, and 3.4% of *cis*-1-iodo-2-(perfluoroethyl)cyclohexane. The side products were unequivocally identified by t.o.f. mass spectrum analysis[29] of g.l.c. separated components. The infrared spectrum also showed a strong carbonyl band at 5.99–6.02 μ (doublet) attributed to the unsaturated ketone. Subsequent fractions, b.p. 50° (5.2 mm. to 2.0 mm.), totaled 53.0 g. and contained 28.1 g. of *trans* and 24.5 g. of *cis* adduct (40% conversion; *trans*–*cis*, 1.15; total recovery 95%) according to g.l.c. analysis. The pot residue was 6.2 g. of a viscous dark liquid condensation product.

The dark adduct mixture was passed down activated alumina and carbon and the colorless material redistilled. Careful fractionation in column A afforded *trans* isomer, b.p. 58° (5.5 mm.) (96% pure), and *cis* isomer, b.p. 68° (5.5 mm.) (99% pure, g.l.c. analysis).

When less pure cyclohexene (2.0 moles, 98.6%) was used (see following experiment) the conversion fell to 14% of the adducts. When the amount of cyclohexene (99%) was reduced to 64 g. (0.8 mole), and 64 g. (0.8 mole) of benzene was added, the conversion to adducts was reduced to 15%.

(29) Time-of-flight (t.o.f.) analyses were performed by Dr. D. O. Miller and Dr. F. Kitson, to whom I am indebted for assistance in obtaining and interpreting these data.

(30) E. T. McBee, R. D. Battershell, and H. P. Braendlin, *J. Org. Chem.*, **28**, 1131 (1963).

Crystalline *cis*-1-iodo-2-(perfluoroheptyl)cyclohexane by X-Ray-Induced Reaction.—Cyclohexene (24.6 g., 0.3 mole, 98.6% by g.l.c., containing 1.3% of methylcyclopentene by t.o.f. analysis) and 1-iodoperfluoroheptane (49.6 g., 0.1 mole, containing about 10% of an isomeric iodoperfluoroheptane by g.l.c.) was sealed under nitrogen in a 300-ml. steel tube fitted with a collar device for rotating in front of a gold target impinged upon by an electron beam from a Van de Graf accelerator.[31] After 3.5 hr. at 25° and 30,000 rads/min. dose rate, a sample (nearly colorless) showed about 20% conversion (90% yield) to adducts; after 5.75 hr. at 45,000 rads/min., the reaction mixture was sampled and distilled. There was evidence of decomposition, since white fumes and dark blue liquid was obtained. The recovery of 1-iodoperfluoroheptane was 28 g. (73%), and the yield of isomeric adducts was 23 g. (41% conversion). There was about 4 g. (10%) of $C_7F_{15}H$ formed and isolated as an azeotrope (with cyclohexene) which separated into two layers. The isomeric mixture of adducts partly solidified when cooled to 5° for 1 day. When placed on a cold Hirsch funnel, 0.8 g. of solid *cis* isomer was collected; 18.0 g. of liquid mixture was recovered. Recrystallization from dichloromethane at −70° gave 0.4 g. of *cis* isomer, m.p. (sinter 45°) 46–47° (g.l.c., 95% pure).

Preparative scale g.l.c. of the isomeric mixture gave the solid *cis* and the pure liquid *trans* isomer which distilled at b.p. 74° (0.7 mm.); $n^{25}D$ 1.3933.

G.l.c. Separation of Isomeric Adducts.[32]—The most suitable conditions found for the separation of these sensitive materials by g.l.c. was as follows. A 12-ft. by 0.75-in. column packed with 20% of tricresyl phosphate on "Chromasorb" was heated to 150° while helium at 1550 ml./min. was used as a carrier gas to elute 1-ml. quantities of *trans* and *cis* adducts. The colorless material was transferred to ampoules without appreciable darkening, and kept dark and cold. An attempt to purify the product mixture using similar conditions with a polypropylene glycol column packing satisfactory for analysis failed because the liquid did not elute properly. Properties and analysis of adducts are listed in Table III.

Relative Rate of Reaction of CF_3I and $CF_3CF_2CF_2I$ with Cyclohexene.—Iodotrifluoromethane (3.92 g., 0.02 mole) was weighed in a small brass cylinder, and condensed into a 400-ml. steel shaker tube (with a Hastelloy C liner) in which had been placed 16.4 g. (0.20 mole) of cyclohexene, 5.92 g. (0.02 mole) of 1-iodoperfluoropropane, and 0.33 g. (0.002 mole) of ABN. The tube was heated to 80° for 20 hr. while shaking, cooled to 25°, vented, and the liquid product (23.0 g.) sampled for g.l.c. analysis (1-m. "TCP" column, 125°, 53 ml./min. of helium). The areas of the component peaks were converted to per cent conversion by calculation using the factors obtained from a similar mixture.[33] The products were a mixture of (perfluoroalkyl)cyclohexenes (R_f = CF_3 and C_3F_7-), *ca.* 2.5% conversion (on total R_fI); *trans* isomer C (1.77 g., 23.5%); *trans* isomer E (0.10 g., 1.75% based on CF_3I); *cis* isomer D (1.69 g., 22.3%); *cis* isomer F (0.06 g., 0.85%); TMSN (0.129 g., 47% on ABN); and coupled products (two peaks; *ca.* 2.3% on total R_fI). The disproportionation products were identified by comparison with the previously isolated compounds,[6] and are the sum of the mixture obtained. The ratio of adducts from $CF_3CF_2CF_2I$ to adducts from CF_3I was 17.6; the ratio of E to F was 2.06 and of C to D, 1.05. The efficiency of addition in total moles of adducts was 4.83. For comparison, with CF_3I and cyclohexene alone under similar conditions the efficiency was 2.67; with $CF_3CF_2CF_2I$ and cyclohexene, 7.91.

Distillation of 22.5 g. (94.3% of total) gave CF_3I (collected in the −70° trap, 1.3 g.); $CF_3CF_2CF_2I$ (0.83 g.); cyclohexene (14.0 g.); and a mixture of the two pairs of adducts, b.p. 56–66° (4.5–3.5 mm.); 3.57 g. (theory, 3.61 g.). The residue and hold-up was 0.56 g. G.l.c. analysis showed that the ratio of adducts in the distilled sample was 18.6 to 1 in close agreement with the results given above.

Relative Rate of Addition of $CF_3CF_2CF_2I$ and $(CF_3)_2CFI$ to Cyclohexene. (a) **At 65° with ABN Initiator.**—Cyclohexene (8.21 g., 0.10 mole), 1-iodoperfluoropropane (2.96 g., 0.01 mole), 2-iodoperfluoropropane (2.96 g., 0.01 mole), and ABN (0.164 g., 0.0010 mole) were heated at 65°. The per cent conversions to adducts obtained are plotted as a function of time in Fig. 3. At the conclusion of the experiment the product mixture was a light yellow color. After 11–20 hr. about 2–4% of (perfluoropropyl)cyclohexenes was present in the product mixture.

Precisely the same conditions were used with 1-iodoperfluoropropane or 2-iodoperfluoropropane *alone* in separate experiments. The rate of total product formation is plotted in Fig. 1, 2, and 4. There was no change in the isomer ratio with time in either case. There was no (perfluoropropyl)cyclohexene obtained from reaction of 1-iodoperfluoropropane, but a 2–3% conversion to a (perfluoroisopropyl)cyclohexene mixture occurred with 2-iodoperfluoropropane. A variable amount of R_fH was lost by the sampling technique, and no attempt was made to measure the quantity present.

Over-all reaction rates were also determined in cyclohexane solution. Cyclohexane (Spectro Grade, 5.89 g., 0.070 mole), 2-iodoperfluoropropane (2.96 g., 0.01 mole), cyclohexene (0.82 g., 0.01 mole), and ABN (0.082 g., 0.0005 mole) was heated at 65°, samples taken, and analyzed. The conversion to adducts attained 10.5% of A and 4.5% of B after 17 or 23 hr. For the same reaction time 9.0 % conversion [on $(CF_3)_2$ CFI] to iodocyclohexane was obtained and about 1% of (perfluoroisopropyl)cyclohexenes. The solution was slightly yellow and the crystalline hydriodide salt was formed.

1-Iodoperfluoropropane under these conditions gave a 15% conversion to C and D in 17 hr., 17% conversion in 24 hr., and 18.4% conversion in 29 hr. The (perfluoropropyl)cyclohexenes were formed after 21-hr. reaction time (about 1% conversion).

2-Iodoperfluoropropane, cyclohexane, and ABN (same amounts as before; no cyclohexene) gave iodocyclohexane as follows: 1 hr., 4.45% conversion [on $(CF_3)_2CFI$]; 2 hr., 6.73%; 3 hr., 9.79%; 4 hr., 12.0%; 5 hr., 16.0% (or 0.0013 mole). The amount of ABN decomposed during this time (half-life, 4 hr. at 74°) was *ca.* 0.00025 mole; therefore, about 6 moles of iodocyclohexane was produced for each mole of ABN decomposed.

(b) **At 130° with Di-*t*-butyl Peroxide Initiator.**—1-Iodoperfluoropropane (40 g., 0.135 mole), 2-iodoperfluoropropane (21.0 g., 0.71 mole), cyclohexene (not treated with alumina, 164 g. 2.00 moles), and di-*t*-butyl peroxide (6.0 g., 0.04 mole) were heated in a Hastelloy C-lined shaker tube at 130° for 15 hr. The ratio of adducts was ascertained before and after work up by g.l.c. analysis. The recovered iodoperfluoroalkane cuts (16.0 g.) contained a large number of components. The distilled *cis* and *trans* adducts (30.8 g., 40% total conversion) comprised: A, 33.2% conversion and B, 15.5% [from $(CF_3)_2CFI$]; and C, 21.3% and D, 18% conversion (from $CF_3CF_2CF_2I$). The ratio of adducts (A + B/C + D) was 0.653, whereas the ratio of reactants was 0.526; hence, the rate of adduct formation from 2-iodoperfluoropropane was 1.24 times greater. Because of the large number of volatile products obtained no estimate of the ratio of abstraction to addition could be made.

Azonitrile-Induced Isomerization and Disproportionation of A.—A mixture of 0.1951 g. (0.000516 mole) of A, 4.1 g. (0.0050 mole) of cyclohexene, and ABN (0.0827 g., 0.000504 mole) was heated in a bath at 71°. The relative amounts were estimated from the areas in comparison with cyclohexene. Initially only A (4.45% by weight) and cyclohexene (95.4% by weight) were present. After 1 hr. the composition was cyclohexene (93%), 1- and 3-(perfluoroisopropyl)1-cyclohexene[6] mixture (0.5%), A (2.8%), B (1.3%), TMSN (0.5%), and "coupled" product[6] (0.5%). After 3, 5, 10, or 22 hr., the composition was cyclohexene (95%), olefin mixture (0.5%), A (3.0%), TMSN, and "coupled" product (2.5%).

Relative Rates of Addition and Abstraction of $CF_3CF_2CF_2I$ or of $(CF_3)_2CFI$ with 1-Heptene.—1-Perfluoropropyl-2-iodoheptane (H) was prepared from 1-heptene (4.0 g., 0.04 mole), 1-iodoperfluoropropane (6.0 g., 0.02 mole), and ABN (0.03 g., 0.0002 mole) kept at 65° for 6 hr. in a 10-ml. steel cylinder, which was evacuated to 0.5 mm. at −70°. The liquid was sampled at −70° for g.l.c. analysis (2-m. "R" column; 150°; 15 p.s.i. of helium pressure) and distilled in column B, b.p. 86° (10 mm.); $n^{25}D$ 1.4072, $d^{25}D$ 1.5608; 6.5 g. (84% recovery). Moles of $H/CF_3CF_2CF_2H$ from area ratio × weight/area factor (1.2 for both substances) was 104/1. There was only 0.0022% of $CF_3CF_2CF_2I$ unreacted. A 99% yield of H was shown by g.l.c. analysis. Retention time was 19.4 min.

Anal. Calcd. for $C_{10}H_{14}F_7I$: C, 30.4; F, 33.7; H, 3.56; I, 32.2. Found: C, 30.5; F, 33.6; H, 3.8; I, 31.9.

1-Isoperfluoropropyl-2-iodo-heptane (G) was prepared under the conditions used previously, and also in cyclohexane solution.

(31) The technique and equipment was that used by Dr. F. W. Stacey, to whom I am indebted for assistance.

(32) I am indebted to J. B. Robson for assistance.

(33) The weight/area factors for the product mixture were very similar to those given for adducts A to D in similar mixtures.

No further reaction occurred after 1 hr. at 65°, and all the 2-iodoperfluoropropane was used up (g.l.c. analysis of samples). Distillation in column B gave G, b.p. 78° (10 mm.); $n^{25}D$ 1.4075; 7.1 g. (90% recovery). Retention time was 14.6 min. Moles G/$(CF_3)_2CHF$ was 192; yield of G was better than 99%.

1-Heptene (1.95 g., 0.02 mole), 2-iodoperfluoropropane (11.4 g., 0.038 mole), and ABN (0.03 g., 0.0002 mole) under these conditions gave by distillation, G (6.8 g., 86% recovery), and $(CF_3)_2$-CFI (5.4 g.). G.l.c. analysis showed that $(CF_3)_2CFH$ (0.12 g., 2.1% conversion), G (99% conversion), and no 1-heptene were present. Moles of G/$(CF_3)_2CFH$ was 33.5.

Anal. Calcd. for $C_{10}H_{14}F_7I$: C, 30.5; F, 33.7; H, 3.56; I, 32.2. Found: C, 30.4; F, 33.3; H, 3.8; I, 31.9.

2-*endo*-Iodo-3-*exo*-trifluoromethylnorbornane (J) and 2,2′-Bis-(3-iodo-3′-Trifluoromethylnorbornyl).—Iodotrifluoromethane (9.8 g., 0.05 mole), norbornene (9.0 g., 0.1 mole), and ABN (1.0 g., 0.0061 mole) were kept at 80° for 15 hr. while shaking. Fractionation gave norbornene (1.65 g.), J [b.p. 87° (20 mm.) or 72° (6.0 mm.); $n^{25}D$ 1.4851; 10.2 g. (60%)], and 2,2′-bis(3-iodo-3′-trifluoromethylnorbornyl) [b.p. 106° (0.3 mm.); $n^{25}D$ 1.5238; 4.2 g. (22%)]. G.l.c. analysis showed that J contained about 5% of TMSN. The liquid was twice cooled to 5°, filtered from solid TMSN and passed over activated alumina. TMSN was reduced to 1.6%, but was not completely removed (high carbon analysis).

Anal. Calcd. for $C_8H_{10}F_3I$: C, 33.12; H, 3.47; F, 19.65; I, 43.75. Found: C, 33.8; H, 3.5; F, 19.8; I, 42.7.

Anal. Calcd. for $C_{15}H_{20}F_3I$: C, 46.9; H, 5.24; I, 33.0; mol. wt., 384.2. Found: C, 46.9; H, 5.1; I, 33.8; mol. wt. (ebullioscopic in acetone), 365.

1-Trifluoromethyl-2-iodoheptane (K) and 1-Trifluoromethyl-4-iodo-8-pentylnonane.—CF_3I (9.8 g., 0.05 mole), 1-heptene (10.0 g., 0.1 mole), and ABN (1.0 g., 0.0061 mole) were kept at 80° while shaking for 15 hr. Distillation in column B gave K, b.p. 72° (10 mm.); $n^{25}D$ 1.4398 (9.0 g., 68% yield) and CF_3CH_2-$CH[(CH_2)_4CH_3]CH_2CHI(CH_2)_4CH_3$, b.p. 94–96° (0.25 mm.); $n^{25}D$ 1.4597 (4.90 g., 25% yield). G.l.c. analysis of K showed that 5% of an isomeric substance was present. TMSN was removed by filtration and chromatography on alumina. The 2 to 1 telomer was redistilled in a sublimer cup, b.p. 80° (0.15 mm.).

Anal. Calcd. for $C_8H_{14}F_3I$: C, 32.7; H, 4.8; F, 19.4; I, 43.1. Found: C, 32.7; H, 4.8; F, 19.7; I, 42.6.

Anal. Calcd. for $C_{17}H_{28}F_3I$: C, 45.9; H, 7.2; F, 14.5; I, 32.3. Found: C, 46.1; H, 7.0; F, 13.9; I, 32.4.

Relative Rates of Reaction of Cyclohexene and 1-Heptene and of Norbornene and 1-Heptene with 1-Iodoperfluoropropane.—1-Heptene (1.04 g., 10.6 mmoles), cyclohexene (1.00 g., 12.3 mmoles), 1-iodoperfluoropropane (3.06 g., 10.3 mmoles), and AVN[9] (0.025 g., 0.1 mmole) were divided among 6 tubes sealed *in vacuo* at −70° and heated at 70 ± 1° in an oil bath for the period indicated. The amount of reaction was determined by g.l.c. analysis having previously obtained the characteristic retention times and weight/area factors. Less than 30% of the $CF_3CF_2CF_2I$ was used up in 4 hr. The ratio of H to C and D taken from the areas under the curves were at the times given: 0.25 hr., 14.0; 1.0 hr., 11.5; 2 hr., 10.1; 3 hr., 8.5. The ratios reflect the changing reactant composition, and the low over-all conversion the retarding effect of the cyclic olefin and its adducts on the radical-induced addition.

1-Heptene (0.98 g., 10.0 mmoles), norbornene (0.94 g., 10.0 mmoles), 1-iodoperfluoropropane (3.32 g., 11.2 mmoles), and AVN[9] (0.025 g., 0.1 mmole) were used as before. Almost complete reaction of 1-iodoperfluoropropane resulted. The ratio of H to the norbornene adduct[1] L taken from the areas under the curves were as follows: 0.25 hr., 0.98; 0.5 hr., 1.05; 1.0 hr., 1.05; 2 hr., 1.15; 3.0 hr., 1.10. Very little discriminaton between olefins was observed and no retardation of addition.

1-Iodoperfluoropropane and Cyclopentadiene.—1-Iodoperfluoropropane (29.6 g., 0.1 mole) and freshly distilled cyclopentadiene (6.6 g., 0.1 mole), kept at −70° (obtained by thermal cracking of cyclopentadiene dimer), and ABN (0.2 g., 0.0008 mole) were heated to reflux under nitrogen in a flask fitted with a −70° reflux condenser in an oil bath at 73–76° for 20 hr. (inside temperature 64–70°). The mixture turned green in color. G.l.c. analysis showed that none of the 1-iodoperfluoropropane was used up, but that about one-half of the cyclopentadiene was gone. Distillation gave 4.5 g. of viscous oil residue, but no volatile adducts.

1-Iodoperfluoropropane (35.2 g., 0.12 mole), cyclopentadiene (1.0 g., 0.015 mole), 1-heptene (10.0 g., 0.1 mole), and ABN (0.2 g., 0.0008 mole) were heated as before for 8 hr. at reflux temperature (52–53°). G. l.c. analysis showed that very little reaction had occurred. Distillation gave 27.4 g. of unchanged 1-iodoperfluoropropane and 8.2 g. of 1-heptene. There was a residue of 2.8 g. Without cyclopentadiene, these reactants gave in 4 hr. an 84% conversion to H.

***trans*-1-Iodo-2-(perfluorobutyl)cyclopentane (M).**—1-Iodoperfluorobutane (52.0 g., 0.15 mole), cyclopentene (34 g., 0.47 mole) and ABN (1.64 g., 0.01 mole) sealed in a heavy wall Pyrex glass tube *in vacuo* were heated at 75–82° for 7.5 hr. The red liquid (80.3 g.) was fractionated in column B. Cyclopentene and 1-iodoperfluorobutane codistilled, b.p. 36–39°; $n^{25}D$ 1.3929; 48.5 g. An intermediate cut, b.p. 54–82° (20 mm.), $n^{25}D$ 1.4030, 1.3 g., and (M), b.p. 86–88° (21 mm.), $n^{25}D$ 1.4045, 21.9 g. (38% conversion; about 75% yield on R_fI) distilled, leaving a hold-up of 0.95 g. and a residue of 1.1 g. The −70° trap contained 12.2 g. of 1-iodoperfluorobutane (total recovered, 24.6 g. from g.l.c. analysis). The product fractions were filtered from TMSN at 5° and redistilled. G.l.c. analysis (using a 2-m. "R" column; 150°; 27 ml./min. of helium) showed one substance (99.2%) at a retention time of 10.5 min. The ultraviolet spectrum in CH_3OH gave λ_{max} at 263 mμ (ε 461.2).

Anal. Calcd. for $C_9F_9H_8I$: C, 26.1; H, 1.95; I, 30.65. Found: C, 26.2; H, 2.0; I, 30.3.

The recovered mixture (48.3 g.) containing 13.6 g. (0.04 mole) of 1-iodoperfluorobutane and 35.3 g. (0.52 mole) of cyclopentene was placed in a heavy wall Pyrex glass tube as before. After a 31-hr. exposure to direct sunlight in August (ambient temperatures to 35°), the liquid (44.5 g.) was removed from a dark, solid deposit, filtered through activated carbon, and distilled. A mixture of cyclopentene and 1-iodoperfluorobutane (b.p. 41–45°; $n^{25}D$ 1.4013; 21.7 g.) and dark colored liquid M, b.p. 60–65° (10 to 5 mm.), 11.2 g. (42% conversion), was obtained. Decomposition of material in the pot flask was observed. The trap liquid (8.0 g.) was mostly 1-iodoperfluorobutane.

1-(Perfluorobutyl)-1-cyclopentene (N) and 3-(Perfluorobutyl)-1-cyclopentene (O).—M (5.0 g., 0.012 mole) and tri-*n*-butylamine (3.7 g., 0.020 mole) were heated in column B for 1 hr. at 150°, and then to 200° while taking off distillate, b.p. 126–130°; $n^{25}D$ 1.3401; 2.97 g. The column hold-up (0.60 g.) was pulled over by reducing the pressure. After washing with 10% hydrochloric acid and drying over magnesium sulfate the mixture of N and O (3.24 g., 94%) distilled, b.p. 124–126°; $n^{25}D$ 1.3386. An infrared spectrum showed a vinyl stretching band at 3.22 μ and bands at 6.10 and 10.05 μ.

Anal. Calcd. for $C_9H_7F_9$: C, 37.8; H, 2.5; F, 59.8. Found: C, 37.8; H, 2.4; F, 60.2.

G.l.c. analysis (using a 2-m. bis-2-methoxyethyl phthalate (20%) on 60–80 mesh "Chromasorb" column at 65°; 46 ml./min. of helium) showed two substances were present; 16.1% at 12.1 min. retention time and 83.3% at 14.65 min.

The proton n.m.r. spectrum, taken with a Varian Associates A-60 spectrometer at 60 Mc. with tetramethylsilane internal reference, gave vinyl proton resonances for two different olefins. There was a distorted three-line resonance of one vinyl proton (0.18 proton area) centered at −380 c.p.s., two vinyl proton resonances at −358 and −343 c.p.s. (0.79 and 0.70 proton area) and a broad proton resonance band of the H—C—R_f at −240 to −180 c.p.s. (0.88 proton area). The vinyl proton resonance of the Δ^1 olefin was also at lower field than the two vinyl proton resonances for the Δ^2 olefin in the related Δ^1 and Δ^2-(perfluoropropyl)cyclohexene isomers.[6]

Some Chemical Transformations and Conformations in the Cycloheptadecanone Series[1]

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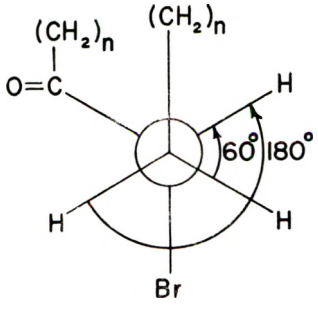
Received May 8, 1963

Cycloheptadec-9-en-1-one (I) was converted to cycloheptadeca-1,9-dione (VI) and to 2-bromocycloheptadeca-1,10-dione (VIII). Dehydrobromination of the latter which was shown to have a quasi-axial conformation yielded a mixture of α,β- and β,γ-unsaturated diketones IX and X. The double bond was found to be *trans* in both IX and X while infrared data indicated that IX existed as an *S-cis, S-trans* mixture.

As part of an investigation of the conformation of large-ring unsaturated ketones we have studied the dehydrobromination of 2-bromocycloheptadeca-1,10-dione (VIII). Synthesis of this substance was effected by a straight-forward route (Chart I) involving the addition of hypobromous acid to civetone[2] (cycloheptadec-9-en-1-one)(I) followed by chromic acid oxidation of the intermediate bromohydrin (VII). The requisite bromo diketone VIII, which was obtained as an oil solidifying only below room temperature, was homogeneous on thin-layer chromatography (silica gel) and gave the proper elemental analysis, while its infrared spectrum (Table I) indicated a C—Br/C=O angle of about 90° (quasi-axial conformation)[3] in accord with the findings of Leonard and Owens[4] in 2-bromocycloalkanones containing 11–15 carbon atoms. The least strained conformation of VIII about C-1,2,3 would appear to be one with dihedral angles of 60° and 180° (pictured in Newman projection) which places the bromine atom and the polymethylene groups attached to the C-3 carbon at maximum distance from each other.



Dehydrobromination of the bromo ketone (VIII) with powdered calcium carbonate in boiling dimethylformamide yielded, in a number of runs, ratios of about 3:2 to 3:1 of the α,β-unsaturated ketone IX and an accompanying by-product which was shown to be the β,γ-unsaturated ketone X, as well as significant quantities of more polar materials which were not investigated further. The two unsaturated ketones, obtained as oils, were readily separable by thin-layer chromatography with the β,γ-isomer being the faster moving substance.

The α,β-unsaturated ketone IX gave a satisfactory elemental analysis and exhibited the anticipated mass number 264 as the principal molecular ion in the mass spectrum,[5] while catalytic reduction resulted in the uptake of just one mole of hydrogen with the formation of cycloheptane-1,9-dione (VI) in high yield. In the ultraviolet spectrum, determined in ethanol solution, a maximum appeared at 227 mμ (ε 13,800) which was shifted to 220 mμ in isooctane (ε 12,050). A bis-semicarbazone was obtained with λ_{max} 230 mμ (ε 24,400) and 263 mμ (ε 22,500), the higher wave-length maximum being due to the α,β-unsaturated semicarbazone moiety[6] while the 230-mμ maximum is clearly due to the saturated semicarbazone group.[6,7] The infrared spectrum of IX (Fig. 1), which was determined in carbon tetrachloride solution, showed a strong carbonyl band at

TABLE I

INFRARED SPECTRA OF CYCLOHEPTADECANE DERIVATIVES[a]

Substituent	C=O	H | C=C | H	$-CH_2-$	$CH_2-C=O$	$-(CH_2)_n-$
1-Keto	1715		1458, 1442 (sh)[b]	1407	728
1-Keto-Δ^9 (I)	1710	972	1463, 1442	1417	722
1-Keto-9-Br-10-OH (VII)	1712		1457, 1445	1410	725
1,9-Diketo (VI)	1712		1460, 1442	1410	722
2-Br-1,10-diketo (VIII)	1714, 1711		1460, 1440	1410	725
Δ^2-1,10-Diketo (IX)	1710, 1692, 1667	1625, 985	1465, 1445	1412	725
Δ^3-1,10-Diketo (X)	1712	973	1463, 1440	1410	725

[a] Determined as a liquid film and reported as cm.$^{-1}$. Estimated accuracy of readings ±2 cm.$^{-1}$. [b] Poorly resolved in 1430–1450-cm.$^{-1}$ region. Ref. 13 reports bands at 1450 and 1438 cm.$^{-1}$ in carbon tetrachloride.

(1) Supported in part by Grant T-185, American Cancer Society.

(2) Purchased from the Firmenich Co., Geneva, Switzerland, and stated by the manufacturer to consist of a mixture of *cis* and *trans* isomers in a 1:2 ratio.

(3) In liquid film and in carbon tetrachloride a split carbonyl peak with maxima at 1711 and 1714 cm.$^{-1}$ was observed, the higher frequency peak being assigned to the α-bromo ketone group. This small shift denotes that the C–Br bond possesses little if any *syn*-skew character (see ref. 4).

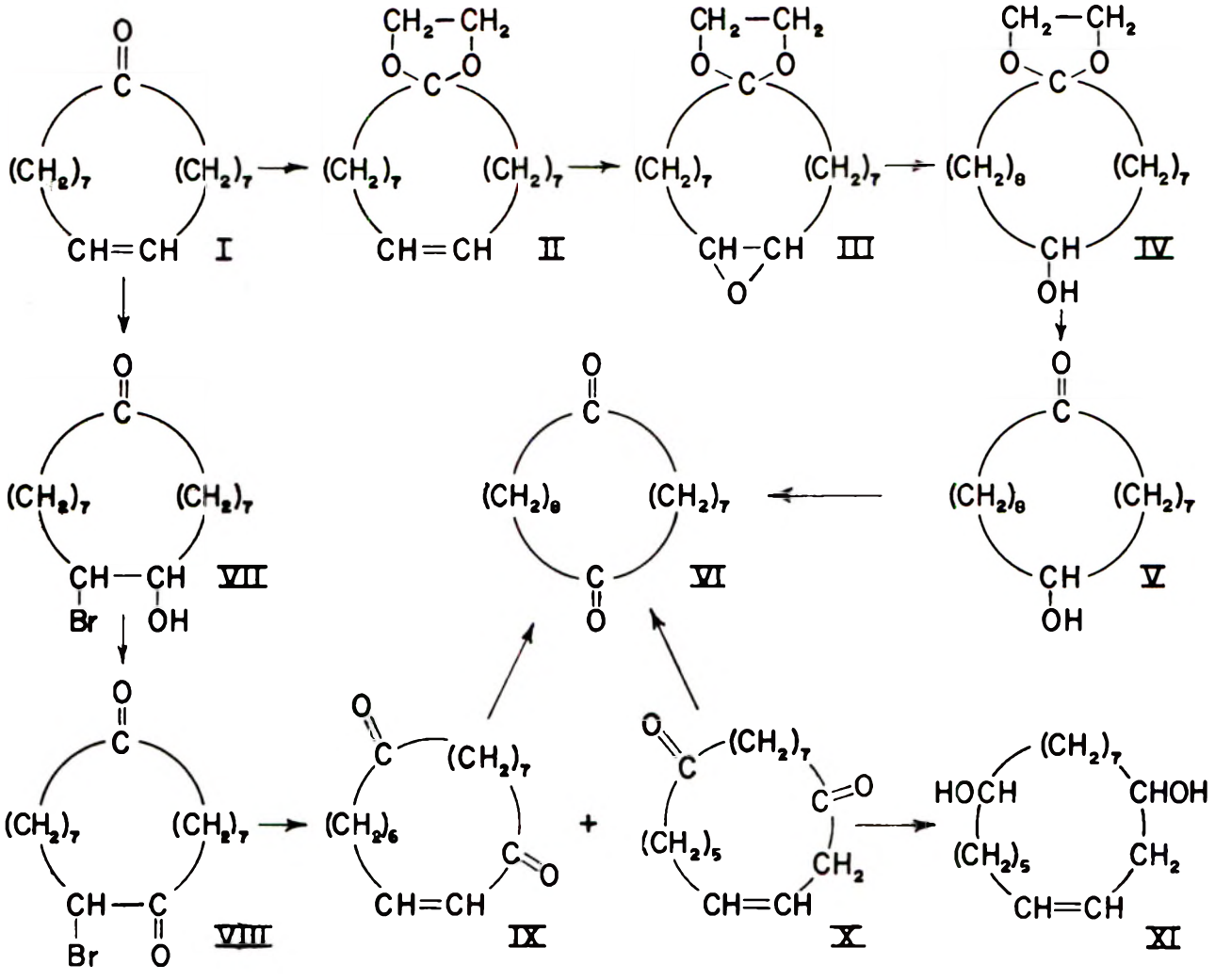
(4) N. J. Leonard and F. H. Owens, *J. Am. Chem. Soc.*, **80**, 6039 (1958).

(5) We are grateful to Dr. H. Budzikiewicz and Prof. Carl Djerassi, Stanford University, for the mass spectrometric analyses.

(6) L. Dorfman, *Chem. Rev.*, **53**, 85 (1953).

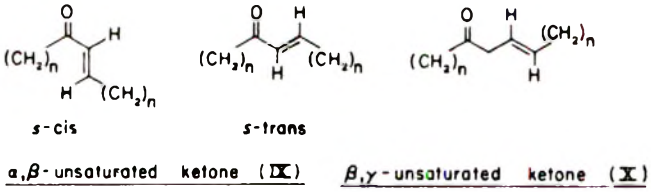
(7) The abnormally high ε at 230 mμ, instead of the expected[6] 13,000–14,000, may be attributed to the contribution of the unsaturated semicarbazone at that wave length. Testosterone semicarbazone, for example, (λ_{max} 270 mμ, ε 22,700) exhibits an ε-value of 7,200 at 230 mμ.

CHART I



1714 (saturated ketone), a considerably weaker band at 1670 (unsaturated ketone), an intense band at 1624 of about one-half the area of the 1670 band (C=C stretching), and a strong band at 987 cm.$^{-1}$ characteristic of a *trans* double bond. Neither in film nor in carbon disulfide was a band characteristic of a *cis* olefin found, which is in accord with the finding of Leonard and Owens[4] that in rings of greater than ten carbon atoms the *trans* olefin is greatly favored over the *cis* compound.

In the carbonyl region, apart from the bands described, a weaker but definite band appeared at 1695 (CCl_4 $CHCl_3$), 1693 (film), and 1692 cm.$^{-1}$ (CS_2). This band does not appear to be due to an impurity since all samples of IX as well as a sample of the monoketone cycloheptadec-2-en-1-one exhibited a peak at this position. It is probable that IX exists as a mixture of *S-cis* and *S-trans* isomers and the peak at 1695 cm.$^{-1}$ is due to the *S-cis* conformation while the 1670 cm.$^{-1}$ band may be assigned to the *S-trans* unsaturated ketone. These two conformations are



s-cis *s*-trans

α,β-unsaturated ketone (IX) β,γ-unsaturated ketone (X)

The propensity of *S-cis* unsaturated ketones to rearrange to the β,γ-unsaturated isomers has been noted by Noack and Jones[8] and would account for the presence of significant quantities of X in the crude dehydrobromination mixture. However, it must be noted that the extinction coefficient of IX in the ultraviolet (ε 13,800) is unusually high[9] if a significant portion of compound is present in an *S-cis* configuration. Additional support for the presence of *S-cis* isomer comes from the pronounced intensity of the C=C stretching frequency band at 1624 cm.$^{-1}$ in the infrared, which is consistent[10] for an *S-cis* and not for an *S-trans* ketone. The C=C stretching frequency band for the *S-trans* compound may be concealed beneath this 1624 cm.$^{-1}$ band, or a shoulder appearing at about 1640 cm.$^{-1}$ may be due to the *S-trans* compound. The possibility cannot be excluded, however, that the 1695-cm.$^{-1}$ peak is not, in fact, a carbonyl band and is instead a combination band or a Fermi resonance band due to the absorption at 987 and 725 cm.$^{-1}$.[11]

The principal features of interest in the n.m.r. spec-

(8) K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

(9) The extinction coefficient of *S-cis* α,β-unsaturated ketones is reported to range between 4700–7200; R. B. Turner, D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951), and references therein.

(10) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960); K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2201 (1961).

(11) The broad band appearing at 725 cm.$^{-1}$ was also found in cycloheptadecanone and in cycloheptadecane-1,9-dione and may be attributed to a rocking mode of the $(CH_2)_n$ groups.

trum of IX (Fig. 2) were the vinylic proton peaks, the C-2 proton appearing as a doublet at 357 and 372.5 c.p.s., while the C-3 proton appeared as a sextet spaced between 393 and 422.5 c.p.s.[12] The coupling constant of the doublet, J = 15.5 c.p.s., is the order that would be expected for a pair of *trans* protons.

The β,γ-unsaturated diketone X, which had no strong selective absorption in the ultraviolet, exhibited in the infrared a single intense carbonyl band at 1718 cm.$^{-1}$ (CCl_4) and a band at 971 cm.$^{-1}$ characteristic of a *trans* olefin (Fig. 1). As in the case of IX no evidence was found for the presence of a *cis* olefin. Both the α,β- and β,γ-isomers showed a band at 1410 cm.$^{-1}$ due to the methylene groups adjacent to the carbonyl functions[13] with the more pronounced peak being present in the spectrum of X. Although a satisfactory elemental analysis could not be obtained for X, a crystalline bissemicarbazone with correct analysis was prepared. The derivative had only a single maximum at 229 mμ (ϵ 20,800) which demonstrated that the double bond had not conjugated. Catalytic reduction of X gave an almost quantitative yield of cycloheptadeca-1,9-dione which established that no skeletal rearrangement had occurred during dehydrobromination and left the β,γ-structure as the only reasonable one. The n.m.r. spectrum (Fig. 3), which was confirmatory for this structure, exhibited the olefinic protons as a series of at least six lines centered at 313 c.p.s. with the outer peaks separated by 10 c.p.s. The doubly activated methylenic protons appeared as a doublet (containing additional unresolved fine structure) at 171 and 176 c.p.s. while broad absorption centered at 137.5 c.p.s. is attributed to the balance of methylene groups adjacent to the carbonyl functions. Base-catalyzed exchange carried out in methanol-d_4 supported these assignments since the peaks in the 171–176-c.p.s. region disappeared the most rapidly, as would be expected for the doubly activated methylene position, followed then by diminution of absorption in the 137 c.p.s. region. The deuterated material was reisolated after sixteen hours of deuterium exchange and showed, in the infrared, complete disappearance of the aforementioned α-methylene absorption at 1410 cm.$^{-1}$ and appearance of the anticipated C–D bands in the 2000–2200-cm.$^{-1}$ region. The β,γ-isomer X is schematically depicted with no conformational implications since it is not known whether or not the carbonyl and double bond are coplanar.

The mass spectrum[5] of X was anomolous. In two different analyses the compound demonstrated a molecular ion peak at the anticipated position of mass 264, but the major peak appeared at mass 250 in one run and at 262 in the second run. Since in each case the samples were stored in glass for approximately one month prior to the mass spectral determination it is not known whether chemical modification occurred on storage or if the differences are due to some variation in analytical procedure. For additional mass spectral investigation, X was reduced with lithium aluminum hydride to the unsaturated diol XI which exhibited

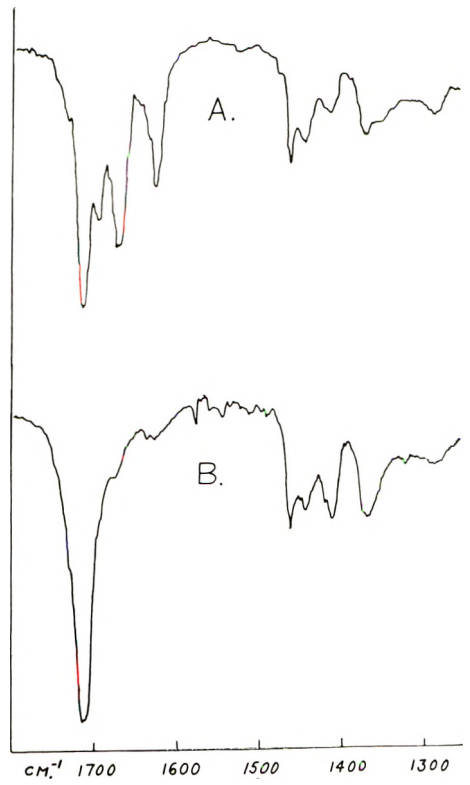


Fig. 1.—The infrared spectrum of A, cycloheptadec-2-ene-1,10-dione (IX); and B, cycloheptadec-3-ene-1,10-dione (X) determined in carbon tetrachloride.

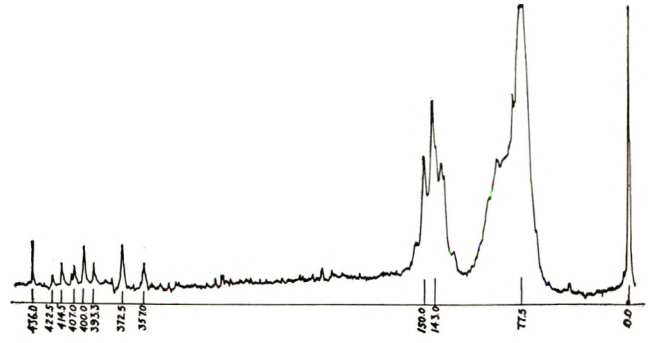


Fig. 2.—N.m.r. spectrum[12] of cycloheptadec-2-ene-1,10-dione (IX) determined in deuteriochloroform (c.p.s.).

a principal mass peak at 250. The loss of mass 18 is almost certainly due to the elimination of water, a behavior not unexpected for a β,γ-unsaturated alcohol.

The partial conversion of IX to X was readily demonstrable by treating the α,β-unsaturated ketone with calcium carbonate in dimethylformamide or by stirring an ether or benzene solution of the substance with alkaline alumina. The α,β-unsaturated ketone remained the predominant isomer in each case but because of low recovery due to the formation of polar by-products it is not possible to state whether or not this is a reflection of the true stability of the two isomers. It was also possible to effect the partial conversion of the β,γ-unsaturated to the α,β-unsaturated isomer under identical conditions but with extremely low product recovery.

It would appear to be pertinent to comment on the structure of the large-ring α,β-unsaturated monoketones (C_{19} to C_{14}) which have been reported[4] to exhibit unusually low ϵ-values in the ultraviolet and whose infrared spectra indicate the presence of both satu-

(12) We wish to thank Mr. Thomas Wittstruck for the n.m.r. determinations which were carried out in deuteriochloroform solution with tetramethylsilane as internal standard, utilizing a Varian 4302 60 Mc./sec. spectrometer. Peak positions are reported in c.p.s. downfield from the standard.

(13) G. Chiurdoglu, Th. Doehard, and B. Tursch, *Bull. soc. chim. France*, 1322 (1960).

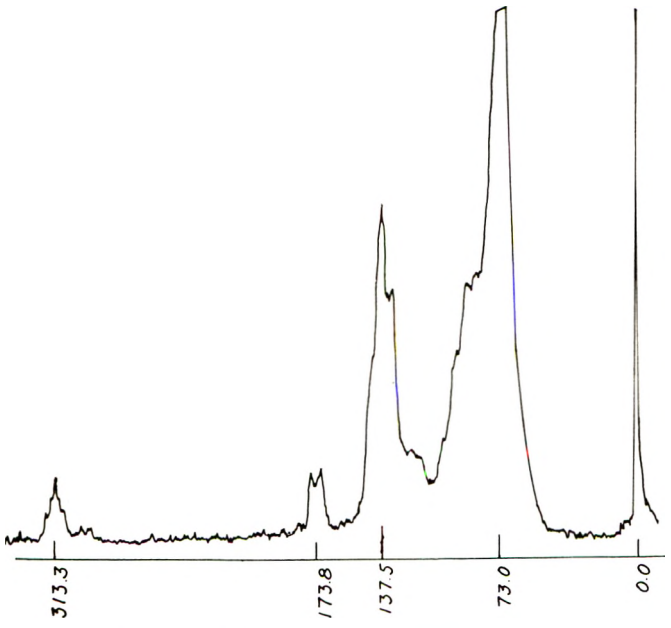


Fig. 3.—N.m.r. spectrum[12] of cycloheptadec-3-ene-1,10-dione (X) determined in deuteriochloroform (c.p.s.).

rated and unsaturated carbonyl functions, while semicarbazones derived from these substances possess ultraviolet spectral maxima characteristic of saturated rather than unsaturated carbonyl derivatives. These results, which have been explained[4] on the basis of steric inhibition of resonance, are probably due to a preponderance of β,γ-unsaturated isomer in the unsaturated ketone mixture.

The synthesis of cycloheptadeca-1,9-dione (VI) and an unsuccessful attempt to prepare the requisite bromo diketone VIII *via* this compound are also briefly documented (Chart I). Civetone (I) was converted by conventional means to the cycloethylene ketal[14] II which on treatment with monoperphthalic acid gave the 9,10-oxido ketal III. Reduction of III with lithium aluminum hydride in ether solution produced the hydroxyketal IV, and acid hydrolysis of the ketal moiety yielded the ketol V as a *d,l*-pair. It should be noted that attack of hydride on the oxide at either C-9 or C-10 yields the same compound. Chromic acid oxidation of the ketol gave cycloheptadecane-1,9-dione (VI) as a crystalline solid.[15] Attempts to monobrominate VI led invariably to polyhalogenated substances.

Experimental[16]

1-Ethylenedioxycycloheptadec-9-ene (II).—A sample of civetone[3] (I) (10.0 g.) was dissolved in benzene (200 ml.) containing ethylene glycol (20.0 ml.) and *p*-toluenesulfonic acid (200 mg.), and the solution was boiled for 20 hr. with continuous separation of water. The cooled solution, after washing with dilute bicarbonate and water, was taken to dryness, leaving a crystalline residue of II, m.p. 36–41°[17]; yield, 12.0 g.; no carbonyl absorption in the infrared.

1-Ethylendioxy-9-hydroxycycloheptadecane (IV).—The ketal from the foregoing procedure (11.9 g.) in ether (100 ml.) at 0° was treated with a cold solution of monoperphthalic acid (2 equiv.) in ether (300 ml.), and the mixture was stored in a refrigerator for 25 hr. Titration indicated the uptake of 1 equiv. of peracid. The solution was washed with sodium bicarbonate solution, then water, and dried over sodium sulfate. Evaporation gave 1-ethylenedioxy-9,10-oxidocycloheptadecane (III) (12.5 g.) as an oil solidifying below room temperature. Without purification, III was taken up in dry ether (100 ml.) and added to a suspension of lithium aluminum hydride (5.0 g.) in ether (200 ml.). The mixture was boiled for 7 hr. and then allowed to stand for 16 hr. at room temperature. Saturated sodium sulfate solution was cautiously added dropwise until solid adhered to the sides of the reaction vessel, and then solid sodium sulfate was added. The ether solution was decanted, the residue was thoroughly washed with ether, and the combined solutions were evaporated yielding 11.5 g. of IV, m.p. 50–52°. An analytical sample was obtained by recrystallization from pentane, m.p. 51–52°.

Anal. Calcd. for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.30; H, 11.71.

9-Hydroxycycloheptadecanone (V).—The hydroxyketal IV (2.0 g.) was allowed to stand in a mixture of acetone (30 ml.), water (2.0 ml.), and 10% hydrochloric acid (1.0 ml.) for 5 hr. at room temperature. Dilution with water and ether extraction gave V, 1.28 g., m.p. 76–77°. The melting point was unchanged on further crystallization from pentane.

Anal. Calcd. for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.20; H, 12.12.

Cycloheptadecane-1,9-dione (VI).—A solution of V (0.2 g.) in 5 ml. of acetone (previously distilled from potassium permanganate) was cooled in an ice bath and treated dropwise with Jones' reagent[18] (8 *N* chromic acid in sulfuric acid) until the color of the reagent persisted. The mixture was allowed to stand at 0° for 5 min. before the addition of water and isolation of product by ether extraction; yield, 0.18 g., m.p. 62–64°. Crystallization from aqueous acetone gave the analytical sample of VI, m.p. 63–65°.[15] The infrared bands of interest are listed in Table I (see p. 3103).

Anal. Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.46; H, 11.37.

9-Bromo-10-hydroxycycloheptadecanone (VII).—Civetone (0.25 g.) was dissolved in a mixture of purified dioxane (3.0 ml.) and dilute perchloric acid (0.4 ml., 0.5 *N*). N-Bromoacetamide (0.18 g.) was added in one portion, and the resulting clear solution was left for 1.5 hr. at room temperature. The excess N-bromo reagent was destroyed by the addition of dilute sodium bisulfite and the product isolated by ether extraction. The extract was washed with water, dried over sodium sulfate, and evaporated leaving the bromohydrin (VII) as a colorless oil; yield, 0.3 g. The analytical sample, obtained as an oil, was prepared by chromatography on a silica gel thin-layer plate utilizing 97% benzene–3% ethyl acetate as solvent. Apart from the infrared bands listed in Table I, hydroxyl absorption was seen at 3540 cm.$^{-1}$ (film).

Anal. Calcd. for $C_{17}H_{31}BrO_2$: C, 58.79; H, 9.00. Found: C, 59.01; H, 8.82.

2-Bromocycloheptadeca-1,10-dione (VIII).—Crude bromohydrin (VII) (0.3 g.) was dissolved in acetone (15 ml.) and treated with 0.8 ml. of Jones' reagent.[18] After 5-min. reaction at room temperature a few drops of methanol were added to destroy the excess chromic acid, and the mixture was diluted with water. The bromo diketone was extracted with ether, and the extract was washed, dried, and evaporated *in vacuo*, leaving 0.24 g. of VIII as an oil which crystallized only upon cooling below room temperature. The material was essentially homogeneous on thin-layer chromatography with 97% benzene–3% ethyl acetate as solvent. An analytical specimen was obtained as an oil by column chromatography on silica gel with benzene as the eluting solvent: ultraviolet, $\lambda_{max}^{CH_3OH}$ 299 mμ; infrared, see Table I; n.m.r., quartet centered at 243 c.p.s.[12] due to coupling of the C-2 proton with the two protons at C-3. A first-order analysis indicates coupling constants of J = 8.7 and 6.2 c.p.s.

Anal. Calcd. for $C_{17}H_{29}BrO_2$: C, 59.13; H, 8.47. Found: C, 59.38; H, 8.61.

Cycloheptadec-2-ene-1,10-dione (IX).—The bromo diketone VIII (0.3 g.) was heated for 6 hr. in a boiling, stirred mixture of finely powdered calcium carbonate (0.4 g.) and dimethylformamide (10 ml.). The cooled mixture was filtered and, after the

(14) M. Stoll, J. Hulstkamp, and A. Rouve, *Helv. Chim. Acta*, **31**, 543 (1948).

(15) M. Stoll, M. Hinder, and L. Ruzicka, *ibid.*, **31**, 1176 (1948), reported VI as a liquid.

(16) Melting points are uncorrected. We are very grateful to Mr. Neville Bacon for infrared determinations which were carried out on a Beckman IR-7 with Bausch and Lomb replica grating.

(17) Lit.[14] m.p. of *cis* isomer, 19–21°; *trans* isomer, 49–50°.

(18) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

addition of water to the filtrate, the dehydrobromination products were extracted with ether. The washed and dried ether solution was taken to dryness leaving a yellow oil which was purified by chromatography on silica gel plates[19] with 18% ethyl acetate–82% benzene as developing solvent. Apart from traces of starting bromo compound and polar material remaining at the origin, two major zones were detected. The more polar zone, which had moved about 50% of the length of the plate, was eluted with ether yielding 90 mg. of α,β-unsaturated diketone IX as an oil. Rechromatography in the same system gave an analytical specimen: λ_{max}^{EtOH} 227 mμ (ϵ 13,800); $\lambda_{max}^{isooctane}$ 220 mμ (ϵ 12,050); mass spectrum, principal peak 264. The infrared spectrum peaks are shown in Fig. 1 and Table I, while the n.m.r. spectrum is shown in Fig. 2.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.05; H, 10.41.

A bissemicarbazone of IX was prepared by treatment with excess semicarbazide hydrochloride in aqueous alcohol containing sodium acetate. The semicarbazone, after recrystallization from methanol–water melted at 225° dec.; λ_{max}^{EtOH} 230 mμ (ϵ 24,400) and 263 mμ (ϵ 22,500).

Anal. Calcd. for $C_{19}H_{34}N_6O_2$: C, 60.29; H, 9.05; N, 22.20. Found: C, 60.54; H, 9.19; N, 21.16.

Cycloheptadec-3-ene-1,10-dione (X).—The less polar zone from the dehydrobromination of VIII had moved about 60% of the length of the silica gel plate. Elution of this zone with ether gave 65 mg. of the β,γ-unsaturated ketone X as an oil which showed no strong selective absorption in the ultraviolet. The infrared spectrum peaks are shown in Fig. 1 and Table I and the n.m.r. spectrum in Fig. 3. The mass spectral determination is noted in the discussion section. A satisfactory elemental analysis could not be obtained with carbon values consistently running about 2% low.

A bissemicarbazone of X, prepared as described under IX, underwent gradual decomposition when heated above 250° and exhibited λ_{max}^{EtOH} 229 mμ (ϵ 20,800).

Anal. Calcd. for $C_{19}H_{34}N_6O_2$: C, 60.29; H, 9.05; N, 22.20. Found: C, 59.80; H, 9.44; N, 22.03.

Equilibration of IX and X. A.—A solution of α,β-unsaturated ketone IX (45 mg.) in dimethylformamide (3 ml.) was treated with calcium carbonate (0.1 g.) and boiled for 5 hr. Conventional work-up and thin-layer chromatography yielded 6.2 mg. of β,γ-unsaturated compound X and 25 mg. of IX.

B.—A solution of 25 mg. of IX in 5 ml. of benzene was stirred for 25 hr. with 0.25 g. of Woelm alumina, activity grade I. Removal of alumina, followed by thin-layer chromatography gave 4.0 mg. of X and 7.1 mg. of IX.

C.—The equilibration of a small sample of β,γ-unsaturated isomer X as described in B led to the formation of the α,β-unsaturated isomer which was characterized by thin-layer chromatography and by infrared spectrum. While quantitative data was not obtained, the two isomers appeared to be present in about equal quantities but recovery was extremely low.

Reduction of IX to Cycloheptadecane-1,9-dione (VI).—The reduction of 24 mg. of IX was carried out in 2 ml. of absolute ethanol over 25 mg. of 5% palladium-on-barium sulfate at 20 p.s.i. and 25°. After 2 hr. the catalyst was removed and washed with acetone, and the combined solutions were treated with water to the point of turbidity. Chilling afforded 15 mg. of VI, m.p. 63–65°,[5] which was identical in all respects with the sample prepared by the oxidation of V.

Reduction of X to Cycloheptadecane-1,9-dione.—The catalytic reduction of 20 mg. of X carried out exactly as described in the preceding section, gave 11 mg. of VI, m.p. 64–65°, whose infrared spectrum chromatographic behavior and mass spectral pattern were identical with an authentic sample. The crystalline, but low melting mother liquors, were shown by chromatography and mass spectrum to consist almost exclusively of VI with only small amounts of impurities.

Cycloheptadec-3-ene-1,10-diol (XI).—A solution of 24 mg. of cycloheptadec-3-ene-1,9-dione (X) in 5 ml. of dry ether was added to 25 mg. of lithium aluminum hydride in 5 ml. of ether, and the mixture was stirred for 1 hr. at room temperature. The work-up was carried out with sodium sulfate as described under the preparation of IV. Crystallization of the residue from pentane yielded 20 mg. of the crystalline diol, m.p. 73–75°, ν_{max}^{KBr} 3 70 (OH), 989 cm.$^{-1}$ (HC=CH). Although XI is undoubtedly a mixture of 1,10-*cis* and -*trans* diols, only one spot appeared on thin-layer chromatography. An analytical specimen, from pentane, melted at 78° and exhibited the main peak in the mass spectrum at 250.

Anal. Calcd. for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 75.67; H, 11.96.

Deuterium Exchange of X.—A 25-mg. sample of X was dissolved in 0.25 ml. of methanol-d_4 and the n.m.r. spectrum traced in the conventional manner and also scanned on an oscilloscope. The C-2 methylene group appeared in the 175-c.p.s.[2] region while the balance of methylene groups adjacent to ketonic functions appeared in the 135-c.p.s. region. A drop of sodium deuteriomethoxide solution was added and the spectrum followed on the oscilloscope. Exchange was seen to occur most rapidly in the 175-c.p.s. region while protons in the 135-c.p.s. region exchanged more slowly. Partial isomerization to the α,β-unsaturated ketone was seen to be a much slower process. After standing for 16 hr. the deuterated X was reisolated by thin-layer chromatography. The infrared (film) demonstrated complete disappearance of the 1410-cm.$^{-1}$ band (CH_2—C=O), saturated carbonyl absorption at 1700 cm.$^{-1}$ and *trans* double bond absorption at 975 cm.$^{-1}$.

(19) For spotting, the silica gel layer was 0.25 mm. thick, while for preparative purposes a 1-mm. layer was utilized.

Alkylations of Phenylacetic Esters with Halides by Means of Sodium Amide in Liquid Ammonia. Comparisons with Alkylations of Phenylacetic Acid[1a]

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Received April 8, 1963

Ethyl phenylacetate was alkylated with alkyl and aralkyl halides through the sodio ester, which was prepared by means of sodium amide in liquid ammonia. The methyl, *n*-butyl, benzyl, and the α- and β-phenylethyl derivatives were obtained in high yields but the α,β-diphenylethyl derivative was produced in only fair yield along with stilbene. Similarly, *t*-butyl phenylacetate was alkylated with representative halides through the sodio ester. The α-phenylethylation of both the ethyl and *t*-butyl phenylacetates afforded largely the corresponding *erythro* isomers. Evidence was obtained that the latter alkylation is stereospecific. The alkylated ethyl and *t*-butyl phenylacetates were hydrolyzed by alkali and acid, respectively. The present method of alkylation appears preferable to earlier methods for the synthesis of alkylated phenylacetic esters and, also, for the preparation of certain of the corresponding carboxylic acids. Alkylations of the sodio esters are compared with those of disodiophenylacetate, which has a greater tendency to effect side reactions with certain of the halides. In contrast to sodio ethyl phenylacetate, disodiophenylacetate reacted with β-phenylethyl bromide to give mainly styrene.

A number of alkylations of ethyl phenylacetate have previously been effected with alkyl halides by means of basic reagents, but the yields generally have not been very satisfactory.[2] Three of the best yields have been 35% with ethyl bromide by potassium in ether,[2] 38% with benzyl chloride by potassium hydroxide in certain acetals or ethers,[2] and 45% with *n*-butyl bromide by sodium in ether and toluene.[3]

In the present investigation alkylations of this ester were accomplished in much better yields by means of sodium amide in liquid ammonia (equation 1).

$$C_6H_5CH_2COOC_2H_5 \xrightarrow[\text{liq. } NH_3]{NaNH_2} \underset{\text{I}}{C_6H_5\overset{Na}{C}HCOOC_2H_5} \xrightarrow{RX} \underset{\text{II}}{C_6H_5\overset{R}{C}HCOOC_2H_5} \quad (1)$$

As indicated, ethyl phenylacetate was converted to its sodio derivative I with a molecular equivalent each of the reagent and of the halide.

The results are summarized in Table I. Alkylations with the first six halides listed in this table afforded the corresponding monoalkylation products II in good to excellent yields (69–91%). The liquid products were shown by v.p.c. to be essentially pure, though that from methyl iodide evidently contained a trace of the corresponding dimethylation derivative. The alkylation products II generally afforded good to excellent yields on saponification (see Experimental).

The α-phenylethylation was of particular interest since the formation of diasteroisomers of II (R = α-phenylethyl) was possible. Actually only one isomer was isolated, its yield being 70%. On the basis of the corresponding results with *t*-butyl phenylacetate described later, this isomer may be assumed to have the *erythro* configuration. Saponification of this isomer evidently brought about some epimerization, since both the *erythro* and *threo* acids were obtained.

Although the alkylation of sodio ester I with β-phenylethyl bromide was unaccompanied by appreciable β-elimination (see Table I), that of I with α,β-diphenylethyl chloride was accompanied by considerable β-elimination to form stilbene (Scheme A).

SCHEME A

$$C_6H_5\overset{Na}{C}HCOOC_2H_5 + C_6H_5CH_2\overset{C_6H_5}{C}HCl$$

liq. alkylation; NH_3 β-elimination

II (R = α,β-diphenylethyl) $C_6H_5CH{=}CHC_6H_5$

This experiment afforded the *erythro* isomer of II and stilbene in yields of 32 and 39%, respectively. Also, an oil was obtained that appeared to consist of alkylation product (15%). Saponification of the pure *erythro* isomer, as well as that of the oil, yielded a mixture of the *erythro* and *threo* acids.

Similarly *t*-butyl phenylacetate was alkylated through its sodio intermediate III to form IV in yields of 72–93% (Table II). Acid-catalyzed hydrolysis of the alkylation products IV afforded good to excellent yields of the corresponding carboxylic acids (see Experimental).

$$\underset{\text{III}}{C_6H_5\overset{Na}{C}HCOOC(CH_3)_3} \qquad \underset{\text{IV}}{C_6H_5\overset{R}{C}HCOOC(CH_3)_3} \quad (2)$$

Like the sodio ethyl ester I, the sodio *t*-butyl ester III underwent α-phenylethylation to form largely (72–73%) one of the two possible diastereoisomers which, in this case, was shown to have the *erythro* configuration. This was accomplished by acid-catalyzed hydrolysis, which occurred without epimerization to form the corresponding *erythro* carboxylic acid (equation 3).

$$\underset{\substack{\text{erythro}}}{C_6H_5\overset{C_6H_5CHCH_3}{C}HCOOC(CH_3)_3} \xrightarrow[\text{dioxane}]{HCl} \underset{\substack{\text{erythro}}}{C_6H_5\overset{C_6H_5CHCH_3}{C}HCOOH} \quad (3)$$

Actually the yield of the *erythro* alkylated ester IV (R = α-phenylethyl) must have been at least 80%, since treatment of the crude product[4] with *p*-toluene-

(1) (a) Supported in part by the National Science Foundation; (b) Union Carbide and Carbon Chemicals Co. Fellow, 1961–1963.

(2) See A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 284 (1957).

(3) A. L. Mndzhoyan, O. L. Mndzhoyan, E. R. Bagdasaryan, and V. A. Mnatsakanyan, *Dokl. Akad. Nauk Arm. SSR*, **30**, 97 (1960); *Chem. Abstr.*, **55**, 3508*h* (1961).

(4) An attempted analysis of the crude ester product by v.p.c. was unsuccessful, since pure *erythro* ester, as well as the pure *threo* ester, underwent epimerization under these conditions.

TABLE I

ALKYLATIONS OF ETHYL PHENYLACETATE WITH HALIDES BY SODIUM AMIDE IN LIQUID AMMONIA TO FORM ESTERS II (SEE EQUATION 1)

Halide	Moles of each reactant	Time, hr	Ethyl esters II	Yield, %	B.p. (mm) or m.p., °C. Found	B.p. (mm) or m.p., °C. Literature
Methyl iodide	0.1[a]	0.5	2-Phenylpropanoate	69[b]	115–118 (19)	229–230 (atm.)[c]
n-Butyl bromide	0.2	1	2-Phenylhexanoate	91	76–77 (0.1)	114–119 (4)[d]
Benzyl chloride	0.1	1	2,3-Diphenylpropanoate	85	115–116.5 (0.13)	325 (atm.)[e]
Benzhydryl chloride	0.1	6	2,3,3-Diphenylpropanoate	76[f]	122–123	120[g]
α-Phenylethyl chloride	0.05	2	2,3-Diphenylbutanoate	70[h]	88–89.5	91–92[i]
β-Phenylethyl bromide	0.05	10	2,4-Diphenylbutanoate	87[j]	113–114 (0.05)	
α,β-Diphenylethyl chloride	0.05	12	2,3,4-Triphenylbutanoate	32[k]	90–92	91.5–92.5[l]

[a] A 10% excess (0.11 mole) of sodium amide was used. [b] Purity (v.p.c.) 97% (see Experimental). [c] W. Wislicenus and R. v. Schrötter, *Ann.*, **424**, 215 (1921). [d] Ref. 3. [e] A. Meyer, *Ber.*, **21**, 1306 (1888). [f] A 50% yield was obtained in 2 hr. [g] E. P. Kohler and G. Heritage, *Am. Chem. J.*, **33**, 153 (1905). [h] Presumably the *erythro* isomer. [i] W. R. Brasen and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 395 (1957). [j] A low yield was obtained when the chloride was used (see Experimental). [k] *erythro* isomer. Stilbene (39%) was also obtained (see Experimental). [l] Ref. 20.

TABLE II

ALKYLATIONS OF *t*-BUTYL PHENYLACETATE WITH HALIDES BY SODIUM AMIDE IN LIQUID AMMONIA TO FORM ESTERS IV (SEE EQUATION 2)

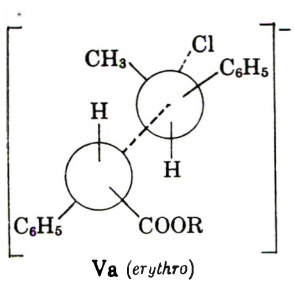
Halide	Moles of each reactant	Time, hr.	*t*-Butyl Esters IV[a] Yield, %	B.p. (mm.) or m.p., °C.	Formula	C Calcd.	C Found	H Calcd.	H Found
n-Butyl bromide	0.1	1	86	93 (1.0)	$C_{16}H_{24}O_2$	77.37	77.15	9.74	9.72
Benzyl chloride	0.1	1	93	38.5 (−40)[b]	$C_{19}H_{22}O_2$	80.81	81.13	7.86	7.80
Benzhydryl chloride	0.05	6	78[c]	127–128[d]	$C_{25}H_{26}O_2$	83.76	83.97	7.31	7.34
α-Phenylethyl chloride	0.08	0.25	72–73[e]	136–136.5[f]	$C_{20}H_{24}O_2$	81.04	81.29	8.16	8.28

[a] See Table I for names of the acid portions of the esters. [b] Recrystallized from methanol–water. [c] A 52% yield was obtained in 2 hr. [d] Recrystallized from 95% ethanol. [e] *erythro* isomer. [f] Recrystallized from methanol.

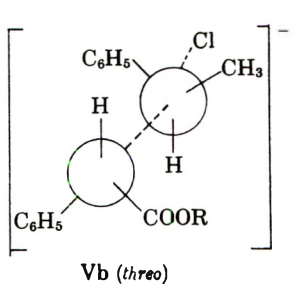
sulfonic acid in refluxing toluene afforded the *erythro* acid in this yield based on the starting ester or halide. Also there was obtained a mixture of the *erythro* and *threo* acids (11%) and the pure *threo* acid (1%).

Interestingly, the α-phenylethylation of sodio *t*-butyl phenylacetate (III), and presumably also that of sodio ethyl phenylacetate (I), appears to be stereospecific. Thus, blank experiments involving treatment of the *threo* isomer of IV (R = α-phenylethyl) with the starting sodio ester III or sodium amide failed to afford an isolable amount of the *erythro* isomer (see Experimental). The *threo* isomer of IV employed in these blank experiments was obtained by treating the *erythro* isomer with a catalytic amount of potassium amide in ether, and then separating the resulting mixture of the *erythro* and *threo* isomers.

A possible explanation of the predominant formation of the *erythro* isomer is that the α-phenylethylation, which presumably involves the Sn2 type of mechanism, has a more favorable transition state leading to this isomer than that leading to the *threo* isomer. The transition states may be assumed to have configurations similar to those of the alkylation products as represented by Va and Vb for the *erythro* and *threo* isomers, respectively (R = C_2H_5, $C(CH_3)_3$).



Va (*erythro*)



Vb (*threo*)

The present method of alkylation of phenylacetic esters by means of sodium amide in liquid ammonia appears superior to earlier methods. Thus, our yields of *n*-butylation and benzylation products of ethyl phenylacetate (see Table I) were twice the best of those reported previously (see introduction).

Incidentally, *t*-butyl acetate[5] and triethylcarbinyl diethylacetate[6] previously have been alkylated satisfactorily with halides in liquid ammonia by means of lithium amide and potassium amide, respectively.

Comparison with Alkylations of Phenylacetic Acid.—The alkylations of phenylacetic esters described above compliment earlier alkylations of phenylacetic acid by means of two molecular equivalents of sodium amide in liquid ammonia (equation 4).[7-9]

$$C_6H_5CH_2COOH \xrightarrow[\text{liq. } NH_3]{2NaNH_2} \underset{\text{VI}}{C_6H_5\overset{Na}{C}HCOONa} \xrightarrow[\text{2. acid}]{\text{1. RX}} \underset{\text{VII}}{C_6H_5\overset{R}{C}HCOOH} \quad (4)$$

Alkylations of disodio salt VI with *n*-butyl bromide, and benzyl and α-phenylethyl chlorides have afforded VII in yields of 65–88%, which are comparable to those (70–93%) of II and IV obtained in corresponding alkylations of sodio esters I and III (see Tables I and II). Moreover, like the α-phenylethylation of sodio ester III, that of disodio acid VI is evidently stereospecific to form largely the corresponding *erythro* isomer of VII[8]; in fact, the yield of this isomer is about the same (80%) as that obtained in the α-phenylethylation of the sodio ester III followed by hydrolysis (see preceeding section).

However, alkylations of disodio salt VI with benzhydryl, β-phenylethyl, and α,β-diphenylethyl halides

(5) K. Sisido, Y. Kazama, H. Kodama, and H. Nozaki, *J. Am. Chem. Soc.*, **81**, 5817 (1959).
(6) C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 3837 (1956).
(7) C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 4942 (1956).
(8) C. R. Hauser, D. Lednicer, and W. R. Brasen, *ibid.*, **80**, 4345 (1958).
(9) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).

have not been as satisfactory as those of sodio ester I or III with these halides. This is because the dianion VI, which is presumably a stronger base than the monoanion of I or III, effects side reactions involving the α-hydrogen of the first halide and the β-hydrogen of the second and third halides as described subsequently.

The reaction of disodio salt VI with benzhydryl chloride has been shown to form not only the corresponding alkylation product VII (51%) but also tetraphenylethylene (39%).[7] The latter product arose through self-alkylation of the halide, followed by β-elimination.[10] None of this side reaction was observed in the alkylation of sodio ester I or III with benzhydryl chloride, in which the corresponding alkylation product II or IV was obtained in yields of 76–78% (see Tables I and II).[11]

The reaction of disodio salt VI with β-phenylethyl chloride has afforded the corresponding alkylation product VII in only 45% yield,[9] compared to the 87% yield of alkylation product II from sodio ester I and β-phenylethyl bromide[12] (see Table I). We have observed that alkylation of disodio salt VI with β-phenylethyl chloride is accompanied by β-elimination to form styrene, and that relatively more β-elimination occurs with the bromide (Scheme B).

SCHEME B

$$\mathrm{VI} + \mathrm{C_6H_5CH_2CH_2X} \xrightarrow[\text{alkylation}]{\text{liq. } NH_3} \begin{cases} \mathrm{VII\ (R = CH_2CH_2C_6H_5)} \\ \mathrm{X = Cl,\ yield\ 39\text{–}45\%} \\ \mathrm{X = Br,\ yield\ <11\%} \end{cases} \quad \underset{\beta\text{-elimination}}{} \quad \begin{cases} \mathrm{C_6H_5CH{=}CH_2} \\ \mathrm{X = Cl,\ yield\ 13\%} \\ \mathrm{X = Br,\ yield\ 67\%} \end{cases}$$

The reaction of disodio salt VI with α,β-diphenylethyl chloride has afforded none of the corresponding alkylation product VII; instead β-elimination occurred to form stilbene (75%).[13] Even sodio ester I undergoes considerable β-elimination with this halide, though the corresponding alkylation product II was obtained in fair yield (see Table I).

It should be pointed out that benzhydrylation and β-phenylethylation of sodio ester I or III, followed by hydrolysis, has afforded better over-all yields of the corresponding phenylacetic acid derivatives VII than the direct alkylation of disodio salt VI.

Although the alkyl derivatives of phenylacetic acid VII would generally be prepared by direct alkylation of disodiophenylacetate VI or through the sodio ester I or III (see preceeding section), the method of choice for acid VII where R is α,β-diphenylethyl involves the alkylation of sodiophenylacetonitrile with α,β-diphenylethyl chloride, followed by hydrolysis.[14] Actually, hydrolysis of the alkylated nitrile with acid and alkali have afforded the *erythro* and *threo* isomers of the acid in over-all yields of 71 and 72%, respectively.[14]

Experimental[15]

Alkylations of Ethyl Phenylacetate (Table I).—To a stirred suspension of 0.05–0.2 mole of sodium amide[16] in 250–500 ml. of commercial, anhydrous liquid ammonia was added a molecular equivalent of ethyl phenylacetate in 25–50 ml. of dry ether, followed after 10–15 min. by a molecular equivalent of the appropriate halide in 25–50 ml. of dry ether. After stirring for the appropriate length of time, using a Dry Ice–acetone condenser for longer periods, a slight excess of a molecular equivalent of ammonium chloride was added, and the ammonia was evaporated on the steam bath as an equal volume of ether was added. The resulting ethereal suspension was cooled, acidified with 100 ml. of 3 *N* hydrochloric acid, and stirred for 15 min., followed by separation of the two layers. The ethereal layer was washed with saturated sodium bicarbonate solution, followed by saturated sodium chloride solution, and then combined with two ethereal washings of the original aqueous solution. The ethereal solution of the product was dried over anhydrous magnesium sulfate, and the solvent was removed. The residue was distilled *in vacuo* or recrystallized. Data and results are summarized in Table I or as described later.

In the experiment with methyl iodide employing the slight excess of sodium amide (see Table I), the ethereal solution of the reaction product was washed with saturated sodum bisulfite solution to remove the brown color (iodine) before drying. After drying, the solvent was removed and the residue was distilled *in vacuo*. A vapor phase chromatogram (5-ft. Apiezon L column) of a sample of the distillate showed that it consisted of 97% of ethyl 2-phenylpropanoate, 3% of ethyl 2-methyl-2-phenylpropanoate, and no ethyl phenylacetate. When the methylation was effected without the slight excess of reagent (3-hr. reaction period), the product (58% yield) was shown by v.p.c. to consist of 93% of ethyl 2-phenylpropanoate, 2% of ethyl 2-methyl-2-phenylpropanoate, and 5% of ethyl phenylacetate.

In the experiments with *n*-butyl bromide and benzyl chloride the residues were distilled *in vacuo* to give ethyl 2-phenylhexanoate and ethyl 2,3-diphenylpropanoate, respectively. Vapor phase chromatograms of samples of each of these products showed only a single peak, indicating that each was essentially pure.

In the experiments with benzhydryl and α-phenylethyl chlorides, the residues were recrystallized from methanol–water and 95% ethanol, respectively, to yield ethyl 2,3,3-triphenylpropanoate and ethyl *erythro*-2,3-diphenylbutanoate, each product being obtained in two crops.

In the experiment with β-phenylethyl bromide, a few crystals of hydroquinone were added to the dried ether solution of the product and the solvent was then removed. A vapor phase chromatogram of the crude residue showed a large peak corresponding to the monoalkylation product II (R = β-phenylethyl), small peaks for ethyl phenylacetate and β-phenylethyl bromide, but no noticeable peak for styrene. Distillation of the crude residue afforded the pure alkylation product (87%), b.p. 113–116° (0.06 mm.). A vapor phase chromatogram of the distillate showed only one peak. The boiling point of an analytical sample was 113–114° (0.05 mm.).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.38; H, 7.75.

In the experiment with α,β-diphenylethyl chloride, the residue was distilled *in vacuo* to recover 1.93 g. (24%) of ethyl phenylacetate, b.p. 115–118° (20 mm.) [lit.[17] b.p. 132–138° (32 mm.)] and give 3.54 g. (39%) of *trans*-stilbene,[18] b.p. 97–100° (1 mm.)

(10) See C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(11) Sodio ester I underwent alkylation with benzhydryl bromide in about the same yield as with the chloride under similar conditions (2 hr., footnote *f*, Table I). Neither tetraphenylethylene nor tetraphenylethane was detected by v.p.c. The latter hydrocarbon (39%) has been obtained along with the alkylation product (21%) in the reaction of disodio salt VI with benzhydryl bromide; ref. 7, footnote 7.

(12) β-Phenylethyl chloride afforded, under similar conditions (see Table I), only a 48% yield of alkylation product as determined by v.p.c. A trace of styrene was also detected.

(13) C. R. Hauser, C. F. Hauser, and P. J. Hamrick, Jr., *J. Org. Chem.*, **23**, 1713 (1958).

(14) D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **80**, 3409 (1958).

(15) Analyses are by Dr. Ing. Schoeller, Kronach, West Germany, and Galbraith Microanalytical Laboratories, Knoxville, Tennessee. Melting points and boiling points are uncorrected. An F & M Model 500 programmed temperature gas chromatograph, using a 2-ft. silicone gum rubber column except where noted, was used to produce the vapor phase chromatograms. The carrier gas was helium.

(16) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(17) I. Heilbron, "Dictionary of Organic Compounds," Vol. IV, Oxford University Press, New York, N. Y., 1953, p. 96.

(18) This stilbene evidently arose from the reaction of sodio ester I with the α,β-diphenylethyl chloride, and not from the possible thermal elimination, since this halide has been distilled without apparent decomposition at 127–129° (0.5 mm.); see C. R. Hauser, S. W. Kantor, and W. R. Brasen *J. Am. Chem. Soc.*, **75**, 2660 (1953).

TABLE III

SAPONIFICATIONS OF ALKYLATION PRODUCTS II TO FORM CARBOXYLIC ACIDS

Ester II, R	Carboxylic acid	Yield, %	B.p. (mm.) or m.p., °C. Found	B.p. (mm.) or m.p., °C. Literature
Methyl[a]	2-Phenylpropanoic	20 (91)[b]	153–155 (21)	155 (21)[c]
n-Butyl	2-Phenylhexanoic	57 (92)[b]	170–178 (19)	180–183 (20)[d]
Benzyl	2,3-Diphenylpropanoic	97	84–85[e]	82[f]
Benzhydryl	2,3,3-Triphenylpropanoic	94	221.5–222[g]	221.5–222[f]
α-Phenylethyl	2,3-Diphenylbutanoic	(96)[b,h]	130–170	187–187.5,[i] 135[j]
β-Phenylethyl	2,4-Diphenylbutanoic	67 (99)[b]	70.5–72[k]	72–73[l]
α,β-Diphenylethyl[m,n]	2,3,4-Triphenylbutanoic	85 (95)[b]	145–150	131–135,[o] 159–160[p]

[a] 0.02 mole of potassium hydroxide used. [b] Crude yield. [c] S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 171 (1961). [d] Ref. 3. [e] Recrystallized from ether–hexane. [f] Ref. 7. [g] Recrystallized from methanol. [h] Fractionally recrystallized from ethanol–water to yield *erythro* isomer (52%, m.p. 184–186°) and *threo* isomer (33%, m.p. 125–128°). [i] *erythro* isomer, ref. 8. [j] *threo* isomer, ref. 8. [k] Recrystallized from hexane. [l] Ref. 9. [m] 0.005 mole of ester and 0.02 mole of potassium hydroxide used in each case. [n] Data refer to the crystalline ester (m.p. 90–92°). The same quantities of oil (see Experimental) and base gave an 84 (94)% yield of acids, m.p. 145–147°. [o] *erythro* isomer, ref. 14. [p] *threo* isomer, ref. 14.

[lit.[19] b.p. 166–167° (12 mm.)]. After crystallization from methanol–chloroform the stilbene melted at 122–124°, m.m.p. 121–124° (lit.[13] m.p. 126–127°). Crystallization of the pot residue from methanol–water afforded 5.42 g. (32%) of ethyl *erythro*-2,3,4-triphenylbutanoate, m.p. 88–89° and 90–92° after recrystallization from ethanol. Evaporation of the mother liquor left 4.08 g. (15%) of an oil, which presumably consisted at least partly of the pure *threo* isomer, since it has been reported as an oil.[20]

Saponification of Alkylation Products II (Table III).—Solutions of 0.01 mole of esters II and 5.6 g. (0.1 mole) of potassium hydroxide in 25 ml. of 95% ethanol were refluxed for 24 hr. The ethanol was removed by distillation, and the residue dissolved in water. After the aqueous solution was extracted once with ether to remove any unchanged ester, it was chilled and acidified with concentrated hydrochloric acid. Three ether extracts of the aqueous solution were washed with saturated sodium chloride solution, combined, and dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled *in vacuo* or recrystallized from an appropriate solvent (see Table III).

The residue from the saponification of ethyl *erythro*-2,3-diphenylbutanoate was fractionally crystallized from ethanol–water to give 1.24 g. (52%) of *erythro*-2,3-diphenylbutanoic acid, m.p. 184–186°, and 0.79 g. (33%) of *threo*-2,3-diphenylbutanoic acid, m.p. 125–128°.

The residue from the saponification of ethyl *erythro*-2,3,4-triphenylbutanoate was recrystallized from 95% ethanol to give 1.28 g. (85%) of acid, m.p. 145–150°, which was apparently a mixture of the *erythro* and *threo* acids, m.p. 131–135° and 159–160°,[14] respectively. Similarly, saponification of the oil (footnote *o*, Table III) gave 1.23 g. (84%) of a mixture of the acids, m.p. 145–147°.

***t*-Butyl Phenylacetate.**—This ester was prepared by an adaption of the method described previously for *t*-butyl acetate.[21]

A solution of 45 g. of *t*-butyl alcohol and 75 g. of dimethylaniline in 200 ml. of dry ether was treated with 93 g. of phenylacetyl chloride. After refluxing 1 hr., the reaction mixture was cooled and treated with water. The ethereal layer was washed with 3 *N* hydrochloric acid, 10% sodium bicarbonate solution, and water, and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled to give *t*-butyl phenylacetate (44%), b.p. 108–110° (15 mm.) [lit.[22] b.p. 110° (15 mm.)].

Alkylations of *t*-Butyl Phenylacetate (Table II).—These alkylations were effected and worked up essentially as described earlier for the corresponding alkylations of ethyl phenylacetate.

In the experiment with *n*-butyl bromide, the residue was distilled *in vacuo* and the distillate was shown to be pure by v.p.c.

In the experiments with benzyl, benzhydryl, and α-phenylethyl chlorides, the residues were recrystallized from appropriate solvents (see Table II).

Acid-Catalyzed Hydrolysis of Alkylation Products IV (Table IV).—Solutions of 0.005–0.01 mole of esters IV in 25 ml. of dioxane and 5 ml. of concentrated hydrochloric acid were refluxed for 2 hr. After cooling, the reaction mixture was diluted with ether and the resulting solution was extracted with cold 5% sodium hydroxide solution. The aqueous alkaline extract was washed with ether, chilled, and acidified with concentrated hydrochloric acid. The resulting mixture was extracted three times with ether, and the combined ethereal extract was dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled *in vacuo* or recrystallized from an appropriate solvent (see Table IV).

TABLE IV

ACID-CATALYZED HYDROLYSIS OF ALKYLATION PRODUCTS IV TO FORM CARBOXYLIC ACIDS

Ester IV R	Carboxylic acid	Yield, %	B.p. (mm.) or m.p., °C. Found	B.p. (mm.) or m.p., °C. Literature[a]
n-Butyl	2-Phenylhexanoic	78	173–178 (19)	180–183 (20)
Benzyl	2,3-Diphenylpropanoic	62	93–96	95.5–96.5
Benzhydryl	2,3,3-Triphenylpropanoic	99	221.5–222.5	221.5–222
α-Phenylethyl	2,3-Diphenylbutanoic	75 (88)[b,c]	188–189[c]	187–187.5[c]

[a] See Table III for references and recrystallization solvents. [b] Crude yield. [c] *erythro* isomer.

α-Phenylethylation of *t*-Butyl Phenylacetate and Hydrolysis of Crude Product.—This alkylation was carried out on the 0.05-mole scale as indicated above to give a 96% yield of solid crude product. A portion (2.96 g., 0.01 mole) of the crude product was dissolved in 50 ml. of dry toluene containing 0.5 g. (0.0026 mole) of *p*-toluenesulfonic acid monohydrate. The solution was refluxed, until the evolution of isobutylene had ceased. After cooling, the reaction mixture was diluted with an equal volume of ether and washed with water to remove the acid catalyst. The organic layer was extracted with two portions of 10% sodium hydroxide solution which were combined, chilled, and acidified with concentrated hydrochloric acid. The acidified aqueous solution was extracted three times with ether, the combined extract dried over anhydrous magnesium sulfate, and the solvent removed to leave 2.17 g. (91%) of crude 2,3-diphenylbutanoic acids, m.p. 175–185°. A portion (2.13 g.) of this residue was crystallized from ethanol–water to yield 1.70 g. (80%) of *erythro*-2,3-diphenylbutanoic acid, m.p. 184–186°. There was also obtained a second crop (0.24 g., 11%), m.p. 120–145°; and a third crop (0.03 g., 1%) m.p. 123–128°, which showed no depression upon admixture with an authentic sample of *threo*-2,3-diphenylbutanoic acid (see Table III for lit. melting points).

***threo*-*t*-Butyl 2,3-Diphenylbutanoate.**—The *threo* isomer was prepared by refluxing 8.9 g. (0.03 mole) of *erythro*-*t*-butyl 2,3-diphenylbutanoate in 300 ml. of dry ether containing a suspension of 0.006 mole of potassium amide for 2 hr. essentially as described previously for *erythro*- and *threo*-2,3-diphenylbutyronitrile.[8] Removal of the solvent from the dried ethereal solution of the product gave a residue which was fractionally crystallized from methanol to afford the *erythro* (55%) and the *threo* (14%) isomers.

(19) See ref. 17, p. 375.

(20) H. M. Crawford, J. C. Davidson, and M. A. Plunkett, *J. Am. Chem. Soc.*, **66**, 2010 (1944).

(21) C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. C. Shivers, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 142.

(22) D. L. Yabroff and C. W. Porter, *J. Am. Chem. Soc.*, **54**, 2453 (1932).

The *threo-t*-butyl 2,3-diphenylbutanoate (white cubes) melted at 99–100.5°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.92; H, 8.02.

A mixture of the *threo* isomer and the *erythro* isomer (m.p. 136–136.5°) melted at 88–104°. Hydrolysis of 0.2 g. of *threo-t*-butyl 2,3-diphenylbutanoate by the dioxane–hydrochloric acid method (see preceding section) yielded *threo*-2,3-diphenylbutanoic acid (94%), m.p. 134–136° (see Table IV for literature melting point and reference).

Failure of *threo-t*-Butyl 2,3-Diphenylbutanoate to Undergo Epimerization in Liquid Ammonia. (A) With Sodio *t*-Butyl Phenylacetate.—To a stirred suspension of 0.01 mole of sodium amide in 100 ml. of liquid ammonia was added 1.41 g. (0.01 mole) of *t*-butyl phenylacetate in 10 ml. of dry ether, followed, after 15 min., by 0.053 g. (1.79 mmoles) of finely powdered *threo-t*-butyl 2,3-diphenylbutanoate (washed in with 5 ml. of dry ether). After stirring for 2 hr., the reaction mixture was neutralized with ammonium chloride, and the ammonia was replaced with ether. The resulting ethereal suspension was worked up as described before for the alkylations of ethyl and *t*-butyl phenylacetates. The residue left after removal of the solvent from the dried ethereal solution was distilled *in vacuo* to remove the *t*-butyl phenylacetate. Recrystallization of the pot residue from methanol–water yielded *threo-t*-butyl 2,3-diphenylbutanoate, m.p. 91–94°. Upon admixture with an authentic sample (m.p. 96–98°) it melted 94–97°. None of the *erythro* isomer (m.p. 136–136.5°) was found.[23]

(B) With Sodium Amide.—To a stirred suspension of 0.609 mmole of sodium amide in 100 ml. of liquid ammonia was added 0.1504 g. (0.501 mmole) of *threo-t*-butyl 2,3-diphenylbutanoate in 10 ml. of dry ether. After stirring for 2 hr., the reaction mixture was worked up as described before for the alkylation of ethyl and *t*-butyl phenylacetates. Removal of the solvent from the dried ethereal solution of the product gave a residue which was crystallized from methanol–water to yield 0.0726 g. (48%) of recovered *threo-t*-butyl 2,3-diphenylbutanoate, m.p. 92–96°. Upon admixture with an authentic sample (m.p. 96–98°) it had m.p. 94–97°. None of the *erythro* isomer (m.p. 136–136.5°) was found.[23]

Alkylation of Phenylacetic Acid. (A) With β-Phenylethyl Chloride.—To a green stirred suspension of 0.05 mole of disodiophenylacetate (VI), prepared from 0.1 mole of sodium amide and 6.81 g. (0.05 mole) of solid phenylacetic acid in 250 ml. of liquid ammonia, was added 7.03 g. (0.05 mole) of β-phenylethyl chloride in 25 ml. of dry ether. After 1 hr., the reaction mixture was neutralized with ammonium chloride and the ammonia replaced with ether. The resulting ether suspension was extracted twice with 5% sodium hydroxide solution and after addition of a few crystals of hydroquinone, the ethereal solution was dried over anhydrous magnesium sulfate. A portion of the solvent was removed and the solution was chilled, followed by the addition of a slight excess of 10% bromine–carbon tetrachloride solution. The excess bromine was decomposed with 10% sodium bisulfite solution and the layers were separated. The organic layer was washed with 10% sodium bisulfite solution and water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue recrystallized from ethanol–water to yield 2.36 g. (13%) of styrene dibromide, m.p. 71–72° (lit.[24] m.p. 72–73°).

The alkaline extract of the reaction product mentioned before was worked up as described previously to give recovered phenylacetic acid (33%) and 2,4-diphenylbutanoic acid (39%).[9]

(B) With β-Phenylethyl Bromide.—The alkylation was performed as described above, except that 9.26 g. (0.05 mole) of β-phenylethyl bromide was used. The ethereal layer was worked up to yield 12.24 g. (67%) of styrene dibromide, m.p. 72–73.5°, after crystallization from ethanol–water. The yield of 2,4-diphenylbutanoic acid was less than 11%.

(23) Since the *erythro* isomer is less soluble than the *threo* isomer in the solvent system employed, any *erythro* isomer present should have precipitated as the first crop.

(24) C. R. Hauser, J. C. Shivers, and P. S. Skell, *J. Am. Chem. Soc.*, **67**, 409 (1945).

Ethylenediketene Dimer

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Received May 9, 1963

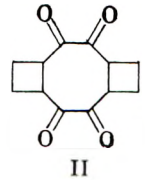
The ethylenediketene dimer obtained from the dehydrochlorination of adipyl dichloride has been reinvestigated and assigned the structure IV. Products derived from this dimer by hydrolysis and oxidation have been identified. The pertinence of this structural information to modes of reaction of alkylketenes is discussed.

In 1912, Staudinger announced Wedekind's discovery that adipyl dichloride reacts with triethylamine to give a $C_{12}H_{12}O_4$ compound, corresponding to a dimer of ethylenediketene (I).[1] Thirteen years later, Wedekind and co-workers published the details of this reaction and of their attempts to determine the structure of the

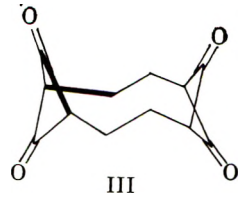
I

dimer.[2] The $C_{12}H_{12}O_4$ compound, m.p. 141–142°, reacted with phenylhydrazine to give a bisphenylhydrazone, with alkaline peroxide to give both a diacid of m.p. 170–171° ($C_{10}H_{14}O_4$) and an acidic substance of m.p. 81–82° ($C_6H_{10}O_5$)[3], and with aqueous acid to give adipic acid.

Two structures for the dimer (II and III) were suggested for consideration; the biscyclobutanedione III was favored. No attempt was made to assign structures to the diacid of m.p. 170–171° or the acidic substance of m.p. 81–82°.



II



III

Assigning structures to the three compounds, $C_{12}H_{12}O_4$, $C_{10}H_{14}O_4$, and $C_6H_{10}O_5$, appeared difficult. An experimental reinvestigation of these compounds provided new analytical, chemical, and spectral data which were sufficient to resolve the problem.

Results and Discussion

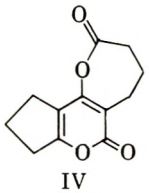
The ethylenediketene dimer was prepared and found to have m.p. 142–144° and the molecular formula C_{12}-

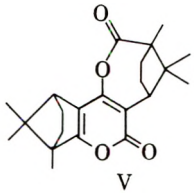
(1) H. Staudinger, "Die Ketene," Ferdinand Enke, Stuttgart, 1912, p. 19.

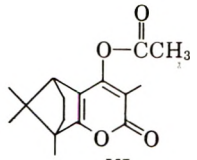
(2) E. Wedekind, M. Miller, and C. Weinard, *J. prakt. Chem.*, [2] **109**, 161 (1925).

(3) There are two apparent misprints in the analytical data reported for the compound of m.p. 81–82° (ref. 2, p. 171): the first sample for combustion is evidently 0.1023 g. rather than 0.1203 g., and the calculated carbon and hydrogen percentages correspond to $C_6H_{10}O_5$, rather than to $C_6H_{10}O_3$ as printed.

$H_{12}O_4$. The structure IV may be assigned to the dimer from a comparison of the ultraviolet and infrared spectral data for the compound [λ_{max}^{EtOH} 313 mμ (ε 7800); $\nu_{max}^{CH_2Cl_2}$ 1765, 1710, 1640, and 1575 cm.$^{-1}$] with that for V[4] [λ_{max}^{EtOH} 326 mμ (ε 9300); $\nu_{max}^{CH_2Cl_2}$ 1761, 1692, 1631, and 1565 cm.$^{-1}$] and VI[4] [λ_{max}^{EtOH} 324 mμ (ε 10,500); $\nu_{max}^{CH_2Cl_2}$ 1773, 1706, 1626, and 1567 cm.$^{-1}$].

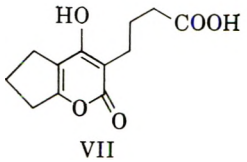

IV

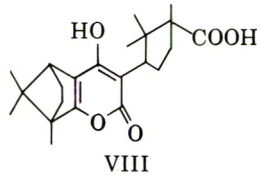

V


VI

Treatment of the dimer IV with alkaline peroxide according to the procedure of Wedekind and coworkers[2] gave the diacid of m.p. 170–171°. The elemental analysis, molecular weight, and neutralization equivalent of the compound indicated that it was $C_{12}H_{14}O_5$, rather than $C_{10}H_{14}O_4$. Direct hydrolysis of the dimer IV with aqueous sodium hydroxide also gave the diacid, thus confirming that the conversion process is hydrolysis, not oxidation.

The $C_{12}H_{14}O_5$-diacid may be formulated as VII since the infrared spectrum, containing bands at 1707, 1660, 1628, and 1562 cm.$^{-1}$, clearly indicates that the α-pyrone structure of IV survived hydrolysis.[5] The comparable infrared bands at 1689, 1653, 1621, and 1550 cm.$^{-1}$ reported for the acid VIII[4] may be viewed as supporting a similar structural assignment for VII.

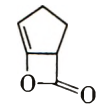

VII


VIII

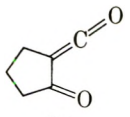
The acidic substance of m.p. 81–82° was isolated and found to be $C_5H_8O_4$, rather than $C_6H_{10}O_5$. The infrared spectrum of the compound suggested that it might be an impure specimen of glutaric acid and this possibility was confirmed by paper chromatographic analysis. No effort was made to isolate and identify the substance mixed with the glutaric acid.

The formation of the dimer IV from the dehydrochlorination of adipyl dichloride is worth comment. Long-chain α,ω-diacid chlorides may be dehydrochlorinated to give materials that probably are β-lactone intramolecular alkylketene dimers.[6] The short-chain α,ω-diacid chlorides do not behave similarly. They give polymers when dehydrochlorinated and left to react in aprotic media[6,7], or, as in the present work, dimers based on an α-pyrone structure.

Two main possibilities may be considered responsible for this diffrence in behavior. It may be that the short-chain α,ω-diacid chlorides cannot give intramolecular ketene condensation products (such as IX from ethylenediketene) for steric reasons; or it may be that a hypothetical intermediate such as X would condense intramolecularly with the nearby ketene function and subsequently eliminate hydrogen chloride to give XI and, eventually, dimers of XI,[8] and a β-lactone is not obtained because an α,ω-diketene is never involved.


IX

$O{=}C{=}CH{-}CH_2CH_2{-}\bar{C}H{-}COCl$
X


XI

Experimental tests of these two rationalizations are now in progress.

Experimental[9]

Ethylenediketene Dimer.[2]—A solution of 105 g. (1.15 equiv.) of adipyl dichloride in 1250 ml. of absolute ether was placed in a dry 2-l. three-necked flask; this flask was equipped with a reflux condenser, mechanical stirrer, addition funnel, nitrogen line, and drying tube. Triethylamine (119 g., 1.17 moles, freshly distilled from α-naphthyl isocyanate) was added to the stirred mixture in an atmosphere of nitrogen during 70 min. Three days later the ethereal solution from the reaction was separated from insoluble polymer and salt by inverted filtration and concentrated to give a colorless solid. Two recrystallizations from benzene gave the ethylenediketene dimer of m.p. 142–144° (lit.[2] m.p. 141–142°) (2.8 g., 4.4% yield).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49; mol. wt., 220. Found: C, 65.22; H, 5.51; mol. wt., 215.

The compound had n.m.r. absorptions only in the region between 110 and 190 c.p.s. below tetramethylsilane and λ_{max}^{EtOH} 313 mμ (ε 7800); $\nu_{max}^{CH_2Cl_2}$ (selected) 1765, 1710, 1640, 1575, 1370, 1225, 1195, 1110, 1070, 1050, 1035, and 965 cm.$^{-1}$.

Hydrolysis Product from Ethylenediketene Dimer.—The dimer of m.p. 142–144° (583 mg.) was covered with 5 ml. of water and treated with 1.43 g. of sodium peroxide according to the method of Wedekind, *et al.*[2] Acidification of the reaction mixture gave a colorless solid which was recrystallized from water to afford 283 mg. (45%) of hydrolysis product having m.p. 168–170°. The analytical sample had m.p. 169.5–171° (lit.[2] m.p. 170–171°), λ_{max}^{EtOH} 298 mμ (ε 11,400), shifted to 292 mμ on addition of sodium hydroxide; ν_{max}^{KBr} (selected) 1707, 1660, 1628, and 1562 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92; mol. wt., 238; neut. equiv., 119. Found: C, 60.48; H, 5.87; mol. wt., 241; neut. equiv., 121.

When 73 mg. of the dimer and 1 ml. of 5% aqueous sodium hydroxide were combined and heated for 40 min. at 80°, a clear solution was obtained which was cooled and acidified to give 83 mg. (105%) of crude diacid, m.p. 169–171°; the infrared spectrum of this material was identical with that of the diacid of m.p. 169.5–171° obtained previously.

Oxidation Product from Ethylenediketene Dimer.—The mother liquor of the acidified reaction mixture from 583 mg. of dimer (IV) and 1.43 g. of sodium peroxide (*cf.* previous section) was extracted ten times with 10-ml. portions of ether. The combined ether extracts were washed once with saturated sodium chloride, dried over calcium sulfate, filtered, and concentrated to

(4) P. Yates and E. A. Chandross, *Tetrahedron Letters*, No. **20**, 1 (1959); E. A. Chandross and P. Yates, *Chem. Ind.* (London), 149 (1960).

(5) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p. 52.

(6) A. T. Blomquist and R. D. Spencer, *J. Am. Chem. Soc.*, **69**, 472 (1947); **70**, 30 (1948).

(7) For example, see J. C. Sauer, *ibid.*, **69**, 2444 (1947).

(8) See ref. 4, and W. R. Hatchard and A. K. Schneider, *ibid.*, **79**, 6261 (1957).

(9) Melting points are uncorrected. Analyses are by J. Nemeth and associates, Urbana, Ill.

give 191 mg. of colorless crystals, m.p. 80–83° (lit.[2] m.p. 81–82°). Recrystallization from benzene gave material of m.p. 83–84° (partial melt; clear melt at 190°).

Anal. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10; neut. equiv., 66. Found: C, 45.73; H, 6.09; neut. equiv., 72.

Examination of this material by infrared spectroscopy and paper chromatography with 1-propanol–concentrated ammonium hydroxide–water (60:20:20 by volume) as developer indicated that it was mostly glutaric acid (R_f 0.52). No acidic impurities were detected by paper chromatography; the infrared spectra of the oxidation product and glutaric acid were similar, but not superimposable.

The Ferric Chloride Oxidation of 5-Substituted o-Semidines and the Polarographic Properties of the Products

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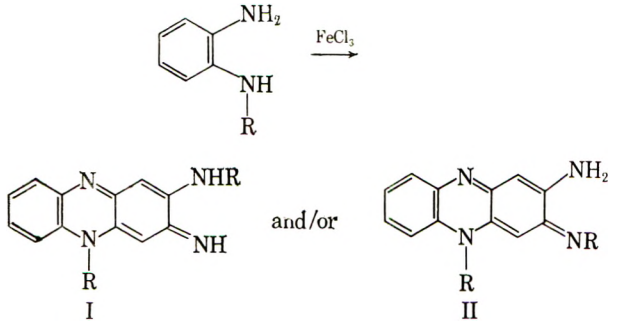
Contribution No. 1524 from the Department of Chemistry, University of California, Los Angeles 24, California

Received April 30, 1963

The ferric chloride oxidation of 5-substituted *o*-semidines (2-aminodiphenylamines) yielded 7-substituted 2-amino-3,5-dihydro-5-phenyl-3-phenyliminophenazines as main products, with elimination of one of the 5-substituents of the starting *o*-semidine. Condensation of these phenazine derivatives with ketones led to characteristic Schiff bases. Some polarographic properties of these phenazine derivatives were studied and the effect of substituents on the half-wave potentials was found to be in good agreement with Hammett's σ-values.

The ferric chloride oxidation of mono-*N*-substituted *o*-phenylenediamines has been investigated by Barry *et al.*,[1-3] who have proven that the main oxidation products are phenazine derivatives existing in two isomeric structures I and II which are formed either as a mixture or separately, depending on the nature of the starting amine.

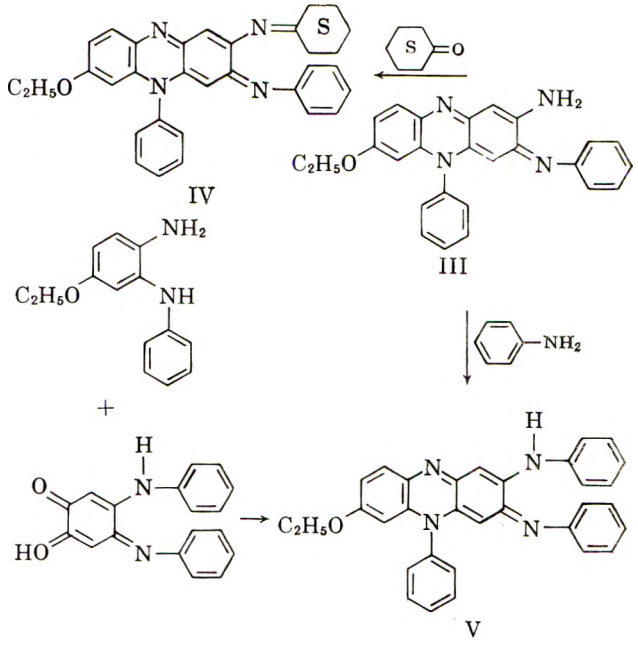


In the oxidation of 2-amino-5-chlorodiphenylamine one chlorine atom is eliminated and only the 7-chloro-II-isomer is formed.

In this laboratory, oxidation products of substituted 2-aminodiphenylamines (*o*-semidines) had been investigated previously as to their suitability as internal indicators in redox titrations. The present paper reports on compounds obtained by the ferric chloride oxidation of some 5-substituted 2-aminodiphenylamines and some of their polarographic properties.

A series of 5-substituted 2-aminodiphenylamines (as the hydrochlorides) were oxidized in aqueous alcoholic solution with ferric chloride. The 5-substituents included various halogen and alkoxy groups. These *o*-semidines were obtained by reduction of the corresponding substituted 2-nitrodiphenylamines, which in turn were prepared by the reaction of substituted anilines with substituted *o*-dinitro- or *o*-halonitrobenzenes. The oxidation products were separated and purified by liquid column chromatography on alumina.

On the basis of the previously cited prior investigations, the deeply colored main oxidation products were expected to be phenazine derivatives with structures analogous to the preceeding I- or II-isomers. This was indeed supported by the elemental analyses of these compounds which also indicated that in each case one of the 5-substituents had been eliminated in the oxidation. Since it seemed not altogether certain whether an alkoxy group would be eliminated in the same fashion as one of the chlorine atoms in the previously mentioned oxidation of 2-amino-5-chlorodiphenylamine, the structure of the main oxidation product of 2-amino-5-ethoxydiphenylamine was determined as 2-amino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine (III) by the following reactions.



Treatment of this oxidation product with aniline (analogous to Barry, *et al.*,[4]) yields compound V, which was independently synthesized by condensation of 2-amino-5-ethoxydiphenylamine with 4,5-dianilino-*o*-quinone. This proved a structure analogous to either

(1) V. C. Barry, J. G. Belton, J. F. O'Sullivan, and D. Twomey, *J. Chem. Soc.*, 888 (1956). This paper includes a literature survey of earlier work.

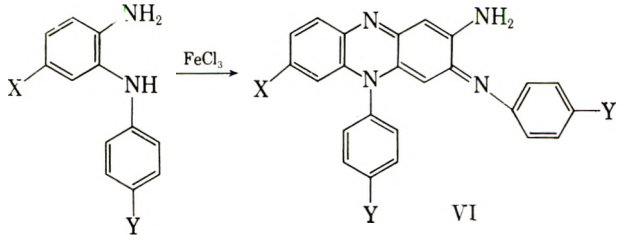
(2) V. C. Barry, J. G. Belton, J. F. O'Sullivan, and D. Twomey, *ibid.*, 893 (1956).

(3) V. C. Barry, J. G. Belton, J. F. O'Sullivan, and D. Twomey, *ibid.*, 896 (1956).

(4) V. C. Barry, J. C. Belton, J. F. O'Sullivan, and D. Twomey, *ibid.*, 895 (1958).

I or II,[4] with the ethoxy group in the 7-position. Structure III (II-isomer) was verified by the condensation of the oxidation product with cyclohexanone to the green Schiff base IV. In a control experiment, a similar green compound was obtained from cyclohexanone and the oxidation product of 2-amino-5-chlorodiphenylamine, for which the structure of a 7-chloro-II-isomer had been ascertained previously.[4]

The formation of green Schiff bases (described in detail later) with cyclohexanone was used subsequently to establish the structure of II-isomers for the oxidation products from other 5-substituted 2-aminodiphenylamines. The newly prepared compounds VI together with the corresponding starting materials are shown.



VI

where X = F, Br, I, —OCH_3, —OC_2H_5 for Y = H
and X = —OCH_3 for Y = F, Cl, —OCH_3

2-Aminodiphenylamines with a substituent in the 5-position have, it seems, a tendency to form II-isomers on oxidation, provided that the substituent can be eliminated in the reaction. A 5-methyl group would be expected to be very difficult to displace and, in fact, the oxidation product of 2-amino-5-methyldiphenylamine had properties quite different from those of either the I- or II-isomers. The chromatogram of the crude base had a development pattern unlike any of the other investigated compounds. Elution of the orange major band gave a bright red compound which dissolved easily in benzene forming a yellow-orange solution. Three other bands on elution gave yellow-green fluorescent, violet, and blue solutions in benzene. The structure of the major constituent has yet not been determined. Similar observations were reported[5] for the oxidation of 2-amino-4-methyldiphenylamine where the stable methyl group in the 4-position also prevents the formation of the phenazine skeleton which involves both the 4- and 5-positions of the starting amine.

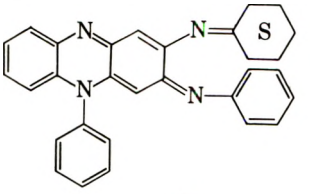
On the other hand, the lack of a substituent in the 5-position of the starting amine causes the formation on oxidation of either a mixture of both isomers or the I-isomer exclusively, as has been shown by Barry, *et al.*[1,3]

Schiff Bases from II-Isomers by Condensation with Cyclohexanone.—As previously mentioned, the reaction of the II-isomers with cyclohexanone in acid solutions resulted in the formation of green compounds which were distinctly different from the glyoxalino derivatives obtained by Barry, *et al.*,[1,6] in reactions of I-isomers with ketones. These glyoxalines were described as yellow to orange-red compounds which were quite soluble, exhibited a greenish yellow fluorescence in solution, and when chromatographed on alumina formed a rather fast moving band on elution with benzene.

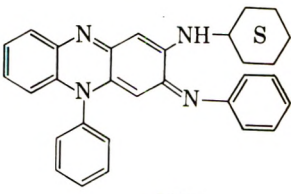
(5) V. C. Barry, J. G. Belton, M. L. Conalty, and D. Twomey, *Nature* **162**, 622 (1948).

(6) V. C. Barry, J. G. Belton, J. F. O'Sullivan, and D. Twomey, *J. Chem. Soc.*, 3347 (1956).

From the experimental results, it appears quite clear that these green compounds are Schiff bases of type VII. The new carbon–nitrogen double bond of the cyclohexylideneamino group can then be responsible for the color difference between the Schiff bases and the parent II-isomers by extending the resonance system of the phenazine skeleton. The color change of the Schiff bases from green to red in hydroxylic solvents (especially rapid in the presence of traces of acid) suggests a protonation of the cyclohexylideneamino double bond, thus interrupting the conjugation with the phenazine system and possibly initiating the addition of water (or alcohol) to form amino-hydroxyl (or amino-alkoxy) ketals.



VII



VIII

Further substantiation of the structure of these green compounds as Schiff bases was obtained from hydrogenation experiments on the Schiff base of 2-amino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine. The chromatographic behavior of this substance was very similar to that of compound IV. The infrared spectrum of this new compound had a single band in the N–H region, thus suggesting the presence of a secondary amine. Both elementary analysis and infrared spectrum indicated that the cyclohexyl group had been preserved in the molecule. Similar results also were obtained for the methoxy analog.

From the foregoing evidence, it appears that during the reduction of the Schiff base VII both the quinoidal system and the carbon–nitrogen double bond of the cyclohexylideneamino group are hydrogenated and in the reoxidation only the quinoidal system is reformed. The structure of the new compound can then be represented correctly by formula VIII.

Thus the formation of the Schiff base, its reduction and reoxidation leads in effect to an alkylation of the free amino group of the original II-isomer. The nature of the *N*-substituent thus introduced will, obviously, depend on the structure of the carbonyl compound employed in the formation of the Schiff base.

Some Polarographic Properties of These Phenazine Derivatives.—The substituted 2-amino-3-anilino-5-phenylphenazinium chlorides described earlier are compounds which, in alcoholic solutions, are intensely red. This property suggested their possible use as internal redox indicators. Preliminary studies have indicated the feasibility of these compounds in the titration of dissolved oxygen with chromium(II) and europium(II) solutions. In these cases, the phenazine is reduced rapidly to a greenish yellow solution of the semiquinone in acid solution. The reduction product in turn is readily reoxidized by oxygen to the colored phenazine. However, their surprisingly low solubility in water and aqueous alcoholic solutions compared to other 5-phenylphenazinium compounds, such as the commercial safranines and phenosafranine, discouraged such use.

However, it still remained possible to determine the effect of a substituent group in terms of the difference

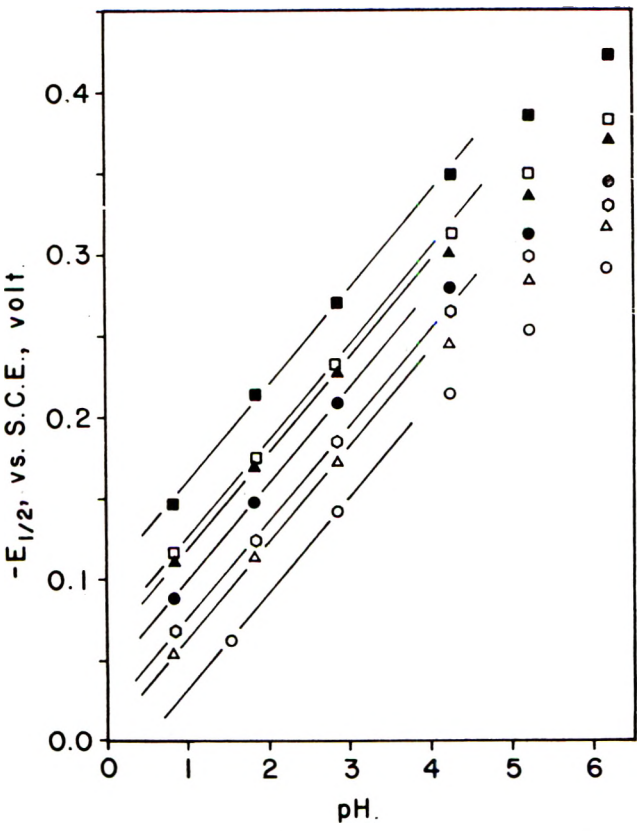
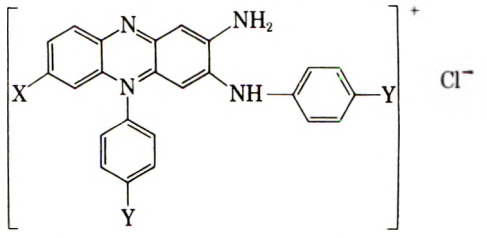


Fig. 1.—Half-wave potential–pH dependence of substituted 2-amino-3-anilino-5-phenylphenazinium chlorides: ■ X = Y = $-OCH_3$; □ X = $-OCH_3$, Y = H; ▲ X = $-OCH_3$, Y = F; ● X = $-OCH_3$, Y = Cl; ⬡ X = Y = H; △ X = F, Y = H; and ○ X = Br, Y = H.

in the reduction potential between the substituted and unsubstituted compounds. Polarographic techniques provided a means for such an investigation.

As representative compounds for study, those that had the structure that follows were considered, where



X = H, F, and Br for Y = H; X = $-OCH_3$ for Y = H, F, Cl, and $-OCH_3$. The choices were guided somewhat by Hammett's σ-values for *para* substitution. The polarographic data reported here were obtained at a concentration of 0.25 m*F* in 3:1 95% ethanol–water solutions with lithium acetate–nitric acid buffers and with lithium nitrate added to increase the ionic strength to 0.25 *M*. The choices for solvent composition and supporting electrolyte were governed by solubility considerations.

In experiments to determine the effects of concentration, solutions 0.50 and 0.75 m*F* gave waves similar to those obtained with the 0.25 m*F* solution. Likewise, half-wave potentials obtained over the ionic strength range of 0.05 to 0.25 *M* were the same after corrections were applied for changes in pH and *iR* drop.

It was found advisable to prepare the ethanolic solutions just prior to the polarographic runs. A small prewave was observed with some of the solutions that had been allowed to stand for one or two days. These waves were $^1/_{20}$–$^1/_{25}$ the height of the main wave and occurred at a potential about 0.2 volt more positive. Among the solutions that were set aside for one to two months, that of the bromo (X = Br, Y = H) compound did not develop such a wave while the prewave of the fluoro (X = F, Y = H) compound increased slightly. The analogous waves of the methoxy (X = $-OCH_3$, Y = H) and methoxyfluoro (X = $-OCH_3$, Y = F) phenazinium chlorides in a month's period had increased to about a third of the height of the original main wave. In all cases, the total height of the two waves remained about constant. The cause of the anomalous waves has not been established.

The experimental half-wave potentials are summarized in Table I. The pH values are "apparent" ones obtained with a glass electrode. The estimated precision for the pH measurements and the half-wave potentials are ±0.02 pH units and ±2 mv., respectively.

TABLE I

MEASURED HALF-WAVE POTENTIALS (S.C.E.) AT VARIOUS pH VALUES

A. Dimethoxy (X = Y = $-OCH_3$)

pH	0.85	1.88	2.88	4.28	5.26	6.24
$-E_{1/2}$, v.	0.147	0.214	0.271	0.349	0.386	0.423

B. Methoxy (X = $-OCH_3$, Y = H)

pH	0.86	1.88	2.85	4.29	5.25	6.23
$-E_{1/2}$, v.	0.117	0.175	0.233	0.313	0.350	0.383

C. Methoxyfluoro (X = $-OCH_3$, Y = F)

pH	0.86	1.86	2.88	4.26	5.25	6.23
$-E_{1/2}$, v.	0.111	0.170	0.228	0.301	0.336	0.371

D. Methoxychloro (X = $-OCH_3$, Y = Cl)

pH	0.85	1.86	2.88	4.27	5.26	6.23
$-E_{1/2}$, v.	0.089	0.148	0.209	0.280	0.313	0.345

E. Unsubstituted (X = Y = H)

pH	0.87	1.87	2.88	4.28	5.26	6.23
$-E_{1/2}$, v.	0.068	0.124	0.185	0.265	0.298	0.330

F. Fluoro (X = F, Y = H)

pH	0.85	1.86	2.88	4.26	5.25	6.20
$-E_{1/2}$, v.	0.054	0.114	0.173	0.245	0.284	0.317

G. Bromo (X = Br, Y = H)

pH		1.57	2.88	4.27	5.25	6.20
$-E_{1/2}$, v.		0.065	0.142	0.215	0.254	0.292

The tabular data is presented graphically in Fig. 1. The $-E_{1/2}$ *vs.* pH slope, for all compounds, in the low pH region is, within experimental error, 0.059 volt/pH unit, and at higher pH values decreases, approaching 0.030 volt/pH unit.

In Table II, the substituent effects in terms of the half-wave potentials are summarized as differences, $\Delta E_{1/2}$, between a substituted compound and the selected reference compound. $(\Delta E_{1/2})_1$ represents the compounds with Y = H and X = substituent with the unsubstituted compound (X = Y = H) as the reference and $(\Delta E_{1/2})_2$ represents those with X = $-OCH_3$ and Y = substituent with the methoxy (X = $-OCH_3$, Y = H) compound as the reference. The $\Delta E_{1/2}$ values are

the average differences in the region where the $-E_{1/2}$ *vs.* pH slope is 0.059 volt/pH unit. The shifts in the half-wave potentials are in the direction expected if one considers the electron donating and withdrawing tendencies of the substituents. Good correlation with the Hammett σ-values for *para* substitution[7] is shown in Fig. 2.

Table II

Changes in the Half-Wave Potential Resulting from Substituent Effects

Compound	$(\Delta E_{1/2})_1$	$(\Delta E_{1/2})_2$
Dimethoxy (X = Y = —OCH_3)	...	−0.035
Methoxy (X = —OCH_3, Y = H)	−0.050	0.000
Methoxyfluoro (X = —OCH_3, Y = F)	...	0.006
Methoxychloro (X = —OCH_3, Y = Cl)	...	0.027
Unsubstituted (X = Y = H)	0.000	...
Fluoro (X = F, Y = H)	0.011	...
Bromo (X = Br, Y = H)	0.043	...

In order to determine the reversibility of the waves and the mechanism of the electroreduction of the phenazinium chlorides, a preliminary hydrogenation experiment was performed. A plot of $-E_{d.m.e.}$ *vs.* log $i/(i_d - i)$ had indicated a one-electron reduction in the low pH region and a two-electron reduction at higher pH values. This was consistent with pH data in Fig. 1 since a one-electron reduction to a semiquinone would require one proton. Hydrogenation of a sample at low pH with palladium-on-charcoal catalyst gave a deep green solution typical of those of semiquinones. Similar treatment of a solution at higher pH values resulted in a yellow-green solution. A polarogram of a low pH solution partially hydrogenated had a composite anodic–cathodic wave with no inflection in the vicinity of the residual current, hence, indicating reversibility between the semiquinone and the phenazine. Further investigations are currently being undertaken to determine electron spin resonance and chronopotentiometric characteristics and the effect of other X- and Y-substituent combinations on Fig. 2 type plots.

Experimental

The Ferric Chloride Oxidation of 5-Substituted *o*-Semidines. I. Synthesis of Substituted 2-Nitrodiphenylamines. Starting Materials.—Aniline and *p*-anisidine were redistilled under reduced pressure from a small amount of zinc dust. *p*-Chloroaniline was used without further purification. All were Eastman White Label. *p*-Fluoroaniline was prepared by tin–hydrochloric acid reduction of *p*-fluoronitrobenzene, obtained by thermal decomposition of the tetrafluoroborate diazonium salt of *p*-nitroaniline.[8]

3,4-Dinitrohalobenzenes were prepared by nitration of the appropriate 1-halo-3-nitrobenzene with a mixture of sulfuric and fuming nitric acids. The chloro compound was purified by reduced pressure distillation, b.p. 115 (0.3), 120 (0.6), and 127° (1 mm).[9] The bromo, m.p. 58.0–58.5° (lit.[10] 59.4, 59–59.5°), and iodo, m.p. 73–74° (lit.[11] 74°), were recrystallized from 95% ethanol.

2,4-Difluoronitrobenzene was prepared according to Finger and Kruse.[12] 3,4-Dinitrotoluene was obtained through a two-step oxidation of 4-amino-3-nitrotoluene with Caro's acid[13] and fuming nitric acid[14] followed by reduced pressure molecular distillation and recrystallization from methanol, m.p. 58.3–59.0°.

2-Nitrodiphenylamine (Eastman Kodak 3906) was recrystallized from 95% ethanol.

5-Chloro-2-nitrodiphenylamine.—A solution of 102 g. (0.5 mole) of 1-chloro-3,4-dinitrobenzene and 140 ml. (1.5 moles) of aniline in 500 ml. of 95% ethanol was allowed to stand for 72 hr. The product was filtered, washed with cold ethanol until free of dark discolorations, digested with 3 *N* hydrochloric acid, and recrystallized from ethanol. Yield was 81 g. (65%), m.p. 112.2–112.6° (cor.) (lit.[15] 108.5°, from 2,4-dichloronitrobenzene, 110°[16]).

5-Bromo-2-nitrodiphenylamine.—1-Bromo-3,4-dinitrobenzene (125 g., 0.5 mole) treated as the preceding chloro analog gave 85 g. (57%) of product, m.p. 117.9–118.9° (cor.) (lit.[17] 116°).

5-Iodo-2-nitrodiphenylamine.—3,4-Dinitroiodobenzene (50 g., 0.17 mole) treated as the previous chloro analog gave 21 g. (36%) of product, m.p. 113.5–114.0° (lit.[18] 111°).

5-Chloro-4′-methoxy-2-nitrodiphenylamine.—One hundred grams (0.5 mole) of 1-chloro-3,4-dinitrobenzene treated with *p*-anisidine by the procedure given in the previous section for 5-chloro-2-nitrodiphenylamine, gave on recrystallization from 95% ethanol, 86 g. (62%) of product, m.p. 115.9–116.4°. The analytical sample on further recrystallization from petroleum ether (J. T. Baker, b.p. 20–40°) gave m.p. 115.7–116.2°.

Anal. Calcd. for $C_{13}H_{11}O_3N_2Cl$: C, 56.02; H, 3.98; N, 10.05. Found: C, 56.23; H, 3.89; N, 10.06.

4′,5-Dichloro-2-nitrodiphenylamine.—A solution of 20.3 g. (0.1 mole) of 1-chloro-3,4-dinitrobenzene and 41.5 g. (0.3 mole) of *p*-chloroaniline in 150 ml. of 95% ethanol was heated at 40–50° for 4 hr. The crystalline product obtained upon cooling was filtered, washed with cold ethanol, digested with 3 *N* hydrochloric acid, and recrystallized from ethanol. Yield was 15 g. (53%), m.p. 158.0–158.5° (lit.[16] from 2,4-dichloronitrobenzene, 156°).

5-Fluoro-2-nitrodiphenylamine.[19]—In a modification of the Suschitzky procedure, a solution containing 17 g. (0.11 mole) of 2,4-difluoronitrobenzene and 30 ml. (0.33 mole) of aniline in 100 ml. of 95% ethanol was allowed to stand for 48 hr. Refluxing was prevented by the precipitation of insoluble plates, later identified as aniline hydrofluoride, $C_6H_5NH_2 \cdot 4HF$, by infrared spectrophotometric comparison with an authentic sample.[20] The mixture of crystals obtained upon cooling was isolated and extracted with ethyl ether. The ether was removed and the de-

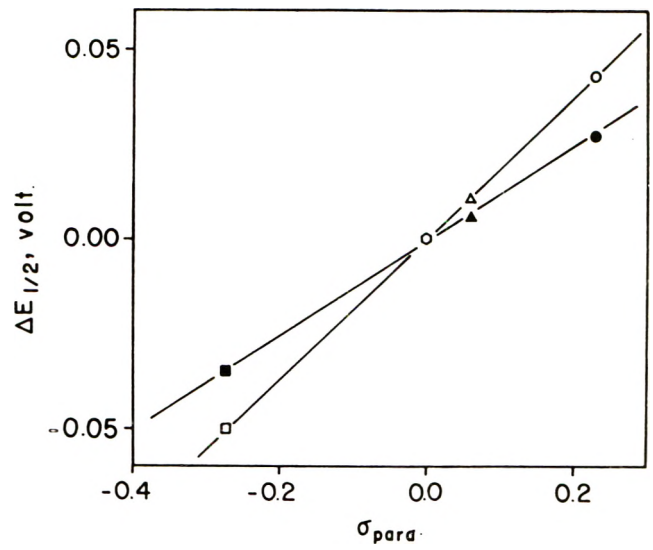


Fig. 2.—Plot of $\Delta E_{1/2}$ values of Table II *vs.* substituent constants, σ_{para}. Legend: same as in Fig. 1.

(7) *E.g.*, H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(8) A. Roe, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 193.

(9) For preparations involving recrystallization, see, *e.g.*, A. Laubenheimer, *Ber.*, **9**, 760 (1876).

(10) W. Korner, *Gazz. chim. ital.*, **4**, 349 (1874); A. Mangini, *ibid.*, **66**, 675 (1936).

(11) R. S. Kapil, *J. Chem. Soc.*, 4127 (1959).

(12) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956).

(13) W. D. Langley, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 334.

(14) J. Meisenheimer and E. Hess, *Ber.*, **52**, 1161 (1919).

(15) A. Laubenheimer, *ibid.*, **9**, 760 (1876).

(16) V. F. Borodkin, *Zh. Prikl. Khim.*, **21**, 987 (1948).

(17) P. Jacobson and R. Grosse, *Ann.*, **303**, 323 (1898).

(18) P. Jacobson, F. K. Fertsch, and F. Heubach, *ibid.*, **303**, 330 (1898).

(19) H. Suschitzky, *J. Chem. Soc.*, 3042 (1953).

(20) J. F. T. Berliner and R. M. Hann, *J. Phys. Chem.*, **32**, 1142 (1928).

sired product was recrystallized from 95% ethanol. Yield was 18 g. (73%), m.p. 92.0–93.5° (lit.[19] 93–94°).

5-Chloro-4′-fluoro-2-nitrodiphenylamine.—A mixture of 26 g. (0.23 mole) of *p*-fluoroaniline, 47 g. (0.23 mole) of 1-chloro-3,4-dinitrobenzene, and 33 g. (0.4 mole) of sodium acetate in 250 ml. of 95% ethanol was refluxed on a steam bath for 12 hr. Upon cooling, the solid was isolated, washed with cold ethanol, water, and 10% sodium bicarbonate solution, digested with 3 *N* hydrochloric acid, and recrystallized twice from ethanol. Yield was 15 g. (25%), m.p. 110.0–110.6°.

Anal. Calcd. for $C_{12}H_8N_2O_2ClF$: C, 54.05; H, 3.02; N, 10.51. Found: C, 54.22; H, 3.31; N, 10.76.

5-Methoxy-2-nitrodiphenylamine.—To 25 g. (0.085 mole) of 5-bromo-2-nitrodiphenylamine was added a solution prepared by dissolving 5 g. (0.22 mole) of sodium in 375 ml. of absolute methanol. The resulting solution was refluxed for 48 hr. Upon cooling, the crystalline product was isolated, washed with water, and recrystallized from 95% ethanol. Yield was 18.5 g. (89%), m.p. 112.5–113.2°. The analytical sample on further recrystallization had m.p. 112.6–113.3°.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.81; H, 5.20; N, 11.25.

4′-Fluoro-5-methoxy-2-nitrodiphenylamine.—5-Chloro-4′-fluoro-2-nitrodiphenylamine (6 g., 0.023 mole) was treated with sodium methoxide solution (5 g. of sodium in 250 ml. of methanol) as before. Upon two recrystallizations from methanol, the yield was 5 g. (87%), m.p. 112.2–112.7°.

Anal. Calcd. for $C_{13}H_{11}N_2O_3F$: C, 59.54; H, 4.23; N, 10.68. Found: C, 59.84; H, 4.31; N, 10.77.

4′-Chloro-5-methoxy-2-nitrodiphenylamine.—4′,5-Dichloro-2-nitrodiphenylamine (5.7 g., 0.02 mole) was treated with sodium methoxide solution (9 g. of sodium in 800 ml. of methanol) as before. Upon recrystallization from methanol, the yield was 4.8 g. (86%), m.p. 131.4–131.9°.

Anal. Calcd. for $C_{13}H_{11}N_2O_3Cl$: C, 56.02; H, 3.98; N, 10.05. Found: C, 56.25; H, 4.19; N, 9.86.

4′,5-Dimethoxy-2-nitrodiphenylamine.—5-Chloro-4′-methoxy-2-nitrodiphenylamine (40 g., 0.144 mole) was treated with sodium methoxide solution (10 g. of sodium in 750 ml. of methanol) as before. Recrystallization from 95% ethanol gave 38 g. (97%) of product, m.p. 105.6–106.2°. The analytical sample on further recrystallization from ethanol had m.p. 106.0–106.5°.

Anal. Calcd. for $C_{14}H_{14}O_4N_2$: C, 61.30; H, 5.15; N, 10.21. Found: C, 61.17; H, 5.21; N, 10.29.

5-Ethoxy-2-nitrodiphenylamine.—To 29 g. (0.117 mole) of 5-chloro-2-nitrodiphenylamine in a pressure bottle was added a solution prepared by dissolving 6 g. (0.26 mole) of sodium in 400 ml. of commercial absolute ethanol. The bottle was sealed and heated at 100° for 48 hr. Upon cooling, the crystalline product was isolated, washed with 3 *N* hydrochloric acid, and recrystallized from 95% ethanol with the aid of charcoal. Yield was 24 g. (71%), m.p. 107.5–108.0° (lit.[21] 106–106.5°).

5-Methyl-2-nitrodiphenylamine.—Ten grams (0.055 mole) of 3,4-dinitrotoluene, 15 ml. (0.16 mole) of aniline, and 5 g. of sodium acetate in 50 ml. of nitrobenzene was heated 48 hr. at 150°. The nitrobenzene was removed by steam distillation and the residue extracted with ethyl ether. The product, obtained by drying the extract and evaporating the solvent, was placed on alumina (Merck 71707) with benzene and eluted with *n*-pentane. Upon recrystallization from light petroleum (Skelly B), the yield was 7 g. (56%), m.p. 109–110°. The analytical sample on further recrystallization had m.p. 111.2–111.6°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.72; H, 5.08; N, 12.23.

The structure was confirmed by infrared spectrophotometric comparison with an authentic sample obtained by desulfonation of barium 4-anilino-2-methyl-5-nitrobenzenesulfonate, m.p. 110°.[22]

II. Synthesis of Substituted 2-Amino-3,5-dihydro-5-phenyl-3-phenyliminophenazines. General.—The 2-nitrodiphenylamines were reduced to the amine by hydrogenation in 95% ethanol with 0.5 g. of 10% palladium-on-charcoal (Matheson Coleman and Bell 5865) as catalyst unless otherwise stated.

Melting point determinations (uncorrected) were made on a Kofler micro hot stage (A. H. Thomas Co.) and the reported decomposition points are temperatures at which the crystals appeared to deform. The compounds discolored when heated above 200°.

The alumina used in the chromatographic purifications were Merck chromatographic grade 71707, Woelm basic (Brockmann) activity grade I, and Harshaw 90% catalyst 0101P. The Harshaw product was neutralized with ethyl acetate, washed with water and methanol, dried, and activated by heating for several days at 150°. The hydrochlorides of the substituted phenazines were prepared by treating a solution of the compound in methanol with a slight excess of hydrochloric acid. The salt thus obtained was recrystallized twice from methanol.

All these compounds have rather low solubility in alcohols, are moderately soluble in benzene, dichloromethane and acetic acid, and are very sparingly soluble in ether, and insoluble in water and carbon tetrachloride. All 7-alkoxylated bases form crystals with a green luster while the 7-halogenated ones are brown. The hydrochlorides of these compounds are needles or plates with golden green luster and dissolve in alcohols to give violet-red solutions, while the solutions of the free bases in organic solvents are red-brown.

The microanalyses were performed by Dr. Adalbert Elek and Miss Heather King.

2-Amino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine.—Three grams of 2-amino-5-ethoxydiphenylamine hydrochloride, obtained by hydrogenation of 5-ethoxy-2-nitrodiphenylamine in 95% ethanol and subsequent precipitation in anhydrous ethyl ether with gaseous hydrogen chloride, was dissolved in 220 ml. of 3:1 95% ethanol–water and oxidized with a solution containing 7 g. of ferric chloride hexahydrate in 70 ml. of water. After stirring for 3.5 hr., the crude hydrochloride was isolated, dissolved in methanol, and precipitated as the free base with ammonium hydroxide. The 2.25 g. of base thus obtained was chromatographed on alumina (450 g. of Woelm activity III) with benzene. The major red band gave, on elution and recrystallization from benzene 1.78 g. (77%) of crystals with a greenish luster, dec. pt. 245–248°.

Anal. Calcd. for $C_{26}H_{22}N_4O$: C, 76.82; H, 5.46; N, 13.78; C_2H_5O, 11.09. Found: C, 76.58; H, 5.36; N, 13.57; C_2H_5O, 10.83.

The hydrochloride was obtained as needles with a golden green luster.

Anal. Calcd. for $C_{26}H_{22}N_4O\cdot HCl$: C, 70.50; H, 5.23. Found: C, 70.31; H, 5.32.

Material from a second red band, much slower moving and narrow, was obtained by extrusion and treatment of the adsorbent with benzene–methanol. This material (after removal of solvent) was rechromatographed with benzene on alumina (Woelm activity IV). Similarly to the original chromatogram, two bands were observed, a broad red band and a slow narrow one. Elution and recrystallization of the first band gave 0.15 g. of material which was identical with the earlier product when compared by decomposition point and infrared spectrophotometry (potassium bromide pellet).

This behavior suggests the presence of an equilibrium between two isomeric structures of the same compound, one being more strongly absorbed than the other, causing the observed separation of bands on the column. In solution, however, the equilibrium seems to be re-established rapidly, thus preventing ready isolation of the pure isomers. These results were obtained regardless of whether or not the solutions, prior to chromatography, were heated to the boiling point of benzene or maintained at room temperature. Similar behavior was observed with the methoxy and the dimethoxy (X = Y = $-OCH_3$) analogs.

2-Anilino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine.—(A) A mixture of 0.37 g. of 2-amino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine hydrochloride, 0.11 g. of aniline hydrochloride, and 6 ml. of aniline was refluxed for 12 min. The crude product, obtained by pouring the cooled reaction mixture into ethyl ether, was isolated, dissolved in methanol, and precipitated as the free base with ammonium hydroxide. The base was chromatographed on alumina (Woelm activity III) with benzene. Two strong bands developed, the faster being the desired product and the other larger band the unchanged starting material. The product, when rechromatographed on activity II alumina and recrystallized from benzene–methanol, resulted in 0.068 g. (17%) of brown crystals.

(B) A solution of 1.6 g. of 2-amino-5-ethoxydiphenylamine hydrochloride and 1.8 g. of 4,5-dianilino-*o*-quinone (from the oxidative condensation of catechol and aniline with potassium

(21) P. Jacobson, F. C. Fertsch, and W. Fischer, *Ber.*, **26**, 681 (1893).
(22) C. Schraube and E. Romig, *ibid.*, **26**, 575 (1893).

iodate,[23] m.p. 193°) in 100 ml. of 95% ethanol was refluxed for 2 hr. Upon cooling, the product was isolated, recrystallized from 95% ethanol, converted to the free base with ammonium hydroxide, and chromatographed on alumina (Woelm activity III) with benzene. The product obtained from elution of the rapid major band was recrystallized from benzene. Yield was 1.6 g. (55%) of brown crystals, dec. pt. 252–254°.

Anal. Calcd. for $C_{32}H_{26}N_4O$: C, 79.28; H, 5.43; N, 11.61; C_2H_5O, 9.34. Found: C, 79.16; H, 5.29; N, 11.40; C_2H_5O, 9.30.

The hydrochloride was obtained as needles with greenish luster.

Anal. Calcd. for $C_{32}H_{26}N_4O$·HCl: C, 74.05; H, 5.24. Found: C, 74.16; H, 5.33.

The decomposition points and infrared spectra (potassium bromide pellets) of both preparations were identical.

2-Amino-3,5-dihydro-7-methoxy-5-phenyl-3-phenyliminophenazine.—To the solution obtained by hydrogenating 3 g. of 5-methoxy-2-nitrodiphenylamine in 120 ml. of 95% ethanol was added 2 ml. of hydrochloric acid and then an oxidizing solution containing 8 g. of ferric chloride hexahydrate in 80 ml. of water. After stirring for 2 hr., the mixture was diluted with water and crude hydrochloride, which crystallized, was isolated, dissolved in methanol, and precipitated as the free base with ammonium hydroxide. The base, 1.7 g., was chromatographed on alumina (500 g. of Merck with 8 wt. % of water added) with benzene as solvent and 95:1 benzene–ether as eluent. Elution of the major band, removal of solvent and recrystallization from benzene gave 1.52 g. (62%) of crystals with a greenish luster, dec. pt. 252–254°.

Anal. Calcd. for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28; CH_3O, 7.91. Found: C, 76.58; H, 5.14; N, 14.30; CH_3O, 7.81.

The hydrochloride was obtained as needles with greenish luster.

Anal. Calcd. for $C_{24}H_{20}N_4O$·HCl: C, 70.00; H, 4.93. Found: C, 69.98; H, 5.36.

2-Amino-5-*p*-anisyl-3-*p*-anisylimino-3,5-dihydro-7-methoxyphenazine was obtained in 72% yield from 4′,5-dimethoxy-2-nitrodiphenylamine by the above procedure as crystals with greenish luster, dec. pt. 258–260°.

Anal. Calcd. for $C_{27}H_{24}N_4O_3$: C, 71.66; H, 5.34; CH_3O, 20.58. Found: C, 71.65; H, 5.21; CH_3O, 20.51.

The hydrochloride was obtained as needles with greenish luster.

Anal. Calcd. for $C_{27}H_{24}N_4O_3$·HCl·H_2O: C, 63.96; H, 5.38; Cl, 6.99. Found: C, 64.24; H, 5.24; Cl, 7.07.

2-Amino-3,5-dihydro-5-*p*-fluorophenyl-3-*p*-fluorophenylimino-7-methoxyphenazine was obtained in 77% yield from 4′-fluoro-5-methoxy-2-nitrodiphenylamine by the above procedure as crystals with greenish luster, dec. pt. 244–246°.

Anal. Calcd. for $C_{25}H_{18}N_4OF_2$: C, 70.08; H, 4.23; CH_3O, 7.24. Found: C, 70.17; H, 4.37; CH_3O, 7.31.

The hydrochloride was obtained as needles with a golden green luster.

Anal. Calcd. for $C_{25}H_{18}N_4OF_2$·HCl: C, 64.59; H, 4.12. Found: C, 64.30; H, 4.42.

2-Amino-5-*p*-chlorophenyl-3,5-dihydro-3-*p*-chlorophenylimino-7-methoxyphenazine.—A solution of 4 g. of 4′-chloro-5-methoxy-2-nitrodiphenylamine, 12 g. of iron filings, and 4 ml. of acetic acid in 220 ml. of 50% ethanol was refluxed for 1.5 hr. and extracted with ethyl ether. The ethereal phase was dried with sodium hydroxide and the hydrochloride of the product precipitated with hydrogen chloride gas. The amine hydrochloride thus obtained (3.6 g.) was treated by the previous procedure. Yield of crystals with greenish luster was 2.3 g. (80%), dec. pt. above 250°.

Anal. Calcd. for $C_{25}H_{18}N_4OCl_2$: C, 65.08; H, 3.93; N, 12.15; Cl, 15.37. Found: C, 65.29; H, 4.16; N, 12.09; Cl, 15.22.

Hydrogenation of 4′-chloro-5-methoxy-2-nitrodiphenylamine with palladium catalyst and subsequent oxidation gave a compound corresponding to the product from 2-amino-5-methoxydiphenylamine.

The hydrochloride was obtained as plates with a golden green luster.

Anal. Calcd. for $C_{25}H_{18}N_4OCl_2$·HCl·0.5H_2O: C, 59.24; H, 3.98; Cl, 20.98. Found: C, 59.36; H, 4.01; Cl, 20.82.

2-Amino-3,5-dihydro-7-fluoro-5-phenyl-3-phenyliminophenazine.—To the solution obtained by hydrogenating 5 g. of 5-fluoro-2-nitrodiphenylamine in 150 ml. of 95% ethanol was added 2.3 ml. of hydrochloric acid and an oxidizing solution containing 14 g. of ferric chloride hexahydrate in 150 ml. of water. After stirring for 90 min., the hydrochloride of the crude product was precipitated by the addition of water, isolated, dissolved in methanol, and precipitated as the free base with ammonium hydroxide. The 3.2 g. of product thus obtained was chromatographed on alumina (500 g. of Merck with 10 wt. % of water added) with benzene. The main reddish brown band was eluted and rechromatographed on more active alumina. Upon recrystallizing twice from benzene, the yield of dark brown crystals was 1.65 g. (40%), dec. pt. 250–252°.

Anal. Calcd. for $C_{24}H_{17}N_4F$: C, 75.77; H, 4.51; N, 14.73. Found: C, 75.84; H, 4.55; N, 14.74.

The hydrochloride was obtained as plates with greenish luster.

Anal. Calcd. for $C_{24}H_{17}N_4F$·HCl: C, 69.14; H, 4.35. Found: C, 69.30; H, 4.45.

2-Amino-3,5-dihydro-7-iodo-5-phenyl-3-phenyliminophenazine.—5-Iodo-2-nitrodiphenylamine was reduced with tin–hydrochloric acid[18] and converted to the hydrochloride by gaseous hydrogen chloride precipitation in anhydrous ethyl ether. Catalytic hydrogenation was unsuccessful with this compound.

A solution of 3.4 g. of 2-amino-5-iododiphenylamine hydrochloride in 150 ml. of 95% ethanol was oxidized by stirring for 3 hr. with a solution containing 6.3 g. of ferric chloride hexahydrate in 60 ml. of water. The hydrochloride of the crude product was precipitated by the addition of water, isolated, and recrystallized from methanol; yield, 2.35 g. Conversion to the free base with ammonium hydroxide gave 1.9 g. of brown crystals which, when chromatographed on alumina (300 g. of Merck with 8 wt. % of water added) with benzene, yielded 1.3 g. (62%) of product, dec. pt. 269–272°.

Anal. Calcd. for $C_{24}H_{17}N_4I$: C, 59.02; H, 3.51; N, 11.47; I, 25.99. Found: C, 59.20; H, 3.53; N, 11.41; I, 25.86.

The hydrochloride was obtained as needles with golden green luster.

Anal. Calcd. for $C_{24}H_{17}N_4I$·HCl: C, 54.92; H, 3.46. Found: C, 54.79; H, 3.53.

2-Amino-7-bromo-3,5-dihydro-5-phenyl-3-phenyliminophenazine.—To a solution obtained by hydrogenating 11.7 g. of 5-bromo-2-nitrodiphenylamine in 200 ml. of 95% ethanol was added an oxidizing solution containing 30 g. of ferric chloride hexahydrate and 2 ml. of hydrochloric acid in 30 ml. of water. After standing 48 hr., the solution was chilled, yielding 3.5 g. of crude hydrochloride. Fifteen grams of the hydrochloride thus prepared was converted with ammonium hydroxide in 95% ethanol to 8.6 g. of crude free base which in turn was chromatographed on alumina (2 kg. of Harshaw with 10 wt. % of water added) with benzene. The product obtained by elution of the main band was recrystallized twice from dichloromethane–methanol as follows. After adding an equal volume of methanol to a warm solution of the base in 300 ml. of dichloromethane, the resulting solution was reduced to 300 ml. and allowed to cool. The yield was 4.8 g., dec. pt. gradual above 200°.

Anal. Calcd. for $C_{24}H_{17}N_4Br$: C, 65.31; H, 3.88. Found: C, 65.47; H, 4.00. The hydrochloride was obtained as needles with dark green luster.

Anal. Calcd. for $C_{24}H_{17}N_4Br$·HCl: C, 60.33; H, 3.80. Found: C, 60.19; H, 3.86.

2-Amino-7-chloro-3,5-dihydro-5-phenyl-3-phenyliminophenazine.—5-Chloro-2-nitrodiphenylamine was treated similarly to the bromo analog.[24]

The hydrochloride was obtained as plates with greenish luster.

Anal. Calcd. for $C_{24}H_{17}N_4Cl$·HCl: C, 66.52; H, 4.19. Found: C, 66.62; H, 4.25.

2-Amino-3,5-dihydro-5-phenyl-3-phenyliminophenazine.—2-Nitrodiphenylamine was hydrogenated and the resulting diamine was precipitated as the hydrochloride from anhydrous ethyl ether with gaseous hydrogen chloride. The 2-aminodiphenylamine hydrochloride thus obtained was oxidized with ferric chloride by the procedure of Barry, *et al.*,[3] and chromatographed on alumina (3 g. of base on 700 g. of Merck with 10 wt. % of water added) with benzene. The deep red band gave, on elution and recrystallization from dichloromethane–methanol, dark red plates, dec. pt. 258–260°.

Anal. Calcd. for $C_{24}H_{18}N_4$: C, 79.53; H, 5.01. Found: C, 79.71; H, 4.84.

The hydrochloride was obtained as plates with greenish luster.

Anal. Calcd. for $C_{24}H_{18}N_4$·HCl·0.5H_2O: C, 70.66; H, 4.94; Cl, 8.69. Found: C, 70.39; H, 5.10; Cl, 8.31.

(23) F. Kehrmann and M. Cordone, *Ber.*, **46**, 3009 (1913).

(24) *Cf.* ref. 3.

A second broad orange band resulted from 2-anilino-3,5-dihydro-3-imino-5-phenylphenazine, m.p. 200° (lit.[1] 202–203°).

Anal. Calcd. for $C_{24}H_{18}N_4$: C, 79.53; H, 5.01. Found: C, 79.60; H, 4.93.

The hydrochloride was obtained as plates with greenish luster.

Anal. Calcd. for $C_{24}H_{18}N_4$·HCl: C, 72.26; H, 4.80. Found: C, 72.22; H, 4.93.

III. **Condensation of 7-Substituted 2-Amino-3,5-dihydro-5-phenyl-3-phenyliminophenazines with Cyclohexanone.**—The preparation of the 7-chloro compound is given in detail. Other compounds were prepared in like manner with similar yields. All the compounds are green crystals with bluish luster which gradually decompose on heating above 220° without a distinct melting point.

The green products obtained from the II-isomers are only slightly soluble in cold benzene and dichloromethane giving green, nonfluorescent solutions, insoluble in ether and carbon tetrachloride, very sparingly soluble in water with a red color, and slightly soluble in alcohols. Concentrated alcoholic solutions are green and upon dilution became red with fluorescence. When an attempt was made to chromatograph these compounds in benzene solution on alumina (Woelm, basic, activity III), the compounds immediately changed to a red form which was adsorbed very strongly and could not be eluted with benzene. The infrared spectra of these green substances (obtained with potassium bromide pellets on the Beckman IR-4 instrument with lithium fluoride optics) do not show any bands in the region of the N–H stretch frequencies, thus indicating that all the amino groups were fully substituted. The elementary analyses correspond to 1:1 condensation products between the parent II-isomers and cyclohexanone with the elimination of one molecule of water.

Addition of sodium hydroxide solution to the red alcoholic solutions of the protonated Schiff bases returns the green color. The color change occurs between pH 9 and 12 depending on the nature of the 7-substituent.

7-Chloro-2-cyclohexylideneamino-3,5-dihydro-5-phenyl-3-phenyliminophenazine.—A solution of 0.20 g. of 2-amino-7-chloro-3,5-dihydro-5-phenyl-3-phenyliminophenazine, 0.5 g. of polyphosphoric acid, and 0.5 ml. of cyclohexanone (Eastman Kodak 972) in 20 ml. of 95% ethanol was refluxed for 2 hr. The red reaction mixture was made alkaline with 10% sodium hydroxide solution and the green product precipitated by the addition of water. The crude Schiff base was isolated, washed with water, dried, and repeatedly recrystallized from benzene. The yield was 0.20 g. (85%).

Anal. Calcd. for $C_{30}H_{25}N_4Cl$: C, 75.53; H, 5.28; Cl, 7.43. Found: C, 75.35; H, 5.41; Cl, 7.23.

7-Bromo-2-cyclohexylideneamino-3,5-dihydro-5-phenyl-3-phenyliminophenazine.

Anal. Calcd. for $C_{30}H_{25}N_4Br$: C, 69.08; H, 4.83; Br, 15.32. Found: C, 68.95; H, 5.10; Br, 15.63.

2-Cyclohexylideneamino-3,5-dihydro-7-fluoro-5-phenyl-3-phenyliminophenazine.

Anal. Calcd. for $C_{30}H_{25}N_4F$: C, 78.24; H, 5.47; N, 12.17. Found: C, 78.39; H, 5.59; N, 12.09.

2-Cyclohexylideneamino-3,5-dihydro-7-iodo-5-phenyl-3-phenyliminophenazine.

Anal. Calcd. for $C_{30}H_{25}N_4I$: C, 68.38; H, 4.43; N, 9.86; I, 22.33. Found: C, 63.57; H, 4.53; N, 9.90; I, 22.24.

2-Cyclohexylideneamino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine.

Anal. Calcd. for $C_{32}H_{30}N_4O$: C, 78.98; H, 6.21; N, 11.51; C_2H_5O, 9.26. Found: C, 78.87; H, 6.08; N, 11.55; C_2H_5O, 9.05.

Hydrogenation of a solution containing 0.15 g. of the Schiff base, 0.2 g. of palladium catalyst, and a few drops of 10% sodium hydroxide solution in 75 ml. of absolute ethanol followed by the removal of the catalyst, air reoxidation, and reduction of volume, gave, upon addition of water and some sodium hydroxide solution, a precipitate which was chromatographed with benzene on alumina (Woelm activity III). The effluent of a rapid orange band was reduced in volume, dried, and rechromatographed on activity II alumina. Recrystallization from benzene–Skellysolve B gave 0.041 g. of 2-cyclohexylamino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine as brown needles, m.p. 225–227°.

Anal. Calcd. for $C_{32}H_{32}N_4O$: C, 78.65; H, 6.60; N, 11.47; C_2H_5O, 9.20. Found: C, 78.39; H, 6.53; N, 11.61; C_2H_5O, 9.00.

A second brown-red band was identified by its infrared spectrum as 2-amino-3,5-dihydro-7-ethoxy-5-phenyl-3-phenyliminophenazine, the hydrolysis product of the Schiff base.

2-Cyclohexylideneamino-3,5-dihydro-7-methoxy-5-phenyl-3-phenyliminophenazine.

Anal. Calcd. for $C_{31}H_{28}N_4O$: C, 78.78; H, 5.97; CH_3O, 6.56. Found: C, 78.68; H, 6.30; CH_3O, 6.48.

A hydrogenation–reoxidation sequence similar to that described for the 7-ethoxy analog gave, from 0.31 g. of Schiff base, 0.056 g. of 2-cyclohexylamino-3,5-dihydro-7-methoxy-5-phenyl-3-phenyliminophenazine, m.p. 218–220°.

Anal. Calcd. for $C_{31}H_{30}N_4O$: C, 78.44; H, 6.37; N, 11.81; CH_3O, 6.54. Found: C, 78.43; H, 6.37; N, 11.91; CH_3O, 6.60.

2-Cyclohexylideneamino-3,5-dihydro-5-phenyl-3-phenyliminophenazine.

Anal. Calcd. for $C_{30}H_{26}N_4O$: C, 81.42; H, 5.92; N, 12.66. Found: C, 81.33; H, 5.87; N, 12.62.

Others.—Similar green products were obtained when the oxidation products of 2-amino-4′,5-dimethoxydiphenylamine, 2-amino-4′-fluoro-5-methoxydiphenylamine, and 2-amino-4′-chloro-5-methoxydiphenylamine were reacted with cyclohexanone in the manner described. These Schiff bases, however were not analyzed.

Polarography. Materials.—The substituted phenazine hydrochlorides have been described. All inorganic reagents were reagent grade and were used without further purification. Nitrogen used for purging sample solutions free of oxygen was 99.9% dry-grade (Liquid Carbonic Corp.) which was scrubbed with vanadous chloride solution and water.[25] The nitrogen was further conditioned by passage through a 5-ml. sample of the supporting electrolyte. Ethanol was 190 proof alcohol (U. S. Industrial Chemicals) distilled from dilute sulfuric acid, then from silver nitrate–potassium hydroxide[26] through 15-plate perforated-plate vacuum-jacketed column with a built-in electronically controlled head.[27]

Apparatus.—The polarograph was a recording instrument constructed in the Department and previously described by Crowell, *et al.*[28] The cell was of the Pecsok–Juvet type[29] and thermostated at 25.00 ± 0.05°.

The pH data were obtained with a Beckman Model G pH meter in conjunction with a Beckman 40498 glass electrode immersed in the solutions compartment and using the cell calomel electrode. The assembly was standardized against Beckman buffer solutions.

Solutions.—The polarograms were obtained in 3:1 95% ethanol–aqueous buffer mixtures. The buffer solutions were sodium acetate–nitric acid systems prepared analogously to Walpole's[30] sodium acetate–hydrochloric acid solutions. The total acetate concentration was 0.2 *F* and appropriate amounts of lithium nitrate were added to increase the ionic strength to 1 *M*.

The ethanolic solutions were 0.333 m*F* in the organic compound. Hence, on 3:1 dilution, the resulting solutions were nominally 0.25 m*F* in the phenazine derivative and 0.25 *M* in ionic strength. No corrections were made for the volume contractions.

Polarogram Measurements.—The half-wave potentials were obtained graphically using the maxima of the oscillations. Buffer blanks were used to estimate the residual current when in the region of the mercury dissolution potential. The precision of the graphical data was about ±2 mv.

Acknowledgment.—We are much indebted to Professor W. R. Crowell for assistance with electrochemical problems and for the use of his polarographic equipment. This work was supported in part by the National Science Foundation through Grant G-7318.

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The Estimation of Hammett Substituent Constants[1]

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Received March 18, 1963

Hammett substituent constants can be estimated from the equation, $\sigma_{XG_2} = m\sigma_X + c$, where X is some substituent, G_2 is a group to which it is attached, m is the slope, and c the intercept. This equation has been shown to apply with G_2 equal to O, S, NH, CO, and *o*-, *m*-, and *p*-phenylene. This equation greatly increases the number of σ-values available, and also makes possible the estimation of σ-values for groups for which experimental determination by means of the pK_a of the corresponding substituted benzoic acid would be difficult.

In the course of work on other problems, values of the Hammett substituent constants[3] for certain groups were required. In order to develop useful methods of estimating substituent constants, relationships between series of substituent constants were sought. McDaniel[4a] and Bauld[4b] have pointed out that certain series of substituents show a linear relationship between $\sigma_{m\text{-}X}$ and $\sigma_{p\text{-}X}$. These relationships, while theoretically interesting, are of limited use in predicting new substituent constants. We have sought for relationships between substituent constants for structurally related substituents.

We can consider almost any reaction series to which the Hammett equation is applicable as consisting of a substituent X, and a reaction site Y; both of which are attached to some group G. Thus, for substituted benzoic acids, X represents the substituent, Y the carboxyl group, and G the phenylene group. In some reaction series we may find it convenient to divide G into the sub-groups G_1, G_2, ... G_n. In the cinnamic acids, for example, we may choose to consider the series to be of the form XGY where G is the styrylene group, or of the form XG_2G_1Y, where G_1 is the *trans*-vinylene group and G_2, the phenylene group. If we write the Hammett equation in its most general form

$$Q_X = \rho\sigma_X + Q_H \tag{1}$$

where Q is the quantity being correlated, we can now consider two ways of correlating data for the series described above. In the first case, we may consider the substituent constant to include only the effect of X, the reaction constant accounting for G_2G_1Y and the reaction conditions. In the second case, we may include G_2 with the substituent constant, leaving the reaction constant to account for G_1Y and the reaction conditions. Thus in the first case, the unsubstituted compound may be written as HG_2G_1Y, whereas in the second case, it would be written as HG_1Y. Then for a given X, the Hammett equation would be written for the first case as

$$Q_X = \rho_{G_1G_2}\sigma_X + Q_{HG_1G_2} \tag{2a}$$

while for the second case,

$$Q_{XG_2} = \rho_{G_1}\sigma_{G_2X} + Q_{HG_1} \tag{2b}$$

obviously

$$Q_{XG_2} \equiv Q_X \tag{2c}$$

Combining 2a and 2b and rearranging, gives

$$\sigma_{G_2X} = \frac{\rho_{G_1G_2}}{\rho_{G_1}}\sigma_X + \frac{Q_{HG_2G_1} - Q_{HG_1}}{\rho_{G_1}} \tag{3a}$$

or

$$\sigma_{G_2X} = m\sigma_X + c \tag{3b}$$

This implies a straight line relationship between the two constants. At first glance, this relationship appears obvious and uninteresting. If we choose certain G_2 values however, this relationship could provide us with σ-values which are otherwise difficult to obtain. When for example, G_2 is the carbonyl group, it should be possible to calculate σ_m and σ_p for the chlorocarbonyl(COCl) group. Such a value would be difficult to obtain by measurement of an ionization constant. Again, if G_2 is an oxygen atom, the σ-values for the hypobromite(BrO) group could be calculated.

To test eq. 3b, least mean square correlations of σ_{G_2X} have been made with $\sigma_{m\text{-}X}$, $\sigma_{p\text{-}X}$, and σ_{IX} for G_2 equal to *o*-, *m*-, and *p*-phenylene, carbonyl, oxygen, sulfur, and imino.

The results of these correlations are given in Table III, and the σ-constants used are given in Table II. The reaction series studied are listed in Table I.

TABLE I

SERIES CORRELATED

1	*m*-XCO	X = OH, H, NH_2, O^-, Me, OMe, OEt, Ph
2	*m*-XO	X = H, Ac, Me, CF_3, Et, Ph
3	*m*-XNH	X = Me, Ac, Et, Bu, Bz, H, OH, NH_2
4	*m*-XS	X = CF_3, Me, Ac, H
5	*p*-XCO	X = OH, NH_2, O^-, Me, OMe, OEt, Ph
6	*p*-XO	X = CF_3, Me, Ac, Et, Pr, Bu, H
7	*p*-XNH	X = Me, Ac, Et, Bu, Bz, H, OH, NH_2
8	*p*-XS	X = CF_3, Me, Ac, Et, *i*-Pr, CN, H
9	*p*-X(*p*-C_6H_4)-X	X = NO_2, Cl, Br, OH, Me, OMe, H, NH_2
10	*p*-X(*m*-C_6H_4)	X = NO_2, Cl, Br, OH, Me, OMe, H
11	*p*-X(*o*-C_6H_4)	X = H, Me, OH, OMe, Cl, NO_2

Discussion

The results of the correlations show that σ_{XG_2} is indeed a linear function of $\sigma_{m\text{-}X}$, $\sigma_{p\text{-}X}$, or σ_{IX}. In some cases it is not yet possible to determine which of the three σ_X-constants gives the best correlation. It should be pointed out that the Hammett $\sigma_{m\text{-}X}$ and $\sigma_{p\text{-}X}$ values are not necessarily identical with the values of σ_X of eq. 3. However σ_X may be represented by

$$\sigma_X = \lambda_I + \delta_R$$

The data do not warrant the use of a four-parameter equation. They were, therefore, studied in terms of $\sigma_{m\text{-}X}$, $\sigma_{p\text{-}X}$, and σ_I. This is equivalent to $\lambda = 1$,

(1) (a) Abstracted from part of the Doctoral Dissertation of M. Charton, Stevens Institute of Technology; (b) presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

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TABLE II

SUBSTITUENT CONSTANTS USED IN CORRELATIONS

X	σ_m	σ_p	σ_I
H	0[a]	0[a]	0[a]
Me	−0.069[b]	−0.170[b]	−0.05[c]
Et	−0.07[b]	−0.157[b]	−0.05[c]
Pr	−0.05[d]	−0.126[e]	−0.02[f]
i-Pr	−0.07[d]	−0.151[b]	−0.03[f]
Bu	−0.07[d]	−0.161[e]	−0.02[f]
Ph	0.06[b]	−0.01[b]	0.10[c]
CF_3	0.43[b]	0.54[b]	0.41[c]
Ac	0.376[b]	0.502[b]	0.28[c]
Bz	0.343[g]	0.459[e]	0.29[h]
CO_2Me	0.315[e]	0.436[i]	0.30[c]
CO_2Et	0.37[b]	0.45[b]	0.30[c]
CO_2H	0.37[b]	0.45[b]	0.30[c]
CO_2^-	−0.1[h]	0.0[e]	[h]
CHO	0.382[j]		
$CONH_2$	0.280[e]	0.36[k]	[h]
CN	0.615[l]	0.660[b]	0.58[c]
OH	0.121[h]	−0.37[b]	0.25[c]
OMe	0.115[b]	−0.268[b]	0.25[c]
OEt	0.1[b]	−0.24[b]	0.27[h]
OPr	0.1[b]	−0.25[b]	
OBu	0.1[b]	−0.32[b]	
OCF_3	0.36[m]	0.32[m]	
OAc	0.39[b]	0.31[b]	
O^-	−0.708[e]	−0.519[e]	−0.80[h]
OPh	0.252[b]	(−0.028)[e]	
		(−0.320)[b]	
NH_2	−0.16[b]	−0.26[b]	0.10[b]
NHMe	−0.302[e]	−0.592[e]	
		(−0.84)[b]	
NHEt	−0.240[e]	−0.607[n]	
NHBu	−0.344[e]	−0.512[n]	
NHOH	−0.044[e]	−0.399[e]	
$NHNH_2$	−0.31[e]	−0.550[e]	
NHAc	0.21[h]	0.00[b]	
NHBz	0.217[e]	0.078[e]	
SH	0.25[b]	0.15[b]	0.25[c]
SMe	0.15[b]	0.00[h]	0.25[c]
SEt		0.03[b]	0.25[c]
S(*i*-Pr)		0.07[b]	0.25[c]
SCN		0.52[b]	
SAc	0.39[h]	0.44[h]	
SCF_3	0.35[m]	0.38[m]	
NO_2	0.710[b]	0.778[b]	0.63[c]
Cl	0.373[b]	0.227[b]	0.47[c]
Br	0.391[b]	0.232[b]	0.45[c]
F	0.337[b]	0.062[b]	0.52[c]
I	0.352[b]	0.27[r]	0.39[c]
$SiMe_3$	−0.04[b]	−0.07[b]	−0.12[c]
SO_2Me	0.60[b]	0.72[b]	0.59[c]
SOMe	0.52[b]	0.49[b]	0.52[c]
2-MeC_6H_4		−0.025[p]	
2-HOC_6H_4		−0.090[p]	
2-$MeOC_6H_4$		−0.004[p]	
2-ClC_6H_4		0.126[p]	
2-$O_2NC_6H_4$		0.173[p]	
3-$O_2NC_6H_4$		0.183[q]	
3-ClC_6H_4		0.092[p]	
3-BrC_6H_4		0.093[q]	
3-HOC_6H_4		0.033[p]	
3-MeC_6H_4		0.008[p]	
3-$MeOC_6H_4$		0.045[p]	
4-$O_2NC_6H_4$		0.229[q]	
4-ClC_6H_4		0.081[q]	
4-BrC_6H_4		0.083[q]	
4-HOC_6H_4		−0.242[q]	
4-$H_2NC_6H_4$		−0.303[q]	
4-MeC_6H_4		−0.048[q]	
4-$MeOC_6H_4$		−0.088[q]	

[a] By definition. [b] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). [c] R. W. Taft, Jr., and I. C. Lewis *J. Am. Chem. Soc.*, **80**, 2436 (1958). [d] Calculated from $\sigma_m = (\sigma_p + 2\sigma_I)/3$. Footnote *c*. [e] See ref. 3b. [f] Calculated from $\sigma_I = \sigma^*/6.23$: R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960). [g] W. N. White, R. Schlitt, and D. Gwynn, *J. Org. Chem.*, **26**, 3613 (1961). [h] Calculated from $\sigma_I = (3\sigma_m - \sigma_p)/2$. Footnote *c*. [i] M. Charton and H. Meislich, *J. Am. Chem. Soc.*, **80**, 5940 (1958). [j] See ref. 3a. [k] Calculated from data of J. D. Roberts and C. M. Regan, *ibid.*, **76**, 939 (1954). [l] M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *ibid.*, **81**, 4226 (1959). [m] L. M. Yagupolskii and L. N. Yagupolskaya, *Dokl. Akad. Nauk SSSR*, **134**, 1381 (1960). [n] M. Charton, Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, p. 78-P. [o] H. H. Jaffé, L. D. Freedman, and G. O. Doak, *J. Am. Chem. Soc.*, **75**, 2209 (1953). [p] Calculated from correlation of K_a of *trans-m-* and *p*-cinnamic acids. These results will be reported elsewhere. [q] E. Berliner and L. H. Liu, *J. Am. Chem. Soc.*, **75**, 2417 (1953). [r] R. A. Robinson and K. P. Ang, *J. Chem. Soc.*, 2314 (1959).

$\delta = 0$; $\lambda = 1$, $\delta = {}^1/_3$ to ${}^1/_2$; $\lambda = 1$, $\delta = 1$; for σ_I, σ_m, σ_p, respectively.

Results of Correlations.—When G_2 is *meta* or *para* –O, –NH, or –CO, the best correlation is obtained with the $\sigma_{m\text{-}X}$-constants. In the case of G_2 = –CO, this is in accord with the observation that vinylidene reaction series are correlated by the $\sigma_{m\text{-}X}$-constants,[5] as the carbonyl group may be considered to be a hetero vinylidene group. When G_2 is *m*- or *p*-S, the best correlation is obtained with the $\sigma_{p\text{-}X}$-constants. It is premature to attempt to account for the difference in behavior between S and –O, –NH or –CO. It has been pointed out by one of the referees, however, that those series which show significant correlation with σ_p contain, except for H, only carbon substituents, and he has suggested that the $\sigma_{m\text{-}X}$ values be used for all calculations of new σ-constants in series 1 through 8. As there is no way to evaluate this proposal from the available data, values of m_m and c_m are given as footnotes to Table III.

For G_2 equal to *p*-phenylene, best results were obtained with $\sigma_{p\text{-}X}$ as is expected. Similarly, for *m*-phenylene best results were obtained with $\sigma_{m\text{-}X}$. In accord with the successful correlation of *o*-phenylene reaction series (in which no steric effect is present) with the σ_p-constants,[6a] best results for the *o*-phenylene series were obtained with $\sigma_{p\text{-}X}$.

It should be noted that when G_2 is –CO the correlations are very sensitive to the value for X = O^-. Exclusion of this value from series 1 and 5 gives poorer correlation, and best results are now obtained with σ_p. The results are still significant, however (90% and 95% confidence levels for series 1 and 5, respectively). The difficulty in these series is the small range of σ_{XG_2} when the value for O^- is excluded (0.10 and 0.14 n-units, respectively for series 1 and 5 as compared with 0.29, 0.53, 0.24, 0.69, 0.74, and 0.52 for series 2, 3, 4, 6, 7, and 8, respectively).

Calculation of New Substituent Constants.—The values of *m* and *c* given in Table III are for the σ_X-constant which gave the best correlation, as deter-

(4) (a) D. H. McDaniel, *J. Org. Chem.*, **26**, 4692 (1961); (b) N. L. Bauld, Abstracts, 139th Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

(5) M. Charton, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, p. 91-Q.

(6) (a) M. Charton, *Can. J. Chem.*, **38**, 2493 (1960); (b) A. C. Farthing and B. Nam, "Steric Effects of Conjugated Systems," Academic Press, New York, N. Y., 1958, p. 131 and ref. 3.

TABLE III

RESULTS OF CORRELATIONS

Series	G_2	r_m[a]	r_p[a]	r_I[a]	s[b]	m	c	n	d
1	*m*-CO	0.943	0.544	0.904	0.0581	0.553	0.329	1.61	−0.538
2	*m*-O	0.956	0.935	0.945	0.0427	0.555	0.156	1.65	−0.246
3	*m*-NH	0.982	0.803	0.874	0.0467	1.11	−0.187	0.871	0.165
4	*m*-S[c]	0.933	0.962	0.880	0.0362	0.290	0.222	3.19	−0.692
5	*p*-CO	0.942	0.576	0.904	0.0637	0.546	0.422	1.62	−0.693
6	*p*-O	0.969	0.953	0.955	0.0808	1.29	−0.218	0.727	0.163
7	*p*-NH	0.938	0.738	0.894	0.107	1.33	−0.476	0.662	0.322
8	*p*-S[d]	0.978	0.988	0.954	0.0358	0.567	0.128	1.72	−0.216
9	*p*-C_6H_4	0.828	0.970	0.634	0.0457	0.384	−0.0262	2.45	0.0626
10	*m*-C_6H_4	0.984	0.857	0.941	0.0128	0.237	0.00792	4.09	−0.0249
11	*o*-C_6H_4	0.867	0.933	0.778	0.0402	0.221	0.0211	3.94	−0.0787

[a] r = correlation coefficient. [b] s = standard deviation. [c] $m_m = 0.393$, $c_m = 0.213$. [d] $m_m = 0.719$, $c_m = 0.103$.

TABLE IV

CALCULATED SUBSTITUENT CONSTANTS

	—G₂ = O—		—G₂ = NH—		—G₂ = S—	
X	σ_m	σ_p	σ_m	σ_p	σ_m	σ_p
F	0.34	0.22	0.19	−0.03	0.24	0.16
Cl	0.36	0.26	0.23	0.02	0.29	0.26
Br	0.37	0.29	0.25	0.04	0.29	0.26
I	0.35	0.24	0.20	−0.01	0.30	0.28
CN	0.50	0.58	0.50	0.34	0.41	0.50
$SiMe_3$	0.13	−0.27	−0.23	−0.53	0.20	0.09
NO_2	0.55	0.70	0.60	0.47	0.45	0.57
SMe	0.24	−0.02	−0.02	−0.28	0.22	0.13
SOMe	0.44	0.45	0.39	0.22	0.36	0.41
SO_2Me	0.49	0.56	0.48	0.32	0.43	0.54

mined by the value of r. These are the preferred values for use in estimating new σ_{XG_2}-values.

To illustrate the utility of the method, a number of new substituent constants have been calculated for groups for which experimental determination would be difficult. These values are given in Table IV.

It is also possible to calculate new values of σ_X from the appropriate σ_{XG_2}. For this purpose the equation

$$\sigma_X = n\sigma_{XG_2} + d \qquad (4)$$

is required, n and d being the slope and intercept obtained by linear regression of σ_X on σ_{XG_2}[3b] (that is, by assuming σ_{XG_2} free of error). Values of n and d are given in Table III.

It has been reported (see footnote *f*, Table II) that σ_I and σ_R values can be estimated from the equations

$$\sigma_I = (3\sigma_m - \sigma_p)/2 \qquad (5)$$

TABLE V

CALCULATED VALUES OF m

Series	G_1	G_2	ρ_{G_1}	$\rho_{GG_{12}}$	m (calcd.)	m (observed)
11	*trans*-C_2H_2	*o*-C_6H_4	1.64[a]	0.389[b]	0.237	0.221
10	*trans*-C_2H_2	*m*-C_6H_4	1.64[a]	0.466[b]	0.284	0.237
9a	*trans*-C_2H_2	*p*-C_6H_4	1.64[a]	0.466[c]	0.284	0.384
9b	*p*-C_6H_4	*p*-C_6H_4	1.415[b]	0.482[b]	0.341	0.384

[a] See footnote *p*, Table II. [b] See ref. 3b. [c] See ref. 6a.

TABLE VI

CALCULATED VALUES OF c

Series	$Q_{HG_2G_1}$	Q_{HG_1}	c (calcd.)	c (observed)
11	−4.413[a]	−4.448[b]	0.0213	0.0211
10	−4.447[c]	−4.448[b]	0.000610	0.00792
9a	−4.447[c]	−4.448[b]	0.000610	−0.0262
9b	−5.636[c]	−5.627[c]	−0.00636	−0.0262

[a] See ref. 6a. [b] See footnote *p*, Table II. [c] See ref. 3b.

TABLE VII

t TESTS OF m AND c

Series	tm	Confidence level	tc	Confidence level
11	0.375	20	0.014	20
10	2.452	90	1.508	80
9a	2.561	95	1.658	80
9b	1.097	70	1.226	70

and

$$\sigma_p = \sigma_I + \sigma_R \qquad (6)$$

Calculation of m and c.—The existence of a linear relationship between σ_{XG_2} and σ_X does not in itself constitute proof of the validity of eq. 3, as the observed linear relationships might be purely empirical. Although this would not in the slightest diminish their utility, it is of interest to determine whether or not the derivation of eq. 3 is valid. One test of its validity is the calculation of m and c from the appropriate values of ρ and Q_H. Calculated values of m and c are given in Tables V and VI for G_2 equal to *o*-, *m*-, and *p*-phenylene.

To determine the significance of the difference between the calculated and observed values of m and c, t tests were performed.[7] The values of t and the confidence levels obtained are given in Table VII. In general, the results of the t tests support the validity of eq. 3. In 9a and 10, however, the calculated and observed values of m and significantly different. As the $\rho_{G_1G_2}$ and $Q_{HG_1G_2}$ values for 9a and 10 are identical and represent an average of *m*-phenylene and *p*-phenylene, it is more reasonable to compare average

(7) A. Hald, "Statistical Theory with Engineering Applications," John Wiley and Sons, Inc., New York, N. Y., 1952, p. 540.

observed m- and c values with the calculated values. For these series, $\bar{m} = 0.311$, $\bar{c} = -0.0914$. These average values are obviously in good agreement with the calculated values of m and c.

Equation 3 is thus supported, at least for series 9, 10, and 11. Although it is true that these are the series least likely to deviate from the equation, it is nevertheless encouraging to find such agreement.

Acknowledgment.—The author wishes to acknowledge helpful discussion of the content of this paper with Professor H. H. Jaffé, University of Cincinnati.

Thiolesters by Anhydride Reduction with Hydrogen Sulfide

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Received May 2, 1963

Phthalic anhydride (or acid) can be reduced by hydrogen sulfide to thiophthalide in high yields. Hydrogen may be substituted for part of the hydrogen sulfide. The reaction appears general, but gives lower yields for other anhydrides. Reduction of cyclohexane-1,2-dicarboxylic anhydride gives 3,4,5,6-tetrahydrothiophthalide. Other aromatic acids or nitriles are reduced completely to hydrocarbon, while aliphatic acids are inert under reaction conditions. While metal sulfides may catalyze the reaction, they are not essential. In their absence, a homogeneous reduction with hydrogen is realized.

In the course of studying the oxidation of organic compounds with sulfur and water, but in the absence of a base, it was found that the reaction was reversible.[1] For example, toluene is oxidized by sulfur and water at 315°. A similar equilibrium exists in the reaction

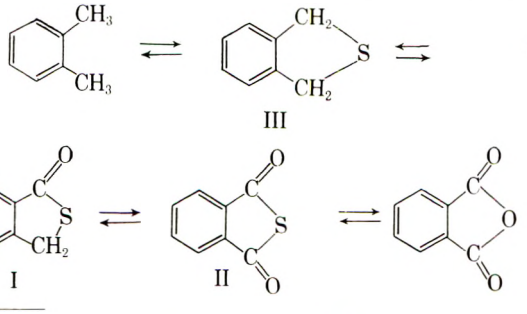
$$C_6H_5CH_3 + 3S + 2H_2O \rightleftharpoons C_6H_5CO_2H + 3H_2S \qquad (1)$$

producing nitriles from hydrocarbon, sulfur, and ammonia.[2]

$$C_6H_5CH_3 + 3S + NH_3 \rightleftharpoons C_6H_5CN + 3H_2S \qquad (2)$$

In the reverse reactions, a carboxylic acid or nitrile is reduced to a hydrocarbon with hydrogen sulfide. Sulfur is also formed. By adding hydrogen to the system, sulfur is converted to hydrogen sulfide which tends to drive the reaction to completion. The over-all reaction is reduction of a carboxyl or nitrile group to a methyl group by hydrogen, with hydrogen sulfide as a catalyst. Reduction begins at about 150° but reaches a practical rate at about 250°. Such reductions have not been reported previously. They may have only limited practical value but do have theoretical significance. For example, the system hydrogen, water, benzoic acid, and hydrogen sulfide contains no solid catalyst and hence represents an example of homogeneous catalysis, a relative rarity in reduction by hydrogen. Nitrile reduction represents a similar situation. The number of other groups capable of reduction in this way has not yet been fully explored.

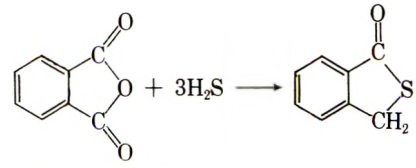
Of greater interest is the reduction of phthalic anhydride from which a number of intermediate compounds were isolated. The yield of any one may be enhanced by the proper choice of conditions and the recycling of undesired intermediates. These intermediate compounds shed light on a probable mechanism of sulfur oxidations. The major reaction sequence involves the following compounds, all of which have been isolated (run 10, Table I).



(3)

III I II

Small amounts of *o*-toluic acid also have been found. It has not been established whether this is part of the above sequence or a competing reaction. The most stable entity at 315° in the presence of water, sulfur, and hydrogen sulfide is thiophthalide (I). It can be obtained in 94% yields by reduction of phthalic anhydride or phthalic acid.



(4)

I

Some typical results are given in Table I. The reverse reactions, the oxidation of *o*-xylene to thiophthalide with sulfur and water, has been described.[1]

An example of the spectrum of intermediates (3) is given in run 10 of Table I. In this case, their concentrations were enhanced by adding *o*-xylene to the system and limiting the amount of hydrogen sulfide employed. As a result, the major products were thiophthalic anhydride (II), thiophthalide (I), and *o*-xylylene sulfide (III); identification was by a high mass spectrometer. Minor peaks matched masses for di- and trithiophthalic anhydride. Benzoic acid, a major product, probably resulted from decarboxylation of phthalic acid at this temperature. Reduction of the intermediate thiophthalic anhydride with hydrogen sulfide at atmospheric pressure gave thiophthalide.

Table I shows that hydrogen sulfide alone as the reducing agent gives good yields of thiophthalide over the temperature range of 175–315°. Conversions increase with temperature while yields decrease. Above 315°, decarboxylation and reduction to *o*-xylene and *o*-xylylene sulfide occurs. The ratio of hydrogen sulfide

(1) W. G. Toland, *J. Org. Chem.*, **26**, 2929 (1961).
(2) W. G. Toland, *ibid.*, **27**, 869 (1962).

TABLE I

REDUCTION OF PHTHALIC ANHYDRIDE TO THIOPHTHALIDE

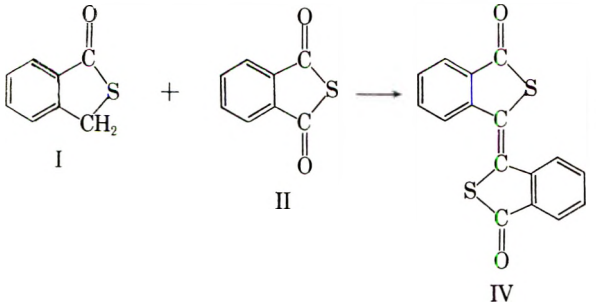
Run no.	1	2	3	4	5	6	7	8	9	10
Charge, moles										
Phthalic anhydride	4.0	4.0	1.0	1.0	2.0	10	2.0	2.0	2.0	2.0
H_2S	4.3	8.2	10	10	10	20	2.1	0.5	3.0	1.0
Hydrogen	0	0	0	0	0	0	11.5	7.0	7.9	2.0[a]
Water	100	100	100	100	0	0	0	100	100	100
Conditions										
Temperature, °C	175	200	80–260	290–315	260	260	260	260	260	315
Time at temp., min.	120	120	120	50	60	120	60	120	145	120
Products, moles										
H_2S	1.7	1.65		6.82	4.44	1.62		0.36	1.41	
Sulfur	1.25	3.2	1.24	1.16	4.44	4.11	0	0	0	
Hydrogen							9.8	5.6		1.5[a]
Phthalic acid	3.52	2.14	0.37	0.042	0	3.46	0.91	1.77	0.59	1.0
Benzoic (B) or toluic (T) acid	0	0	0	0.05 (T)	0	2.1[b]	0	0	0.03 (T)	0.5 (B)
Other					3.0 (H_2O)	11.5 (H_2O)	0.69[c]		0.072[d]	0.07[c]
Tar, grams		20.3	3.0	16.8	0	138.2	11.2	6.6	12.1	0.07[d]
Thiophthalide	0.452	1.68	0.565	0.69	1.91	2.1	0.23	0.10	1.07	0.22
Conversion of phthalic anhydride, %	12.0	47.2	62.8	95.8	100	65.5	55.2	12.8	70.8	50.0
Yield of thiophthalide, mole %										
on H_2S	51.7	77.1		65.2	101.2			214.0	202.0	
on phthalic anhydride	94.2	90.3	89.9	72.2	94.1	64.2[b]	20.4	38.5	74.3	22.0

[a] *o*-Xylene (substituted for H_2). [b] Δ3,3′-Bithiophthalide. [c] Thiophthalic anhydride. [d] *o*-Xylylene sulfide.

to phthalic anhydride (or acid) is not critical; but since three moles are required per mole of phthalic anhydride or acid to form thiophthalide, at least this ratio is preferred. Above 10:1 molar ratios, additional hydrogen sulfide probably has little effect. Except in the reduction of thiophthalic anhydride, only autogenous pressures were studied.

In the reduction of phthalic anhydride, water may be used as a solvent, as shown in runs 1–4. Apparently, the tendency to form cyclic structures is so strong in this case that the opportunity for hydrolysis to open chain species has little effect on the course or degree of reduction.

In one attempt to scale up the reaction (run 6) the reduction took a different course. This could have resulted from an insufficient amount of hydrogen sulfide to complete the conversion, poor mixing of the larger quantities in the same size vessel, or possibly subsequent reactions occurring in the still pot during product distillation. In any event, a condensation occurred, probably between thiophthalide and thiophthalic anhydride with loss of water, to give Δ-3,3′-bithiophthalide (IV) in 64% yield. Oxidation of Δ-3,3′-bithiophthalide with sulfur and water gave phthalic acid in 74% yield.

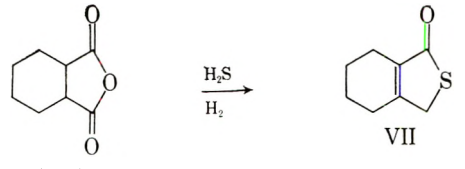


I II IV (5)

The formation of sulfur in the reduction of phthalic anhydride could lead to side reactions with thiophthalide. However, it was shown that under reaction conditions sulfur reacts with hydrogen to form hydrogen sulfide. It was shown that hydrogen in the absence of hydrogen sulfide does not react with phthalic acid. When both hydrogen and hydrogen sulfide are present, thiophthalide is formed in yields at least twice those theoretically obtainable from the hydrogen sulfide alone (runs 8 and 9). In such cases, hydrogen sulfide serves both as a reagent and as a catalyst for the reduction.

The reaction of hydrogen sulfide with 4-cyclohexene-1,2-dicarboxylic anhydride (V) and 1-cyclohexene-1,2-dicarboxylic anhydride (VI) gave thiophthalide in 65% and 91% yields, respectively. The sequence of reactions in these transformations is complex. First, double bond isomerization of the unsaturated cyclic anhydrides (or the corresponding acids) may occur. Second, and more important, sulfur produced during the carbonyl reduction is available to dehydrogenate the partially saturated ring. In addition, any of these tetrahydrophthalic anhydrides (or corresponding acids) which are dehydrogenated by sulfur to phthalic anhydride (or phthalic acid) can be reduced under these reaction conditions to thiophthalide. Anhydride initially reduced by the hydrogen sulfide to thiolactone may be dehydrogenated similarly to thiophthalide.

When a *hydrogen–hydrogen sulfide* mixture was used for reduction of 4-cyclohexene-1,2-dicarboxylic anhydride, a mixture of thiophthalide and the unexpected and previously unreported 3,4,5,6-tetrahydrothiophthalide (VII) was produced. The same products were isolated from the hydrogen sulfide reduction of cyclohexane-1,2-dicarboxylic anhydride (VIII), (Table II). When a *hydrogen–hydrogen sulfide* mixture is used for reduction of VIII, the ratio of VII to I increases.



VIII VII (6)

TABLE II

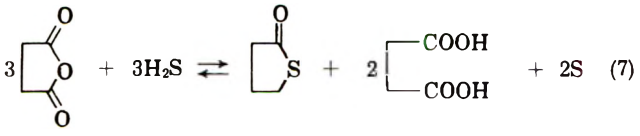
REDUCTION OF CYCLOHEXANE AND CYCLOHEXENE-1,2-DICARBOXYLIC ANHYDRIDES

Anhydride	Reducing agent	% Yield, thiophthalide (I)	% Yield, tetrahydrothiophthalide (VII)
4-Cyclohexene-1,2-dicarboxylic anhydride	H_2S	65	
	H_2S–H_2[a]	23	29
1-Cyclohexene-1,2-dicarboxylic anhydride	H_2S	91	
Cyclohexane-1,2-dicarboxylic anhydride	H_2S	21	25
	H_2S–H_2	23	34
	H_2S–H_2[a]		47

[a] Steel-lined autoclave used.

When, instead of the usual glass-lined autoclave, an unlined steel one was used, only VII was found. Apparently the autoclave walls act as a catalytic surface and allow the hydrogen to easily reduce any sulfur formed.

The reduction of succinic anhydride by hydrogen sulfide gave γ-thiolbutyrolactone (IX) in 24% yield.



From the over-all equation 7 it is apparent that only 33% of the succinic anhydride can be converted to γ-thiolbutyrolactone since the water formed in the reaction hydrolyzes succinic anhydride to succinic acid. In contrast to *o*-phthalic acid, the carboxyl groups in succinic acid may assume conformations unfavorable for anhydride formation. When succinic acid was subjected to the reducing conditions, only 3.6% of the succinic acid was converted to γ-thiolbutyrolactone.

In the same manner acetic anhydride gave a product which was 7.4 mole per cent ethyl thiolacetate. Hydrogen sulfide reduction of benzoic anhydride in the presence of hydrogen at 177° gave a product containing 9 mole per cent benzyl thiolbenzoate, 36 mole per cent benzene, 51 mole per cent benzoic acid, and traces of other materials. When the temperature was raised to 260°, toluene was the product. Benzoic acid required temperatures of greater than 300° to be reduced to toluene, but under these conditions lauric acid was unchanged. Reaction of hydrogen sulfide with phthalimide gave no identifiable products and dibenzoyl amine (made *in situ* from benzoic acid and benzonitrile) yielded only toluene.

Discussion

The initial step in this type of reduction has been described. Hydrogen sulfide reacts with anhydrides below 100° in the presence of tertiary amine accelerators and between 120 and 160° over activated carbon to produce thiocarboxylic acids.[3] Sulfonic acids apparently also function as catalysts.[4] No reduction is involved in this first step, but rather replacement of one oxygen by a sulfur.

Catalytic reduction of a variety of functional groups to thiols using hydrogen with hydrogen sulfide has been described.[5] Keto- and aldehydocarboxylic acids, anhydrides, esters, and amides are reduced to mercaptocarboxylic compounds. Levulinic acid, for example, gives γ-mercaptovaleric acid and its thio lactone. The anhydride group, however, apparently is unaffected under the conditions of keto group reduction. Simple aldehydes and ketones, thio ketones, thio acids, and cyano groups are all reduced to mercaptans at temperatures up to about 300° but give hydrocarbons above this temperature.

Reductions have been observed in studies of the Willgerodt reaction. When acetophenone is treated with aqueous ammonium sulfide, it gives a mixture of α-phenylethyl mercaptan, α-phenylethyl disulfide, styrene, ethylbenzene, diphenylthiophene, and free sulfur.[6] The sulfide reduction of ketones is complicated by subsequent reactions, some of which may involve the free sulfur produced initially. Similarly, 1-acetylacenaphthene is reduced to 1-ethylacenaphthene in 67% yield by ammonium polysulfide with little of the expected Willgerodt product, 1-acenaphthenacetamide being formed.[6]

While a carbonyl function is also reduced to a methylene in anhydride reduction, it cannot occur by any of the mechanisms proposed to date for such reductions. The reduction of phthalic anhydride cannot proceed through either an olefinic[7] or a thioepoxide[8] intermediate. The reduction of anhydrides may actually parallel more closely the mechanism involved in sulfate reduction by bisulfide to give thiosulfate[9] and ultimately polysulfide.[10]

An abbreviated schematic series of steps (Scheme 1) illustrates a potential path of phthalic anhydride reduction consistent with known sulfur chemistry. Many reactive reducing species may be present in the reaction mixture. In this reaction scheme examples of several are used: hydrogen sulfide, reaction 1; sulfur, reaction 7; and hydrogen polysulfide, a species formed by reaction of sulfur with hydrogen sulfide, reaction 4. Beginning with the thioanhydride group, the sequence is illustrated in Scheme 1.

A possible reaction sequence for the reduction of cyclohexane-1,2-dicarboxylic anhydride (VIII) is presented in Scheme 2. Intermediate X is formed as suggested in reaction 7 in Scheme 1. However, with X and alternative reaction path, hydrogen sulfide elimination to XI, is possible. Rearrangement of the double bond into conjugation with the carbonyl group gives 3,4,5,6-tetrahydrothiophthalide (VII). Sulfur formed in reactions 6 and 20 can dehydrogenate VII to thiophthalide (I). When hydrogen is also present, it can react with sulfur, reducing the amount of VII oxidized. When the reaction was carried out in an unlined steel

(3) (a) H. Behringer and H. W. Stein, German Patent 800,412 (November 6, 1950); (b) H. Behringer and H. W. Stein, German Patent Application No. B 388 IV d/120 (October, 1949); (c) H. Behringer, German Patent Application No. B 854 d/120 (November, 1949).

(4) J. C. McCool, U. S. Patent 2,587,580 (March 4, 1952).

(5) M. W. Farlow, W. A. Lazier, and F. K. Signaigo, *Ind. Eng. Chem.*, **42**, 2547 (1950).

(6) (a) C. Willgerodt, *Ber.*, **21**, 534 (1888); (b) E. Baumann and E. Fromm, *ibid.*, **28**, 907 (1895); (c) L. F. Fieser and G. W. Kilmer, *J. Am. Chem. Soc.*, **62**, 1354 (1940).

(7) M. Carmack and D. F. Degar, *ibid.*, **68**, 2029 (1946); J. A. King and F. H. McMillan, *ibid.*, **68**, 525, 632 (1946).

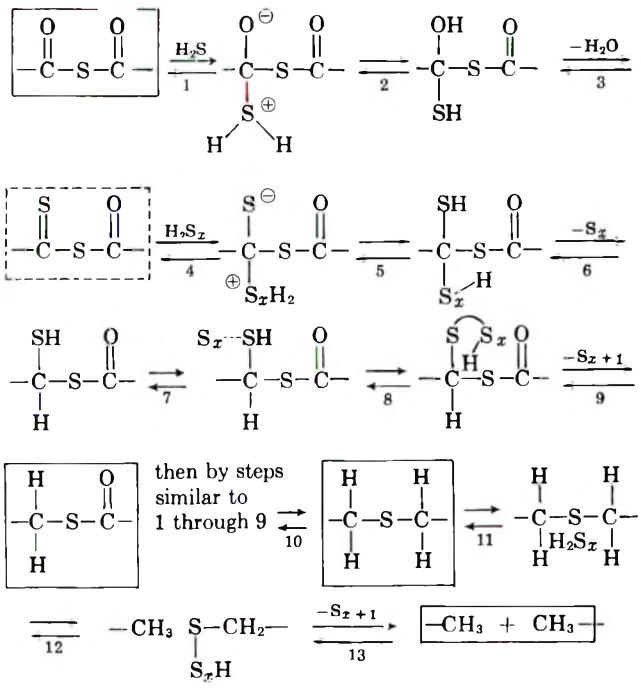
(8) M. A. Naylor and A. W. Anderson, *ibid.*, **75**, 6392 (1953).

(9) W. G. Toland, *ibid.*, **82**, 1911 (1960).

(10) R. E. Davis, *ibid.*, **80**, 3565 (1958).

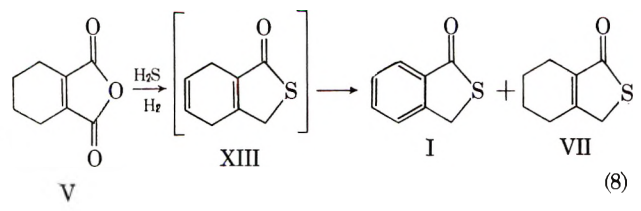
SCHEME 1

(Dotted species seen in mass spectra; solid lined species isolated.)



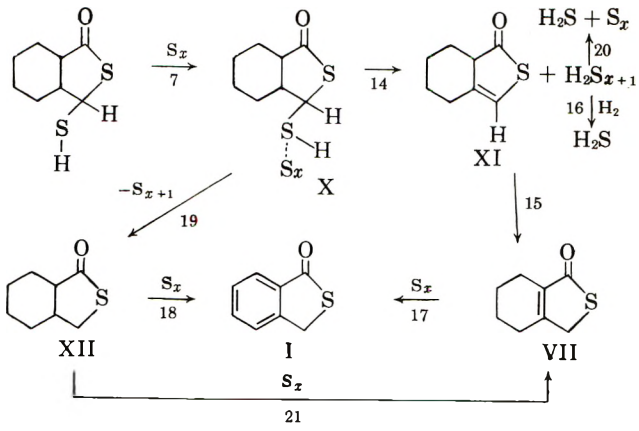
autoclave whose walls can catalyze the hydrogen–sulfur reaction, the yield of VII increased considerably. The alternate path, reactions 19 and 21, in which hexahydrothiophthalide (XII) is formed and then selectively dehydrogenated to VII seems unlikely since no XII was found. This would require the dehydrogenation of the completely saturated XII to VII to be more facile than dehydrogenation of the tetrahydrothiophthalide (VII) to thiophthalide (I). However, steps 18 and 19 cannot be ruled out in these cases in which no 3,4,5,6-tetrahydrothiophthalide (VII) is found.

The hydrogen sulfide–hydrogen reduction of 4-cyclohexene-1,2-dicarboxylic anhydride (V) gave a mixture of thiophthalide (I), 23% yield, and 3,4,5,6-tetrahydrothiophthalide (VII), 29% yield. The reduction of cyclohexane-1,2-dicarboxylic anhydride (VIII) under essentially the same conditions gave only VII; no thiophthalide was found. It is unlikely, then, that VII is the precusor of the thiophthalide found in the reduction of 4-cyclohexene-1,2-dicarboxylic anhydride. A possible reaction path for this unusual transformation involves formation of an intermediate, 3,6-dihydrothiophthalide (XIII), which disproportionates to I and



VII. Partial prior hydrogenation of 4-cyclohexene-1,2-dicarboxylic anhydride to cyclohexane-1,2-dicarboxylic anhydride cannot be dismissed, but it is not likely, especially in the absence of a catalyst other than the metal autoclave walls.

SCHEME 2



Experimental

All runs were conducted in 4.5-l. 316-steel rocking autoclaves equipped with bursting disk, pressure gage, thermowell, bleed valve, and heating jacket.

Reagents were added to the bomb directly where possible. Hydrogen sulfide (and hydrogen) was pressured in after sealing the head. Contents were shaken while heating to temperature which took about 1 hr. After the specified reaction time, the autoclave was allowed to cool overnight to room temperature. Gaseous products were withdrawn through a caustic scrubber to absorb hydrogen sulfide and carbon dioxide. A Dry Ice trap was used when volatile products were expected, and in the phthalic anhydride reduction a wet test meter was used to measure unconverted hydrogen. Liquid and solid products were then worked up as indicated for each type of product.

Phthalic Anhydride Reduction.—Table I summarizes these runs. In those cases where water was used, products were isolated as follows. They were first steam distilled. A chloroform extraction then separated all thiophthalide, benzoic, and toluic acids, as well as other organic by-products. Sulfur partially dissolved in the chloroform, but the bulk of it was recovered by filtration of the chloroform–water mixture. Unchanged phthalic acid was recovered from the water phase by crystallization and by evaporation of the filtrates to dryness. The chloroform solution was extracted with aqueous sodium bicarbonate to remove benzoic and toluic acids, which were isolated by acidifying with dilute mineral acid, filtering, washing, and drying. Identity was established by neutralization equivalent. The remaining chloroform solution was then distilled through a 1-ft. glass helices-packed column. Distillation of the thiophthalide fraction was done at reduced pressure (10–50 mm. of mercury) and select cuts were analyzed by high mass spectrometry, saponification and neutralization equivalents, and elemental analysis for sulfur. Still residues were analyzed for free and total sulfur. By-product tars were found here.

Those runs done with no water present were worked up by diluting with benzene, azeotropically distilling water of reaction, and then fractionally distilling through a 4-ft. zigzag column under reduced pressure.

The green-yellow needles of Δ-3,3′bithiophthalide (IV), m.p. 335°, lit.[11] m.p. 332–333°, obtained in run 6 were soluble only in nitrobenzene and ethyl benzoate. Sublimation gave orange-yellow needles.

In run 9, *o*-xylylene sulfide (III), b.p. 90–100° (2–4 mm.), lit.[12] b.p. 106–107° (9 mm.), was obtained as a yellow oil. The compound was further purified by steam distillation done under an atmosphere of nitrogen.

Anal. Calcd. for C_8H_8S (136.21): C, 70.54; H, 5.29; S, 23.54. Found: C, 69.90; H, 6.05; S, 23.0.

Δ-3,3′-Bithiophthalide (IV) Oxidation.—Δ3,3′-Bithiophthalide (32.8 g., 0.111 mole), sulfur (32 g., 1 g.-atom), and water (1800 g., 100 moles) were charged to the autoclave. The autoclave was held at 260° for 2 hr. The product of the reaction was filtered while still hot, giving a dark solid (27.5 g.) whose analysis showed 79% free sulfur; the aqueous filtrate was partially

(11) S. Gabriel and E. Lenpold, *Ber.*, **31**, 2646 (1898).

(12) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Inst. Petrol.*, **40**, 76 (1954).

evaporated and then chilled to yield crude phthalic acid (27.2 g., 0.164 mole, 74%).

Thiophthalic Anhydride (II) Reduction.—Thiophthalic anhydride was prepared from phthalic anhydride and sodium sulfide as described by Reissert and Halle.[13] Hydrogen sulfide was passed through the thiophthalic anhydride (5.0 g., 0.030 mole) for 6 hr. as the reaction mixture was heated to 260°. The reaction took place at atmospheric pressure. Ether extraction of the cooled reaction product left sulfur (0.34 g., 0.011 g.-atom). Mass spectrometry analysis of the residue left after evaporation of the ether showed the following (in mole per cent): thiophthalic anhydride, 87; thiophthalide, 3.0; toluic acid, 0.9; and benzoic acid, 0.2.

Succinic Anhydride Reduction.—Succinic anhydride (200 g., 2.0 moles) and hydrogen sulfide (500 g., 15 moles) were heated in an autoclave at 260° for 1 hr. and then allowed to cool slowly overnight. The foul smelling reaction product was extracted with benzene and filtered, leaving succinic acid (58 g., 0.20 mole) and sulfur (42.5 g., 1.34 g.-atoms). The succinic acid was identified by its infrared spectrum and the percentage sulfur present was determined by free sulfur analysis. The filtrate was distilled, giving γ-thiolbutyrolactone (48.55 g., 0.475 mole, 24%), b.p. 53–57° (4 mm.), $n^{20}D$ 1.5219–1.5296. Redistillation gave pure γ-thiolbutyrolactone, b.p. 57° (4 mm.), $n^{20}D$ 1.5277; lit.[14] b.p. 56–57° (4 mm.), $n^{20}D$ 1.5240; $\nu C{=}O$ 1725 cm.$^{-1}$ in carbon tetrachloride.

Anal. Calcd. for C_4H_6SO (102.16): C, 47.02; H, 5.92; S, 31.39. Found C, 46.99; H, 5.91; S, 31.42.

Succinic Acid Reduction.—A mixture of succinic acid (237 g., 2.01 moles) and hydrogen sulfide (320 g., 9.4 moles) was charged to an autoclave. The autoclave was heated to 269° and held at this temperature for 2 hr. The autoclave was allowed to cool slowly overnight before it was vented. The crude product (257 g.), which was a mixture of crystals and black oil, was extracted with benzene (1 l.). Distillation of the benzene extract gave γ-thiolbutyrolactone (7.4 g., 0.072 mole, 3.6%), b.p. 45–56° (1 mm.). The benzene-insoluble material was extracted with hot water and separated from the insoluble tar. Evaporation of the water gave succinic acid, (137 g., 1.16 moles, 58% recovery), m.p. 182–184°, which was identified by its infrared spectrum in Nujol.

Acetic Anhydride Reduction.—Acetic anhydride (510 g., 5.0 moles) and hydrogen sulfide (510 g., 15 moles) were charged to an autoclave. The mixture was heated to 260° for 2 hr. After cooling and venting the unchanged hydrogen sulfide, the mixture was filtered to remove sulfur (59.9 g., 1.86 g.-atoms) and then fractionally distilled through a 36-in. helices-packed column. Ethyl thiolacetate, b.p. 117°, lit.[15] b.p. 116–117° was obtained by washing out the acetic acid in the distillate with water and then redistilling.

The composition, in mole per cent, indicated by mass spectrometry analysis of the crude reaction mixture was acetic acid, 89; ethyl thiolacetate, 7; diethyl disulfide, 1; *n*-butyl mercaptan, 0.8; ethyl mercaptan, 0.6; *n*-propyl mercaptan, 0.2; and methyl mercaptan, 0.1.

Benzoic Anhydride, Benzoic Acid, *m*-Toluic Acid Reduction.—A mixture of benzoic anhydride (56.6 g., 0.250 mole) benzene (780 g., 10 moles), and hydrogen sulfide (34 g., 1.0 mole) was charged to an autoclave. Hydrogen was pressured in to 1500 p.s.i.g. and then the autoclave was heated to 177° for 2 hr. After cooling and venting the autoclave, the benzene was distilled, and the residue (71.9 g.) was allowed to cool. The composition, in mole per cent, of the residue as determined by mass spectrometry analysis was benzene, 36; benzoic acid, 51; benzyl thiolbenzoate, 9; benzoic anhydride, 3; benzyl mercaptan, 1; and a trace of toluene.

A similar run at 260° gave almost all toluene. Benzoic acid was unreactive at 260°, but at about 300° was reduced to toluene in 68% yield. Under similar reducing conditions at 340°, *m*-toluic acid gave *m*-xylene in 13% yield; lauric acid was recovered unchanged.

Phthalimide Reduction.—Phthalimide (148 g., 1.0 mole) and hydrogen sulfide (204 g., 6 moles) were charged to an autoclave. After heating for 2 hr. at 260°, the reaction mixture was slowly allowed to cool. The resulting dark mixture yielded no identifiable products.

Benzonitrile–Benzoic Acid Mixture Reduction.—Benzonitrile (103 g., 1.0 mole), benzoic acid (122 g., 1.0 mole), and hydrogen sulfide (200 g., 5.9 moles) were charged to an autoclave which was heated for 2 hr. at 280° and then allowed to cool slowly. Other than toluene (48 g.), only benzoic acid was recovered from the reaction.

Reduction of V, VI, and VIII.—The reduction of compounds V, VI, and VIII was done as follows. The carboxylic anhydride was put in a 4.5-l. glass-lined autoclave. Hydrogen sulfide, and hydrogen when used, was then charged to the autoclave which was placed in the rocker. Heat was applied until the temperature of the autoclave reached 260°. After 2 hr. at 260°, the rocker was stopped, and the autoclave was allowed to cool overnight. The hydrogen sulfide was vented into aqueous sodium hydroxide and the product was removed from the autoclave.

4-Cyclohexene-1,2-dicarboxylic Anhydride (V) Reduction. A.—4-Cyclohexene-1,2-dicarboxylic anhydride (304 g., 2.00 moles) and hydrogen sulfide (390 g., 11.5 moles) were allowed to react as described above. The crude product was a viscous red-brown oil containing water, 9.6 g. (0.53 mole), which was separated. The remaining oil (350 g.) was analyzed by integration of the vapor phase chromatograph trace and was estimated to be 65% (211 g., 1.41 moles) thiophthalide. Vacuum distillation of the crude product gave thiophthalide, b.p. 105–120° (1 mm.), m.p. 49–52°, in only 45% yield before the material in the pot resinified.

B.—4-Cyclohexene-1,2-dicarboxylic anhydride (322 g., 2.15 moles), hydrogen sulfide (150 g., 4.4 moles), and hydrogen (to 1000 p.s.i.g.) were allowed to react in a 2.5-l. stainless steel autoclave. The crude product (380 g.), a viscous deep red oil, was diluted with benzene and extracted with 10% aqueous sodium hydroxide. The benzene solution was evaporated, leaving a red oil (171 g.) estimated to be 56% 3,4,5,6-tetrahydrothiophthalide (96 g., 0.63 mole, 29%) and 44% thiophthalide (75 g., 0.50 mole, 23%) by integration of the vapor phase chromatography trace. A 12-ft. 25% GE SF-96 silicone-on-firebrick column was used in vapor phase chromatograph separations.

1-Cyclohexene-1,2-dicarboxylic Anhydride (VI) Reduction.—1-Cyclohexene-1,2-dicarboxylic anhydride (125 g., 0.822 mole) and hydrogen sulfide (300 g., 8.8 moles) were allowed to react as described previously. The deep red crude product (144 g.) was filtered, leaving a yellow solid (2.4 g.), m.p. 202–215° with apparent water evolution. The water layer (8.1 g., 0.45 mole) in the filtrate was separated and the thiophthalide content of the organic layer (122 g.) was estimated to be 92% (112 g., 0.746 mole, 91%) by integration of the vapor phase chromatograph trace.

Cyclohexane-1,2-dicarboxylic Anhydride (VIII) Reduction. A.—Cyclohexane-1,2-dicarboxylic anhydride (308 g., 2.00 moles) and hydrogen sulfide (340 g., 10 moles) were allowed to react as described previously. The crude product was a deep red oil with a light colored solid suspended in it. The solid was separated, and the filtrate (150 g.) was estimated to consist of 51% 3,4,5,6-tetrahydrothiophthalide (76.5 g., 0.50 mole, 25%) and 42% thiophthalide (63.0 g., 0.42 mole, 21%) by integration of the vapor phase chromatography trace.

B.—Cyclohexane-1,2-dicarboxylic anhydride (250 g., 1.62 moles), hydrogen sulfide (300 g., 8.8 moles), and hydrogen (to 800 p.s.i.g.) were allowed to react as described previously. The solid in the deep red oil was separated and washed with benzene, giving a white solid diacid (120 g., 0.70 mole, 43%), m.p. 180–215°, neutralization equivalent 86.6, calculated for cyclohexane dicarboxylic acid, 86.1. This was probably a mixture of *cis*- and *trans*-cyclohexane-1,2-dicarboxylic acids, m.p. 190–196° dec.[16] and 215–221°,[17] respectively. The benzene in the filtrate was evaporated under a stream of nitrogen to give a red oil (143 g.) which was estimated from the integrated vapor phase chromatography trace to be 60% 3,4,5,6-tetrahydrothiophthalide (85 g., 0.55 mole, 34%) and 40% thiophthalide (58 g., 0.38 mole, 23%).

C.—Cyclohexane-1,2-dicarboxylic anhydride (385 g., 2.50 moles), hydrogen sulfide (170 g., 5.0 mole), and hydrogen (to 900 p.s.i.g.) were allowed to react in a 2.5-l. steel autoclave as described previously. The product was a deep red oil containing white solid. The solid was separated and then washed with benzene, leaving light greenish white crystals (200 g., 1.16 mole,

(13) A. Reissert and H. Halle, *Ber.*, **44**, 3029 (1911).
(14) C. M. Stevens and D. S. Tarbell, *J. Org. Chem.*, **19**, 1996 (1954).
(15) R. B. Baker and E. E. Reid, *J. Am. Chem. Soc.*, **51**, 1568 (1929).
(16) W. Reppe, O. Schlechting, K. Kluger, and T. Toepel, *Ann.*, **560**, 57 (1948).
(17) M. S. Newman and H. A. Loyd, *J. Org. Chem.*, **17**, 579 (1952).

47%), m.p. 214–228°, of *trans*-cyclohexane-1,2-dicarboxylic acid. The viscous red filtrate was estimated by integration of the vapor phase chromatography trace to be 90% 3,4,5,6-tetrahydrothiophthalide (179 g., 1.16 moles, 47%). The benzene wash solution was added to the viscous red oil and the resulting solution extracted with 5% aqueous sodium bicarbonate. The benzene was then evaporated and the oil cooled to 0°. The oil partially crystallized, and a sticky yellow solid was collected. Two recrystallizations of the yellow solid from methanol (with charcoal) gave 3,4,5,6-tetrahydrothiophthalide as white crystals (74 g., 0.48 mole, 19%), m.p. 36–43°. Further recrystallizations gave white crystals, m.p. 42–43°; λ_{max} in 95% ethanol: 233 mμ (log ε 4.02), 258 inflection (3.43); $\nu_{C=O}$ 1690, $\nu_{C=C}$ 1655 cm.$^{-1}$ in carbon tetrachloride. The nuclear magnetic resonance spectrum[18] showed the following absorptions (in τ-values, tetramethylsilane external standard): 8.25, quartet, unconjugated methylene; 7.70, diffuse multiplet, vinyl methylene; 6.17, singlet, split slightly, vinyl methylene adjacent to sulfur; calculated area ratio 2:2:1; observed, 2.1:2.1:1.

Anal. Calcd. for $C_8H_{10}OS$ (154.31): C, 62.26; H, 6.53; S, 20.68. Found: C, 61.98; H, 6.48; S, 20.52. The molecular weight as determined by mass spectrometry was 154.

When this reaction was repeated in a freshly reamed autoclave, the product oil after separation of the solid diacid, was estimated to contain 69% 3,4,5,6-tetrahydrothiophthalide and 21% thiophthalide.

(18) The n.m.r. spectrum was obtained on a Varian A-60 spectrometer.

2-Amino-5,6-dihydro-1,3-oxazines. The Reduction of Carboxylic Esters with Sodium Borohydride[1]

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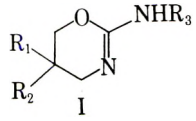
Received June 21, 1963

Several 5-substituted 2-amino-5,6-dihydro-1,3-oxazines (Table III) were prepared by the cyclization of the appropriately substituted 1,3-amino alcohols (Table II) with cyanogen bromide. The amino alcohols were prepared most readily by a two-step process: (1) sodium borohydride reduction of α-substituted cyanoacetates to the novel hydracrylonitriles (Table I), and (2) lithium aluminum hydride reduction of these to the requisite amino alcohols. A side product of step 1 has been shown to result from the reduction of the nitrile function with sodium borohydride.

The 2-amino-5,6-dihydro-1,3-oxazine system (I) has apparently received little attention. In 1890 Gabriel and Lauer[2] described the parent compound (I, $R_1 = R_2 = R_3 = H$) and more recently Najer and co-workers[3] reported the synthesis of several N-substituted derivatives (I, $R_1 = R_2 = H$; R_3 = alkyl, aryl, and aralkyl). Our interest in this system concerned the possible biological activity of analogs in which the 5-position was substituted (*e.g.*, I, $R_1 = R_2$ = phenyl; $R_3 = H$).

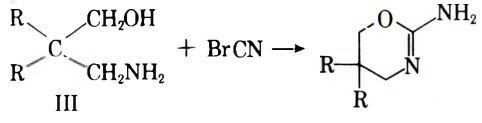


I

$R_3NHCONHCH_2CH_2CH_2Cl$

II

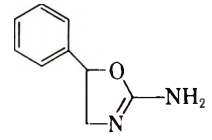
The general method employed by the earlier workers was cyclization of the appropriately N-substituted N′-γ-chloropropylureas (II) in boiling water. Our approach was the cyclization of 2-substituted 1,3-amino alcohols (III) with cyanogen bromide. The



III

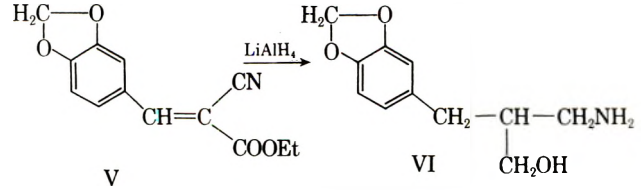
analogous reaction between 1,2-amino alcohols and cyanogen bromide to give the corresponding 2-aminooxazolines (*e.g.*, IV) has been reported.[4]

The requisite 1,3-amino alcohols were in general new compounds. In the search for a method of preparation,



IV

we were attracted by the report[5] that lithium aluminum hydride reduces α,β-unsaturated cyanoacetates (*e.g.*, V) to the corresponding saturated amino alcohols (VI). Numerous attempts to reproduce these results led only to poor yields of colored oils from which none of the desired amino alcohols could be isolated.[6] Two exceptions were noted, namely, ethyl methylphenylcyanoacetate and ethyl diphenylcyanoacetate (see XXXI and XXXII, respectively, Table II). Evidently, disubstitution of the α-position of ethyl cyanoacetate allows reduction with lithium aluminum hydride to proceed satisfactorily.



V VI

The desired amino alcohols were finally obtained by either of the two following methods.

1. Nickel-catalyzed hydrogenation of the α,β-unsaturated cyanoacetates (*e.g.*, V) to give the corresponding amino esters (*e.g.*, VII).[7] The latter sub-

(1) Presented in part at the Fourth Delaware Valley Regional Meeting, Philadelphia, Pa., January 25–26, 1962.

(2) S. Gabriel and S. Lauer, *Ber.*, **23**, 95 (1890).

(3) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France*, 611 (1959).

(4) G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952); R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 444 (1961); G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszowski, N. M. Kelley, and J. McGowan, *J. Med. Chem.*, **6**, 266 (1963).

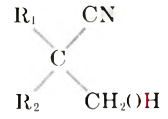
(5) A. Dornow, G. Messwarb, and H. H. Frey, *Ber.*, **83**, 445 (1950).

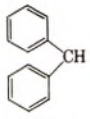
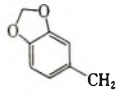
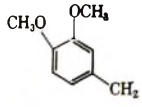
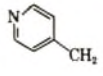
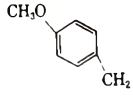
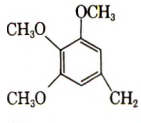
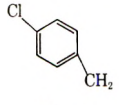
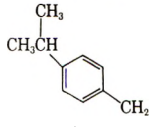
(6) The extraordinary work-up and isolation techniques employed by Dornow, *et al.*, and the generally poor yields reported suggest that they experienced similar difficulties.

(7) R. R. Burtner and J. W. Cusie, *J. Am. Chem. Soc.*, **65**, 262 (1943), used a similar method to reduce methyl diphenylcyanoacetate to the amino ester.

TABLE I

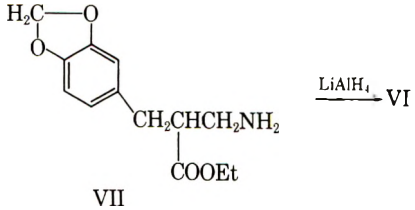
HYDRACRYLONITRILES



Compound no.	R_1	R_2	M.p. or b.p. (mm.), °C.	Recrystd. from	Yield, %	Formula	Calcd.	Found
XII		H	104–105	Ether–pet. ether	80	$C_{16}H_{15}NO$	C 80.98 H 6.37 N 5.90	C 80.85 H 6.45 N 5.65
VIII[i]		H	153 (0.5)		96	$C_{11}H_{11}NO_3$	N 6.83	N 6.62
XXII		H	95.5–96.5	EtOH	91	$C_{12}H_{15}NO_3$	C 65.14 H 6.83 N 6.33	C 65.02 H 6.82 N 6.12
XXIII		H	68–69	$CHCl_3$–ether	68	$C_9H_{10}N_2O$	C 66.65 H 6.22	C 66.81 H 6.46
XXIV		H	43.5–44.5 135° (0.1)		90	$C_{11}H_{13}NO_2$	C 69.09 H 6.85	C 69.30 H 6.80
XXV		H	90 (0.1)		50	$C_{10}H_{11}NO$	C 74.51 H 6.88 N 8.69	C 74.28 H 7.12 N 8.96
XXVI		H	65–66	EtOH	94	$C_{13}H_{17}NO_4$	C 62.14 H 6.82 N 5.57	C 62.41 H 7.08 N 5.40
XXVII		H	138–48 (0.1)		50	$C_{10}H_{10}ClNO$	N 7.16	N 6.77
XXVIII		H	140–142 (0.1)		81	$C_{13}H_{17}NO$	N 6.89	N 6.74
XIV	C_6H_5	C_6H_5	65–66	Ether–pet. ether	85[a]	$C_{15}H_{13}NO$	C 80.69 H 5.87 N 6.27	C 80.58 H 6.08 N 6.18

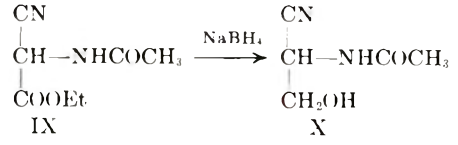
[a] Prepared from diphenylacetonitrile and formaldehyde (see Experimental).

stances were readily converted to the amino alcohols (*e.g.*, VI) with lithium aluminum hydride with none of the previously described difficulties.

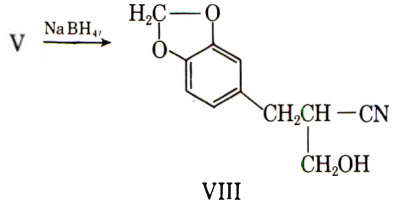


VII

2. Chemical reduction of the α,β-unsaturated cyanoacetates with sodium borohydride to the corresponding saturated hydracrylonitriles (*e.g.*, VIII). A related reduction, namely, that of ethyl α-acetamidocyanoacetate (IX) to α-acetamidohydracrylonitrile (X) with sodium borohydride, has been reported.[8] The hydracrylonitriles (VIII) were then reduced to the desired amino alcohols with lithium aluminum hydride.

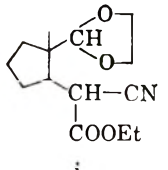


IX X



VIII

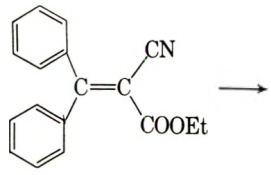
(8) L. Berlinguet, *Can. J. Chem.*, **33**, 1119 (1955); G. W. K. Cavill and F. B. Whitfield, *Proc. Chem. Soc.*, 380 (1962), report the sodium borohydride reduction of i to the corresponding cyano-alcohol. No experimental details are given. We thank Dr. Richard K. Hill of Princeton University for bringing this report to our attention.



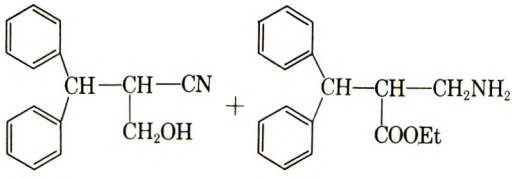
i

While method 1 afforded adequate yields of amino alcohols for subsequent cyclization, method 2 was used almost exclusively when it became clear that in terms of yields and simplicity of operation it was the more satisfactory.

A basic by-product in the reduction of ethyl α-cyano-β-phenylcinnamate (XI) with sodium borohydride in diglyme was identified as ethyl α-diphenylmethyl-β-alaninate (XIII), isolated in 8% yield. This product was identical with that obtained by catalytic



XI



XII 80 %

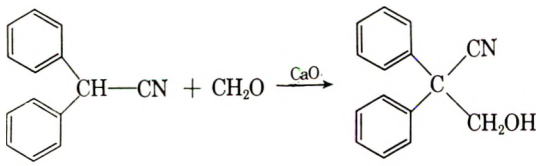
XIII 8 %

(nickel) hydrogenation of XI. Apparently, this is the first reported instance of the reduction of a nitrile with sodium borohydride. It is interesting to note that with isopropyl alcohol (the usual solvent for these reductions), a negligible amount of basic product was obtained. The scope of this side reduction has yet to be studied.

The hydracrylonitriles (Table I) were found to be surprisingly stable to heat; *e.g.*, several of them were purified by distillation at temperatures around 150°; they form the usual derivatives, *e.g.*, tosylates, urethans, carbamates. They are readily hydrolyzed with alkaline peroxide to the corresponding hydracrylamides and with thionyl chloride they are converted to the corresponding β-chloropropionitriles.

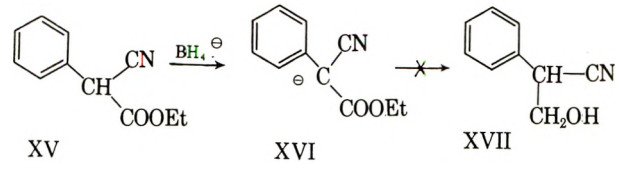
Two cases that follow are worthy of further note.

1. While ethyl diphenylcyanoacetate is converted to diphenylhydracrylonitrile (XIV) with sodium borohydride, the yield is poor (*ca.* 40%). A better method for preparing XIV is condensation of diphenylacetonitrile with formaldehyde in the presence of a base such as calcium oxide.



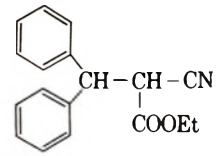
XIV

2. Ethyl phenylcyanoacetate (XV) was recovered unchanged when treated with sodium borohydride. The vigorous evolution of gas when the reagents are brought together suggests the formation of anion XVI which is apparently resistant to further attack by BH_4^-.[9] Wheeler and Wheeler[10] report that carboxylate ion may likewise inhibit attack of BH_4^- at another center of the molecule.



XV XVI XVII

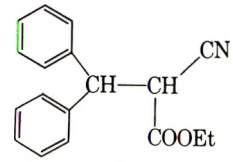
Conversions of carboxylic esters to the corresponding primary alcohols with sodium borohydride are not generally observed[11] although exceptions have been noted.[12] That the α,β-unsaturation has little to do with the reduction of the ester function is evident from the fact that both ethyl diphenylcyanoacetate and ethyl α-cyano-β-phenylhydrocinnamate (XVIII)[13] are reduced to the respective hydracrylonitriles with sodium borohydride and it is likely that the first step in the reduction of α,β-unsaturated cyanoacetates is attack of hydride ion at the β-position.[14] Since several diethyl malonates studied in this laboratory were found to



XVIII

be totally resistant to the action of sodium borohydride, one must conclude that the strongly electron-withdrawing nitrile function plays a major role in the facile reductions observed here, probably by enhancing the electrophilic character of the carbethoxy function (see XIX).

(9) Ethyl α-cyano-β-phenylhydrocinnamate (ii), while possessing an α-hydrogen, is reduced to the corresponding hydracrylonitrile (XII) with sodium borohydride. This would indicate that an α-phenyl group such as that present in XV makes the α-hydrogen appreciably more acidic towards sodium borohydride.



ii

(10) D. M. S. Wheeler and M. M. Wheeler, *J. Org. Chem.*, **27**, 3796 (1962).

(11) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949). For reductions in the presence of aluminum chloride, boron trichloride, and lithium iodide, see H. C. Brown and B. C. Subba Rao, *ibid.*, **77**, 3164 (1955); H. C. Brown, U. S. Patent 2,945,886; R. Paul and N. Joseph, *Bull. soc. chim. France*, 550 (1952), respectively. Presumably, these additives do not enhance the reductive powers of sodium borohydride but convert it, *in situ*, to a more reactive hydride. For example, the addition of lithium halide produces lithium borohydride [H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.* **77**, 6209 (1955)], a reagent which readily reduces esters [R. F. Nystrom, S. W. Chaikin, and W. G. Brown, *ibid.*, **71**, 3245 (1949)].

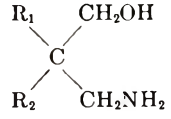
(12) See N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 503. The examples include two steroidal methyl esters and several methyl uronates. See also, J. Kollonitsch, O. Fuchs, and V. Gabor, *Nature*, **175**, 346 (1955). These authors give no examples or experimental details.

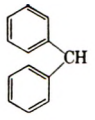
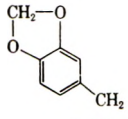
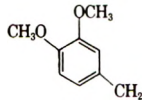
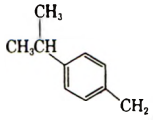
(13) E. P. Kohler and M. Reimer, *Am. Chem. J.*, **33**, 333 (1905).

(14) H. Le Moal, R. Carrié, and M. Bargain, *Compt. rend.*, **251**, 2541 (1960), report that potassium borohydride in methanol reduces ethyl α-cyano-β-phenylcinnamate (XI) to the dihydro compound, *i.e.*, XVIII.

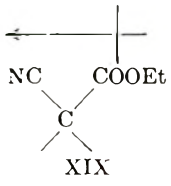
TABLE II

3-AMINO-1-PROPANOLS

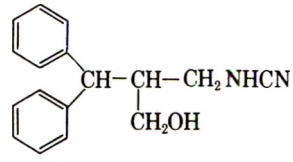


Compound no.	R_1	R_2	M.p., °C.	Recrystd. from	Yield, %	Formula	Calcd.	Found
XXIX		H	157–159[a]	EtOH–ether	87[b] 86[e]	$(C_{16}H_{19}NO)_2C_4H_4O_4$[c]	N 4.68	N 4.39
VI		H	173–174[d]	MeOH	40	$(C_{11}H_{15}NO_3)_2C_4H_4O_4$	N 5.24	N 5.14
XXX		H	162–163	MeOH	40	$C_{12}H_{19}NO_3 \cdot C_4H_4O_4$	N 4.10	N 4.35
XXXI	C_6H_5	CH_3	114 subl.	MeOH	42[f]	$C_{10}H_{15}NO \cdot C_4H_4O_4$	C 59.77 H 6.81 N 4.98	C 59.93 H 7.00 N 4.86
XXXII	C_6H_5	C_6H_5	176–177[g]	Aqueous EtOH	71[h]	$C_{15}H_{17}NO \cdot C_4H_4O_4$	N 4.08	N 4.30
XXXIII		H	152 then 171–172	MeOH–ether	43	$C_{13}H_{21}NO \cdot HCl$	N 6.76	N 6.65

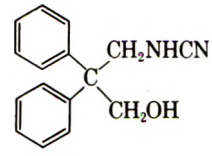
[a] The free base melts 99.5–104.5°. [b] Using ethyl α-diphenylmethyl-β-alaninate as starting material, the yield was 77%. [c] $C_4H_4O_4$ refers to fumaric acid. [d] Dornow, *et al.*, ref. 4, report m.p. 140° for the oxalate salt. [e] Using ethyl α-(3,4-methylenedioxybenzyl) alanine as starting material, the yield was 40%. [f] Ethyl methylphenylcyanoacetate was starting material. [g] The free base melts 108–108.5°. [h] Using ethyl diphenylcyanoacetate as starting material, the yield was 47%.



XIX



XX

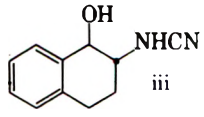


XXI

Reduction of the acrylonitriles with lithium aluminum hydride afforded the requisite, 1,3-amino alcohols in good yields (Table II). These subsequently reacted with cyanogen bromide to give the desired 2-amino-1,3-oxazines in moderate yields (Table III). In most cases, the intermediate cyanamide alcohol could be isolated and in one case (XX) it was characterized. This behavior contrasts sharply with that observed in the case of 1,2-amino alcohols,[4] where the intermediate cyanamide alcohols cyclize spontaneously in every reported case.[15]

Cylization of the intermediate cyanamide alcohols was found to occur readily upon treatment with anhydrous hydrogen chloride. In one case (XXI), however, cyclization took place spontaneously, a probable consequence of the two phenyl groups forcing the cyanamide and alcohol functions closer together.

(15) A private communication from G. I. Poos, and J. D. Rosenau of these laboratories, reveals that at least one exception to this has been found, namely, iii, which is obtained from the corresponding amino alcohol upon treatment with cyanogen bromide. The details of this and other related work will appear elsewhere.



iii

Experimental

All melting points are uncorrected and were taken on a Thomas–Hoover capillary melting point apparatus.

The starting α,β-unsaturated cyanoacetates were prepared from the appropriate aldehydes and ethyl cyanoacetate by known methods.[16] Ethyl diphenylcyanoacetate was prepared from ethyl chlorodiphenylacetate and mercurous cyanide.[17] Ethyl methylphenylcyanoacetate was prepared by methylating ethyl phenylcyanoacetate.[18]

The descriptions which follow are general methods and applicable to all examples in Table I–III unless otherwise noted.

Hydracrylonitriles (Table I). Method A.—To a stirred, cooled (15°) solution of 3.6 g. (0.1 mole) of sodium borohydride in 50 ml. of diglyme was added over a period of 15 min. a solution of 10 g. (0.036 mole) of ethyl α-cyano-β-phenylcinnamate in 50 ml. of diglyme. The temperature was allowed to reach room temperature and stirring maintained for 3 hr. after which the mixture was poured over water and extracted with ether several times. The combined organic solutions were washed twice with 2 *N* HCl and finally once with water. After drying over anhydrous sodium sulfate and concentration *in vacuo* there remained 7.5 g. of a crystalline residue, m.p. 90–100°, which was recrystallized from ether–petroleum ether to give 6.8 g. (80%) of analytically pure α-diphenylmethylhydracrylonitrile, m.p. 104–105°;

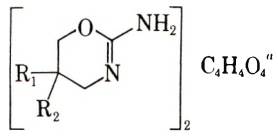
(16) E. J. Cragoe, Jr., C. M. Robb, and J. M. Sprague, *J. Org. Chem.*; **15**, 381 (1950); F. D. Popp, *ibid.*, **25**, 646 (1960).

(17) A. Bickel, *Ber.*, **22**, 1537 (1889).

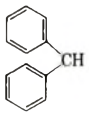
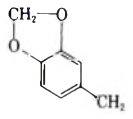
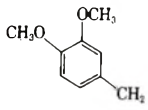
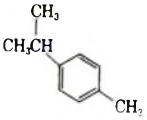
(18) S. Wideqvist, *Chem. Zentr. II*, 1184 (1943).

TABLE III

2-AMINO-5,6-DIHYDRO-1,3-OXAZINES



$C_4H_4O_4$[a]

Compound no.	R_1	R	M.p., °C.	Recrystd. from	Yield, %	Formula	Calcd.	Found
XXXIV		H	209–211	*b*	65	$(C_{17}H_{18}N_2O)_2C_4H_4O_4$	C 70.35 H 6.22 N 8.64	C 70.29 H 6.43 N 8.53
XXXV		H	178–180	Aqueous EtOH	40	$(C_{12}H_{14}N_2O_3)_2C_4H_4O_4$	C 57.53 H 5.52 N 9.59	C 57.59 H 5.76 N 9.16
XXXVI		H	196.5–197	EtOH	46	$(C_{13}H_{18}N_2O_3)_2C_4H_4O_4$	C 58.43 H 6.54	C 58.55 H 6.58
XXXVII	C_6H_5	CH_3	234 dec.	Aqueous EtOH	50	$(C_{11}H_{14}N_2O)_2C_4H_4O_4$	N 11.28	N 11.04
XXXVIII	C_6H_5	C_6H_5	248 dec.	*b*	65	$(C_{15}H_{16}N_2O)_2C_4H_4O_4$	C 69.66 H 5.85 N 9.03	C 69.66 H 5.85 N 8.68
XXXIX		H	194.5 dec.	MeOH	70	$(C_{14}H_{20}N_2O)_2C_4H_4O_4$	N 9.65	N 9.63

[a] $C_4H_4O_4$ signifies fumaric acid. [b] Purified by boiling in ethanol or 2-propanol.

λ_{max}^{KBr} 2.86, 3.25, 3.35, 3.41, 4.39, 6.22, 6.65, 6.84 μ; λ_{max}^{MeOH} 221, 263 mμ; ϵ 9800, 230. The analytical data are reported in Table I.

The aqueous acidic washes of the reaction mixture were made basic with concentrated sodium hydroxide solution and extracted with ether. The organic solution was worked up in standard fashion to yield 1 g. of oil which was converted to a hydrochloride salt, m.p. 199–201°. The yield was 0.85 g. (8%). Comparison with an authentic sample showed this material to be ethyl α-diphenylmethyl-β-alaninate hydrochloride.

Method B.—To a stirred, cooled (15°) suspension of 11.4 g. (0.3 mole) of sodium borohydride in 50 ml. of 2-propanol was added over 5 min. a solution of ethyl α-cyano-β-phenylcinnamate in 200 ml. of 2-propanol. After stirring for 8 hr., the excess borohydride was destroyed with dilute acetic acid and most of the 2-propanol removed *in vacuo*. From this point, the reaction was worked up as previously described in method A. The yield of α-diphenylmethylhydracrylonitrile was comparable to that obtained from the diglyme system, although the amount of basic material obtained was negligible.

Method C (for α,α-Diphenylhydracrylonitrile Only).—To a stirred mixture of 25 g. (0.13 mole) of diphenylacetonitrile, 11.5 g. (0.38 mole) of paraformaldehyde, 30 ml. of water, and 100 ml. of tetrahydrofuran was added in several portions 5.5 g. (0.1 mole) of calcium oxide. The temperature rose to about 30° after which it returned to room temperature and stirring was continued for 8 hr.

The mixture was then made slightly acidic with formic acid and concentrated to near dryness *in vacuo*. The residue was diluted with water and extracted several times with ether after which the combined ether solutions were washed with water, dried over anhydrous potassium carbonate, and concentrated to dryness leaving about 30 g. of an oil which slowly crystallized. The yield of pure crystalline α,α-diphenylhydracrylonitrile (recrystallized from ether–petroleum ether) was only about 15 g. (52%), although if the crude product is treated with lithium aluminum hydride a 71% yield of the corresponding amino alcohol, *i.e.* 3-amino-2,2-diphenyl-1-propanol is obtained.

α,α-Diphenylhydacrylonitrile has the following physical properties: m.p. 65–66°; λ_{max}^{KBr} 2.88, 3.25, 3.40, 4.44, 6.24, 6.67, 6.88 μ. The analytical data are reported in Table I.

Amino Alcohols (Table II).—To a stirred suspension of 3.9 g. (0.1 mole) of lithium aluminum hydride in 75 ml. of anhydrous ether was added, over a convenient period, a solution of 9 g. (0.03 mole) of α-diphenylmethylhydracrylonitrile (or an equivalent amount of ethyl α-diphenylmethyl-β-alaninate) in 100 ml. of ether. After stirring for 5 hr., the excess hydride was destroyed with water, the ether solution filtered and concentrated to dryness. The residue, 6.5 g., was recrystallized from ether–hexane to give 6.1 g. (79%) of pure 3-amino-2-diphenylmethyl-1-propanol, m.p. 99.5–104.5°; λ_{max}^{KBr} 3.14, 3.40, 3.45, 6.24, 6.65, 6.85 μ.

Where the amino alcohols were oils or difficultly recrystallizable, they were converted to a convenient salt (see Table II) and characterized.

2-Amino-5,6-dihydro-4*H*-1,3-oxazines (Table III).—To a stirred, cooled (10°) mixture of 8 g. (0.03 mole) of 3-amino-2-diphenylmethyl-1-propanol and 5.6 g. (0.06 mole) of sodium acetate in 100 ml. of methanol was added drop by drop a solution of 3.6 g. (0.034 mole) of cyanogen bromide in 50 ml. of methanol. The homogeneous mixture was then stirred for 8 hr.

The solution was concentrated to near dryness and the residue treated with cold concentrated aqueous sodium hydroxide. The mixture was then extracted with ether several times after which the combined ether solutions were washed once with water, dried over anhydrous potassium carbonate and evaporated to dryness. The crystalline residue was recrystallized from benzene to give 7.4 g. (84%) of 2-diphenylmethyl-3-hydroxypropylcyanamide, m.p. 91–92° (with subsequent resolidification and fusion at 205°); λ_{max}^{KBr} 2.98, 3.19, 3.40, 4.46, 6.23, 6.66, 6.68 μ.

Anal. Calcd. for $C_{17}H_{18}N_2O$: N, 10.52. Found: N, 10.31.

When the previously described substance was dissolved in ether and treated with anhydrous hydrogen chloride, a hygroscopic solid precipitated. From this 5.1 g. of the free amine, m.p. 197–200°, was obtained.[19] This was converted to a fumarate salt, m.p. 209–211°; the yield was 3 g. (31%); λ_{max}^{KBr} 3.04, 3.40, 5.88, 6.50, 6.84 μ. The analytical data are reported in Table III.

Ethyl α-Diphenylmethyl-β-alaninate Hydrochloride.—In a stainless steel autoclave was placed 10 g. (0.036 mole) of ethyl α-cyano-β-phenyl cinnamate, about 10 g. of triethylamine, about 2 g. of sponge nickel catalyst (Davison Chemical Co.), and 150

(19) Whether this was the product obtained upon melting 2-diphenylmethyl-3-hydroxypropylcyanamide (note its melting point) was not investigated.

ml. of absolute ethanol. The autoclave was then shaken under 1,000 lb. of hydrogen pressure at 100° for 1 hr.

After filtration, the solution was concentrated *in vacuo* and the oily residue taken up in ether and separated into basic and neutral fractions. The basic fraction was converted to its hydrochloride salt and recrystallized from ethanol–ether to give 5.8 g. (50%) of analytically pure ethyl α-diphenylmethyl-β-alaninate hydrochloride, m.p. 200–202°; λ_{max}^{KBr} 3.50, 5.80, 6.15, 6.22, 6.29, 6.65, 6.84 μ; λ_{max}^{MeOH} 258 mμ, ε 475.

Anal. Calcd. for $C_{18}H_{21}NO_2$·HCl: C, 67.59, H, 6.94; N, 4.38. Found: C, 67.89; H, 7.01; N, 4.36.

Acknowledgment.—We wish to thank Dr. George I. Poos who suggested the original problem for helpful discussions, and Mrs. Mary Christie for the spectroscopic data and nitrogen analyses.

Reactions of Acetylenic Esters with Enamines

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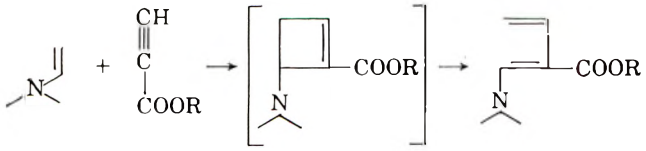
Received June 10, 1963

Enamines derived from cyclic ketones react with ethyl propiolate or dimethyl acetylenedicarboxylate to produce intermediate cyclobutene adducts which have, in several cases, been isolated. These cyclobutenes on heating, undergo bond rearrangement with expansion of the cyclic ketone ring by two carbon atoms. In at least one case, however, treatment with dilute acid in the cold results in a second reaction course to form a Michael-type adduct of the ester and cyclic ketone. Reactions of dimethyl acetylenedicarboxylate with enamines derived from β-diketones and β-keto esters also are described.

Since the introduction by Stork and co-workers[1] in 1954 of a relatively general procedure for the alkylation of carbonyl compounds *via* their enamine derivatives, reactions of the latter with a wide variety of electrophiles have been studied by various investigators.[1] Although alkylations with electrophilic olefins, reported in 1956[2], have been widely studied,[1] little, until recently, has been known about the corresponding reactions of enamines with electrophilic acetylene compounds. The earliest report of such a reaction, in abstract form,[3] indicates that enamines react with conjugated acetylenic esters to produce an intermediate cyclobutene adduct, which rearranges in such a manner as to interpose the two acetylenic carbon atoms between the erstwhile olefinic carbons of the enamine. We had been independently studying this reaction for



some time with both cyclic and acyclic[4] enamines when we became aware of the activities of two other groups of investigators in this field. Bose and Minah[5] have reported on reactions of enamines of cyclic ketones with dimethyl acetylenedicarboxylate and with methyl propiolate to yield ring-expanded products by an analogous process, and a pending paper by Berchtold[6] is concerned with the dimethyl acetylenedicarboxylate reaction in similar cases. In spite of some duplication in these investigations, we present our findings on reactions of cyclic enamines here, for they include certain unique results, among these the *isolation of several of the intermediate cyclobutene adducts.* In addition we have found that the cyclobutenes may, at least in certain cases, be converted *either* to the ring-expanded derivatives,[5,6] *or* (on hydrolysis) *to the unsaturated keto esters corresponding to Michael-type additions of acetylenic esters to ketones.* In addition, we report here reactions of acetylenic esters with various acyclic enamines derived from β-diketones or β-keto esters, the courses of which are widely diverse in nature.

The early experiments with ethyl propiolate were carried out by addition of the ester to a dioxane solution of 1-pyrrolidinocyclopentene (**1a**) at ambient temperature, and subsequent heating of the mixture on the steam bath. Removal of solvent allowed isolation of the crystalline 1-pyrrolidino-2-carbethoxy-1,3-cycloheptadiene (**3**). The structure of this substance was indicated by infrared bands at 1661 and 1605 cm.$^{-1}$ (Nujol) representing C=O and C=C absorptions, respectively. In the n.m.r. spectrum[7] the C-3 proton was observed as a doublet at 6.45 δ ($J_{3,4}$ = 10.1) and H-4 as a triplet of a doublet at 5.70 δ ($J_{3,4}$ = 10.1, $J_{4,5,5}$ = 6.4). Chemical confirmation of the structure was obtained in several ways. Mild acid hydrolysis of the enamine group resulted in the formation of the keto–enol mixture (**4**), which was reduced catalytically to the known[8] 2-carbethoxycycloheptanone (**6**). This keto ester was identified by its reaction with phenylhydrazine to yield the solid phenylpyrazolone derivative,[8] and by its hydrolysis and decarboxylation to cycloheptanone, the semicarbazone of which was compared with an authentic sample. The sequence of reactions also was carried out in reversed order, partial hydrogenation preceding the mild hydrolysis to yield the same product.

When, on the other hand, ethyl propiolate and **1a** were allowed to react below room temperature and the

(1) *Cf.* G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963), for a recent survey.

(2) G. Stork and H. Landesman, *ibid.*, **78**, 5128 (1956).

(3) K. C. Brannock, Abstracts of Papers, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, p. 450.

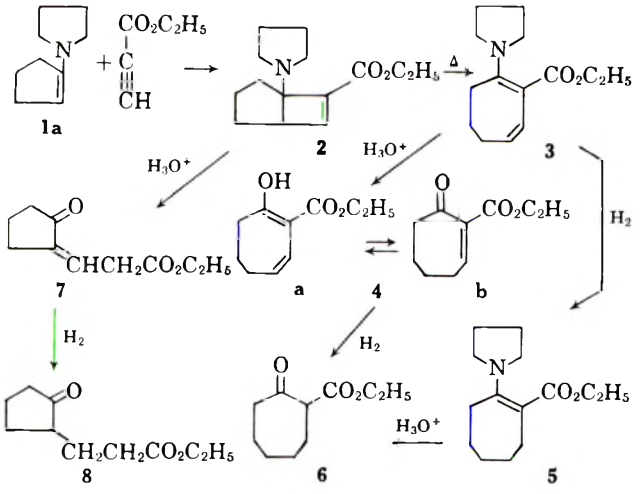
(4) *Cf.* C. F. Huebner and E. Donoghue, *J. Org. Chem.*, **28**, 1732 (1963).

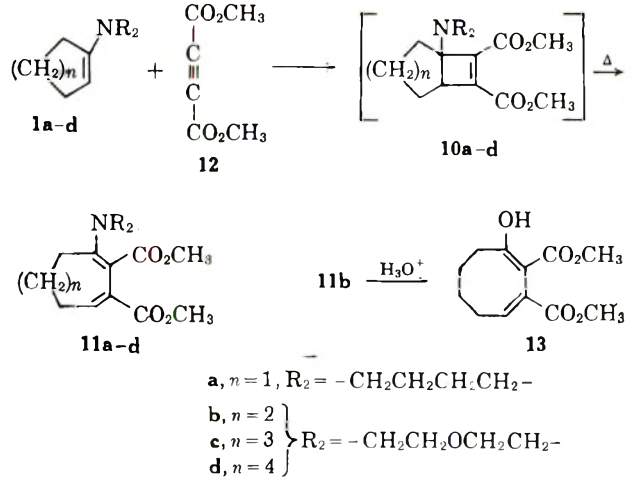
(5) A. K. Bose and G. L. Minah, Metropolitan Regional Meeting of the American Chemical Society, Newark, N. J., January 28, 1963.

(6) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963). We wish to thank Dr. Berchtold who, through Dr. F. Greene, made a copy of his paper available to us before publication, on submission of the previous manuscript[4] from this laboratory.

(7) Spectra were obtained with the Varian A-60 spectrometer at 60 Mc./sec. using tetramethylsilane as internal reference. Chemical shifts are quoted in field-independent δ-units (p.p.m.) where δ is defined by the relationship $\delta = 10^6|H_{ref} - H|/H_{ref}$; coupling constants ($J$) are expressed in c.p.s.

(8) W. Dieckmann, *Ber.*, **55**, 2485 (1922).



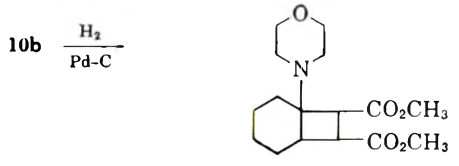


reaction mixture was treated with dilute acetic acid *without heating*, the Michael-type adduct **7** was obtained. Its structure, indicated by infrared absorption bands at 1730 (ester C=O) and 1660 cm.$^{-1}$ (C=C—C=O) and by a single vinyl proton signal appearing in the n.m.r. spectrum as a triplet at 6.37 δ (J = 7), was further established by partial hydrogenation to ethyl β-(2-oxocyclopentyl)propionate (**8**). The identity of this reduction product with the substance as prepared unequivocally by reaction of **1a** with ethyl acrylate[1] was demonstrated by comparison of spectra and of solid derivatives.

Isolation of 5-pyrrolidino-6-carbethoxybicyclo[3.2.0]-hept-6-ene (**2**) was effected by reaction of **1a** and the acetylenic ester in absolute ether at about 15°. Removal of the solvent at low temperature yielded essentially pure **2** as an oil. The n.m.r. spectrum of the compound in deuteriobenzene solution showed one vinyl proton which appeared as a *singlet* (J < 1) 41 c.p.s. upfield from the benzene proton (impurity in C_6D_6). Such a signal is to be expected for the vinyl proton in **2**, since its dihedral angle with the bridgehead proton is close to 90°, as seen on examination of models. Heating the deuteriobenzene solution resulted in a change of the spectrum and the appearance of signals characteristic of **3**. Treatment of the oily cyclobutene **2** with dilute acetic acid, on the other hand, resulted in the formation of the cyclopentanone **7**, isolated and characterized by the usual criteria. In this connection it is of interest that treatment of **2** with dilute *hydrochloric* acid under similar conditions did not effect this rearrangement and hydrolysis; little or no nonbasic material could be extracted from the acidic medium. Although it was not possible to crystallize **2** as such, or to prepare a solid acid salt as a derivative, the substance was readily converted to a crystalline, stable methiodide **9**. The n.m.r. spectrum of this derivative again showed the single vinyl proton as a single (δ = 7.35) and the other spectral data were consistent with the proposed structure.

Reactions of enamines (**1a–d**) were also carried out with dimethyl acetylenedicarboxylate (**12**)[9] to yield, after heating, the corresponding ring expansion products **11**. One such material (**11b**) was hydrolyzed by mild acid to produce the corresponding enol **13**.

In another experiment, the acetylenic ester and 1-morpholinocyclohexene (**1b**) were allowed to react in deuteriobenzene below 25°. The n.m.r. spectrum of the solution, determined 30 min. after mixing, showed the complete absence of vinyl protons, a finding consistent only with structure **10b**. Refluxing an aliquot of the solution produced **11b**, isolated, in this case, in 21% yield. Another portion of the solution was evaporated at low temperature to produce **10b** as an oil. Hydrogenation resulted in the uptake of one mole of hydrogen to yield the corresponding cyclobutane **14**, isolated as the hydrochloride. The cyclobutene **10b** is apparently stable indefinitely in benzene, but in diglyme solution even at room temperature, conversion to **11b** takes place in good yield within several days.



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Reactions of dimethyl acetylenedicarboxylate with enamines derived from β-diketones and β-keto esters were also studied. It was not necessarily expected that these reaction courses would be analogous to those described, since the more complex enamines, being vinylogous amides, differ considerably from the simpler vinylamines in their reactivities.[10] In the event, the reactions were found to be diverse and complex in nature, and indeed, the structures of some of the products cannot yet be formulated with complete certainty.

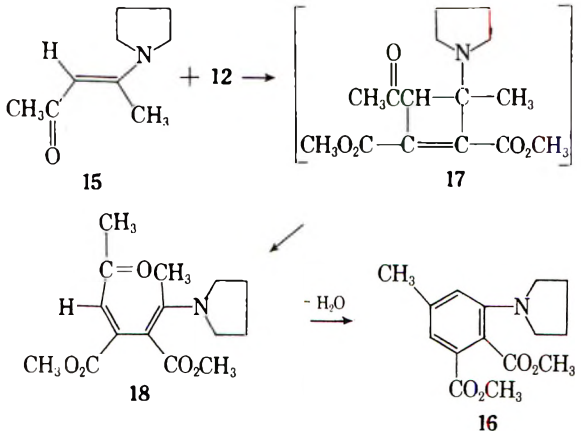
The first of these transformations was found to lead to a new synthesis of the benzene ring under unusually mild conditions.[4] Thus, addition of **12** to 4-pyrrolidinopenten-3-one-2 (**15**)[10,11] in tetrahydrofuran results in an

(9) After this report had been submitted, a detailed paper by Brannock [K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963)] appeared in print. Since this, together with the work of Berchtold [G. A. Berchtold and G. F. Uhlig, *ibid.*, **28**, 1459 (1963)], is concerned with these same reactions, we limit our description here to significant variations in approach.

(10) N. J. Leonard and J. A. Adamik, *J. Am. Chem. Soc.*, **81**, 595 (1959).

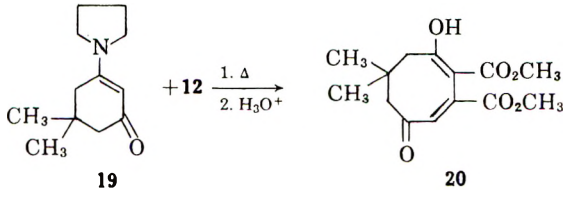
(11) Ultraviolet and n.m.r. data indicate that β-dialkylamino-α,β-unsaturated ketones and esters exist predominantly in the geometric form with the amino and carbonyl groupings *trans* to one another, unlike the corresponding incompletely alkylated amines, which exist in a *cis*, chelated configuration [*cf.* G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 3914 (1961)]. Thus, the *trans* configuration of **15** is reflected in its high extinction coefficient [λ_{max} 310 mμ (ϵ 32,900)] relative to that of 4-aminopenten-3-one-2 [*vide infra*, λ_{max} 298 mμ (ϵ 18,310)]. Further, deshielding of the methyl group protons by the adjacent (*cis*) acetyl function in the former is reflected in a downfield shift of the n.m.r. signal (2.52 *vs.* 1.90 δ). Several other examples of this preferred configuration, not directly pertinent to this investigation, have been observed in this laboratory.

exothermic reaction. Dilution of the mixture with water yields dimethyl-3-pyrrolidino-5-methylphthalate (16) in 60% yield. The reaction presumably proceeds *via* the cyclobutene 17 and diolefin 18. The presence of water appears to accelerate the conversion of 18 to 16, since evaporation of the tetrahydrofuran yields an oil which only slowly produces crystalline 16. The structure of the product was indicated by the n.m.r. spectrum, which revealed signals for two isolated aromatic protons at 6.94 and 6.62 δ with indications of *meta* splitting, and a three-proton singlet at 2.27 δ attributable to an aromatic methyl group.



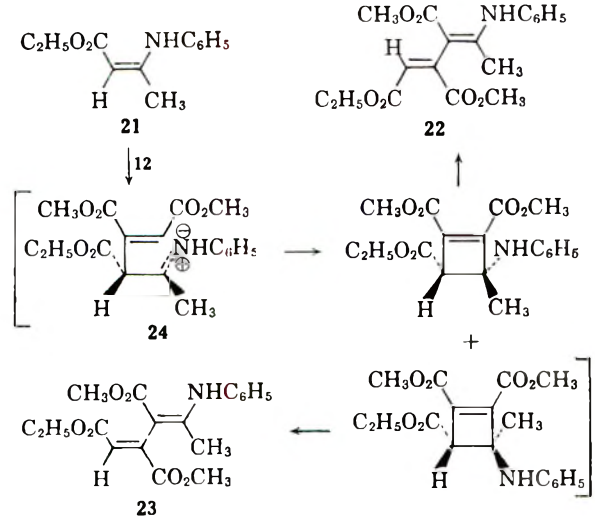
A detailed n.m.r. study of the reaction course was carried out as described for the preparation of 2. Molar equivalents of 15 and 12 were mixed in deuteriobenzene at a temperature below 25°, and the spectrum was measured at intervals. The vinyl proton signal of 15 at 4.78 δ disappeared slowly as the strength of the vinyl proton signal of 18 (6.63 δ) increased. After 20 min. the conversion to 18 was 27% complete and after 2 hr., 67%. The sum of the two protons taken at different times was always equal to 1/21 of the total proton count, thus indicating that no measurable concentration of the cyclobutene 17 accumulated. The formation of 17 is thus slower and its breakdown much more rapid than in the case of the cyclobutenes derived from simple enamines. The geometric structure indicated for 18 is preferred, since the position of the vinyl proton signal indicates deshielding by the β-carbomethoxyl group. Further, the shift of the $CH_3C{=}C$ signal from 2.48 for 15 to 1.80 δ for 18 indicates a marked change in environment, implying that the CH_3 is no longer *cis* to a C=O group. It is noteworthy that 18 is the only one of the four possible geometric isomers which can undergo direct ring closure.

Reaction of an enamine of a cyclic β-diketone was exemplified in 5,5-dimethyl-1-pyrrolidinocyclohexen-1-one-3 (19), which on treatment with dimethyl acetylenedicarboxylate and subsequent hydrolysis yielded 2,3-dicarbomethoxy-7,7-dimethyl-1-hydroxy-5-oxo-1,3-



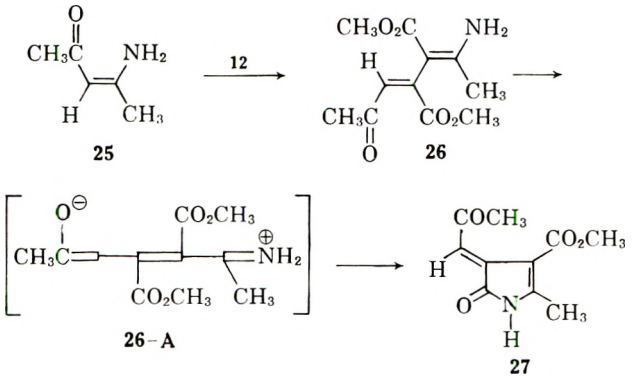
cyclooctadiene (20). The structure of the product follows from spectral data (*vide infra*).

The reaction of ethyl 3-anilinocrotonate (21) with 12 in deuteriobenzene was characterized by the slow disappearance of the vinyl proton signal of 21 at 4.86 δ and no measurable accumulation of a cyclobutene. Two new vinyl proton signals appeared, the stronger at 5.92 and a second at 6.87 δ. As estimated by the disappearance of 21, reaction was 25% complete after 2.5 hr., and 68% complete after 6 hr. On work-up of the reaction mixture it was possible to isolate 22, the major diene, by crystallization. When the reaction was run in diglyme solution and the temperature was allowed to reach 85°, on the other hand, the diene 23 was formed in larger amount. Structural assignments are based on spectral measurements. The infrared spectra of both 22 and 23 show strongly bonded NH groups, even in dilute solution. This result was confirmed by the positions of the NH signals in the n.m.r. spectra. These were observed at 11.45 and 11.33 δ, respectively. The carbomethoxyl and amino groups must therefore be *cis*. The vinyl proton of 23 appears farther downfield in the n.m.r. spectrum; this proton is therefore *cis* to the β-carbomethoxy group and more deshielded. Corroborative evidence is obtained from the ultraviolet spectra. Diene 22 with an all *trans* extended chromophore would be expected to have the larger extinction coefficient, as is observed.[11] It may be noted that the two geometric isomers 22 and 23 cannot arise from a single cyclobutene intermediate unless partial inversion at a carbon atom takes place during its breakdown. Another possibility would be intervention of 24, a type of intermediate proposed by Stork,[1] which can lead to the two cyclobutenes, and, in turn, yield 22 and 23.

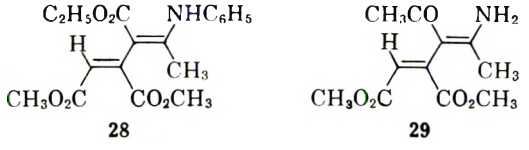


Reaction of 12 with 4-aminopenten-3-one-2 (25) was followed by n.m.r. measurements in a similar manner, and the slow formation of two dienes was again noted. These were characterized by vinyl proton signals at 5.89 and 7.21 δ, in a ratio of 2.1 to 1. In this case only the former compound (26) was isolated in pure form. Assignment of structure is analogous to that for 22. Although 26 may be recrystallized from anhydrous ethanol, treatment with water at room temperature converts it to the amide 27. Seemingly water must function as a proton-donating solvent facilitating the

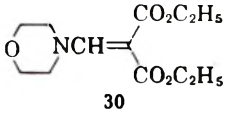
conversion of **26** *via* **26-A** to a geometric isomer capable of ring closure. The depicted stereochemistry of **27** is preferred, since the position of the vinyl proton signal far downfield at 7.13 δ indicates strong deshielding by a β-carbonyl group. It may be noted that neither **22** nor **23** undergoes lactamization under the conditions used in formation of **27**.



It must be mentioned that reaction of **21** and **25** with dimethyl acetylenedicarboxylate by the Michael route, rather than *via* the cyclobutenes can not be entirely excluded by these data. The products which would be obtained, **28** and **29**, are isomeric with the above structures, and it has not been possible to distinguish chemically between the possibilities. However, since all of the enamines derived from simple ketones as well as **15** derived from a diketone react *via* the cyclobutene with interposition of two carbon atoms in the chain, it is more satisfactory to view the reactions of **21** and **25** in the same way.



Finally, it may be noted that while reactions of **12** with enamines derived from β-diketones or β-keto esters proceed much more slowly than with simple enamines, introduction of another electronegative group, as in the case of **30**, prevents reaction altogether. No temperature rise was noted on mixing **30** and **12** in diglyme, and the malonic ester derivative was recovered from the reaction mixture after twenty-four hours.



Experimental[12]

1-Pyrrolidino-2-carbethoxy-1,3-cycloheptadiene (3).—Ethyl propiolate (9.80 g.) in 40 ml. of dioxane (purified by passage through alumina) was added slowly under nitrogen to a solution of 13.75 g. of 1-pyrrolidinocyclopentene[1] and a trace of hydroquinone in 40 ml. of purified dioxane. Heat was evolved and a small quantity of solid precipitated from the solution. The mixture was warmed on the steam bath for 15 min., during which period it turned red and the solid redissolved. Removal of solvent *in vacuo* left, after thorough drying *in vacuo*, 23.75 g. of semicrystalline solid. This was triturated thoroughly with cold, low-boiling petroleum ether. The resulting yellow crystals were separated by filtration and recrystallized from cyclohexane; yield of pure product 8.53 g., m.p. 100.5–101.5°; λ_{max} (log ϵ) 220 (3.87), 271 (4.00), and 340 mμ (4.04); λ_{min} (log ϵ) 243 (3.66), 295 mμ (3.29).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.17; H, 9.01; N, 5.56.

Hydrolysis of 3.— Compound **3** (5.88 g.) was stirred under nitrogen for 12–18 hr. with a mixture of 5 ml. of glacial acetic acid, 25 ml. of water, and a trace of hydroquinone. The product was extracted into ether and the extracts were washed successively with 5% hydrochloric acid, water, and saturated brine. The dried extract was filtered through a pad of Darco, the solvent was evaporated, and the residue distilled to yield 2.99 g. of colorless liquid **4**, b.p. 85–88° (0.5 mm.). This product, like the other cyclic β-keto esters, gives a dark blue color with ferric chloride. The ultraviolet spectrum exhibited maxima at 229 (3.92), and 287 (3.65), while a minimum was observed at 252 mμ (3.05). The infrared spectrum (liquid film) showed strong absorption bands at 1640 and 1605 cm.$^{-1}$ and a shoulder at 1728 cm.$^{-1}$. The n.m.r. spectrum reveals that **4** is about 70% in the enolic form **4a**, as indicated by the intensity of the OH proton signal far downfield (12.9 δ). For the enolic modification H-3 is revealed as a doublet at 6.12 δ ($J_{3,4}$ = 12) which, in turn, is split into two triplets (J = 1.2), presumably because of long-range coupling with C-5. The vinyl proton at C-4 appears as a triplet of a doublet at 5.53 δ ($J_{4,3}$ = 12, $J_{4,5,5}$ = 4.5). The ketonic modification is best formulated as **4b**, as seen by the signal of a single vinyl proton at C-3, a poorly resolved triplet at 7.17 δ. Two CH_3 groups are seen as triplets at 1.27 and 1.30 δ (J = 6.5) as a consequence of the equilibrium mixture.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.20; H, 7.83.

Hydrogenation of 4.—The mixture of tautomers (895 mg.) was hydrogenated in ethanol solution at atmospheric pressure in the presence of 0.25 g. of 10% palladium on carbon. Hydrogen uptake was quantitative in 1 hr. Separation of the catalyst and removal of solvent afforded a quantitative yield of 2-carbethoxycycloheptanone as a pale yellow oil, which was hydrolyzed and decarboxylated by refluxing for 2 hr. with a mixture of 25 ml. of 5% aqueous sulfuric acid and 0.5 ml. of ethanol. The resulting 0.5 g. of cycloheptanone was converted to the semicarbazone, m.p. 161–164° (lit.[13] m.p. 163°), undepressed on admixture with an authentic sample.

In another experiment, 85 mg. of hydrogenation product was heated with 55 mg. of phenylhydrazine in 1 ml. of ethanol for 45 min. at steam-bath temperature, during which period the ethanol was allowed to evaporate. The resulting solid mass was washed with ether and recrystallized from ethanol to yield 20 mg. of the phenylpyrazolone derivative, m.p. 213–214° (lit.[8] m.p. 210°).

1-Pyrrolidino-2-carbethoxycycloheptene (5).—Compound **3** (4.70 g.) was hydrogenated at atmospheric pressure using 0.25 g. of 10% palladium on carbon in 50 ml. of absolute ethanol. The reduction was interrupted when 1 mole of hydrogen had been absorbed. The usual work-up afforded an oily residue which crystallized on standing. Recrystallizations from *n*-hexane (Darco) afforded 1.38 g. of colorless plates, m.p. 63.5–64.5°. The ester carbonyl was observed at 1662 cm.$^{-1}$ (Nujol), and the ultraviolet spectrum showed a maximum at 322 (3.67) and a minimum at 265 mμ (2.61).

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.92; H, 9.83; N, 5.77.

Mild acid hydrolysis of the cycloheptene produced 2-carbethoxycycloheptanone, as shown by its conversion to the phenylpyrazolone derivative.

Formation of 7.—Ethyl propiolate (2.45 g.) in 10 ml. of purified dioxane was added under nitrogen with swirling to 3.44 g. of 1-pyrrolidinocyclopentene (**1a**) in 10 ml. of dioxane, the temperature being maintained at about 15°. The mixture was allowed to stand for 45 min. at this temperature, then 10 ml. of water and 3 ml. of acetic acid were added, and the solution was stirred overnight. After evaporation of the dioxane *in vacuo*, the residue was extracted into ether, and the extracts were washed successively with 5% HCl, water, and saturated brine. Evaporation of the dried extracts after addition of

(12) Melting points and boiling points are uncorrected. Ultraviolet spectra (wave lengths expressed in mμ, extinction coefficients as log ϵ) were determined in ethanol, and n.m.r. spectra, in deuteriochloroform, unless otherwise indicated.

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 316.

hydroquinone left a residue which could be only partially distilled. Considerable decomposition and polymerization took place on heating. The product was obtained as a yellow oil, b.p. 108–112° (0.55 mm.). The ultraviolet spectrum of the somewhat impure material exhibited maxima at 240 (3.93) and 315 (2.64) and a minimum at 228 mμ (2.35). The single vinyl proton appeared as a triplet at 6.37 δ (J = 7). Each band of the triplet was split again into a triplet by long-range coupling with the adjacent ring CH_2 (J = 2.5). The side-chain CH_2 appeared as a doublet at 3.11 δ (J = 7).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 64.83; H, 7.44.

For characterization **7** was converted to its 2,4-dinitrophenylhydrazone by conventional methods.[14] The orange-red plates, m.p. 138.5–139.5° from ethanol, showed infrared absorption (Nujol) at 1744 cm.$^{-1}$. In the ultraviolet, maxima were observed at 240–255 (4.21), 266 (417), 290 (3.97), and 384 (4.51), while the minimum appeared at 312 mμ (3.76).

Anal. Calcd. for $C_{16}H_{18}N_4O_6$: C, 53.03; H, 5.01; N, 15.46. Found: C, 53.30; H, 5.10; N, 15.41.

Ethyl β-(2-Oxocyclopentyl)propionate (8).—The unsaturated keto ester (365 mg.) was hydrogenated at atmospheric pressure in the presence of 0.1 g. of 10% palladium-on-carbon in 50 ml. of 95% ethanol. The usual work-up afforded **8** as a colorless oil which was converted to its 2,4-dinitrophenylhydrazone, m.p. 88–89.5°, from ethanol. Compound **8** was also prepared by reaction of **1a** with ethyl acrylate by the method employed by Stork[1] for the corresponding methyl ester. The infrared spectrum was identical with that of the reduction product. The dinitrophenylhydrazone had m.p. 90–90.5°, undepressed on admixture with the derivative from the reduction product.

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.44; H, 5.45; N, 15.25.

5-Pyrrolidino-6-carbethoxybicyclo[3.2.0]hept-6-ene (2).—Compound **1a** (13.75 g.) and ethyl propiolate (9.80 g.) were separately dissolved in 50-ml. portions of anhydrous ether, and the solutions were chilled in an ice bath. The ester solution was added over a 10-min. period to the enamine in a nitrogen atmosphere. A small quantity of amorphous, polar solid precipitated, which was separated by filtration. The orange filtrate was kept at ice-bath temperature for 1 hr. and then filtered through a pad of Darco. The solvent was evaporated *in vacuo* at ice-bath temperature. The resulting oil resisted crystallization, but was relatively pure **2**, as shown by spectral examination. The infrared spectrum of the liquid showed a carbonyl band at 1710 cm.$^{-1}$ and a C=C band at 1610 cm.$^{-1}$. The ultraviolet spectrum exhibited maxima at 220 (3.78) and 283 (3.12) and a minimum at 260 mμ (2.95).

Conversion of 2 to the Michael Adduct 7.—A mixture of 2.36 g. of the cyclobutene, 8 ml. of purified dioxane, 4 ml. of water, and 1.2 ml. of acetic acid was stirred overnight at room temperature in a nitrogen atmosphere. The mixture, initially homogeneous, separated into two layers during the reaction. Evaporation of the dioxane *in vacuo* was folllowed by addition of water and extraction into ether, washing the extracts with 5% hydrochloric acid, water, and brine, and drying and evaporation of solvent to yield 1.6 g. of oil. Distillation *in vacuo* yielded 0.42 g. of yellow oil, b.p. about 94° (0.2 mm.), together with considerable polymeric residue. The infrared spectrum of the liquid was identical with that of the adduct prepared earlier. The keto ester was converted to its 2,4-dinitrophenylhydrazone, m.p. 138–139.5°. The infrared spectrum of this derivative also agreed in all details with the compound referred to above.

In a separate experiment 7.05 g. of the cyclobutene was stirred for 4 hr. with 35 ml. of 5% hydrochloric acid. Extraction of the solution with ether yielded only a very small quantity of polar oil and none of the desired keto ester.

5-Pyrrolidino-6-carbethoxybicyclo[3.2.0]hept-6-ene Methiodide (9).—A solution of 0.47 g. of the amine in 10 ml. of dry benzene was added to a solution of 0.56 g. of methyl iodide in the same solvent. The mixture was allowed to stand overnight and the resulting dirty yellow needles were separated by filtration and washed with benzene. There was obtained 0.43 g. of crude product, m.p. 100–104°. The analytical sample was prepared by recrystallizations from ethyl acetate containing a little isopropyl alcohol. The resulting white needles had m.p. 116–117.5°. The infrared spectrum showed bands at 1710 and 1610 cm.$^{-1}$. In the n.m.r., aside from the vinyl proton singlet mentioned earlier, a feature of interest was the N-methyl group signal at 3.60 δ.

Anal. Calcd. for $C_{15}H_{24}NO_2I$: C, 47.75; H, 6.42; N, 3.72. Found: C, 47.56; H, 6.38; N, 3.67.

1-Morpholinocyclooctene (1d).—This enamine, b.p. 147–149° (14 mm.), was prepared in 50% yield by the method used by Djerassi and Tursch[15] for 1-morpholinocyclohexene.

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.19. Found: C, 73.18; H, 10.47; N, 7.59.

1-Morpholino-2,3-dicarbomethoxy-1,3-cyclooctadiene (11b).—Dimethyl acetylenedicarboxylate (2.55 g.) was carefully added to 3.0 g. of 1-morpholinocyclohexene[1] (**1b**) in 3 ml. of "diglyme." A spontaneous exothermic reaction ensued with the temperature rising to *ca.* 105°. The solution was allowed to cool, and the product was separated by filtration and recrystallized from chloroform–acetone; yield 50%, m.p. 210–212°. The ultraviolet spectrum exhibited λ_{max} (log ε) 303 (4.06) and a plateau at 312–324 mμ (4.05), while the infrared spectrum (Nujol) showed carbonyl absorptions at 1714 and 1680 cm.$^{-1}$ and C=C absorption at 1614 cm.$^{-1}$. In the n.m.r. spectrum the vinyl proton appeared as a quartet at 6.75 δ (J = 7.3, 9.6).[16]

Anal. Calcd. for $C_{16}H_{25}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.87; H, 7.72; N, 4.60.

1-Pyrrolidino-2,3-dicarbomethoxy-1,3-cycloheptadiene (11a). From the requisite enamines this product, as well as **11c** and **11d** (*vide infra*), were prepared in like manner and in similar yield. Compound **11a** had m.p. 135–138° after recrystallizations from ethanol–water. The ultraviolet spectrum showed λ_{max} (log ε) 324 (4.04), while infrared bands were found at 1718, 1683, and 1605 cm.$^{-1}$. The vinyl proton signal appeared as a triplet (or a quartet with the center peaks superimposed) at 6.83 δ (J = 7).

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.76; H, 7.60; N, 4.98.

1-Morpholino-2,3-dicarbomethoxy-1,3-cyclononadiene (11c).—This compound, after recrystallization from methanol, had m.p. 152–155°, but was contaminated by an unknown impurity, as shown by the n.m.r. spectrum. In this case the vinyl proton signal was observed at 6.05 δ (J = 4, 12).[16] The ultraviolet maximum was observed at 328 mμ (4.11).

Anal. Calcd. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.20; H, 7.59; N, 4.43.

1-Morpholino-2,3-dicarbomethoxy-1,3-cyclodecadiene (11d).—After recrystallizations from ethanol–water the compound had m.p. 114–115°, λ_{max} (log ε) 326 mμ (4.14). The infrared absorptions were observed at 1722, 1690, and 1630 cm.$^{-1}$ and the vinyl proton signal at 5.82 δ (J = 4, 12).[16]

Anal. Calcd. for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.06; N, 4.15. Found: C, 63.83; H, 8.05; N, 4.11.

1-Hydroxy-2,3-dicarbomethoxy-1,3-cyclooctadiene (13).—One-half gram of **11b** was allowed to stand for several hours at room temperature in 5 ml. of 15% aqueous hydrochloric acid, with occasional swirling. Momentary solution was followed by turbidity and crystallization of the enolic product, which was separated by filtration and recrystallized from acetone–water; yield, 95%. The substance, m.p. 60–64°, gave a deep purple color with ferric chloride. The infrared spectra in chloroform and in Nujol gave no indication of hydroxyl absorption, apparently because of strong internal hydrogen bonding. Infrared bands were observed at 1725, 1663, and 1609 cm.$^{-1}$, while the ultraviolet maximum was seen at 254 mμ (4.00). In the n.m.r. the chelated hydroxyl proton appeared at 12.7 and the vinyl proton at 6.98 δ (J = 7.1, 9.4).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.26; H, 6.95.

6-Morpholino-7,8-dicarbomethoxybicyclo[4.2.0]oct-7-ene (10b).—A solution of 0.234 g. of dimethyl acetylenedicarboxylate in 2.34 ml. of deuteriobenzene was mixed with a solution of 0.25 g. of **1b** in 2.5 ml. of the same solvent. The characteristic triplet at 4.68 δ (J = 3.1) due to the vinyl proton of **1b** was completely absent from the n.m.r. spectrum determined 30 min. after mixing, and no new vinyl proton signals appeared.

Based on these observations, a large-scale preparative experiment was run in an attempt to isolate the cyclobutene or a derivative. A solution of 7.6 g. of the ester in 75 ml. of benzene was added slowly with cooling (5–7°) to 8.0 g. of **1b** in 30 ml. of

(14) Ref. 13, p. 219.

(15) C. Djerassi and B. Tursch, *J. Org. Chem.*, **27**, 1041 (1962).

(16) These coupling constants must retain a certain degree of uncertainty because of the extreme difficulty in analyzing the remainder of the complex spectrum.

benzene. The final volume of the solution was 168 ml. A 25-ml. aliquot of the solution was refluxed for 4 hr. and evaporated to dryness. The crystals of **11b**, after filtration and washing with ether, weighed 0.51 g. (21%), m.p. 210–212°. Another 38-ml. aliquot of the benzene solution was evaporated at reduced pressure to yield crude **10b** as an orange oil. Attempts to crystallize the product as the base or as its hydrochloride or methiodide salt were unsuccessful. Although the preparation contained neither starting material nor eight-membered enamine **11b**, as shown by thin-layer chromatography, purification by chromatography on alumina was not successful. The major component, though obtained in a fairly pure state, appeared to generate another minor component on further treatment. The nature of these transformations is unknown.[17]

In another experiment 2.34 g. of the acetylenic ester in 2.5 ml. of diglyme was added dropwise to a solution of 2.5 g. of **1b** in 2.5 ml. of the same solvent, keeping the temperature at 5–7°. The mixture (9.5 ml.) was placed in the refrigerator overnight. An aliquot (7.5 ml.) was then heated to 130° for 10 min. On cooling, 1.22 g. (34%) of **11b** was obtained, m.p. 210–212°. The remainder of the solution was allowed to stand at room temperature for 3 days, during which period **11b** was slowly produced. The yield of crystalline material at the end of this period was 0.52 g.

6-Morpholino-7,8-dicarbomethoxybicyclo[4.2.0]octane Hydrochloride (14).—The remainder of the benzene solution referred to in the previous section (105 ml.) was shaken with hydrogen at 40 p.s.i. in the presence of 1 g. of 10% palladium on charcoal for 3 hr. After separation of the catalyst the benzene was stirred with 12 ml. of 15% aqueous hydrochloric acid for 2 hr. The aqueous extract was made alkaline with ammonia, the product was extracted into ether, and the solvent was removed from the dried extracts. Addition of 6 *N* ethanolic hydrogen chloride to the residue yielded a solid hydrochloride which, after recrystallization from ethanol weighed 4 g. and had m.p. 193–194°. The ultraviolet spectrum showed only end absorption, while in the infrared ester carbonyl absorptions were observed at 1754 and 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{25}NO_5$.HCl: C, 55.31; H, 7.48; N, 4.03. Found: C, 55.06; H, 7.31; N, 4.23.

Dimethyl 3-Pyrrolidino-5-methylphthalate (16).—Dimethyl acetylenedicarboxylate (4.7 g.) was added over a period of several minutes to a solution of 5 g. of 4-pyrrolidinopenten-3-one-2 (**15**)[10] in 10 ml. of warm tetrahydrofuran. An exothermic reaction took place, after which the mixture was heated 15 min. on the steam bath, then poured into water. The resulting solid was collected by filtration and recrystallized from methanol to yield 5.4 g. of **16**, m.p. 82–84°. The ultraviolet spectrum had λ_{max} (log ϵ) 236 (4.21), 274 (3.90), and 347 (3.54), and λ_{min} (log ϵ) 259 (3.86) and 301 mμ (2.89). The infrared spectrum (Nujol) showed ester carbonyl absorptions at 1732 and 1713 with aromatic absorption at 1605 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.25; H, 6.85; N, 5.01.

For the spectral studies a solution of 0.18 g. of dimethyl acetylenedicarboxylate in 1.8 ml. of deuteriobenzene was added over a period of several minutes to a solution of 0.15 g. of **15** in 1.5 ml. of deuteriobenzene while keeping the temperature at 5°. After mixing, the reaction was warmed to 25° and the n.m.r. spectrum was measured at intervals.

2,3-Dicarbomethoxy-7,7-dimethyl-1-hydroxy-5-oxo-1,3-cyclooctadiene (20).—To a solution of 5 g. of **19**[16] in 20 ml. of diglyme maintained at 60°, 3.68 g. of dimethyl acetylenedicarboxylate was added dropwise, after which the mixture was heated at steam-bath temperature for 30 min. The contents were poured into water and the oil was extracted into ether, the ether removed, and the residue treated with 15 ml. of 15% hydrochloric acid for 1 day. A crystalline material gradually separated which was recrystallized from ethanol; m.p. 147–149°. The n.m.r. spectrum of **20** indicates a chelated hydroxyl proton at 13.1 δ, split by long-range coupling with one of the adjacent methylene protons (J = 1.6). The vinyl hydrogen signal appears at 6.55 δ (J = 1.4), coupled with a C-6 proton. The C-6 methylene signal was observed as a quartet (AB type) at 2.50 δ (J = 12.1). The high field proton of this quartet was split into a doublet by long-range coupling (J = 1.4) with H-4. The C-8 methylene signal was also observed as a quartet (AB type) at 2.30 δ (J = 11.4). The lowfield proton in this case was split into a doublet (J = 1.6) by coupling with the hydroxyl proton. This long-range coupling disappears on addition of deuterium oxide. Strong infrared bands are observed at 1745, 1727, and 1603 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.83; H, 6.39.

Ethyl 5-Anilino-3,4-dicarbomethoxy-*trans,cis*-2,4-hexadienoate (22) and Ethyl 5-Anilino-3,4-dicarbomethoxy-*cis,cis*-2,4-hexadienoate (23).—A solution of 0.19 g. of **12** in 1.9 ml. of deuteriobenzene was added to a solution of 0.25 g. of ethyl 3-anilinocrotonate (**21**) in 2.5 ml of deuteriobenzene under the conditions described in the preceding experiment. Since the downfield band in the n.m.r. spectrum was somewhat obscured by incompletely deuterated solvent, the deuteriobenzene was removed after the reaction was complete (24 hr.) and the spectrum determined in deuteriochloroform. Integration of the vinyl protons showed **22** and **23** to be present in a ratio of 1.4 to 1.0. A solution of 6.1 g. of **12** in 60 ml. of benzene was then added dropwise to a solution of 8.0 g. of **21** in 80 ml. of benzene while keeping the reaction temperature at 5°. The mixture was then allowed to warm to room temperature. After allowing it to stand for 48 hr., the solvent was removed *in vacuo*, and the residue was recrystallized twice from methanol–water to yield 5.0 g. of **22**, m.p. 88–90°. The ultraviolet spectrum showed maxima at 256 (4.07), 302 (3.73), and 342 (3.74) and minima at 230 (3.93), 289 (3.70), and 318 mμ (3.71). The infrared spectrum in methylene chloride showed a broad bonded NH band at 3250 to 3000 cm.$^{-1}$ which was unaltered on dilution. Pertinent features of the n.m.r. spectrum were the vinyl proton signal at 6.00 δ and the CH_3—C=C signal at 2.08 δ.

Anal. Calcd. for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.43 H, 6.16; N, 3.95.

A solution of 5.0 g. of **12** in 5 ml. of diglyme was added to 7.2 g. of **21** in 5 ml. of diglyme in small portions; the temperature rose to 85°. The mixture was then heated on the steam bath for 15 min. and poured into water. The resulting oil was extracted with ether and the extract was dried and evaporated. The residue crystallized on standing. Recrystallization from methanol gave 5.7 g. of **23**, m.p. 72–74°, depressed to 55–65° on admixture with **22**. The ultraviolet spectrum showed maxima at 254 (4.07), 312 (3.49), and 336–360 plateau (3.46); and minima at 230 (3.99) and 294 mμ (3.45). The infrared spectrum in methylene chloride showed a broad band at 3250 to 3000 cm.$^{-1}$ which was unaltered on dilution. Features of the n.m.r. spectrum were the vinyl proton signal at 6.89 δ and the CH_3—C=C signal at 2.08 δ.

Anal. Calcd. for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.10; H, 6.04; N, 4.02.

6-Amino-4,5-dicarbomethoxy-*trans,cis*-3,5-heptadien-2-one (26).—A solution of 18.6 g. of **12** in 10 ml. of anhydrous tetrahydrofuran was added in small portions to 13.0 g. of **25** in 10 ml. of tetrahydrofuran over several minutes. The temperature rose to 85°. After an hour, about half of the tetrahydrofuran was removed by distillation, and the residue was chilled to effect crystallization. Recrystallization from ethyl acetate gave 12 g. of **26**, m.p. 115–116°. The ultraviolet absorption spectrum was characterized by a maximum at 300 (4.12) and a minimum at 257 mμ (3.34). The infrared spectrum in methylene chloride showed a strongly-bonded NH at 3140 and a weakly bonded NH at 3430 cm.$^{-1}$, neither of which changed on dilution. The n.m.r. spectrum showed a vinyl proton signal at 5.92 δ and a CH_3—C=C signal at 2.12 δ.

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.83. Found: C, 54.46; H, 6.50; N, 5.73.

Methyl 2-Methyl-5-oxo-4-(2-oxo-propylidene)-2-pyrroline-3-carboxylate (27).—When a portion of the tetrahydrofuran reaction mixture containing **26** was poured into water, a pale yellow, crystalline substance separated. Recrystallization from ethanol yielded **27**, m.p. 179–181°. Conversion of **26** to **27** could also conveniently be carried out in 90% yield by solution of the former in minimum boiling water and collection of product on cooling. The ultraviolet spectrum showed maxima at 267 (3.98) and 363 (3.69), and minima at 224 (3.35) and 306 mμ (3.16). The compound dissolved in aqueous sodium hydroxide with a deepening of the color-maximum 434. The n.m.r. spectrum showed the vinyl proton signal at 7.14 δ.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.57; H, 5.35; N, 6.57.

Attempted Reaction of Diethyl 4-Morpholinylmethylene-

(17) Compound **10b** had an R_f value of 0.47, while the minor component ran at 0.56 on aluminum oxide G, using 1:1 benzene–methylene chloride as solvent.

malonic Ester (30) with 12.—A mixture of 5 g. of 30[18] and 2.76 g. of 12 were mixed in 10 ml. of diglyme. No temperature rise was noted. After 24 hr. at room temperature, the reaction was diluted with water and unchanged 30 recovered, m.p. 58–61°.

(18) C. D. Hurd and L. T. Sherwood, *J. Org. Chem.*, **13**, 471 (1948).

Acknowledgment.—The authors wish to express their sincere appreciation to Miss Natalie Cahoon and co-workers for spectra determinations and to Mr. George Robertson and co-workers for analytical results.

Reactions of Mercaptoamines. I. With Isocyanates and Isothiocyanates[1]

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Received May 3, 1963

Isothiocyanates reacted with 2-mercaptoethylamine hydrochloride to give S-substituted products, the hydrochlorides of S-2-aminoethyl N-alkyldithiocarbamates. With free 2-mercaptoethylamine, one mole of phenyl isothiocyanate gave the N-substituted product, 1-(2-mercaptoethyl)-3-phenyl-2-thiourea, and two moles gave the N,S-disubstituted product. All aliphatic isothiocyanates gave disubstituted products, the 1-[2-(N-alkyldithiocarbamoyl)ethyl]-3-alkyl-2-thioureas, regardless of the relative amount of isothiocyanate. The disubstituted products were cleaved by silver nitrate to one mole of the isothiocyanate and the silver mercaptide of the 1-(2-mercaptoethyl)-3-alkyl-2-thiourea, from which the free thiourea was obtained by treatment with sodium sulfide. Isocyanates, regardless of relative amount, reacted with 2-mercaptoethylamine to give the N,S-disubstituted products. Cleavage with silver nitrate afforded the 1-(2-mercaptoethyl)-3-alkylureas.

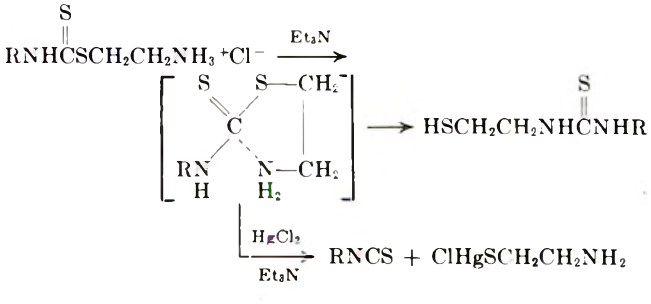
The behavior of isocyanates and isothiocyanates toward active hydrogen compounds has been studied since the earliest days of organic chemistry, and it is well known that both react vigorously with amines, and that isocyanates also react, somewhat less vigorously, with alcohols and water.[2] In contrast, isothiocyanates are so relatively unreactive toward hydroxyl-containing compounds that aqueous media often are used in their preparation,[3] and their reaction with hydroxyalkyl amines gives hydroxyalkyl thioureas.[4] Both isocyanates and isothiocyanates have been reported to react with thiols,[5] but there is no evidence to indicate how readily these reactions proceed relative to reaction with the amino group. Consequently there was no *a priori* way of predicting how compounds containing both the thiol and the amino function would react with isocyanates and isothiocyanates. This question became of importance in connection with the proposed preparation of a number of 2-mercaptoethyl ureas and thioureas for testing as radioprotective drugs, and an examination of the reaction of 2-mercaptoethylamine with isocyanates and isothiocyanates was undertaken.

The reaction with isothiocyanates was studied first, since there seemed to be a better chance of directing this reaction preferentially to one or the other functions of the 2-mercaptoethylamine molecule. When a solution of 2-mercaptoethylamine hydrochloride in ethanol (pH 5 to Hydrion test paper) was treated with phenyl or *n*-butyl isothiocyanate, there was no reaction. However, when a few drops of aqueous sodium hydroxide were added, raising the pH to 6–6.5, vigorous exothermic reaction took place and solid products crystallized. Analysis indicated that these products

$$HSCH_2CH_2NH_3^+Cl^- + RNCS \longrightarrow RNHC(=S)SCH_2CH_2NH_3^+Cl^-$$

were the result of reaction at the thiol function, that is, that they were the hydrochlorides of S-2-aminoethyl N-phenyldithiocarbamate (72% yield) and N-*n*-butyldithiocarbamate (74%), respectively. This structure assignment was confirmed by their chemical behavior and by the fact that 2-dimethylaminoethanethiol hydrochloride, which can react only at the thiol function, reacted vigorously with phenyl isothiocyanate at pH 6. Treatment of an aqueous solution of the product with base gave free S-(2-dimethylamino)ethyl N-phenyldithiocarbamate in 66% yield.

The dithiocarbamates derived from 2-mercaptoethylamine were much less stable. The hydrochlorides dissolved in water to give clear solutions, but the solutions underwent rapid hydrolysis. In a few minutes cloudiness appeared, and the characteristic odor of the parent isothiocyanate became strongly noticeable. When the hydrochlorides were treated with an equivalent of weak base, they rearranged to the corresponding N-substituted derivatives of 2-mercaptoethylamine, giving



1-(2-mercaptoethyl)-3-phenyl-2-thiourea (77%) and somewhat impure 1-(2-mercaptoethyl)-3-*n*-butyl-2-thiourea (77%). This rearrangement appears to be exactly analogous to the known rearrangement of S-acyl 2-mercaptoethylamine derivatives.[6,7] As a preparative route to 2-mercaptoethylthioureas this reaction was less satisfactory than other techniques to be de-

(1) This work was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-193-MD-2174.

(2) I. D. Morton and E. Hoggarth, "Chemistry of Carbon Compounds," Vol. IB, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, The Netherlands, 1952, p. 939.

(3) M. L. Moore and F. S. Crossley, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 599.

(4) F. B. Dains, R. Q. Brewster, I. L. Malm, A. W. Miller, R. V. Maneval, and J. A. Sultzaberger, *J. Am. Chem. Soc.*, **47**, 1981 (1925).

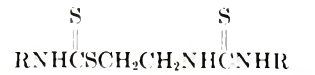
(5) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, pp. 201 and 238.

(6) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 3425 (1951).

(7) T. Wieland and E. Bokelmann, *Ann.*, **576**, 20 (1952).

TABLE I

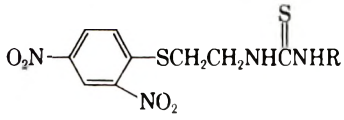
1-[2-(N-ALKYLDITHIOCARBAMOYL)ETHYL-3-ALKYL]-2-THIOUREAS



R	Yield, %	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
CH_3	74	136–138	32.26	5.86	18.81	43.06	32.49	5.92	18.69	43.24
C_2H_5	78	124.5–126.5	38.21	6.82	16.71	38.25	38.10	6.85	16.71	38.11
i-C_3H_7	87	128–129.5	42.97	7.58	15.04	34.42	43.04	7.69	14.88	34.25
n-C_4H_9	100	98–101.5	46.87	8.19	13.66	31.28	47.02	8.10	13.57	31.46
n-C_7H_{15}	99	91–92.5	55.19	9.52	10.73	24.56	55.11	9.49	10.78	24.59
C_6H_5	98	150.5–152.5	55.30	4.93	12.09	27.68	55.15	5.02	11.95	27.85

TABLE II

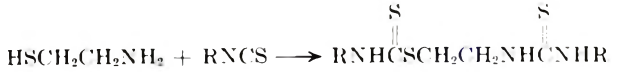
2,4-DINITROPHENYL SULFIDE DERIVATIVES OF 1-ALKYL-3-(2-MERCAPTOETHYL)-2-THIOUREAS



R	Yield, % Thiourea	Yield, % Deriv.	M.p., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
CH_3	57	53	158–160	37.97	3.83	17.71	20.27	38.05	3.89	17.68	20.38
C_2H_5	58	73	142.5–145	39.99	4.27	16.96	19.41	40.02	4.30	16.83	19.12
n-C_4H_9	47	69	135–137	43.56	5.06	15.63	17.89	43.66	4.88	15.50	18.00
n-C_7H_{15}	66	90	145.5–146.5	47.98	6.04	13.99	16.01	48.17	6.16	14.04	15.88

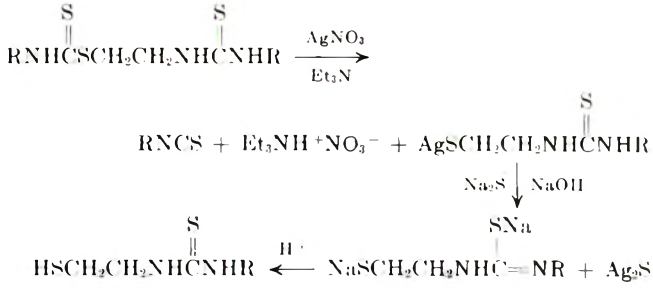
scribed later. The free dithiocarbamates apparently required a finite period to rearrange, for when a suspension of S-2-aminoethyl N-phenyldithiocarbamate hydrochloride in acetone was treated with triethylamine and then immediately with a solution of mercuric chloride in acetone, phenyl isothiocyanate was obtained in 41% yield. This could have been obtained only from the dithiocarbamate by metal ion-assisted mercaptan elimination.[8] Regeneration of the isothiocyanate in this reaction constitutes excellent proof that the structure of the dithiocarbamate was correctly assigned.

When free 2-mercaptoethylamine was treated with an equimolar amount of phenyl isothiocyanate, reaction took place at the amino function, and 1-(2-mercaptoethyl)-3-phenyl-2-thiourea was obtained in 91% yield. It was expected that this reaction could be extended to the aliphatic isothiocyanates and that a series of 2-mercaptoethylthioureas could be prepared easily. However, aliphatic isothiocyanates invariably reacted at both functions of 2-mercaptoethylamine even when present in deficient amount, and the products were the 1-[2-(N-alkyldithiocarbamoyl)ethyl]-3-alkyl-2-thioureas. Products of this type were prepared



from a number of aliphatic isothiocyanates and from phenyl isothiocyanate when it reacted with 2-mercaptoethylamine in a 2:1 ratio. The properties of these materials are summarized in Table I. The excellent yields reported were obtained with a 2:1 isothiocyanate to 2-mercaptoethylamine mole ratio.

Since the 1-[2-(N-alkyldithiocarbamoyl)ethyl]-3-alkyl-2-thioureas were easily prepared and easily purified by recrystallization, they appeared to be excellent starting materials for the preparation of 2-mercaptoethylthioureas. Basic hydrolysis removed the dithiocarbamoyl group, but the 2-mercaptoethylthioureas were obtained in impure form. A more satisfactory preparative procedure was to treat the N,S-disubstituted products with silver nitrate in acetonitrile. The N-alkyldithiocarbamoyl function was cleaved by this treatment and the thiourea function was unaffected, the products being one mole of alkyl isothiocyanate and the silver mercaptide of the 2-mercaptoethyl thiourea. This preparation is another example of the



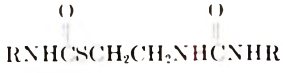
metal ion-assisted mercaptan elimination reaction,[8] one in which the mercaptan is the product of interest and not the isothiocyanate. Silver ion could not be eliminated completely from the mercaptide by treatment with hydrogen sulfide, but, when the mercaptide was triturated with a solution of sodium sulfide and sodium hydroxide, silver sulfide was precipitated completely. Acidification of the filtrate gave the 2-mercaptoethylthiourea in relatively pure form. In this manner the 1-alkyl-3-(2-mercaptoethyl)-2-thioureas were prepared in which the alkyl group was methyl, ethyl, isopropyl, *n*-butyl, and *n*-heptyl. All but the isopropyl compound were liquids at room temperature.

When an attempt was made to distil 1-(2-mercaptoethyl)-3-*n*-butyl-2-thiourea at reduced pressure, material came over at 102–120° (1.5 mm.) and solidified in the receiver. This solid gave an infrared spectrum quite different from that of the thiourea. It appeared that cyclization to 2-*n*-butylamino-2-thiazoline had occurred, and this was confirmed when the thiazoline was prepared by treating 2-aminoethanol with *n*-butyl iso-

(8) A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 71 (1963).

TABLE III

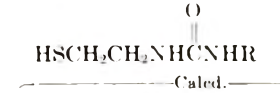
1-[2-(N-ALKYLTHIOLCARBAMOYL)ETHYL]-3-ALKYLUREAS



			Calcd.				Found			
R	Yield, %	M.p., °C.	C	H	N	S	C	H	N	S
n-C_3H_7	94	138–139	48.55	8.56	16.99	12.96	48.72	8.65	16.72	13.16
n-C_4H_9	82	127.5–130	52.33	9.15	15.26	11.64	52.18	8.98	15.41	11.48
n-$C_{12}H_{25}$	100	129.5–131	67.28	11.50	8.41	6.41	67.16	11.36	8.54	6.60
$C_2H_5O_2CCH_2$	83	131–133.5	42.97	6.31	12.53	9.56	43.08	6.49	12.58	9.40
C_6H_5	96	196.5–200	60.93	5.43	13.32	10.17	60.76	5.58	13.31	10.19

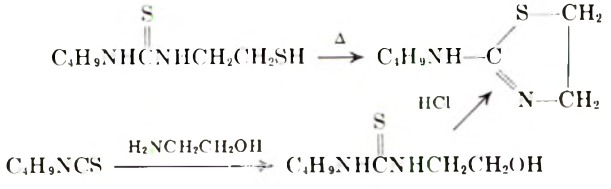
TABLE IV

1-(2-MERCAPTOETHYL)-3-ALKYLUREAS

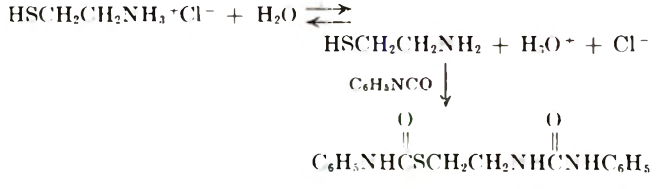


			Calcd.				Found			
R	Yield, %	M.p., °C.	C	H	N	S	C	H	N	S
n-C_3H_7	87	120–121	44.41	8.70	17.27	19.76	44.58	8.56	17.08	19.83
n-C_4H_9	85	75.5–77	47.69	9.15	15.90	18.19	47.48	9.01	16.06	18.32
n-$C_{12}H_{25}$	79	98–99	62.45	11.18	9.71	11.11	62.24	11.08	9.79	11.22
$C_2H_5O_2CCH_2$	59	85.5–87	40.76	6.84	13.58	15.54	40.69	6.69	13.38	15.70
HO_2CCH_2	71	149.5–150.5	33.70	5.66	15.72	17.99	33.76	5.70	15.83	17.99
C_6H_5	99	141.5–143	55.07	6.16	14.28	16.33	55.18	6.23	14.22	16.19

thiocyanate and treating the product with hydrochloric acid. Since most of the 2-mercaptoethylthioureas could not be purified either by crystallization or by distillation, they were characterized as 2,4-dinitrophenyl sulfides (Table II).

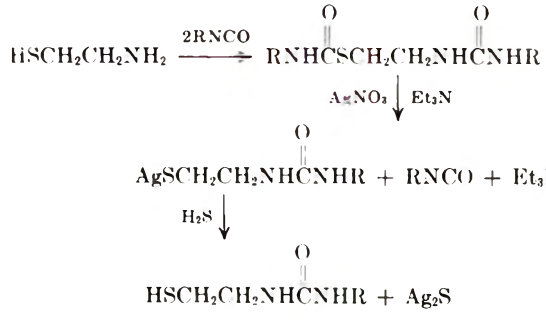


The isocyanates had an even stronger tendency than the isothiocyanates to react at both ends of the 2-mercaptoethylamine molecule. When phenyl isocyanate was added to a suspension of 2-mercaptoethylamine hydrochloride in acetonitrile no reaction took place. When a little water was added the 2-mercaptoethylamine hydrochloride hydrolyzed sufficiently to react, and the N,S-disubstituted product, 1-[2-(N-phenylthiolcarbamoyl)ethyl]-3-phenylurea, was formed, along with some *sym*-diphenylurea from reaction of the isocyanate with water. Free 2-mercaptoethylamine re-

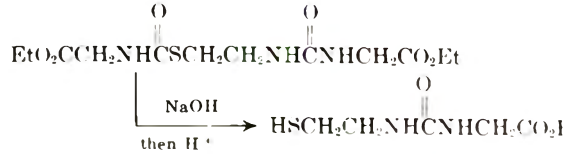


acted with one mole of phenyl isocyanate to give a 48% yield (based on 2-mercaptoethylamine) of the N,S-disubstituted material as the sole product. With two moles of isocyanate the yield was 96%. When the sodium salt of 2-mercaptoethylamine reacted with the isocyanate, the disubstituted compound was again the principal product, but a 34% yield of 1-(2-mercaptoethyl)-3-phenylurea was obtained also. A better route to the mercaptoethylurea (99% yield) was cleavage of 1-[2-(N-phenylthiolcarbamoyl)ethyl]-3-phenylurea with silver nitrate, followed by treatment of the silver mercaptide with aqueous sodium sulfide or alcoholic hydrogen sulfide.

Extension of this reaction to other isocyanates provided a very general route to 1-(2-mercaptoethyl)-3-alkylureas. Reaction of 2-mercaptoethylamine with two moles of isocyanate, followed by cleavage of the N,S-disubstituted product with silver nitrate or mercuric chloride and treatment of the mercaptide with sulfide gave good yields of mercaptoethylureas.



The N,S-disubstituted compounds from *n*-propyl, *n*-butyl, and *n*-dodecyl isocyanates and from ethyl isocyanatoacetate were prepared, and all were cleaved to the corresponding mercaptoethylureas by the metal ion-assisted reaction. In addition, 1-[2-(N-ethoxycarbonylmethylthiolcarbamoyl)ethyl]-3-ethoxycarbonylmethylurea was hydrolyzed directly to 1-(2-mercaptoethyl)-3-carboxymethylurea in 71% yield by treatment with aqueous base. Recently 1-(2-mercaptoethyl)-3-methylurea has been prepared by treating cystamine (the disulfide of 2-mercaptoethylamine) with methyl isocyanate and subjecting the prod-



uct to electrolytic reduction.[9] Unless equipment for such reduction is readily available, the technique here described will be found more convenient. Properties of the 1-[2-(N-alkylthiolcarbamoyl)ethyl]-3-alkylureas are summarized in Table III, and those of the 1-(2-mercaptoethyl)-3-alkylureas in Table IV.

Experimental[10]

S-(2-Aminoethyl) N-Phenyldithiocarbamate Hydrochloride.—To a solution of 12.5 g. (0.11 mole) of 2-mercaptoethylamine hydrochloride in 100 ml. of 95% ethanol (pH 5.5) was added 13.5 g. (0.10 mole) of phenyl isothiocyanate at 23°. There was no apparent reaction. When 5 drops of 10% sodium hydroxide solution was added (pH 6) the temperature began to rise. At 38° solid began to precipitate, and at 40° the mixture set up solid. After 2 hr. the temperature had fallen back to room temperature. An additional 50 ml. of ethanol was added, and the solid was recovered by suction filtration. Cooling the filtrate in ice brought down more solid, also recovered by suction filtration. The solids were combined and dried in air. The crude S-(2-aminoethyl) N-phenyldithiocarbamate hydrochloride thus recovered amounted to 17.9 g. (72%) and melted at 155–162°. The solid was recrystallized twice from 95% ethanol to give pure product, m.p. 160–164° dec.

Anal. Calcd. for $C_9H_{13}N_2S_2Cl$: C, 43.45; H, 5.27; N, 11.26; S, 25.77. Found: C, 43.23; H, 5.20; N, 11.18; S, 25.91.

S-(2-Aminoethyl) N-*n*-Butyldithiocarbamate Hydrochloride.—2-Mercaptoethylamine hydrochloride (12.5 g., 0.11 mole) and 11.5 g. (0.10 mole) of *n*-butyl isothiocyanate reacted as described previously to give 17.0 g. (74%) of S-(2-aminoethyl) N-*n*-butyldithiocarbamate hydrochloride, m.p. 151–155°. Two recrystallizations from absolute ethanol gave pure product, m.p. 153–156°.

Anal. Calcd. for $C_7H_{17}N_2S_2Cl$: C, 36.74; H, 7.49; N, 12.25; S, 28.02; Cl, 15.50. Found: C, 36.77; H, 7.57; N, 12.24; S, 28.13; Cl, 15.38.

S-(2-Dimethylamino)ethyl N-Phenyldithiocarbamate.—2-(Dimethylamino)ethyl mercaptan hydrochloride (7.1 g., 0.05 mole) and 6.8 g. (0.05 mole) of phenyl isothiocyanate reacted as described previously, and the reaction mixture was poured into 200 ml. of ice water. When the mixture was made strongly basic a solid separated. After recovery and drying it amounted to 7.9 g. (66%), m.p. 109–113°. Two recrystallizations from 95% ethanol gave 4.9 g. of pure S-(2-dimethylamino)ethyl N-phenyldithiocarbamate, m.p. 110.5–112.5°.

Anal. Calcd. for $C_{11}H_{16}N_2S_2$: C, 54.96; H, 6.71; N, 11.66; S, 26.67. Found: C, 54.82; H, 6.76; N, 11.87; S, 26.46.

1-(2-Mercaptoethyl)-3-phenyl-2-thiourea.—To a solution of 6.8 g. (0.06 mole) of 2-mercaptoethylamine hydrochloride in 35 ml. of 95% ethanol was added a solution of 2.4 g. (0.06 mole) of sodium hydroxide in 4 ml. of water. Sodium chloride precipitated. To this mixture at 23° was added 6.8 g. (0.05 mole) of phenyl isothiocyanate. The temperature rose rapidly to 39°, then dropped slowly. After 2 hr. the reaction mixture was poured into 200 ml. of ice water, and a solid separated. After recovery by suction filtration and drying *in vacuo* the crude 1-(2-mercaptoethyl)-3-phenyl-2-thiourea amounted to 9.7 g. (91%), m.p. 105–114°. Two recrystallizations from 95% ethanol raised the melting point to 113–116.5°.

Anal. Calcd. for $C_9H_{12}N_2S_2$: C, 50.91; H, 5.70; N, 13.20; S, 30.20. Found: C, 50.74; H, 5.60; N, 13.41; S, 30.48.

1-[2-(N-*n*-Butyldithiocarbamoyl)ethyl]-3-*n*-butyl-2-thiourea.—To a suspension of 11.4 g. (0.10 mole) of 2-mercaptoethylamine hydrochloride in 25 ml. of 95% ethanol was added a solution of 4.0 g. (0.10 mole) of sodium hydroxide in 5 ml. of water. A new solid came out of solution. To this mixture was then added 23.1 g. (0.2 mole) of *n*-butyl isothiocyanate. The temperature rose rapidly from 33° to 75°, then dropped back to 30° over about an hour. The reaction mixture was then poured into 400 ml. of ice water. The solid which separated was recovered by suction filtration and dried *in vacuo*. The crude 1-[2-(N-*n*-butyldithiocarbamoyl)ethyl]-3-*n*-butyl-2-thiourea amounted to 30.8 g. (100%). The entire sample was recrystallized from 150 ml. of acetonitrile to give 17.5 g. of purified material, m.p. 98–101.5°. A second recrystallization of a portion from acetonitrile did not change the melting point.

Anal. Calcd. for $C_{12}H_{25}N_3S_3$: C, 46.87; H, 8.19; N, 13.66; S, 31.28. Found: C, 47.02; H, 8.10; N, 13.57; S, 31.46.

1-(2-Mercaptoethyl)-3-*n*-butyl-2-thiourea.—To a solution of 55.4 g. (0.18 mole) of 1-[2-(N-*n*-butyldithiocarbamoyl)ethyl]-3-*n*-butyl-2-thiourea in 250 ml. of acetonitrile was added 18.2 g. (0.18 mole) of triethylamine and, with vigorous stirring, a solution of 30.6 g. (0.18 mole) of silver nitrate in 75 ml. of acetonitrile. The gray-brown silver derivative which separated was recovered by suction filtration and washed with acetonitrile. The damp solid was triturated with a solution of 60.1 g. (0.25 mole) of sodium sulfide nonahydrate to which 100 ml. of 10% sodium hydroxide solution had been added. The black silver sulfide which was formed was removed by filtration and washed with water. A yellow oil separated when the filtrate was made acid with 5 *N* hydrochloric acid, and was extracted into two 200-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate, and on evaporation left 16.4 g. (47%) of yellow liquid 1-(2-mercaptoethyl)-3-*n*-butyl-2-thiourea.

An attempt was made to distil a 5.5-g. sample of the crude thiourea at reduced pressure. At 1.5 mm. and a pot temperature of 150–170°, material distilled at 102–120° (1.5 mm.) and solidified in the receiver. There was obtained 2.5 g. of white solid, m.p. 61–66°. The infrared spectrum of this material was identical to that of 2-*n*-butylamino-2-thiazoline. Yield of thiazoline produced in this pyrolysis was 55%.

To a solution of 1.9 g. (0.01 mole) of crude thiourea in 25 ml. of 95% ethanol was added 4 ml. of 10% sodium hydroxide solution (0.01 mole) and a solution of 2.0 g. (0.01 mole) of 1-chloro-2,4-dinitrobenzene in 35 ml. of ethanol. The solution was heated to boiling and filtered hot, and on cooling deposited a yellow solid. The 2,4-dinitrophenyl sulfide derivative of 1-(2-mercaptoethyl)-3-*n*-butyl-2-thiourea amounted to 2.5 g. (69%), m.p. 135–137°. Two recrystallizations from 95% ethanol gave purified solid, m.p. 135–137°.

Anal. Calcd. for $C_{13}H_{18}O_4N_4S_2$: C, 43.56; H, 5.06; N, 15.63; S, 17.89. Found: C, 43.66; H, 4.88; N, 15.50; S, 18.00.

2-*n*-Butylamino-2-thiazoline.—To a solution of 9.2 g. (0.15 mole) of 2-aminoethanol in 50 ml. of 95% ethanol was added slowly 17.3 g. (0.15 mole) of *n*-butyl isothiocyanate. The temperature was held at 30–45° by cooling. After standing 3 hr., the reaction mixture was poured into 300 ml. of ice–water, and an oil separated. The oil was extracted into two 100-ml. portions of ether, and the ether solution was dried over anhydrous magnesium sulfate. Evaporation of the ether left 21.3 g. (81%) of crude 1-*n*-butyl-3-(2-hydroxyethyl)-2-thiourea.

To the crude thiourea (0.077 mole) was added 66 ml. (0.77 mole) of concentrated hydrochloric acid, and the resulting homogeneous solution was heated under reflux for 7 hr. The solution was cooled in ice and made strongly basic with a solution of 35 g. of sodium hydroxide in 50 ml. of water. A white solid separated and was recovered by suction filtration and dried. The crude 2-*n*-butylamino-2-thiazoline amounted to 17.2 g. (90%) and melted at 64–67.5°. A sample recrystallized from 1:1 ethanol–water melted at 67–69°.

Anal. Calcd. for $C_7H_{14}N_2S$: C, 53.12; H, 8.92; N, 17.71; S, 20.26. Found: C, 52.97; H, 8.96; N, 17.83; S, 19.99.

Rearrangement of S-(2-Aminoethyl) N-Phenyldithiocarbamate Hydrochloride.—In 50 ml. of anhydrous acetonitrile was suspended 7.5 g. (0.03 mole) of S-(2 aminoethyl) N-phenyldithiocarbamate hydrochloride, and 4.0 g. (0.04 mole) of triethylamine was added. On trituration all the solid went into solution, and a new solid crystallized. After 2 hr. the mixture was poured into 300 ml. of water, and an oil separated and crystallized. After recovery and drying the solid amounted to 4.9 g. (77%), m.p. 111.5–114°. Its infrared spectrum was identical with that of an authentic sample of 1-(2-mercaptoethyl)-3-phenyl-2 thiourea.

1-(2-Mercaptoethyl)-3-isopropyl-2-thiourea.—The procedure for 1-(2-mercaptoethyl)-3-*n*-butyl-2-thourea was followed with 28.0 g. (0.10 mole) of 1-[2-(isopropyldithiocarbamoyl)ethyl]-3-isopropyl-3-thiourea, 17.0 g. (0.10 mole) of silver nitrate, 10.1 g. (0.10 mole) of triethylamine, and 28.8 g. (0.12 mole) of sodium sulfide nonahydrate. There was obtained 12.6 g. (71%) of crude 1-(2-mercaptoethyl)-3-isopropyl-2-thiourea, m.p. 102–103°. Two recrystallizations from 95% ethanol gave pure material, m.p. 102–103.5°.

(9) K. Schimmelschmidt, H. Hoffmann, and E. Mundlos *Ber.*, **96**, 38 (1963).

(10) All melting points are corrected and boiling points are uncorrected. Microanalyses by Galbraith Laboratories, Knoxville, Tennessee.

Anal. Calcd. for $C_6H_{11}N_2S_2$: C, 40.41; H, 7.91; N, 15.71; S, 35.96. Found: C, 40.58; H, 7.94; N, 15.79; S, 36.17.

1-[2-(N-Phenylthiolcarbamoyl)ethyl]-3-phenylurea.—To a suspension of 6.8 g. (0.05 mole) of 2-mercaptoethylamine hydrochloride in 50 ml. of acetonitrile was added 5.1 g. (0.05 mole) of triethylamine. A new solid came out of solution. To the resulting suspension was added 6.0 g. (0.05 mole) of phenyl isocyanate. The temperature rose rapidly from 25° to 53°, then dropped back to 25° over about 90 min. The reaction mixture was poured into 200 ml. of ice water and a solid separated. After recovery by suction filtration and drying, the 1-[2-(N-phenylthiolcarbamoyl)-ethyl]-3-phenylurea amounted to 7.6 g. (96%), m.p. 165–189°. A portion of this solid was recrystallized three times from 95% ethanol to give material melting at 196.5–200°.

Anal. Calcd. for $C_{16}H_{17}O_2N_3S$: C, 60.93; H, 5.43; N, 13.32; S, 10.17. Found: C, 60.76; H, 5.58; N, 13.31; S, 10.19.

1-(2-Mercaptoethyl)-3-phenylurea.—In a solution of 4.6 g. (0.0457 mole) of triethylamine in 75 ml. of acetonitrile was suspended 14.4 g. (0.0457 mole) of 1-[2-(N-phenylthiolcarbamoyl)-ethyl]-3-phenylurea. To the suspension was added a solution of 7.8 g. (0.0457 mole) of silver nitrate in 25 ml. of acetonitrile. The mixture was triturated for an hour, an intense odor of phenyl isocyanate becoming apparent. The pH at this point was about six. When 2 ml. of triethylamine was added, bringing the pH to 7.5, the isocyanate odor rapidly disappeared.

The solid silver mercaptide was recovered by suction filtration and washed with 25 ml. of acetonitrile. While still damp it was added to a solution of 18.0 g. (0.075 mole) of sodium sulfide nonahydrate in 75 ml. of water. Black silver sulfide appeared rapidly when the mixture was triturated. When conversion appeared to be complete, the silver sulfide was recovered by suction filtration, washed with 25 ml. of water, and air-dried. The aqueous filtrate was made strongly acid with 5 *N* hydrochloric acid, and a copious cream colored precipitate came down. This was recovered by suction filtration, washed with 25 ml. of water, and air-dried. The acetonitrile filtrate from the original reaction was poured into 300 ml. of water, and a white solid, presumably by-product 1,3-diphenylurea, came out. It was recovered by suction filtration and dried.

The silver sulfide recovered amounted to 6.2 g. (theory 5.7 g.). The by-product 1,3-diphenylurea amounted to 3.7 g. (77%), m.p. 221–228°. After recrystallization from ethanol it melted at 236–243°. The crude 1-(2-mercaptoethyl)-3-phenylurea amounted to 8.9 g. (99%). Recrystallization from 75 ml. of ethanol gave 7.2 g. of relatively pure material, m.p. 141–143°. Two more recrystallizations from ethanol gave an analytical sample, m.p. 141.5–143°.

Anal. Calcd. for $C_9H_{12}ON_2S$: C, 55.07; H, 6.16; N, 14.28; S, 16.33. Found: C, 55.18; H, 6.23; N, 14.22; S, 16.19.

1-(2-Mercaptoethyl)-3-carboxymethylurea.—To 16.8 g. (0.05 mole) of 1-[2-(N-ethoxycarbonylmethylthiolcarbamoyl)ethyl]-3-ethoxycarbonylmethylurea was added 80 ml. of 10% sodium hydroxide solution (0.20 mole). The solid went into solution rapidly, and the solution became warm. After an hour the solution was filtered and cooled in ice, and 40 ml. of 5 *N* hydrochloric acid was added slowly. Gas evolved vigorously, and a solid crystallized. It was recovered by suction filtration and dried in a vacuum oven. The crude 1-(2-mercaptoethyl)-3-carboxymethylurea amounted to 6.3 g. (71%), m.p. 143–147°. The crude product was dissolved in 60 ml. of hot ethanol, and the solution was filtered to remove a small amount of sodium chloride. Cooling brought down 3.7 g. of purified urea, m.p. 147–149°. A portion was recrystallized a second time from ethanol to give an analytical sample, m.p. 149.5–150.5°.

Anal. Calcd. for $C_5H_{10}O_3N_2S$: C, 33.70; H, 5.66; N, 15.72; S, 17.99. Found: C, 33.76; H, 5.70; N, 15.83; S, 17.99.

The Dealkylation of Aromatic Amines

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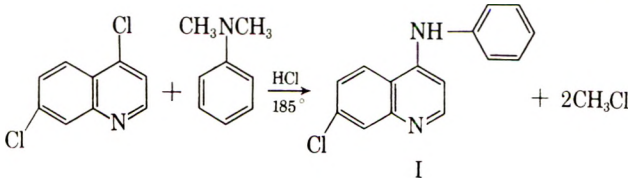
Received April 22, 1963

Tertiary aromatic amines were dealkylated smoothly to secondary aromatic amines at about 150° by passing hydrogen bromide through the molten salt. Secondary aromatic amines were converted to anilines at about 200°. All the rates followed pseudo first-order kinetics which made possible a comparative study among a number of tertiary amines under varying conditions.

We observed the rather unusual results of an attempted Friedel–Crafts reaction. *para* Substitution in dimethylaniline was anticipated but instead the product I was isolated in good yield. Obviously a dealkylation



I

had occurred prior to the coupling process, and this paper reports our study of the dealkylation process.

Many methods of dealkylation are available.[3-11] Only a few methods deal with the direct action of a mineral acid on an alkylamine,[12] stemming mainly from the work of Hickinbottom,[13,14] who found that N-methylaniline, heated in a slow stream of hydrogen chloride, yields aniline. Monoalkylaniline hydrobromides decompose between 250–300° with the elimination of the alkyl group as olefin and alkyl bromide. Tertiary alkyl groups are removed readily by acids at 110–140°.[15] Treatment of N-methylaniline under Zeisel conditions results in a yield of only 3% methyl iodide. N-Butylaniline is unaffected by 19 *N* sulfuric acid at 140° for 30 hours. An interesting application

(1) Abstracted from the Ph.D. thesis of R. A. C., National Defense Education Act Fellow, 1959–1962.

(2) To whom correspondence should be addressed.

(3) Cyanogen bromide: H. A. Hagemann, "Organic Reactions," Vol. 7, John Wiley and Sons, New York, N. Y., 1953, pp. 198–262.

(4) Acetyl bromide: W. Staedel, *Ber.*, **19**, 1947 (1886).

(5) Lead tetraacetate: H. von Foerst, "Neuere Methoden der Preparativen Organischen Chemie," Band 2, Verlag Chemie Weinheim, Germany, 1949, p. 267.

(6) Manganese dioxide: H. B. Henbest and J. W. Stratford, *Chem. Ind.* (London), 1170 (1960).

(7) Potassium ferricyanide: T. D. Perrine, *J. Org. Chem.*, **16**, 1303 (1951).

(8) Silicon tetrabromide: H. Breederveld, *Rec. trav. chim.*, **78**, 589 (1959).

(9) Tetranitromethane: E. Schmidt and H. Fischer, *Ber.*, **53**, 1537, (1920).

(10) Occasional nitration or halogenation: E. E. Ayling, J. H. Gorvin, and L. E. Hinkel, *J. Chem. Soc.*, 755 (1942).

(11) Zinc or cobalt halides: C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 615–618.

(12) The Hofmann–Martius rearrangement[13] concerns the direct action of a mineral acid, but, since it is carried out in a sealed tube at a high temperature and involves rearrangement, it is not included in the discussion.

(13) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans Green and Co., New York, N. Y., 1948, p. 306.

(14) P. Sabatier and G. Gaudion, *Compt. rend.*, **165**, 309 (1917).

(15) W. J. Hickinbottom, *J. Chem. Soc.*, 1070 (1933).

$$C_6H_5NH(CH_2)_4NHC_6H_5 \xrightarrow[230^\circ]{HBr} C_6H_5NH_2{\cdot}HBr +$$

tetrahydroquinoline hydrobromide

of dealkylation in preparative work has been reported recently.[16]

The purpose of this paper is to determine the mildest conditions under which dealkylation occurs with mineral acid and to run several comparative studies to understand the scope of the reaction. Without going into the details of the development of the procedure, the following conditions were found most useful: hydrogen bromide as a gas was introduced into the molten salt maintained at *ca.* 150°; the rate of dealkylation of tertiary alkyl amines at this temperature was quite rapid and independent of the flow rate of hydrogen bromide above 200 ml./min. Remarkably, the rates in this medium of molten aromatic amine–hydrobromide salt through which hydrogen bromide was passing to maintain the hydrogen bromide concentration and to sweep out alkyl bromide, followed pseudo first-order kinetic laws as shown in Experimental and in Table I. The rates of dealkylation of secondary aromatic amines were sufficiently slow at this temperature so that pure secondary amines could be isolated. Nevertheless, secondary aromatic amines could be dealkylated smoothly at a higher temperature, *ca.* 195°. All the facts established in this study are listed below:

Table I

Rates of Dealkylation of Tertiary to Secondary Amines by Hydrogen Bromide at 156°[a]

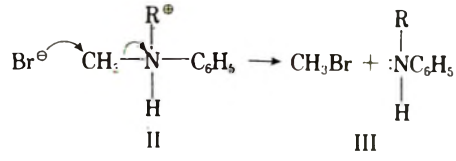
N,N-Amines	k, min.$^{-1}$	$t_{1/2}$, min.
Dimethylaniline	0.012	58
Di-*n*-propylaniline[b]	0.0031	223
Dimethyl-*m*-chloroaniline	0.016	43
Dimethyl-*p*-toluidine	0.0058	119
Dimethyl-*o*-toluidine	0.021	34
Diethylaniline[c]	Very slow, 20% dealkylation in 2 hr.	

[a] Pseudo first-order rates at flow rate of hydrogen bromide 425 ml./min. ± 25 ml. [b] 20% silicone gum rubber used for stationary phase in g.l.c. [c] 10% Carbowax used for stationary phase.

1. Tertiary aromatic amines are dealkylated more readily than secondary aromatic amines.
2. Hydrogen bromide is more effective than hydrogen chloride.
3. The sequence of ease of elimination of alkyl groups is in the order: methyl > *n*-propyl > ethyl in tertiary aromatic amines.
4. A small but appreciable amount of isopropyl bromide was isolated in addition to *n*-propyl bromide in the dealkylation of di-*n*-propylaniline.
5. Electron-attracting groups in the aromatic ring increase the rate of dealkylation and *vice versa*.
6. *ortho* Substituents increase the rate of dealkylation to a greater extent than any other factor.
7. Aliphatic amines are more resistant to dealkylation and are not dealkylated in any useful manner by this procedure.[17] Cyclic amines such as N-methylpiperidine and nicotine gave polymeric products, and tri-*n*-butylamine was largely unaffected.

(16) G. B. Russell, G. J. Sutherland, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, **27**, 4375 (1962).

The preceding facts were accumulated under conditions to stress the synthetic rather than the mechanistic aspects of dealkylation. Nevertheless, the facts are suggestive of a simple mechanism which has been useful in carrying out the preceding work and in predicting these and other results. We believe that the reaction is remarkably akin to a solvolytic reaction of the S$_N$2 type reverting to the S$_N$1 type as the alkyl group is changed.



II III

The nitrogen atom in II is tetrahedral and in III is tending toward the trigonal planar structure, *i.e.*, R and H in the same plane as the benzene ring. Thus, a driving force exists in II to be transformed to the resonance-stabilized III. The driving force possibly could explain the more facile dealkylation of aromatic amines compared to aliphatic amines. If the R group in II is an alkyl group rather than a hydrogen atom, some steric crowding may exist, and this would explain the more facile dealkylation of tertiary amines compared to secondary amines.[18] Obviously, the reactivity sequences: HBr > HCl > H_2SO_4 for acids and *m*-chloro > hydrogen > *p*-methyl for aromatic substituents, should hold as long as the mechanism is S$_N$2. A methyl group should dealkylate in preference to an ethyl or other primary alkyl groups, and this prediction has been found to be true in the demethylation of kairoline (see Experimental). In our interpretation, the S$_N$2 mechanism reverts in part to the S$_N$1 mechanism with the introduction of a propyl group, judging from the faster rate of dealkylation and the isolation of a small amount of isopropyl bromide in the reaction of di-*n*-propylaniline with hydrogen bromide. Unquestionably, the tertiary alkyl group must dealkylate by the S$_N$1 mechanism.[15,19]

Whether the working hypothesis can be accepted as a mechanism remains to be seen. But disregarding this point, we were impressed in this work by the ease of cleavage of the carbon–nitrogen bond and the resemblance of the cleavage to that of the carbon–oxygen bond.

The experimental work was facilitated greatly by the gas chromatographic techniques described in the next section.

(17) Other comments on dealkylation of aliphatic amines are to be found in C. D. Hurd, "The Pyrolysis of Carbon Compounds," A.C.S. Monograph 50, Chemical Catalog Co., New York, N. Y., 1929, pp. 310–329, and in reference by C. Ainsworth and N. R. Easton, *J. Org. Chem.*, **27**, 4118 (1962).

(18) If steric crowding exists in II when R is an alkyl group, a greater steric crowding effect should be present in a quaternary ammonium salt which should therefore dealkylate more easily with hydrogen bromide than II. We propose to test this prediction, although an example has been noted: A. T. Babayan, M. G. Indzhikyan, Z. G. Gegelyan, and A. A. Grigoryan, *Dokl. Akad. Nauk Arm. SSR*, **35**, 67 (1962); *Chem. Abstr.*, **58**, 5543 (1963). $C_6H_5NHCH_3 + CH_3{=}CH{-}CH_2NR_2 \longrightarrow$ $C_6H_5N(CH_3)CH_2CH{=}CH_2 + R_2NH$

(19) Anchimerically assisted groups also should be cleaved easily from the nitrogen atom by the S$_N$1 mechanism. Such a cleavage has been observed with a norbornane lactam using 5% hydrochloric acid: L. H. Zalkow and C. D. Kennedy, *J. Org. Chem.*, **28**, 852 (1963).

TABLE II

RETENTION TIMES OF AROMATIC AMINES[a]

Aromatic amine	B.p., °C.	Retention time, sec.	Aromatic amine	B.p., °C.	Retention time, sec.
Aniline	184	122	*m*-Toluidine	203	184
N-Methylaniline	196	138	N,N-Dimethyl-*m*-toluidine	212	132
N,N-Dimethylaniline	193	98	*o*-Chloraniline	209	242
o-Toluidine	201	142	N,N-Dimethyl-*o*-chloroaniline	206	120
N-Methyl-*o*-toluidine	208	178	*m*-Chloroaniline	230	484
N,N-Dimethyl-*o*-toluidine	185	56	N-Methyl-*m*-chloroaniline	235	492
p-Toluidine	200	172	N,N-Dimethyl-*m*-chloroaniline	232	300
N-Methyl-*p*-toluidine	211	196	2,6-Xylidene	214	242
N,N-Dimethyl-*p*-toluidine	211	132	N,N-Dimethyl-2,6-xylidene	196	52
N-Ethylaniline	205	160	N-*n*-Propylaniline	222	210
N,N-Diethylaniline	215	124	N,N-Di-*n*-propylaniline	245	210
			N-Methylpiperidine	107	26

[a] The conditions are given in g.l.c. analysis section. Most curves are Gaussian in shape with about 1-cm. width at base of curve.

Experimental

The Reaction of Dimethylaniline and 4,7-Dichloroquinoline.[20]—This experiment led to the subsequent results reported here. N N-Dimethylaniline (0.3 mole) and 4,7-dichloroquinoline (0.1 mole) were heated to 100° whereupon a slow stream of hydrogen chloride was passed beneath the surface. The temperature climbed rapidly to 160° and after heat of neutralization had spent itself external heating was applied to maintain a temperature of 185°. After 2 hr. the mixture was cooled, poured into water, filtered, and washed with more water. The brown precipitate (26.2 g.) was recrystallized from ethanol containing an equal volume of hydrochloric acid. The crystalline hydrochloride (m.p. 295–300°; neut. equiv., 293) was converted to the free base by dissolving in ethanol and adding 0.1 *N* sodium hydroxide solution until the solution was basic. The white platelets were collected by filtration, washed thoroughly with water, air-dried and sublimed under reduced pressure, m.p. 207–207.5°, mixture melting point with 4-phenylamino-7-chloroquinoline, synthesized from aniline and 4,7-dichloroquinoline, the same.

Apparatus and General Procedure for Dealkylation.—The constant temperature bath was a three-necked two-piece 2-l. resin kettle equipped with thermometer, condenser, and a 200 × 25 mm. test tube. The test tube, inserted in one of the necks of the resin flask, was long enough to be bathed in the vapors of the refluxing liquid. A gas inlet tube for hydrogen halide entered the side of the test tube and terminated at the bottom in a sintered glass disk to give a well distributed flow of hydrogen halide. Temperatures in the apparatus could be maintained within 0.5° over long periods of time.

The pure amine (0.25 mole) was placed in the test tube to which a drying tube was attached. Dry hydrogen halide was passed through the amine until the hydrohalide had precipitated. The heat was dissipated with a water bath. To prevent pressure building up when the hydrohalide solidified, the hydrogen halide was by passed by opening the closed end of a Y tube in the piping system. The test tube was now placed in the constant temtemperature bath, the drying tube being replaced by a condenser. The temperature of the bath fell about 15° but was regained in about 3–5 min. When the hydrohalide melted, the safety valve was closed again to pass hydrogen halide through the molten salt. The exit hydrogen halide was led to a water trap.

To obtain rates an aliquot was removed from the test tube at appropriate intervals with a 1-ml. glass dipper and dissolved in water. The aliquot was made strongly basic and thoroughly extracted with ether. The ether layer was dried with solid potassium hydroxide and evaporated by means of a Rinco evaporator. The amine residue, about 0.5 g., was analyzed by gas–liquid chromatography when all aliquots had been accumulated. It was unnecessary to withdraw exact amounts of aliquot as analysis was based on the ratio of tertiary to secondary or primary amines.

G.l.c. Analysis.—Temperatures: column 230°; Gowmac detector, 217°. Column: 6 ft., ¼ in. copper tubing packed with 60–80-mesh Chromosorb W, containing 5% polyethylenebenzonitrile as a stationary phase.[21] Flow rate: 90 ml. of He/min. Detector current: 100 ma. Sample volume: 5 μl. The retention times are given in Table II.

Where separation was not brought about by the polyethylene benzonitrile resin, such a mixture of dipropylaniline and propylaniline, other resins that are specified were utilized.

Considerable study was done on calibration curves using known percentages of tertiary amine dissolved in secondary amine.[1] In all cases, the approximate area (peak height × 0.5 peak width at base of peak) was linear with respect to the concentration of tertiary amine. Therefore, rates were obtained by plotting log area of the tertiary amine peak *vs.* time.[22]

Results of Kinetic Studies Using Optimum Conditions for Dealkylation.—Hydrogen bromide was found to be more reactive than hydrogen chloride. A temperature of 156° (b.p. of 3-heptanol) and a flow rate of hydrogen bromide of 400 ml./min. were selected for comparison conditions. (The rate of dealkylation was independent of flow rate as low as 200 ml./min.; below this flow rate, however, the rate of dealkylation was dependent on flow rate.) All rates followed pseudo first-order rate kinetics. A typical rate is shown with N,N-dimethylaniline (k = 0.012 min.$^{-1}$; $t_{1/2}$ = 58 min.).

Time (min.)	Log area
17	0.89
30	0.82
43	0.76
59	0.67
73	0.61
90	0.52

At this temperature, negligible amounts of primary amines were formed, perhaps amounting to a few per cent in the case of the fastest dealkylating amine. Thus the dealkylation rate is mainly that of tertiary aromatic amine degrading to secondary amine. The comparative results using optimum conditions are shown in Table I.

Direct Comparison of Hydrogen Chloride and Hydrogen Bromide as Dealkylating Agents.—A direct comparison was made on dimethylaniline at a temperature of 177° and a flow rate of 146 ml./min.

HCl: k = 0.015 min.$^{-1}$; $t_{1/2}$ = 46 min.
HBr: k = 0.021 min.$^{-1}$; $t_{1/2}$ = 33 min.

Dealkylation of N-methylaniline.—As stated earlier, the rates of dealkylation of secondary amines are much slower than tertiary amines. A comparison was made at 195° at an approximate flow-rate of 100 ml./min. of hydrogen chloride.

(20) We are indebted to Mr. W. Carl Dyer for making the initial run on this reaction.

(21) The resin was made by the condensation of equimolecular quantities of benzonitrile and ethylene bromide following the conditions for bromination of acetophenone reported by D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Syn.*, **40**, 7 (1960).

(22) This method of analysis placed emphasis on accurate delivery of 5μg. samples for g.l.c. Therefore, two or three samples were injected, and the average area for the tertiary amine was used to obtain rates. Usually, all areas were identical.

N,N-Dimethylaniline[23]: $k = 0.014$ min.$^{-1}$; $t_{1/2} = 50$ min.

N-Methylaniline: Very slow; kinetics complicated by appearance of N,N-dimethylaniline, reaching 10% by weight of total amine fraction at end of 1 hr. This means that rate of alkylation of N-methylaniline is faster than its rate of dealkylation, the latter being extremely slow. To demonstrate this, methyl chloride was passed through molten N-methylaniline hydrochloride at 195° and at a flow rate af 154 ml./min. After 3 hr., an aliquot contained 20% tertiary amine. This experiment demonstrates that the reverse reaction, alkylation, is slow under the conditions of dealkylation. Besides being slow it does not become important until the concentration of secondary amine is high.

The Isolation of the Alkyl Bromide from Dealkylation of N,N-Di-*n*-propylaniline.—The effluent hydrogen bromide containing alkyl bromide was passed through an efficient trap cooled with ice–water–salt mixture. The condensate was washed with cold water, separated, and dried. Analysis by gas chromatography (oven temperature, 93°; 10% SE-30 stationary phase, 32 ml./min. He flow rate, retention time for *n*-propyl bromide = 154 sec., retention time for isopropyl bromide = 126 sec.) showed 96% *n*-propyl bromide, 4% isopropyl bromide, and no propylene bromide. Pure *n*-propyl bromide did not isomerize when subjected to conditions identical with isolation procedure.

Demethylation of N-Methyltetrahydroquinoline (Kairoline) to Tetrahydroquinoline.—To show that methyl groups are removed preferentially, kairoline (0.2 mole) was treated with hydrogen chloride at 195° for 13 hr. Recovery of the basic product gave tetrahydroquinoline (0.19 mole, free from tertiary amine as denoted by g.l.c., benzenesulfonamide m.p. 65.6–66.5°, lit. m.p. 67°).

Attempts to Dealkylate Aliphatic Amines.—Regardless of changes in conditions and irrespective of the addition of catalysts or trapping agents such as 4,7-dichloroquinoline or 2,4-dinitrochlorobenzene, the dealkylation of nicotine and of N-methylpiperidine led only to black, polymeric tars. The attempted dealkylation of tri-*n*-butylamine at 195° for 6 hr. gave approximately 1% *n*-butyl bromide.

(23) One notes that the rate of dealkylation at 195° is about the same as the rate at 177°. Part of this similarity is caused by different flow rates. But, another factor is that hydrogen chloride is not as soluble at higher temperatures in the melt. Thus, an increase in temperature does not necessarily increase the rate appreciably. An experiment to determine the amount of hydrogen chloride dissolved showed that 1 equivalent of hydrogen chloride dissolved per 1 equivalent of amine.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this work.

The Swamping Catalyst Effect. V. The Halogenation of Aromatic Acid Derivatives[1]

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Received June 24, 1963

A study of the halogenation of the aluminum chloride complexes of acid derivatives using excess aluminum chloride was undertaken. All the following acid derivatives were halogenated as aluminum chloride complexes. Methyl benzoate gave 86% methyl 3-bromobenzoate on monobromination and 89% methyl 2,5-dibromobenzoate on dibromination. *p*-Toluyl chloride gave 85% methyl 3,5-dibromo-4-toluate on dibromination. Methyl *p*-toluate gave 71% 3-chloro-4-toluic acid on chlorination and 65% methyl 3-iodo-4-toluate on iodination. Coumarin gave 74% 6-bromocoumarin. Benzonitrile gave 64% 3-bromobenzonitrile on monobromination and 79% 2,5-dibromobenzonitrile on dibromination. N-Methyl- and N,N-dimethylbenzamides gave poor yields in bromination. Methyl *o*-toluate gave a mixture of halogenated products which could not be separated easily. The preceding procedure is probably the best method of direct introduction of chlorine or bromine into aromatic acid derivatives.

One may ask the question: how is *m*-bromobenzoic acid obtained? The immediate answer would seem to be direct bromination of benzoic acid. This pathway is fraught with obstacles. The halogenation is very slow and incomplete, and the temperature of halogenation is high enough to bring about sublimation of unreacted benzoic acid.[4] To quote one source,[5] "direct halogenation is seldom successful and scarcely ever used" with aromatic acids.

We have now found that direct halogenation of the aromatic acid esters or chlorides can be carried out with eminent success using the swamping catalyst effect as shown.

$$C_6H_5COOCH_3 + 2AlCl_3 + Br_2 \xrightarrow{65^\circ} m\text{-}BrC_6H_4COOCH_3(86\%) + HBr$$

The swamping catalyst effect entails halogenation of the aluminum chloride complex with a highly reactive halogenation species, either X^+ itself, or the ion pair, $X^+AlCl_3X^-$. The halogenating species cannot be obtained unless more than one equivalent, and preferably two equivalents, of aluminum chloride are used.[6] No solvent is employed.

(1) Part IV: B. R. Suthers, P. H. Riggins, and D. E. Pearson, *J. Org. Chem.*, **27**, 447 (1962).

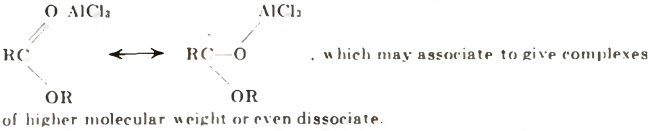
(2) Abstracted mainly from the Ph.D. thesis of W. E. S., 1962.

(3) Abstracted in part from the Ph.D. thesis of B. R. S., 1961.

(4) H. Hübner and G. Weiss, *Ber.*, **6**, 175 (1873); P. S. Varma and P. B. Panicker, *J. Indian Chem. Soc.*, **7**, 503 (1930).

(5) G. M. Dyson, "Manual of Organic Chemistry," Vol. I, Longmans, Green and Co., New York, N. Y., 1950, p. 590.

(6) In an earlier paper,[7] we stated that a unique part of the swamping catalyst effect with ketones was the formation of an eight-membered ring between two moles of acetophenone and two moles of aluminum chloride. From further study of the literature on complexes,[8] we believe that these structures are somewhat variable[9] and it is best to consider the complex simply as a Lewis salt: $R_2C{=}O \cdot AlCl_3 \longleftrightarrow R_2\overset{+}{C}{-}O\overset{-}{A}lCl_3$ or



, which may associate to give complexes of higher molecular weight or even dissociate.

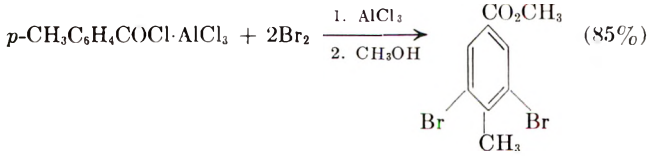
(7) D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper, *J. Org. Chem.*, **23**, 1412 (1958).

(8) Ester–aluminum chloride complexes: M. F. Lappert, *J. Chem. Soc.*, 817 (1961); 542 (1962); J. Vanderhoek, *Baskerville Chem. J. City Coll. N. Y.*, **10**, No. 1, 13 (1960). Acid chloride–aluminum halide complexes: B. N. Menshutkin, *J. Russ. Phys. Chem. Soc.*, **42**, 1310 (1911); E. P. Kohler, *Am. Chem. J.*, **24**, 385 (1900); J. Boeseken, *Rec. trav. chim.*, **19**, 19 (1900); N. N. Lebedev, *Zh. Obshch. Khim.*, **21**, 1788 (1951); *Chem. Abstr.*, **46**, 6586 (1952); W. Nespital, *Z. physik. Chem.* (Leipzig), **16B**, 153 (1932); B. P. Susz and J. J. Wuhrmann, *Helv. Chim. Acta*, **40**, 971 (1957), and earlier papers. Nitrile–aluminum halide complexes: I. Kablukov and A. S. A. Khanov, *J. Russ. Phys. Chem. Soc.*, **41**, 1755 (1910); *Chem. Abstr.*, **5**, 1419 (1911); R. Müller and G. Wersitsch, *Z. anorg. allgem. Chem.*, **208**, 304 (1932); R. E. Van Dyke and T. S. Harrison, *J. Am. Chem. Soc.*, **73**, 402 (1951).

(9) S. C. J. Olivier, *Rec. trav. chim.*, **37**, 205 (1918); H. Ulich, *Z. physik. Chem.*, Bodenstein-Festband, 423 (1931).

As noted in halogenation of the ketone–aluminum chloride complexes,[7] we found that the acid derivative–aluminum chloride complexes were deactivated toward substitution, gave *meta* oriented products, but had very poor control of the orientation. They behaved as though the directive influence of the complexed group was purely inductive in nature. Any other group attached to the aromatic nucleus seemed to control the orientation. Thus, in the dibromination of methyl benzoate, the reaction was as follows.

The first bromine substitution which is in the *meta* position controls the orientation of the second bromine substitution. But with *p*-toluyl chloride (and very likely with the ester), the reaction was as follows.



The inductive effect of the methyl group, perhaps combined with the small steric effect of the complexed ester grouping, predominates over the orientation influence of the first bromine atom introduced. Chlorination also can be carried out as demonstrated by the preparation of 3-chloro-4-toluic acid in 71% yield. Iodination using iodine monochloride gave methyl 3-iodo-4-toluate in 65% yield. Coumarin, if brominated without complexing with aluminum chloride, yields 3,4-dibromocoumarin which can be dehydrobrominated to 3-bromocoumarin.[10a] The coumarin–aluminum chloride complex, on the other hand, gave 6-bromocoumarin in good yield.[11]

The second question one may ask is whether other methods of directly halogenating aromatic acids are available. The Derbyshire–Waters method[12] is quite comparable in respect to yields and orientation. The only decision to be made is whether one prefers concentrated sulfuric acid and silver sulfate as a medium or anhydrous aluminum chloride.

Considerable literature does exist on the halogenation of acid derivatives using small amounts (or no) catalyst. The chlorination of benzoyl chloride with small amounts of ferric chloride yields a mixture of about 80% *meta*- and 20% *ortho*-chlorobenzoyl chloride.[13] The chlorination of methyl benzoate leads first to benzoyl chloride and then on the addition of ferric chloride to chloro-substituted benzoyl chlorides.[14] Iodination of phthalic anhydride in fuming sulfuric acid of course is a well known process leading to tetraiodophthalic anhydride.[15]

With no many processes available for the halogenation of aromatic acids, one must discriminate among them. We suggest that for laboratory preparation of *meta*-chloro- or bromo-substituted acids the swamping catalyst method be used starting with the ester or acid chloride but for the preparation of *meta*-iodo acids the Derbyshire–Waters method be used.

The swamping catalyst method appears to be quite superior to other methods for preparing *m*-halobenzonitriles. For example in this paper, *m*-bromobenzonitrile was prepared in 64% yield on monobromination and 2,5-dibromobenzonitrile in 79% yield on dibromination. Gas phase bromination of benzonitrile leads to a mixture of monobrominated isomers.[16] *p*-Bromobenzonitrile is obtained in small yield using heterogeneous conditions with sulfuric acid.[17] Earlier reports mention poor yields or complex products from the halogenation of benzonitrile in sealed tubes.[18] None of these results appears comparable to those of the swamping catalyst technique.

Among other acid derivatives investigated in halogenation were N-methyl- and N,N-dimethylbenzamide. They were much more difficult to brominate, particularly N-methylbenzamide. Nevertheless, the *meta*-brominated products were obtained in 30 and 50% yields, respectively.

Experimental

General Procedure.—The apparatus and conditions described in *Organic Syntheses* were employed.[19] Unless otherwise stated, 0.3 mole of acid derivative and 0.8 mole of finely divided, anhydrous aluminum chloride were mixed to form the complex and then 0.35 mole (or 0.7 mole for dihalogenation) of halogen was added dropwise or by passing under the surface.

The halogenated acid chloride complexes, in the halogenation of acid chlorides, were decomposed by dropwise addition of methanol to the flask cooled in ice rather than by transfer of the complex to ice and water. Thus, the halogenated acid chloride complexes were isolated as methyl esters.

Methyl 3-Bromobenzoate.—The gray complex from methyl benzoate and aluminum chloride was brominated smoothly at 60° by dropwise addition of bromine over a period of about 1 hr. The 3-bromo ester was obtained in 85% yield, m.p. 30–31°, after fractionation, b.p. 138–140° at 10 mm., and one recrystallization from hexane.

The red complex from benzoyl chloride and aluminum chloride was brominated in the same manner and after decomposition with methanol yielded 86% methyl 3-bromobenzoate, m.p. 30–31°.

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(10) E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Publishing Co., New York, N. Y., 1959; (a) Vol. IVB, 877; (b) Vol. IVC, 1569.

(11) A report is given in the literature that bromine water yields 6-bromocoumarin: J. Read and W. G. Reid, *J. Chem. Soc.*, 745 (1928).

(12) D. H. Derbyshire and W. A. Waters, *ibid.*, 3694 (1950); J. H. Gorvin, *Chem. Ind.* (London), 910 (1951); A. M. Fleifel, *J. Org. Chem.*, **25**, 1024 (1960).

(13) E. Hope and G. C. Riley, *J. Chem. Soc.*, **123**, 2470 (1923); *m*-bromobenzoyl chloride using bromine and chlorine: E. C. Britton and R. M. Tree, U. S. Patent 2,607,802, (Aug. 19, 1952); *Chem. Abstr.*, **47**, 5437 (1953); for chlorination of benzoic acid in a sealed tube, see J. T. Bornwater and A. F. Holleman, *Rec. trav. chim.*, **31**, 221 (1912).

(14) E. Katzschmann, German Patent 1,097,973 (January 26, 1961); *Chem. Abstr.*, **55**, 24685 (1961); Heyden Newport Chemical Co., British Patent 831,051 (March 23, 1960); *Chem. Abstr.*, **54**, 24556 (1960); S. I. Burmistrov and L. G. Zagorskaya, *J. Gen. Chem. USSR*, **32**, 1253 (1962).

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(17) P. S. Varma and N. B. Sen-Gupta, *J. Indian Chem. Soc.*, **10**, 593 (1933).

(18) C. Engler, *Ann.*, **133**, 144 (1865); L. H. Friedberg, *ibid.*, **158**, 29 (1871); V. Merz and W. Weith, *Ber.*, **16**, 2890 (1883); addition of chlorine in sunlight: T. Van Der Linden, *Rec. trav. chim.*, **53**, 47 (1934).

(19) D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Syn.*, **40**, 7 (1960).

Methyl 2,5-Dibromobenzoate.—Two equivalents of bromine were employed. The crude product was fractionated to remove the monobrominated ester, and the dibrominated ester collected at 94–96° at 0.5 mm., m.p. 39–40° after one recrystallization from hexane. From methyl benzoate the yield was 84%, and from benzoyl chloride it was 45%, the difference in the yield being caused by less complete bromination of the benzoyl chloride complex. A portion of the 2,5-dibromo ester was saponified in 89% yield to 2,5-dibromobenzoic acid, m.p. 154–155°, lit.[20] m.p. 153°.

Methyl 3,5-Dibromo-4-toluate.—The crude product (95 g., b.p. 131–151° at 2 mm.) obtained from 0.3 mole of *p*-toluyl chloride, was recrystallized from methanol several times to yield 78 g. (85%) of methyl 3,5-dibromo-4-toluate, m.p. 87.5–88.5°; sapon. equiv., 311; calcd. 308. A portion of the ester yielded 3,5-dibromo-4-toluic acid, m.p. 238–239° after saponification and recrystallization from methanol, lit.[21] m.p. 235–236°, mixture melting point the same with a sample of the acid prepared from 3,5-dibromo-4-methylacetophenone.[7]

3-Chloro-4-toluic acid.—The chlorination was carried out as described previously[7] starting with methyl *p*-toluate. The reaction mixture was quenched with water rather than methanol and yielded 71% 3-chloro-4-toluic acid, m.p. 201–202° after one recrystallization from aqueous ethanol, lit.[22] m.p. 200–202°.

Methyl 3-Iodo-4-toluate.—Because of the tendency of iodine monochloride to dissociate to chlorine and iodine in the presence of aluminum chloride,[7] the reaction conditions were made as mild as possible. To 0.4 mole of anhydrous aluminum chloride was added 0.13 mole of methyl 4-toluate. The complex was heated to 65°, the usual reaction temperature, and then cooled to room temperature. Iodine monochloride (0.14 mole) was added over a period of 8 hr., the mixture stirred an additional 4 hr. and quenched with 165 g. of methanol added dropwise while the flask was cooled. Fractional distillation of the residue from the dry, neutral ether extract gave 7 g. (26%) of methyl 3-chloro-4-toluate, b.p. 85–87° at 2 mm., $n^{25}D$ 1.5253; and 22 g. (65%) of methyl 3-iodo-4-toluate, m.p. 28–29°, lit.[23] m.p. 28°, sapon. equiv., 279, 281; calcd. 277. The acid melted at 210–211°, lit.[22] m.p. 205–206°.

Attempted Preparation of 5-Bromo-2-toluic Acid.—The bromination of methyl *o*-toluate under swamping conditions led to a mixture of methyl bromo-*o*-toluate esters which could not be separated by fractionation in a Helipak filled column. Both 3-bromo- and 5-bromo-2-toluic acids were isolated in poor yield from the saponified mixture. Chlorination of methyl *o*-toluate also gave an inseparable mixture.

6-Bromocoumarin.—The crude product was collected at 144–155° (1 mm.). It was recrystallized from ethanol to obtain 74% of colorless, fine needles, m.p. 165–166°, lit.[24] m.p. 164°. The mixture melting point with a sample made from the Perkin condensation of 5-bromosalicylaldehyde and acetic anhydride was also the same. 3,4,6-Tribromocoumarin, m.p. 318–319°, was made from 6-bromocoumarin and bromine in carbon bisulfide, lit.[24] m.p. 316°.

3-Bromobenzonitrile.—The yellow complex between benzonitrile (0.43 mole) and aluminum chloride (0.85 mole) was brominated at 60° using 0.43 mole of bromine. The addition took 30 min. and was followed by a heating period of 11 hr. (probably an excessive heating time). Benzonitrile (8 g., 19%) was removed at 46–50° (2 mm.) and the residue dissolved in hexane, decolorized with Norit, and chilled. After filtration and air-drying 3-bromobenzonitrile (50 g., 64%) was obtained, m.p. 37–38°, lit.[25] m.p. 38°. The benzamide, prepared from the nitrile, melted at 156–156.5°, lit.[22] m.p. 155°. When the bromination was run with iron as a catalyst, in place of aluminum chloride, only benzonitrile and *sym*-triphenyltriazine (27%, m.p. 231–232°, lit.[10b] m.p. the same) were obtained.

2,5-Dibromobenzonitrile.—The ratios of reagents were aluminum chloride 3.5 moles, benzonitrile 1.1 moles and bromine 3.1 moles. The bromine addition was carried out at 60° for 3 hr. followed by another 3-hr. heating period. The product was distilled up to 120° (2 mm.). The distillate was fractionally crystallized from benzene to yield 235 g. (79%) of 2,5-dibromobenzonitrile, m.p. 144–145°, lit.[26] m.p. 132°.

Anal. Calcd. for $C_7H_3Br_2N$: Br, 61.2. Found: Br, 61.2.

2,5-Dibromobenzoic acid, m.p. 156–157°, lit.[20] m.p. 153°, was obtained by hydrolysis of the nitrile. 2,5-Dibromoacetophenone, m.p. 40–41°, lit.[20] m.p. the same, was prepared from the nitrile by addition of methylmagnesium iodide. The oxime, m.p. 139–140°, was rearranged to 2,5-dibromoacetanilide, m.p. 171–172°, lit.[28] m.p. the same. The infrared spectrum of 2,5-dibromobenzonitrile showed a peak at 820 cm.$^{-1}$ and none at 780 cm.$^{-1}$, which is to be expected of two adjacent aromatic hydrogens.

Competitive Bromination of Acetophenone with Methyl Benzoate and with Benzoyl Chloride under Swamping Conditions.—A mixture of acetophenone (0.05 mole) and methyl benzoate (0.05 mole) was added dropwise to aluminum chloride (0.2 mole). While the fluid complex was maintained at 65°, bromine (0.05 mole) was added dropwise in 95 min. Gas chromatography of the four components,[29] the two starting materials, *m*-bromoacetophenone, and methyl *m*-bromobenzoate indicated that methyl benzoate was brominated at least twice as readily as acetophenone. Similarly, it was shown that acetophenone was brominated at least twice as rapidly as benzoyl chloride.

3-Bromo-N-methylbenzamide.—The green complex of N-methylbenzamide and aluminum chloride did not brominate at temperatures lower than 120°. With the higher temperature of reaction more tar was obtained. However, 3-bromo-N-methylbenzamide was isolated in 30% yield, m.p. 96–97° from aqueous methanol, mixture melting point with a sample prepared from *m*-bromobenzoyl chloride and methylamine the same.

3-Bromo-N,N-dimethylbenzamide.—The brown complex between aluminum chloride and N,N-dimethylbenzamide was brominated at 75°. The titled compound was obtained in 50% yield m.p. 52–53°, mixture melting point with an authentic sample from *meta*-bromobenzoyl chloride and dimethylamine the same.

Anal. Calcd. for $C_9H_{10}BrNO$: Br, 35.1. Found: Br, 35.7.

3-Bromo-4-ethylacetophenone.—By the regular procedure[19] this compound was obtained in 59% yield, b.p. 106–107° at 1.7 mm., $n^{25}D$ 1.5669.

Anal. Calcd. for $C_{10}H_{11}BrO$: Br, 35.2. Found: Br, 35.2.

The oxime from hexane melted at 70–70.5° and the 2,4-dinitrophenylhydrazone at 194–194.5°.

Acknowledgment.—We are indebted to the National Science Foundation for a grant in support of this work.

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(25) H. Rupe and F. Bernstein, *Helv. Chim. Acta*, **13**, 457 (1930).

(26) A. Claus and A. Weil, *Ann.*, **269**, 223 (1892). It is interesting that other work of the senior author has been reported in error.[27]

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(28) H. L. Wheeler and W. Valentine, *Am. Chem. J.*, **22**, 277 (1899).

(29) A 12-ft. column packed with 30–60-mesh Chromosorb containing 20% by weight of Craig polyethylene succinate ester was used. The oven temperature was 194° and flow rate 50 ml./min. The retention times were: methyl benzoate, 17.4 min.; acetophenone, 20.8 min.; methyl *m*-bromobenzoate, 53.8 min.; *m*-bromoacetophenone, 68.2 min.

Structure of the 2:2 Condensation Product of Nitromethane and Cyclohexanone

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Received December 31, 1962

The 2:2 condensation product of nitromethane and cyclohexanone is shown by (1) appropriate degradative experiments, (2) the synthesis of the key degradation products XV and II, and (3) n.m.r. studies of the location of the double bond, to have structure I.

Isolation of a high-melting crystalline solid $C_{14}H_{20}N_2O_3$ (I) from condensation of nitromethane with cyclohexanone, catalyzed by secondary amines, has been reported from several sources.[2-7] Nightingale and her students have investigated the generality of formation of high-melting condensation products, analogous to I, from other aliphatic nitro compounds and cyclic ketones. Nitromethane is unique among the nitro compounds which were investigated, because nitroethane, 1-nitropropane, and phenylnitromethane gave no solid products with cyclohexanone analogous to I.[5] Compounds analogous to I are obtained, however, from condensations of nitromethane with cyclopentanone (8–24%)[5,7] cycloheptanone (51%),[7] and cyclooctanone (1%),[7] as well as with the substituted cyclohexanones, 3-methylcyclohexanone (1%)[4] (but not with 2-methylcyclohexanone[5]), 4-methylcyclohexanone (5–40%),[4,5,7] 4-isopropylcyclohexanone (40%),[7] 4-*sec*-butylcyclohexanone (23%),[7] 4-*t*-butylcyclohexanone (34%),[7] and 4-cyclohexylcyclohexanone (20%).[7] Secondary amines used as catalysts (with the yields given for formation of I from nitromethane and cyclohexanone) include piperidine[4] (8–14,[5] 20%[7]), piperazine (67%),[7] 2-methylpiperazine (27%),[7] pyrrolidine (23%),[7] morpholine (22%),[7] hexamethyleneimine (24%),[7] diethylamine (19%),[3] and di-*n*-propylamine,[5] but neither the primary amine, methylamine,[4] nor the tertiary amine, triethylamine,[7] nor tetramethylammonium hydroxide,[7] nor sodium ethoxide,[5] catalyzed the formation of I. Compound I also has been obtained from condensation of nitromethane with the other cyclohexanone reaction products,[3] 1-(nitromethyl)cyclohexanol (4%)[3,5] and 1-(nitromethyl)cyclohexene,[5] and with the enamines,[8] 1-piperidinocyclohexene (10%),[6] 1,4-bis(1-cyclohexenyl)piperazine (22%),[7] and 1-hexamethyleneiminocyclohexene (43%).[7]

In 1958 Nightingale, Reich, and Erickson reported an extensive study of the reactions of I, and proposed the partial structure $C_{13}H_{18}NO{\cdot}(C{=}O)NHOH$.[5] They suggested further that I contained a C=N group and a $-\overset{|}{C}{=}\overset{|}{C}-$ group, both of which are unconjugated. After the appearance of this publication, work aimed at a complete elucidation of the structure of I was begun in our laboratory. The results of the functional group determination and the proof of the atomic skeleton (structure I in Chart 1), which are described in detail here, have been presented previously in a Communication.[9] Shortly after submission of our Communication, we had established the location of the olefinic double bond, making it possible for Nightingale and her co-workers to utilize the complete structure of I in her most recent paper.[7] Recently, House and Magin[10] have reported independent degradative experiments which demonstrate the same atomic skeleton for I, but by a different and complementary route proceeding through selective reduction of the double bond (of IV). From n.m.r. data (on IV and IVa), they narrowed possible locations of the olefinic double bond to a single position in either cyclohexane ring; the final, correct choice was based on the difficulty of writing a rational mechanism to place the double bond in the other cyclohexane ring.[10]

The Functional Groups.—The acidic hydrolysis of I to $C_{14}H_{19}NO_3$ (IV[11]), which corresponds to the hydrolysis of an oximino group, was previously formulated as the conversion of a hydroxamic acid to the corresponding carboxylic acid.[5] It followed then that the monomethyl derivative $C_{15}H_{21}NO_3$ (IVa), formed by action of potassium hydroxide and methyl iodide on IV, was the methyl ester of the carboxylic acid IV.[5] In the present work, methylation of IV to IVa (obtained as dimorphic forms both melting at 95–96°) has also been accomplished with diazomethane,[12] but attempted esterification of IV with methanol containing sulfuric acid gave only unchanged IV.[13] Failure of the acid-catalyzed esterification, and the low frequencies of infrared bands possibly attributable[5] to a carboxyl group in IV and to a methoxycarbonyl group in IVa, cast doubt on the presence of these functional groups.

Compounds IV and IVa, like compound I,[5] contain a carbon to carbon double bond, as shown by the olefinic band present in their infrared spectra, and by the two vinyl proton resonances present in the n.m.r. spectra of I and IVa. Catalytic hydrogenation of both IV and IVa over Raney nickel at two atmospheres gave the same neutral product $C_{14}H_{21}NO_2$ (XV), the conversion being carried out under much milder conditions than in the high-pressure hydrogenation previously

(1) (a) National Science Foundation Graduate Fellow, June, 1960–June, 1962, and du Pont Summer Fellow, 1st Summer Session, 1962; (b) from the Ph.D. thesis of Richard J. Sundberg, University of Minnesota, August, 1962; *Dissertation Abstr.*, **24**, 85 (1963).

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(5) D. V. Nightingale, D. A. Reich, and F. B. Erickson, *ibid.*, **23**, 236 (1958).

(6) Z. Eckstein, A. Sacha, and W. Sobótka, *Bull. Acad. Polon. Sci., Ser. Sci., Chim., Geol. Geograph.*, **7**, 295 (1959); *Roczniki Chem.*, **34**, 1329 (1960).

(7) D. V. Nightingale, S. Miki, D. N. Heintz, and D. A. Reich, *J. Org. Chem.*, **28**, 642 (1963).

(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(9) W. E. Noland and R. J. Sundberg, *Tetrahedron Letters*, 295 (1962).

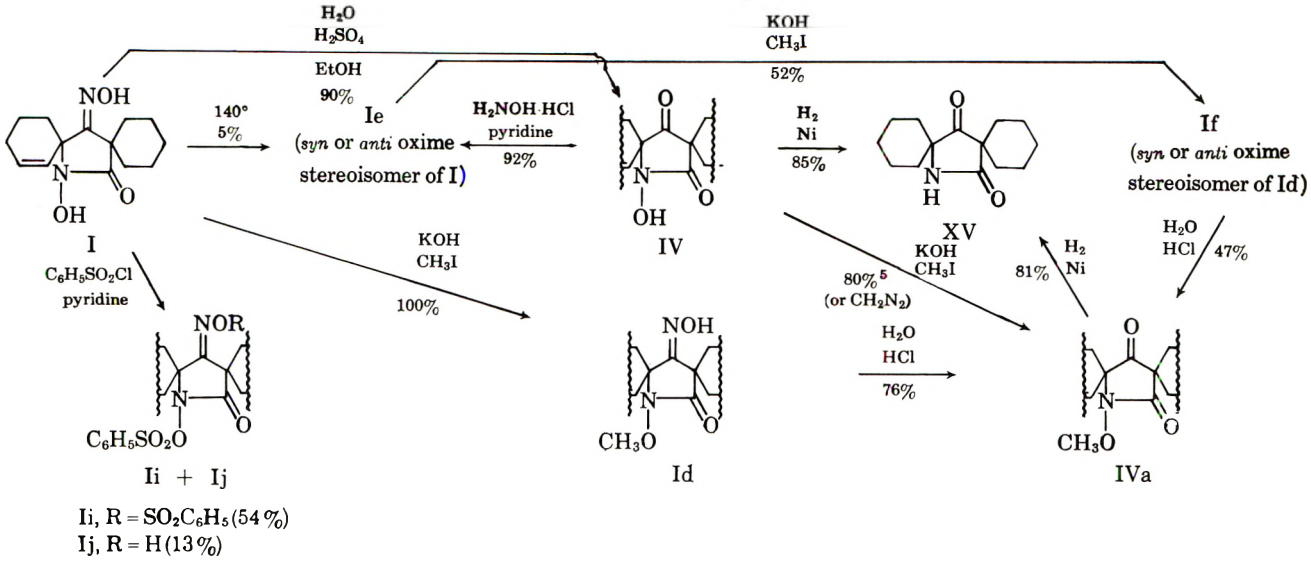
(10) H. O. House and R. W. Magin, *J. Org. Chem.*, **28**, 647 (1963).

(11) Wherever appropriate, our usage of roman numeral designations corresponds to that of Nightingale (ref. 5). With new compounds numbers have been chosen so as not to conflict with numbers already assigned to members of the Nightingale series.

(12) Experiment performed by Vernon D. Parker, University of Minnesota, 1959.

(13) Experiment performed by Allan M. Huffman, University of Minnesota, 1959.

CHART I



employed.[5] Hydrogenolysis of the acidic hydroxyl group in IV and of the related methoxyl group in IVa under mild conditions is incompatible with the formulation of IV as a carboxylic acid and of IVa as its methyl ester. The acidity and ease of hydrogenolysis of the hydroxyl group, and the position of the amide carbonyl band in the infrared spectra, are all consistent, however, with the structure in I and IV of a five-membered ring N-hydroxylactam, which was resistant to hydrolysis. The remaining nitrogen and oxygen atom of I must then be a part of the oximino group which undergoes hydrolysis. The position of the oxime band in the infrared spectrum of I, and of the ketone carbonyl band in IV, in the methyl derivative IVa, and in the product XV, all indicate that a ketoxime group in I has undergone hydrolysis to a five-membered ring ketone.[14]

Catalytic hydrogenation of I over Raney nickel at two atmospheres and room temperature gave the primary aminolactam $C_{14}H_{24}N_2O$ (II) under much milder conditions than in the high-pressure hydrogenation previously employed.[5] This leaves a single oxygen atom in a five-membered ring amide carbonyl group. In some hydrogenation experiments, reduction stopped partially or completely before saturation of the carbon nitrogen double bond, giving as the product, the iminolactam $C_{14}H_{22}N_2O$ (IIg). Hydrogenation of IIg over fresh Raney nickel catalyst completed the reduction to II. Hydrolysis of IIg with aqueous ethanolic sulfuric acid gave the ketolactam XV. Oxidation of II with chromium trioxide in acetic acid, or with aqueous potassium permanganate, also gave XV. Conversely, XV was converted to II by oximation (to XVc, $C_{14}H_{22}N_2O_2$) and subsequent catalytic hydrogenation over Raney nickel at two atmospheres pressure.

An attempt to reconvert the ketone IV to the oxime I by oximation gave, instead, Ie ($C_{14}H_{20}N_2O_3$) the *syn* or *anti* stereoisomer of I. Partial isomerization of I to Ie was effected by refluxing I in xylene. A small amount of Ie, along with I, was also isolated from an incomplete oxidation of I with aqueous potassium permanganate at 95°. That the isomerization of I to Ie during the oxidation is not due solely to action of the alkali generated is suggested by the quantitative recovery of I from an aqueous 10% potassium hydroxide solution at room temperature. Catalytic hydrogenation of Ie under the conditions used for I also gave the aminolactam II, proving that I and Ie have the same atomic skeleton. Methylation of I and Ie with potassium hydroxide and methyl iodide gave isomeric methyl derivatives $C_{15}H_{22}N_2O_3$, Id and If, respectively. Both isomers were hydrolyzed with aqueous hydrochloric acid to IVa, proving that the difference between Id and If (and, thus, of their parent compounds I and Ie) must lie in the stereochemistry of the oxime group. Completion of the series of transformations described previously confirmed that I is an unsaturated, five-membered ring ketoxime N-hydroxylactam.

The Atomic Skeleton: by Degradation.—For degradation, the primary aminolactam II, obtained by low-pressure hydrogenation of I, was chosen as a subject for study. Dimethylation of II with formaldehyde and formic acid[15] gave an N,N-dimethylaminolactam $C_{16}H_{28}N_2O$ (IId), which was converted to its methiodide IIe ($C_{17}H_{31}N_2OI$). Application of the Hofmann degradation to IIe produced a displacement product, $C_{14}H_{23}NO_2$ (XIV), in which the trimethylammonium group has been replaced by a hydroxyl group. The product XIV had been obtained previously by Nightingale, Reich, and Erickson[5] by high-pressure hydrogenation of the keto N-methoxylactam IVa. In the present work the same transformation has been effected *via* the sodium borohydride reduction of XV. Application of the Hofmann degradation to IIe in ethylene glycol also produced a displacement product, $C_{16}H_{27}NO_3$ (IIf), in which the trimethylammonium group has been replaced by a 2-hydroxyethoxyl group derived from ethylene glycol. The fact that application of the Hofmann degradation to IIe did not result in formation of an olefinic elimination product, but produced instead the displacement products XIV and

(14) In the infrared spectra of the ketolactams IV, IVa, and XV (as well as of M-IVa, IVc-e, IVg-j) the five-membered ring ketone carbonyl band at 1736–1767 cm.$^{-1}$ is of medium intensity, always much less intense than the strong lactam carbonyl band in the region of 1650–1701 cm.$^{-1}$. This marked intensity difference is reminiscent of that in anhydrides and imides, and led to the infrared evidence for the five-membered ring ketone carbonyl group being overlooked in the original work (ref. 5).

(15) H. T. Clarke, H. B. Gillespie, and S. Z. Weissbaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

CHART 2

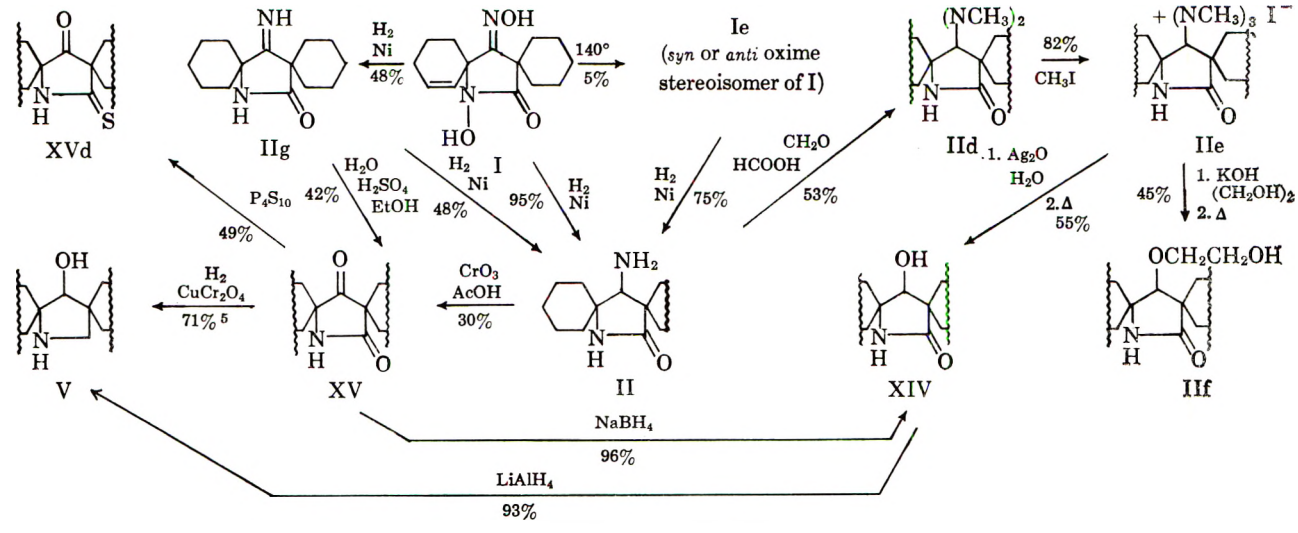
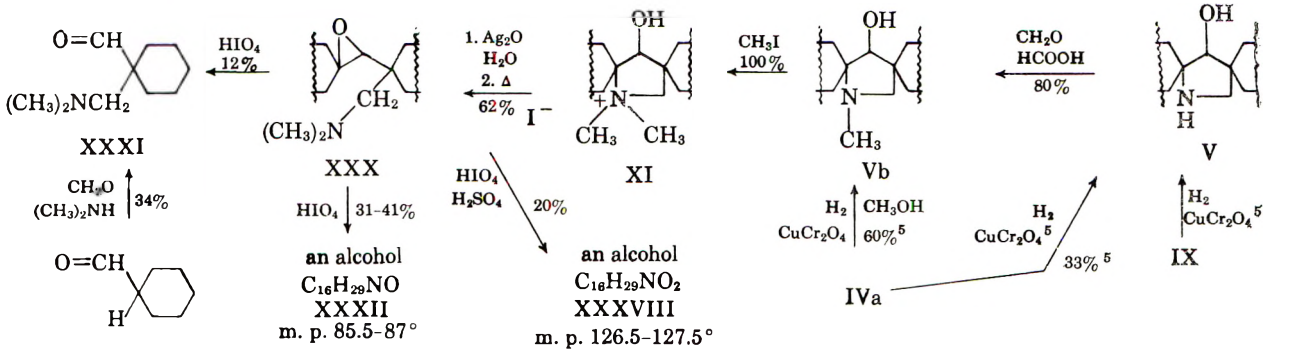


CHART 3



IIf, strongly suggests that the carbon bearing the trimethylammonium group in IIe (and, correspondingly, the carbon bearing the hydroxyl group of XIV and the amino group of II and IId) is attached to carbons bearing no hydrogens.

Attention was then turned to degradative procedures involving the second nitrogen of II, the nitrogen atom still present in the lactam group of XIV and XV. Lithium aluminum hydride reduction of XIV gave the hydroxyamine $C_{14}H_{25}NO$ (V), in which the lactam group has been reduced to an amino group. The product V had been obtained previously by Nightingale, Reich, and Erickson[5] by high-pressure hydrogenation of XV, of IVa, and of the unsaturated hydroxyamine $C_{14}H_{23}NO$ (IX). Methylation of V with formaldehyde and formic acid[15] gave the hydroxy-N-methylamine $C_{15}H_{27}NO$ (Vb). Compound Vb has been obtained previously by Nightingale, Reich, and Erickson[5] by high-pressure hydrogenation of IVa in methanol solution, in which the methanol apparently acted as a methylating agent. Conversion of Vb to its known methiodide $C_{16}H_{30}NOI$ (XI)[5] and application of the Hofmann degradation produced a colorless oil, the epoxy-N,N-dimethylamine $C_{16}H_{29}NO$ (XXX), an intramolecular displacement product. Formation of epoxides by intramolecular displacement under Hofmann degradation conditions is characteristic of β-hydroxyamine methiodides.[16a] Consequently, in XI and its precursors V and Vb, the hydroxyl group corresponding to the primary amino group of II must be beta to the amino nitrogen.

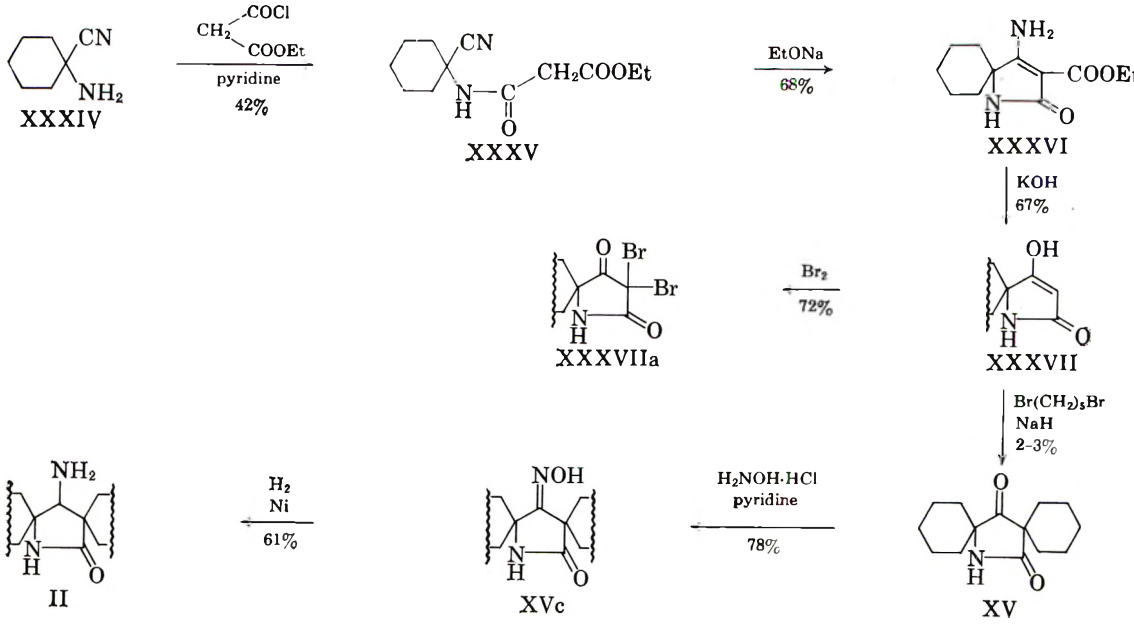
Reaction of the epoxide XXX with periodic acid gave, in addition to an isomeric rearrangement product XXXII and an oxidation product $C_{16}H_{29}NO_2$ (XXXVIII), the known cleavage product, 1-dimethylaminomethylcyclohexanecarboxaldehyde[17] (XXXI). The identity of the cleavage product XXXI was established by comparison of its methiodide (XXXIa) with the methiodide of a synthetic sample prepared by a Mannich reaction[17] from cyclohexanecarboxaldehyde. Isolation of XXXI as a cleavage product proves the structure of the epoxyamine (see XXX), if the plausible assumption is made that the remaining six carbons not present in the cleavage fragment XXXI were part of a second cyclohexane ring. Such an assumption is consistent with the already established fact that the hydroxyl carbon atom in XIV must be attached only to quaternary carbons. The second of the quaternary carbons, not present in XXXI, can, therefore, be part of a cyclohexane ring connected through a spiro junction to the hydroxyl carbon and the nitrogen atom of XIV.[18] This conclusion is strongly supported by the n.m.r. spectrum of the precursor XV, which contains a

(16) (a) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 352 (1960); (b) 380 (1960).

(17) C. Mannich, B. Lesser, and F. Silten, *Ber.*, **65**, 378 (1932).

(18) Cleavage of XXX with periodic acid would be expected to yield cyclohexanone as well as XXXI, but all attempts to isolate cyclohexanone from the reaction as its 2,4-dinitrophenylhydrazone were unsuccessful. When cyclohexanone was treated under the conditions of the periodic cleavage, an attempt to isolate it as its 2,4-dinitrophenylhydrazone was equally unsuccessful. It is assumed, therefore, that under the conditions of the periodic acid cleavage cyclohexanone undergoes iodination or further oxidation.

CHART 4

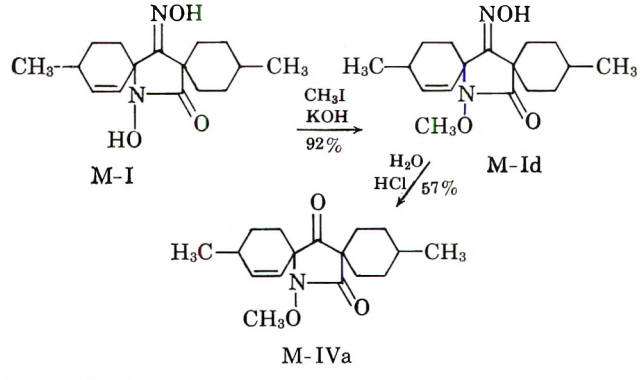


single large peak at 8.31 τ, attributed to the twenty essentially equivalent methylene protons of the two cyclohexane rings. Assignment of structure XXX to the epoxyamine permits assignment of structural formulas to its precursors XI, Vb, V, XIV, and the key compounds XV and II, as well as to their derivatives XVc, IId, IIe, IIf, and IIg (see Charts 2–4).

The Atomic Skeleton: by Synthesis of XV and II.—The ketolactam XV was chosen as the target compound for a synthetic proof of the atomic skeleton of I. The synthesis began with 1-aminocyclohexanecarbonitrile (XXXIV), obtained by action[19] of ammonia on cyclohexanone cyanohydrin. Acylation with ethyl chloroformylacetate in pyridine gave XXXV (see Chart 4) as an oil, which was cyclized with sodium ethoxide to XXXVI (isolated in dimorphic forms).[20] Alkaline hydrolysis of XXXVI, with accompanying decarboxylation, gave XXXVII.[20,21] Dialkylation of XXXVII with 1,5-dibromopentane, catalyzed by sodium hydride in N,N-dimethylformamide,[26] gave XV in 2–3% yield.[27,30] The synthetic sample of XV was identical, as shown by mixture melting point and infrared comparison, with the sample obtained by degradation of I. As XV has been converted to II, synthesis of XV also constitutes a total synthesis of II (Chart 4). Since II is derivable from I under mild conditions by low-pressure hydrogenation, it is assumed that the atomic skeleton proved to be present in II is also present in I.

Location of the Olefinic Double Bond: the Complete Structure of I.—Action of strong alkali at 200° on IV gave cyclohexanecarboxylic acid, also characterized as its amide. This acid cleavage of the β-ketolactam group (and subsequent hydrolysis of the N-hydroxyamide linkage) proves that the olefinic double bond is not present in the right-hand cyclohexane ring of IV and its precursor I (as written in Chart 1). To differentiate between the two possible positions in the left-hand ring, the n.m.r. spectrum of the more soluble derivative IVa was compared with that

CHART 5



(19) R. A. Jacobson, *J. Am. Chem. Soc.*, **67**, 1996 (1945).

(20) The Nujol infrared spectra of the two dimorphs of XXXVI show that they are in the enol form in the solid state. Likewise, XXXVII is largely but not entirely enolized in the solid state. This is shown by the presence in the Nujol infrared spectrum of a weak five-membered ring ketone carbonyl band at 1764 and a medium inflection at 1677 cm.$^{-1}$, attributed to an unconjugated lactam carbonyl band; and strong conjugated lactam and conjugated double bond bands at 1655 and 1595 cm.$^{-1}$, which are attributed to the enol form. The ultraviolet spectra of XXXVI and XXXVII show that the two compounds also exist as enols in ethanol solution; the ultraviolet spectra compare favorably with those of related enolic tetramic[22] and tetronic[23,24] acids. In agreement with its enolic structure, compound XXXVII reacts almost instantaneously with bromine in water to form a dibromide XXXVIIa, as does the related γ,γ-dimethyltetramic acid, 4-hydroxy-5,5-dimethyl-3-pyrrolin-2-one.[25]

(21) Synthesis of XXXVII has analogy in the synthesis of 3,4-dihydroxy-2-pentenoic acid γ-lactone (γ-methyltetronic acid), in which the 1-(ethoxycarbonyl)ethyl ethyl ester of malonic acid was cyclized by the action of sodium in toluene, with accompanying loss of the ethoxycarbonyl group: L. J. Haynes and A. H. Stanners, *J. Chem. Soc.*, 4103 (1956).

(22) R. N. Lacey, *ibid.*, 850 (1954).

(23) E. R. H. Jones and M. C. Whiting, *ibid.*, 1419 (1949).

(24) R. N. Lacey, *ibid.*, 832 (1954).

(25) S. Gabriel, *Ber.*, **47**, 3033 (1914).

(26) H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers, and R. W. DeNet, *J. Org. Chem.*, **26**, 644 (1961).

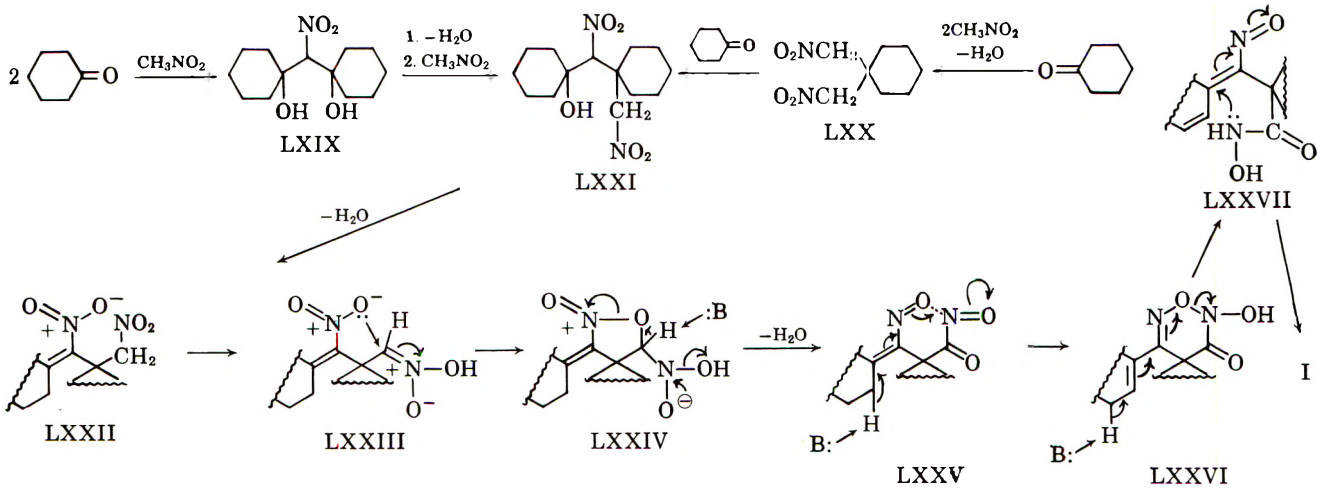
(27) The low solubility and high crystallinity permitted XV to be isolated without difficulty. The low yield may be due in part to intermolecular dialkylation, leading to polymerization, and in part to O-alkylation. O-Alkylation occurs to the exclusion of C-alkylation in methylation with dimethyl sulfate of a related ambident anion,[28] the sodium salt of 3,4-dihydroxy-2-methyl-2-butenoic acid γ-lactone (the sodium salt of α-methyltetronic acid).[29]

(28) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

(29) L. J. Haynes and J. R. Plimmer, *Quart. Rev.* (London), **14**, 309 (1960).

(30) Synthesis of spiro systems from enolate anions by dialkylation has also been accomplished previously: M. Mousseron, R. Jacquier, and H. Christol, *Bull. soc. chim. France*, 346 (1957).

CHART 6



of M-IVa, its 3,11-dimethyl homolog. For this purpose, M-I[31] (Chart 5), formed by condensation of nitromethane with 4-methylcyclohexanone was methylated (to M-Id) and then hydrolyzed to M-IVa, analogous to the conversion of I to Id to IVa.

The n.m.r. spectrum of M-IVa shows clearly that the double bond is not in the 10,11-position, as such a structure would contain only one vinyl proton, rather than the two seen to be present. The n.m.r. spectra of I, IVa, and M-IVa all contain two doublets (J = 9–10.7 c.p.s.), a simple one centered at 4.67–4.75 τ (C-9 olefinic proton, which has no adjacent aliphatic protons) and a more complex one centered at 3.84–4.01 τ (C-10 olefinic proton). The C-10 proton is coupled to two C-11 protons in I and IVa, accounting for the complexity of the doublet. With M-IVa, in which the C-10 proton is coupled to the single C-11 proton, each member of the C-10 proton doublet is itself a finely split doublet (J = 3.1 c.p.s.). The similarity of the vinyl proton region in the n.m.r. spectra of I, IVa, and M-IVa shows that the double bond is in the same position in all three compounds, and cannot have rearranged during the acid hydrolysis of I to IV, or during the alkaline methylation of IV to IVa. With location of the double bond in the 9,10-position, it is now possible to assign complete structural formulas to I, IVa, and M-IVa, and to their unsaturated derivatives, including Id, Ie, If, IV, IX, M-I, and M-Id (Charts 1, 5, 7). By analogy with the structure of I, it is assumed that similar structures may be assigned to the related condensation products of nitromethane with cyclopentanone,[5,7] cycloheptanone,[7] cyclooctanone,[7] and 3-[32] and 4-alkylsubstituted[5,7,32] cyclohexanones.

A Plausible Mechanism for Formation of Compound I.—Formation of I from nitromethane and cyclohexanone probably proceeds (Chart 6) through the key intermediate LXXI, which could be formed either (1) *via* the 2:1 condensation product LXX (which has been isolated from a reaction in which I was also formed[3]), or (2) *via* the 1:2 adduct LXIX. From LXXI there would follow a series of steps (possibly proceeding in the order LXXII–LXXVII shown[33]), involving intramolecular oxygen transfer, dehydration, and oxidation–reduction, culminating in a second key intermediate LXXVII, which could readily isomerize to I. Transformation of the nitromethyl group of LXXI to the hydroxamic acid group of LXXVII is seen to be an example of the Victor Meyer reaction, which usually occurs under strongly acidic conditions.[34,35]

Ancillary Degradative Experiments.—Reduction of IV with lithium aluminum hydride gave diastereoisomeric amino alcohols $C_{14}H_{23}NO$, IXa (isolated as dimorphic forms, m.p. 129–131° and 133–134°) and IXb (m.p. 150–152°), and a reduction intermediate $C_{14}H_{21}NO_2$, the nitrone IXc (Chart 7), analogous to the saturated derivative recently described by House and Magin.[16] Diastereoisomer IXa is assigned the structure in which the 7-hydroxyl group and the 9,10-double bond are attached *cis* to the central pyrrolidine ring (Chart 8). The n.m.r. spectrum of IXa differs from that of IXb in (1) the 0.18 τ relative deshielding in IXa of the two 9,10-double bond protons by the *cis* 7-hydroxyl group, (2) the 0.07 τ relative deshielding in IXb of the *cis* C–H proton (at 6.59 τ) of the secondary alcohol by the C-9 double bond proton, and (3) the difference in chemical shift in IXa between the two C-15 methylene protons, which gives rise to a 4-peak AB pattern (J = 11.3 c.p.s.) centered at 7.15 τ, while IXb gives only a single sharp peak at 7.15 τ. It is likely that IXc is stereochemically related to IXb, since with reduction under more vigorous conditions the yield of IXc decreased from 21 to 4% while that of IXb increased from 20 to 33%, but the yield of IXa changed only slightly, from 15 to 13%. Comparison of the infrared spectra shows that the reduction product IX,[5] m.p. 140–141°, of Nightingale and Reich[36] consisted predominantly of the less soluble diastereoisomer IXb.

Methylation of a crude mixture of diastereoisomers IX with formaldehyde and formic acid[15] gave a corresponding mixture of the methyl derivatives (IXg). The separate diastereoisomers IXa and IXb were methylated with methyl iodide to the corresponding methiodides IXe and IXd, both of which showed a marked tendency to crystallize as 2:1 complexes with

(31) Formerly designated as compound XXI (ref. 5); now compound M-I (ref. 7).

(32) D. V. Nightingale, F. B. Erickson, and J. M. Shackelford, *J. Org. Chem.*, **17**, 1005 (1952).

(33) We wish to thank a referee for suggesting the sequence LXXIII–LXXVI.

(34) H. B. Hass and E. F. Riley, *Chem. Rev.*, **32**, 373 (1943).

(35) W. E. Noland, *ibid.*, **55**, 137 (1955).

(36) Donald A. Reich, Ph.D. thesis (with Dorothy V. Nightingale), University of Missouri, June, 1956, p. 34; *Dissertation Abstr.*, **16**, 2313 (1956).

CHART 7

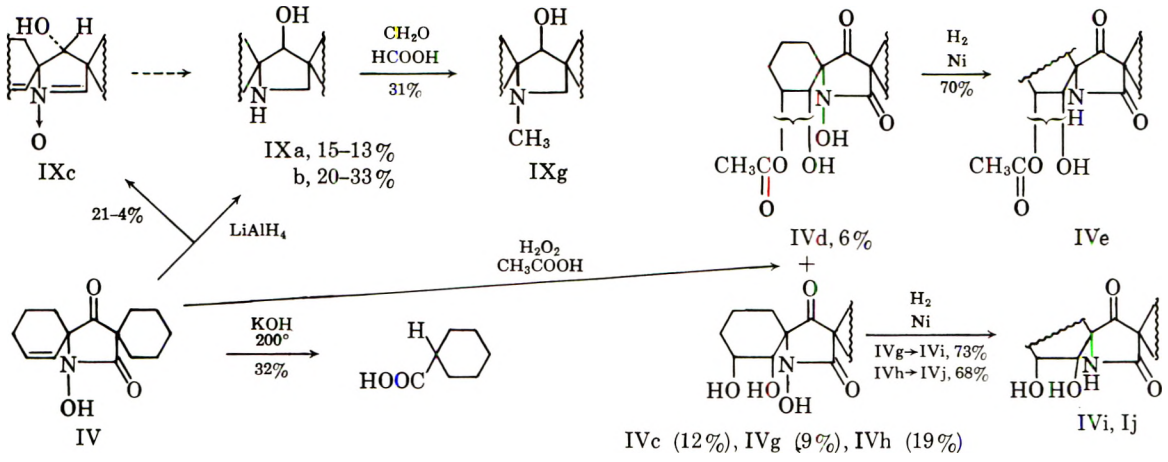
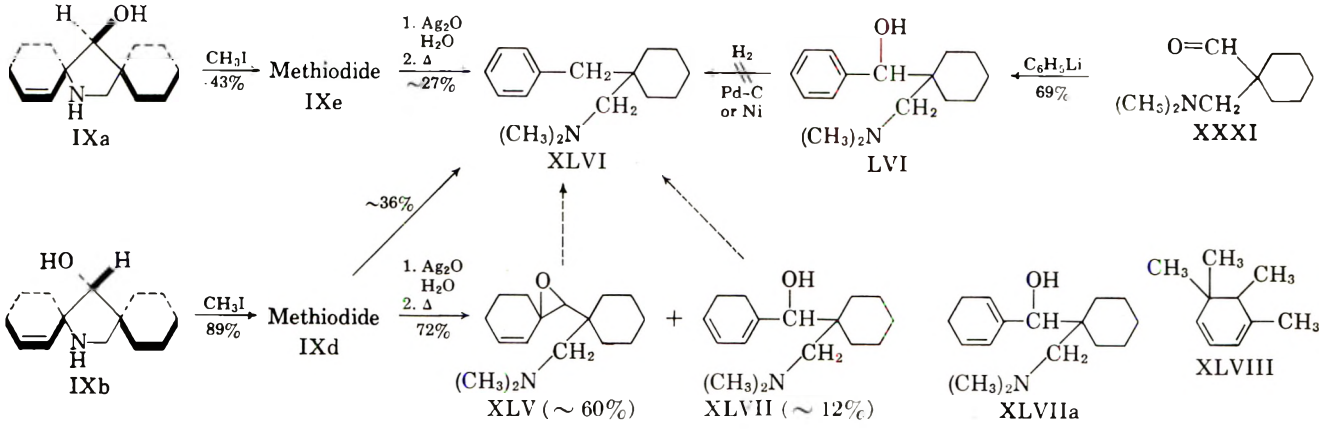


CHART 8



benzene from ethanol–benzene solution. Pyrolysis of the methohydroxide of IXd gave on one occasion a distillable oil $C_{16}H_{27}NO$, which, from the n.m.r. and infrared spectra, appears to consist largely of the epoxide XLV (Chart 8), with a small amount of the isomeric conjugated diene alcohol XLVII (or, less likely, the isomer XLVIIa). The ultraviolet spectrum of the oil, using α-pyronene (XLVIII) as a model,[37] indicates the presence of 16% conjugated diene. Pyrolysis on other occasions of the methohydroxides of IXd and IXe gave in the distillate impure oils, having aromatic ultraviolet spectra and identical infrared spectra. The oils, purified through the crystalline picrate (XLVIa), were shown to consist largely of the aromatized product $C_{16}H_{25}N$ (XLVI) assumed to result from pyrolytic dehydration of the intermediates XLV and XLVII. The aromatic ultraviolet spectrum of XLVI agrees well with those of toluene[38] and 1-(1-dimethylaminomethylcyclohexyl)-1-phenylmethanol (LVI), prepared by action of phenyllithium on 1-dimethylaminomethylcyclohexanecarboxaldehyde (XXXI). Attempts to provide an independent synthesis of XLVI by converting LVI to XLVI were unsuccessful; highly sterically hindered benzyl alcohols are reported to resist hydrogenolysis.[39]

Additional Derivatives.—Action of benzenesulfonyl chloride in pyridine on I gave both a monobenzenesulfonyl derivative $C_{20}H_{24}N_2O_5S$ (Ij), and a dibenzenesulfonyl derivative $C_{26}H_{28}N_2O_7$ (Ii) analogous to the diacetyl derivative Ia.[3,5] The monobenzenesulfonyl derivative is assigned the N-hydroxylactam benzenesulfonate structure (Ij in Chart 1) on the basis of the position of the hydroxyl band in the infrared spectrum, and the fact that it was recovered unchanged (76%) from attempted reaction with hydrochloric acid under conditions known to effect Beckmann rearrangement of oxime sulfonate esters.[40] Reaction of II with nitrous acid gave $C_{14}H_{20}N_2O_2$ (VII), which has a strong, conjugated ultraviolet spectrum, and OH or NH bands as well as an amide carbonyl band in the infrared spectrum. Fusion of XV with tetraphosphorus decasulfide gave a monothioamide $C_{11}H_{21}NOS$ (XVd, Chart 2), as shown by the five-membered ring ketone carbonyl band in the infrared spectrum.

Oxidation[41] of IV with peracetic acid has been reported[5] to yield a compound $C_{16}H_{23}NO_7$, m.p. 219–221°. Working with a larger ratio of hydrogen peroxide and acetic acid, we isolated instead a hydroxy acetate $C_{16}H_{23}NO_6$ (IVd, m.p. 242–246°) and three isomeric glycols $C_{14}H_{21}NO_5$ (Chart 7): IVc (m.p. 220–221°), IVg (m.p. 235–237°), and IVh (m.p. 240–243°, sublimes). As IVg and IVh were isolated after alkaline saponification, one of them may be derived from IVd; IVh was

(37) λ_{max} in isooctane: 263 mμ (log ε 3.76); R. T. O'Connor and L. A. Goldblatt, *Anal. Chem.*, **26**, 1726 (1954).

(38) (a) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949); (b) T. W. Campbell, S. Linden, S. Godshalk, and W. G. Young, *ibid.*, **69**, 880 (1947).

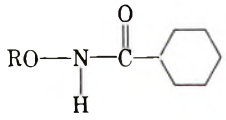
(39) W. H. Hartung and R. Simonoff, *Org. Reactions*, **7**, 268 (1953).

(40) L. G. Donaruma and W. Z. Heldt, *ibid.*, **11**, 1 (1960).

(41) We have found that ozonolysis of IV and IVa in ethyl acetate solution, followed by oxidation with hydrogen peroxide, gave oils which failed to crystallize.

most readily isolated as a sodium salt monohydrate (IVf). Oxidation of IV with performic acid gave, after saponification, IVg and IVh (as IVf). Formation of a total of three glycols implies that, unless double bond migration[42] or skeletal rearrangement has occurred, in addition to the expected two *trans* isomers, one of the *cis* forms was also obtained, a fact which can be rationalized in terms of anchimeric assistance by the neighboring N-hydroxyl group. Catalytic hydrogenation of IVd, IVg, and IVh over Raney nickel at two atmospheres and room temperature gave the hydrogenolysis products IVe, IVi, and IVj, containing one less oxygen atom, analogous to the conversion of IV to XV.

During the course of this work cyclohexanehydroxamic acid (LXXIX) and its methyl derivative (LXXX) were prepared for examination as model compounds.



LXXIX, R = H
LXXX, R = CH_3

Experimental

Melting points were determined on a calibrated Kofler micro hot stage. Where not specified, the drying agent used for organic solutions was anhydrous magnesium sulfate.

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 1 (I).—The procedure used was essentially that of Nightingale, Reich, and Erickson,[5] except that the reflux period was increased from 30 to 72 hr., and the catalyst, piperidine, was added occasionally during the reflux period. The product consisted of small white needles, m.p. 271–274° sublimes (29%), lit.[7] 24%; lit.[3] m.p. 270–271°, lit.[7] 273–274° dec. (sublimes); ν_{OH} 3180 m infl., 3080 m, 2650 m, (KBr), 3070 s, 2650 w (Nujol), $\nu_{C=N}$ 1690 m (KBr), 1693 m (Nujol), $\nu_{C=O,\ C=C}$ 1655 s, 1639 s (KBr), 1654 s, 1641 s (stronger) cm.$^{-1}$ (Nujol).[13] The n.m.r. spectrum of a saturated solution in N,N-dimethylformamide[43a] contains the most intense absorption (in τ; 1 τ = 56.44 c.p.s.) in the aliphatic methylene proton region as a complex with a major peak at 8.35 and a lesser peak at 8.13. In the vinyl proton region there is a doublet (4.78, and stronger peak at 4.61; J = 9.6 c.p.s.) centered at 4.70, and a more complex multiplet having its strongest peak at 4.01. In a 1:1 solution of chloroform-*d* and dimethyl sulfoxide-d_6[43b] (in τ; 1 τ = 100 c.p.s.) there is a central peak at 8.19, with side peaks at 8.39 and 7.89 (16.4 protons). The two vinyl protons appear as a doublet (4.77, and stronger peak at 4.68; J = 9 c.p.s.) centered at 4.73, and a more complex doublet (stronger peak at 3.96, and 3.87; J = 9 c.p.s.) centered at 3.94, and the two hydroxyl protons appear as sharp singlets at +0.56 and −0.67.

Anal.[13] Calcd. for $C_{14}H_{20}N_2O_3$ (264.32): C, 63.61; H, 7.63; N, 10.60. Found: C, 63.83; H, 7.71; N, 10.52.

Diacetyl Derivative of I: 14-Acetoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Acetyloxime (Ia).[3,12]—A solution of I (2.00 g., 0.00756 mole) in acetic anhydride (50 cc., 0.53 mole) was refluxed for 10 min., and the excess acetic anhydride was evaporated under aspirator pressure. The white residue was recrystallized from ethanol–water, yielding white crystals (2.15 g., 82%), m.p. 129–130°; lit.[3,5] m.p. 128–129°; ν_{OH} none, $\nu_{C=O,\ C=N}$ 1804 s and 1790 s (doublet), 1733 s, $\nu_{C=C}$ 1655 mw cm.$^{-1}$ (Nujol).

Anal.[13] Calcd. for $C_{18}H_{24}N_2O_5$ (348.39): C, 62.05; H, 6.94; N, 8.04. Found: C, 62.28; H, 7.08; N, 8.03.

Benzenesulfonyl Derivatives of I.—Action of benzenesulfonyl chloride (10 cc., 0.079 mole) on I (2.00 g., 0.00756 mole) in refluxing pyridine (100 cc.) gave a mixture of benzenesulfonyl derivatives as a brown oil, which was dissolved in 1:1 benzene–methylene chloride (8 cc.) and chromatographed on alumina. Elution with benzene removed a clear yellow oil which quickly solidified to a white solid (Ii, 2.22 g., 54%), m.p. 125–127°. Elution with methylene chloride removed an orange crystalline solid (Ij, 0.41 g., 13%), m.p. 190°.

Two recrystallizations of Ii from ethanol–water yielded **14-benzenesulfonyloxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-benzenesulfonyloxime (Ii, dibenzenesulfonyl derivative of I)** as a granular white solid, m.p. 124–125°; ν_{OH} none, $\nu_{C=O}$ 1745 m, ν_{OSO_2} 1381 s, 1195 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{26}H_{28}N_2O_7S_2$ (544.63): C, 57.33; H, 5.18; N, 5.14; S, 11.78. Found: C, 57.35; H, 5.19; N, 4.80; S, 12.14.

Four recrystallizations of Ij from methanol–water yielded **14-benzenesulfonyloxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-oxime (Ij, monobenzenesulfonyl derivative of I)** as white prisms, m.p. 184–187° dec.; ν_{OH} 3290 m, $\nu_{C=O}$ 1727 s, $\nu_{C=N}$ 1647 m, ν_{OSO_2} 1389 s, 1190 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{20}H_{24}N_2O_5S$ (404.47): C, 59.39; H, 5.98; N, 6.93; S, 7.93. Found: C, 59.74; H, 5.90; N, 6.79; S, 8.39.

Methyl Derivative of I: 14-Methoxy-14-azadispiro[5.1.5.2]-pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 1 (Id).—Methyl iodide (28 g., 0.197 mole) was added to a solution of I (37.0 g., 0.140 mole) and potassium hydroxide (9.25 g., 0.165 mole) in methanol (350 cc.), and the resulting solution refluxed for 2.5 hr. The solution was then concentrated by distilling methanol (~150 cc.), and diluted with boiling water (350 cc.). Fine white needles (39.3 g., 100%), m.p. 183–185°, crystallized. Two recrystallizations from methanol–water yielded fine white needles, m.p. 185–186°; ν_{OH} 3210 ms, 3060 m, $\nu_{C=N,\ C=O}$ 1689 s, $\nu_{C=C}$ 1647 ms cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$ (278.34): C, 64.72; H, 7.97; N, 10.07. Found: C, 64.67; H, 7.98; N, 10.22.

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 2 (Ie). (A) **From Oximation of IV.**—A solution of IV (6.07 g., 0.0244 mole) and hydroxylamine hydrochloride (4.0 g., 0.057 mole) in pyridine (25 cc.) and absolute ethanol (25 cc.) was refluxed for 36 hr. At fourteen convenient intervals during the reflux period, one-fourteenth of each of the following was added: hydroxylamine hydrochloride (28.0 g., 0.403 mole), pyridine (140 cc.), and absolute ethanol (140 cc.). At the end of the reflux period, the solvents were evaporated in a stream of air. The residual mushy solid was extracted successively with water and chloroform, leaving behind nearly pure crystalline solid (5.93 g., 92%). Recrystallization from ethyl acetate–light petroleum ether (b.p. 60–68°) yielded fine needles, m.p. 262–264°, having an infrared spectrum different from that of I; ν_{OH} 3360–2360 ms (very broad), $\nu_{C=N}$ 1696s, $\nu_{C=O}$ 1673s, $\nu_{C=C}$ 1655 ms infl. cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{20}N_2O_3$ (264.32): C, 63.61; H, 7.63; N, 10.60. Found: C, 63.57; H, 7.58; N, 10.44.

(B) **From Partial Thermal Isomerization of I in Xylene.**—A mixture of I (2.0 g.) and xylene (80 cc.) was refluxed for 72 hr., but remained heterogeneous throughout the period. Then the hot mixture was quickly filtered, removing unchanged I (1.53 g., 76%), m.p. 276–278°, identified by its infrared spectrum (Nujol). Upon being cooled overnight, the filtrate deposited a mixture of I and Ie (0.11 g., 5%), m.p. 250–256° dec., the presence of Ie being shown in particular by the shape of the carbonyl band, and of the doublet in the 950–900-cm.$^{-1}$ region.

(C) **From Partial Thermal Isomerization of I in Xylene in the Presence of Chloranil.**—A mixture of I (3.0 g.), chloranil (5.6 g.), and xylene (150 cc.) was refluxed for 13 hr., and then filtered while hot. The filtrate deposited a dark brown solid (1.17 g.) after a time. This solid was dissolved in aqueous potassium hydroxide and the mixture filtered to remove an insoluble black tar. The filtrate was treated with charcoal, and then acidified, causing precipitation of a light tan powder (1.13 g., 38%), m.p. 260–262° (sublimes above 200°), having an infrared spectrum (Nujol) indicating it to be predominantly Ie. Fractional crystallization from ethyl acetate–light petroleum ether (b.p. 60–68°) separated unchanged I (0.34 g., 11% recovery) and Ie (0.14 g., 5%), as shown by their infrared spectra (Nujol). Recrystallization of the Ie from ethyl acetate–light petroleum ether yielded small white needles, m.p. 262–263° dec. (sublimes above 200°), having an infrared spectrum (Nujol) identical with that of the sample prepared by oximation of IV.

(42) Double bond migration in acetic acid is unlikely, because it did not occur during the hydrolysis of I to IV in aqueous ethanolic sulfuric acid.

(43) Spectrum determined (a) by George B. Bodem, University of Minnesota, August 5, 1959; (b) by LeRoy F. Johnson, Varian Associates, Palo Alto, Calif., November 27, 1962.

Anal. Found: C, 63.25; H, 7.79; N, 10.52.

Methyl Derivative of Ie: 14-Methoxy-14-azadispiro[5.1.5.2]-pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 2 (If).—Methylation of Ie (0.22 g., 0.00083 mole) essentially as described previously for methylation of I to obtain Id gave white crystals (0.12 g., 52%), m.p. 184–186° sublimes. Recrystallization from methanol–water yielded a white powder, m.p. 185–186°; ν_{OH} 3210 m, 3080 vw, $\nu_{C=N}$, $_{C=O}$ 1692 s, $\nu_{C=C}$ 1658 m cm.$^{-1}$ (Nujol). The infrared spectrum is different from that of Id.

Anal. Calcd. for $C_{15}H_{22}N_2O_3$ (278.34): C, 64.72; H, 7.97; N, 10.07. Found: C, 64.75; H, 8.05; N, 10.23.

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (IV).—The compound was prepared essentially according to the procedure of Nightingale, Reich, and Erickson,[5] except that the reflux period was decreased from 53 to 24 hr., and ethanol was added in order to decrease the solvent volume required. The crystalline product was dissolved in methylene chloride (in which any unchanged I is insoluble), and the solution was dried, treated with charcoal, and concentrated. Dilution with hot light petroleum ether (b.p. 60–68°) yielded white crystals (90%), m.p. 174–175°; lit.[5] 91%, m.p. 170–172°; ν_{OH} 3060 m, 2690 w (KBr), 3060 m, 2690 w, 3360–2200 m (very broad) in Nujol, 3040 m, 2660 w (halocarbon oil), $\nu_{C=O}$ 1755 ms, 1676 s (KBr), 1752 m, 1676 s (Nujol), 1750 ms, 1675 s (halocarbon oil), $\nu_{C=C}$ 1648 ms (KBr), 1646 m (Nujol), 1645 ms cm.$^{-1}$ (halocarbon oil).[13]

Anal.[13] Calcd. for $C_{14}H_{19}NO_3$ (249.30): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.67; H, 7.75; N, 5.71; neut. equiv., 232, 242.

14-Methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (IVa). (A) From Methylation of IV with Potassium Hydroxide and Methyl Iodide.—The preparation of IVa in 80% yield by methylation of IV with potassium hydroxide and methyl iodide has been described by Nightingale, Reich, and Erickson.[5] These authors report that IVa, like I and IV, gives a purple color with ferric chloride solution. In our hands IVa, like Id, does not give a positive ferric chloride test. The positive reaction previously observed with IVa may possibly have been due to the presence of unmethylated IV as a contaminant in the IVa.

(B) From Methylation of IV with Diazomethane.[12]—An ethereal solution of diazomethane[44] was prepared by adding N-nitroso-N-methylurea (10.3 g., 0.100 mole) to a mixture of aqueous 50% potassium hydroxide solution (30 cc.) and ether (100 cc.) at 5°. The distilled ethereal solution of diazomethane was added to IV (2 g., 0.0080 mole), with swirling, until no more gas evolution was observed. The ether was evaporated and the grayish residue was recrystallized from methanol–water, yielding white platelets, m.p. 89–91°, having an infrared spectrum (Nujol) which showed the product to be IVa.

(C) From Acidic Hydrolysis of Id.—Compound Id (0.32 g., 0.00115 mole) was stirred with a solution of concentrated hydrochloric acid (14 cc.) in water (86 cc.) at 90° on a steam bath. After 3.5 hr. the mixture had become homogeneous, but stirring and heating were continued for 1 more hr. The solution was then allowed to cool to room temperature, and long needles crystallized (0.23 g., 76%), m.p. 86–90°, having an infrared spectrum (Nujol) identical with that of a sample prepared by methylation of IV as described in part A. Recrystallization from methanol–water yielded a sample, m.p. 92–94°, which gave no depression in m.m.p., 92–94°, with a sample of m.p. 95–96° prepared by methylation of IV as described in part A; lit.[5] m.p. 95–96°.

(D) From Acidic Hydrolysis of If.—Hydrolysis of If (0.20 g., 0.00072 mole) as described for Id in part C gave needles (0.09 g., 47%), m.p. 95–95.5°, which gave no depression in m.m.p., 95–96°, with a sample of m.p. 95–96° prepared by methylation of IV as described in part A.[5] The infrared spectra of the two samples (Nujol) were identical.

(E) Dimorphism of IVa.—Compound IVa was obtained in two dimorphic forms, both melting at 95–96°, but having different infrared spectra (Nujol). The spectrum of dimorph A is characterized by three sharp bands of relative intensity (going toward lower frequency) m, s, s around 735 cm.$^{-1}$, while dimorph B has sharp bands of relative intensity m, s, m in the same region.

Dimorph A, m.p. 95–96°, was obtained by crystallization from ethanol–water; $\nu_{C=O}$ 1751 ms, 1701 s; $\nu_{C=C}$ 1650 m cm.$^{-1}$ (Nujol).[12] The n.m.r. spectrum of a 10% solution in carbon tetrachloride contains the most intense absorption (in τ; 1 τ = 56.44 c.p.s.) in the aliphatic methylene proton region, as a complex with a major peak at 8.34 and lesser declining peaks at 8.06 and 7.88. There is a sharp peak at 6.15 (14-methoxyl group protons). The two vinyl protons appear as a doublet (4.76, and stronger peak at 4.58; J = 10.1 c.p.s.) centered at 4.67, and a more complex doublet (stronger peak at 3.94, and 3.75; J = 10.7 c.p.s.) centered at 3.85.

Anal.[12] Calcd. for $C_{15}H_{21}NO_3$ (263.33): C, 68.41; H, 8.04; N, 5.32. Found: C, 68.63; H, 8.01; N, 5.35.

Dimorph A, upon recovery from refluxing in acetic anhydride, crystallized as dimorph B, m.p. 95–96°,[12] thus constituting dimorph interconversion in one direction. Recrystallization of IVa, prepared as described in part A,[5] from methanol–water also gave dimorph B, m.p. 95–96°[13]; $\nu_{C=O}$ 1748 m, 1698 s (Nujol, halocarbon oil); $\nu_{C=C}$ 1643 mw cm.$^{-1}$ (Nujol, halocarbon oil).

Anal. Found: C, 68.39; H, 8.03; N, 5.43.

7-Amino-14-azadispiro[5.1.5.2]pentadecan-15-one (II). (A) From Low-Pressure Hydrogenation of I.—Compound I (8.58 g., 0.0324 mole) in ethanol (250 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature. Compound I was not completely soluble in the original solution, but dissolved completely as the hydrogenation proceeded. Hydrogen uptake ceased after 43 hr. of shaking, when the pressure drop corresponded to 123% of the calculated amount, but shaking was continued for an additional 24 hr. The catalyst was filtered off and washed with hot 95% ethanol. The combined ethanol filtrate and washings were concentrated and diluted with hot water, causing crystallization of clusters of fine white needles (7.3 g., 95%), m.p. 193–195°. Several recrystallizations from ethanol–water yielded fine white needles, m.p. 195–196°, lit.[5] m.p. 192–193°; ν_{NH} 3160 m, 3040 mw (KBr), 3150 m, 3050 mw (Nujol), 3130 and 3030 mw (halocarbon oil), $\nu_{C=O}$ 1676 s (KBr), 1678 s (Nujol), 1673 s cm.$^{-1}$ (halocarbon oil).

Anal. Calcd. for $C_{14}H_{24}N_2O$ (236.35): C, 71.14; H, 10.24; N, 11.85. Found: C, 70.95; H, 10.18; N, 11.89.

(B) From Low-Pressure Hydrogenation of Ie.—Compound Ie (1.00 g., 0.00378 mole) dissolved in absolute ethanol (200 cc.) was hydrogenated as described in part A. After filtration of the catalyst, the combined ethanol filtrate and washings were evaporated to dryness, and the residue was dissolved in chloroform. The chloroform solution was extracted with dilute hydrochloric acid, and the acid extract made alkaline with sodium hydroxide. Extraction with chloroform, drying, and evaporation of the chloroform gave a hard white solid (0.67 g., 75%), m.p. 193–195°, which gave no depression in m.m.p., 193–195°, with a sample of m.p. 193–196° prepared from I. The infrared spectra (Nujol) of the two samples were identical.

(C) From Low-Pressure Hydrogenation of IIg.—Compound IIg (0.45 g., 0.00192 mole) was hydrogenated and the reaction mixture worked up essentially as described in part B, giving white needles (0.22 g., 48%), m.p. 193–196°, having an infrared spectrum (Nujol) identical with that of a sample prepared from I.

(D) From Low-Pressure Hydrogenation of XVc.—Compound XVc (1.00 g., 0.00400 mole) in ethanol (200 cc.) was hydrogenated and the reaction mixture worked up as described in part B, giving a hard white solid (0.58 g., 61%), m.p. 192–194°. Recrystallization from ethanol–water gave a sample which gave no depression in m.m.p., 193–196°, with a sample of m.p. 193–196° prepared from I. The infrared spectra (Nujol) of the two samples were identical.

Monoacetyl Derivative of II: 7-Acetamido-14-azadispiro-[5.1.5.2]pentadecan-15-one (IIa).[5,45]—A solution of II (0.90 g., 0.00380 mole) in acetic anhydride (25 cc., 0.265 mole) was heated on a steam bath for 20 min. The solution was then poured into ice water and the precipitated white solid filtered off. One recrystallization from ethanol–water yielded colorless plates (0.58 g., 55%), m.p. 277–278°, lit.[5] m.p. 271–272°; ν_{NH} 3330 m, 3140 m, 3040 m, $\nu_{C=O}$ 1683 s, 1651 s cm.$^{-1}$ (Nujol).

Diacetyl Derivative of II: 7-Diacetylamino-14-azadispiro-[5.1.5.2]pentadecan-15-one.[5,45]—A solution of II (1.07 g., 0.00453 mole) in acetic anhydride (25 cc., 0.265 mole) was refluxed for 3 hr. After the solution had cooled to room temperature and had been kept for 2 days, the white crystals, m.p. 226–227°, were filtered off. Addition of water to the filtrate caused separation of most of the product (total 0.50 g., 34%); lit.[5] m.p.

(44) (a) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 969–971; (b) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(45) Experiment first performed by Roger D. Johnson, National Science Foundation Undergraduate Research Participant, University of Minnesota, summer, 1959, with support from NSF Grant G-8179.

224.5–226°; ν_{NH} 3310 ms, 3100 mw, $\nu_{C=O}$ 1728 s, 1703 s, 1644 s cm.$^{-1}$ (Nujol).

Action of Nitrous Acid on II: Preparation of VII.—Sufficient hydrochloric acid was added to a mixture of II (3.00 g., 0.0127 mole) and water (375 cc.) to dissolve completely the solid. The pH was then adjusted to 4–5 by addition of aqueous potassium hydroxide solution. The solution was cooled in an ice bath and a cold solution of sodium nitrite (2.63 g., 0.0381 mole) in water (375 cc.) was added gradually. The solution was stirred at room temperature for 30 hr. and then filtered, giving a yellow solid (2.41 g.), having an infrared spectrum (Nujol) very similar to that of the analytical sample. Two crystallizations from methanol–water, and a final recrystallization from ethanol–water, yielded white crystals, m.p. 261–262° dec. (sealed capillary); λ_{max} mμ (log ε) in 95% ethanol: 225 (4.15), 277 (3.95); $\nu_{NH\ or\ OH}$ 3330 m, 3190 w, 3110 m, $\nu_{C=O}$ 1681 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{20}N_2O_2$ (248.32): C, 67.71; H, 8.12; N, 11.28. Found: C, 67.79; H, 8.30; N, 10.98.

Incomplete Hydrogenation of I: Preparation of 14-Azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-Imine (IIg).—Compound I (10.0 g., 0.0378 mole) in ethanol (250 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature. Hydrogen uptake ceased after 72 hr. of shaking, but the pressure drop corresponded to only 93% of the calculated amount. The hydrogenation solution, which contained a white precipitate, was heated to boiling to dissolve the precipitate. Then the catalyst was filtered off and the filtrate concentrated, diluted with hot water, and allowed to cool to room temperature. The resulting white crystalline precipitate (4.28 g., 48%), m.p. 214,° was recrystallized twice from ethanol–water, and then twice from methylene chloride–light petroleum ether (b.p. 60–68°), yielding white needles, m.p. 209–210° sublimes; ν_{NH} 3130 ms, 3040 m, $\nu_{C=O}$ 1698 s, $\nu_{C=N}$ 1661 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{22}N_2O$ (234.33): C, 71.75; H, 9.46; N, 11.96. Found: C, 71.75; H, 9.27; N, 11.32.[46]

14-Azadispiro[5.1.5.2]pentadecane-7,15-dione (XV). (A) From Low-Pressure Hydrogenation of IV.[45]—Compound IV (10.0 g., 0.0401 mole) in 95% ethanol (200 cc.) solution was hydrogenated over Raney nickel at 2 atm. and room temperature for 6 hr. The hydrogenation solution, which contained precipitated product, was heated to boiling to dissolve the precipitate. Then the catalyst was filtered off and washed with hot ethanol. Concentration and cooling of the combined filtrate and washings gave colorless needles (8.06 g., 85%), m.p. 238–239°. Three recrystallizations from ethanol–water yielded glistening white needles, m.p. 244–245°, lit.[5] m.p. 233–234°; ν_{NH} 3150 m, 3060 m, $\nu_{C=O}$ 1754 m, 1695 s cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 3% solution in deuteriochloroform contains a single, large peak at 8.31 ± 0.01 τ.

Anal. Calcd. for $C_{14}H_{21}NO_2$ (235.32): C, 71.45; H, 9.00; N, 5.95. Found: C, 71.60; H, 9.22; N, 5.91.

(B) From Low-Pressure Hydrogenation of IVa.—Compound IVa (0.18 g., 0.00068 mole) in methanol (100 cc.) solution was hydrogenated over Raney nickel at 2 atm. and room temperature for 42 hr. The mixture was then heated to 55° and the catalyst filtered off. The filtrate was concentrated to about 15 cc. and diluted with water, causing precipitation of a white solid (0.13 g., 81%) in two crops, m.p. 225–236° and 235–237°. The infrared spectrum (Nujol) is identical with that of a sample prepared from IV. Recrystallization of the white solid from ethanol–water gave a sample, m.p. 235–237°, which gave no depression in m.m.p., 241–243°, with a sample of m.p. 243–244° prepared from IV.

(C) From Oxidation of II with Chromium Trioxide.—Chromium trioxide (2.7 g., 0.027 mole) was stirred with glacial acetic acid (80 cc.). The resulting violet-brown solution was decanted from a small amount of undissolved residue and added over a period of 1 hr., with occasional warming on a steam bath, to a solution of II (2.0 g., 0.0085 mole) in glacial acetic acid (30 cc.). Then the resulting solution was diluted with water until it became cloudy, and cooled overnight. The resulting precipitate was crystallized from ethanol–water, giving a solid (0.60 g., 30%) in two crops, m.p. 238–240° and 230–237°. One recrystallization from ethanol–water gave a sample, m.p. 236–238°, which gave no depression in m.m.p., 236–238°, with a sample of m.p. 240–241° prepared from IV. The infrared spectra of the two samples (Nujol) were identical.

(46) The compound gave low and erratic nitrogen analyses.

Oxidation of II (2.0 g.) with refluxing aqueous potassium permanganate solution added in portions also gave XV (16%), along with unchanged II (36%).

(D) From Acidic Hydrolysis of IIg.—A mixture of IIg (1.00 g., 0.00427 mole) and a solution of concentrated sulfuric acid (10 cc.) in ethanol (20 cc.) and water (30 cc.) was refluxed for 20 hr. The mixture remained inhomogeneous throughout the reflux period. The hot mixture was filtered. After the filtrate had cooled, white needles precipitated (0.286 g.,), m.p. 235–237°. Additional solid (0.14 g.; total, 0.426 g., 42%) was obtained by recrystallization of the filtered solid from ethanol–water. The infrared spectrum (Nujol) is identical with that of a sample prepared from IV.

Oxime of XV: 14-Azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-Oxime (XVc).—Compound XV (3.0 g., 0.0128 mole) and hydroxylamine hydrochloride (2.0 g., 0.029 mole) in pyridine (15 cc.) and absolute ethanol (15 cc.) was refluxed for 37 hr. At seven convenient intervals during the reflux period, one seventh of each of the following was added: hydroxylamine hydrochloride (7.0 g., 0.101 mole), pyridine (35 cc.), and absolute ethanol (35 cc.). At the end of the reflux period the solvents were evaporated in a stream of air. The residual solid was extracted with water to dissolve salts, and the remaining solid was refluxed with 3 25-ml. portions of 90% ethanol to extract unchanged XV. The residue (2.50 g., 78%) was recrystallized twice from dioxane–ethanol–water, yielding a white powder, m.p. 320–322° uncorrected (sealed tube); ν_{OH} 3240 m infl., ν_{NH} 3140 m, 3050 m, $\nu_{C=O}$ 1698 s, $\nu_{C=N}$ 1667 ms cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{22}N_2O_2$ (250.33): C, 67.17; H, 8.86; N, 11.19. Found: C, 67.18; H, 8.90; N, 11.01.

Action of Tetraphosphorus Decasulfide on XV: 14-Azadispiro[5.1.5.2]pentadecan-7-one-15-thione (XVd).—Compound XV (0.50 g., 0.00212 mole) and tetraphosphorus decasulfide (0.75 g., 0.00169 mole) were fused over a small flame. Additional tetraphosphorus decasulfide (0.25 g., 0.00056 mole) was added and the fusion was repeated. After the fused mass had cooled, it was crushed and stirred with dilute hydrochloric acid. The undissolved solid was dissolved in ethanol, and the solution treated with charcoal and filtered. The filtrate deposited brownish needles (0.26 g., 49%), m.p. 240–250°. Three recrystallizations from absolute ethanol yielded colorless needles, m.p. 248–249°; ν_{NH} 3130 m, $\nu_{C=O}$ 1748 m, 1669 w, $\nu_{C=S}$ 1512 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NOS$ (251.38): C, 66.88; H, 8.42; N, 5.57. Found: C, 66.39; H, 8.06; N, 5.73.

7-Dimethylamino-14-azadispiro[5.1.5.2]pentadecan-15-one (IId).—For the purpose of methylation,[15] a solution of II (5.7 g., 0.0241 mole), aqueous 35% formaldehyde solution (14 cc., 0.16 mole), and aqueous 88% formic acid (14 cc., 0.33 mole) was refluxed for 15 hr. The solution was then concentrated by passing a stream of air over the heated solution. The residual white solid was dissolved in dilute hydrochloric acid and the acidic solution extracted with chloroform. The acidic aqueous layer was made alkaline with sodium hydroxide and extracted with chloroform. The extract was dried and evaporated to dryness. Recrystallization of the residual white solid from light petroleum ether (b.p. 60–68°) gave white crystals (3.4 g., 53%) in two crops, m.p. 152–156° and 150–153°. Four more recrystallizations from light petroleum ether yielded fine white needles, m.p. 156–158°; ν_{NH} 3150 m, 3050 w, $\nu_{C=O}$ 1684 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}N_2O$ (264.40): C, 72.68; H, 10.67; N, 10.60. Found: C, 72.59; H, 10.47; N, 10.04, 10.21.

Methiodide (IIe) of IId.—Compound IId (7.1 g., 0.0268 mole) and methyl iodide (23 g., 0.162 mole) in benzene (100 cc.) were refluxed for 44 hr. During this time additional methyl iodide (46 g., 0.324 mole) was added in two portions. Filtration of the reaction mixture gave IIe (4.51 g.), m.p. 222–228°. Filtration of the reaction mixture after additional reflux periods of 48 and 24 hr. gave more IIe (4.43 g.; total, 8.94 g., 82%), m.p. 216–226°. Three recrystallizations from absolute ethanol yielded white needles, m.p. 226–230°; ν_{NH} 3270 m, $\nu_{C=O}$ 1695 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{31}N_2OI$ (406.35): C, 50.24; H, 7.69; N, 6.89. Found: C, 50.28; H, 7.68; N, 6.21, 6.28.

7-Hydroxy-14-azadispiro[5.1.5.2]pentadecan-15-one (XIV). (A) From the Displacement Reaction of Hydroxyl Ion on IIe.—Silver oxide, freshly prepared[16b] from silver nitrate (2.17 g., 0.128 mole) and sodium hydroxide (0.55 g., 0.137 mole), was added to a solution of IIe (2.17 g., 0.00534 mole) in aqueous 10% methanol (100 cc.). The resulting mixture was stirred for 1.5 hr. and

filtered. The filtrate was concentrated by distillation of the water under reduced pressure, taking precautions to avoid excessive foaming, and then was distilled under reduced pressure to dryness at about 100°. The brown residue was extracted with a mixture of water and chloroform. The chloroform layer was washed with dilute hydrochloric acid, dried, and evaporated, giving a clear, colorless, viscous oil, which soon crystallized. Recrystallization from chloroform–light petroleum ether (b.p. 60–68°) gave a white solid (0.70 g., 55%), m.p. 200–208°. One more recrystallization of part of the crystals from chloroform–light petroleum ether yielded XIV as white prisms, m.p. 215–217° sublimes, lit.[5,47] m.p. 190–191°; ν_{OH} 3360 m, ν_{NH} 3170 m, 3050 vvw infl., $\nu_{C=O}$ 1686 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{23}NO_2$ (237.33): C, 70.85; H, 9.77; N, 5.90. Found: C, 70.69; H, 9.69; N, 5.84.

The major portion of the original crystals, m.p. 200–208°, and an oily residue isolated from the mother liquors were combined, dissolved in chloroform, and chromatographed on alumina. Elution with 1:1 benzene–chloroform removed an unidentified white semisolid (0.06 g.). Elution with chloroform removed a solid which, after recrystallization from chloroform–light petroleum ether (b.p. 60–68°), gave XIV (0.43 g., 34%), m.p. 218–219° sublimes.

(B) **From Reduction of XV with Sodium Borohydride.**—A solution of sodium borohydride (3.0 g., 0.0079 mole) in absolute ethanol (100 cc.) was added dropwise to a suspension of XV (37.9 g., 0.161 mole) in absolute ethanol (1000 cc.). The mixture was refluxed for 0.5 hr. and then additional sodium borohydride (3.0 g., 0.0079 mole) in absolute ethanol (50 cc.) was added, and refluxing was continued for an additional 1.75 hr. The volume of the solution was reduced by distillation to about 300 cc. and hot 2% hydrochloric acid (275 cc.) was added. The resulting solution was decanted from a gummy white solid, and the solution concentrated and cooled, giving white prisms (36.5 g., 96%), m.p. 216–217° sublimes,[47] which gave no depression in m.m.p., 216–218° sublimes, with a sample of m.p. 215–217° sublimes, prepared from IIe (part A). The infrared spectra (Nujol) of the two samples were identical, and were also identical with the infrared spectrum of a sample[48] of m.p. 198–199° sublimes[47] prepared by hydrogenation of IVa at 177 atm. and 230° over copper chromium oxide.[5]

7-(2-Hydroxyethoxy)-14-azadispiro[5.1.5.2]pentadecan-15-one (IIf).—In an attempt to effect a Hofmann elimination reaction,[49] a solution of IIe (4.25 g., 0.0104 mole) and potassium hydroxide (42.0 g., 0.75 mole) in ethylene glycol (225 cc.) and water (42 cc.) was refluxed for 6 hr. The solution was cooled, diluted with water, and extracted with ether. The ether extract was washed with dilute hydrochloric acid, dried, and evaporated, leaving a yellow oil which soon crystallized, giving a gray solid (1.31 g., 45%), m.p. 146–150°. Two recrystallizations from ethanol–water yielded fine white needles, m.p. 150–157°; ν_{OH} 3390 mw, ν_{NH} 3180 m, 3050 w, $\nu_{C=O}$ 1692 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{27}NO_3$ (281.38): C, 68.29; H, 9.67; N, 4.98. Found: C, 68.34; H, 9.76; N, 5.02.

7-Hydroxy-14-azadispiro[5.1.5.2]pentadecane (V).—A solution of XIV (36.5 g., 0.154 mole) in anhydrous tetrahydrofuran (500 cc.) was added dropwise to a suspension of lithium aluminum hydride (7.9 g., 0.208 mole) in ether (950 cc.), and then the mixture was refluxed, with stirring, for 26 hr. The excess lithium aluminum hydride was decomposed by addition of absolute ethanol, and then water (150 cc.) was added dropwise with vigorous stirring, causing formation of a heavy white precipitate. The ether–tetrahydrofuran solution was decanted, and the residual precipitate was washed twice with ether. The combined decanted ether solution and washings were extracted with dilute hydrochloric acid, and the acidic extract was made alkaline with sodium hydroxide and cooled. The resulting white crystalline precipitate was filtered and dried, giving a solid (32.0 g., 93%), m.p. 169–170°. Sublimation at 130° (4 mm.) yielded fine white needles, m.p. 166.5–167.5°, lit.[5,47] m.p. 162–163°; $\nu_{NH,\,OH}$ 3390 s, 3320 w (3500–3200, very broad) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{25}NO$ (223.35): C, 75.28; H, 11.28; N, 6.27. Found: C, 75.01; H, 11.25; N, 6.36.

7-Hydroxy-14-methyl-4-azadispiro[5.1.5.2]pentadecane (Vb).—For the purpose of methylation,[15] a mixture of V (32.0 g., 0.144 mole), aqueous 35% formaldehyde, and aqueous 88% formic acid was stirred at 90° for 17 hr. Concentrated hydrochloric acid (30 cc.) was added, and the solution was concentrated by distillation until the residue became viscous. The residue was then dissolved in water and washed with ether. The water layer was made alkaline with sodium hydroxide and kept for several hr., with occasional stirring, during which time an oil separated. The mixture was extracted with light petroleum ether (b.p. 60–68°), and the extract dried and evaporated, leaving a clear oil. The oil was dissolved in an equal volume of light petroleum ether (b.p. 30–60°), and solution cooled for several hours in a freezer, causing crystallization of a hard white solid (27.6 g., 80%), m.p. 75–78°, lit.[5] m.p. 79–81°; ν_{OH} 3150 s, 2680 w cm.$^{-1}$ (Nujol).

Methiodide (XI) of Vb.—Compound XI has been prepared previously in unstated yield in absolute ethanol solution.[5] In the present work, the use of ether as solvent resulted in precipitation of the product in quantitative yield. A solution of Vb (10.0 g., 0.0422 mole) and methyl iodide (11.5 g., 0.081 mole) in ether (40 cc.) was kept at room temperature for 12 hr. A white solid began to precipitate soon after the addition of methyl iodide. After 12 hr., additional methyl iodide (4.6 g., 0.032 mole) in ether (20 cc.) was added, and the mixture was kept at room temperature for 2 days more. The precipitate was then filtered off, being obtained as a white microcrystalline solid (16.4 g., 102%), m.p. 190–195°, lit.[5] m.p. 186–187°; ν_{OH} 3290 s cm.$^{-1}$ (Nujol).

2-(1-Dimethylaminocyclohexyl)-1-oxaspiro[2.5]octane (XXX).—Silver oxide, freshly prepared[16a] from silver nitrate (16.6 g., 0.098 mole) and sodium hydroxide (4.2 g., 0.105 mole), was added to a solution of XI (16.4 g., 0.0433 mole) in aqueous 43% methanol (280 cc.). The resulting mixture was stirred vigorously for 3 hr. and then filtered. The filtrate was concentrated by distilling off the solvents at aspirator pressure. In order to prevent foaming, the filtrate was added gradually to the distilling flask from a pressure equalized dropping funnel at a rate such that only a small volume of solution was present in the distilling flask at any time. When the concentrate became viscous, the aspirator was replaced by a vacuum pump. As the pyrolysis proceeded, a colorless, slightly viscous liquid distilled (7.30 g., 67%). Redistillation yielded a sample (6.70 g., 62%), b.p. 135–140° (0.5 mm.), $n^{25}D$ 1.4939; ν_{OH} none, $\nu_{C=O}$ none, on the liquid.

Anal. Calcd. for $C_{16}H_{29}NO$ (251.40): C, 76.44; H, 11.63; N, 5.57. Found: C, 76.47, 76.46; H, 11.61, 11.83; N, 6.53, 6.40, 5.54.

Picrate (XXXa) of XXX.—During an unsuccessful attempt to prepare the N-oxide of XXX, a solution of XXX (0.50 g., 0.00199 mole) and aqueous 30% hydrogen peroxide (2.0 cc.) in methanol (6 cc.) was kept at room temperature for 20 hr. Then platinum black was added to decompose the peroxide, and the mixture was kept for an additional 10 hr. A saturated solution (10 cc.) of picric acid in ethanol was added, causing formation of a yellow precipitate (0.80 g., 82%), m.p. 176–180°. Two recrystallizations from absolute ethanol yielded yellow plates, m.p. 178–180°.

Anal. Calcd. for $C_{22}H_{32}N_4O_8$ (480.51): C, 54.99; H, 6.71; N, 11.66. Found: C, 55.33; H, 6.44; N, 11.58.

Methiodide (XXXc) of XXX.—A solution of XXX (4.0 g., 0.0159 mole) and methyl iodide (4.6 g., 0.0324 mole) in ether (10 cc.) and light petroleum ether (b.p. 60–68°, 10 cc.) was stirred at room temperature overnight. More methyl iodide (4.6 g., 0.0324 mole) was added and the solution was refluxed for 24 hr. and kept at room temperature for an additional 24 hr. Filtration removed a white solid (4.82 g., 77%) in two crops, m.p. 161–165° and 163–165°. As attempted recrystallization from ethanol–ethyl acetate produced decomposition, the crude product was vacuum dried for analysis, yielding a white powder, m.p. 163–165°; ν_{OH} 3450 mw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{32}NOI$ (393.35): C, 51.91; H, 8.20. Found: C, 51.34; H, 8.09.

1-Dimethylaminomethylcyclohexanecarboxaldehyde (XXXI). (A) **From XXX by Periodic Acid Cleavage.**—Sodium periodate (5.35 g., 0.0250 mole) was added to a solution of XXX (5.00 g., 0.0199 mole) in water (100 cc.) containing concentrated sulfuric acid (2.5 cc.), causing separation of an oil. The mixture was

(47) The variation in reported melting points, particularly of XIV, but also of other compounds in this series, including I, V, and XV, is attributed primarily to the extensive sublimation which occurs prior to the actual melting point.

(48) We are indebted to Prof. Dorothy V. Nightingale of the University of Missouri for sending us a sample of XIV, prepared as described in ref. 5.

(49) P. L. Julian, E. W. Meyer, and H. C. Printy, *J. Am. Chem. Soc.*, **70**, 887 (1948).

stirred at room temperature. At intervals, aliquots (2 cc. each) were removed and titrated for periodic acid with standard arsenite and iodine solutions.[50] The amount of sodium periodate consumed at the end of 2 hr. was 0.86 g. (0.00402 mole, 20% of theoretical), and at the end of 5 hr. a total of 1.23 g. (0.00575 mole, 29%) had been consumed. At this point 50 cc. of a solution prepared from sodium periodate (5.35 g., 0.0250 mole), concentrated sulfuric acid (2.5 cc.), and water (100 cc.) was added, and the mixture was stirred at room temperature for an additional 2 hr. The mixture was then made alkaline with sodium bicarbonate and extracted with ether. The ether layer was extracted with dilute hydrochloric acid. The ether layer was then concentrated and treated with 2,4-dinitrophenylhydrazine reagent, but the precipitate which formed melted over a wide range and could not be purified by recrystallization (see under XXXVIII).

The dilute hydrochloric acid layer was made alkaline with sodium hydroxide, and extracted with ether. The ether was distilled and the residue vacuum distilled. The first fraction of the distillate was **1-dimethylaminomethylcyclohexanecarboxaldehyde (XXXI)** (0.38 g., 12%), b.p. 75–80° (2 mm.), $n^{30}D$ 1.4655, having an infrared spectrum on the oil identical, except for a band at 1687 m cm.$^{-1}$, with that of the sample prepared from cyclohexanecarboxaldehyde. The second fraction of the distillate consisted primarily of an **alcohol $C_{16}H_{29}NO$ (XXXII)** (1.57 g., 31%), b.p. 160° (2 mm.), $n^{25}D$ 1.5119; ν_{OH} 3210 mw (very broad), $\nu_{C=O}$ 1722 mw cm.$^{-1}$ on the liquid. The infrared spectrum, including the carbonyl band at 1722 mw cm.$^{-1}$, indicates that the sample was contaminated with XXXI. See subsequent discussion for preparation of the methiodide (XXXIIa) from this sample of XXXII.

(B) From Cyclohexanecarboxaldehyde.—Essentially by the general procedure of Mannich, Lesser, and Silten,[17] a mixture of cyclohexanecarboxaldehyde (Columbia Organic Chemicals Co., Inc., Columbia, S. C.; 15.0 g., 0.134 mole), *sym*-trioxane (5.4 g., 0.18 mole as CH_2O), dimethylamine hydrochloride (10.0 g., 0.123 mole), and absolute ethanol (6 cc.) was refluxed for 1 hr. More *sym*-trioxane (5.4 g., 0.18 mole CH_2O) was added and the mixture was refluxed for an additional hour. The mixture was then diluted with ether, and the resulting two-phase system was extracted with dilute hydrochloric acid. The acid extract was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried, the ether was then distilled, and the residual liquid was distilled, yielding a colorless liquid (7.20 g., 34%), b.p. 90° (7 mm.), $n^{25}D$ 1.4659; lit.[17] b.p. 102–104° (17 mm.); $\nu_{C=O}$ 1719 s cm.$^{-1}$ on the liquid.

Methiodide of XXXI: (1-Formylcyclohexyl)methyltrimethylammonium Iodide (XXXIa). (A) From XXXI Obtained from XXX by Periodic Acid Cleavage.—Methyl iodide (4.60 g., 0.0324 mole) was added to a solution of XXXI (0.29 g., 0.00182 mole) in ether (9 cc.). A white microcrystalline solid (0.338 g., 60%), m.p. 231–233°, was filtered off. This solid had an infrared spectrum (Nujol) identical with that of the sample prepared from XXXI obtained from cyclohexanecarboxaldehyde. Recrystallization from absolute ethanol–benzene yielded glistening white plates, m.p. 236–237°, having an infrared spectrum (Nujol) identical with that of the unrecrystallized product.

(B) From XXXI Obtained from Cyclohexanecarboxaldehyde.—According to the procedure described in part A, XXXI (1.00 g., 0.00628 mole), obtained from cyclohexanecarboxaldehyde, gave a white microcrystalline solid (1.01 g., 52%), m.p. 227–232°. Two recrystallizations from absolute ethanol–benzene yielded glistening white plates, m.p. 239–240°, lit.[17] m.p. 223°; $\nu_{C=O}$ 1725 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{11}H_{22}NOI$ (311.21): C, 42.45; H, 7.13; N, 4.50. Found: C, 42.67; H, 7.06; N, 4.57.

Alcohol $C_{16}H_{29}NO$ (XXXII) and Its Methiodide (XXXIIa). (A) From Attempted Deoxygenation[51] of XXX with Acetic Acid in the Presence of Sodium Iodide and Zinc Dust.—A solution of sodium iodide (2.1 g., 0.0140 mole), sodium acetate (0.7 g.), and water (0.4 cc.) in acetic acid (5 cc.) was cooled in an ice bath and zinc dust (2.1 g., 0.032 g.-atom) was added. Compound XXX (1.00 g., 0.00398 mole) was added dropwise, with stirring, over a period of about 10 min., and then the mixture was allowed to warm to room temperature over a period of 2 hr. The mixture was filtered, diluted with water, and extracted with ether. The ether layer was washed with aqueous sodium carbonate solution and then extracted with dilute hydrochloric acid. The hydrochloric acid extract was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried and evaporated, giving a white solid (0.537 g., 54%), m.p. 62–85°. Two recrystallizations from light petroleum ether (b.p. 30–60°) in a Dry Ice–acetone bath yielded the **alcohol $C_{16}H_{29}NO$ (XXXII)**, m.p. 85.5–87°, having an infrared spectrum (Nujol) identical with that of the unrecrystallized sample; ν_{OH} 3150 m, $\nu_{C=O}$ none cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 12% solution in carbon tetrachloride contains (in $\tau \pm 0.01$ average deviation, with areas relative to 29 protons given in parentheses; 1 τ = 56.44 c.p.s.) a major peak at 8.55 (10.1 protons, attributed to an intact cyclohexane ring) and an associated peak at 8.39 (3.9), a peak at 7.99 (4.0), a sharp peak at 7.68 (6.7, the 6 protons of the two N-methyl groups), two sharp peaks (possibly the lower half of an AB pattern due to the N-methylene protons) at 7.36 (0.9) and 7.14 (0.4), a sharp peak at 6.22 (1.1 proton, the CH proton of a secondary alcohol), and the two broader singlets at 4.47 (1.0 vinyl proton) and 3.90 (1.0 vinyl proton).

Anal. Calcd. for $C_{16}H_{29}NO$ (251.40): C, 76.44; H, 11.63; N, 5.57. Found: C, 76.68; H, 11.63; N, 5.89.

Attempted hydrogenation of XXXII in methanol at 2 atm. over palladium on calcium carbonate or Raney nickel gave unchanged XXXII in recoveries of 31%, m.p. 83–87°, and 46%, respectively.[52]

Reaction of this sample of XXXII (0.10 g., 0.00040 mole) with excess methyl iodide in ether gave a white solid precipitate (0.048 g., 31%), m.p. 190–221°. Recrystallization from absolute ethanol–benzene yielded the **methiodide (XXXIIa) of XXXII** (0.018 g., 11%), m.p. 216–219°, having an infrared spectrum (Nujol) identical with that of the sample of XXXIIa prepared by methylation of XXXII obtained from attempted deoxygenation of XXX with triphenylphosphine (part B).

(B) From Attempted Deoxygenation[53] of XXX with Triphenylphosphine.—Compound XXX (1.00 g., 0.00398 mole) and triphenylphosphine (1.05 g., 0.00400 mole) were heated together at 200° for 40 min. Distillation of the product at 155–158° (1 mm.) gave an oil, which was dissolved in ether and extracted with dilute hydrochloric acid. The hydrochloric acid layer was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried and evaporated, giving the **alcohol $C_{16}H_{29}NO$ (XXXII)** as an impure oil, identified by comparison of its infrared spectrum (Nujol) with that of pure XXXII obtained from XXX as described in part A. Reaction of the oil with excess methyl iodide in ether gave a white microcrystalline solid precipitate (0.60 g., 38%), m.p. 218–223°. Two recrystallizations from absolute ethanol–benzene yielded the **methiodide (XXXIIa) of XXXII** as fluffy white needles, m.p. 220–222°; ν_{OH} 3330 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{32}NOI$ (393.35): C, 51.91; H, 8.20; N, 3.56. Found: C, 52.17; H, 8.36; N, 3.59.

(C) Methiodide (XXXIIa) of XXXII Obtained from XXX by Attempted Periodic Acid Cleavage.—Reaction of XXXII (1.57 g., 0.00625 mole), obtained in the form of an oil as the major product from the attempted periodic acid cleavage of XXX, with excess methyl iodide in ether soon caused precipitation of a small amount of XXXIa, having an infrared spectrum (Nujol) identical with that of the sample of XXXIa prepared from XXXI obtained from cyclohexanecarboxaldehyde. After filtration of the XXXIa, the filtrate was kept at room temperature for one day, and then the precipitated XXXIIa (1.02 g., 41%), m.p. 218–220°, was filtered off. Recrystallization from absolute ethanol–benzene yielded the **methiodide (XXXIIa) of XXXII** as white needles, m.p. 221–223°, having an infrared spectrum (Nujol) identical with that of the sample prepared from XXXII obtained from attempted deoxygenation of XXX with triphenylphosphine (part B).

Alcohol $C_{16}H_{29}NO_2$ (XXXVIII) from XXX by Periodic Acid Cleavage and Oxidation.—Sodium periodate (3.9 g., 0.0182 mole) was added to a solution of XXX (4.0 g., 0.0159 mole) in water (25 cc.) containing concentrated sulfuric acid (1.8 cc.), causing separation of an oil. The mixture was stirred at room

(50) E. L. Jackson, *Org. Reactions*, **2**, 361 (1944).

(51) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

(52) This failure of XXXII to hydrogenate and the apparent absence of olefinic unsaturation in the infrared spectrum led to the description of XXXII in our Communication[9] as a "saturated alcohol." The n.m.r. spectrum, as noted, shows the presence of two vinyl protons.

(53) G. Wittig and W. Haag, *Ber.*, **88**, 1654 (1955).

temperature for 9 hr. Aqueous 25% sulfuric acid (20 cc.) was then added, causing the oil to dissolve and the brown color of iodine to develop. The brown solution was then extracted rapidly with ether, and the dark ether extract was treated with aqueous sodium thiosulfate, causing partial decolorization. The acidic aqueous layer was made alkaline with sodium hydroxide, and the brown oil which separated was extracted with ether. Evaporation of the ether extract left a brown oil, which, after being kept and scratched, partially crystallized. The remaining oil was decanted from the crystals and distilled, giving 1-dimethylaminomethylcyclohexanecarboxaldehyde (**XXXI**), b.p. 70° (0.7 mm.), $n^{29}D$ 1.4732, having an infrared spectrum on the liquid identical with that of the sample prepared from cyclohexanecarboxaldehyde. The infrared spectrum (Nujol) of the methiodide (**XXXIa**), m.p. 224–227°, was also identical with that of the methiodide of XXXI prepared from cyclohexanecarboxaldehyde.

The crystallized fraction of the oil was dissolved in methylene chloride, treated with charcoal, and then recrystallized from ethanol–water, giving a sample (0.86 g., 20%), m.p. 120–126°. Two recrystallizations from ethanol–water yielded the **alcohol** $C_{16}H_{29}NO_2$ (**XXXVIII**) as glistening white platelets, m.p. 126.5–127.5°; ν_{OH} 3280 s, 2660 m (broad) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{16}H_{29}NO_2$ (267.40): C, 71.86; H, 10.93; N, 5.24. Found: C, 71.99; H, 10.86; N, 5.22.

The original ether extract, which had been treated with sodium thiosulfate, was evaporated. The residue was treated with 2,4-dinitrophenylhydrazine reagent, giving a reddish solid. Two recrystallizations from ethanol yielded a red powder, m.p. 213.5–216.5°; ν_{NH} 3320 mw, 3120 mw, $\nu_{C=N}$ 1629 s, $\nu_{C=C}$ 1600 s cm.$^{-1}$ (Nujol). This compound is not cyclohexanone 2,4-dinitrophenylhydrazone (lit.[54] m.p. 160.5–161.5°).

Anal. Found: C, 39.35; H, 3.09.

When cyclohexanone was treated under the conditions of the periodic acid cleavage, followed by treatment with 2,4-dinitrophenylhydrazine reagent, cyclohexanone 2,4-dinitrophenylhydrazone was still not isolated. Instead, a red compound was isolated, having an infrared spectrum (Nujol) almost identical with that of the 2,4-dinitrophenylhydrazone isolated from the periodic acid cleavage of XXX. Thus, it was not possible to establish that cyclohexanone is a product of the periodic acid cleavage of XXX.

1-Aminocyclohexanecarbonitrile (**XXXIV**).—This compound, previously prepared by other methods,[55–57] was prepared[19] by passing ammonia through cyclohexanone cyanohydrin[58] ($n^{23}D$ 1.4635, m.p. 30–33°; 100 g., 0.798 mole) for 6 hr., with cooling in an ice bath during the initial exothermic stage of the reaction. At the end of the 6 hr., the reaction flask was stoppered and kept at room temperature for 15 hr., after which ammonia was passed through the solution for 5 hr. more. Then nitrogen was passed through the solution for 3 hr. to remove excess ammonia. The residual oil was dissolved in benzene (in later runs, ether was used to facilitate subsequent isolation of solvent free XXXV) and the solution extracted with water. The benzene layer was dried and the benzene evaporated, leaving a yellowish orange oil (61 g., 61%); ν_{NH} 3560 m infl., 3370 ms, 3320 ms, 2660 w, 1614 ms, $\nu_{C=N}$ 2230 w, $\nu_{C=O}$ 1706 m cm.$^{-1}$ on the liquid. As the compound is reported to be unstable towards heat and distillation,[57] further purification was not attempted.

1-(2-Ethoxycarbonylacetamido)cyclohexanecarbonitrile (**XXXV**).—Ethyl chloroformylacetate[59,60] (29.8 g., 0.198 mole) was added dropwise, with stirring, over a period of 1 hr. to a solution of 1-aminocyclohexanecarbonitrile (prepared as described previously from 45.0 g., 0.359 mole, of cyclohexanone cyanohydrin) in anhydrous pyridine (100 cc.) and benzene (200 cc.). The resulting mixture of orange solution and white precipitate was stirred at room temperature for 24 hr. and then washed successively with 10% hydrochloric acid and aqueous sodium bicarbonate solution. The benzene layer was dried and evaporated, leaving an orange oil (21.7 g., 42% from 1-aminocyclohexanecarbonitrile). The oil was chromatographed on alumina and eluted with benzene, yielding a yellow oil, $n^{24}D$ 1.4839; ν_{NH} 3320 ms, $\nu_{C=N}$ 2230 w, $\nu_{C=O}$ 1736 s, 1667 s cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{12}H_{18}N_2O_3$ (238.28): C, 60.48; H, 7.61; N, 11.76. Found: C, 59.87; H, 7.69; N, 11.01.

4-Amino-3-ethoxycarbonyl-1-azaspiro[4.5]dec-3-en-2-one (**XXXVI**).—A solution of sodium ethoxide prepared from sodium (0.37 g., 0.0161 g.-atom) in absolute ethanol (5 cc.) was added to a solution of XXXV (2.75 g., 0.0116 mole) in absolute ethanol (5 cc.). The resulting solution was refluxed for 3 hr., and then a solution of concentrated hydrochloric acid (1.6 cc.) in hot water (10 cc.) was added. Dimorph A (1.88 g., 68%) crystallized in two crops, m.p. 263–265° dec. and 267–269° dec. Recrystallization from ethanol yielded **dimorph B** as a granular white solid, m.p. 269–273° dec., having an infrared spectrum (Nujol) different from that of dimorph A; λ_{max} mμ (log ϵ) in 95% ethanol: 220 (4.27), 269 (4.12); ν_{NH} 3400 mw, 3330 m, 3040 m, 1580 ms, $\nu_{C=O}$ 1702 s, 1660 s, $\nu_{C=C}$ 1628 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$ (238.28): C, 60.48; H, 7.61; N, 11.76. Found: C, 60.68; H, 7.65; N, 11.84.

Dimorph B was reconverted to Dimorph A by dissolving Dimorph B in chloroform and allowing the solution to evaporate slowly to dryness. The residue had an infrared spectrum (Nujol) identical, except for a band at 1724 mw cm.$^{-1}$ in the former, with that of Dimorph A obtained by recrystallizing the sample from chloroform. By recrystallization from chloroform **dimorph A** was obtained as a white powder, m.p. 267–270° dec.; λ_{max} mμ (log ϵ) in 95% ethanol: 220 (4.25), 269 (4.11); ν_{NH} 3370 m, 3170 ms, 1552 ms, $\nu_{C=O}$ 1675 s, 1659 s, $\nu_{C=C}$ 1623 cm.$^{-1}$ (Nujol).

Anal. Found: C, 60.40; H, 7.28.

4-Hydroxy-1-azaspiro[4.5]dec-3-en-2-one (**XXXVII**).—Compound XXXVI (8.3 g., 0.0348 mole) was dissolved in a solution of potassium hydroxide (8.0 g., 0.143 mole) in water, and the resulting solution was refluxed for 1 hr. Concentrated hydrochloric acid was added until the solution became just acidic. Cooling caused precipitation of a white powder (3.9 g., 67%), m.p. 220–222°. Recrystallization from hot water yielded a white powder, m.p. 219–220°; λ_{max} mμ (log ϵ) in 95% ethanol: 261 (3.78); ν_{NH} 3180 m, ν_{OH} 3500–2160 mw (very broad), $\nu_{C=O}$ 1764 w, 1677 m (infl.), 1655 s, $\nu_{C=C}$ 1595 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_{13}NO_2$ (167.20): C, 64.65; H, 7.84; N, 8.38. Found: C, 64.72; H, 8.01; N, 8.35.

Dibromo Derivative of XXXVII: 3,3-Dibromo-1-azaspiro[4.5]decane-2,4-dione (**XXXVIIa**).—A solution of XXXVII (0.040 g., 0.000239 mole) in ethanol (2 cc.) was diluted with hot water (20 cc.), and bromine (1 drop) was added to the warm solution, causing a white precipitate to form almost instantaneously. Filtration gave a white powder (0.056 g., 72%), m.p. 243–248° dec. (sublimes). Three recrystallizations from methanol yielded small white prisms, m.p. 246–250° dec. (sublimes); ν_{NH} 3160 m, 3060 m, $\nu_{C=O}$ 1778 m, 1707 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_{11}NO_2Br_2$ (325.02): C, 33.26; H, 3.41; N, 4.31. Found: C, 33.07; H, 3.54; N, 4.26.

Synthesis of 14-Azadispiro[5.1.5.2]pentadecane-7,15-dione (**XV**).—A solution of XXXVII (2.55 g., 0.0152 mole) in freshly distilled N,N-dimethylformamide (100 cc.) was added dropwise to a suspension of solid sodium hydride (0.74 g., 0.0308 mole) in N,N-dimethylformamide[25] (100 cc.). Then the resulting solution was stirred until hydrogen evolution became very slow (about 1 hr.). The solution was then transferred to a dropping funnel. This solution and a solution of 1,5-dibromopentane (3.90 g., 0.0170 mole) in N,N-dimethylformamide (50 cc.) were then dropped into a flask maintained at 110° at rates such that the two reagents were always present in nearly equivalent amounts. The addition was complete in 10 hr., and the solution was then refluxed for 12 hr. The solvent was removed under reduced pressure, leaving a semisolid orange residue. The residue was partitioned between dilute aqueous potassium hydroxide solution and chloroform. The orange chloroform solution was then washed with dilute hydrochloric acid, dried, and the chloroform evaporated, leaving an oil. The oil was redissolved in chloroform (30 cc.) and hot light petroleum ether (b.p. 60–68°) was added. A brown oil separated rapidly. The supernatant liquid was decanted from the oil after about 15 min., and was allowed to evaporate. The residual orange-white solid, m.p.

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150–200°, was dissolved in ethanol (7 cc.), hot water (7 cc.) was added, and the solution was filtered quickly. Upon cooling of the solution, fine white needles (0.123 g., 3%), m.p. 233–241°, separated. The infrared spectrum (Nujol) of the white needles was identical with that of a sample of XV prepared by hydrogenation of IV. In another similar experiment, XV, m.p. 236–239°, was isolated in 2% yield. The infrared spectrum (Nujol) of this sample was also identical with that of the sample of XV, m.p. 236–238°, prepared by hydrogenation of IV, and there was no depression in m.m.p., 236–239°.[47]

In contrast to the successful reactions catalyzed by sodium hydride, an attempt to synthesize XV by catalyzing the condensation of XXXVII with 1,5-dibromopentane with potassium *t*-butoxide in refluxing solutions of benzene and N,N-dimethylformamide was unsuccessful. The only crystalline solid isolated was unchanged XXXVII, in 42% recovery, having an infrared spectrum (Nujol) identical with that of the starting material.

Cyclohexanecarboxylic Acid from Acid Cleavage of IV. (A) Under Wolff–Kishner Conditions.—A solution of IV (8.00 g., 0.0321 mole), potassium hydroxide (8.4 g., 0.150 mole), and hydrazine (95%, 25 cc.) in diethylene glycol (150 cc.) was refluxed for 8 hr. The condenser was then removed and the vapors allowed to escape until the temperature of the boiling solution reached 195°. Refluxing was then resumed for an additional 10 hr. The hot solution was poured into hot water (500 cc.) and acidified. After being kept at room temperature for several hours, the acidic solution was extracted with chloroform. The chloroform extract was dried and evaporated, leaving an oil. The oil was distilled, giving a colorless liquid (0.38 g., 9%), b.p. 81–83° (0.9 mm.), m.p. 28°; lit.[61,62] m.p. 27–29°, lit.[63,64] 29–30°. The infrared spectrum was identical with that of authentic cyclohexanecarboxylic acid.

(B) With Potassium Hydroxide in Diethylene Glycol.—A solution of IV (10.0 g., 0.0401 mole) and potassium hydroxide (10.0 g., 0.178 mole) in water (10 cc.) and diethylene glycol (120 cc.) was refluxed for 2 hr. The condenser was then removed and the vapors allowed to escape until the temperature of the boiling solution reached 200°. Refluxing was then resumed for an additional 16 hr. The dark solution was poured into hot water, kept at room temperature for 24 hr., washed with chloroform, and acidified. The acidic solution was extracted with chloroform, and the chloroform extract dried and evaporated, leaving a dark oil. The oil was distilled, giving a colorless liquid (2.42 g.), b.p. 83–88° (0.7 mm.), estimated from the infrared spectrum to contain about 70% cyclohexanecarboxylic acid (32% yield). A portion of the liquid (2.2 g.) was refluxed with thionyl chloride (10 cc., 0.14 mole) for 30 min. The resulting brown solution was poured into ammonia, giving a precipitate (0.91 g.), m.p. 130–170° sublimes. Recrystallization from chloroform–light petroleum ether (b.p. 60–68°) yielded **cyclohexanecarboxamide** (0.34 g., 7% based on IV), m.p. 188–190° sublimes; lit.[62,63] m.p. 184°, lit.[61] 185–186°. The infrared spectrum (Nujol) was identical with that of an authentic sample.

14-Hydroxy-3,11-dimethyl-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime (M-I).[12,31]—Compound M-I was obtained in 5% yield, essentially according to the procedure of Nightingale, Reich, and Erickson,[5] as a white solid, m.p. 276–279°. Recrystallization from 95% ethanol yielded a white powder, m.p. 277–279°; reported 5%,[32] 9%,[5] 15–40%[7]; m.p. 257–258° dec.,[7,32] 272–274°[7]; ν_{OH} 3180 ms, 3060 ms, $\nu_{C=N}$ 1695 ms, $\nu_{C=O}$ 1653 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{24}N_2O_3$ (292.37): C, 65.72; H, 8.27; N, 9.58. Found: C, 65.72; H, 8.30; N, 9.56.

Methyl Derivative of M-I: 14-Methoxy-3,11-dimethyl-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime (M-Id).—Methyl iodide (11.4 g., 0.080 mole) was added to a solution of M-I (5.0 g., 0.0171 mole) and potassium hydroxide (0.95 g., 0.0169 mole) in methanol (50 cc.) and the resulting solution refluxed for 4 hr. About half of the methanol was then boiled off, and the concentrated solution was diluted to the point of cloudiness with hot water. Fluffy yellow crystals (4.82 g., 92%, m.p. 180–190°) separated. Two recrystallizations from methanol–water yielded fluffy white needles, m.p. 192–194°; ν_{OH} 3210 m, 3050 vw, $\nu_{C=O}$ 1692 s, $\nu_{C=C}$ 1645 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{26}N_2O_3$ (306.39): C, 66.64; H, 8.55; N, 9.14. Found: C, 66.90; H, 8.69; N, 9.22.

14-Methoxy-3,11-dimethyl-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (M-IVa).—A suspension of M-Id (2.0 g., 0.065 mole) in a solution of concentrated hydrochloric acid (10 cc.) in methanol (10 cc.) and water (20 cc.) was refluxed for 2 hr., but the mixture did not become homogeneous. Additional concentrated hydrochloric acid (10 cc.) in methanol (20 cc.) and water (10 cc.) was added and refluxing was continued for 12 more hr., during which time the mixture became homogeneous. Some of the methanol was then boiled off, and the concentrated solution was diluted with hot water and allowed to cool. Colorless needles (1.07 g., 57%), m.p. 121–124°, crystallized. Two recrystallizations from methanol–water yielded white needles, m.p. 128–129°; $\nu_{C=O}$ 1764 m, 1701 s, $\nu_{C=C}$ 1639 mw cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 10% solution in carbon tetrachloride contains (in $\tau \pm 0.01$ average deviation; 1 τ = 56.44 c.p.s.) a strong peak at 8.97 and a lesser peak at 8.86 (3- and 11-methyl group protons), a very strong peak at 8.39 with lesser declining peaks at 8.26, 8.05, and 7.86 (ring protons on saturated carbon atoms), and a sharp peak at 6.16 (14-methoxyl group protons). The two vinyl protons appear as a doublet (J = 10.2 c.p.s.) at 4.84 and 4.66 (stronger); and another doublet (J = 10.7 c.p.s.) at 4.10 (stronger) and 3.91, each member of which is itself a finely split doublet (J = 3.1 c.p.s.).

Anal. Calcd. for $C_{17}H_{25}NO_3$ (291.38): C, 70.07; H, 8.65; N, 4.81. Found: C, 70.11; H, 8.80; N, 4.88.

The Two Diastereoisomers (IXa and IXb) of 7-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene (IX) and the Nitrone, 7-Hydroxy-14-azadispiro[5.1.5.2]pentadeca-9,14-diene 14-Oxide (IXc).—A solution of IV (18.00 g., 0.0723 mole) in anhydrous tetrahydrofuran (120 cc.) was added dropwise to a stirred suspension of lithium aluminum hydride (7.5 g., 0.198 mole) in anhydrous ether (600 cc.). The resulting mixture was refluxed for 71 hr. Then the excess lithium aluminum hydride was destroyed by adding moist ether and absolute ethanol. Cold water (90 cc.) was then added to the vigorously stirred suspension. After 15 min. of stirring, the ether layer was decanted from the coagulated white precipitate, and the residual solid was washed with ether. The combined ether decantate and washings were extracted with dilute hydrochloric acid, and the acidic extract was made alkaline with sodium hydroxide. The alkaline solution was extracted with chloroform and the extract dried and evaporated, leaving an oil. The oil was dissolved in hot light petroleum ether (b.p. 60–68°) and, upon cooling, it crystallized as a white solid (14.2 g., 89%), m.p. 115–132°. The solid was dissolved in 1:1 benzene–chloroform and chromatographed on a column of alumina (4 × 30 cm.). Elution with solutions of 0–20% chloroform in benzene removed a white solid, in fractions melting from 128–135°. Crystallization from light petroleum ether gave **diastereoisomer IXa** (2.34 g., 15%), m.p. 129.5–131°. Three recrystallizations from light petroleum ether yielded glistening white plates, m.p. 129–131°; $\nu_{OH,NH}$ 3500–2300 s (very broad), 3100 m, $\nu_{C=C}$ 1639 vw cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 7% solution in deuteriochloroform contains (in $\tau \pm 0.02$ average deviation; 1 τ = 56.44 c.p.s.) a complex in the aliphatic methylene proton region, with the major peak at 8.57, a medium strong peak at 8.25, a sharp strong peak at 8.19, and a medium weak peak at 8.00; a 4 peak AB pattern at 7.38 w, 7.18 m, 7.11 m, and 6.91 w, centered at 7.15 (J = 11.3 c.p.s.); and a sharp medium peak at 6.66. The two vinyl protons appear as a doublet (J = 10.7 c.p.s.) at 4.46 and 4.27 (stronger), and a more complex doublet (J = 10.2 c.p.s.) at 4.09 (stronger) and 3.91.

Anal. Calcd. for $C_{14}H_{23}NO$ (221.33): C, 75.97; H, 10.47; N, 6.33. Found: C, 76.04; H, 10.31; N, 6.56.

In another run, crystallization of IXa from light petroleum ether (b.p. 60–68°) produced what is assumed to be a dimorphic form, m.p. 133–134°, having an infrared spectrum (Nujol) different from that of a previous sample; $\nu_{OH,NH}$ 3450–2370 s (very broad), 3110 s, $\nu_{C=C}$ 1639 vw cm.$^{-1}$ (Nujol). Attempts to prepare an analytical sample of the second form by recrystallization from light petroleum ether only reconverted it to the first form.

Elution with solutions of 25–33% chloroform in benzene removed fractions melting from 144–152°. Crystallization from light petroleum ether (b.p. 60–68°) gave **diastereoisomer IXb** (3.12 g., 20%), m.p. 150–152°. Three recrystallizations from light petroleum ether yielded colorless needles, m.p. 150–152°; $\nu_{OH,NH}$ 3400–2400 s (very broad), 3060 m, $\nu_{C=C}$ 1639 vw cm.$^{-1}$

(61) M. Markownikoff, *Ber.*, **25**, 3355 (1892).
(62) O. Aschan, *Ann.*, **271**, 231 (1892).
(63) J. S. Lumsden, *J. Chem. Soc.*, **87**, 90 (1905).
(64) G. S. Hiers with R. Adams, *J. Am. Chem. Soc.*, **48**, 2385 (1926).

(Nujol). The n.m.r. spectrum of a 9% solution in deuteriochloroform contains (in $\tau \pm 0.01$ average deviation; 1 τ = 56.44 c.p.s.) a complex with the major peak at 8.58, a medium peak at 8.30, a medium weak peak at 8.10, and a medium strong peak at 7.80; a sharp medium peak at 7.15; and a sharp weaker medium peak at 6.59. The two vinyl protons appear as a doublet (J = 9.6 c.p.s.) at 4.64 and 4.47 (strongest), and a more complex doublet (J = 11.9 c.p.s.) at 4.27 (stronger) and 4.06.

Anal. Found: C, 75.96; H, 10.37; N, 6.55.

Elution with chloroform removed a third product, which was crystallized from benzene, giving the nitrone **IXc** (3.60 g., 21%), m.p. 182–184°. Three recrystallizations from benzene yielded colorless prisms, m.p. 182.5–184.5°; λ_{max} mμ (log ϵ) in 95% ethanol: 241 (3.93); $\nu_{OH.NH}$ 3090 s, $\nu_{C=C}$ 1647 w, $\nu_{C=N+}$ 1577 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_2$ (235.32): C, 71.45; H, 9.00; N, 5.95. Found: C, 71.57; H, 8.99; N, 6.06.

In another run under slightly more severe conditions, in which 70% more lithium aluminum hydride, 275% more tetrahydrofuran, and only half as much ether were used, and the reflux time was extended by 21 hr., the yields were 13% of IXa, 33% of IXb, and 4% of the nitrone IXc.

Methyl Derivatives of IX: Mixture of the Two Diastereoisomers of 7-Hydroxy-14-methyl-14-azadispiro[5.1.5.2]pentadecane (IXg).—For the purpose of methylation,[15] a solution of the crude mixture of diastereoisomers of IX (15.0 g., 0.0679 mole) in aqueous 35% formaldehyde solution (50 cc., 0.58 mole) and aqueous 88% formic acid (50 cc., 1.16 mole) was refluxed for 20 hr. Dilute aqueous hydrochloric acid was added, and the solution was washed with chloroform and made alkaline with sodium hydroxide. The alkaline solution was extracted with light petroleum ether (b.p. 60–68°), and the extract dried and evaporated, leaving a brown oil. Distillation of the oil at 135–140° (0.3 mm.) gave a very viscous yellow oil, which soon solidified to a hard white solid (4.92 g., 31%), m.p. 70–73°. Three crystallizations from light petroleum ether (b.p. 60–68°) yielded white plates, m.p. 75–88°; ν_{OH} 3110 m, $\nu_{C=C}$ 1639 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{25}NO$ (235.36): C, 76.54; H, 10.71; N, 5.95. Found: C, 76.66; H, 10.68; N, 6.04.

Methiodide (IXe) of IXa.—Potassium hydroxide (1.0 g., 0.018 mole) was added to a solution of IXa (1.80 g., 0.00814 mole) and methyl iodide (9.1 g., 0.0642 mole) in absolute ethanol (50 cc.), and the solution was kept at room temperature for 48 hr. The precipitated potassium iodide was filtered off, and the filtrate was concentrated and diluted with hot benzene, causing precipitation of white needles (1.32 g., 43%), m.p. 214–216°. Two recrystallizations from absolute ethanol–benzene yielded white needles, m.p. 216–217°; ν_{OH} 3330 m, $\nu_{C=C}$ 1642 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}NOI$ (377.31): C, 50.93; H, 7.48; N, 3.71. Found: C, 51.12; H, 7.47; N, 3.69.

Partial evaporation of the benzene mother liquor gave a benzene complex as plates (0.80 g., 24%), m.p. 195–197°. Two recrystallizations from ethanol–benzene yielded plates, m.p. 189–193°; ν_{OH} 3250 s, $\nu_{C=C}$ 1642 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}NOI \cdot {}^1/_2C_6H_6$ (416.37): C, 54.80; H, 7.51; N, 3.36. Found: C, 54.82; H, 7.62; N, 3.31.

Heating the benzene complex (0.41 g., 0.0098 mole) to 190° expelled benzene and left a white powder (0.37 g., 100%), m.p 215–217°, having an infrared spectrum (Nujol) identical with that of the uncomplexed sample.

Methiodide (IXd) of IXb.—Methylation of IXb (2.50 g., 0.0113 mole) with methyl iodide and potassium carbonate in methanol, and work-up in a manner similar to that described previously for the preparation of IXe, gave a benzene complex as lustrous plates (4.20 g., 89%), m.p. 120–150°, resolidifying and then remelting at 228–230°. Two recrystallizations from absolute ethanol–benzene yielded lustrous plates, m.p. 144–147°, resolidifying and remelting at 225–227°; ν_{OH} 3220 ms, $\nu_{C=C}$ 1634 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}NOI \cdot {}^1/_2C_6H_6$ (416.37): C, 54.80; H, 7.51; N, 3.36. Found: C, 54.47; H, 7.48; N, 3.55.

Heating the benzene complex (0.20 g., 0.00048 mole) to 200° caused it to melt and resolidify to a hard, granular white solid (0.17 g., 94%), m.p. 225–227°; ν_{OH} 3230 s, $\nu_{C=C}$ 1645 vw cm.$^{-1}$ (Nujol). The infrared spectrum (Nujol) is different from that of the diastereoisomer IXe.

Anal. Calcd. for $C_{16}H_{28}NOI$ (377.31): C, 50.93; H, 7.48; N, 3.71. Found: C, 51.00; H, 7.47; N, 3.99.

Recrystallization of the uncomplexed sample from ethanol–benzene regenerated the benzene complex, as shown by its infrared spectrum (Nujol).

Mixture of 2-(1-Dimethylaminomethylcyclohexyl)-1-oxaspiro[2.5]oct-4-ene (XLV) and 1-(Cyclohexa-1,3-dienyl)-1-(1-dimethylaminomethylcyclohexyl)methanol (XLVII).—Silver oxide, freshly prepared[16b] from silver nitrate (8.4 g., 0.0494 mole) and sodium hydroxide (3.0 g., 0.075 mole), was added to a solution of IXd benzene complex (9.73 g., 0.0233 mole) in water (60 cc.). The mixture was filtered, and the filtrate concentrated at 30 mm. and then pyrolyzed by distillation at 1 mm., giving an oil (4.17 g., 72%), b.p. 142–145° (1 mm.). Redistillation gave a sample, b.p. 137–140° (0.6 mm.), $n^{25}D$ 1.5098; λ_{max} mμ (log ϵ) in 95% ethanol: 267 (2.97); ν_{OH} 3130 mw (broad), $\nu_{C=C}$ 1639 vw cm.$^{-1}$ on the liquid. The n.m.r. spectrum of a 7.5% solution in carbon tetrachloride contains (in $\tau \pm 0.01$ average deviations; 1 τ = 56.44 c.p.s.) complex aliphatic proton absorption, with the strongest peak at 8.59; and major peaks at 8.12 m, 7.78 s, 7.69 ms, 7.59 m, and 7.40 w; a very weak peak at 6.09 (CH proton of the secondary alcohol group in XLVII); olefinic peaks consisting of a sharp doublet (proton at the 4-position of the double bond in XLV; J = 11.3 c.p.s.) at 5.08 and 4.88 (stronger); and a larger more complex multiplet (proton at the 5-position of the double bond in XLV, plus the olefinic protons in XLVII) containing a pair of stronger peaks at 4.22 and 4.14 and a lesser peak at 3.94.

Anal. Calcd. for $C_{16}H_{27}NO$ (249.38): C, 77.06; H, 10.91; N, 5.62. Found: C, 77.10; H, 10.89; N, 5.64.

Picrate (XLVa) from the Mixture of XLV and XLVII.—A saturated solution of picric acid in 95% ethanol (5 cc.) was added to a solution of the mixture of XLV and XLVII (0.25 g., 0.00100 mole) in 95% ethanol (5 cc.), causing crystallization of glistening yellow plates (0.32 g., 67%), m.p. 214–215°. Recrystallization from 95% ethanol yielded yellow plates, m.p. 214–217°; ν_{OH} 3320 ms cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{22}H_{30}N_4O_8$ (478.49): C, 55.22; H, 6.32; N, 11.70. Found: C, 55.19; H, 6.34; N, 11.68.

1-Benzyl-1-dimethylaminomethylcyclohexane (XLVI). (A) **From IXd.**—Silver oxide, freshly prepared[15b] from silver nitrate (4.2 g., 0.0247 mole) and sodium hydroxide (1.5 g., 0.037 mole), was added to a slurry of IXd benzene complex (4.30 g., 0.0103 mole) in water (30 cc.), and the mixture was stirred for 3 hr. The mixture was filtered, and the filtrate concentrated at 30 mm. and then pyrolyzed by distillation at 1 mm. Redistillation of the colorless distillate gave a colorless oil (1.10 g., 46%), b.p. 129–135° (2 mm.), $n^{28}D$ 1.5161; λ_{max} mμ (log ϵ) in 95% ethanol: 255 infl. (2.97), 262 (3.01), 265 (3.01), 269 infl. (2.99); ν_{OH} 3340 m, $\nu_{C=O}$ 1715 m, $\nu_{C=C}$ 1592 w cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{16}H_{25}N$ (231.27): C, 83.05; H, 10.89; N, 6.05. Found: C, 80.28; H, 10.89; N, 6.74.

As the sample was obviously impure, it was purified through the picrate XLVIa, described subsequently. The picrate XLVIa (0.77 g., 0.00167 mole) was shaken with aqueous 5% sodium hydroxide solution until it dissolved. The resulting yellow orange solution was extracted with light petroleum ether (b.p. 60–68°) and with ether, and the combined extracts dried and evaporated, leaving a colorless oil. Distillation at a bath temperature of 180° (0.5 mm.) yielded a colorless oil (0.33 g., 86%), $n^{28}D$ 1.5235; λ_{max} mμ (log ϵ) in 95% ethanol: 248 infl. (2.29), 255 (2.30), 260 (2.33), 265 (2.23), 269 (2.13); $\nu_{C=C}$ 1590 m cm.$^{-1}$ on the liquid.

Anal. Found: C, 82.61; H, 10.94; N, 6.32.

(B) **From IXe.**—Silver oxide, freshly prepared[16b] from silver nitrate (2.1 g., 0.0123 mole) and sodium hydroxide (0.8 g., 0.020 mole), was added to a slurry of IXe (1.70 g., 0.00451 mole) in water (20 cc.), and the mixture was stirred for 1.5 hr. The mixture was filtered, and the filtrate concentrated and pyrolyzed as described in part A, giving as the distillate an oil (0.15 g., 14%), having an infrared spectrum identical with that of the crude sample isolated from IXd, as described in part A. The residual oil which did not distill from the reaction flask was treated with a saturated solution of picric acid in 95% ethanol, giving a picrate (0.40 g., 19%), m.p. 169–171°, having an infrared spectrum (Nujol) identical with that of the picrate (XLVIa) of XLVI from IXd, described subsequently.

Picrate (XLVIa) of XLVI.—A crude sample of XLVI (0.56 g., 0.00242 mole), prepared from IXd, gave a picrate (1.02 g., 91%), m.p. 168–170°. Two recrystallizations from 95% ethanol yielded yellow prisms, m.p. 170–172°; ν_{OH} none (Nujol).

Anal. Calcd. for $C_{22}H_{28}N_4O_7$ (460.48): C, 57.38; H, 6.13; N, 12.17. Found: C, 57.37; H, 6.00; N, 12.16.

1-(1-Dimethylaminomethylcyclohexyl)-1-phenylmethanol (LVI).—Phenyllithium (0.0159 mole) was prepared by adding a solution of bromobenzene (2.5 g., 0.0159 mole) in anhydrous ether (5 cc.) to lithium metal (0.25 g., 0.036 g.-atom) in ether (15 cc.). The resulting mixture was refluxed until the lithium had completely dissolved (4 hr.) and then a solution of 1-dimethylaminomethylcyclohexanecarboxaldehyde (XXXI, 2.50 g., 0.0157 mole) in ether (10 cc.) was added dropwise. The solution was stirred at room temperature for 16 hr. and then hydrolyzed with dilute hydrochloric acid. The ether layer was separated, extracted with dilute hydrochloric acid, and the acid extract combined with the acidic aqueous layer. The acidic layer was then made alkaline with sodium hydroxide and extracted with methylene chloride. The extract was dried, evaporated, and distilled, yielding a colorless, very viscous oil (2.66 g., 69%), b.p. 152–157° (1–2 mm.), $n^{25}D$ 1.5348; λ_{max} mμ (log ε) in 95% ethanol: 247 infl. (2.38), 253 (2.36), 259 (2.36), 265 (2.23), 268 infl. (1.98); ν_{OH} 3150 w, 3570–2370 m (very broad), $\nu_{C=C}$ 1600 w cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{16}H_{25}NO$ (247.37): C, 77.68; H, 10.19; N, 5.66. Found: C, 77.43; H, 9.99; N, 5.93.

Attempted Hydrogenolysis of LVI to XLVI. (A) By Reduction of the Corresponding Chloride.—A solution of LVI (0.50 g., 0.00202 mole) and thionyl chloride (4 cc., 0.055 mole) in benzene (2 cc.) was kept at room temperature for 1 hr. and then refluxed for 1.5 hr. Benzene (10 cc.) was added and then boiled off to remove excess thionyl cloride. Addition of light petroleum ether (b.p. 60–68°) caused precipitation of an oil, which was separated and washed with ether. Then anhydrous ether (10 cc.) and lithium aluminum hydride (0.20 g., 0.0053 mole) were added and the mixture was kept at room temperature for 24 hr. The excess hydride was destroyed by addition of ethanol and the product, assumed to be an oil, isolated as a picrate (0.26 g.). Recrystallization from 95% ethanol yielded yellow prisms, m.p. 156–157°; ν_{OH} none, ν_{NH} 2700 w cm.$^{-1}$ (Nujol). The elemental analyses show that the desired product was not obtained.

Anal. Calcd. for $C_{22}H_{28}N_4O_7$ (460.48): C, 57.38; H, 6.13; N, 12.17. Found: C, 54.22; H, 5.73; N, 8.03.

(B) By Catalytic Hydrogenolysis. (1) With Palladium on Charcoal in Concentrated Hydrochloric Acid.—A solution of LVI (0.30 g.) in concentrated hydrochloric acid (7 cc.) was hydrogenated at 2 atm. over palladium-on-charcoal (0.1 g.) at room temperature for 17 hr. The solution was diluted with water, filtered, and washed with chloroform. The aqueous acidic layer was made alkaline with sodium hydroxide and extracted with chloroform. Drying and evaporation of the chloroform layer left unchanged LVI, as shown by its infrared spectrum.

(2) With Raney Nickel.—A solution of LVI (1.00 g.) in absolute ethanol (150 cc.) was refluxed with Raney nickel (8.0 g.) for 4 hr. Removal of the catalyst and evaporation of the ethanol left unchanged LVI (0.80 g., 80%), having an infrared spectrum identical with that of the starting material.

Oxidation of IV with Peracids. (A) 9,10,14-Trihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 1, IVc) and 10(?)-Acetoxy-9(?),14-dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (IVd) by Oxidation of IV with Peracetic Acid.—A solution of IV (3.90 g., 0.0157 mole) and aqueous 30% hydrogen peroxide (10 cc., 0.10 mole) in glacial acetic acid (50 cc.) was kept at 90° for 5 hr. Platinum black was then added to destroy excess peroxides, and the solvents were removed under reduced pressure, leaving a brown oil, which soon solidified to a glass. The glass was dissolved in ethyl acetate–chloroform, and the solution was concentrated and more chloroform added to the warm concentrate. Upon cooling of the solution, crystals formed (0.52 g., 12%), m.p. 220–223°. Two recrystallizations from ethyl acetate–chloroform, followed by two recrystallizations from methanol–ethyl acetate, yielded IVc as fine white needles, m.p. 220–221°; ν_{OH} 3390 ms, 3060 w, 3220–2450 m (very broad), $\nu_{C=O}$ 1767 m, 1675 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.39; H, 7.53; N, 4.90.

The mother liquor from the isolation of IVc was concentrated, producing crystals (0.32 g., 6%), m.p. 244–250°. Recrystallization from methanol–ethyl acetate yielded IVd as small white plates, m.p. 242–246° dec.; ν_{OH} 3060 ms, $\nu_{C=O}$ 1736 s, 1692 s, 1629 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{23}NO_6$ (325.35): C, 59.06; H, 7.13; N, 4.31. Found: C, 58.49; H, 6.99; N, 4.91.

(B) Sodium 9,10-Dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione-14-hydroxylate (IVf) and 9,10,14-Trihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 2, IVg). (1) By Oxidation of IV with Peracetic Acid.—A mixture of IV (20.0 g., 0.0804 mole) in aqueous 30% hydrogen peroxide (45 cc., 0.44 mole) and glacial acetic acid (150 cc.) was kept at 90° for 4 hr. and at room temperature for 10 hr. The resulting solution was stirred with platinum black for several hours to destroy excess peroxides, and the solvents were evaporated. The residual glass was then dissolved in methanol (200 cc.) and treated with hydrogen at 2 atm. over Raney nickel[65] at room temperature for 12 hr. The catalyst was then filtered off and the filtrate concentrated to a volume of about 50 cc. Sodium hydroxide (20 g., 0.50 mole) and water (10 cc.) were added and the alkaline solution was refluxed for 2 hr. Dilute hydrochloric acid (3 *N*, 15 cc.) was then added cautiously to the hot solution. Upon cooling of the solution needles formed (4.92 g., 19%), which decomposed above 220° without melting. Three recrystallizations from 95% ethanol yielded IVf as fine white needles, which decomposed above 215° without melting; ν_{OH} 3370 s, 2620 m (very broad), $\nu_{C=O}$ 1748 m, 1639 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{20}NO_5Na \cdot H_2O$ (323.32): C (after allowing for 0.5 C atom in the residue as Na_2CO_3), 50.14; H, 6.86; N, 4.33. Found: C, 50.48; H, 6.83; N, 4.24.

The mother liquor from the isolation of IVf was acidified with hydrochloric acid and extracted with chloroform. The extract was dried, concentrated, and diluted with light petroleum ether (b.p. 60–68°), causing precipitation of a solid (3.02 g., 13%), m.p. 215–220°. Extraction of the solid with hot 1:2 chloroform–light petroleum ether (b.p. 60–68°) left undissolved a white solid (2.10 g., 9%), m.p. 230–235°. Two recrystallizations from methanol–ethyl acetate yielded IVg as a granular white solid, m.p. 235–237°; ν_{OH} 3280 ms, 3130 w, $\nu_{C=O}$ 1757 m, 1672 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.19; H, 7.23; N, 4.76.

(2) By Oxidation of IV with Performic Acid.—A mixture of IV (8.30 g., 0.0333 mole) in aqueous 30% hydrogen peroxide (20 cc., 0.20 mole) and aqueous 90% formic acid (80 cc.) was stirred at room temperatre for 2 hr. Then more 30% hydrogen peroxide (20 cc., 0.20 mole) and 90% formic acid (80 cc.) were added, and stirring at room temperature was continued for 6 hr. more, during which time the mixture became homogeneous. A catalytic amount of platinum black was then added and the mixture was stirred at room temperature for 12 hr. to destroy excess peroxides. The mixture was filtered, and the filtrate was concentrated under reduced pressure in a rotary evaporator, giving a brown oil. Aqueous 10% sodium hydroxide solution was added to the oil, and the resulting mixture of brown solution and solid precipitate was kept at 90° for 1.5 hr. The mixture was then filtered, and the tan solid was washed with a small amount of cold water. The solid (3.27 g., 0.0101 mole, 30%) was shown to be IVf by comparison of its infrared spectrum (Nujol) with that of IVf from the oxidation of IV with peracetic acid, described in part 1.

Acidification of the combined alkaline filtrate and water wash with concentrated hydrochloric acid gave IVg (2.17 g., 23%), m.p. 227–239°, identified by comparison of its infrared spectrum (Nujol) with that of IVg from the oxidation of IV with peracetic acid, described in part 1. Recrystallization from methanol–ethyl acetate gave a sample, m.p. 241–244°.

(C) 9,10,14-Trihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 3, IVh), from Acidification of IVf.—Compound IVf (0.20 g., 0.00062 mole) was stirred with hydrochloric acid (2.4 *N*, 5 cc.) for 5 min. The mixture was filtered, giving a white powder (0.14 g., 80%), m.p. 235–238° sublimes. Two crystallizations from methanol–ethyl acetate yielded IVh as glistening white needles, m.p. 240–243° sublimes; ν_{OH} 3230 ms, 3110 ms, $\nu_{C=O}$ 1760 m, 1672 s cm.$^{-1}$ (Nujol). The infrared spectrum (Nujol) was different from those of IVc and IVg.

Anal. Calcd. for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.40; H, 7.41; N, 4.89.

10(?)-Acetoxy-9(?)-hydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (IVe).—Compound IVd (0.90 g., 0.00277 mole) dissolved in 95% ethanol (100 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature for 8 hr. The mixture

(65) Apparently in this case the catalyst was deactivated by reaction products; see the preparation of IVj and IVi for the successful hydrogenolysis of IVf and IVg.

was then heated, the catalyst filtered off, and the filtrate concentrated and diluted with hot water. Upon cooling, glistening white needles separated (0.60 g., 70%), m.p. 261–264°. Recrystallization from ethanol–water yielded white needles (0.25 g., 29%), m.p. 268–270°; ν_{OH} 3440 ms, ν_{NH} 3150 m, 3060 m, $\nu_{C=O}$ 1751 ms, 1689 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{23}NO_5$ (309.35): C, 62.12; H, 7.49; N, 4.53. Found: C, 62.36; H, 7.69; N, 4.54.

9,10-Dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 2, IVi).—Compound IVg (1.38 g., 0.00487 mole) dissolved in 95% ethanol (120 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature for 24 hr. The catalyst was filtered off and the filtrate evaporated to dryness. Crystallization of the residue from methanol–ethyl acetate gave crystals (0.95 g., 73%), m.p. 289–292°. Recrystallization from methanol–ethyl acetate yielded fine white needles, m.p. 290–292°; ν_{OH} 3340 m, ν_{NH} 3130 m, 3040 w, $\nu_{C=O}$ 1751 m, 1650 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.64; H, 8.00; N, 5.25.

9,10-Dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 3, IVj).—Compound IVf (2.0 g., 0.0062 mole) was converted to IVh by stirring with aqueous 10% hydrochloric acid (50 cc.) for 10 min. The white solid (IVh) was then filtered off, dissolved in ethanol (50 cc.), and hydrogenated over Raney nickel at 2 atm. and room temperature for 24 hr. The catalyst was filtered off and the filtrate evaporated to dryness. Crystallization from ethanol–ethyl acetate–light petroleum ether (b.p. 60–68°) gave a white solid (1.13 g. 68%), m.p. 178–180°. Two recrystallizations from ethyl acetate–light petroleum ether yielded a granular white solid, m.p. 178–180°; ν_{OH} 3310 m, $\nu_{C=O}$ 1748 mw, 1681 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 63.19; H, 8.18; N, 4.83.

Cyclohexanehydroxamic Acid (LXXIX).—The product, prepared in 38% yield from cyclohexanecarbonyl chloride[66] according to a procedure for benzohydroxamic acid,[67] was crystallized twice from chloroform, giving matted white needles, m.p. 136–137°; lit.[68] 65%, lit.[58] m.p. 132°, lit.[69] 132–133°; $\nu_{NH,OH}$ 3160 s, 3010 m, $\nu_{C=O}$ 1658 s, ν, 1538 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_7H_{13}NO_2$ (143.18): C, 58.72; H, 9.15; N, 9.78. Found: C, 58.53; H, 9.06; N, 9.92.

Methylation of LXXIX: Preparation of N-Methoxycyclohexanecarboxamide (LXXX).—A solution of cyclohexanehydroxamic acid (1.4 g., 0.0098 mole), potassium hydroxide (0.6 g., 0.011 mole), and methyl iodide (2.0 g., 0.0141 mole) in methanol (10 cc.) was refluxed for 2 hr. The solution was then evaporated to dryness in a rotary evaporator. The residue was extracted with light petroleum ether (b.p. 60–68°), and the extract filtered, concentrated, and cooled, causing precipitation of feathery needles (0.23 g., 15%), m.p. 73–75°. Two recrystallizations from light petroleum ether yielded feathery white needles, m.p. 77–79°; ν_{NH} 3170 s, $\nu_{C=O}$ 1650 s, ν, 1513 m cm.$^{-1}$ (Nujol)

Anal. Calcd. for $C_8H_{15}NO_2$ (157.21): C, 61.12; H, 9.62; N, 8.91. Found: C, 60.87; H, 9.53; N, 9.07.

Acknowledgment.—We wish to thank Professor Dorothy V. Nightingale for informing us of current work in her laboratory related to this structure determination, and for her friendly interest in the progress of the work.

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The Preparation and Stereospecific Rearrangement of Spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane]. The Effect of a Nonclassical Intermediate[1]

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Received May 3, 1963

The addition of dimethylsulfoxonium methylide in dimethyl sulfoxide to bicyclo[2.2.1]hept-2-en-7-one occurs in a stereospecific manner to yield spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane]. This epoxide is rearranged stereospecifically with retention of configuration at the migration terminus by the action of heat and/or Lewis acids to yield bicyclo[2.2.1]hept-2-ene-*syn*-7-carboxaldehyde. The structures of the epoxide and aldehyde are established by chemical and physical means. A mechanism for the rearrangement is suggested which incorporates a nonclassical intermediate.

Norton[2] reports that bicyclo[2.2.1]hept-2-en-7-one (2) reacts with the nitrogen-containing nucleophiles, hydroxylamine, semicarbazide, and 2,4-dinitrophenylhydrazine with exceptional ease. Therefore, when searching for a suitable starting material for the preparation of some 7-functionally substituted bicyclo[2.2.1]-hept-2-enes, we decided to examine the reactions of this ketone with some nucleophiles in which the attacking atom would be carbon rather than nitrogen. One of the more interesting nucleophiles, whose reactivity toward ketones has recently been demonstrated, is dimethylsulfoxonium methylide.[3] We report here the results of our investigation into the reaction of dimethylsulfoxonium methylide in dimethyl sulfoxide with bicyclo[2.2.1]hept-2-en-7-one (2).

Results

Bicyclo[2.2.1]hept-2-en-7-one (2) was first prepared and characterized by Norton.[2] The final step in his synthetic scheme involved the oxidation of bicyclo-[2.2.1]hept-2-en-7-ol (of unspecified configuration but probably *anti*) with chromic acid in acetone.[4] The ketone, obtained in 38% yield, was identified by its infrared and ultraviolet spectra, its facile reaction with hydroxylamine, 2,4-dinitrophenylhydrazine, and semicarbazide, and by its reduction with lithium aluminum hydride back to bicyclo[2.2.1]hept-2-en-7-ol. As the starting point for our synthesis we used bicyclo[2.2.1]-hept-2-en-*anti*-7-ol (1), prepared in 21% over-all yield from bicyclo[2.2.1]heptadiene by the procedure

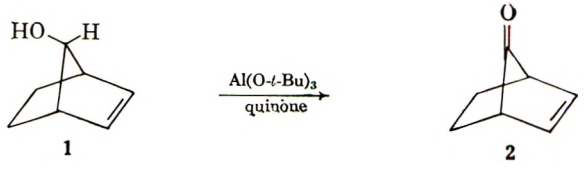
(1) (a) Portions of this work have been presented at the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November, 1962, and at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963 (Abstracts of meeting, p. 25M); (b) Since there are presently no accepted conventions for designating the stereochemistry of 7-substituted bicycloheptenes we will arbitrarily refer to those in which the functional group of the 7-substituent and the bicycloheptene double bond are on the same side of the plane defined by the 1, 4, and 7 carbons as *syn*, those in which they are on opposite sides as *anti*.

(2) C. J. Norton, Ph.D. thesis, Harvard University, 1955, pp. 103, 126 ff.

(3) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867, 868, 3782 (1962).

(4) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and W. G. Wood, *J. Chem. Soc.*, 2407 (1951).

of Story.[5] Our attempts to oxidize this alcohol with chromium trioxide in pyridine,[6] and with aluminum *t*-butoxide in an acetone–benzene mixture,[7] led primarily to the recovery of unchanged starting material. When the oxidation was carried out with chromic acid in an acetone–water–sulfuric acid mixture according to the procedure of Jones, *et al.*,[8] a very complex mixture was obtained. By carrying out the oxidation with aluminum *t*-butoxide in benzene, using quinone as a hydrogen acceptor[9] we were able to prepare bicyclo[2.2.1]hept-2-en-7-one (**2**) from bicyclo[2.2.1]-hept-2-en-*anti*-7-ol (**1**) in 73% yield.

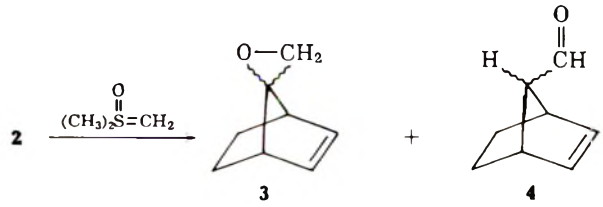


1 **2**

The infrared spectrum of our material and the melting point and ultraviolet spectrum of its 2,4-dinitrophenylhydrazone, were all identical to those reported by Norton.[2] The ultraviolet spectrum of the pure ketone was not. Norton reports that his material showed a strong absorption in the short wave-length region of the spectrum, λ_{max}^{EtOH} 233 mμ (ε 1300), as well as the more normal absorption at a longer wave length, $\lambda_{max}^{isooctane}$ 275 mμ (ε 33). Norton attributed this unusual short wave-length absorption to "a very unique transannular interaction between the nonconjugated double bond and the carbonyl group."[10] This ultraviolet absorption has been widely quoted[11]; the short wavelength band has been suggested to arise from the charge transfer $\pi \rightarrow \pi^*$ transition,[11,12] and has been the object of considerable theoretical speculation. Consequently, we were disturbed when the ultraviolet spectrum of our ketone in 95% ethanol exhibited no detectable maximum at 233 mμ or thereabouts, but rose gradually to ε 2700 at 200 mμ. At 233 mμ the molar extinction coefficient was approximately 250. The absorption of our material at longer wave length was quite similar to that of Norton's, *i.e.*, λ_{max}^{EtOH} 272 mμ (ε 38.9). The fact that the gas chromatographic analysis of our material showed it to be pure led us to conclude that we had indeed prepared bicyclo[2.2.1]hept-2-en-7-one.[13] We have no explanation for the short wave-length absorption observed by Norton.[14]

When a solution containing a stoichiometric amount of dimethylsulfoxonium methylide in dimethyl sulfoxide[3] was allowed to react with bicyclo[2.2.1]hept-2-en-7-one (**2**), a gas chromatographic analysis of the products on a silicone oil 200 column at 110° showed the presence of two compounds, **3** and **4**. On this column the retention time of **3** was 0.82 times that of **4**; its peak area relative to **4** was 0.053, although this ratio could be changed from 1.2 to 0 by varying the conditions of analysis, *i.e.*, column, column and preheater temperature, flow rate.

Both of these compounds were neutral and each had the empirical formula, $C_8H_{10}O$. The infrared spectrum of **3** confirmed the presence of a double bond (6.17 μ) and a vinyl hydrogen (3.26, 14.25 μ), and the absence of a hydroxyl or carbonyl function. Hence the oxygen must be present as an epoxide or as an ether. The presence of absorptions at 3.19, 7.19, 10.95, and 11.84 μ, which could be attributed to a terminal epoxide,[15] and the strong C–O stretching vibrations at 10.18 and 10.57 μ confirm this. Compound **4** showed strong absorptions at 3.26 and 14.35 (vinyl hydrogen), 3.70 (aldehydic hydrogen), 5.81 (carbonyl), and 6.12 μ (double bond). This evidence, taken collectively, indicates that compound **3** is a spiro[bicyclo[2.2.1]-hept-2-ene-7,2′-oxacyclopropane],[16] and that compound **4** is a bicyclo[2.2.1]hept-2-ene-7-carboxaldehyde.



3 **4**

These structures were established chemically in the following manner. The reduction of **3** with lithium aluminum hydride affords a single unsaturated alcohol, $C_8H_{12}O$ (**5**), which is identical to the single alcohol produced by the reaction of **2** with methylmagnesium iodide followed by hydrolysis. Compound **4** is oxidized by silver oxide to a bicyclic unsaturated carbox-

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(11) *E.g.*, S. Winstein, L. DeVries, and R. Orloski, *J. Am. Chem. Soc.*, **83**, 2020 (1961), and references cited therein.

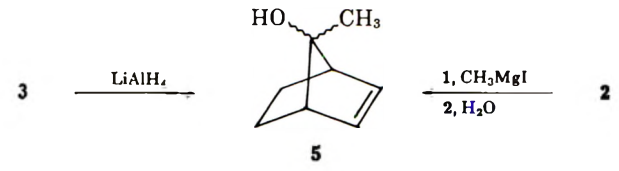
(12) (a) M. Simonetta and S. Winstein, *ibid.*, **76**, 18 (1954); (b) H. Labhart and G. Wagnière, *Helv. Chim. Acta*, **42**, 2219 (1959); R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962).

(13) The n.m.r. spectrum of this material seems compatible with this structure, *e.g.*, two vinyl protons split into a triplet (3.50 τ, J = 2.3 c.p.s.) by at least two other hydrogens, two bridgehead protons split into a quintet (7.25 τ) by at least three other hydrogens, and four methylene hydrogens which appear as a complex absorption (7.8–9.1 τ). While the vinyl hydrogen resonance of this ketone appears at a lower field than do those of the other 7-substituted bicyclo[2.2.1]hept-2-enes which we have examined, it is reported that the vinyl hydrogen resonances of both *anti*-7-chloro- and *syn*-7-bromobicyclo[2.2.1]hept-2-ene occur at an even lower field, *i.e.*, 3.15 τ [L. Kaplan, H. Kwart, and P. von R. Schleyer, *J. Am. Chem. Soc.*, **82**, 2341 (1960)]. It is known that both the chemical shifts and the coupling constants of hydrogens in bicyclic compounds are quite sensitive to changes in their steric and/or electronic environment [O. L. Chapman, *ibid.*, **85**, 2014 (1963)]. The fact that the vinyl hydrogens in bicyclo[2.2.1]hept-2-en-7-one appear as a triplet which shows evidence of further splitting is quite characteristic of symmetric 7-substituted bicyclo[2.2.1]heptenes (see Experimental).

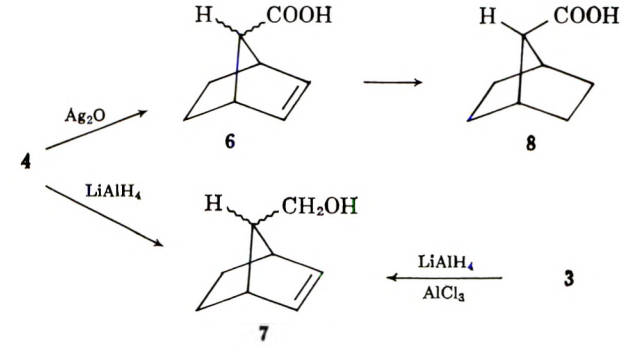
(14) (a) J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 710 (1963), report that 1,5,5-trimethylbicyclo[2.2.1]hept-2-en-7-one shows an $n \rightarrow \pi^*$ absorption, λ_{max}^{EtOH} 270 mμ (ε 58), but only an ill-defined absorption at short wave lengths rising to ε 3000 at *ca.* 200 mμ. These authors report a private communication from R. Orloski whose reexamination of the spectrum of bicyclo[2.2.1]hept-2-en-7-one shows it to be similar to that of 1,5,5-trimethylbicyclo[2.2.1]hept-2-en-7-one; (b) K. V. Scherer, Jr., Abstracts of the 144th National Meeting of the American Chemical Society, Los Angeles, April, 1963, p. 61M, reports that the ultraviolet spectrum of Δ^5-dihydrodicyclopentadien-8-one, run in isooctane, exhibits shoulders at 203.0 (2900) and 215 mμ (ε 800), and shows a maximum at 269 mμ (ε 30.6); (c) P. G. Gassman and P. G. Pape, *Tetrahedron Letters*, No. 1, 9 (1963), have recently reported an ultraviolet spectrum for bicyclo[2.2.1]hept-2-en-7-one similar to that which we found.

(15) (a) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1963, pp. 36, 155; (b) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960); (c) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(16) When bicyclo[2.2.1]hept-2-en-7-one is allowed to react in the presence of excess dimethylsulfoxonium methylide, a compound which we believe to be spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclobutane] is formed in good yield. We shall discuss this reaction in a separate communication since it does not bear directly on this work.



ylic acid, $C_8H_{10}O_2$ (**6**), and is reduced by lithium aluminum hydride to a single unsaturated alcohol, $C_8H_{12}O$ (**7**), which is different from **5**, but which is identical to the single unsaturated alcohol formed when the epoxide **3** was reduced with lithium aluminum hydride in the presence of aluminum trichloride.[17] The unsaturated acid **6** can be catalytically hydrogenated to the known bicyclo[2.2.1]heptane-7-carboxylic acid (**8**).[18]

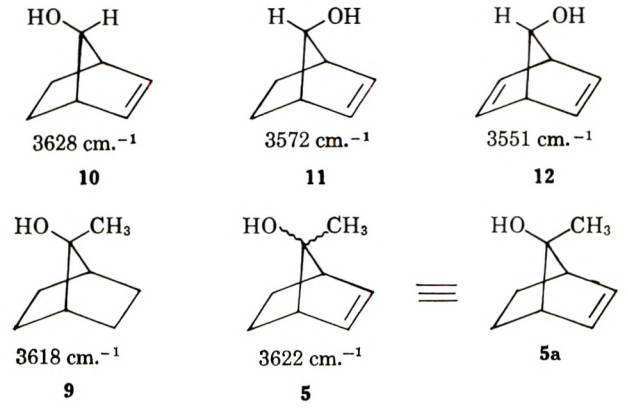


The fact that the normal product from the reaction of dimethylsulfoxonium methylide with a non-α,β-unsaturated ketone is an epoxide,[3] and that the composition of the reaction mixture obtained from this reagent and bicyclo[2.2.1]hept-2-en-7-one was dependent upon the conditions of analysis, led us to suspect that the aldehyde was being formed from the epoxide by rearrangement during gas chromatography.

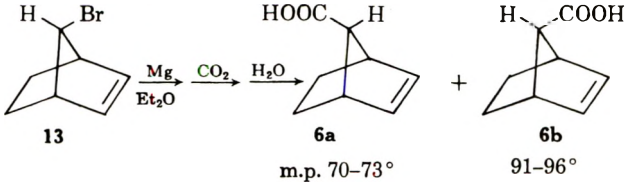
In order to test this idea, we reduced a portion of the reaction mixture with lithium aluminum hydride. A gas chromatographic analysis of this reaction product showed the presence of only the tertiary alcohol **5**. No primary alcohol **7** was formed in this reduction; therefore, the reaction mixture prior to reduction could have contained no aldehyde **4**. When the same reaction mixture was treated with boron trifluoride etherate or with aluminum trichloride, it was possible to isolate small quantities of aldehyde, though the principal product(s) was apparently polymeric in nature. The epoxide can be smoothly rearranged to the aldehyde by chromatography on Merck acid-washed alumina.

Having thus established that the epoxide **3** could be rearranged by heat and/or Lewis acids to a single aldehyde **4**, we decided to investigate the stereochemistry of this reaction. In order to observe this stereochemistry, it was necessary only to establish the configuration of the epoxide **3** and of the aldehyde **4**. This was done in the following manner.

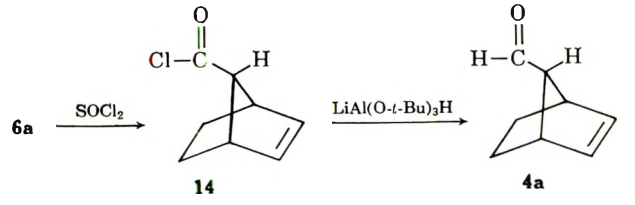
A high-dilution infrared spectrum of the tertiary alcohol **5**,[19] shows that the principal oxygen–hydrogen stretching frequency occurs at 3622 cm.$^{-1}$. The oxygen–hydrogen stretching frequency of 7-methylbicyclo[2.2.1]heptan-7-ol (**9**), prepared by catalytic reduction of **5**, occurs at 3618 cm.$^{-1}$. The fact that the oxygen–hydrogen stretching vibration of both the saturated and the unsaturated alcohol occurs at approximately the same frequency is indicative that the hydroxyl group of **5** must be on the opposite side of the bridge from the double bond.[20] This conclusion is substantiated by the spectra of the related bicyclic alcohols **10**–**12**.[19] Thus the unsaturated tertiary alcohol **5** is 7-methylbicyclo[2.2.1]hept-2-en-*anti*-7-ol (**5a**). Since the lithium aluminum hydride reduction used to prepare **5a** from the epoxide **3** could not have affected the stereochemistry at the C-7 position, it follows that both the epoxide and the alcohol have the same configuration. The epoxide **3** is thus spiro[bicyclo[2.2.1]-hept-2-en-*anti*-7,2′-oxacyclopropane] (**3a**).



The bicyclo[2.2.1]hept-2-ene-7-carboxylic acid (**6**), m.p. 94–100°, prepared by oxidation of the aldehyde **4** is identical to one of the carboxylic acids, m.p. 91–96°, prepared from *syn*-7-bromobicyclo[2.2.1]hept-2-ene (**13**) and assigned the *syn* configuration **6b** by Sauers.[21]



The 2,4-dinitrophenylhydrazone of aldehyde **4** melts broadly at 126–134°, but well below the 150–151° reported by Wilt and Levin for the 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]hept-2-ene-*anti*-7-carboxaldehyde (**4a**) prepared from **6a** *via* the acid chloride **14**.[22]



These results indicate that the configuration of our aldehyde is *syn*, *i.e.*, **4b**. However, the stereochemical assignments of Sauers, and hence of Wilt and Levin, are not based upon chemical evidence but upon the melting points of the bicyclo[2.2.1]hept-2-ene-7-carboxylic acids (**6a**,**b**) and upon the relative retention

(17) E. L. Eliel and D. W. Delmonte, *J. Am. Chem. Soc.*, **80**, 1744 (1958).

(18) (a) H. Kwart and L. Kaplan, *ibid.*, **76**, 4072 (1954); (b) L. Kaplan, Ph.D. thesis, University of Delaware, 1953.

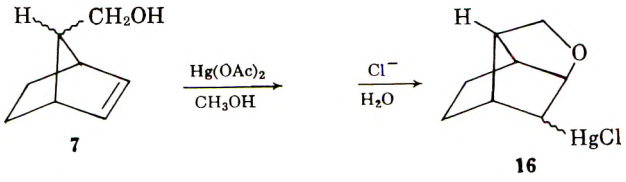
(19) This spectrum was determined on a Perkin-Elmer Model 421 grating infrared spectrophotometer by Dr. L. P. Kuhn of the Ballistics Research Laboratory, Aberdeen Proving Ground, Md.

(20) Ref. 15a, p. 31, ref. 1–7.

(21) R. R. Sauers, *Chem. Ind.* (London), 176 (1960).

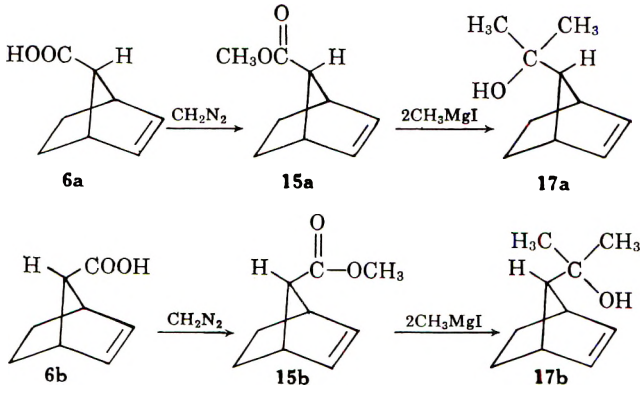
(22) J. W. Wilt and A. A. Levin, *J. Org. Chem.*, **27**, 2319 (1962).

times of their two methyl esters **15a,b** when gas chromatographed upon diethylene glycol and diethylene glycol–silver nitrate columns. Although we had no reason to doubt their conclusions, we desired a more direct indication of the stereochemistry of our bicyclo[2.2.1]hept-2-ene-7-carboxaldehyde. Since both iodolactonization, using an aqueous solution of iodine, potassium iodide, and sodium bicarbonate, and lactonization in the presence of a strong acid, have been reported to cause rearrangements with bicyclo[2.2.1]-heptenecarboxylic acids,[23,24] we decided to turn our attention to the primary alcohol **7** produced from the aldehyde **4** by chemical reduction. When this alcohol is treated with mercuric acetate in methanol,[25] conditions which do not cause isomerization of the alcohol, the mercuric ion rapidly disappears, and treatment of the reaction mixture with aqueous sodium chloride causes the precipitation of a white solid, m.p. 176–180°, which we believe to be the chloromercuri tricyclic ether (**16**) of undetermined configuration.



7 **16**

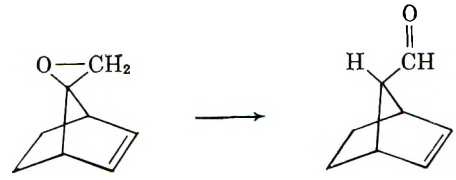
The bicyclo[2.2.1]hept-2-ene-7-methanol prepared by the lithium aluminum hydride reduction of the lower melting of Sauers' acids **6a**, and thus presumably of *anti* configuration, reacts, but does not form a tricyclic ether under these conditions. In addition, each of Sauers' two acids, *i.e.*, **6a,b**, was converted *via* its methyl ester **15a,b** to the corresponding tertiary alcohol **17a,b**, respectively. The high-dilution infrared spectrum of the tertiary alcohol **17b** shows a strong intramolecular hydrogen bond (3577 cm.$^{-1}$) and a weak nonbonded hydroxyl absorption (3617 cm.$^{-1}$), while the alcohol **17a**, derived from the lower melting of Sauers' acids, **6a**, shows only a broad nonbonded hydroxyl absorption at 3618–3629 cm.$^{-1}$.[19]



6a **15a** **17a**

6b **15b** **17b**

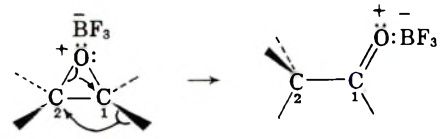
We believe that these data confirm both chemically and physically the stereochemistry of the two bicyclo[2.2.1]hept-2-ene-7-carboxylic acids (**6a,b**) the esters **15a,b**, the tertiary alcohols **17a,b**, the primary alcohols **7a,b**, and the aldehydes **4a,b**. It is now clear that the aldehyde which we have observed as a rearrangement product of spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (**3a**) is bicyclo[2.2.1]hept-2-ene-7-*syn*-carboxaldehyde (**4b**), and that this rearrangement has occurred with *retention* of configuration at the bridge carbon, C-7.



3a **4b**

Discussion

Heat or catalysis by a Lewis acid can cause an epoxide to rearrange to an aldehyde or ketone.[26] The course of the reaction is determined by the direction of ring opening and by the relative migratory aptitudes of the substituents. Electron releasing groups can enhance the rate of the reaction and promote cleavage of an adjacent carbon–oxygen bond by stabilizing the incipient positive charge in the transition state of the rate determining step. These electronic effects can be accommodated by a concerted, unimolecular process (path A) for which bond-breaking is more important in the transition state than is bond-making.[26b] By analogy with other 1,2-nucleophilic rearrangements,

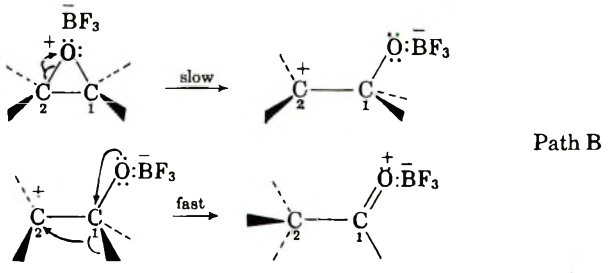


epoxide-to-carbonyl conversions should normally follow this concerted path, and should undergo inversion at the migration terminus (C-2) in the process.[26,27] The boron trifluoride-catalyzed isomerizations of 5α,6α-epoxycholestane to coprostan-6-one, 5β,6β-epoxycoprostane to cholestan-6-one, 4α,5α-epoxycholestane to coprostan-4-one, and 4β,5β-coprostane to cholestan-4-one provide well defined examples of this type of reaction.[28] Other examples are known.[29] Clearly the rearrangement of spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (**3a**) with retention of configuration at the migration terminus to bicyclo[2.2.1]hept-2-ene-*syn*-7-carboxaldehyde (**4b**) cannot follow such a concerted path.

(23) J. A. Berson and A. Remanick, *J. Am. Chem. Soc.*, **83**, 4947 (1961).
(24) S. Beckmann and H. Geiger, *Chem. Ber.*, **94**, 48 (1961).
(25) H. B. Henbest and J. B. Nicholls, *J. Chem. Soc.*, 221 (1959).

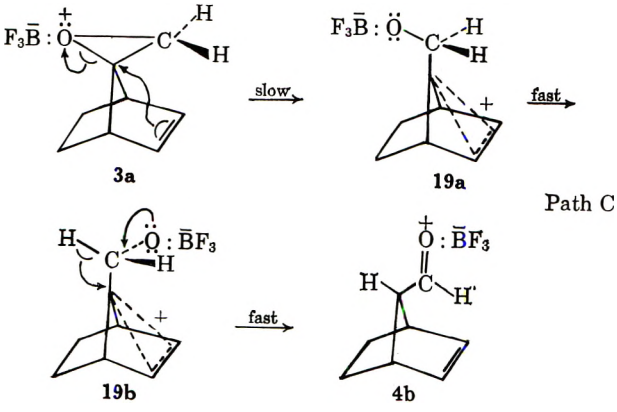
(26) These rearrangements have been reviewed by (a) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," R. C. Elderfield, Ed., Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 47–54; and by (b) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).
(27) (a) C. K. Ingold, "Structure, and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 478, 511; (b) P. D. Bartlett, "Organic Chemistry, An Advanced Treatise," H. Gilman, Ed., Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 59ff.
(28) (a) H. B. Henbest and T. F. Wrigley, *J. Chem. Soc.*, 4596 (1957); (b) C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers, *ibid.*, 630 (1959).
(29) (a) P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, G. F. Woods, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton, and G. H. Thomas, *ibid.*, 2921 (1953); (b) J. Elks, R. M. Evans, C. H. Robinson, G. H. Thomas, and L. J. Wyman, *ibid.*, 2933 (1953); (c) E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.*, **78**, 183 (1956); (d) H. B. Henbest and T. F. Wrigley, *J. Chem. Soc.*, 4765 (1957); (e) R. C. Cookson and J. Hudec, *Proc. Chem. Soc.*, 24 (1957); (f) H. Linde and K. Meyer, *Experientia*, **15**, 238 (1958); *Helv. Chim. Acta*, **42**, 897 (1959); (g) A. Lardon, H. P. Sigg, and T. Reichstein, *ibid.*, **42**, 1457 (1959); (h) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4657 (1960); (i) M. Shiota, T. Ogihara, and Y. Watanake, *Bull. Chem. Soc., Japan*, **34**, 40 (1961).

Conceptually, an epoxide–carbonyl rearrangement could follow a nonconcerted path B whose slow first step would be analogous to that of an acid-catalyzed epoxide cleavage,[26b] and whose fast second step would resemble that of a nonconcerted pinacol rearrangement[30] or of a semipinacolic deamination.[31]



Path B

The presence in the molecule of groups which could strongly stabilize the developing positive charge at the migration terminus, C-2, should favor reaction by path B relative to the concerted route (path A).[26b] We believe that the π-electrons of the double bond in spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (**3a**) exert such an effect, and cause the rearrangement of this epoxide to follow the nonconcerted path C. Thus the first and probable rate-determining step would consist of the heterolysis of the C-7 oxygen bond, assisted by the coordinated Lewis acid and by a backside "push" from the π-electrons, to form the intermediate ion **19a**. The C-7–C-8 bond of this intermediate could then rotate with a minimum of steric interference to a conformation **19b** that would allow the migrating nucleophile (hydride) to attack the delocalized carbonium ion from the preferred *anti* side.[32] The resulting aldehyde **4b** would then have the same configuration at C-7 as the starting epoxide **3a**.



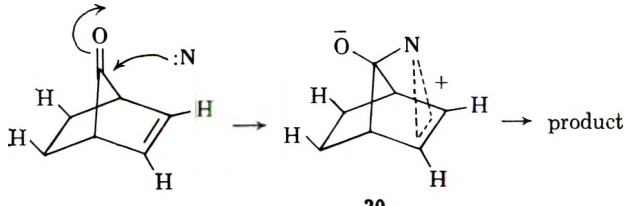
3a **19a** **19b** **4b**

Path C

We believe that this represents the first clear case of an epoxide–carbonyl rearrangement which occurs with complete retention of configuration at the migration terminus.[33]

It seems probable that the highly stereospecific nature of this rearrangement together with the almost total absence of a conformational effect in the intermediates (**19**) will combine to make this system ideal for the study of relative migratory aptitudes. We plan to extend this work to some related nucleophilic rearrangements and to some other bicyclic ketones.

It is interesting to note that bicyclo[2.2.1]hept-2-en-7-one (**2**) reacts with methylmagnesium iodide and with dimethylsulfoxonium methylide (possibly also with diazomethane[1a]) in a stereospecific manner. In each case the product formed, *anti*-alcohol **5a** or *anti*-epoxide **3a**, respectively, is the result of a nucleophilic addition to the carbonyl from the side of the double bond. We do not know whether this observed stereospecificity is due to steric or to electronic effects, but we suspect that both may be important. Attack from the side of the double bond is probably less sterically hindered than is attack from the side of the *exo* hydrogens. Since the nucleophiles which we have studied possess no net charge prior to reaction, coulombic repulsion by the π-electrons of the double bond is probably not an important factor. The dipolar intermediate **20** which results from the attack of a neutral nucleophile, :N, on the ketone **2** from the side of the double bond, is probably more stable than that which would result from attack on the opposite side of the molecule. Not only is the negative charge on the oxygen farther removed from the region of high π-electron density, but the positive charge which is developed on the nucleophile can be partially delocalized by these π-electrons. We expect to be in a better position to evaluate the relative importance of these effects when we have examined the reaction with a greater variety of nucleophiles.



2 **20**

Experimental[34]

Bicyclo[2.2.1]hept-2-en-7-one (2).[35]—Ten grams of aluminum *t*-butoxide (Aceto Chemical Co.) was added to a solution of 10 g. of bicyclo[2.2.1]hept-2-en-*anti*-7-ol (**1**)[5] and 16 g. of *p*-benzoquinone in 300 ml. of dry benzene. The mixture was heated at reflux and an additional 10-g. portion of aluminum *t*-butoxide was added in small increments over a 24-hr. period. Heating was continued for an additional 50 hr. The reaction mixture was cooled and 200 ml. of 3 *N* hydrochloric acid was added. After filtration of the reaction mixture through a Celite

(30) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 602.

(31) (a) Ref. 30, pp. 602ff; (b) B. M. Benjamin, H. S. Schaeffer, and C. J. Collins, *J. Am. Chem. Soc.*, **79**, 6160 (1957).

(32) (a) S. Winstein, M. Shatavsky, C. Norton, R. B. Woodward, *ibid.*, **77**, 4183 (1955); (b) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956); (c) S. Winstein and A. T. Stafford, *ibid.*, **79**, 505 (1957); (d) S. Winstein and C. Ordonneau, *ibid.*, **82**, 2084 (1960).

(33) There are some examples of acid-catalyzed oxide cleavages which occur with retention of configuration at the migration terminus (see ref. 26b, pp. 756ff). In each case this retention can be attributed to restricted rotation about the C-1–C-2 bond (path B) either because of bridged-ion formation by a neighboring aryl or acyl group, or because of a conformational or steric effect. Such effects are not present in path C.

(34) Melting and boiling points are uncorrected. Microanalyses were performed by either Bernhardt Mikroanalytisches Laboratorium, Mülheim, or Gailbraith Laboratories, Incorporated, Knoxville, Tenn. Except where noted, infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics. Ultraviolet spectra were recorded on a Cary, Model 14M, spectrophotometer, using 1-cm. quartz cells. The nuclear magnetic resonance spectra were recorded on a Varian A-60 n.m.r. spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed with a Perkin-Elmer vapor fractometer, Model 154D, or an F & M Model 500 linear temperature programmed gas chromatograph.

(35) We thank Dr. O. R. Vail for working out the experimental details of this preparation; abstracted from the Ph.D. dissertation of Oakley R. Vail, University of South Carolina, 1963.

mat, the aqueous layer was discarded, and the benzene layer was washed successively with six 150-ml. portions of 3 *N* hydrochloric acid, enough 5% sodium hydroxide solution to extract the hydroquinone, and two 50-ml. portions of saturated sodium chloride solution. The benzene solution was dried over anhydrous potassium carbonate, the solvent was removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure; b.p. 54–56° (17 mm.); yield, 7.2 g. (73%).

Anal. Calcd. for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.45; H, 7.55.

Infrared[15a]: λ_{max}^{film} 3.27, 14.30 (>C=CH—); 5.62 (>C=O in 7-ketobicyclo[2.2.1]heptane); 6.15 μ (>C=C<); in agreement with Norton.[36]

N.m.r.: $\nu_{max}^{CCl_4}$ 3.50, triplet, J = 2.5 c.p.s. (2 >C=C*H*—); 7.25, quintet (2 ≻C—H, bridgehead); 7.5–9.1 τ, multiplet (2 ≻C*H*H, 2 >CH*H*).

Ultraviolet: λ_{max}^{EtOH} 272 mμ (ϵ 38.9); $\lambda_{inflection}^{EtOH}$ 222 mμ (ϵ 465).[2,14a]

The 2,4-dinitrophenylhydrazone, prepared by the method of Shriner, Fuson, and Curtin,[37] and recrystallized from ethanol, melted at 135–135.5° (lit.[2] m.p. 134–135°).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 54.16; H, 4.20; N, 19.44. Found: C, 54.35; H, 4.09; N, 19.31.

Ultraviolet: λ_{max}^{EtOH} 224 (ϵ 19,700); 358 mμ (24,000).[2]

Spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (3a).—Eleven grams of trimethylsulfoxonium iodide[3] was added, in small portions to a nitrogen-blanketed, stirred suspension of 1.20 g. of sodium hydride (supplied as a 53% dispersion in mineral oil by Metal Hydrides, Inc.) in 40 ml. of dimethyl sulfoxide. When the evolution of hydrogen had ceased, a solution of 5.40 g. of bicyclo[2.2.1]hept-2-en-7-one in 20 ml. of dimethyl sulfoxide was added dropwise with cooling. The reaction mixture was stirred at room temperature for 1 hr., diluted with 100 ml. of water, and extracted with three 50-ml. portions of pentane. The pentane extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation at atmospheric pressure, and the product was distilled under vacuum; b.p. 60–61° (28 mm.); yield, 4.32 g. (72%).

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.31; H, 8.23.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 3.19, 7.91, 10.95, 11.84 (>C(O)—CH_2?); 3.25, 14.25 (—C=C*H*—); 6.17 (>C=C<); 10.18, 10.57 μ (C—O?).

N.m.r.: $\nu_{max}^{CCl_4}$ 3.86, triplet, J = 2.1 c.p.s. (2 >C=C*H*—); 7.23, singlet, (2 >C(O)—CH_2); 7.75, quintet (2 ≻C—*H*, bridgehead); 7.9–8.3, multiplet (2 >C*H*H); 8.8–9.1 τ, multiplet (2 >CH*H*).

7-Methylbicyclo[2.2.1]hept-2-en-*anti*-7-ol (5a). A. From Spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (3a).—To a stirred slurry of 40 mg. of lithium aluminum hydride in 1 ml. of anhydrous ether was added a solution containing 80 mg. of epoxide in 2 ml. of anhydrous ether. The mixture was heated at reflux for 6 hr., cooled, and then decomposed with water and 15% sodium hydroxide solution. The precipitated salts were removed by filtration, and the solvent was distilled from the filtrate through a 10-cm. Vigreux column. The residue was purified by sublimation at 60° (90 mm.) to give 47 mg. (58%) of white needles, m.p. 74–76°. Gas chromatographic analysis on the silicone oil column, both separately and as a mixture with bicyclo[2.2.1]hept-2-ene-*syn*-7-methanol (**7b**) and bicyclo[2.2.1]-hept-2-ene-*anti*-7-methanol (**7a**), from which it was well resolved, showed the resulting alcohol to be 99% pure. A small sample was resublimed for analysis.

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.17; H, 9.84.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 2.77, 2.90 (O—H); 3.26, 14.04 (>C=CH—); 6.14 (>C=C<); 7.29 (C—CH_3); 8.9 μ (C—O). $\nu_{max}^{CCl_4}$ 3622 cm.$^{-1}$ (nonbonded O—H).[19]

N.m.r.: $\nu_{max}^{CCl_4}$ 4.06, triplet, J = 2.5 c.p.s. (2 >C=C*H*—); 7.71, quintet (2 ≻C—H, bridgehead); 7.9–8.2, multiplet (2 >C*H*H); 8.5, singlet (shifted to 7.84 by the addition of a drop of trifluoroacetic acid; 1 O—*H*); 8.71, singlet (3 —CH_3); 8.8–9.3 τ, multiplet (2 >CH*H*).

B. From Bicyclo[2.2.1]hept-2-en-7-one (2).—Methylmagnesium iodide was prepared from 56 mg. of magnesium and 300 mg. of methyl iodide in 5 ml. of anhydrous ether.

A solution of 205 mg. of the ketone in 3 ml. of ether was added slowly to the Grignard reagent. After the addition was complete, the reaction mixture was heated at reflux for 1 hr. The mixture was cooled, the complex was decomposed by the addition of water and wet sodium sulfate, and the precipitated salts were removed by filtration. The ethereal filtrate was dried over anhydrous sodium sulfate. A gas chromatographic analysis on the silicone oil column revealed the presence of unchanged starting material (40%) and one other component (60%) which had the same retention time as the alcohol **5a** prepared by the reduction of the epoxide with lithium aluminum hydride. The infrared spectrum of this component, collected from the gas chromatographic column, was identical with that of the tertiary alcohol **5a**, prepared from the epoxide **3a**.

The solvent was removed from the reaction by distillation through a 10-cm. Vigreux column, and the unchanged bicyclo-[2.2.1]hept-2-en-7-one (**2**) was recovered by distillation at 73 mm. The residual alcohol was purified by sublimation at 60° (80 mm.); yield, 83 mg. (41%); m.p. 74–76°.

7-Methylbicyclo[2.2.1]heptan-7-ol (9).—A 20-mg. sample of the tertiary alcohol **5a** was hydrogenated at atmospheric pressure in 95% ethanol using 5% palladium on charcoal as a catalyst. The hydrogenated sample was purified by sublimation at 60° (90 mm.); m.p. 97–98°.

Anal. Calcd. for $C_8H_{14}O$: C, 76.29; H, 10.91. Found: C, 76.14; H, 11.18.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 2.77, 2.90 (O—H); 7.29 (C—CH_3); ~8.8 μ (C—O?). The maxima at 3.26, 6.14, and 14.04 μ, present in the spectrum of the unsaturated alcohol **5a** were missing from this spectrum.

The n.m.r. spectrum was too complex to analyze but showed a peak whose position varied with added trifluoroacetic acid (1 O—*H*), a total of 14 H's, and no vinyl hydrogens.

Bicyclo[2.2.1]hept-2-ene-*syn*-7-carboxaldehyde (4b). A. By Rearrangement of the Epoxide 3a during Gas Chromatography.—When the epoxide **3a** was subjected to gas chromatographic analysis on the silicone rubber column (110°, 120 ml. He/min.) two compounds were detected with retention times of 3.0 and 4.2 min. The ratio of the area of the first to the second peak was 1.0 under these conditions. When the silicone oil column was used for analysis of the epoxide (110°, 150 ml. of He/min.), two peaks were again observed with retention times of 8.6 and 10.5 min., but the ratio of their areas was now 0.053.

These peak-area ratios were difficult to duplicate. They varied with the conditions of the analysis, *i.e.*, column and preheater temperature, flow rate, and sometimes changed drastically after a given column had been used for the analysis and/or collection of other materials.

The first component was collected from the silicone rubber column. Its infrared spectrum showed all the absorptions present in the spectrum of spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (**3a**) plus an additional small peak at 5.81 μ which was presumed to arise from a trace of aldehyde contaminant formed by rearrangement of the epoxide in the postheater of the gas chromatograph.

The second component was obtained by collection from the silicone oil column. By using a 30-μl. sample, it was possible to collect 15–18 mg. (60–70%) of this material from each injection.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 3.26, 14.10 (>C=CH—); 3.55, 3.70 (—C*H*O); 5.81 (>C=O); 6.15 μ, weak, (>C=C<).

N.m.r.: $\nu_{max}^{CCl_4}$ 0.36, doublet, J = 2.5 c.p.s. (1 —C*H*O); 3.96, triplet, J = 1.8 c.p.s. (2 >C=C*H*—); 6.83, poorly defined sextet (2 ≻C—H, bridgehead); 7.88, broad singlet (1 >C*H*—CHO); 8.0–9.2 τ, multiplet (2 >C*H*H, 2 >CH*H*).

This material was found to be very unstable. Upon even brief exposure to air it was rapidly oxidized to the corresponding carboxylic acid **6b**. The rate of this oxidation could be conveniently followed by n.m.r. Because of its instability, we were unable to obtain a good analysis of this material.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner[37] and recrystallized from ethanol, melted at 126–130°.

Anal. Calcd. for $C_{14}H_{14}O_4N_4$: C, 55.63; H, 4.67; N, 18.54. Found: C, 55.42; H, 4.68; N, 18.54.

B. By Rearrangement of the Epoxide 3a on Alumina.—A 300-mg. sample of the epoxide **3a** was dissolved in 5 ml. of pentane and chromatographed on a 1 × 15 cm. column packed with 12

(36) Ref. 2, Plate IV.

(37) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, New York, N. Y., 1956, p. 219.

g. of Merck acid-washed alumina. The column was eluted with 30 ml. of pentane followed by 10% ether in pentane. Ten-milliliter fractions were collected. All of the nonpolymeric material eluted in fractions 5 through 10. An infrared analysis of fraction 5 indicated the presence of some unrearranged epoxide. Fractions 6–10 were combined and concentrated by distillation of most of the solvent through a 10-cm. Vigreux column at atmospheric pressure. The remainder of the material, when short-path distilled at ~90° (7 mm.) in a semimicro still, yielded 53 mg. (18%) of a material whose infrared spectrum was identical with the aldehyde **4b** collected from the gas chromatograph.

C. By Rearrangement with Lewis Acids.—Small samples of the epoxide **3a**, collected from the silicone rubber column and containing about 10% of the aldehyde **4b** as a contaminant, were treated with ethereal solutions of boron trifluorode etherate and of aluminum trichloride at room temperature. After the solutions had been allowed to stand for about 15 min. they were washed with aqueous base and analyzed by gas chromatography on the silicone rubber column at 80°. Neither of the reaction mixtures showed any epoxide; each showed small amounts of the aldehyde **4b** together with a large amount of very high boiling material, probably polymer, which was not identified. No isomeric aldehyde was detected.

Bicyclo[2.2.1]hept-2-ene-*syn*-7-carboxylic Acid (6b).—A 100-mg. sample of the aldehyde (**4b**), collected from the silicone oil column at 110°, was dissolved in 1.5 ml. of methanol. Water (1 ml.) and of silver nitrate (360 mg.) were added. The mixture was stirred to dissolve the silver nitrate, and 200 mg. of sodium hydroxide was added. Stirring was continued at room temperature for 2 hr. The precipitated silver and silver oxide were removed by filtration and washed with water. The combined filtrate and washings was saturated with sodium chloride, and the still basic solution was extracted with ether to remove any unchanged aldehyde. The solution was acidified and extracted with ether in a small continuous extractor for 24 hr. The ethereal extract was dried over anhydrous sodium sulfate, the solvent was removed by distillation through a 10-cm. Vigreux column, and the residue was purified by sublimation at 80° (5 mm.) to yield 90 mg. (80%) of a white crystalline acid, m.p. 94–100°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.32; H, 7.20.

Infrared[15a]: λ_{max}^{KBr} 3.37 broad (O—H); 5.70 (—COOH, monomeric); 5.86 (—COOH, dimeric); 6.05 (>C=C<); 14.30 μ (>C=C*H*—).

The methyl ester (15b) was prepared by treating a small sample of the acid **6b** with an ethereal solution of diazomethane. When analyzed by gas chromatography on the Carbowax column at 170°, conditions which will separate and resolve the methyl esters of the *syn*- and *anti*-bicyclo[2.2.1]hept-2-ene-7-carboxylic acids, only one ester was found. The infrared spectrum was determined on a sample of this ester **15b** collected from the Carbowax column.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 3.26, shoulder, 14.17, broad, (>C=C*H*—); 5.76 (—C*O*—O—); 6.17 μ, very weak (>C=C<).

Bicyclo[2.2.1]heptane-7-carboxylic Acid (8).—A small sample of the unsaturated acid **6b** was hydrogenated at atmospheric pressure in 95% ethanol using 5% palladium on charcoal as catalyst. The catalyst was removed by filtration, the solvent was distilled through a 10-cm. Vigreux column, and the residual acid was purified by sublimation at 85° (5 mm.) to yield a new acid, m.p. 72–75° (lit.[18] m.p. 77.5–78.5°).

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 3.38 μ, broad (O–H); 5.71 μ (–COOH, monomeric); 5.87 μ (–COOH, dimeric). This spectrum showed no evidence of a double bond and was in good agreement with the infrared spectrum (KBr) reported by Kwart and Kaplan for bicyclo[2.2.1]heptane-7-carboxylic acid.[18]

Bicyclo[2.2.1]hept-2-ene-*syn*-7-methanol (7b). A. From Bicyclo[2.2.1]hept-2-en-*syn*-7-carboxaldehyde (4b).—To a stirred slurry of 100 mg. of lithium aluminum hydride in 3 ml. of anhydrous ether was added 240 mg. of aldehyde **4b** in 5 ml. of anhydrous ether. The reaction mixture was stirred at reflux for 2 hr., cooled, and decomposed by the addition of water and 15% aqueous sodium hydroxide. The precipitated salts were removed by filtration and washed with ether. The ethereal solution was concentrated to about 0.5 ml. by distillation of the solvent through a 10-cm. Vigreux column. A gas chromatographic analysis of this concentrate on the Ucon column at 140° showed the presence of only one compound whose retention time was different from that of the starting material **4b** or the tertiary alcohol **5a**. This product was collected from the Ucon column, yield 130 mg. (53%).

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.46; H, 9.90.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 2.75, 3.00 (O–H); 3.27, 14.05, broad (>C=C*H*—); 6.16 (>C=C<); 9.78 μ, broad (–CH_2–OH). This spectrum was identical with that of the alcohol formed by esterification and lithium aluminum hydride reduction of the higher-melting of Sauers' bicyclo[2.2.1]hept-2-ene-7-carboxylic acids (**6b**).[21]

N.m.r.: $\nu_{max}^{CCl_4}$ 4.15, poorly defined assymmetric quartet (2 >C=C*H*—); 6.3–6.7, broad, concentration dependent (1 —CH_2O*H*); 6.62, doublet, J = 7 c.p.s. (2 —C*H*$_2$—OH); 7.29, poorly defined doublet, J = 2 c.p.s. (2 >C$_1$—*H*, bridgehead); 8.1–9.2 τ, complex multiplet (1 >C$_7$—*H*, 2 >C*H*H, 2 >CH*H*).

B. From Spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2′-oxacyclopropane] (3a).[17]—To a cold slurry of 15 mg. of lithium aluminum hydride in 2 ml. of anhydrous ether was added a cold solution of 32 mg. of aluminum trichloride in 2 ml. of anhydrous ether. The mixture was cooled to −10° in an ice–salt bath, and a solution of 100 mg. of epoxide **3a** in 3 ml. of anhydrous ether was added dropwise to the stirred slurry. The reaction mixture was stirred for 30 min. in the ice–salt bath and then at room temperature for an additional 30 min. A 15% solution of sodium hydroxide was added, the precipitated salts were removed by filtration, and the filtrate was dried over anhydrous magnesium sulfate.

A gas chromatographic analysis of the ethereal solution on the silicone oil column showed the presence of bicyclo[2.2.1]hept-2-ene-*syn*-7-methanol (**7b**) (90%), 7-methylbicyclo[2.2.1]hept-2-en-*anti*-7-ol (**5a**) (4%), and 6% of two unidentified components. No bicyclo[2.2.1]hept-2-ene-*anti*-7-methanol (**7a**) could be detected.

The ethereal solution was concentrated to about 1 ml. by distillation of the solvent through a 10-cm. Vigreux column, and the primary alcohol **7b** was isolated by collection from the silicone oil column. The yield of pure material isolated in this manner was 41 mg. (40%).

The infrared spectrum of this material was identical to that of the alcohol prepared by the reduction of the aldehyde **4b**, *i.e.*, **7b**.

The formation of the tertiary alcohol **5a** could be completely suppressed by using twice as much aluminum trichloride. However, under these conditions the proportion of unidentified material was increased to about 20%, and the proportion of the primary alcohol **7b** was reduced to 80% of the product mixture.

C. From the Higher-Melting of Sauers' Acids (6b).—A solution of a small amount of the higher-melting of the two bicyclo[2.2.1]hept-2-ene-7-carboxylic acids,[21] (m.p. 94–100°) in ether was treated with a stoichiometric amount of ethereal diazomethane. The solution was dried over anhydrous magnesium sulfate and treated with an excess of lithium aluminum hydride in 2 ml. of anhydrous ether. The mixture was heated under reflux for 1 hr., and enough 15% sodium hydroxide was added to decompose the complex and the excess hydride. The ethereal solution was decanted from the precipitated salts, dried over anhydrous magnesium sulfate, and analyzed by gas chromatography on the silicone oil column. Only one compound was present, the retention time and infrared spectrum of which were identical to those of the alcohol **7b** prepared by reduction of the aldehyde **4b**.

Bicyclo[2.2.1]hept-2-ene-*anti*-7-methanol (7a).—A solution of 25 mg. of bicyclo[2.2.1]hept-2-ene-*anti*-7-carboxylic acid[21] (m.p. 70.5–71.5°) in 0.5 ml. of ether was treated with a stoichiometric amount of ethereal diazomethane. The solution was dried over anhydrous magnesium sulfate and added dropwise to a stirred slurry of 30 mg. of lithium aluminum hydride in 1 ml. of ether. The mixture was heated under reflux for 1 hr. A 15% solution of sodium hydroxide was added, the precipitated salts were removed by filtration, and the filtrate was concentrated to about 0.2 ml. through a 2-in. Vigreux column. Gas chromatographic analysis of the product on the silicone oil and on the Ucon column showed the presence of only one component. The product was collected from the silicone oil column; yield, 13 mg. (60%).

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.57; H, 9.83.

Infrared[15a]: λ_{max}^{film} 3.00 (O—H); 3.29, 14.30, broad (>C=C*H*—); 6.22 (>C=C<); 9.79 μ, broad (CH$_2$—OH).

N.m.r.: $\nu_{max}^{CCl_4}$ 3.94, triplet, J = 2 c.p.s. (2 >C=C*H*—); 6.77, doublet, J = 7 c.p.s. (2 —C*H*$_2$OH); ~7, singlet, concentration dependent (1 —CH$_2$O*H*); 7.32, poorly defined quartet

(2 >C_1—H, bridgehead); 8.0–9.3 τ, complex multiplet (1 >C_7—H, 2 >C*H*H, 2 >CH*H*).

α,α-Dimethylbicyclo[2.2.1]hept-2-ene-*syn*-7-methanol (17b).—A solution of 80 mg. of bicyclo[2.2.1]hept-2-ene-*syn*-7-carboxylic acid (6b) in 2 ml. of ether was treated with a stoichiometric amount of ethereal diazomethane. The solution was dried over anhydrous magnesium sulfate and then was added dropwise to 5 ml. of an ethereal solution of methylmagnesium iodide, prepared from 110 mg. of magnesium turnings and 700 mg. of methyl iodide. The reaction mixture was heated under reflux for 3 hr., stirred at room temperature overnight, and cooled in an ice bath. Ten milliliters of water and 500 mg. of sodium sulfate were carefully added, the mixture was shaken in a separatory funnel, the two layers were separated, and the aqueous layer was washed with 10 ml. of ether. The combined ethereal solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated to about 1 ml. by distillation of the solvent through a 10-cm. Vigreux column.

A gas chromatographic analysis of this concentrate on the silicone oil column at 140° showed the presence of the tertiary alcohol **17b** (95%) and some relatively volatile compounds (5%) which were probably formed by dehydration of the tertiary alcohol during the work-up and/or analysis. The alcohol **17b** was isolated by collection from the silicone oil column at 140° and was purified for analysis by distillation in a semimicro short-path still heated in an oil bath at 90–95° under 10 mm. pressure. The yield was 46 mg. (52%) of collected material.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.94; H, 10.31.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 2.79 (O—H); 3.27, 14.02 (>C=C*H*—); 7.26, 7.36, 8.25, 8.35 (>C(CH_3)$_2$); 6.12 (>C=C<); 8.81 μ (>C—OH). $\nu_{max}^{CCl_4}$ 3617 cm.$^{-1}$, weak (free O—H); 3577 cm.$^{-1}$, strong (π-electron, hydrogen-bonded O—H).[19]

N.m.r.: $\nu_{max}^{CCl_4}$ 4.03, triplet, J = 2 c.p.s. (2 >C=C*H*); 7.10, poorly defined doublet (2 >C_1—*H*, bridgehead); 8.29, singlet (1 O—*H*) superimposed on a multiplet at 8.0–8.5, (1 >C_7—H, 2 >C*H*H); 8.9–9.3, multiplet (2 >CH*H*) superimposed on a singlet at 8.97 τ (6 —CH_3).

α,α-Dimethylbicyclo[2.2.1]hept-2-ene-*anti*-7-methanol (17a).—This alcohol was prepared in the same manner as the *syn* isomer **17b** starting with 150 mg. of a mixture of bicyclo[2.2.1]hept-2-ene-7-*syn*- and 7-*anti*-carboxylic acids (35% *syn*, 65% *anti*).[21] The resulting mixture of tertiary alcohols was separated by gas chromatography on the Ucon column at 135°. The yield was 24 mg. (14%) of the *syn* alcohol (identical in all respects with **17b** as described) and 58 mg. (35%) of the *anti* alcohol **17a**. An analytical sample of **17a** was obtained by distillation of the collected material in a semimicro short-path still heated in an oil bath at 90–95° under 10-mm. pressure.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.76; H, 10.61.

Infrared[15a]: $\lambda_{max}^{CCl_4}$ 2.76, 2.85 (O—H); 3.27, 14.23 (>C=C*H*—); 6.14 (>C=C<); 7.35 (C—CH_3); 8.10, 8.23 (C(CH_3)$_2$); 8.72 μ (>C—OH?). $\nu_{max}^{CCl_4}$ 3618–3629 cm.$^{-1}$, broad (nonbonded O—H).[19]

N.m.r.: $\nu_{max}^{CCl_4}$ 3.89, triplet, J = 2 c.p.s. (2 >C=C*H*—); 7.23, poorly defined doublet (2 >C_1—*H*, bridgehead); 8.85 τ, singlet (—CH_3). The remainder of the spectrum was too complex to make definite assignments, but the total integrated peak area between 7.8 and 9.3 τ corresponded to twelve hydrogens.

2-Chloromercuri-9-oxatricyclo[4.3.0.0^{3,7}]nonane (16).—To a solution of 22 mg. of bicyclo[2.2.1]hept-2-ene-*syn*-7-methanol (**7b**) in 0.2 ml. of methanol was added 53 mg. of anhydrous mercuric acetate.[25] After the solution had stood at room temperature for 90 min., a test for the presence of mercuric ion, using 15% sodium hydroxide and a small sample of the solution, was negative. A solution of 20 mg. of sodium chloride in 0.5 ml. of 50% methanol was added to the reaction mixture. A white precipitate formed immediately. The precipitate was filtered and dried to yield 41 mg. (64%) of product which melted with decomposition from 176–180°. After two recrystallizations from benzene the melting point was unchanged.

Anal. Calcd. for $C_8H_{11}OHgCl$: C, 26.75; H, 3.09; O, 4.45; Hg, 55.69. Found: C, 27.61; H, 3.36; O, 4.63; Hg, 55.05.

The infrared spectrum, determined in a potassium bromide pellet, was too complex to analyze properly (thirty strong peaks between 6.75 and 13.0 μ). However, it did not show any evidence for a hydroxyl, a methoxyl, or a double bond.

Gas Chromatographic Analysis.—The following columns were used for the gas chromatographic work described herein: a 0.25 in. × 8 ft. coiled stainless steel tube packed with 25% Dow-Corning silicone oil 200 on 60–80-mesh Chromasorb P; a 0.25 in. × 8 ft coiled copper tube packed with 20% General Electric SE 30 silicone rubber on 80–100-mesh acid-washed firebrick; a 0.25 in. × 6 ft. double hairpin copper tube packed with 15% Carbowax 20M on 80–100-mesh neutral firebrick; a 0.25 in. × 7 ft. coiled copper tube packed with 20% Ucon, water insoluble, on 60–80-mesh Chromasorb P. Helium was used as a carrier gas at flow rates ranging from 50–100 ml./minute.

Nuclear Magnetic Resonance Spectra.—During the course of this work we have examined the n.m.r. spectra of fifteen symmetric, 7-substituted bicyclo[2.2.1]hept-2-enes, nine of which are reported here. A characteristic feature in each of these spectra is the resonance of the two vinyl hydrogens, H-2 and H-3, whose gross appearance is that of a triplet centered at 3.86 to 4.13 τ (but see ref. 13) and split by 1.8 to 2.4 c.p.s. It has also been reported that the vinyl hydrogen resonance of bicyclo[2.2.1]hept-2-ene appears as "an unsymmetrical triplet" centered at 4.06 τ.[38] The gross appearance of the vinyl hydrogen resonance as a triplet in these spectra instead of as a more complex A_2X_2 pattern,[39] can probably be attributed to the fact that the coupling between a vinyl hydrogen and the nearest bridgehead hydrogen is of the same approximate magnitude as the coupling between the two vinyl hydrogens themselves, *i.e.*, $J_{12} \sim J_{23}$,[40] The values which we report must therefore approximate the average of the vinyl bridgehead and the vinyl–vinyl couplings, *i.e.*, $(J_{12} + J_{23})/2$, and are probably accurate to about 0.5 to 1.0 c.p.s. The presence of further fine splitting in the vinyl resonance region of most of our spectra is evidence that the longer range couplings which have been reported in the case of bicyclo[2.2.1]heptadiene,[40,41a] 5-substituted bicyclo[2.2.1]hept-2-enes,[41b] and 5-substituted 7-isopropylidenebicyclo[2.2.1]hept-2-enes[41c] are also present in the symmetric, 7-substituted bicyclo[2.2.1]-heptenes. We have observed that this further splitting of the vinyl hydrogen resonance in each of these compounds is more pronounced in the *syn* isomers and can thus serve as an indication of molecular configuration.

We note that most of the "average" vinyl couplings, *i.e.* $(J_{12} + J_{23})/2$, which we find are smaller than those reported elsewhere, *e.g.*, J_{12} = 2.2–3.3 c.p.s.,[40,41a] J_{23} = 3.45–6.0 c.p.s.[40,41a,c] We suspect that this may be due in part to the fact that our spectra were usually determined from solutions which were quite dilute and which had not been degassed.[34]

Acknowledgment.—The authors are indebted to Dr. L. P. Kuhn of the Ballistics Research Laboratory, Aberdeen Proving Ground, who carried out the infrared studies of hydrogen bonding reported herein, and to Prof. M. R. Willcott of Emory University for helpful discussions of the n.m.r. spectra. We are pleased to acknowledge the financial support given this work by the Petroleum Research Fund of the American Chemical Society, Grant No. 911-A4, and an institutional grant to the University of South Carolina from the National Science Foundation for the purchase of a Varian A-60 n.m.r. spectrometer.

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Hydrocarbon Chlorinations with Phosphorus Pentachloride[1]

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Received June 27, 1963

Phosphorus pentachloride smoothly chlorinates a variety of alkylated aromatic and aliphatic hydrocarbons in either a thermal or catalyzed (benzoyl peroxide) reaction according to $RH + PCl_5 \rightarrow RCl + HCl + PCl_3$ to yield benzylic chlorides and aliphatic chlorides, respectively. Cumene, while reacting rapidly, undergoes a variety of side reactions which greatly diminish the yield of monochlorinated product. Mesitylene substitutes mainly by an ionic process to give 2,4,6-trimethylchlorobenzene. Competitive experiments show that this chlorinating system has about the same selectivity as photochlorination. Olefins react readily with PCl_5 at elevated ($\sim$100°) temperatures *via* an ionic mechanism to give high yields of dichloro derivatives in which *trans* addition to the double bond has occurred.

Only a few reports[2,3] concerning the reactions of phosphorus pentachloride with nonolefinic hydrocarbons have appeared. These involved highly arylated compounds such as triphenylmethane and diphenylmethane which reacted readily under conditions conducive to free-radical reactions (high temperatures) to yield trityl chloride and diphenylmethyl chloride, respectively. The availability and relative ease of handling of PCl_5 made a more extensive study appear to be worthwhile and part of this paper presents the results of such an investigation made with a variety of alkylated benzenes and aliphatic hydrocarbons under different experimental conditions.

On the other hand, the reaction of PCl_5 with olefins has received considerable attention.[4-13] For the most part these reactions have been directed towards the synthesis of olefinic phosphonic acid derivatives or their β-chloro derivatives. In certain instances, however, dichlorinated compounds were also detected among the products.[8,12] Reactions of this type have been reinvestigated in order to determine whether the chlorination could be made to be predominant and, if so, whether the addition would be stereoselective.

Results

The hydrocarbon chlorination data are compiled in Table I. Chlorobenzene showed no detectable reaction even after prolonged treatment and as a matter of convenience it or *o*-dichlorobenzene were often used as solvents.

The aliphatic compounds cyclohexane and *n*-heptane dissolved very little PCl_5 even at their boiling points and the thermal reactions gave very low yields of chlorinated products. When the reactions were run under homogeneous conditions in *o*-dichlorobenzene solvent, the yields obtained in the thermal reactions were increased significantly over those obtained in the absence of a solvent, but they were still quite low compared with those obtained under the same conditions with the alkylated aromatic compounds. In general the per cent chlorination under these conditions varied directly with the time of reaction. The decreased yields with these compounds mostly can be attributed to the lower reflux temperatures prevailing during the experiments. When the reactions were catalyzed by small amounts of benzoyl peroxide the rates of chlorination were greatly increased.

The yields of chlorinated products obtained with the alkylated aromatic derivatives also varied with the time of reaction but were always much higher than those encountered with the lower boiling aliphatic systems. While the rates could be increased by catalysis with benzoyl peroxide, good yields were obtained with $\sim$16-hour reaction periods *via* the thermally induced reaction. Thus, toluene reacted readily by the thermal or catalyzed reaction to give good (60–70%) yields of benzyl chloride. Similar behavior was exhibited by *p*-xylene and 60–70% yields of *p*-methylbenzyl chloride were obtained. In the presence of an excess of PCl_5 it was possible to chlorinate the second methyl group to give α,α'-dichloro-*p*-xylene. No evidence for the formation of benzal dichlorides was found.

Ethylbenzene yielded α-phenethyl chloride almost exclusively with only 0.5% of the β-derivative being formed. Similarly, *p*-ethyltoluene reacted smoothly to give a mixture of *p*-methyl-α-phenethyl chloride and *p*-ethylbenzyl chloride (34.8% and 25.2%, respectively). Only small traces of the β-phenethyl derivative were found.

Cumene reacted very readily and hydrogen chloride was rapidly evolved in large quantities. Upon work-up, however, it was found (either on a small scale with analysis by v.p.c. or in a preparative reaction) that only low or modest yields (20–30%) of the expected phenyldimethylcarbinyl chloride were obtained and that the major products were a mixture of compounds which were relatively high boiling, 120–135° (15 mm.). This mixture was examined *via* n.m.r. The lower boiling component, 120–130° (15 mm.), showed evidence of a benzylic or conjugated $-CH_2Cl$ (sharp singlet at τ 5.65), an uncoupled methyl group (τ 8.0), along with much smaller quantities of vinyl protons (centered at τ 3.78). The higher boiling portion, 130–135° (15 mm.), showed a diminished methyl singlet (τ 7.98),

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TABLE I
HYDROCARBON CHLORINATIONS

Hydrocarbon	Moles hydrocarbon / moles PCl_5	Solvent[c]	Temp., °C.	Time, hr.	Products, % yield based on PCl_5
Chlorobenzene	2		120	12	99% Recovery of C_6H_5Cl
Cyclohexane	1.56	ODCB	90	8	$C_6H_{11}Cl$ (13)
Cyclohexane	3		88	5	$C_6H_{11}Cl$ (~1)
Cyclohexane[a]	3	ODCB	88	7	$C_6H_{11}Cl$ (70.2)
Cyclohexane	2	ODCB	88	13	$C_6H_{11}Cl$ (20)
n-Heptane	3		90	8	Mixed chloroheptanes (~2)
n-Heptane	3	ODCB	90	14	Mixed chloroheptanes (23)
n-Heptane[a]	3	ODCB	90	8	Mixed chloroheptanes (73.2)
p-Xylene	1.2		110	10	*p*-Methylbenzyl chloride (30.8) + α,α'-dichloro-*p*-xylene (6.5)
p-Xylene	1.0	C_6H_5Cl	110	16	*p*-Methylbenzyl chloride (67.3) + α,α'-dichloro-*p*-xylene (0.2)
p-Xylene	0.6		110	16	*p*-Methylbenzyl chloride (50.4) + α,α'-dichloro-*p*-xylene (14.8)
Toluene	3		100	16	Benzyl chloride (65.1)
Toluene[a]	3		100	7	Benzyl chloride (72.1)
Ethylbenzene	4		105	16	α-Phenethyl chloride (60) + β-phenethyl chloride (0.5)
p-Ethyltoluene	2		105	16	*p*-Methyl-α-phenethyl chloride (34.8) + *p*-ethylbenzyl chloride (25.2)
Mesitylene	1.5		110	16	2,4,6-Trimethylchlorobenzene (37) + 3,5-dimethylbenzyl chloride (25.2)
Mesitylene	1.0	C_6H_5Cl	110	16	2,4,6-Trimethylchlorobenzene (35) + 3,5-dimethylbenzyl chloride (23)
Mesitylene	1.2	MDNB	90	10	2,4,6-Trimethylchlorobenzene (63)
Mesitylene[a,b]	3		88	8	3,5-Dimethylbenzyl chloride (59.2) + 2,4,6-trimethylchlorobenzene (3) + dichloronated product (1.1)
Toluene + ethylbenzene	4		115	16	Benzyl chloride (34.8) + α-phenethyl chloride (28.4) + β-phenethyl chloride (0.5)
Toluene + cyclohexane	5.6		88	13	Benzyl chloride (4.85) + cyclohexyl chloride (22.6)
Toluene + cyclohexane[a]	2	MDNB	85	8	Benzyl chloride (8) + cyclohexyl chloride (17.6)
Cumene	2		110	14	Phenyldimethylcarbinyl chloride (28.5) + higher chlorinated products

[a] Reaction catalyzed with benzoyl peroxide. [b] Reaction with SO_2Cl_2 instead of PCl_5. [c] ODCB = *o*-dichlorobenzene; MDNB = *m*-dinitrobenzene.

two very small $-CH_2Cl$ (tentatively assigned) peaks at τ 5.65 and τ 5.80 and only very small quantities of vinyl protons. Neither the n.m.r. nor infrared spectra indicated any significant amounts of ring chlorination and it is concluded that the major products of the cumene–PCl_5 reaction were a mixture of highly chlorinated derivatives containing some chloro olefins (*vide infra*).

Mesitylene underwent substitution very readily in the thermal reaction to give a 60–70% total yield of products in which the ring chlorinated isomer, 2,4,6-trimethylchlorobenzene, was predominant. In contrast, a chlorination with SO_2Cl_2 catalyzed by benzoyl peroxide gave mainly 3,5-dimethylbenzene chloride with only ~3% ring chlorination. When the reaction was conducted in the presence of *m*-dinitrobenzene, 2,4,6-trimethylchlorobenzene was obtained as the sole product in 63% yield (by actual isolation).

A series of competitive experiments were performed with excesses of equimolar mixtures of toluene and ethylbenzene, and toluene with cyclohexane. The former gave a mixture containing benzyl chloride (34.8%), α-phenethyl chloride (28.4%), and only 0.5% of β-phenethyl chloride. The latter mixture gave 22.6% cyclohexyl chloride and 4.85% benzyl chloride when reacted thermally without solvent and 17.6% cyclohexyl chloride and 8% benzyl chloride when reacted in the presence of *m*-dinitrobenzene and catalyzed by benzoyl peroxide.

In all of these reactions phosphorus trichloride and hydrochloric acid were products and each was isolated and/or trapped and identified. In all cases distillation could be carried out virtually to completion with only negligible residues remaining. This along with n.m.r. and infrared spectral data is excellent evidence for the lack of formation of organophosphorus compounds in these reactions.

Three olefins, octene-1, cyclohexene, and *trans*-stilbene, were investigated and the results are shown in Table II. The yields listed were based upon actual isolation of the products. Octene-1 was very readily converted to 1,2-dichlorooctane in 83% yield at the reflux temperature (91°) of the reaction mixture (using chlorobenzene as solvent). Only negligible amounts of other products were obtained.

TABLE II
OLEFIN CHLORINATIONS

Hydrocarbon	Moles PCl_5 / moles olefin	Solvent	Temp., °C.	Time, hr.	% yield based on PCl_5[a]
Octene-1	0.5	C_6H_5Cl	91	6	1,2-Dichlorooctane (83)
Cyclohexene	1	MDNB[b]	80	10	*trans*-1,2-Dichlorocyclohexane (87)
trans-Stilbene	0.5	C_6H_5Cl	124	12	*meso*-1,2-Dichlorostilbene (85) + *dl*-1,2-dichlorostilbene (13.1)

[a] Yields based on actual isolation of products. [b] Actually a catalytic amount (0.05 mole) was used.

The reaction with cyclohexene was conducted in the presence of a small amount of *m*-dinitrobenzene and an 87% yield of *trans*-1,2-dichlorocyclohexane was obtained. None of the *cis* isomer was detected and if it was present it was there in very small quantities. There is a small but significant difference in boiling points of the two isomers[14] but only a single peak was found *via* v.p.c.

Two isomers (in nearly quantitative total yield) were found when *trans*-stilbene reacted with PCl_5 at reflux (124°) in chlorobenzene. The major component was *meso*-1,2-dichlorostilbene (85%) while the minor component was the *dl* mixture (13.1%). When the *dl* mixture was heated in chlorobenzene in the presence of catalytic amounts of PCl_5, it was found that no detectable amount of isomerization had occurred.

Discussion

The competitive reaction between cyclohexane and toluene in photochlorination has been reported.[15] With toluene assigned a relative reactivity value of 1.0 per replaceable methyl hydrogen, it was found that each hydrogen in cyclohexane was 2.8 times as reactive. This result demonstrates that resonance stabilization is not important in the transition state which in turn reflects the highly exothermic nature of the reactions of carbon–hydrogen bonds with chlorine atoms.[16] With PCl_5 in a thermal reaction, the reactivity per C–H in cyclohexane was found to have a value of 3.0 compared to the methyl C–H bonds in toluene again with an assigned relative reactivity of 1.0. Thus, the systems are very similar in their over-all behavior. This then implies that the attacking radical in the PCl_5 reaction is either a chlorine atom or a substance with about the same activity as a chlorine atom. The following scheme (equations 1–7) seems reasonable.

$$PCl_5 \rightleftharpoons PCl_3 + Cl_2 \quad (1)$$

$$Cl_2 \rightleftharpoons 2Cl\cdot \text{ thermal reaction} \quad (2)$$

$$R\cdot + PCl_5 \longrightarrow RCl + \cdot PCl_4 \text{ catalyzed reaction} \quad (3)$$

$$PCl_4 + RH \longrightarrow HPCl_4 + R\cdot \quad (4)$$

$$HPCl_4 \longrightarrow HCl + PCl_3 \quad (5)$$

$$\cdot PCl_4 \rightleftharpoons PCl_3 + Cl\cdot \quad (6)$$

$$Cl\cdot + RH \longrightarrow R\cdot + HCl \quad (7)$$

It is difficult *per se* to distinguish whether steps 4 and 5 are important or whether $\cdot PCl_4$ first decays rapidly to $PCl_3 + Cl\cdot$ as in step 6. The competitive experiments imply that step 6 is the important one, although the depicted equilibria may be of considerable importance and many reactive species may be involved in a complex manner.[17] Interestingly, the same question appears with chlorinations conducted with sulfuryl chloride[18] wherein most, but not all, of the results are explicable by a step involving $SO_2Cl\cdot \rightarrow SO_2 + Cl$.

The relative rates of the thermal reactions varied directly with temperature. This result is entirely consistent with steps 1 and 2. The ability of PCl_5 to chlorinate a variety of hydrocarbons in a thermal reaction is one of the areas in which it differs fundamentally from other chlorinating agents such as sulfuryl chloride.[19] This of course is partly due to the higher reflux temperatures available by use of this reagent.

A benzoyl peroxide-catalyzed competitive experiment between cyclohexane and toluene was performed in the presence of *m*-dinitrobenzene. As expected, the over-all yields were decreased because nitrated aromatic solvents are poor media for radical substitution reactions.[20] The results showed that under these conditions toluene was 1.8 times more reactive per CH_3 hydrogen than was cyclohexane, a result practically opposite that obtained in the reaction conducted in the absence of *m*-dinitrobenzene. It has been previously reported that certain solvents (usually aromatic) can form complexes with chlorine atoms to lower their energy and increase their selectivity.[21,22] It is quite probable that a type of coordination occurs in this system and involves the nitro compound. Whether this might involve $\cdot PCl_4$ or $\cdot Cl$ or both cannot be estimated.

While the chlorinations of most of the hydrocarbons took place smoothly to yield the expected products there were significant exceptions. Cumene reacted readily but only a relatively small yield of the expected phenyldimethylcarbinyl chloride was isolated. Most of the product was a more extensively chlorinated mixture. Cumene, of course, can be chlorinated readily either photochemically with chlorine[15] or with sulfuryl chloride[15] to give predominantly the tertiary chloride. The results with PCl_5 are interpretable on the basis of a series of dehydrohalogenation reactions catalyzed by PCl_5 with subsequent additions of chlorine across the double bonds.

$$R_2C(Cl)CH_3 + PCl_5 \longrightarrow R_2\overset{+}{C}CH_3PCl_6^-$$

$$R_2\overset{+}{C}CH_3PCl_6^- \longrightarrow R_2C{=}CH_2 + HCl + PCl_5$$

$$R_2C{=}CH_2 + PCl_5 \longrightarrow R_2CCl{-}CH_2Cl + PCl_3$$

Ability of PCl_5 to function as a Lewis acid (albeit a weak one) is well established,[23] while the halogen addition to olefins is discussed subsequently.

Mesitylene when chlorinated by sulfuryl chloride gave good yields of 3,5-dimethylbenzyl chloride with only about 3% ring chlorination. On the other hand, the thermal reaction with PCl_5 gave a mixture which was predominantly the ring substituted compound, 2,4,6-trimethylchlorobenzene (in a ratio of about 1.5:1). When the reaction was conducted in the presence of *m*-dinitrobenzene the product was exclusively 2,4,6-trimethylchlorobenzene. It is quite evident that in this case an ionic reaction competes with the free-radical substitution. The addition of a polar com-

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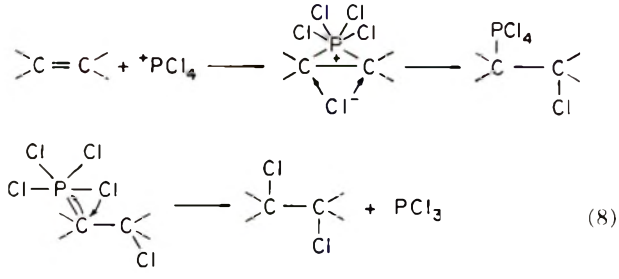
(15) G. A. Russell and H. C. Brown, *ibid.*, **77**, 4578 (1955).
(16) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 370.
(17) As pointed out by one of the referees, the bond reactivity data, obtained from competitive chlorination experiments between toluene and cyclohexane, tend to support step 6, but the isomer distributions of the products obtained from the chlorination of ethylbenzene and *p*-ethyltoluene do not. Whether the marked preference for benzylic substitution in these compounds is due to reaction with $\cdot PCl_4$, which would be expected to be less reactive than $Cl\cdot$, or to an energy lowering coordination[21,22] of $Cl\cdot$ and/or $\cdot PCl_4$ with the ring prior to hydrogen abstraction is not discernible from the present data. Experiments designed to help clarify these interesting observations are in progress.
(18) Ref. 16, pp. 380–381.
(19) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 2142 (1939).
(20) Ref. 16, p. 352.
(21) G. A. Russell, *J. Am. Chem. Soc.*, **80**, 4987 (1958).
(22) C. Walling and M. F. Mayahi, *ibid.*, **81**, 1485 (1959).
(23) M. Boaz, V. Gutmann, and J. R. Masaguer, *Monatsh.*, **92**, 582 (1961).

ponent, *m*-dinitrobenzene, which enhances ionic reactions but strongly inhibits free radical ones,[20] completely suppressed the free-radical path. This apparently is a manifestation of the activity of the mesitylene ring toward electrophilic attack and the reaction is akin to ring chlorinations by other more obvious Friedel–Crafts catalysts as reported by Kovacic.[24-27]

It has been known for a long time[4-13] that PCl_5 reacts with olefins in the cold to give compounds in which the elements of Cl–PCl_4 have been added. Surprisingly, little emphasis has been placed on the use of this reaction for the simple chlorination of olefins, and while a few examples[8,12] of 1,2-dichlorination in the system have been reported, no attempts to investigate the scope and general utility of the reaction have been made.

$$R{-}CH{=}CH_2 + PCl_5 \longrightarrow RCHCl{-}CH{-}PCl_4 \xrightarrow{H_2O} RCHCl{-}CH_2{-}PO_2H$$

Merely heating octene-1 with PCl_5 in chlorobenzene gave 1,2-dichlorooctane in 83% yield (isolated). No evidence for more than trace amounts of other compounds was found. Similarly, cyclohexene when heated with PCl_5 in the presence of *m*-dinitrobenzene gave an 87% yield of 1,2-dichlorocyclohexane which was apparently solely the *trans* isomer (infrared, refractive index, v.p.c.). The reaction of *trans*-stilbene (in chlorobenzene) gave an 85% yield of *meso*-1,2-dichlorostilbene (*trans* addition) and 13.1% of the *dl* mixture (*cis* addition). Thus the reactions proceed very readily and are highly stereoselective. At least in the case of cyclohexene–*m*-dinitrobenzene (and octene-1) they are obviously ionic. It has been postulated that the formation of *gem*-dichloride by reaction of PCl_5 with ketones involves $\overset{+}{P}Cl_4$ from 2 $PCl_5 \rightleftharpoons \overset{+}{P}Cl_4\overset{-}{P}Cl_6$.[28] Based on this argument, it would be expected that $\overset{+}{P}Cl_4$ would add to olefins to form a bridged cationic intermediate. Attack of a chloride ion on this would be from the side opposite of the very bulky PCl_4 group, thus giving the over-all *trans* addition. This is of course basically the mechanism accepted for ionic halogen additions to olefins. Phosphorus trichloride must then be eliminated by a SNi process as shown in equation 8.



(8)

While *trans*-stilbene would be expected to yield the same result by the same mechanism, small but significant quantities of the *dl* compound arising from *cis* addition were found. Isomerization of the *trans* dichloride to the *cis* dichloride is not thermodynamically favored and, in fact, under normal free-radical conditions, the reverse is found.[29] While many rationalizations could be put forth to explain this result, the simplest and most obvious is that at the somewhat elevated temperature at which this reaction was conducted both a free-radical and ionic addition were operative. This was apparently the situation in the reactions with mesitylene and seems a very reasonable explanation in this case.

Experimental[30]

General.—All of the liquid hydrocarbons used in this study were commercial reagent grade materials which were further purified by distillation from sodium. High purity phosphorus pentachloride (purchased from the Baker and Adamson Division of the Allied Chemical Corporation) was used as received.

The general chlorination procedure followed in all cases was to mix the reagents and then stir and reflux under nitrogen for the times listed in Tables I and II. After cooling, the reaction mixtures were either distilled directly without washing, or poured onto ice, washed with water and dilute $NaHCO_3$ solution, dried over anhydrous $CaCl_2$, and then distilled. Either method of work-up gave essentially the same results. The v.p.c. analyses were performed with a column composed of 10% Apiezon L on Anakrome ABS. Authentic samples for retention time comparisons were commercially available reagent grade compounds or were synthesized by straight forward procedures. N.m.r. spectra were obtained on a Varian A-60 spectrometer, using tetramethylsilane as an internal reference. This instrument was particularly useful and while in all cases isolation and/or v.p.c. were used for the ultimate analysis, in many cases the same results could have been obtained by this method alone. Bond reactivities in the competitive experiments were obtained by use of the nonintegrated expression,[15] $k_s/k_t([SH]/[TH])_{av} = [SCl]/[TCl]$, which corrects for losses of reagents due to causes other than chemical reaction.

A few typical examples of preparative scale experiments are given subsequently.

Chlorination of Ethylbenzene.—Ethylbenzene (135 g., 1.25 moles) was mixed with 62.5 g. of PCl_5 (0.31 mole). The mixing process was exothermic and the temperature rose to 55°. The reaction mixture was then stirred and refluxed (105°) under nitrogen for 16 hr. During this period, HCl was steadily evolved. Without washing[31] the clear light yellow solution which resulted was distilled through a helices-packed column. The first fraction was PCl_3 (b.p. 75° at atmospheric pressure). There was obtained 33 g. of it (77% yield). The next fraction, consisting of unchanged PCl_5 and ethylbenzene, was obtained at 134–135°. The final fraction, with b.p. 93–94° (15 mm.) weighed 24.5 g. The n.m.r. spectra of this colorless liquid was identical with that of an authentic sample of α-phenethyl chloride (quartet at τ 5.18, doublet at τ 8.42 in the proper intensity ratios). Analysis by v.p.c. showed that the product contained about 0.5% of β-phenethyl chloride.

Chlorination of Cyclohexene.—A mixture of cyclohexene (41 g., 0.5 mole), PCl_5 (104 g., 0.5 mole), and *m*-dinitrobenzene (8.4 g., 0.05 mole) was stirred and refluxed at 80° under nitrogen for 10 hr. The reaction mixture was then cooled, washed with water and dilute sodium bicarbonate solution (5%), and then dried over anhydrous calcium chloride. After stripping the unchanged cyclohexene *in vacuo* the product, b.p. 72–75° (15 mm.), was collected. It weighed 34 g. (87%); $n^{30}D$ 1.4873 (lit.[14] $n^{20}D$ 1.4904 for the *trans* isomer).

Anal. Calcd: for $C_6H_{10}Cl_2$: C, 47.1; H, 6.5; Cl, 46.4. Found: C, 47.19; H, 6.61; Cl, 46.21.

The infrared spectrum of this compound was identical with that listed in the literature[14] for the *trans* isomer. Only one peak was found *via* v.p.c.

Chlorination of *trans*-Stilbene.—A solution of *trans*-stilbene (22 g., 0.122 mole) and PCl_5 (51 g., 0.244 mole), in 200 cc. of

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(26) P. Kovacic and A. K. Sparks, *ibid.*, **26**, 2541 (1961).
(27) P. Kovacic, C. Wu, and R. W. Stuart, *J. Am. Chem. Soc.*, **82**, 1917 (1960).
(28) M. S. Newman and L. L. Wood, Jr., *ibid.*, **81**, 4300 (1959).
(29) R. E. Buckles, W. E. Steinmetz, and N. G. Wheeler, *ibid.*, **72**, 2496 (1950).
(30) Melting points are corrected, but boiling points are not. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.
(31) Any unchanged PCl_5 codistilled out of the reaction mixture with the excess hydrocarbons.

chlorobenzene was refluxed (124°) under nitrogen for 12 hr. Upon cooling, 17.5 g. of fine, snow white crystals of *meso*-1,2-dichlorostilbene[28] separated and were isolated (m.p. 193–194). Upon evaporation of the solution to one half its original volume and chilling, a further 8.5 g. of this compound were obtained. The remaining solution was evaporated to dryness and the residue was recrystallized from petroleum ether to yield 4.0 g. of *dl*-1,2-dichlorostilbene[28] (m.p. 90–91°).

Chlorination of Cumene.—A solution of cumene (240 g., 2 moles) and PCl_5 (208 g., 1 mole) was stirred and refluxed (110°) under nitrogen for 14 hr. Hydrogen chloride was rapidly evolved during this period. After washing with water and $NaHCO_3$ solution, the clear yellow solution which was obtained as distilled through a short packed column. There was obtained 44 g. (28.5%) of phenyldimethylcarbinyl chloride, b.p. 95–96° (15 mm.). N.m.r. showed a sharp singlet at τ 8.22; ratio of aliphatic protons to aromatic protons 6:5. There was also obtained 95 g. of a substance boiling mainly at 120–135° (15 mm.). This colorless liquid showed greatly diminished methyl peaks in its n.m.r. and infrared spectra as well as evidence in the former for $-CH_2Cl$ groups and small amounts of vinyl protons. It was not investigated further. These results were essentially reproducible. From the relative retention times in the v.p.c. analysis it was estimated that a mixture of di- and tri-chlorinated products had been formed.

Catalyzed Chlorination of Cyclohexane.—A mixture of cyclohexane (84 g., 1 mole) and PCl_5 (70 g., 0.33 mole) in 200 cc. of *o*-dichlorobenzene was refluxed (88°) under nitrogen for 7 hr. Small quantities of benzoyl peroxide were added periodically during this time and HCl was evolved. After cooling, the reaction mixture (which was a light yellow color at this point) was poured onto ice water. The organic layer was separated, washed consecutively with water and 5% $NaHCO_3$ solution, and then dried over anhydrous $CaCl_2$. Analysis by v.p.c. indicated a 70.2% yield of cyclohexyl chloride had been formed (based on PCl_5).

Acknowledgment.—We wish to thank Mr. Carl Lindemann for the gas chromatographic analyses and Mr. Paul Kaufman who helped with some of the experimental work.

The Reaction of Ethyl Azodicarboxylate with Conjugated Dienes. II[1,2]

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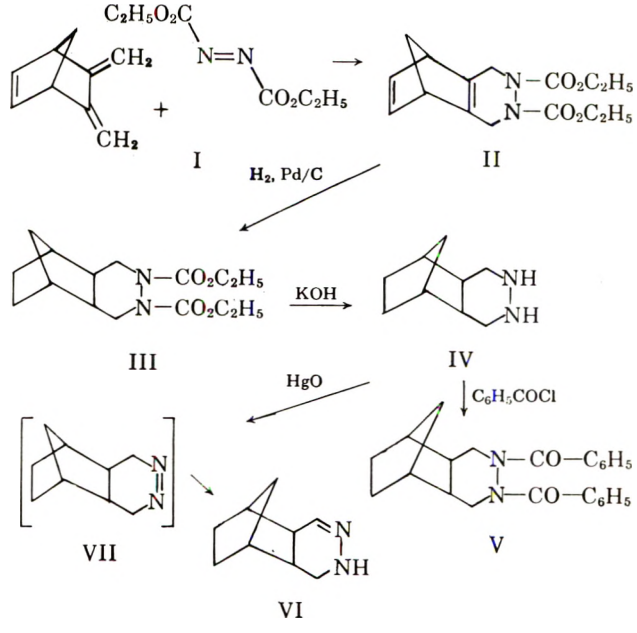
Received June 3, 1963

Further investigations of the reaction of ethyl azodicarboxylate (I) with conjugated dienes have been performed. The reaction of I with 5,6-dimethylenebicyclo[2.2.1]hept-2-ene gave the Diels–Alder adduct 1,2-dicarbethoxy-7,10-methano-1,2,3,6,7,10-hexahydro-4,5-benzopyridazine in 80% yield. Addition of I to bi(1-cyclohexen-1-yl) produced 1,2-dicarbethoxy-3,4,5,6-bis(tetramethylene)-1,2,3,6-tetrahydropyridazine in 80% yield. Treatment of 2,4-dimethyl-1,3-pentadiene with I proceeded by a concerted cyclic mechanism to give a mixture of isomers, 1,2-dicarbethoxy-1-[1-(4-methyl-2-methylene-3-pentenyl)]hydrazine (78.5%) and 1,2-dicarbethoxy-1-[3-(2,4-dimethyl-1,4-pentadienyl)]hydrazine (21.5%). The proofs of structure on the latter compounds were accomplished by instrumental methods and chemical degradation.

In a previous report from this laboratory,[2] it was shown that ethyl azodicarboxylate added to simple conjugated dienes by Diels–Alder or 1,4-addition, whereas, with more highly substituted conjugated dienes addition occurred by a different mechanism with a shift of the double bond.[2-4] The present report describes the results of an extension of these studies to other conjugated diene systems.

The addition of ethyl azodicarboxylate (I) to 5,6-dimethylenebicyclo[2.2.1]hept-2-ene took place with an evolution of heat and gave an 80% yield of the Diels–Alder adduct, 1,2-dicarbethoxy-7,10-methano-1,2,3,6,-7,10-hexahydro-4,5-benzopyridazine (II). The adduct II was hydrogenated over palladium-on-charcoal catalyst in ethanol to form 1,2-dicarbethoxy-7,10-methanodecahydro-4,5-benzopyridazine (III) in 82% yield. Hydrolysis of III was accomplished by refluxing in ethanolic potassium hydroxide solution for 11.5 hours. The cyclic hydrazine, 7,10-methanodecahydro-4,5-benzopyridazine (IV), was thus obtained in 84% yield. The dibenzoyl derivative of IV, 1,2-dibenzoyl-7,19-methanodecahydro-4,5-benzopyridazine (V) was prepared in 80% yield. Oxidation of IV was performed under a nitrogen atmosphere using yellow mercuric oxide in anhydrous ether. The only compound isolated was the cyclic hydrazone, 7,10-methano-Δ^2-octahydro-4,5-benzopyridazine (VI) in 63.5% yield, which was characterized by its infrared and ultraviolet spectra. The isolation of VI indicated that the azo compound VII had probably formed, but facile isomerization to the more stable structure VI, had taken place under the reaction conditions.



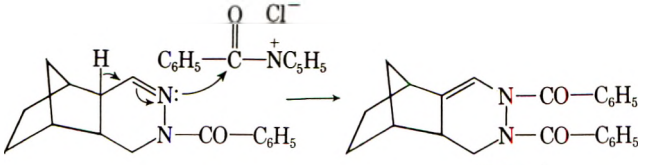
(1) This research was carried out under Grant No. 17836 from the National Science Foundation, whose support is gratefully acknowledged.

(2) For the previous report on this topic see B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **27**, 1947 (1962). The literature pertinent to this subject and leading references to prior investigations can be found in this reference.

(3) Abstracted in part from a thesis by P. E. Beck submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy, to Duquesne University, June, 1963.

(4) B. Franzus and J. H. Surridge, *J. Org. Chem.*, **27**, 1951 (1962).

Preparation of the benzoyl derivative of VI was attempted in pyridine. Instead of the desired monobenzoyl derivative, a compound was isolated, m.p. 179–180°, whose analysis corresponded to $C_{23}H_{22}N_2O_2$. The infrared spectrum of the compound was undefinitive except that it showed no N–H band, and a benzoyl type of carbonyl peak was present. The compound discolored permanganate and absorbed bromine. Further, it easily absorbed one molar equivalent of hydrogen catalytically to produce V. Thus, this compound was formulated as 1,2-dibenzoyl-7,10-methano-Δ^3-octahydro-4,5-benzopyridazine (VIII), which could arise by the following mechanism.

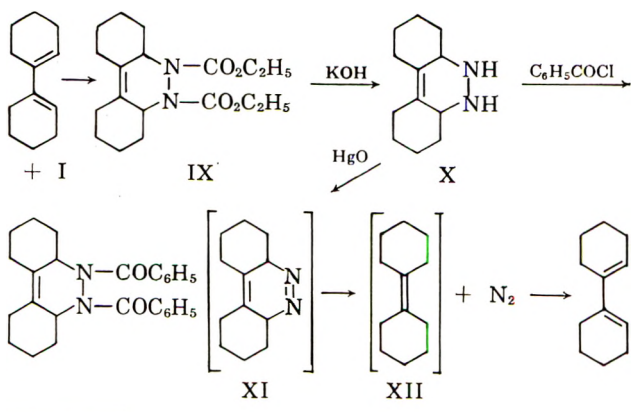


VIII

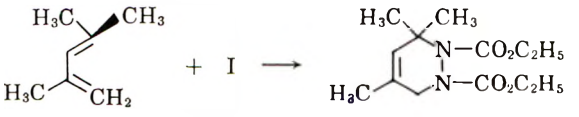
Ethyl azodicarboxylate reacted smoothly at room temperature with the more complex diene, bi(1-cyclohexen-1-yl) to form the Diels–Alder adduct, 1,2-dicarbethoxy-3,4,5,6-bis(tetramethylene)-1,2,3,6-tetrahydropyridazine (IX), in 87% yield. Attempted hydrogenation of IX to the saturated adduct with a variety of catalysts failed and starting IX was reisolated. Other workers[5–7] have found that similar Diels–Alder adducts with this diene also failed to undergo hydrogenation. The failure was attributed to the "blocking effect of the cyclohexane rings on the olefinic linkage. . . .".[5]

The adduct IX was hydrolyzed with potassium hydroxide in refluxing ethylene glycol and gave 66% of the theoretical amount of cyclic hydrazine 3,4,5,6-bis(tetramethylene)-1,2,3,6-tetrahydropyridazine (X). A 78% yield of the dibenzoyl derivative of X was obtained. Oxidation of X was accomplished using yellow mercuric oxide in anhydrous ether. Nitrogen gas was evolved from the oxidation mixture and the only product isolated was the starting diene, bi(1-cyclohexen-1-yl), in 73% yield.

These results indicated that the oxidation of X formed the cyclic unstable azo compound XI, which evolved nitrogen possibly through the biradical XII. However, XII collapsed to the more stable diene by radical shift rather than by closure to the carbocyclic system. Thus, for the synthesis of carbocyclic systems, it appears imperative to use a saturated cyclic hydrazine in the oxidation step.

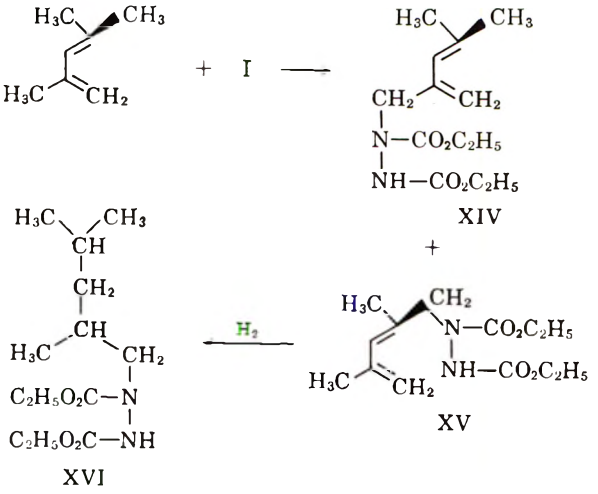


Diels, Blom, and Koll[8] have reported that I, when added to 2,4-dimethyl-1,3-pentadiene, yielded the Diels–Alder adduct, N,N′-dicarbethoxy-3-dimethyl-5-methyltetrahydropyridazine (XIII). Bromine addition to the product furnished resinous material; however, the proposed adduct was not characterized to any further extent.



XIII

Levina, *et al.*,[9] have published a report stating that the reaction of I with 2,4-dimethyl-1,3-pentadiene resulted in a mixture of isomers, 1,2-dicarbethoxy-1-[1-(4-methyl-2-methylene-3-pentenyl)]hydrazine (XIV) and 1,2-dicarbethoxy-1-[1-(2,4-dimethyl-2,4-pentadienyl)]hydrazine (XV). Hydrogenation of this mixture purportedly gave rise to a single product, 1,2-dicarbethoxy-1-(2,4-dimethyl-*n*-pentyl)hydrazine (XVI). These Russian workers assumed that the adduct (isomer mixture XIV and XV) arose from radical addition but presented no supporting evidence or definitive structure proof.



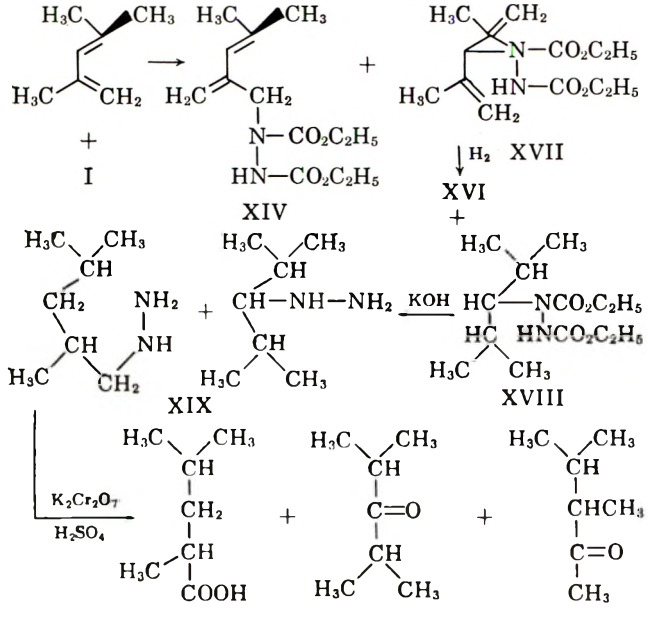
Thus, a reinvestigation of this diene system was undertaken in order to clarify the addition of I to 2,4-dimethyl-1,3-pentadiene and to prove rigorously the structure of the product or products.

In this laboratory, when I was mixed with 2,4-dimethyl-1,3-pentadiene in benzene solution, adduct formation took place with an evolution of heat and an 87% yield of purified product was isolated. The infrared spectrum of this product showed bands at 2.90 μ (N–H), and in the carbonyl region at 5.70–5.80 μ (shoulder) and at 5.85 μ. The ultraviolet spectrum of this material exhibited a maximum at 232 mμ (ϵ 6800) which indicated that the product contained 80% of a highly substituted conjugated diene. Gas chromatography showed the product was actually a mixture of two products with the composition of 21.5 and 78.5%,

(5) N. L. Drake and C. N. Kraebel, *J. Org. Chem.*, **26**, 41 (1961).
(6) F. Bergman, H. Eschinazi, and M. Neeman, *ibid.*, **8**, 185 (1943).
(7) K. Alder, H. Rickert, and E. Windemuth, *Ber.*, **71**, 2451 (1938).
(8) O. Diels, J. H. Blom, and W. Koll, *Ann.*, **443**, 242 (1925).
(9) R. Y. Levina, U. S. Skabarow, and M. H. Kuzmin, *Dokl. Akad. Naul SSSR*, **131**, 1080 (1962).

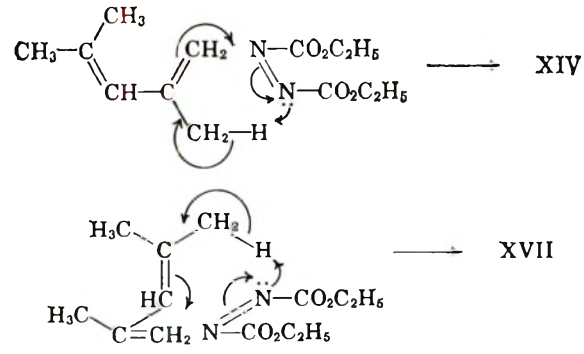
respectively. Assignment of the structures to these products as XIV, the 78.5% component, and 1,2-dicarbethoxy-1-[3-(2,4-dimethyl-1,4-pentadienyl)]hydrazine (XVII), the 21.5% component was made on the basis of the ultraviolet data and the ensuing evidence. The isomer mixture, XIV and XVII, absorbed two molar equivalents of hydrogen to furnish a 90.5% yield of product. Gas chromatography of the latter material showed that the composition was 14% of 1,2-dicarbethoxy-1-[3-(2,4-dimethyl-*n*-pentyl)]hydrazine (XVIII) and 86% of XVI. Hydrolysis of the saturated mixture (XVIII and XVI) with potassium hydroxide in refluxing ethylene glycol furnished an 82.5% yield of the alkyl hydrazine mixture XIX. The mixture was oxidized with potassium dichromate in dilute sulfuric acid solution. From the acidic fraction of the oxidation mixture, 2,4-dimethylpentanoic acid was isolated and characterized as the amide.

The neutral fraction of the oxidation mixture was subjected to gas chromatography. This analysis showed that besides peaks due to ether and water, two other components were present in a ratio of 21.7 to 78.3%. An authentic sample of diisopropyl ketone had the same retention time as the former component. That the latter peak was due to 3,4-dimethyl-2-pentanone was determined from chemical evidence. The neutral fraction gave a positive iodoform test. A semicarbazone derivative was prepared and corresponded to 3,4-dimethyl-2-pentanone. The fact that 3,4-dimethyl-2-pentanone was found in the reaction mixture was consistent with prior observations. Fry[10] has reported that diisopropyl ketone, when subjected to acid conditions, undergoes rearrangement to 3,4-dimethyl-2-pentanone.



The results thus have shown that the addition of I to 2,4-dimethyl-1,3-pentadiene took place by a route other than the Diels–Alder reaction, namely by the cyclic mechanism already postulated.[2] (See col. 2.)

Because of the structural nature of this diene, its reaction with I led to two addition products. The cyclic mechanism proceeded with a shift of the double bond; however, even with the double bond shift, the



major product retained conjugation. The high percentage of this product can be easily rationalized on the basis of steric factors.

That the addition of I to 2,4-dimethyl-1,3-pentadiene took place by the cyclic mechanism and not by free-radical addition was substantiated by the fact that when the reaction was carried out in the presence of a free-radical inhibitor, hydroquinone, the course of the reaction remained unchanged. The adduct exhibited the same infrared and ultraviolet spectra as the product which was obtained without the inhibitor. The adducts that formed under both conditions also had identical gas chromatograms.

Experimental[11]

1,2-Dicarbethoxy-7,10-methano-1,2,3,6,7,10-hexahydro-4,5-benzopyridazine (II).—To 8.0 g. (0.068 mole) of 5,6-dimethylenebicyclo[2.2.1]hept-2-ene[12] was added 8.7 g. (0.05 mole) of ethyl azodicarboxylate (I).[13] The slightly yellow crude product was distilled and gave 11.59 g. (80%) of the colorless liquid II, b.p 138–140° (0.26 mm.), $n^{26}D$ 1.4668, d^{25} 1.1673.

Anal. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.59. Found: C, 61.51; H, 7.10; N, 9.67.

1,2-Dicarbethoxy-7,10-methanodecahydro-4,5-benzopyridazine (III).—The adduct II, (17.0 g., 0.058 mole) was hydrogenated over 0.7 g. of 10% palladium on charcoal in 120 ml. of ethanol at 59 p.s.i. on a Parr apparatus. Two molar equivalents of hydrogen were absorbed. The solution was filtered and the ethanol was removed under vacuum. The residual liquid was distilled and yielded 14.13 g. (82%) of III, b.p. 151° (0.32 mm.), $n^{26}D$ 1.4930, d^{25} 1.1492.

Anal. Calcd. for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16. Found: C, 60.66; H, 8.28.

7,10-Methanodecahydo-4,5-benzopyridazine (IV).—A solution of 45 g. of potassium hydroxide in 250 ml. of 95% ethanol containing 37.9 g. (0.128 mole) of III was refluxed for 11.5 hr. The precipitated potassium carbonate was filtered from the cooled mixture and the ethanol was removed under vacuum. The residual liquid was distilled and furnished 16.23 g. (84%) of IV, b.p. 122° (6.7 mm.), $n^{27}D$ 1.5055–1.5100. This material solidified on standing, m.p. 37–40°.

1,2-Dibenzoyl-7,10-methanodecahydro-4,5-benzopyridazine (V).—To 1.55 g. (0.01 mole) of IV in 20 ml. of 10% sodium hydroxide solution, 8 ml. of benzoyl chloride was added slowly with shaking and cooling. After extraction with chloroform, the product was crystallized from hexane. Recrystallization of

(10) A. Fry, M. Eberhardt, and I. Ookuni, *J. Org. Chem.*, **25**, 1252 (1960).

(11) Boiling points and melting points are uncorrected. Microanalyses were performed by A. Bernhardt, Mülheim, Germany. Spectra of the compounds were measured with a Beckman Model DU ultraviolet spectrophotometer and a Perkin-Elmer Model 137 double beam infrared spectrophotometer. Gas chromatographic analyses were performed on an F & M Scientific Corp. Model 21 B dual heater gas chromatographic apparatus using a 10-ft. long, 0.25-in. diameter Celite–silicone grease column.

(12) Prepared by the method of M. A. P. Bowe, R. G. J. Miller, J. B. Rose, and D. G. M. Wood, *J. Chem. Soc.*, 1541 (1960). The authors wish to acknowledge the gift of a generous quantity of dicyclopentadiene from Union Carbide Olefins Co., which was used in the preparation of the precursor, 5,6-di(chloromethyl)bicyclo[2.2.1]hept-2-ene.

(13) Prepared by the method of N. Rabjohn, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 375.

the resulting solid from ethanol–water yielded 2.96 g. (80%) of V, m.p. 173.5–174.5°.

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 76.64; H, 6.71. Found: C, 76.50; H, 6.74.

7,10-Methano-Δ²-octahydro-4,5-benzopyridazine (VI).—A solution of 4.4 g. (0.029 mole) of IV in 70 ml. of anhydrous ether was stirred with 20 g. of mercuric oxide (yellow powder) for 18 hr. under a nitrogen atmosphere. The dark solid was filtered and the ether was removed under vacuum. The residual liquid was distilled to give 2.71 g. (63%) of VI, b.p. 124° (7.5 mm.), which solidified on standing, m.p. 52–53°; λ_{max}^{EtOH} 234–235 mμ (ε 2340). Infrared spectrum (chloroform) bands at 2.90 (N–H) and 6.12 μ (C=N).

1,2-Dibenzoyl-7,10-methano-Δ³-octahydro-4,5-benzopyridazine (VIII).—The cyclic hydrazone VI (0.5 g., 0.0032 mole) in a solution of 20 ml. of benzene and 10 ml. of pyridine to which was added dropwise 1.5 ml. of benzoyl chloride was heated for 1 hr. on a stream bath and the mixture was then poured into water. The benzene layer was separated, washed with sodium carbonate solution and with water, and then dried over anhydrous sodium sulfate. The benzene was concentrated to a small volume and hexane was added. The precipitated white solid, 0.55 g., melted at 177–180°. Recrystallization from ethanol–water gave VIII, m.p. 179–180°. The compound discolored permanganate and also absorbed bromine readily.

Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.98; H, 6.22; N, 7.78.

Hydrogenation of VIII.—The derivative VIII (0.36 g., 0.001 mole) was quantitatively hydrogenated at room temperature and atmospheric pressure over 0.1 g. of 10% palladium-on-charcoal catalyst in 50 ml. of ethanol. One molar equivalent of hydrogen was absorbed. After filtration, the ethanol was evaporated to a small volume and water was added. On cooling, 0.163 g. of a white solid precipitated, m.p. 173.5–174.5°. A mixture melting point with an authentic sample of V was undepressed.

1,2-Dicarbethoxy-3,4,5,6-bis(tetramethylene)-1,2,3,6-tetrahydropyridazine (IX).—One-tenth mole (17.4 g.) of I was added to 19.5 g. (0.12 mole) of bi-(1-cyclohexen-1-yl)[14] dissolved in 30 ml. of benzene. Immediate reaction took place with an evolution of heat. The colorless solution was vacuum concentrated. The residual liquid was distilled and furnished 29.1 g. (87%) of IX, b.p. 167° (0.5 mm.), $n^{26}D$ 1.5060, which solidified on standing, m.p. 43–44°; lit.[15] b.p. 205–206° (8 mm.), $n^{20}D$ 1.5080, m.p. 42–43°).

Anal. Calcd. for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39. Found: C, 64.04; H, 8.22.

Attempted Hydrogenation of IX.—A solution of 20.0 g. (0.06 mole) of IX in 130 ml. of 95% ethanol containing 1.0 g. of 10% palladium-on-charcoal catalyst was placed in a Parr hydrogenation apparatus at 59 p.s.i. and shaken for 16 hr. No drop in gage pressure took place. The catalyst was removed by filtration and Raney nickel was added to the solution. Shaking was continued on the Parr apparatus at 61.5 p.s.i. After 46 hr. no hydrogen had been absorbed. The catalyst was filtered from the solution. Vacuum concentration of the solution followed by evaporative distillation gave 14.6 g. of material, $n^{26}D$ 1.5018. The infrared spectrum of this material was identical with the spectrum of IX.

A similar hydrogenation experiment using rhodium-on-alumina catalyst also failed and starting IX was isolated.

3,4,5,6-Bis(tetramethylene)-1,2,3,6-tetrahydropyridazine (X).—A solution of 37.03 g. (0.11 mole) of IX and 50 g. of potassium hydroxide in 250 ml. of ethylene glycol was refluxed for 13.5 hr. The solution was cooled and 300 ml. of water was added. The resulting solution was extracted with two 200-ml. portions of ether. The combined ether extracts were dried over calcium sulfate, and the ether was removed. The residual liquid was distilled and furnished 14.0 g. (66%) of X, b.p. 110–112° (0.22 mm.), which immediately solidified, m.p. 44–46°; lit.[15] m.p. 45–46°.

The dibenzoyl derivative of X was prepared in 78% yield and melted at 186–188° (from ethanol–water); lit.[15] m.p. 188–189°.

Oxidation of X.—To a solution of X (2.66 g., 0.0139 mole), in 110 ml. of anhydrous ether stirred with a magnetic stirrer was added 8.0 g. of mercuric oxide (yellow powder). Immediate evolution of nitrogen took place and the mercuric oxide darkened. Stirring was continued for 15 hr. after which the solid was filtered and the ether was removed. The crude product, $n^{26}D$ 1.5330, was distilled and gave 1.63 g. (73%) of bi(1-cyclohexen-1-yl), b.p. 116–117° (5.7 mm.), $n^{26}D$ 1.5325; lit.[14] b.p. 101–102° (5.5 mm.), $n^{20}D$ 1.5322. The infrared spectrum of this product was identical with that of authentic bi(1-cyclohexen-1-yl).

Reaction of 2,4-Dimethyl-1,3-pentadiene with I.—One-tenth mole (17.4 g.) of I and 12.5 g. (0.13 mole) of 2,4-dimethyl-1,3-pentadiene[16] were mixed in 30 ml. of benzene. Immediate reaction occurred with an evolution of heat. The colorless solution was vacuum concentrated to yield a thick viscous liquid. Purification by evaporative distillation yielded 22.1 g. (82%) of XIV and XVII, b.p. 132° (0.06 mm.), $n^{26}D$ 1.4742, d^{25} 1.0653[17]; infrared spectrum ($CHCl_3$) bands at 2.90 (N–H), 5.70–5.80 (shoulder), and 5.85 μ (C=O). The ultraviolet spectrum of the product exhibited λ_{max}^{EtOH} 232 mμ (ε 6800) and indicated that 80% of conjugated diene was present.[18]

Gas chromatography of the product gave two peaks with the composition 21.5 and 78.5%, respectively, as determined by the peak area method.[19]

Anal. Calcd. for $C_{13}H_{22}N_2O_4$: C, 57.76; H, 8.20. Found: C, 57.57; H, 8.02.

Addition of I to 2,4-Dimethyl-1,3-pentadiene under Nonradical Conditions.—To a solution of 6.25 g. (0.065 mole) of 2,4-dimethyl-1,3-pentadiene in 20 ml. of benzene containing 0.1 g. of hydroquinone, which was kept under a nitrogen atmosphere, 8.7 g. (0.05 mole) of I was added in one lot. Immediate reaction took place with an evolution of heat. The colorless solution was extracted twice with two 25-ml. portions of 5% sodium hydroxide solution and once with water. The benzene, after drying over anhydrous sodium sulfate, was vacuum concentrated. The residual liquid was distilled evaporatively and gave 10.46 g. (75%) of product, $n^{26}D$ 1.4740. The infrared spectrum of this liquid was identical with that of authentic adduct. The ultraviolet spectrum exhibited λ_{max}^{EtOH} 232 mμ (ε 6600) and indicated that 77% of conjugated diene was present.

Gas chromatography showed this product to have the following composition: 27% of product with retention time of 13 min.; 73% of product with retention time of 18.3 min.[20]

Hydrogenation of XIV and XVII.—The addition product, mixture XIV and XVII, (18.43 g., 0.068 mole) was hydrogenated over 1.0 g. of 10% palladium-on-charcoal catalyst in 130 ml. of ethanol at 59.1 p.s.i. on a Parr apparatus. Two molar equivalents of hydrogen were absorbed. The catalyst was removed by filtration and the ethanol was removed under vacuum. Purification of the clear, viscous liquid by evaporative distillation yielded 16.85 g. (90.5%) of XVI and XVIII, b.p. 163°(0.04 mm.), $n^{26}D$ 1.4450, d^{22} 1.0205; lit.[9] b.p. 169–170° (10 mm.), $n^{20}D$ 1.4530, d^{20} 1.0207. Gas chromatography of the product gave two peaks with the composition of 14 and 86%, respectively, as determined by the peak area method.[21]

Anal. Calcd. for $C_{13}H_{26}N_2O_4$: C, 56.91; H, 9.55. Found: C, 56.87; H, 9.44.

Hydrolysis of XVI and XVIII.—A solution of 38.5 g. (0.14 mole) of mixture XVI and XVIII in 250 ml. of ethylene glycol containing 60 g. of potassium hydroxide was refluxed for 15 hr. The mixture was cooled and 400 ml. of water was added. The resulting solution was extracted with three 300-ml. portions of ether. The combined ether extracts were dried over calcium sulfate, and the ether was removed. The residual liquid distilled and yielded 15.03 g. (82.5%) of the alkyl hydrazine mixture XIX, b.p. 94–104° (18 mm.), $n^{26}D$ 1.4458; lit[9] b.p. 84–85° (25 mm.), $n^{20}D$ 1.4550.

Oxidation of XIX.—To a solution of 50.0 g. (0.17 mole) of potassium dichromate dissolved in 300 ml. of 15% sulfuric acid

(14) Prepared by the method of E. E. Gruber and R. Adams, *J. Am. Chem. Soc.*, **57**, 2555 (1935).

(15) Y. S. Skabarow, M. G. Kuzmin, and R. Y. Levina, *Zh. Obshch. Khim.*, **30**, 2473 (1960).

(16) Purchased from Aldrich Chemical Co., Milwaukee, Wis.

(17) Levina, *et al.*, in ref. 9 reported for the adduct (XIV and XVII): b.p. 172–175° (10 mm.), $n^{20}D$ 1.4760, d^{20} 1.0637. Diels, *et al.*, in ref. 8 reported b.p. 136° (0.5 mm.).

(18) The diene, 2,4-dimethyl-1,3-pentadiene, exhibits λ_{max}^{EtOH} 232 mμ (ε = 8500): J. C. Lunt and F. Sondheimer, *J. Chem. Soc.*, 2957 (1950).

(19) Retention times of the peaks were 13.2 and 19.0 min., respectively. Flow rate of helium was 45 ml. per min. with the column temperature of 220° and the detector temperature of 275°.

(20) Flow rate of helium was 45.5 ml. per min. with the column temperature of 230° and the detector temperature of 268°.

(21) Retention times of the peaks were 13.5 and 15.8 min., respectively. Flow rate of helium was 46 ml. per min. with the detector temperature of 265° and the column temperature of 224°.

solution and stirred with a magnetic stirrer, 15.3 g. (0.117 mole) of XIX was added dropwise. After the addition was completed, the reaction mixture was stirred for 2 hr. and allowed to come to room temperature. The mixture was extracted two times with 200 ml. of ether. The combined ether extracts were washed twice with 200-ml. portions of 5% sodium hydroxide solution and once with water. The ether phase was dried over calcium sulfate. Removal of the ether on a steam bath gave 4.92 g. of crude neutral liquid with a ketonic odor. The infrared spectrum confirmed the presence of a ketone. Gas chromatography of this material showed four peaks. The first two peaks, which were off scale, corresponded to ether and water. The third peak had a retention time of 9.11 min. and the fourth peak had a retention time of 10.64 min.[22] The ratio of the third to fourth peak was 21.7 to 78.3%. An authentic sample of diisopropyl ketone[23] had a retention time of 9.11 min. under the same conditions. This material gave a positive iodoform test. A semicarbazone derivative was prepared, m.p. 111–113°.[24]

The basic extract was acidified and extracted with two 200-ml. portions of ether. The ether was dried over calcium sulfate and then evaporated. The crude residual liquid amounted to 2.5 g. The infrared spectrum of this liquid indicated that a carboxylic acid was present. The amide was prepared from the crude liquid and gave 1.23 g. of 2,4-dimethylpentanoic acid amide, m.p. 88–90° (from petroleum ether); lit.[25] m.p. 90°.

(22) Flow rate of helium was 45.5 ml. per min., with detector temperature of 128° and column temperature of 105°.

(23) Purchased from Eastman Kodak Co.

(24) Reported for 3,4-dimethyl-2-pentanone semicarbazone, m.p. 112°: J. Colonge and K. Mostafar, *Bull. soc. chim. France*, 335 (1939).

(25) M. W. Burrows and W. H. Bentley, *J. Chem. Soc.*, **65**, 512 (1895).

The Reduction of Acid Adducts of Isoquinoline Reissert Compounds[1]

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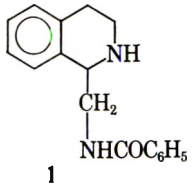
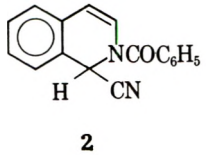
Received June 3, 1963

2-Benzoyl-1,2-dihydroisoquinaldonitrile (isoquinoline Reissert compound) forms adducts with hydrobromic or perchloric acid. Reduction of these adducts either by sodium borohydride or by catalytic hydrogenation affords 2-benzyl-1,2,3,4-tetrahydroisoquinaldamide. The structure of the reduction product is established by an alternative synthesis. A preparation of 2-benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile (dihydroisoquinoline Reissert compound) and the perchlorate salt is described. Whereas isoquinoline Reissert compound yields benzaldehyde on hydrolysis, the dihydro derivative gives only benzoic acid.

1-Benzamidomethyl-1,2,3,4-tetrahydroisoquinoline (**1**) which was of interest to us in connection with another synthetic problem was prepared earlier by Rupe and Frey by drastic reduction of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**2**, isoquinoline Reissert compound).[2,3] Attempts to hydrogenate **2** under milder conditions than Rupe's method failed to yield any discrete reduction products.[4] The recent isolation of a hydrobromide salt (**3**, $X^- = Br^-$) of isoquinoline



1



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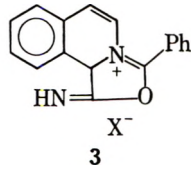
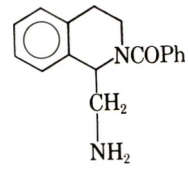


3

Reissert compound suggested that this derivative might be more easily reduced to **1**.[5] In addition to the hydrobromide, a perchlorate salt (**3**, $X^- = ClO_4^-$) of the Reissert compound was prepared. Platinum-catalyzed hydrogenation of **3** ($X^- = ClO_4^-$) at three atmospheres pressure afforded a reduced salt that was converted to the corresponding base, $C_{17}H_{18}N_2O$, formed by the uptake of three moles of hydrogen. The same basic product was obtained unexpectedly on treatment of either salt **3** with sodium borohydride. Although the reduced base was isomeric with Rupe's compound **1**, the failure of our derivative to form an N-nitroso or an acetyl derivative or to yield benzoic acid on hydrolysis excluded **1** and the unrearranged structure **4** from consideration. The first real clue to the structure **5**



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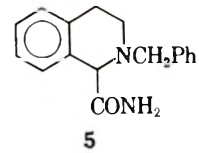
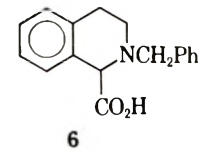


5



6

of the reduction product was obtained when the sulfuric acid-catalyzed hydrolysis mixture was made alkaline; a strong odor of ammonia was observed. A second hydrolysis product ($C_{17}H_{17}NO_2$) proved to be 2-benzyl-1,2,3,4-tetrahydroisoquinaldinic acid (**6**).

Confirmation of structure **5** for the reduced base was obtained by an alternative synthesis (Chart I). The Reissert compound **2** was degraded to isoquinaldamide (**7**), and **7** was hydrogenated in acidic solution to form 1,2,3,4-tetrahydroisoquinaldamide (**8**). A reaction between the reduced amide **8** and benzyl chloride at reflux temperature produced the chloride salt **9** that was converted directly to 2-benzyl-1,2,3,4-tetrahydroisoquinaldamide (**5**). The product from this reaction sequence proved identical by infrared spectra and melting point determinations with the reduction product from the salt.

Further support for **5** as the correct structure of the reduced base was adduced from the n.m.r. spectrum.[6] The salient feature in the spectrum was the unsplit band at τ 5.83 due to a single proton. This can be

(1) (a) We gratefully acknowledge grants in support of this work from the Tennessee Heart Association and the National Institutes of Health (NB-03329); (b) presented in part at the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November 1–3, 1962.

(2) H. Rupe and W. Frey, *Helv. Chim. Acta*, **22**, 673 (1922).

(3) A. Reissert, *Ber.*, **38**, 1603 (1905); W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

(4) W. E. McEwen, R. H. Terss, and I. W. Elliott, *J. Am. Chem. Soc.*, **74**, 3605 (1952).

(5) J. W. Davis, *J. Org. Chem.*, **25**, 376 (1960). Davis referred to **3** as a "Reissert imine"; in this paper the same compounds are called Reissert salts or acid adducts.

(6) The n.m.r. measurements were run in deuteriochloroform with tetramethylsilane as internal reference. We thank Dr. Harold Boaz of the Eli Lilly Research Laboratories, Indianapolis, Ind., for this information.

CHART I

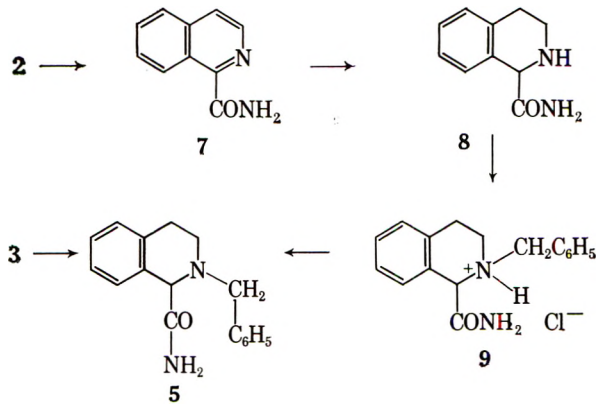
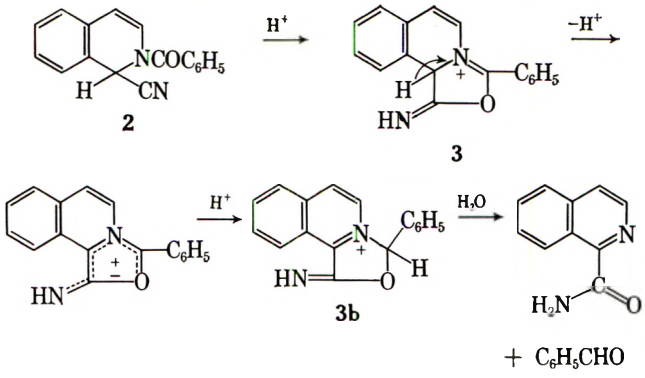
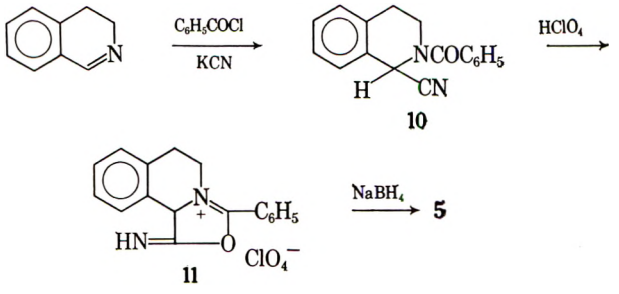


CHART II



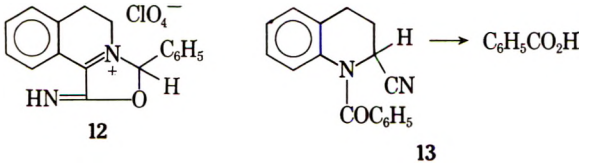
ascribed to the resonance signal from the hydrogen at C-1 in **5**. None of the other models (**1** and **4**) possess this feature. The remainder of the spectrum is in concordance with this assignment.

In connection with these studies it was also of interest to synthesize 2-benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile (**10**, dihydroisoquinoline Reissert compound). Since direct hydrogenation of **2** had failed to yield a simple dihydro product, the preparation of **10** was achieved by treatment of 3,4-dihydroisoquinoline with benzoyl chloride and potassium cyanide. The dihydro Reissert compound **10** afforded a perchlorate salt **11** under the usual conditions.



Borohydride reduction of the salt **11** gave the same product, 2-benzyl-1,2,3,4-tetrahydroisoquinaldamide (**5**), obtained from reduction of the acid adduct **3** of the Reissert compound.

More extensive acid hydrolysis of the dihydroisoquinoline Reissert compound **10** or the salt **11** gave only benzoic acid and no benzaldehyde. This result is in accord with the findings of Collins for the analogous dihydroquinoline Reissert compound **13**.[7]



Structure of the Salts.—The acid adduct **3** of isoquinoline Reissert compound was first proposed as an intermediate in the mechanism of the unique acid-catalyzed hydrolysis whereby the acyl group in the amide state in the Reissert complex is reduced to the corresponding aldehyde (Chart II).[8] Davis' assignment of structure **3** to the hydrobromide salt of isoquinoline Reissert compound is based on the observation that further acid hydrolysis produces benzaldehyde and isoquinaldamide.[5] We concur in the formulation **3** for the salts for the following reasons. First, the results on reduction in which **3** is converted to **5** can most simply be described by a cyclic intermediate (**3** or **3b**) which permits intramolecular transfer of oxygen. Secondly, infrared spectra of **2** and a series of amides related to the Reissert compound show a band at 7.4–7.5 μ that can arise from the N—C=O group frequency vibration. On salt formation this band disappears. Ring closure of the type illustrated in **3** would restrict this group vibration and account for the observed spectral change.

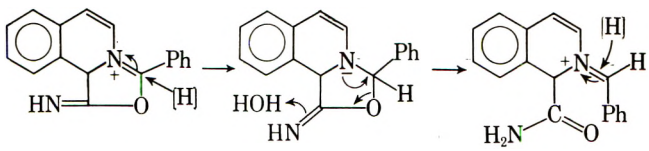
Thirdly, by way of discriminating between **3** and **3b** for the salt we have found that salt formation is reversible. The Reissert compound **2** is rapidly and quantitatively recovered when the salt is treated with base; **3** is a better model for this reaction than **3b** because such a change from **3b** would involve conversion of an isoquinolinium system to a dihydroisoquinoline. Moreover, additional acid appears necessary to complete the hydrolysis of the salt to benzaldehyde and isoquinaldamide; neutral solvents, even boiling water,[5] do not rapidly affect **3**.

Lastly, the formation of an acid adduct **11** from dihydroisoquinoline Reissert compound **10** under the same conditions as for the Reissert compound itself and the properties of the salt **11** have a bearing on this argument. The salt can be represented either by **11** or **12**, but the fact that acid hydrolysis of the salt (or the dihydro Reissert compound) produces only benzoic acid and no benzaldehyde is evidence in favor of **11**. The isomer **12** should be cleaved with water to benzaldehyde, but **11** can be expected to give rise to benzoic acid.

The hypothetical relationship in the hydrolysis mechanism between **3** and **3b**, or **11** and **12** revives the concept that "an important driving force in the reaction is the gain in resonance energy attendant on conversion of the dihydroquinoline to a completely aromatic system." [9]

A plausible series of changes for reductive cleavage of the five-membered ring and intramolecular transfer of oxygen from **3** to produce **5** can be outlined by the following formulas. The reduction by sodium borohydride of the carbon–carbon double bond of the isoquinoline ring in **3** requires little comment. It has been

(7) R. F. Collins, *J. Am. Chem. Soc.*, **77**, 4921 (1955).
(8) R. L. Cobb and W. E. McEwen, *ibid.*, **77**, 5042 (1955).
(9) W. E. McEwen and R. N. Hazlett, *ibid.*, **71**, 1949 (1949).



observed by others when aqueous alcohol is the solvent.[10]

Experimental

Hydrobromide Salt of Isoquinoline Reissert Compound (3).—This compound was prepared by the method of Davis,[5] but samples prepared at different times varied considerably in melting points although the infrared spectra were the same. Typical ranges were: 156–158°, 160–161°, and 166–168° (lit.[5] m.p. 158–160°). The analytical sample had m.p. 159–160°.

Anal. Calcd. for $C_{17}H_{13}N_2OBr$: C, 59.84; H, 3.84; N, 8.21. Found: C, 59.47; H, 4.21; N, 8.26.

Acetonitrile was a satisfactory solvent in place of acetic acid for these salt preparations. When acetic anhydride was used, a mild exothermic reaction ensued on addition of the mineral acid, and only isoquinaldamide hydrobromide was isolated.

Perchlorate Salt of Isoquinoline Reissert Compound.—A solution of 5.0 g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile **2** in 50 ml. of glacial acetic acid was treated with 5 ml. of 70% perchloric acid. A heavy yellow precipitate formed after about 5 min., and the product 5.4 g. (78%), m.p. 202–204°, was collected after 20 min. and washed with ethanol. Recrystallization of the salt from ethanol gave yellow prismatic crystals, m.p. 204–205°.

Anal. Calcd. for $C_{17}H_{13}N_2O_5Cl$: C, 56.57; H, 3.64; N, 7.77. Found: C, 56.98; H, 3.81; N, 8.09.

Hydrolysis of the Hydrobromide Salt of Reissert Compound by Base.—The salt (**3**, 0.10 g.) was dissolved in warm water containing 10% methanol, and the solution was treated with excess ammonium hydroxide. A precipitate formed immediately which was collected, washed with water, and dissolved in hot methanol. On cooling there was obtained 0.71 g. (93%) of isoquinoline Reissert compound, as identified by melting point and infrared spectrum.

Reduction of the Perchlorate Salt of Isoquinoline Reissert Compound. A. Catalytic Hydrogenation.—A suspension of 12 g. (0.033 mole) of isoquinoline Reissert perchlorate salt **3** in 200 ml. of ethanol and 0.3 g. of platinic oxide was hydrogenated at 3 atm. until the uptake of hydrogen virtually ceased (*ca.* 6 hr). The reaction mixture was heated on the steam bath and diluted with water to dissolve the salt. The hot mixture was filtered to remove the catalyst, and the filtrate was allowed to cool. A greenish yellow solid (9.2 g.) separated from the fluorescent green liquid. On recrystallization from ethanol the salt was obtained as pale yellow crystals, m.p. 251° dec.

Anal. Calcd. for $C_{17}H_{19}N_2O_5Cl$: C, 55.67; H, 5.22; N, 7.64. Found: C, 55.31; H, 5.37; N, 7.95.

A solution of 5.0 g. of the reduced salt in hot water was treated with charcoal, filtered, and cooled. To the crystallized salt was added aqueous ammonia, and after 0.5 hr. the flocculent white solid, 32 g. (88%), was collected and recrystallized from ethanol as colorless prisms, m.p. 150–151°. The melting point was undepressed on admixture with the base from borohydride reduction of the salt; moreover, the infrared spectra were identical.

B. Borohydride Reduction.—A hot solution of isoquinoline Reissert perchlorate (4 g.) in aqueous alcohol was treated with 1 g. of potassium borohydride. After 0.5 hr. the mixture was heated to boiling, and water was added almost to the point of turbidity. On standing 2.1 g. (71%) of a white solid was collected and after several recrystallizations gave colorless crystals, m.p. 150–151°; infrared spectrum ($CHCl_3$): 2.83 and 2.95 (monomeric NH_2 asymmetric and symmetric stretch, respectively); 2.90, 3.05, 3.15 (dimeric NH_2—OC stretch); 5.95 μ (amide CO).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.76; N, 10.52. Found: C, 76.80; H, 6.72; N, 10.81.

The same reduction product (63%) was obtained from a parallel reduction of the hydrobromide salt.

A solution of the base in ethanol was mixed with perchloric acid and after a few minutes in an ice bath almost colorless crystals separated from the magenta solution. The product, m.p. 251° dec., was identical with the yellow perchlorate from the catalytic reduction by mixture melting point and infrared spectra.

Acid Hydrolysis of 2-Benzyl-1,2,3,4-tetrahydroisoquinaldamide.—To 0.5 g. of 2-benzyl-1,2,3,4-tetrahydroisoquinaldamide was added 4 ml. of concentrated sulfuric acid and 5 ml. of water. A clear violet-red solution resulted that changed on heating to a deep yellow. The solution was allowed to reflux 1.5 hr. and to stand 12 hr. The acid solution was diluted with water and extracted with ether, but the ether extracts gave no evidence of benzoic acid. The aqueous layer was made strongly alkaline with 20% sodium hydroxide solution, and a strong odor of ammonia was noticed. The basic reaction mixture was acidified slightly with acetic acid, and a small amount of a gum separated. The mixture was extracted with ether (20 ml.), ether–dichloromethane (20 ml.), and dichloromethane (20 ml.). The extracts were combined and evaporated, and the residue was taken up in warm ethanol, filtered, and allowed to cool. The acid was obtained as clusters of fine colorless needles (0.17 g.), m.p. 174–175°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.25. Found: C, 76.30; H, 6.68; N, 5.20.

1,2,3,4-Tetrahydroisoquinaldamide.—Hydrogenation of isoquinaldamide hydrobromide[5] (3.0 g.) in 70% aqueous methanol (150 ml.) was catalyzed by platinic oxide (0.1 g.) at 40 p.s.i. After the theoretical uptake of hydrogen (1 hr.) the reaction was stopped and the catalyst was removed by filtration. The filtrate was made basic with ammonium hydroxide, and 1.5 g. of reduced amide, m.p. 181–183°, was collected. A sample, m.p. 182–183°, was recrystallized for analysis.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.15; H, 6.87; N, 15.90. Found: C, 67.89; H, 6.95; N, 15.78.

2-Benzyl-1,2,3,4-tetrahydroisoquinaldamide.—A suspension of 1.5 g. of 1,2,3,4-tetrahydroisoquinaldamide in 15 ml. of benzyl chloride gave a clear yellow solution during 2 hr. refluxing. After standing 20 hr. the semisolid mixture was diluted with 50 ml. of acetone, and 0.9 g. of an insoluble solid, m.p. 218–222°, was collected and washed with 10 ml. of acetone. The crude salt (0.6 g.) was dissolved in warm water and filtered, and the filtrate was treated with cold 20% sodium hydroxide solution. The amine was collected as a gummy white solid that was recrystallized from aqueous methanol as pale yellow crystals (0.3 g.), m.p. 147–149°. This product proved identical with the compound **5** from reduction of the isoquinoline Reissert salts by mixture melting point and infrared spectra.

2-Benzoyl-1,2,3,4-tetrahydroisoquinaldonitrile (10).[11]—To 200 ml. of dichloromethane and 70 ml. of water were added 10 g. of 3,4-dihydroisoquinoline[12] and 18 g. of potassium cyanide. The mixture was stirred vigorously and cooled in an ice bath while 24 g. of benzoyl chloride was added dropwise over a period of 2 hr. After 6 hr. stirring the layers were separated, and the dichloromethane solution was extracted successively with water, 5% sodium hydroxide, 5% hydrochloric acid, and water again. The solution was dried over sodium sulfate and evaporated under reduced pressure to leave a viscous orange oil. The oil was diluted with 5 ml. of ethanol, cooled, and scratched. Fine crystals began to form after 15 min., the mixture was kept near 0° for 12 hr., and the first crop of crystals (1.5 g.), m.p. 113–115°, was collected. Recrystallization of this product raised the melting point to 114–115°, but it did not correspond to dihydroisoqulnoline Reissert compound **10** and was not studied further.

Anal. Found: C, 79.81; H, 6.47; N, 5.79.

The second and third crops of crystals (7.3 g., m.p. 96–98°), were sticky colorless crystals. Recrystallization from aqueous ethanol and finally ethanol–ether gave the Reissert compound **10** as colorless prisms, m.p. 104–105°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.94; H, 5.37; N, 10.68. Found: C, 78.05; H, 5.66; N, 10.62.

Perchlorate Salt of Dihydroisoquinoline Reissert Compound.—To 1.0 g. of recrystallized dihydroisoquinoline Reissert compound was added glacial acetic acid (5 ml.) until all of the solid dissolved on shaking. The solution was cooled slightly, and 1.5 ml. of 70% perchloric acid was added. After 10 min., the salt precipitated nearly all at once when the solution was scratched.

(10) R. Mirza, *J. Chem. Soc.*, 4400 (1957); J. W. Huffman, *J. Am. Chem. Soc.*, **80**, 5193 (1958).

(11) This general method is described by F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.*, **26**, 4930 (1960).

(12) W. J. Dale, L. Starr, and C. W. Strobel, *ibid.*, **26**, 2225 (1961).

The mixture was chilled 10 min. in an ice bath and the product (1.1 g., m.p. 205–208°), was collected as a bright yellow solid. An analytical sample, m.p. 213–214°, was recrystallized from ethanol; infrared spectrum (KBr): 3.00–3.08 (doublet), 6.05 μ.

Anal. Calcd. for $C_{17}H_{15}N_2O_5Cl \cdot H_2O$: C, 53.63; H, 4.50; N, 7.30. Found: C, 53.41; H, 4.51; N, 7.34.

Borohydride Reduction of Dihydroisoquinoline Reissert Perchlorate Salt.—A suspension of sodium borohydride (0.5 g. in 30 ml. of ethanol) was treated with 0.95 g. of dihydroisoquinoline Reissert perchlorate. The color at first was orange, but this quickly faded on heating. A white solid that remained undissolved after heating 10 min. was dissolved by addition of water. Further dilution with water brought the boiling solution to the point of turbidity, and a small quantity of alcohol was added to give a clear solution. On chilling in an ice–water bath a colorless granular solid was deposited (0.8 g.), m.p. 146–148°; this was raised to 147–149° by recrystallization. This compound was identified as 2-benzyl-1,2,3,4-tetrahydroisoquinaldamide (5) by mixture melting point and infrared spectrum.

Hydrolysis of Dihydroisoquinoline Reissert Compound.—To 0.5 g. of dihydro Reissert compound 10 was added 11 ml. of concentrated hydrochloric acid, and the mixture was allowed to reflux 8 hr. The cooled mixture deposited a feathery colorless solid (0.18 g., 78%), m.p. 118–120°. This product proved to be benzoic acid.

A similar result was obtained when the perchlorate salt 11 was heated with aqueous hydrochloric acid (1:1 by volume) and 2,4-dinitrophenylhydrazine. No benzaldehyde derivative was obtained, but benzoic acid was recovered from the reaction mixture.

Deoxymercuration in the Presence of Both Acid and Iodide Ion[1]

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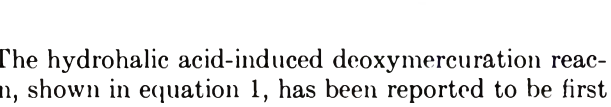
The School of Chemistry of the University of Minnesota, Minneapolis 14, Minnesota

Received May 13, 1963

The deoxymercuration rate of 2-methoxyethylmercuric iodide in solutions containing both hydronium ion and iodide ion contains contributions from terms of the first and second order in iodide as well as a term of the zeroth order in iodide. The rate is of the first order in hydronium ion throughout. A previous report that 2-isopropoxyethylmercuric chloride is inert to perchloric acid (ref. 3) is in error. Substantial differences are found between deoxymercuration rates of 2-methoxyethylmercuric iodide and the corresponding hydroxy compound at all iodide concentrations. This precludes a fast reversible formation of the olefin–mercuric iodide complex and it is suggested that the formation of this complex, in fact, is rate determining.

The hydrohalic acid-induced deoxymercuration reaction, shown in equation 1, has been reported to be first order in hydrochloric acid[2] and also second order in hydrochloric acid.[3] Both of these reports pertain to



(1)

alcohol rich alcohol–water mixtures in which kinetic salt effects may be quite large,[4] and in which incomplete ion-pair dissociation may be a factor.[5] In neither study was the halide ion concentration varied independently of the acid concentration. The present paper reports a study of the deoxymercuration reaction induced by combinations of acid and sodium iodide in water as a solvent (containing 2% methanol). The principal substrate was 2-methoxyethylmercuric iodide, but certain points were established by using 2-hydroxyethylmercuric iodide and 2-isopropoxyethylmercuric chloride.

Results

Rates were measured spectrophotometrically using previously described techniques.[6a] The build-up of absorption at 3200 Å. due to mercuric iodide and its iodide ion complexes was followed. This absorption is primarily due to HgI_4^{-2} and HgI_3^-, which are in equilibrium with HgI_2 in the presence of excess iodide ion. Since the I^- concentration did not change appreciably in the course of any one experiment, the fraction of HgI_2 converted to each absorbing species was fixed and the change in optical density was proportional to the fraction of the reaction which had taken place. Thus the usual form of the integrated first-order rate law (equation 2) could be used.[6b] Plots of $\log \{(D_\infty - D_0)/(D_\infty - D_t)\}$ *vs.* t were precisely linear. (The optical density is D with the subscript indicating the time, t, at which it was measured. The pseudo first-order rate constant is k_1.) The slopes of such plots, obtained graphically, were used to get values of k_1. Substrate concentrations were in the

$$k_1 = \frac{2.303}{(t - t_0)} \log \frac{(D_\infty - D_0)}{(D_\infty - D_t)} \qquad (2)$$

range 10^{-4}–10^{-6} M. All reactions were pseudo first order. The iodide concentration exceeded the substrate concentration by at least a factor of 12 in all experiments and in most by far more than that. The acid concentration was either in excess over the substrate by at least a factor of 100 or else it was held constant by buffering.

All measurements were made at least in duplicate and generally did not differ by more than 5%. In case of discrepancies of 10% or more, the measurement was repeated until the difficulty could be eliminated. This suggests a reliability of about ±5% for cited values of k_1.

All of the rate constants reported in this paper were measured at 25.0 ± 0.1°. All measurements were made in water containing 2% by volume of methanol because the substrates were handled as stock solutions in that solvent.

(1) This work was supported by the Air Force Office of Scientific Research through Contract No. AF 49(638)711. Reproduction in whole or in part is permitted for any purpose of the U. S. Government.

(2) O. W. Berg, W. P. Lay, A. Rodgman, and G. F. Wright, *Can. J. Chem.*, **36**, 358 (1958).

(3) K. Ichikawa, H. Ouchi, and S. Araki, *J. Am. Chem. Soc.*, **82**, 3880 (1960).

(4) S. D. Ross, M. Finkelstein, and R. C. Peterson, *ibid.*, **83**, 5335 (1960).

(5) C. A. Kraus, *J. Chem. Educ.*, **35**, 324 (1951).

(6) (a) M. M. Kreevoy, *J. Am. Chem. Soc.*, **81**, 1099 (1959); (b) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 28.

Rate as a Function of Acid Concentration.—Rates were measured as a function of hydronium ion concentration at two (constant) sodium iodide concentrations, 4.07×10^{-3} and 0.1536 M. The latter is close to the highest iodide ion concentration used in this work. With 4.07×10^{-3} M iodide ion, hydronium ion concentration was varied with perchloric acid. Four determinations were made over the range of acid concentration, 8×10^{-4} to 3×10^{-3} M giving values of k_1 very nearly proportional to the acid concentration. A pseudo second-order rate constant, k_2', is given by $k_1/[H^+]$ and has the value $0.510 \pm .008$ l. mole^{-1} sec.$^{-1}$. This value becomes $0.590 \pm .014$ [$k_2'^0$] when each rate constant is corrected for the ionic strength effects described subsequently.

At the higher iodide ion concentration acetic acid–sodium acetate buffers were used to provide the hydronium ion, and $k_2'^0$ was again invariant under changes in its concentration. (In acetic acid–sodium acetate buffers $k_2'^0$ is defined as $k_1[OCOCH_3^-]/K[HOCOCH_3]$, where K is the thermodynamic dissociation constant of acetic acid and quantities in brackets are concentrations. It is shown, subsequently, that this is equivalent to the similar quantity defined for strong acid.) Four measurements over the range, 5×10^{-6} to 6×10^{-5} M hydronium ion gave a $k_2'^0$ of $1.10 \pm .04 \times 10^2$ l. mole^{-1} sec.$^{-1}$. Sodium acetate concentration was held constant in these experiments and the hydronium ion concentration was varied by varying the acetic acid concentration so that there was no change in the ionic strength within the series. The acetic acid concentration was $< 1.7 \times 10^{-2}$ M. It is shown below that there is no significant catalysis by molecular acetic acid under these conditions.

Experiments designed to test for catalysis by molecular acetic acid were carried out both at low (8×10^{-4} M) and at high (0.170 M) iodide concentration. The ionic strength was not held constant in these experiments but it is shown, subsequently, that $k_2'^0$ is independent of ionic strength to a first approximation when it is determined in acetic acid–sodium acetate buffers. At the low iodide concentration a $k_2'^0$ of 0.140 was obtained in an experiment carried out with 0.325 M acetic acid. The value of $k_2'^0$ predicted from similar experiments with perchloric acid is 0.136. If it is concluded from this that the molecular acetic acid contributes $< 5\%$ of the total rate under these conditions then the molecular acetic acid rate coefficient, $k_2'^{HOAC}$, must be smaller than $k_2'^{H}$, the hydronium ion rate coefficient, by at least a factor of 10^4.

At the higher iodide concentration rates were measured in dilute acetic acid–sodium acetate buffers (both constituents around 5×10^{-3} M) as well as more concentrated buffers (both constituents around 0.1 M) of about the same buffer ratio. A $k_2'^0$ of 1.34×10^2 was obtained with the dilute buffer and 1.25×10^2 with the more concentrated buffer. If it is concluded from this that the molecular acetic acid contributes $< 5\%$ of the total rate in the more concentrated buffers, then the corresponding rate coefficient, $k_2'^{HOAc}$, must be smaller than $k_2'^{H}$ by a factor of at least 10^5.

These results, coupled with similar findings in the absence iodide ion,[6,7] established that $k_2'^0$ is independent of hydronium ion concentration over the whole range of iodide concentrations. They strongly suggest the absence of general acid catalysis.

Rate as a Function of Electrolyte Concentration.—At 3.80×10^{-3} M perchloric acid and 2.33×10^{-3} M sodium iodide, k_1 was studied as a function of electrolyte concentration with added sodium perchlorate, sodium nitrate, and potassium nitrate. The results are shown in Table I.

TABLE I

EFFECT OF ADDED ELECTROLYTE ON k_1 IN 3.8×10^{-3} M PERCHLORIC ACID AND 2.3×10^{-3} M SODIUM IODIDE

Salt	$10^2 \times$ total electrolyte, M[a]	$10^3 k_1$, sec.$^{-1}$	$10^3 k_1^0$, sec.$^{-1}$[b]	$10^3 k_1^0$, sec.$^{-1}$[c]
None	0.61	1.26	1.48	1.47
KNO_3	1.61	1.18	1.47	1.45
KNO_3	3.11	1.07	1.46	1.43
KNO_3	4.61	0.94	1.35	1.30
KNO_3	5.61	0.97	1.43	1.37
KNO_3	8.11	0.95	1.48	1.38
KNO_3	10.61	0.93	1.51	1.38
$NaClO_4$	1.46	1.23	1.55	1.53
$NaClO_4$	3.21	1.05	1.44	1.40
$NaClO_4$	5.69	0.96	1.41	1.35
$NaClO_4$	10.76	0.95	1.58	1.45
$NaClO_4$	20.91	0.94	1.68	1.42
$NaNO_3$	2.61	1.09	1.46	1.43

[a] Since only 1:1 electrolytes are involved this is exactly half the ional strength. [b] Calculated from equations 3 and 4. [c] Calculated from equations 3 and 5.

If two ions of opposite charge are combined to make a formally neutral transition state, equation 3 gives the Brønsted law[8] for k_1^0, the rate constant in infinitely

$$k_1^0 = k_1/f_t^2 \tag{3}$$

dilute electrolyte. Changes in electrolyte concentration should not change k_1^0, although k_1 may vary considerably. The mean ion activity coefficient, $f_\pm$, can be calculated from the Debye–Hückel theory (equation 4)[9] for dilute solutions (ional strength, Γ, $< \sim 0.2$). For more concentrated solutions the extended Debye–Hückel theory[10] (equation 5) may be successful. In both equations 4 and 5 the notation

$$\log f_\pm = -\frac{S_f\sqrt{\Gamma}}{1 + A\sqrt{\Gamma}} \tag{4}$$

is that of Harned and Owen.[9,10]

$$\log f_\pm = -\frac{S_f\sqrt{\Gamma}}{1 + A\sqrt{\Gamma}} - \frac{B\Gamma}{2} + \frac{D'\Gamma^2}{4} \tag{5}$$

Equation 3 has been applied to the present data, using both equations 4 and 5 for $f_\pm$, and the results are shown in Table I. The theoretical value was used for S_f.[11] Empirically obtained values appropriate to hydrogen iodide were used for B, D', and $\dot{a}$,[12] the mean ionic diameter. (The latter is required to evaluate A.) Since these parameters were determined for solutions containing only hydrogen iodide they constitute a source of serious uncertainty in $f_\pm$, particularly at higher ional strengths. Nevertheless the deviations

(7) M. M. Kreevoy and F. R. Kowitt, *J. Am. Chem. Soc.*, **82**, 739 (1960).

(8) J. N. Brønsted, *Z. Physik. Chem.* (Leipzig), **102**, 169 (1922).

(9) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1958, pp. 64–66, 508–512.

(10) Ref. 9, pp. 66–68.

(11) Ref. 9, p. 165.

(12) Ref. 9, p. 510.

from constancy in the k_1^0 values calculated from equations 3 and 5 do not exceed the experimental uncertainty. If equations 3 and 4 are used instead, systematic deviations outside of the experimental uncertainty are observed with ional strengths of 0.2 and higher. Changes of about 25% in k_1 can be observed on going from the lowest to the highest ional strength.

In acetic acid–sodium acetate buffers the hydronium ion concentration is given by $K[\mathrm{HOAc}]/[\mathrm{OAc}^-]f_\pm^{2\mathrm{HOAc}}$. In such a buffer k_2' would be given by $k_1[\mathrm{OAc}^-]f_\pm^{2\mathrm{HOAc}}/K[\mathrm{HOAc}]$. To get the infinite dilution value, k_1^0 would be used, giving $k_1[\mathrm{OAc}^-]f_\pm^{2\mathrm{HOAc}}/K[\mathrm{HOAc}]f_\pm^2$ for $k_2'^0$. However, equation 4 also gives $f_\pm^{\mathrm{HOAc}}$ in moderately dilute solutions if 5.6 Å. is used for $\mathring{a}$.[13] This is not too different from the value of $\mathring{a}$ (5.0 Å.) that permits equation 4 to successfully predict $f_\pm$ up to 0.1 M electrolyte. Thus the two activity coefficient terms cancel to a good approximation in dilute buffers, and $k_2'^0$ is simply given by $k_1[\mathrm{OAc}^-]/K(\mathrm{HOAc}]$.

If the hydronium ion is provided by a strong acid $k_2'/f_\pm^2$ gives k_2'.[4] Equation 5 (or 4 within its range of applicability) can be used to get $f_\pm$. This has been done in obtaining the values of $k_2'^0$ which were measured in perchloric acid solutions.

Rate as a Function of Iodide Concentration.—Values of $k_2'^0$ were obtained at sodium iodide concentrations ranging up to 0.17 M. They are shown in Table II. Table II also shows the acid system, perchloric or acetic acid–sodium acetate, and the quantity $[\mathrm{H}^+]f_\pm^2$ so that the measured values of k_1 can be regenerated from it. In all of these experiments the ratio of molecular acetic acid concentration to hydronium ion concentration was low enough to preclude significant catalysis by acetic acid.

TABLE II

THE INFLUENCE OF $[\mathrm{I}^-]$ ON $k_2'^0$

Acid	$[\mathrm{H}^+]f_\pm^2$, M	$[\mathrm{I}^-]$, M	$k_2'^0$ obsd., l. mole^{-1} sec.$^{-1}$	$k_2'^0$ calcd., l. mole^{-1} sec.$^{-1}$
$HClO_4$	2.47×10^{-3} [a]	None	0.0380[b]	0.038
HOAc	5.62×10^{-4}	8.00×10^{-4}	0.140	0.136
$HClO_4$	2.21×10^{-3}	1.02×10^{-3}	0.159	0.162
$HClO_4$	2.18×10^{-3}	2.03×10^{-3}	0.291	0.292
$HClO_4$	7.95×10^{-3}	2.33×10^{-3}	0.361	0.321
$HClO_4$	2.16×10^{-3}	3.05×10^{-3}	0.432	0.436
$HClO_4$	[c]	4.07×10^{-3}	0.590	0.586
HOAc	5.79×10^{-5}	6.99×10^{-3}	1.082	1.05
HOAc	5.79×10^{-5}	1.40×10^{-2}	2.71	2.48
HOAc	5.79×10^{-5}	2.80×10^{-2}	7.17	6.50
HOAc	5.79×10^{-5}	4.19×10^{-2}	12.64	12.0
HOAc	5.79×10^{-5}	5.59×10^{-2}	20.7	19.1
HOAc	5.79×10^{-5}	7.86×10^{-2}	35.3	34.0
HOAc	5.79×10^{-5}	1.05×10^{-1}	58.8	56.4
HOAc	[c]	1.57×10^{-1}	110	117
HOAc	2.54×10^{-5}	1.70×10^{-1}	134	136
HOAc	2.18×10^{-5}	1.70×10^{-1}	125	136

[a] In the absence of iodide ion the ional strength correction is inappropriate; this is simply the acid concentration. [b] Calculated as described in ref. 6 and 7. This value can be compared with 0.0340 previously reported (ref. 7). The latter is probably more accurate but the former is used for consistency in the present paper. [c] The average of four acid concentrations was used for this point, as described in the section on the variation of the rate with acid concentration.

Casual inspection shows that no constant order with respect to iodide ion will reproduce all of the data in Table II since $k_2'^0$ is nearly proportional to the iodide concentration at low iodide concentration but nearly proportional to its square at high iodide concentration. Further there is a reaction in the absence of iodide. If it is assumed that $k_2'^0$ is governed by equation 6 with the indicated constants it is possible to fit most of the $k_2'^0$ values within their experimental reliabilities. The value of k_2 is that obtained in the absence of iodide ion. Values of k_3 and k_4 were obtained by an iterative process, in which a k_3 value was first obtained by ignoring the square term at low iodide concentration; this value was then used in equation 6 with the high iodide values of $k_2'^0$ to get a value of k_4. The latter was then used in equation 6 to obtain an improved value of k_3. This process was repeated twice more, at which point the values obtained for k_3 and k_4 were no longer changing.

$$k_2'^0 = k_2 + k_3[\mathrm{I}^-] + k_4[\mathrm{I}^-]^2 \qquad (6)$$

$$k_2 = 3.80 \times 10^{-2}\ \text{l. mole}^{-1}\ \text{sec.}^{-1}$$

$$k_3 = 1.19 \times 10^{2}\ \text{l.}^2\ \text{mole}^{-2}\ \text{sec.}^{-1}$$

$$k_4 = 4 \times 10^{3}\ \text{mole}^{-3}\ \text{sec.}^{-1}$$

The $k_2'^0$ values at low iodide concentration, on which k_3 is primarily based, are quite firmly established. All of the known variables which might influence them (ionic strength effects, complexing) have either been eliminated or corrected for. Since they are very well correlated by equation 6, k_3 can probably be considered as reliable as the values of $k_2'^0 \sim \pm 5\%$.

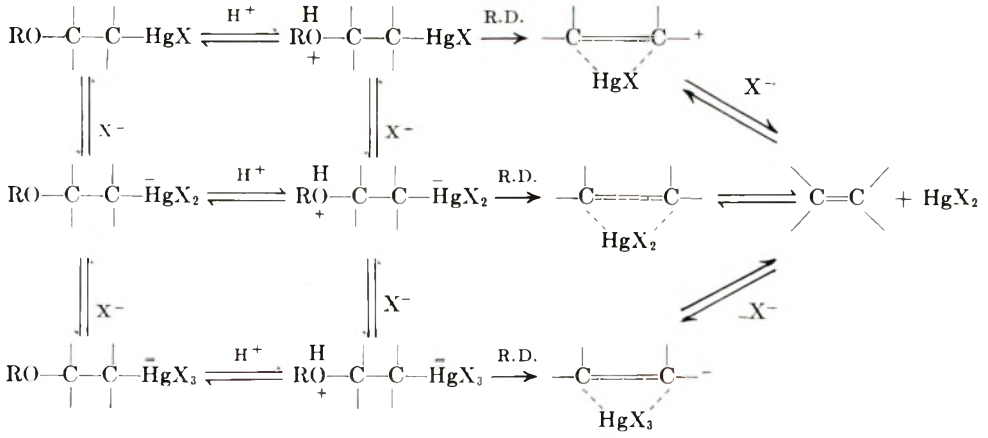
On the other hand a number of difficulties impair the accuracy of $k_2'^0$ values at high iodide concentrations and thereby render k_4 numerically unreliable. Experiments with methylmercuric iodide[14] suggest that a significant fraction of the substrate may be complexed with iodide ion at the higher iodide concentrations, causing $k_2'^0$ to fall below the values that are required to obtain correct values of k_4 from equation 6. Equations 3 and 4 have been experimentally tested only at lower iodide concentrations and equation 4 has been shown to fail at higher electrolyte concentrations, so that the cancellation of the hydrogen iodide and acetic acid activity coefficients may well be imperfect. Neither of these effects, however, call the *reality* of k_4 into question. At high iodide concentrations $k_2'^0$ is five times as large as would be predicted by the combined k_2 and k_3 terms in equation 6. The cancellation of the electrolyte effects is unlikely to be in error by as much as 20%, since the predicted effects themselves are not much larger than this. Complexing would act to *reduce* the apparent values of $k_2'^0$ at high iodide concentrations, and thereby reduce the estimated k_4.

2-Hydroxyethylmercuric Iodide.—Rates were measured for 2-hydroxyethylmercuric iodide at 0.0140 M sodium iodide and 0.130 M sodium iodide. In both cases an acetic acid–sodium acetate buffer was used with $K[\mathrm{HOAc}]/[\mathrm{OAc}^-]$, 5.79×10^{-5}. At the former iodide concentration $k_2'^0$ was 12.3 l. mole^{-1} sec.$^{-1}$ while at the latter it was 240 l. mole^{-1} sec.$^{-1}$. The former is about a factor of 4 larger than that for 2-methoxyethylmer-

(13) H. S. Harned, *J. Phys. Chem.*, **43**, 275 (1939).

(14) M. Visot, unpublished results.

CHART I



curic iodide under comparable conditions and the latter is larger by a factor of about 3.

2-Isopropoxyethylmercuric Chloride.—Rates were measured for the deoxymercuration of 2-isopropoxyethylmercuric chloride by perchloric acid in a mixture containing 79.7% by volume ethanol. The reactions were followed by following the build-up of the mercuric chloride absorption at 2400 Å. Pseudo first-order rate constants were evaluated by means of equation 7. Equation 7 differs from equation 2 by a factor of two in the denominator on the right hand side. This enters because, in the absence of added halide ion, the mercuric halide product is formed by removing a halide ion from a molecule of unreacted starting material, inactivating it.[6a] Because the reactions appeared to be markedly autocatalytic[6a] (none of the other reactions described in this paper are autocatalytic) the initial slopes of plots

$$k_1 = \frac{2.303}{2(t - t_0)} \log \frac{(D_\infty - D_0)}{(D_\infty - D_t)} \qquad (7)$$

of log $(D_\infty - D_t)$ against t were used. The second-order rate constants, k_2, obtained by dividing k_1 by the perchloric acid concentration, were strongly dependent on the perchloric acid concentration, as has previously been observed for reactions of this type[15] in largely alcoholic solutions. As before[15] a plot of log k_2 against the perchloric acid concentration is linear. It has a slope of 0.90, which may be compared with slopes of 0.73 and 1.25 previously reported[15] in 76.8 and 84.0% ethanol, respectively. It has an intercept of -3.478, corresponding to a k_2 of 3.3×10^{-4} in infinitely dilute acid.

Discussion

It is clear from the foregoing that catalysis by none, one, or two halide ions is possible. If a narrow range of iodide concentrations is studied any order between zero and two may be obtained. The iodide ion presumably functions by complexing the mercury atom, which can certainly accommodate at least four ligands in its coordination shell.[16] This is presumably true of the other halide ions as well, although the term of the second order in halide ion will be harder to observe due to the weaker complexing power of chloride and bromide with mercury.

(15) M. M. Kreevoy, J. W. Gilje, and R. A. Kretchmer, *J. Am. Chem. Soc.*, **83**, 4205 (1961).

(16) J. Bjerrum, G. Schwarzenbach, and L. G. Sillen, "Stability Constants," The Chemical Society, London, 1958, p. 121.

The report by Ichikawa and co-workers[3] that hydrochloric acid induced deoxymercuration rates are given by a rate law of the form $k[H^+][Cl^-][S]$ is oversimplified. Their reported observation[3] that 2-isopropoxyethylmercuric chloride does not react with perchloric acid is in error, as shown above. With increasing dilution their observed rates did not fall so fast as required by a square dependence on the hydrochloric acid concentration.[3] This can now be explained on the basis of equation 8. Using 2-isopropoxyethyl-

$$\text{rate} = k_2[H^+][S] + k_3[H^+][Cl^-][S] \qquad (8)$$

mercuric chloride as an example, k_2 was evaluated in 79.7% ethanol from equation 9. This is based on the

$$\log k_2 = 0.90[H^+] - 3.478 \qquad (9)$$

assumption that k_2 will be the same in hydrochloric and perchloric acids. Equation 8 could then be used to obtain k_3. Table III shows the values obtained, along with those originally given by Ichikawa and co-workers.[3] The former are clearly much more nearly constant. However, even equation 8 is still oversimplified by the omission of a term in $[Cl^-]$,[2] as explained above. In the deoxymercuration of 2-acetoxyethylmercuric chloride it is likely that a solvolytic term, of the zeroth order in hydrochloric acid is also present in the rate law.[17]

TABLE III

CALCULATED VALUES OF k_3 FOR HCl DEOXYMERCURATION OF 2-ISOPROPOXYETHYLMERCURIC CHLORIDE IN 80% ETHANOL

[HCl], M	$10^2 \times k_3$[a] $l.^2$ mole^{-2} sec.$^{-1}$	$10^2 \times k_3$[b] $l.^2$ mole^{-2} sec.$^{-1}$
0.0128	8.5	5.8
.0257	6.5	5.1
.0500	5.9	5.8
.0975	5.6	5.5
.1614	5.7	5.6

[a] Taken from ref. 3. [b] Calculated from equation 8.

A general scheme for deoxymercuration in the presence of halide ion is shown in Chart I. The mercuric halide formed will, of course, assume its equilibrium state of complexation with the halide ion present. The orientation and dynamics of the carbon atoms, the oxygen, and the mercury in the transition state is probably very similar to that previously established for the case of deoxymercuration catalyzed only by acid.[7] The

(17) M. M. Kreevoy and G. B. Bodem, *J. Org. Chem.*, **27**, 4539 (1962).

modification suggested by Ichikawa,[3] in which the decomposition of the olefin–mercuric halide complex is rate determining, is definitely excluded by the repeated observations[3] that 2-alkoxyethylmercuric halides and 2-hydroxyethylmercuric halides give rise to unique rates. If the formation of the olefin–mercuric halide complex were fast and reversible a common rate would be observed (or at least a marked tendency of the rates to drift toward a common value as the reaction proceeds). If the formation of the olefin-mercuric halide complex is essentially irreversible, as suggested by Ichikawa, it is, by definition,[18] rate determining.

The observation that 2-acetoxyethylmercuric chloride is converted to 2-ethoxyethylmercuric chloride in ethanolic perchloric acid is mentioned by Ichikawa as evidence for the reversible formation of olefin–mercuric chloride π-complex. However, the facile solvolysis of 2-acetoxyethylmercuric iodide[17] makes it seem likely that this conversion simply proceeds *via* deoxymercuration to ethylene and mercuric chloride followed by readdition to the ethylene.

If the reaction scheme shown previously is correct, then the ratio k_3/k_2 is given by equation 10. It is

$$k_3/k_2 = [*_3]/[*_2][I^-] \quad (10)$$

$*_n \equiv$ Transition state giving rise to k_n

identical in form and analogous in substance with the formation constant for a complex of a metallic ion with iodide ion. In this case, however, the central ion is the transition state containing only one iodine atom. In the same way k_4/k_3 is the formation constant for the transition state containing three iodine atoms from that containing only two. The former ratio, k_3/k_2, has a value, 3.2×10^3 l. mole^{-1}, and the later ratio, k_4/k_3, a value, 34 l. mole^{-1}. It is interesting to compare these with the various complexing constants of the mercuric ion. If the mercury were very weakly bound to the carbon skeleton in the transition state, so that the iodomercuric group resembled HgI^+ when only one iodine atom was present, the formation constants for the complexed transition states would be expected to resemble K_2 and K_3. On the other hand, if the mercury is firmly bound k_3/k_2 and k_4/k_3 might resemble K_3 and K_4, respectively. The values of K_2, K_3, and

$$K_2 = [HgI_2]/[HgI^+][I] \quad (11)$$

$$K_3 = [HgI_3^-]/[HgI_2][I^-] \quad (12)$$

$$K_4 = [HgI_4^=]/[HgI_3^-][I^-] \quad (13)$$

K_4 are 10^{11}, 5×10^3, and 10^2,[16] supporting the hypothesis that the mercury is still firmly bound. This is consistent with the deoxymercuration transition state structure previously proposed,[7] in which the mercury is not being split away from the carbon skeleton in the rate-determining step.

Experimental

The preparation of solvents and acids have been previously described,[19] as has the kinetic method[6] and the preparation of 2-methoxyethylmercuric iodide.[20] The general method of Hofmann and Sand[21] was used to prepare 2-hydroxyethylmercuric iodide, m.p. 145° dec., lit.[21] 147°. The method of Ichikawa and coworkers[3] was used to prepare 2-isopropoxyethylmercuric chloride, m.p. 84.5–86°, lit.[3] 85–86°. Inorganic solutions were made up by weight from the best quality reagents commercially available.

(18) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp. 99–100, 199–201.

(19) M. M. Kreevoy, *J. Am. Chem. Soc.*, **79**, 5929 (1957).
(20) M. M. Kreevoy and L. T. Ditsch, *J. Org. Chem.*, **25**, 134 (1960).
(21) K. A. Hofmann and J. Sand, *Ber.*, **33**, 1641 (1900).

Reactions of Aromatic Carboxylates. I. Evidence for the Intermediacy of Benzyne in the Pyrolyses of *o*-Halobenzoates[1]

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Received May 27, 1963

The formation of benzyne in the pyrolysis of *o*-halobenzoates has been demonstrated by trapping experiments with tetracyclone to form 1,2,3,4-tetraphenylnaphthalene. The intermediacy of benzyne in the formation of xanthone in alkali metal *o*-halobenzoate reactions has been shown by the isolation of two dichloroxanthone isomers in the pyrolysis of potassium 2,4-dichlorobenzoate. 3,4-Benzocoumarin has been found as the major product of the pyrolysis of potassium *o*-iodobenzoate and has been detected in other *o*-halobenzoate systems. The major reaction path can often be polymerization by intermolecular aromatic S_N2 reaction and benzyne-type reactions can be suppressed by temperature control.

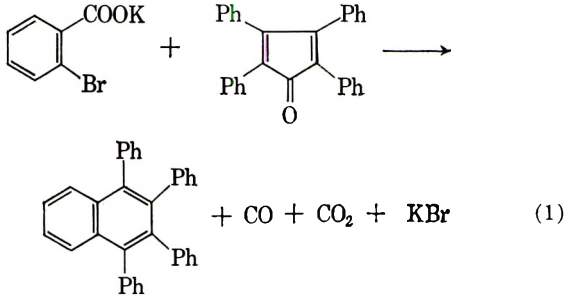
The dismaying violence and the unpredictable products of *o*-halobenzoate pyrolyses have done little to encourage their study until recent years when *o*-halobenzoates have been regarded as potential sources of benzyne.[2] The rationale behind these views[3–6] is that benzyne should be formed from *o*-halobenzoates by a decarboxylation and elimination of halide ion since benzyne is generated in an aromatic system by an initial carbanion formation with a subsequent elimination of a suitable *ortho* group. Attempts to form benzyne from carboxylates with an *ortho* diazonium group[7] and an *ortho* phenyliodonium group[8] have been successful. This paper is a presentation of results which demonstrate the presence of benzyne in the pyrolyses

(1) Presented in part at the 141th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.
(2) The following works are excellent reviews on benzyne: (a) R. Huisgen, "Organometallic Chemistry," H. Zeiss, Ed., Reinhhold Publishing Co., New York, N. Y. 1960, pp. 36–87; (b) J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961); (c) H. Heaney, *Chem. Rev.*, **62**, 81 (1962).
(3) G. Köbrich, *Ber.*, **92**, 2985 (1959).
(4) H. E. Simmons, *J. Org. Chem.*, **25**, 691 (1960).
(5) J. K. Kochi, *ibid.*, **26**, 932 (1961).
(6) G. Köbrich, *Angew. Chem.*, **74**, 428 (1962).
(7) M. Stiles and R. G. Miller, *J. Am. Chem. Soc.*, **82**, 3802 (1960).
(8) E. LeGoff, *ibid.*, **84**, 3786 (1962).

of *o*-halobenzoates and help to define the limits of benzyne-type reactions in these systems.

Simmons[4] found that silver *o*-chlorobenzoate gave a 50% yield of phenyl *o*-chlorobenzoate upon pyrolysis at 212°. A postulated intermediate for an SN2, decarboxylation and proton abstraction route, the silver salt of *o*-(*o*-chlorobenzyloxy)benzoic acid, did not afford phenyl *o*-chlorobenzoate under similar conditions. Supplementing this observation is a recent finding of Köbrich[6] that silver 2-chloro-4-methyl benzoate pyrolyzes to a mixture of *m*- and *p*-cresol esters. Neither of these arguments for the intermediacy of benzyne are fortified with successful attempts to trap benzyne with anthracene, furan, or tetracyclone. A conclusive proof for benzyne would consist of trapping with dienophiles and isolating products of cine-substitution with the appropriate reservations outlined by Heaney.[2c]

Benzyne Trapping.—At the outset of this work, attempts to trap benzyne with anthracene met with the same negative findings as reported by Simmons[4] and Kochi[5] except that a mass spectrum of ether soubles from an *o*-bromobenzoate–anthracene reaction had large peaks at 178 (anthracene), 196 (xanthone), and 254 (possible triptycene). This result encouraged further efforts. Tetracyclone proved to be a suitable dienophile trap for the intermediate benzyne. When potassium *o*-bromobenzoate was heated to 300–315° for five minutes in a nitrogen atmosphere with tetracyclone, 1,2,3,4-tetraphenylnaphthalene was formed (eq. 1). The yields, based on bromobenzoate, ranged from 3.4 to 8.2%. The product gave no melting point depression with an authentic sample[9] and their infrared spectra were superimposable.

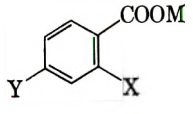


(1)

Other *o*-halobenzoates gave tetraphenylnaphthalene when treated in similar fashion. These results are listed in Table I.

TABLE I

PYROLYSES OF *o*-HALOBENZOATES IN THE PRESENCE OF TETRACYCLONE

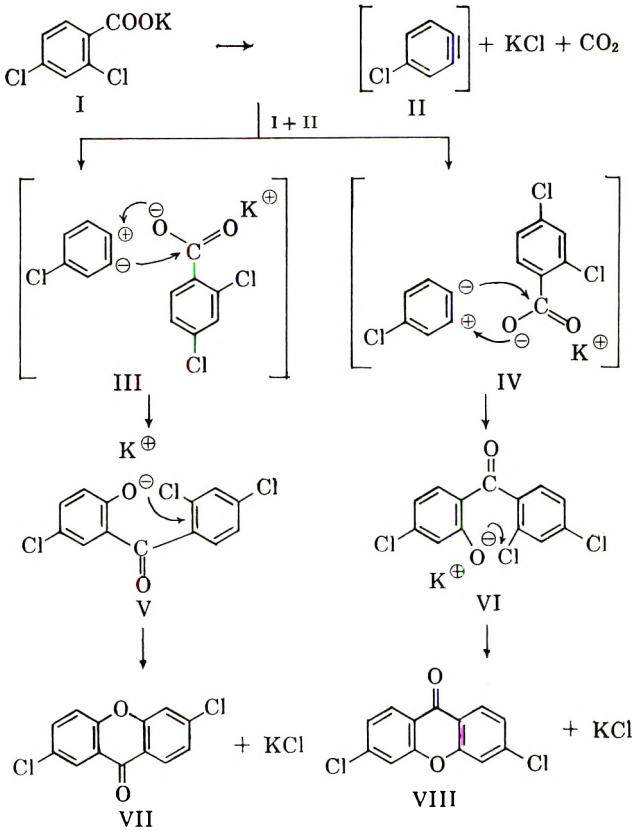


M	X	Y	Yield of tetraphenylnaphthalene, %
K	Br	H	8.2
Cs	Br	H	11.7
K	I	H	4.8
Ag	Cl	H	0.5
Na	Cl	H	6.1
Cs	Cl	Cl	10.5

(9) G. Wittig and E. Knauss, *Ber.*, **91**, 906 (1958).

Benzyne and Xanthone Formation.—In the pyrolysis of alkali metal *o*-halobenzoates, xanthone is usually the major product. This reaction was first reported by Richter in 1883[10] for sodium *o*-chlorobenzoate. Some forty years later xanthone was an unexpected product of the pyrolysis of calcium *o*-chlorobenzoate in 18% yield.[11] Recently Kochi[5] reported yields as high as 70% for xanthone formation from alkali metal *o*-halobenzoates, but maintained that benzyne was not an intermediate.

One of the principal conclusions of this work is that benzyne is an intermediate in xanthone formation. The basis for this statement is the isolation of two xanthones from the pyrolysis of a substituted *o*-halobenzoate. When potassium 2,4-dichlorobenzoate was heated between 300° and 309° for thirty minutes under a nitrogen atmosphere, two dichloroxanthones were formed in 33% yield and 41% selectivity. The only ester isolated from this reaction was *m*-chlorophenyl 2,4-dichlorobenzoate in 10% yield. The two isomeric ketones were present in about 1:1 ratio and were separated by column chromatography. The 3,6-dichloroxanthone isomer (VIII) had the melting point 183–184°.[12] The 2,6-dichloroxanthone isomer (VII) melted at 216–216.5° and matched the product of an independent synthesis. The proof of structure of this latter compound stems from the reaction of potassium 2,4-dichlorobenzoate and potassium *p*-chlorophenolate in hot nitrobenzene with an Ullmann–Goldberg catalyst (Cu/CuCl)[13] to effect *ortho* displacement. Ring cyclization of the resulting derived acids with acetic anhydride and sulfuric acid gave a nonacidic material



(10) R. Richter, *J. prakt. Chem.*, [2] **28**, 273 (1833).

(11) W. Lawson, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **125**, 624 (1924).

(12) M. Julia and G. Tchernoff, *Bull. soc. chim. France*, 546 (1952).

(13) A. A. Goldberg and A. H. Wragg, *J. Chem. Soc.*, 4227 (1958).

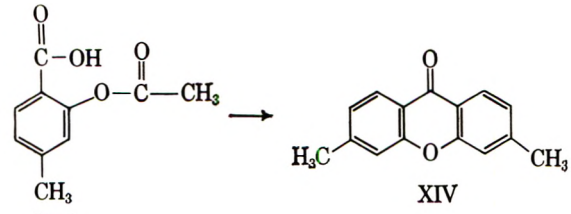
which, after crystallization from ethanol, melted at 215–216° and displayed the same infrared spectrum as the material from the pyrolysis reaction. A mixture melting point of these two products gave no depression.

Two dichloroxanthones are predicted by a benzyne-type reaction. In this mode of reaction chlorobenzyne II is generated and attacked by another 2,4-dichlorobenzoate molecule. A concerted addition of benzoate to benzyne gives a phenolate system which precedes an unexceptional displacement for the xanthone ring closure (VII and VIII). (See p. 3189, col. 2.)

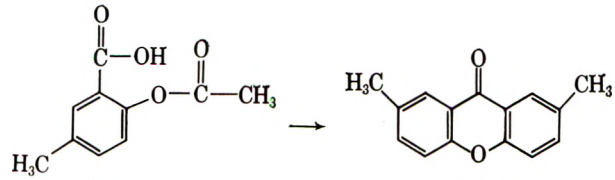
Careful examination of all chromatographic cuts of esters in the potassium 2,4-dichlorobenzoate reaction gave no evidence for the presence of *p*-chlorophenyl 2,4-dichlorobenzoate. Only the *meta* isomer was formed. Both isomers would be predicted to occur if I added nonconcertedly to II to give intermediates such as X which could protonate to give an ester such as XII. Consequently, concertedness in the addition of I to II is suggested, but is not proven. To examine this point further, potassium 2-(2,4-dichlorobenzoyloxy)-5-chlorobenzoate was heated to 310°. The principal product was *p*-chlorophenyl 2,4-dichlorobenzoate. No dichloroxanthones were detected. Since the intermediate anion resulting from decarboxylation of this salt would be the same as one derived from the nonconcerted addition of I to II, concertedness in the dichloroxanthone reaction route is implied strongly. In addition to being evidence against the *cis*-disalicylide route and its variant (*vide infra*), this experiment permits the conclusion that *m*-chlorophenyl-2,4-dichlorobenzoate was not formed in the 2,4-dichlorobenzoate pyrolysis by a benzyne intermediate, but arose from an SN2 reaction on the *o*-chloro group, followed by decarboxylation and proton abstraction (IX → X → XII).

An example of nonconcerted addition of benzoate to benzyne is that of silver 2,4-dichlorobenzoate wherein no xanthone isomers were detected; both chlorophenyl esters were formed. This difference in the potassium and silver experiments lies probably in the nature of the metal carboxylate bond, which dictates the site requirements of attack by the benzyne.

A possible route for xanthone formation involves a double displacement of halogen to form a *cis*-disalicylide (XI), which is reported to decarboxylate to xanthone.[14] In those reactions known to go to xanthones through a *cis*-disalicylide route, only one disubstituted isomer of xanthone is formed. Examples of this effect are the formation of 4,5-dimethylxanthone from *o*-cresyl-*o*-cresotinate,[15] 3,6-dimethylxanthone (XIV) from *o*-acetyl-*m*-cresotic acid (XIII), and 2,7-dimethylxanthone (XVI) from *o*-acetyl-*p*-cresotic acid (XV).[16]

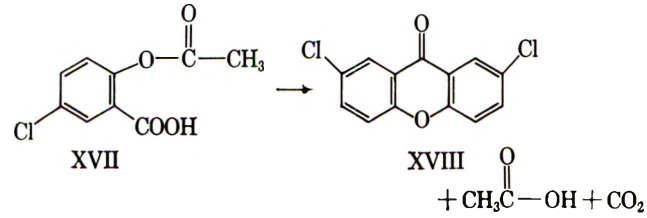


XIII XIV



XV XVI

We have found that only one xanthone isomer, 2,7-dichloroxanthone (XVIII), is formed in the pyrolysis of 5-chloroacetylsalicylic acid (XVII). Consequently,

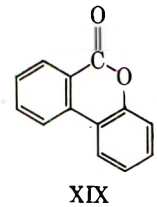


XVII XVIII

the *cis*-disalicylide route does not obtain in the pyrolysis of potassium 2,4-dichlorobenzoate.

A variant of this mechanism involves the initial SN2 product IX which decarboxylates to anion X capable of rearranging to a xanthone VIII *via* an intermediate phenolate.[5] This path is untenable since it also predicts only one isomer, 3,6-dichloroxanthone, in the 2,4-dichlorobenzoate system.

3,4-Benzocoumarin Formation.—When the xanthone reaction was extended, to potassium *o*-iodobenzoate, the yield of xanthone dropped sharply, and an ester was isolated as the main ether-soluble product. The ester was shown to be 3,4-benzocoumarin (XIX) or the δ-lactone of 2′-hydroxydiphenyl-2-carboxylic acid. Yields ranged

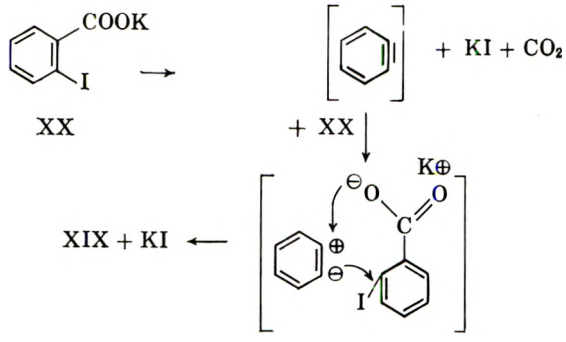


XIX

from 18% to 33%. This ester was also formed in 3.3% yield during a potassium *o*-bromobenzoate pyrolysis carried out under 255-p.s.i. carbon dioxide. Examina-

(14) R. Anschutz, *Ber.*, **52**, 1884 (1919).
(15) M. Schopf, *ibid.*, **25**, 8645 (1892).
(16) L. Anschutz and G. Gross, *ibid.*, **77**, 647 (1944).

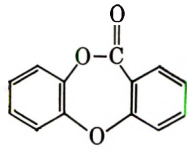
tion of its reaction path was assisted by the pyrolysis of potassium *o*-(*o*-iodobenzoyloxy)benzoate at 240°. The chief product was phenyl *o*-iodobenzoate although 3,4-benzocoumarin and xanthone were formed. Since this salt cannot be the principal intermediate in the *o*-iodobenzoate reaction, a concerted addition—displacement to 3,4-benzocoumarin as well as the addition—



rearrangement to xanthone would seem to be feasible.

3,4-Benzocoumarin does not rearrange to xanthone under the reaction conditions. This finding rules out a long-standing contention[17] that it was an intermediate in the formation of xanthone from phenyl salicylate.

Silver *o*-Iodobenzoate.—One of the more interesting aspects of *o*-halobenzoate reactions is the report of Simmons[4] that during silver *o*-iodobenzoate pyrolysis there is formed a compound that melts at 180–181° and has infrared absorption at 5.65, 5.70, and 5.75 μ. On the basis of the infrared and elemental analyses, the compound was designated as the lactone of *o*-carboxy-*o'*-hydroxydiphenyl ether. Although no material melting at 180–181° was isolated in our experi-



XXI

ments, it is unlikely that the structure assignment is correct for the following reasons.

(1) Structure XXI recently has been prepared by Lewis[18] from 2'-hydroxy-2-phenoxybenzoic acid by lactonization and from *o*-phenyloxybenzoic acid by oxidative coupling. Its melting point is given at 66–69°.

(2) The infrared spectra of depsidones, such as vicanicin, substances known to have the nucleus of XXI, display one carbonyl absorption[19] (5.75 μ).

In our hands, silver *o*-iodobenzoate was pyrolyzed in a nitrogen atmosphere to 3,4-benzocoumarin (10%), xanthone (5%), phenyl *o*-iodobenzoate (5%), phenyl benzoate (10%), and diphenic anhydride (5%).

Nonhalogenated Esters.—One of the esters formed in the pyrolysis of *o*-halobenzoates is phenyl benzoate. This type of product was first mentioned by Kochi[5] for a mixture of lithium *o*-bromobenzoate and lithium 2-chloro-4-methyl benzoate which, after heating to 400°, gave phenyl *p*-toluate. A nonhalogenated ester, *m*-cresyl-*p*-toluate, was formed by the pyrolysis of potassium 2-chloro-4-methyl benzoate.[6] It is possible that these nonhalogenated esters are formed from the expected phenyl *o*-halobenzoates by dehydrohalogenation involving the hydrogen evolved by the charring process. Phenyl benzoate was formed in 3.2% yield during an explosive reaction of potassium *o*-bromobenzoate as well as during a violent silver *o*-iodobenzoate pyrolysis. When the potassium *o*-bromobenzoate reaction was run at a temperature of 300–315° with a carbon dioxide pressure of 100 p.s.i., the yield of phenyl benzoate fell to 0.66%. A mass spectrum of the bomb reaction gases showed 0.4% hydrogen.

Acid–Salt Reaction.—When the pyrolysis of potassium *o*-bromobenzoate was carried out in the presence of *o*-bromobenzoic acid, phenyl *o*-bromobenzoate was obtained in yields of 37 to 46%. The possibility that this proceeds through an SN2 product, *o*-(*o*-bromobenzoyloxy)benzoic acid, is diminished by the observation that the latter acid, under the same reaction conditions, affords a 5.1% yield of phenyl *o*-bromobenzoate. The finding supports, but does not prove, that the ester was formed by concerted addition of the acid to benzene derived from *o*-bromobenzoate.

Polymers.—The formation of polysalicylates by an intermolecular SN2 reaction of the carboxylate on halogen takes place to a considerable degree. To be sure, it accounts for most of the reaction products in certain cases, particularly if the temperature is maintained below that necessary for decarboxylation. When silver *o*-iodobenzoate was heated under vacuum (20 mm.) for one hour between 175–200°, the major portion (88%) of the reaction products was a chloroform-soluble oligomer with a number of average molecular weight of 3150. Similarly, potassium *o*-bromobenzoate afforded an oligomer (molecular weight, 2200) representing 76% of the reaction products by maintaining the temperature at 240° for 30 minutes. The polymer run gave off very little carbon dioxide, whereas maintaining the temperature at 300° gave a quantitative yield (based on the xanthone reaction) of carbon dioxide.

Experimental[20]

Apparatus.—The apparatus for the pyrolytic experiments, unless otherwise noted, consisted of a 25- or 50-ml. reaction flask fitted with two Claisen adapters for gas inlet and a thermocouple lead. An exit tube led to a trap and a 1-in. head of mercury. The system was evacuated and flushed with nitrogen at least five times prior to immersion in a Wood's metal bath. The bath was heated by a Hoskins furnace. All reactions were run with a nitrogen sweep and reaction mixtures were maintained under nitrogen until their internal temperature was 35–40°.

Preparation of Salts.—Salts of the *o*-halobenzoates were prepared by reaction of stoichiometric quantities of acid and potassium hydroxide in water. After removal of water, the salts were washed with ether and dried for 24 hr. at 100° (0.5 mm.) in an Abderhalden pistol. Nujol infrared spectra were taken to ensure removal of water and parent acids.

Potassium 2,4-Dichlorobenzoate.—Potassium 2,4-dichlorobenzoate (4.58 g.) was heated above 300° for 30 min. under a nitrogen atmosphere. The temperature never exceeded 309°. The reaction mixture was a frothing red melt. After cooling, the reaction mass was washed with ether, acetone, and benzene. The washings were combined and stripped to give a residue weighing 1.655 g. The salt material of the reaction was dissolved in water and acidified. A 0.91 g. sample of 2,4-dichlorobenzoic acid was collected. Chromatography on acid-washed alumina

(17) E. Strohbach, *Ber.*, **34**, 4136 (1901).
(18) J. R. Lewis, *J. Chem. Soc.*, 2533 (1962).
(19) S. Nulakantan, T. R. Seshandri, and S. S. Subramanian, *Tetrahedron Letters*, **18**, 597 (1962).

(20) Melting points are uncorrected. Elemental analyses were done by Mr. James Stiles of these laboratories.

with benzene as the eluent gave 275 mg. of material with an ester infrared spectrum in the fore fraction. Two crystallizations from ethanol gave white crystals, m.p. 98.5–99.0°, of *m*-chlorophenyl 2,4-dichlorobenzoate.

Anal. Calcd. for $C_{13}H_7Cl_3O_2$: C, 51.77; H, 2.34; Cl, 35.27. Found: C, 51.67; H, 2.56; Cl, 35.75.

This ester was hydrolyzed to *m*-chlorophenol and 2,4-dichlorobenzoic acid.

The second fraction of the benzene eluent contained a white solid, which melted at 216–216.5° after crystallization from ethanol.

Anal. Calcd. for $C_{13}H_6Cl_2O_2$: C, 58.89; H, 2.28. Found C, 58.63; H, 2.38.

This dichloro ketone was 2,6-dichloroxanthone. Immediately after this fraction came another ketonic material, 3,6-dichloroxanthone. One crystallization of the second ketone gave white crystals melting at 183–184°. Infrared spectra distinguished between the two isomers in the fingerprint region. The 3,6-dichloroxanthone had strong bands (chloroform), 9.38, 10.50, 11.59, and 11.85 μ; whereas, the 2,6-isomer had only one strong band at 10.85 μ. The total weight of dichloroxanthones was 651.6 mg. for a 33% yield and 41% selectivity. The 2,6-isomer fraction weighed 275 mg; the 3,6-isomer fraction weighed 175 mg.; 150 mg. of dichloroxanthones was a mixture of the two isomers. Another 315 mg. came off the column with more polar solvents. The latter were not characterized.

Preparation of 2,6-Dichloroxanthone.—Potassium 2,4-dichlorobenzoate (1.202 g.) and potassium *p*-chlorophenolate (0.949 g.) were heated with copper powder (0.0406 g.) and cuprous chloride (0.0904 g.) in 10 ml. of refluxing nitrobenzene for 20 min. The products were washed with ether, dissolved in dilute base and filtered. Acidification was followed by ether extraction. The acidic ether residue was treated with 5% sodium bicarbonate and re-extracted. Another acidification of the bicarbonate solution gave 566 mg. of a light brown precipitate. This was dissolved in 10 ml. acetic anhydride containing 5 microdrops of concentrated sulfuric acid. After 45 min., the mixture was poured into chilled 5% sodium hydroxide. The precipitate was collected, washed with base followed by water, and dried. It weighed 146 mg. and possessed the same infrared spectrum as the dichloroxanthone (m.p. 216–216.5°) from the 2,4-dichlorobenzoate pyrolysis. Recrystallization from ethanol gave a melting point of 215.5–216.5°. A mixture melting point determination of the two samples showed no depression.

Potassium *o*-Bromobenzoate.—Potassium *o*-bromobenzoate (2.725 g.) was heated to 324° for 5 min. in a nitrogen atmosphere. At the end of this time the mass exploded. The ether-soluble material weighed 788 mg. and were chromatographed on alumina to give 375 mg. of xanthone. Analysis was made by infrared comparison and mixture melting point determination with that of authentic material. The yield was 33.6%.

Potassium *o*-Bromobenzoate (Pressure).—Potassium *o*-bromobenzoate (4.78 g.) was placed in a 300-ml. Aminco bomb under 100-p.s.i. carbon dioxide and heated to 300–312° for 15 min. The maximum pressure was 255 p.s.i.; the final bomb pressure was 162 p.s.i. The mass spectrum of the final gas indicated the presence of 0.4% hydrogen. Acid-washed alumina chromatography separated the nonsalt products as follows: phenyl benzoate (0.55%), xanthone (12.5%), and 3,4-benzocoumarin (3.3%). Analyses were carried out by infrared and vapor phase chromatography. Unidentified oils brought off the column by polar solvents totaled 61% of the total material obtained from the column and had the infrared spectrum of an ester and a ketone.

Potassium *o*-Bromobenzoate (Low Temperature).—Potassium *o*-bromobenzoate (2.380 g.) was heated in a nitrogen atmosphere to 240° for 30 min. Only 8.9 mg. of carbon dioxide was evolved. Ether soluble material of the reaction mixture weighed 0.135 g. and had the infrared spectrum of a mixture of xanthone and phenyl *o*-bromobenzoate. Chloroform soluble material weighed 0.440 g. and had the infrared carbonyl absorption at 5.72 μ. The latter oil was coagulated with chlorotorm and methanol. Unchanged salt was recovered and converted to 0.895 g. of *o*-bromobenzoic acid. The molecular weight of the coagulate was 2200.

***o*-Bromobenzoate–Anthracene.**—Potassium *o*-bromobenzoate (3.228 g.) and anthracene (0.602 g.) were heated between 300 and 325° for 40 min. in a nitrogen atmosphere. The reaction mixture was treated with ether. The ether-soluble material was chromatographed. No triptycene was separated. A mass spectrum of the ether-soluble material had three large peaks at 178 (7200), 196 (3380), and 254 (158). They correspond, respectively, to anthracene, xanthone, and triptycene.

Preparation of 1,2,3,4-Tetraphenylnaphthalene from Potassium *o*-Bromobenzoate.—Potassium *o*-bromobenzoate (3.22 g.) was added slowly in a nitrogen atmosphere to molten tetracyclone (4.2 g.) at 305° for 20 min. The benzene-soluble products were chromatographed on acid-washed alumina. A petroleum ether–benzene eluent (90/10) brought down 0.327 g. of a clear oil which was crystallized with methanol, m.p. 204.5–205.0°. Its melting point was undepressed when mixed with authentic 1,2,3,4-tetraphenylnaphthalene,[9] and its infrared spectrum was superimposable on that of authentic material.

Anal. Calcd. for $C_{34}H_{24}$: C, 94.41; H, 5.59. Found: C, 94.19; H, 5.97.

Silver *o*-Chlorobenzoate and Tetracyclone.—Silver *o*-chlorobenzoate (2.89 g.) and tetracyclone (3.84 g.) were mixed and heated to 210–220° in a nitrogen atmosphere for 1 hr. The reaction products that were benzene-soluble were chromatographed on acid-washed alumina. Elution with a petroleum ether–benzene mixture (70/30) gave 23 mg. of an oil whose infrared was superimposable on that of authentic 1,2,3,4-tetraphenylnaphthalene.

A similar procedure except for the use of temperatures between 275° and 325° was used for mixtures of tetracyclone and other *o*-halobenzoates such as cesium *o*-bromobenzoate, sodium *o*-chlorobenzoate, and potassium *o*-iodobenzoate.

Cesium 2,4-Dichlorobenzoate and Tetracyclone.—Tetracyclone (11.52 g.) and cesium 2,4-dichlorobenzoate (1.62 g.) were mixed and heated in a nitrogen atmosphere between 324–331° for 10 min. Column chromatography of the products gave a fore fraction weighing 0.250 g. and whose infrared in Nujol above 9.0 μ in microns was 9.15 (m), 9.30 (s), 9.96 (m), 10.12 (s), 10.70 (s), 10.90 (m), 11.13 (m), 11.30 (m), 12.0 (s), 12.53 (m), 12.95 (m), 13.42 (s), 14.30 (s), 14.80 (m). The mass spectrum of the oil had the following peaks: 358 (6.1), 398 (7), 468 (35.1), 470 (17.0).

Cesium 2,4-Dichlorobenzoate.—Cesium 2,4-dichlorobenzoate (6.46 g.) was heated in a nitrogen atmosphere between 270° and 297° for 25 min. The acetone-soluble portion of the reaction products was chromatographed to afford 0.245 g. of *m*-chlorophenyl-2,4-dichlorobenzoate, 0.480 g. of mixed dichloroxanthones, and 1.00 g. of material with infrared bands of a ketone and an ester. The respective yields of ester and xanthones were 8.1 and 18%.

Cesium 2,4-Dichlorobenzoate.—Cesium 2,4-dichlorobenzoate (12.93 g.) was heated in a bomb under 100-p.s.i. nitrogen to 325° for 15 min. The maximum pressure was 275 p.s.i.; the final pressure prior to opening of the bomb was 130 p.s.i. Chloroform-soluble material weighed 3.56 g. Chromatography on acid-washed alumina gave dichloroxanthone in 25.6% yield. The 2,6–3,6 isomer ratio was approximately 1. The xanthone accounted for 57.8% of total recovered material. Another 28.9% was ketonic material that came off the column with polar solvents, *e.g.*, ether and methanol.

Silver 2,4-Dichlorobenzoate.—Silver 2,4-dichlorobenzoate (1.649 g.) was heated in a nitrogen atmosphere to 220°, at which point a vigorous evolution of gas took place along with a temperature rise to 240°. After 5 min. the temperature fell to 220° and the reaction flask was removed from the heating bath. Ether washing of the reaction products gave 0.251 g. of material whose infrared was similar to that of a mixture of *m*-chlorophenyl-2,4-dichlorobenzoate and *p*-chlorophenyl-2,4-dichlorobenzoate. Column chromatography did not separate the isomers.

***p*-(*m*)-Chlorophenyl-2,4-Dichlorobenzoate.**—2,4-Dichlorobenzoic acid was converted to the acid chloride with oxalyl chloride, whereupon the latter reacted with an etheral solution of *p*-chlorophenol. After extraction with 5% sodium hydroxide solution, the ether was stripped to a residue which was crystallized twice from methanol, m.p. 225.0–225.5°.

Anal. Calcd. for $C_{13}H_3Cl_2O_2$: C, 51.77; H, 2.34; O, 10.62. Found: C, 52.28; H, 2.73; O, 10.60.

The *m*-chlorophenyl ester was prepared in a similar manner. Its melting point was 99–100°.

Anal. Found: C, 52.08; H, 2.67; O, 10.38.

Potassium 2-(2,4-Dichlorobenzoyloxy)-5-Chlorobenzoate.—2,4-Dichlorobenzoyl chloride (1.91 g.) was added slowly to a cooled solution of 5-chlorosalicylic acid (1.73 g.) in pyridine (15 ml.). After complete addition, the milky mixture was poured into water (150 ml.). The solid was taken up in ether, and the ether solution was washed with 1.2 *N* hydrochloric acid. The ether

extract was crystallized from chloroform to melt at 185.5–186.5°. The infrared spectrum had the following bands in Nujol beyond 5.5 μ: 5.70 (s), 5.82 (s), 6.28 (s), 6.4 (m), 6.7 (s), 6.8 (s), 6.92 (s), 7.02 (m), 7.25 (s), 7.65 (s), 7.80 (m), 7.85 (m), 8.05 (s), 8.20 (s), 8.65 (m), 8.95 (s), 9.12 (s), 9.60 (s), 11.1 (m), 11.25 (m), 11.37 (s), 11.93 (s), 12.23 (m), 12.80 (s), 13.12 (s), 14.09 (s), 14.50 (m), and 14.80 μ (s).

Anal. Calcd. for $C_{14}H_7Cl_3O_4$: C, 48.66; H, 2.04; O, 18.52. Found: C, 48.68; H, 2.50; O, 18.21.

2-(2,4-Dichlorobenzyloxy)-5-chlorobenzoic acid, (1.0 g.), was dissolved in 25 ml. of methanol and 25 ml. of ethyl ether. To this solution was added 300 mg. of potassium *t*-butoxide in 20 ml. of methanol. The mixture was stripped at 60° (14 mm.). Ether was added to the residue and filtration gave a white solid whose infrared (Nujol) in microns beyond 5.5 μ was: 5.75 (s), 6.30 (s), 6.85 (s), 7.10 (s), 7.25 (s), 7.65 (m), 7.70 (s), 7.82 (s), 8.05 (s), 8.35 (s), 8.70 (s), 8.95 (s), 9.05 (s), 9.55 (m), 10.10 (m), 11.22 (s), 11.50 (s), 11.60 (m), 11.85 (m), 12.10 (s), 12.60 (s), 13.05 (m), 13.12 (m), 13.80 (s), 14.25 (w), 14.65 (m).

A portion of the salt was added to acidic water. The resulting precipitate was collected and dried. Its infrared was the same as the starting acid.

The potassium salt (0.094 g.) was heated in a nitrogen atmosphere to 310°. At 285° the salt melted with gas evolution. After 5 min. at 310°, the gas evolution subsided and the reaction pot was removed from heat.

Ether washing of the reaction mass dissolved a whitish oil (0.032 g.) whose infrared was identical with that of *p*-chlorophenyl 2,4-dichlorobenzoate. The ether-insoluble residue was dissolved in dilute acid. Extraction with ether followed. The ether solubles (0.030 g.) had the infrared of a mixture of *p*-chlorophenol and 2,4-dichlorobenzoic acid.

5-Chloroaspirin.—5-Chloroaspirin (2.15 g.) was heated to 275° for 20 min. When acetic acid evolution stopped, the temperature was raised to 328° and held at that point for 30 min. The mass was cooled. An infrared of the products in the reaction pot displayed only ester-type carbonyl. The pot was reheated to 362° for 10 min. Another infrared of this reaction mass showed ester and ketonic carbonyl bonds. Column chromatography separated the ketone from the esters. The yield of 2,7-dichloroxanthone was 20%. Its melting point after methanol crystallization was 224–225°; lit.[21] 226°. The infrared (Nujol) of 2,7-dichloroxanthone in microns beyond 5.5 μ was 6.0 (s), 6.23 (s), 6.85 (s), 7.25 (m), 7.60 (m), 7.75 (s), 7.90 (w), 8.25 (m), 8.55 (m), 8.60 (m), 8.80 (s), 9.20 (m), 10.15 (m), 11.0 (s), 11.25 (w), 12.08 (s), 12.20 (s), 12.72 (m), 13.25 (s), 14.42 (s), 14.60 (s).

Anal. Calcd. for $C_{13}H_6Cl_2O_2$: C, 58.89; H, 2.28; O, 26.75. Found: C, 58.76; H, 2.58; O, 26.90.

3,4-Benzocoumarin.—The method of Wittig and Pieper[22] was used to prepare 3,4-benzocoumarin from fluorenone. 3,4-Benzocoumarin (0.400 g.) was heated in a nitrogen atmosphere to 340–345° for 20 min. The ester (0.390 g.) was recovered unchanged, according to infrared analysis.

***o*-Bromobenzoate–*o*-Bromobenzoic Acid.**—*o*-Bromobenzoic acid (13.936 g.) and potassium *o*-bromobenzoate (2.38 g.) were mixed and heated in a nitrogen atmosphere. The maximum temperature was 315° and the heating time above 300° was 16 min. Chromatography of the nonacidic material on acid-washed alumina gave a fraction of 1.276 g. of phenyl *o*-bromobenzoate. The yield based on *o*-bromobenzoate was 46%.

o-(*o*-Bromobenzoyloxy)benzoic Acid.—Salicylic acid was dissolved in pyridine. To this solution was added *o*-bromobenzoyl chloride dropwise with cooling. After complete addition the mixture was poured into water. A white precipitate was collected, dried, and crystallized three times from benzene to melt at 155–156°.

Anal. Calcd. for $C_{14}H_9BrO_4$: C, 52.36; H, 2.38; O, 19.93. Found: C, 52.61; H, 2.51; O, 19.59.

Infrared (Nujol) of acid in microns above 5.0 μ is as follows: 5.70 (s), 5.85 (s), 5.93 (s), 6.23 (s), 6.30 (s), 6.70 (m), 6.82 (s), 6.95 (m), 7.09 (m), 7.25 (m), 7.60 (s), 7.75 (s), 7.85 (s), 10.85 (s), 11.15 (m), 11.40 (w), 11.68 (w), 11.80 (m), 12.42 (m), 12.65 (m), 12.75 (w), 13.23 (s), 13.55 (s), 14.00 (s), 14.60 (s).

o-(*o*-Bromobenzoyloxy)benzoic acid (1.617 g.) was heated in a nitrogen atmosphere to 335°. The time above 300° was 9 min. Temperatures were taken in the reaction mass. The reaction products were treated with ether and chloroform. The ether-soluble material weighed 1.216 g.; the chloroform-soluble material weighed 0.117 g. These two fractions were combined for a chromatography on acid-washed alumina. Phenyl *o*-bromobenzoate (0.071) g. was recovered from a petroleum ether (30–60°)–benzene mixture (85/15). The total material taken off the column was 0.4948 g. The yield of phenyl *o*-bromobenzoate was 5.1%.

Potassium *o*-Iodobenzoate.—Potassium *o*-iodobenzoate (11.54 g.) was heated in a nitrogen atmosphere between 320° and 330° for 15 min. Upon cooling, the reaction mass was treated with ether. The ether-soluble material weighed 1.81 g. and was chromatographed on acid-washed alumina. The following materials were isolated and identified by infrared spectra and v.p.c.: phenyl *o*-iodobenzoate (0.044 g.), xanthone (0.100 g.), and benzocoumarin (0.704 g.). The yields of xanthone and benzocoumarin based on starting material are 2.5% and 18%, respectively. Two unknown materials were also isolated: a hydrocarbon (0.102 g.) with infrared absorptions at 6.4, 6.95, 8.0, 9.2, 9.75, 9.95, 10.15, and 13.5 μ; an ester (0.065 g.) with infrared absorptions at 5.8, 6.2, 6.85, 7.65, 8.35, 8.6, 9.1 and 10.8 μ.

Potassium *o*-(*o*-Iodobenzoyloxy)benzoate.—*o*-Iodobenzoic acid was converted to its acid chloride by means of oxalyl chloride. The acid chloride was poured into a chilled solution of salicylic acid in pyridine. After addition, the pyridine solution was poured into excess acidic water and the precipitate so formed was collected. Two crystallizations from benzene gave white crystals melting at 147–148°. Its infrared spectrum (Nujol) in microns beyond 5.0 μ is as follows: 5.70 (s), 5.85 (s), 6.23 (s), 6.30 (m), 6.40 (m), 6.70 (m), 6.85 (s), 7.10 (m), 7.25 (m), 7.65 (s), 7.80 (s), 8.05 (s), 8.30 (s), 8.60 (s), 8.82 (s), 9.20 (s), 9.60 (m), 9.85 (s), 10.85 (m), 11.15 (m), 11.80 (m), 12.45 (m), 12.65 (m), 12.80 (m), 13.30 (s), 13.70 (s), 14.10 (s), 14.68 (s).

Anal. Calcd. for $C_{14}H_9IO_4$: C, 45.69; H, 2.47; O, 17.38. Found: C, 45.86; H, 2.17; O, 17.38.

The *o*-(*o*-iodobenzoyloxy)benzoic acid (0.368 g.) was dissolved in ether and treated with 0.100 g. of potassium *t*-butoxide in 10 ml. of *t*-butyl alcohol. The mixture was stripped of solvent at 60° (90 mm.). The residue weighed 0.200 g. and had the following infrared spectrum (Nujol) in microns above 5.0 μ: 5.70 (s), 6.23 (s), 6.40 (s), 6.85 (s), 7.0 (m), 7.30 (s), 7.75 (m), 7.90 (m), 8.15 (s), 8.40 (s), 8.60 (w), 8.70 (m), 8.88 (s), 9.20 (s), 9.25 (m), 9.60 (s), 9.85 (s), 10.50 (w), 10.60 (w), 11.25 (m), 11.50 (w), 11.65 (m), 11.90 (w), 12.25 (m), 12.40 (m), 12.70 (m), 13.50 (s), 13.65 (s), 14.20 (s), 14.50 (w), 14.80 (m).

The potassium *o*-(*o*-iodobenzoyloxy)benzoate (0.200 g.) was heated under a nitrogen atmosphere at 260° for 10 min. The reaction mass, upon cooling, was treated with chloroform. A v.p.c. of the chloroform-soluble material showed the presence of phenyl *o*-iodobenzoate, 3,4-benzocoumarin, phenyl benzoate, and xanthone. The column for this analysis was composed of chromosorb with 5% SE 30 silicone oil and was heated at 260°.

Silver *o*-Iodobenzoate.—Silver *o*-iodobenzoate (2.456 g.), prepared by the reaction of silver nitrate and potassium *o*-iodobenzoate, was heated in a nitrogen atmosphere to 80°, at which point a rapid exothermic reaction took place. The temperature rose to 155°. Diphenic anhydride (0.050 g.) was isolated from the top of the reaction vessel. The ether-soluble reaction products (0.530 g.) were chromatographed on acid-washed alumina. The various chromatographic cuts were examined by v.p.c. on 5% SE 30 on Chromosorb (temp., 266°). The following were identified: phenyl benzoate, phenyl *o*-iodobenzoate, xanthone, and 3,4-benzocoumarin. The yield of 3,4-benzocoumarin was 10%; that of xanthone was 5%; that of phenyl *o*-iodobenzoate was 5%; that of phenyl benzoate was 10%.

Silver *o*-iodobenzoate (4.72 g.) was heated under vacuum to 120°. Gas evolution was vigorous but not violent. Acetone washing of the reaction products afforded 0.161 g. of material with an ester infrared spectrum. Ether washing gave only 0.008 g. Chloroform washing gave 1.631 g. of tacky material. The latter residue was redissolved in 10 ml. of chloroform and poured into petroleum ether (30–60°). A precipitate formed which was filtered and dried. Its melting range was 135–143°. Its molecular weight by ebullioscopic determination with chloroform was 3150. The infrared of this oligomer in Nujol beyond 5.0 μ in microns was as follows: 5.69 (s), 6.21 (m), 6.42 (w), 6.73 (w), 6.85 (s), 7.75 (m), 7.79 (s), 8.01 (s), 8.30 (s), 8.62 (m), 8.90 (m),

(21) H. E. Faith, M. E. Bahler, and H. J. Florestano, *J. Am. Chem. Soc.*, **77**, 543 (1955).

(22) G. Wittig and G. Pieper, *Ber.*, **73**, 295 (1940).

9.01 (w), 9.32 (m), 9.51 (s), 9.77 (m), 11.17 (w), 11.75 (w), 12.80 (w), 13.42 (s), 14.55 (w).

Anal. Found: C, 55.01; H, 3.09; O, 21.78; Ag, 8.85; I, 9.74.

A portion of the oligmer (0.191 g.) was hydrolyzed with base to salicylic acid (0.111 g.).

Acknowledgment.—The author expresses thanks for technical assistance to Mrs. Jean Whittaker and Mr. Eugene White and for encouraging and stimulating discussions to Prof. Cheves Walling, Dr. Archibald P. Stuart, and Dr. Howard P. Angstadt.

Fate of the Carbinol Carbon in the Conversion of Tetrahydrofurfuryl Alcohol to Dihydropyran

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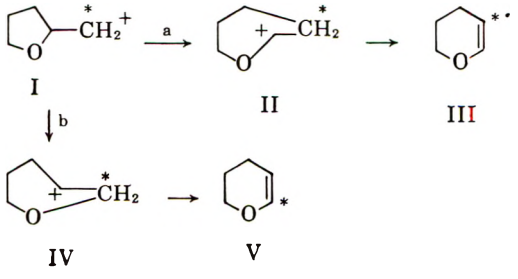
Received June 5, 1963

Tetrahydrofurfuryl alcohol with carbon-14 in the exocyclic carbon atom was prepared by carbonating furyllithium with radioactive carbon dioxide and reducing the resulting furoic(^{14}COOH) acid. Lithium aluminum hydride converted the acid to furfuryl alcohol. Hydrogen over Raney nickel then saturated the ring to give the labeled tetrahydrofurfuryl alcohol. Passing the labeled alcohol over hot alumina produced radioactive dihydropyran. Ozonization cleaved the dihydropyran to formic acid and 4-hydroxybutanal, while nitric acid oxidation of the dihydropyran gave glutaric acid which with hydrazoic acid was degraded to 1,3-diaminopropane. The results of radioactivity assays on these materials showed that the carbon-14 in dihydropyran was located in the 2- and 6-positions. The relations of this distribution to postulated reaction pathways is discussed.

When tetrahydrofurfuryl alcohol is passed over alumina at 350°, dehydration and ring expansion occur to give dihydropyran.[1,2] Although the reaction has been examined and improved by several groups,[3-5] only little evidence useful in defining a mechanism has been obtained. We wish to report work bearing on this aspect of the tetrahydrofurfuryl alcohol–dihydropyran conversion.

In the first stages of the reaction, alumina may be taken to coordinate with one or both of the oxygen atoms in tetrahydrofurfuryl alcohol. We assumed as a working hypothesis that the hydroxyl oxygen is the one involved and, therefore, that the exocyclic carbon atom becomes electron deficient. This presents two rearrangement possibilities, which are formulated here—in terms of the limiting carbonium ion-form I[6]—as paths a and b. Path a proceeds through a Wagner–Meerwein rearrangement with ring expansion (see II) and loss of proton to give the dihydropyran product III. A close analogy may be found in the alumina dehydration of cyclopentylcarbinol to cyclohexene.[10] An added favorable feature is the possibility of delocalization of the positive charge in II to oxygen.[11] Path b has the ring oxygen migrating to the external methylene group to give IV, which on loss of a proton becomes dihydropyran V. An ethylene oxide ring derived from IV could be involved in the rearrangement just as in the conversion of 2-methoxy-2-methylpropyl *p*-bromobenzenesulfonate to isobutyraldehyde.[12] A basis of choice between paths a and b lay in the fact that the former places the exocyclic carbon atom of tetrahydrofurfuryl alcohol at the dihydropyran 3-position (*cf.* III), while the latter places it at the dihydropyran 2-position (*cf.* V). With this in mind, we proceeded to prepare tetrahydrofurfuryl alcohol with carbon-14 in the exocyclic methylene group, to carry out the dehydration–rearrangement, and to locate the carbon-14 in the derived dihydropyran.



In order to obtain the labeled starting alcohol, furyllithium was carbonated with radioactive carbon dioxide. Lithium aluminum hydride converted the resulting furoic(^{14}COOH) acid (VI) to furfuryl alcohol,

(1) The formal names for this compound and its derivatives are cumbersome and unfamiliar. Thus, for the parent compound we have our choice of 5,6(or 2,3)-dihydro-4*H*-pyran, 5,6(or 2,3)-dihydro-γ-pyran, or 5,6(or 2,3)-dihydro-1,4-oxin. For convenience, we have based the naming here on Δ^2-dihydropyran and, wherever possible, have dropped the Δ^2. Note that this scheme automatically places the double bond at the 2,3- rather than the 5,6-position.

(2) R. Paul, *Bull. soc. chim.*, [4] **53**, 1489 (1933).

(3) R. L. Sawyer and D. W. Andrus, *Org. Syn.*, **23**, 25 (1943).

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

(5) C. H. Kline and J. Turkevich, *ibid.*, **67**, 498 (1945).

(6) The tetrahydrofurfuryl cation has been suggested before as a key intermediate: *cf.* Paul,[7] who interpreted his reaction in terms of something resembling the cation, Wilson,[8] and Fried.[9]

(7) R. Paul, *Bull. soc. chim.*, [5] **2**, 745 (1935).

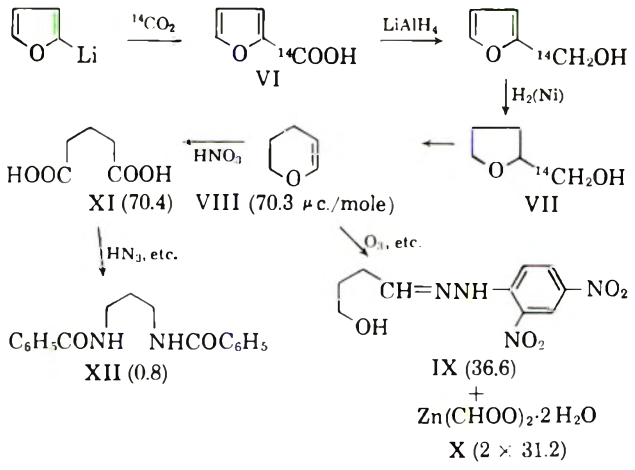
(8) G. J. Baumgartner and C. L. Wilson, *J. Am. Chem. Soc.*, **81**, 2440 (1959); H. P. Thomas and C. L. Wilson, *ibid.*, **73**, 4803 (1951).

(9) J. Fried, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 348.

(10) H. S. Turner and R. J. Warne, *J. Chem. Soc.*, 789 (1953).

(11) Other pertinent analogies involving a carbon shift to the adjacent electron-deficient carbon may be cited. These include diazotization of cyclopentylmethylamine to cyclohexanol [P. A. S. Smith, D. R. Baer, and S. N. Ege, *J. Am. Chem. Soc.*, **76**, 4564 (1954)], of 2-(aminomethyl)-tetrahydrofuran to an "oxidation product" of 5-hydroxypentanal [N. V. Williams, *Chem. Abstr.*, **26**, 3253 (1932); *Bull. acad. sci. USSR, Classe sci. math. nat.*, 1117 (1931)], and of 2-(aminomethyl)-tetrahydropyran to 6-hydroxyhexanal [J. Colonge and P. Corbet, *Bull. soc. chim. France*, 287 (1960); *Compt. rend.*, **247**, 2144 (1958)]. The rearrangement of pinacol to pinacolone over alumina at 320° [W. N. Ipatieff and W. Leontowitsch, *Chem. Zentr. II*, **77**, 87 (1906); *J. Russ. Phys. Chem. Soc.*, **35**, 606 (1903)], the conversion of 4-hydroxy-2,4,6-trimethyl-2,5-cyclohexadienone to trimethylhydroquinone with dilute acid [E. Bamberger and A. Rising, *Ber.*, **33**, 3636 (1900)], and the transformation of 3-ethoxy-2-methyl-2-heptanol to 2,2-dimethylhexaldehyde in hot formic acid [I. Elphimoff-Felkin, *Bull. soc. chim. France*, 497 (1950)] are also related.

(12) S. Winstein, C. R. Lindegren, and L. L. Ingraham, *J. Am. Chem. Soc.*, **75**, 155 (1953). Other examples of the migration of oxygen to an adjacent electron-deficient carbon atom may be found in the solvolysis of tetrahydrofurfuryl tosylate and bromide to 3-hydroxytetrahydropyran [D. Gagnaire, *Bull. soc. chim. France*, 1813 (1960)] and in the isomerization of tetrahydrofurfuryl acetate to 3-acetoxytetrahydropyran in the presence of zinc chloride [D. Gagnaire and A. Butt, *ibid.*, 309 (1961)].

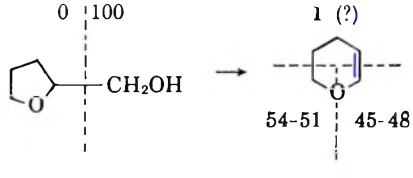


which on hydrogenation over Raney nickel[13] gave the radioactive tetrahydrofurfuryl alcohol VII. Passing this material over hot alumina furnished labeled dihydropyran VIII.

Ozonolysis afforded a convenient way of separating the carbon atoms of positions 2 and 3 of the dihydropyran. The carbon at position-2 emerged as formic acid (collected in the form of the zinc salt X) while the carbon at position 3 emerged as part of 4-hydroxybutanal (collected in the form of its 2,4-dinitrophenylhydrazone IX). Assay showed that the activity of the dihydropyran VIII (70.3 μc./mole) was divided between the two cleavage fragments X and IX (2 × 31.2 and 36.6 μc./mole), respectively. This result was consistent with the operation of path a *and* path b to roughly the same extent.

However, this conclusion was premature. When the radioactive glutaric acid (XI) derived from dihydropyran (VIII) by oxidation was decarboxylated with hydrazoic acid, the 1,3-diaminopropane product (collected as the dibenzoyl derivative XII) was practically devoid of activity.[14] Since the original 3-position of dihydropyran is carried by the dibenzoyl derivative XII, the 3-position cannot be active. Thus, the activity of the 4-hydroxybutanal (as in IX) is seen to reside not at the aldehydic carbon, but instead at the hydroxy end of the C_4 chain, and the activity of dihydropyran VIII is divided not between positions 2 and 3, but instead between positions 2 and 6.

The accompanying diagram summarizes the distribution in terms of per cent activities.[15] Reaction



pathway a is clearly excluded. Pathway b is still admissable but only with modification, for as it stands, it fails to account for the appearance of the exocyclic carbon of tetrahydrofurfuryl alcohol at the dihydropyran 6-position. Possibly path b furnishes dihydropyran-2-^{14}C (V), which subsequently rearranges to a mixture of dihydropyran-2-^{14}C and dihydropyran-6-^{14}C. Work in this area is being continued.

Experimental[16]

Furoic(^{14}COOH) Acid (VI).—Butyllithium was prepared[17] under nitrogen from 27.5 g. (0.20 mole) of dry, redistilled butyl bromide, 3.9 g. (0.56 g.-atom) of lithium wire, and 140 ml. of ether freshly distilled from lithium aluminum hydride. The filtered butyllithium solution was titrated,[18] and 73 ml. containing 0.10 mole of reagent was taken for the metalation of furan.

Furan (34 g., 0.50 mole) was distilled directly into the ethereal butyllithium solution from a mixture of furan and lithium aluminum hydride. A 300-ml., round-bottomed, 3-necked flask provided with a water-cooled condenser, served as the reaction vessel. So far as possible, dry nitrogen blanketed the reaction mixture. After the reaction mixture was diluted with 30 ml. of ether distilled directly from ethereal lithium aluminum hydride, metalation was allowed to proceed at room temperature with occasional short periods of boiling.

The reaction flask, fitted with an efficient induction stirrer,[19] was attached to a vacuum manifold.[19] Carbon dioxide was generated in the line over a 20-min. period by adding 50 ml. of concentrated sulfuric acid to 20.0 g. of dry barium carbonate containing 24.4 μc. of carbon-14. The gas was passed into the stirred furyllithium solution at −60°. Careful warming of the sulfuric acid mixture released all residual carbon dioxide. After a total carbonation time of 40 min., 20 ml. of water was added by drops followed by 30 ml. of 6 *N* sulfuric acid. The mixture was stirred at room temperature for 1 hr., the uncombined carbon dioxide was collected at liquid-nitrogen temperatures, and the flask was removed from the line.

Furoic acid was recovered by batch and continuous extractions with ether. The acid was partially purified by transferring it from the ether solution to aqueous sodium hydroxide and then after acidification back to ether. This ether solution was dried with calcium sulfate and treated with a small amount of activated alumina gel plus 2 g. of decolorizing carbon. Filtration gave a clear, almost colorless solution, from which solvent was stripped by first warming the solution at 50–60° and then drying the residue in a desiccator over phosphorus pentoxide. The solvent-free solid (9.3 g., m.p. 128–130°, neut. equiv. 112–113) was crystallized first from water (decolorizing carbon was used here) and then from carbon tetrachloride to give pure furoic(^{14}COOH) acid (VI) that weighed 8.6 g. (76% based on carbon dioxide) and melted at 133° (cor.).

Anal. Calcd. for $C_5H_4O_3$: C, 53.38; H, 3.6; neut. equiv., 112.1. Found: C, 53.73, 53.61; H, 3.50, 3.56; neut. equiv., 112.3; radioactivity, 242, 247 (av. 245) μc./mole.

The *p*-nitrobenzyl ester[20] of this furoic(^{14}COOH) acid (VI) melted after two recrystallizations from 95% ethyl alcohol at 134–134.5°.

Anal. Calcd. for $C_{12}H_9O_5N$: C, 58.30. Found: C, 58.24, 58.35; radioactivity, 255 μc./mole.

A small sample of the radioactive furoic acid VI was decarboxylated[21] by boiling a mixture of the acid (0.35 g.), copper powder (0.35), and freshly distilled quinoline (4 ml.) for several minutes. The furan in the evolved gases was collected and,

(13) G. Hilly, *Bull. soc. chim.*, [5] **4**, 1630 (1937).

(14) The measured counts per minute was just over the background.

(15) For the purposes of this distribution, the molar activity of the dihydropyran was taken as 69.6 and was arrived at by averaging the molar activities of dihydropyran VIII, glutaric acid XI, and the 2,4-dinitrophenylhydrazone of the derived 5-hydroxypentanal (see Experimental section). If the distribution of activity between positions 2 and 6 of the dihydropyran is based on the activities of zinc formate (X), 1,3-dibenzamidopropane (XII), and dihydropyran (VIII), the distribution comes to 45% at the 2-position and 54% at the 6-position. If the distribution is based in the activities of 4-hydroxybutanal (*cf.* IX), 1,3-dibenzamidopropane (XII), and dihydropyran (VIII), the values come to 48% at the 2-position and 51% at the 6-position. With assay standard deviations of 2–3%, the activity distribution in the dihydropyran 2- and 6-positions is either very close to or is indistinguishable from 1:1.

(16) Melting points are uncorrected unless otherwise indicated. Some of the elementary analyses were performed by C. K. Fitz, 115 Lexington Avenue, Needham Heights 94, Mass.

(17) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **51**, 1499 (1949).

(18) H. Gilman and A. H. Haubein, *ibid.*, **66**, 1515 (1944).

(19) M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert, and P. F. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949.

(20) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 157.

(21) *Cf.* E. C. Wagner and J. K. Simons, *J. Chem. Educ.*, **13**, 265 (1936); H. Gilman and M. B. Louisinian, *Rec. trav. chim.*, **52**, 156 (1933); W. G. Dauben and P. Coad, *J. Am. Chem. Soc.*, **71**, 2928 (1949).

after mixing with maleic anhydride (0.25 g.) and ether (3 ml.), was set aside for 2 days.[22] The precipitated hard, white crystals were collected, rinsed with ether, and dried to give 0.34 g. (68%) of 3,6-endoxy-1,2,3,6-tetrahydrophthalic anhydride, m.p. 124–125° dec.

Anal. Calcd. for $C_8H_6O_4$: C, 57.83; H, 3.64. Found: C, 58.19; H, 3.71; radioactivity, 0.0 μc./mole.

Tetrahydrofurfuryl Alcohol (VII) from Furoic(carboxyl-^{14}C) Acid (VI).—A saturated solution of furoic(carboxyl-^{14}C) acid (5.6 g. or 0.050 mole) in 25 ml. of absolute ether was added dropwise to a stirred mixture of 2.3 g. (0.061 mole) of lithium aluminum hydride in 100 ml. of ether.[23] Two 25-ml. portions of ether served to rinse all the furoic acid into the reaction mixture. The addition required 15 min., after which time the mixture was boiled for 1 hr.

Aqueous sodium hydroxide solution (30 ml. containing 4 g. of base) was added cautiously to the stirred reaction mixture. After removal of the two liquid layers, the white residual solid was shaken with three 10-ml. portions of ether. The combined ether layers were separated and washed several times with 10-ml. portions of water until the washings were neutral. The combined aqueous layer and washings were extracted continuously for 5.5 hr., and the ether extract, after several washings with small portions of water, was combined with the first ether portion. The ether solution, dried at 0° with magnesium sulfate, was carefully concentrated to obtain pale yellow, oily, furfuryl alcohol.

A teaspoonful of Raney nickel[13] wet with methanol was added to a glass vessel containing the furfuryl alcohol in about 5 ml. of ether. Two milliliters of methanol was used to rinse down the Raney nickel. The mixture at 50° was shaken with hydrogen at a pressure of 1300 lb. for 5.5 hr. The hydrogenation mixture was filtered, and the filtrate after concentration was distilled through a 4-in. vacuum-jacketed Vigreux column. Water-white tetrahydrofurfuryl alcohol (VII), boiling at 78–79° (18 mm.), was obtained in a yield of 3.9 g. (77%).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.0; H, 9.60; radioactivity, 241, 241, 245 (av. 242) μc./mole.

Dihydropyran (VIII) from Tetrahydrofurfuryl Alcohol (VII).—The procedure was adapted from Sawyer and Andrus.[3] A glass tube $^3/_8$ in. in diameter was filled for about 60 cm. of its 70-cm. length with Alcoa activated alumina (Grade F-1, 8–14 mesh). The tube, slanted about 20° from the horizontal, was held in a 65-cm. furnace. The upper end of the catalyst tube was fitted with a 3-ml. dropping funnel provided with an inlet for nitrogen and a pressure-equalizing side arm. The lower end of the catalyst tube could be attached to two small cold traps in series.

The catalyst was pretreated[4] by slowly dropping 125 ml. of ordinary dihydropyran through the tube at 100°. Then, at a temperature of approximately 340° (maximum 366°), nitrogen was passed through very slowly for several hours. Finally, 14 ml. of ordinary tetrahydrofurfuryl alcohol was added to the 340° catalyst at a rate of 1 drop every 6 sec. Nitrogen (*ca.* 1 bubble per second) was passed through the hot tube during the addition, which required 0.5 hr., and for 2 hr. thereafter. Emergent material was discarded.

The collecting traps were attached to the end of the pyrolysis tube and were cooled with Dry Ice–acetone. The first trap contained 2 g. of dry potassium carbonate. Radioactive tetrahydrofurfuryl alcohol (VII, 3.81 g.) was added a a rate of 1 drop per second. When almost all had been added, 2.0 ml. of ordinary tetrahydrofurfuryl alcohol was placed in the dropping funnel, and the addition was continued. This rinsing process was repeated with another 2.0-ml. portion and finally with a 0.50-ml. portion of ordinary tetrahydrofurfuryl alcohol. The slow current of nitrogen was maintained during, and for 80 min. after, the addition.

No condensate was found in the second trap. The first trap was warmed to 0°, and the green upper layer of product was transferred to a small vacuum-jacketed Vigreux flask. The lower, aqueous layer was shaken with 0.50 ml. of ordinary dihydropyran, which was then added to the Vigreux flask. The dihydropyran was distilled (b.p. 65–86°) and condensed directly into a cold, 10-ml. distilling flask provided with a short Vigreux column and a fraction cutter. Approximately 40 mg. of lithium aluminum hydride was carefully added to the wet dihydropyran. After standing for 2 hr., the product was distilled. Radioactive dihydropyran (VIII, 5.52 g.) with $n^{21}D$ 1.4399 was collected at b.p. 83.5–84°.

Anal. Calcd. for C_5H_8O: C, 71.39; H, 9.58. Found: C, 70.7; H, 10.0; radioactivity, 70.3 μc./mole.

The 2,4-dinitrophenylhydrazone[24] of 5-hydroxypentanal was prepared by first hydrolyzing dihydropyran (0.11 ml.) in 1 ml. of water containing 1 drop of concentrated hydrochloric acid. The homogeneous solution obtained after 15 min. of shaking by hand and 5 hr. of standing was treated with a freshly prepared solution of 2,4-dinitrophenylhydrazine (0.30 g.), 2.5 ml. of water, 8.0 ml. of absolute alcohol, and 1.5 ml. of concentrated sulfuric acid. The mixture was warmed briefly on the steam bath, set aside overnight at room temperature, and then cooled. The collected solid, on recrystallization from 95% alcohol, afforded bright yellow crystals (0.25 g.) of the 2,4-dinitrophenylhydrazone of 5-hydroxypentanal, m.p. 109.5–110°.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00. Found: C, 46.8; H, 5.0; radioactivity, 68.2 μc./mole.

Cleavage of Dihydropyran VIII by Ozonolysis.—Over a period of 0.5 hr., 0.010 mole of ozone in oxygen was bubbled into a −10° solution of 0.91 ml. (0.010 mole) of radioactive dihydropyran (VIII) in 40 ml. of dry, freshly distilled methylene chloride. The reaction tube was then held in a bath at 25° while a stream of nitrogen directed at the surface of the solution removed volatile materials. Zinc dust (3.7 g. or 0.05 g.atom) and water (10 ml.) were added, and the mixture was stirred overnight at room temperature. The mixture was then heated on the steam bath under a reflux condenser for 2 hr. Filtration gave a clear solution, which was extracted continuously for 2 days with *ca.* 300 ml. of ether.

The aqueous layer was separated, placed on the steam bath, and concentrated under a jet of nitrogen to a volume of 15 ml. Filtration removed a small amount of white solid, and the resulting clear filtrate was concentrated further to 2–3 ml. Addition of 20 ml. of absolute alcohol gave an immediate precipitate of zinc formate dihydrate (X), which was collected after allowing the mixture to stand for 8 days at −10°. The pure white product, washed on the funnel with absolute alcohol and then dried in the air, weighed 0.60 g. (63%).

Anal. Calcd. for $Zn(CHO_2)_2 \cdot 2H_2O$: C, 12.55; H, 3.16; ZnO, 42.5. Found: C, 12.8, 13.15; H, 3.35, 3.3; ash, 42.3, 42.50; radioactivity, 62.1, 62.6, 62.5 (av. 2 × 31.2) μc./mole.

The ether solution from the continuous extraction was concentrated under slightly reduced pressures. To the pale yellow residual oil dissolved in 20 ml. of 95% alcohol was added a freshly prepared solution of 1.2 g. (0.0061 mole) of 2,4-dinitrophenylhydrazine, 6 ml. of concentrated sulfuric acid, 9 ml. of water, and 30 ml. of 95% alcohol. The clear solution was warmed for a short time on the steam and then set aside in the cold for 10 hr. The precipitate was collected and was crystallized first from 95% alcohol and then from aqueous alcohol. The fine, yellow crystals of 4-hydroxybutanal 2,4-dinitrophenylhydrazone (IX), after drying *in vacuo* for 20 hr., weighed 0.74 g. (27%) and melted at 116.5–117°.

Anal. Calcd. for $C_{10}H_{12}N_4O_5$: C, 44.78; H, 4.51. Found: C, 44.75, 44.7; H, 4.61, 4.43; radioactivity, 35.3, 36.8, 37.2, 37.2, 36.6 (av. 36.6) μc./mole.

Glutaric Acid (XI) from Dihydropyran (VIII).[25]—A mixture of 2.5 ml. of water, 1 drop of concentrated nitric acid, and 1.0 g. (0.012 mole) of radioactive dihydropyran (VIII) was shaken for 15 min. The resulting homogeneous solution, after 2 hr. at room temperature, was added dropwise over a 2-hr. period to a cold (0°), stirred mixture of 4.8 g. of concentrated nitric acid and 0.04 g. of sodium nitrite. Stirring was continued for 2.5 hr. at 0°, and thereafter for 7 hr. at room temperature.

The acid mixture in a small evaporating dish was exposed to a current of air overnight. The light brown concentrate (2–3 ml.) was diluted with 5 ml. of water and evaporated on the steam bath in a current of air. The dilution and evaporation was repeated three times. Benzene (20 ml.) plus ether (2 ml.) were added to the last concentrate, and solvent was slowly distilled. Addition of benzene–ether as needed kept the volume of the boiling solution approximately constant. The almost colorless solution was filtered to remove a trace of insoluble solid. The

(22) O. Diels, K. Alder, and E. Naujoks, *Ber.*, **62**, 554 (1929).

(23) *Cf.* R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).

(24) *Cf.* C. L. Wilson, *J. Chem. Soc.*, 52 (1945); G. F. Woods and H. Sanders, *J. Am. Chem. Soc.*, **68**, 2111 (1946).

(25) *Cf.* J. English, Jr., and J. E. Dayan, *Org. Syn.*, **30**, 48 (1950).

clear filtrate, after concentration to 15 ml., was cooled to precipitate glutaric acid. Two recrystallizations from benzene gave 1.1 g. (69%) of glutaric acid (XI), m.p. 93–94°. Another crystallization did not change the melting point.

Anal. Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10; neut. equiv., 66.05. Found: C, 45.57, 45.62; H, 6.04, 6.07; neut. equiv., 66.0; radioactivity, 70.8, 71.4, 69.0, 70.2 (av. 70.4) μc./mole.

1,3-Dibenzamidopropane (XII) from Glutaric Acid (XI).[26]—A mixture of radioactive glutaric acid XII (0.50 g. or 0.0038 mole), sodium azide (1.04 g. or 0.0160 mole) and pure chloroform (25 ml.) was swept with a slow stream of nitrogen. The gases from the reaction mixture were passed up a vertical water-cooled condenser and then into aqueous barium hydroxide. Concentrated sulfuric acid (7 ml. or 0.1 mole) was added by drops to the stirred mixture at *ca.* 64° over a 15-min. period. Stirring and heating were continued for 2 hr.

Aqueous sodium hydroxide (60 ml. of a 15% solution) was added slowly with stirring and cooling. Benzoyl chloride (2.4 g. or 0.017 mole) was added and the mixture was shaken vigorously for 10 min. and intermittently for 5 hr. After an additional 15 hr. at room temperature, the two layers were separated and the organic layer was extracted thoroughly with chloroform. The combined chloroform solutions were dried with magnesium sulfate and boiled to remove all solvent. Two crystallizations of the residual oil from benzene gave 0.63 g. (59%) of 1,3-dibenzamidopropane (XII), m.p. 148.5–149° (cor.).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43. Found: C, 72.6, 72.02; H, 6.39, 6.69; radioactivity, 0.8 ± 0.4 μc./mole.

Radioactivity Measurement.[27]—Samples to be analyzed were burned quantitatively to carbon dioxide and water, which were collected and measured manometrically. The carbon dioxide was bled into a Bernstein–Ballentine tube or an ionization chamber for counting. Individual radioactivity determinations have standard deviations of 2–3%.

Acknowledgment.—We are grateful to Research Corporation for a grant that supported much of this work and to R. Christian Anderson and David R. Christman for their help and advice. Some of the research was performed under the auspices of the U. S. Atomic Energy Commission.

(26) *Cf.* H. Wolff, "Organic Reactions," R. Adams, Ed., Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 307; S. Rothchild and M. Fields, *J. Org. Chem.*, **16**, 1080 (1951).

(27) R. C. Anderson, Y. Delabarre, and A. A. Bothner-By, *Anal. Chem.*, **24**, 1298 (1952).

A Steroidal Internal Displacement Reaction[1]

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Received June 6, 1963

Reaction of 3,5-cyclo-6β-methoxy-17β-tosyloxyandrostan-14α-ol with base yields 3,5-cyclo-6β-methoxy-14-androsten-17α-ol instead of fragmentation products. Base treatment of the *p*-toluenesulfonylhydrazone of 3β-acetoxy-14α-hydroxy-5-androsten-17-one affords the rearranged product 13α,14α-oxido-5-androsten-3β-ol.

The 5,10-, 8,9-, and 13,14-seco steroids contain medium sized rings incorporated into the steroid nucleus. It is desirable to synthesize these compounds in order to evaluate this structural variation on biological properties. An attractive route to a 13,14-seco compound involves fragmentation[2] of an appropriately substituted 1,3-diol monotosylate.

Starting with 5-androstene-3β,14α,17β-triol (I),[3] this was converted to the 3,17-ditosylate II. Selective methanolysis of the more reactive 3β-tosylate afforded the 3,5-cyclo derivative III. The necessary stereochemical arrangement of reactive centers is in principle present in III, *e.g.*, the *trans* antiparallel relationship of C-13–C-14 bond and the departing 17β-tosyloxy group to form a seco ketone by bond fragmentation.

Treatment of the 1,3-diol monotosylate III with potassium *t*-butoxide in boiling *t*-butyl alcohol led to the partial recovery of starting material with no detectable seco ketone as evidenced by the infrared spectrum. These conditions were found to be suitable for the fragmentation reaction in other 1,3-diol monotosylates.[2] Reaction of III under more vigorous conditions, with sodium hydride in tetrahydrofuran, which promoted irreversible alkoxide ion formation at C-14 led to a transformation product IV. The substance IV was characterized by the formation of a monoacetate on acetylation with acetic anhydride. The n.m.r. of IV showed the presence of one vinyl proton (4.84 τ).[4]

The transformation of IV to a substance of known structure was accomplished by acetolysis of the 3,5-cyclo steroid to the 3β-acetoxy-Δ⁵ compound Va. Oxidation of Va with chromic acid led to the known 17-ketone VI.[3]

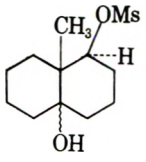
The substance V was also isolated from the reaction mixture and is related to IV by the presence of a 3β-hydroxy-Δ5 system generated from the 3,5-cyclo steroid. This change apparently occurred on the acidic alumina employed in the chromatographic separation.

Formation of the 17α-ol IV can be presumed to arise by intermediate formation of the highly strained 14α,17α-oxide compound VII formed by internal displacement, with attendant inversion at C-17, by the C-14 alkoxide ion. The strained intermediate VII undergoes further base-catalyzed elimination to IV.[5]

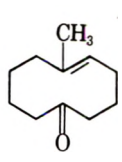
The absence of seco ketonic material arising from the four-center reaction is probably a result of the non-

(1) This investigation was supported by PHSR Grant AM-05183 from the National Institute of Arthritis and Metabolic Diseases.

(2) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957), report the fragmentation of the C-4–C-5 bond on base treatment of 3β-tosyloxy-5α-hydroxycholestane. P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961), also has recently reported the facile fragmentation of the bicyclic 1,3-diol monomesylate (i) to (ii).



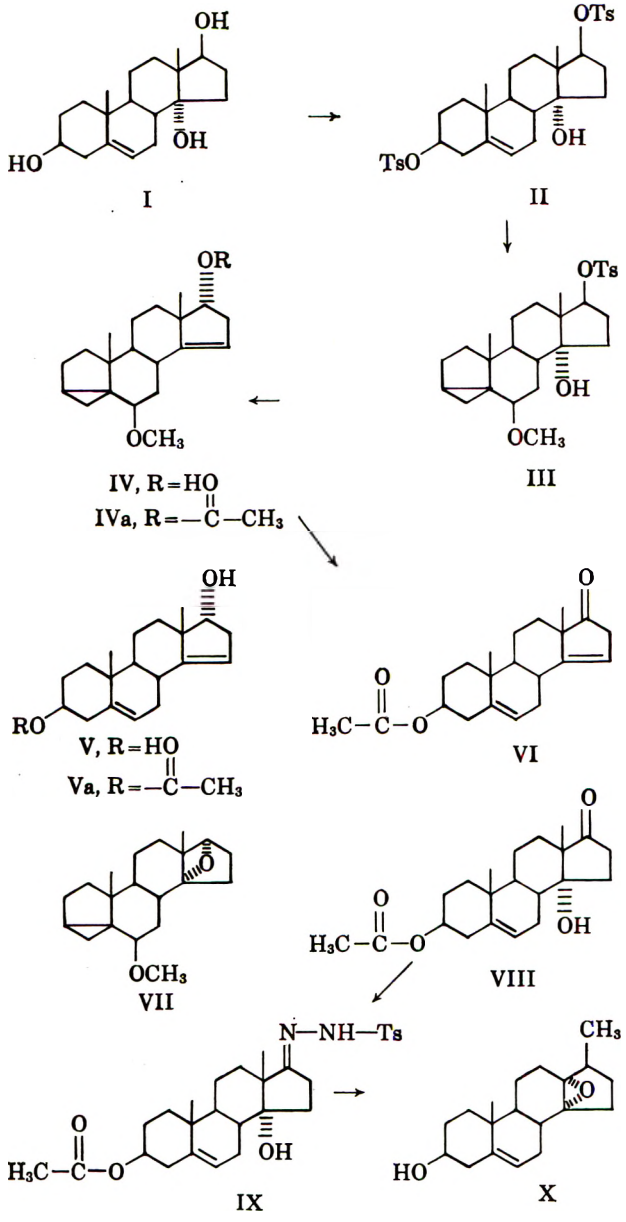
(i)



(ii)

(3) (a) A. F. St. Andre, *et al.*, *J. Am. Chem. Soc.*, **74**, 5506 (1952). The stereochemistry of the hydroxyl at C-14 is alpha in I as demonstrated by (b) S. H. Eppstein, *et al.*, *ibid.*, **80**, 3382 (1958).

(4) The n.m.r. spectrum of 3β-acetoxy-5,14-androstadien-17β-ol showed the C-15 proton signal at 4.81 τ and the C-17α proton signal at 6.0 τ. In compound IV the C-17β proton signal is found at 6.04 τ. We thank Mr. W. V. Anderson for recording the n.m.r. spectra. The spectra were recorded at 60 Mc. on a Varian Associates HR4300 high resolution spectrometer on deuteriochloroform solutions of the steroids.



coplanarity of the reacting centers caused by conformational rigidity of ring D.[6]

It is well established that 1,3-diols undergo fragmentation reactions under acid-catalyzed conditions *via* carbonium ion intermediates.[7] A variant of this fragmentation method was investigated as a means of obtaining the desired 13,14-seco compound. Schechter and Friedman[8] have demonstrated that the base-catalyzed decomposition of *p*-toluenesulfonylhydrazones in protic solvents afford products characteristic of the intermediate formation of carbonium ions. In the present case, possible C-13–C-14 bond fission concerted

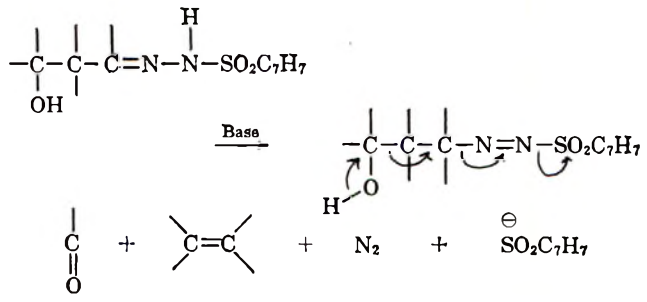


Figure 1

with a carbonium ion generated at C-17 *via* a *p*-toluenesulfonylhydrazone was attempted as a method of obtaining a seco compound. (See Fig. 1.)

Reaction of 3β-acetoxy-5-androsten-14α-ol-17-one[2] (VIII) with *p*-toluenesulfonylhydrazine afforded the hydrazone IX. Decomposition of IX with sodium in boiling ethylene glycol yielded a rearranged oxide X with little or no ketonic material present as judged by the infrared spectrum of the total reaction mixture.

The structure of X was established by the n.m.r. spectrum of X which showed the C-18 methyl signal as a doublet at 9.0 τ ($J \sim 7$ c.p.s.), and by the absence of hydroxyl absorption in the infrared spectrum. No proton signals characteristic of an ethylene oxide type were apparent in the n.m.r., indicating the tetrasubstituted nature of the oxide. The stereochemistry of X is assigned on its probable mode of formation which involves generation of a carbonium ion at C-17, followed by migration of the C-18 angular methyl group and collapse of the ion at C-13 by oxide formation.[9]

Experimental[10]

3β,17β-Ditosyloxy-5-androsten-14α-ol (II).—To a solution of 1.0 g. of the triol I in pyridine was added 3.3 g. of *p*-toluenesulfonyl chloride. The mixture was allowed to stand for 16 hr. at room temperature. The product was precipitated by pouring the reaction mixture into ice–water. Filtration and drying afforded 1.9 g. of crude II. An analytical sample was prepared by repeated crystallization from benzene, m.p. 126–127°, $[\alpha]^{24}D$ −38°; λ_{Nujol} 2.75 (OH), 6.23, 8.4, 8.5 μ (tosylate).

Anal. Calcd. for $C_{37}H_{42}O_7S_2$: S, 10.4. Found: S, 9.95.

3,5-Cyclo-6β-methoxy-17β-tosyloxy-androstan-14α-ol (III).—To a solution of 1.8 g. of the ditosylate II in 200 ml. of methanol and 25 ml. of acetone was added 4.0 g. of anhydrous potassium acetate. The mixture was refluxed for 3 hr. under a nitrogen atmosphere. The solvent was removed under reduced pressure, 200 ml. of water was added, and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and the chloroform was removed under reduced pressure, to yield 1.5 g. of crude III. Crystallization from acetone–hexane gave analytical sample, m.p. 164–166°.

Anal. Calcd. for $C_{27}H_{38}O_3S$: C, 68.32; H, 8.07; S, 6.76. Found: C, 67.88; H, 7.82; S, 6.58.

(5) In footnote 2a discussion of the factors responsible for 1,3-oxide formation from 1,3-diol monosulfonates in fused ring systems is presented. The isomerization of 3α,5α-oxidocholestane to 3α-hydroxy-5-cholestene under mild acidic conditions is also reported.

(6) (a) F. V. Brutcher, Jr., and W. Bauer, Jr., *J. Am. Chem. Soc.*, **84**, 2236 (1962), discuss the three most probable conformations of Ring D in the steroids. Examination of Dreiding molecular models of compound III indicates that the dihedral angle between the departing tosylate group and the C-13–C-14 bond in both envelope and half chair conformations varies from 140–150°. In addition, the increased 1,3 interaction of a solvated 14α-hydroxy anion and the C-17α-hydrogen exerts its effect by further diminishing the dihedral angle and thereby favoring the internal displacement reaction to the 14α,17α-oxide. (b) E. J. Corey, R. B. Mitra, and H. Uda, *ibid.*, **85**, 362 (1963), have utilized fragmentation reactions of appropriately substituted 1,3-hydrindanediol monotosylates for introduction of cyclononene moiety in an elegant total synthesis of *d,l*-caryophyllene and its isomers.

(7) See H. Wasserman, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 375. Direct acid treatment of a C-14α–C17β-diol would be expected to yield a 13,17-seco compound *via* the C-14 carbonium ion intermediate.

(8) H. Schechter and L. Friedman, *J. Am. Chem. Soc.*, **81**, 5512 (1959).

(9) Skeletal rearrangements have been previously observed in *p*-toluenesulfonylhydrazone decompositions. See (a) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); (b) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **56**, 4013 (1954); (c) J. Elks, G. H. Phillipps, D. A. H. Taylor, and L. J. Wyman, *J. Chem. Soc.*, 1739 (1954); (d) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).

(10) Melting points were taken on a Fisher-Johns apparatus. A Perkin-Elmer Infracord was used to obtain infrared spectra. Rotations were determined in chloroform at 1% concentrations unless otherwise stated. Thin layer chromatographic data were obtainec on Merck Silica Gel-G with a chloroform–ether solvent system. The microanalyses were performed by Berkeley Microanalytical Laboratory.

3,5-Cyclo-6β-methoxy-14-androsten-17α-ol (IV) and 5,14-Androstadiene-3β,17α-diol (V).—To a suspension of 0.5 g. of sodium hydride (50% in mineral oil) in 88 ml. of dry tetrahydrofuran under a nitrogen atmosphere was added dropwise a solution of 1.4 g. of III in 50 ml. of dry tetrahydrofuran. The reaction mixture was refluxed for 16 hr. under a nitrogen atmosphere, then cooled to room temperature, and the excess sodium hydride decomposed by dropwise addition of water. An additional 200 ml. of water was added and the mixture was extracted 3 times with 150-ml. portions of chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and taken to dryness under reduced pressure. An infrared spectrum of the residue indicated the absence of carbonyl absorption. The residue was dissolved in benzene and chromatographed on Merck acid washed alumina. Elution with benzene afforded 471 mg. of IV. An analytical sample was prepared by crystallization from hexane, m.p. 128–130°; $[\alpha]^{24}D$ +52; λ_{Nujol} 3.1 μ (–OH); n.m.r.: 8.84 (15-proton), 6.04 doublet (17-proton, J = 5 c.p.s.), 6.65 (methoxy), 8.93 (19-methyl), 8.98 τ (18-methyl).

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.61; H, 9.79.

Elution with chloroform afforded 70 mg. of V. An analytical sample was prepared by crystallization from acetone–ether, m.p. 193–195°, $[\alpha]^{24}D$ −81°; λ_{Nujol} 3.0 μ (–OH); n.m.r.: 4.62 (6-proton), 4.88 (15-proton), 6.04 doublet (17-proton, J = 6 c.p.s.), 8.96 (19-methyl), and 9.0 τ (18-methyl).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.52. Found: C, 79.12; H, 9.79.

3,5-Cyclo-6β-methoxy-14-androsten-17α-ol 17-Acetate (IVa).—To a solution of 0.1 g. of IV in 5 ml. of pyridine was added 5 ml. of acetic anhydride. The solution was allowed to stand for 16 hr. and the solvents were removed under reduced pressure. Attempts to crystallize the oil that remained were unsuccessful. An analytical sample was prepared by sublimation at 100° (0.005 mm.), $[\alpha]^{25}D$ +58; λ_{Nujol} 5.75 and 8.0 μ (CH_3COO—).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.10; H, 8.61.

3β-Acetoxy-5,14-androstadien-17α-ol (Va).—To a solution of 10 mg. of IV in 1.0 ml. of glacial acetic acid was added 1.0 mg. of *p*-toluenesulfonic acid and the reaction mixture was allowed to stand for 4 hr. The mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and the ether removed under reduced pressure, affording 10 mg. of a clear oil, λ_{Nujol}, 2.9 (OH), 5.75 and 8.0 μ (CH_3COO—). Thin layer chromatography of this material revealed that it was homogeneous.

3β-Acetoxy-5,14-androstadien-17-one (VI).—To a solution of 10 mg. of the oil Va in 1 ml. of acetone an acidic solution of chromium trioxide[11] was added dropwise until a slight excess was present. The solution was then filtered through Celite, diluted with water, and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and the solvent was removed under reduced pressure, affording 10 mg. of a clear oil. Thin layer chromatography revealed that the oil was homogeneous and had thin layer chromatographic mobility in two solvent stystems identical to that of an authentic sample of 3β-acetoxy-5,14-androstadien-17-one[3]; λ_{Nujol} 5.75, 8.0 (CH_3COO—), and 5.8 μ (17-ketone).

***p*-Toluenesulfonylhydrazone of 3β-Acetoxy-14α-hydroxy-5-androsten-17-one (IX).**—To a solution of 0.5 g. of 3β-14α-hydroxy-5-androsten-17-one[3] (VIII) in 25 ml. of ethanol was added 0.28 g. of *p*-toluenesulfonylhydrazine and 0.05 g. of *p*-toluenesulfonic acid. The reaction mixture was refluxed for 2 hr. and cooled to room temperature. Under reduced pressure half of the solvent was removed and addition of 50 ml. of ice–water precipitated the product. Filtration and drying afforded 0.389 g. of crude product. An analytical sample was prepared by repeated crystallization from methanol, m.p. 251–252°; λ_{Nujol} 2.8 (14-OH), 3.1, 6.28, 7.1, 7.5, and 8.6 (tosylhydrazone), and 5.75 and 8.0 μ (acetate).

Anal. Calcd. for $C_{27}H_{38}O_5N_2S$: N, 5.5. Found: N, 5.1.

13α,14α-Oxido-5-androsten-3β-ol (X).—To a solution of 0.5 g. of sodium in 75 ml. of dry ethylene glycol under a nitrogen atmosphere was added 0.5 g. of the tosylhydrazone IX. The solution was refluxed for 1 hr. under a nitrogen atmosphere, cooled to room temperature, diluted with 200 ml. of ice–water and extracted with chloroform–ether. The extract was washed with water, dried over sodium sulfate, and the solvent was removed under reduced pressure affording 0.35 g. of residue. An frared spectrum of the residue revealed the absence of carbonyl and tosylhydrazone absorption. Thin layer chromatography showed principally one component. The residue was dissolved in benzene and chromatographed on Merck acid-washed alumina. Elution with ether afforded 127 mg. of X. An analytical sample was prepared by crystallization from dioxane–water, m.p. 139–142°, $[\alpha]^{25}D$ −101°; λ_{Nujol} 2.8 μ (–OH); n.m.r.: 4.57 (6-proton), 9.02 and 9.13 doublet (17-methyl, J = 7 c.p.s.), and 9.02 τ (19-methyl).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found, C, 78.86; H, 9.71.

(11) (a) K. Bowden, *et al.*, *J. Chem. Soc.*, 39 (1946); (b) C. Djerassi, *et al.*, *J. Org. Chem.*, **21**, 1548 (1956).

Organoboron Compounds. XVII.[1] Chemistry of a Compound with Neighboring Borono, Ethynyl, and Amine Functional Groups[2]

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Received May 10, 1963

The synthesis of 2-(*o*-boronophenylethynyl)pyridine (I) and conversion to 2-[β-hydroxy-β-(*o*-boronophenyl)-vinyl]pyridine (II) are reported. Synergetic activity of the borono and amine groups in these molecules was investigated by means of a reaction with chloroethanol.

8-Quinolineboronic acid[4, 5] and 2-(2-boronophenyl)-benzimidazole[1] displace chloride from chloroethanol considerably faster than do equimolar mixtures containing benzeneboronic acid and quinoline or 2-phenylbenzimidazole. The enhanced activity of the former compounds was attributed to cooperative action of the borono and amine functions made possible by the proximity of these groups in a given molecule. As a further test of the role of molecular geometry on the chemical properties of the borono and amine groups, we undertook a study of 2-(*o*-boronophenylethynyl)-pyridine (I). In this molecule the groups are sufficiently separated that direct interaction would not be expected[6]; therefore the reaction pathways available to 8-quinolineboronic acid and the boronophenylbenzimidazole should not be available to compound I.

(1) Paper XVI: R. L. Letsinger and D. B. MacLean, *J. Am. Chem. Soc.*, **85**, 2230 (1963).

(2) This research was supported in part by the National Science Foundation.

(3) Dow Chemical Co. Fellow, Lubrizol Corp. Fellow.

(4) R. L. Letsinger and S. Dandegaonker, *J. Am. Chem. Soc.*, **81**, 498 (1958).

(5) R. L. Letsinger, S. Dandegaonker, W. J. Vullo, and J. D. Morrison, *ibid.*, **85**, 2223 (1963).

(6) On the basis of normal bond lengths and angles it is estimated that the minimum distance separating boron and nitrogen in I would be 4.8 Å., while the minimum distance between hydrogen (of BOH) and nitrogen would be 2.9 Å.

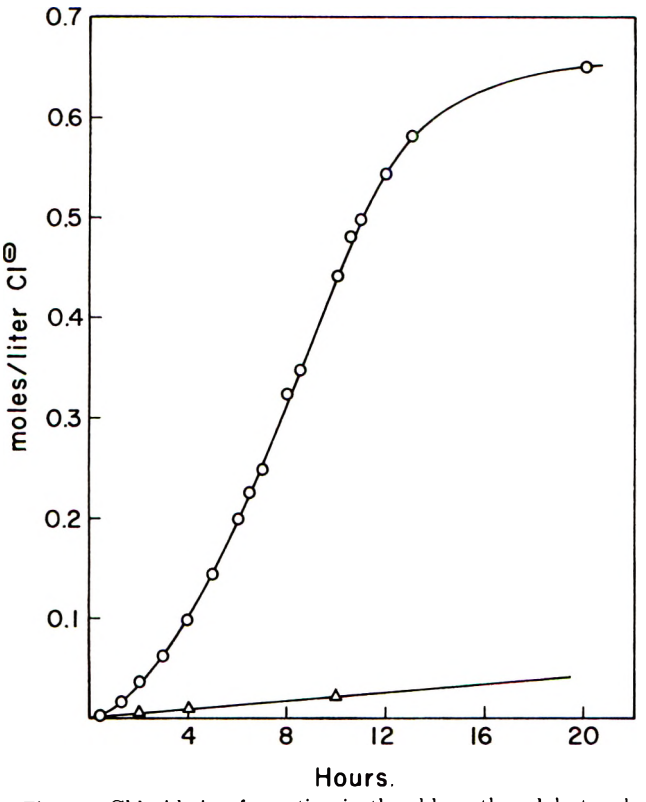
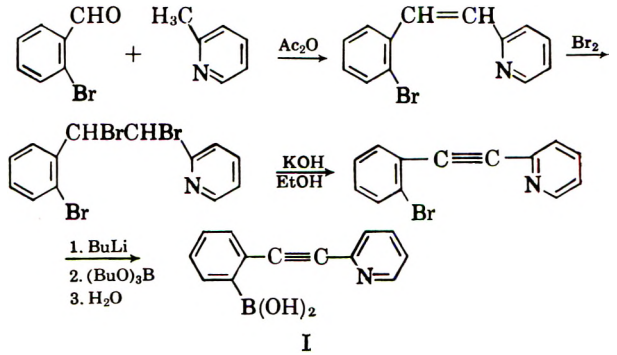


Fig. 1.—Chloride ion formation in the chloroethanol–butanol–collidine system to which 2-(*o*-boronophenylethynyl)pyridine had been added, O; chloride ion formation in a control which did not contain the boron compound, Δ.

CHART I

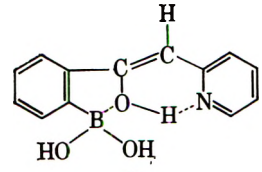


I

2-(*o*-Boronophenylethynyl)pyridine was prepared from *o*-bromobenzaldehyde and 2-picoline by the series of reactions indicated in Chart I. The sequence is similar to that used for the synthesis of 2,2′-tolandiboronic acid.[7] Distinctive bands in the infrared spectrum of I were found at 2.8 (O—H), 4.5 (—C≡C—), and 7.25 and 7.45 μ (region for B—O). Maxima in the ultraviolet region (ethanol solvent) occurred at 274 (ε 16,200), 293 (22,200), 302 (21,700), and 311 mμ (23,000). The compound was further characterized by preparation of a crystalline derivative with *o*-phenylenediamine and by conversion to 2-phenacylpyridine by treatment with hot sulfuric acid.

As in the case of 8-quinolineboronic acid and boronophenylbenzimidazole[1] a chloroethanol–butanol system was used to test for synergetic activity of the borono and amine groups. For this purpose a solution consisting of one millimole of the boron compound, five millimoles of collidine, and five milliliters of 1-butanol, measured at room temperature, was warmed to 88.8° and then brought to a volume of ten milliliters by addition of prewarmed chloroethanol. Aliquots were removed at intervals and titrated for chloride ion by the Volhard procedure. Data from two separate experiments are combined in Fig. 1, along with data for a control reaction in which the boron compound was omitted from the mixture. The curve obtained with this boronophenylethynylpyridine differed in a significant way from those for 8-quinolineboronic acid and the boronophenylbenzimidazole. With the latter compounds the reaction proceeded at a uniform rate from the beginning until the collidine had been converted to the hydrochloride.[1] In contrast, the reaction with compound I was initially very slow, no faster than that of the control. The rate increased over a four-hour period and thereafter was constant until the collidine had been consumed. Throughout the linear portion of the curve the rate (k = 0.60 hr.$^{-1}$)[8] was somewhat greater than that for 8-quinolineboronic acid (k = 0.37 hr.$^{-1}$) and boronophenylbenzimidazole (k = 0.28 hr.$^{-1}$).

This behavior indicates that boronophenylethynylpyridine itself is inactive or of low activity in this system and that in the course of the reaction it is converted to an active compound. In agreement with this idea, a new organoboron compound, assigned structure II, was isolated from a reaction of I with chloroethanol. When this substance was introduced into a fresh portion of the solvent system (chloroethanol–butanol–collidine), the reaction began immediately with no induction period and proceeded at a uniform rate (k = 0.66 hr.$^{-1}$) very close to that corresponding to the linear portion of the curve in Fig. 1.



II

The assignment of structure II rests on analytical data, the formation of a semicarbazone derivative, conversion to 2-phenacylpyridine, and spectral data. The infrared spectrum is consistent with the view that hydroxyl is present (strong absorption at 2.9 μ), that the ethynyl group is absent (no absorption between 4 and 5 μ), that a carbon–carbon double bond is present (strong absorption at 6.2 μ; no bands in the carbonyl region between 5 and 6 μ), and that the boron is tetracoordinated (only weak absorption between 7 and 8 μ). Like 2-phenacylpyridine[9] the substance is yellow; λ_{max}^{EtOH} 383 and 400 (shoulder) mμ.

The transformation of I to II involves addition of –O–H to a carbon–carbon triple bond. An analogous reaction was observed when 2,2′-tolandiboronic acid was heated in an alkaline solution.[7] In that case it was not possible to determine whether the closure involved a five- or six-membered C–B–O ring since

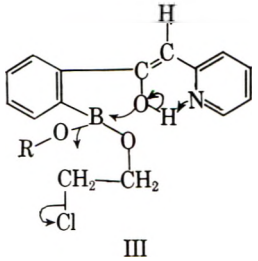
(7) R. L. Letsinger and J. R. Nazy, *J. Am. Chem. Soc.*, **81**, 3013 (1959).

(8) The pseudo zero-order rate constant is 0.062 mole/l./hr.; k is obtained by subtracting the rate for the collidine control reaction and dividing by the molar concentration of the boron compound.

(9) R. F. Branch, *Nature*, **177**, 671 (1956), attributed the yellow color of 2-phenacylpyridine to the presence of an enol tautomer. Since a borono group is a Lewis acid, a neighboring borono group should further stabilize an enol form by coordination with oxygen, as in II.

either type of product would have afforded deoxybenzoin on degradation. With II, however, phenacylpyridine could only reasonably be derived from an intermediate with oxygen alpha to the ring bearing the boron.

The reaction of II with chloroethanol in the presence of excess collidine (relative to II) is a catalytic one since it proceeds until all of the base has been converted to hydrochloride. Though the function of nitrogen in the reaction of II has not yet been uniquely established, formulation III for the operation of the catalyst in the step involving carbon–chlorine fission is attractive. As with 8-quinolineboronic acid[4,10] and the boronophenylbenzimidazole[1] it is assumed that boron functions as a binding site for the alcoholic substrates and that nitrogen serves to increase the nucleophilicity of oxygen bound to boron. Since in II the nitrogen is relatively distant from boron, its effect may be presumed to be transmitted to boron by way of the intervening hydroxyl group. No comparable pathway for interaction of the borono and amine groups is available in compound I, and indeed I appears to be a very poor catalyst for the reaction of chloroethanol with butanol and collidine.



III

Experimental

Infrared spectra were obtained with a Beckman IR-5 spectrometer with the sample in potassium bromide, and ultraviolet spectra were obtained with a Cary Model 11 spectrophotometer. Elemental analyses were performed by Miss Hilda Beck.

o-Bromostilbazole Dibromide.—A mixture of 121.5 g. (0.66 mole) of *o*-bromobenzaldehyde, 61.2 g. (0.66 mole) of 2-picoline and 100 g. (1 mole) of acetic anhydride was refluxed for 10 hr. under a nitrogen atmosphere.[11] The solution was then poured on to ice and acidified with hydrochloric acid. Volatile matter was distilled with steam and the residual solution was made alkaline with sodium hydroxide. The solid which separated on cooling was collected and extracted with hot, dilute hydrochloric acid. *o*-Bromostilbazole hydrochloride separated when the acidic solution was cooled. *o*-Bromostilbazole was liberated by alkaline treatment and was recrystallized from 95% ethanol; weight, 116 g. (68%); m.p. 80–81°. This material was dissolved in carbon disulfide and treated with 25 ml. of bromine. On cooling, 178.6 g. (98% based on bromostilbazole) of bromostilbazole dibromide precipitated, m.p. 153–158°. An analytical sample, m.p. 166–169°, was obtained by recrystallizing a portion of the substance several times from methanol. The remaining material was used for the preparation of *o*-bromophenylethynylpyridine.

Anal. Calcd. for $C_{13}H_{10}Br_2N$: C, 37.1; H, 2.38; N, 3.33. Found: C, 37.1; H, 2.39; N, 3.64.

2-(*o*-Boronophenylethynyl)pyridine.—Dehydrobromination was accomplished by heating 177 g. of *o*-bromostilbazole dibromide with 92 g. of potassium hydroxide in 1600 ml. of absolute ethanol. The solution was then concentrated to about 300 ml., filtered to remove potassium bromide, and further concentrated to 150 ml. Following addition of 200 ml. of water, the mixture was extracted with ether. The crude bromophenylethynylpyridine, obtained as an oil by evaporation of the ether, was purified by formation of the picrate. For this step a solution of bromophenylethynylpyridine (114 g.) in the minimum amount of ethanol was added to 115 g. of picric acid in hot ethanol. The mixture was cooled and filtered, and the precipitate was recrystallized from methanol. The picrate (133 g., m.p. 162–162.5°) was then suspended in 1 l. of water and treated with an aqueous solution containing 13 g. of sodium hydroxide. Extraction with ether, treatment of the ether solution with charcoal, and distillation of the ether afforded 62.5 g. (58.5% based on bromostilbazole dibromide) of 2-(*o*-bromophenylethynyl)pyridine (infrared band, 4.50 μ).

For preparation of the boronic acid, 75 ml. of 1.5 *M* butyllithium in ether was added to 6.2 g. of the bromophenylethynylpyridine in 300 ml. of ether at −70°. A nitrogen atmosphere was used throughout the reaction of the organometallic reagents. After 15 min. an excess (46 g.) of butyl borate was added to the brown solution of the lithium reagent. The solution was stirred an additional 15 min., warmed to 0°, and hydrolyzed by addition of water. Extraction of the ether layer with dilute aqueous potassium hydroxide and neutralization (to pH 6.5) of the extract with hydrochloric acid yielded an oil, which was taken up in chloroform, and extracted with aqueous hydrochloric acid. On addition of sodium carbonate (to pH 6.5) the amphoteric 2-(*o*-boronophenylethynyl)pyridine precipitated; weight, 1.5 g. It was collected by extraction with ether. The analytical sample, obtained by recrystallization from benzene, melted initially at 135°, resolidified on standing, and melted again at 155° on further heating.

Anal. Calcd. for $C_{13}H_{10}BNO_2$: C, 70.0; H, 4.52; N, 6.29; neut. equiv., 223. Found: C,[12] 56.3; H, 4.50; N, 6.04; neut. equiv. (by a potentiometric titration with sodium hydroxide in presence of mannitol), 224.

When hydrogen chloride gas was passed into an ether solution of this boronic acid, an essentially quantitative yield of the amine hydrochloride, m.p. 153.5–154.5°, was obtained. Potentiometric titration of this salt with sodium hydroxide gave a titration curve with two distinct breaks, one for the amine hydrochloride and the other for the boronic acid (mannitol added for second titration). Both gave a value of 263 for the equivalent weight of the hydrochloride, as compared to the calculated value of 260.

***o*-Phenylenediamine Derivative.**—Equimolar amounts of boronic acid I (1.0042 g.) and *o*-phenylenediamine (0.4867 g.) were heated in boiling toluene under conditions to remove the water azeotrope. Concentration of the solution yielded crystals of the *o*-phenylenediamine derivative of 2-(*o*-boronophenylethynyl)-pyridine; weight, 1.0907 g. (82%). It melted at 150–150.5° after recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_{19}H_{13}BN_2$: C, 77.3; H, 4.78; N, 14.24. Found: C[12], 72.2; H, 4.66; N, 13.61.

Conversion to 2-Phenacylpyridine.—A solution of 1.0208 g. of 2-(*o*-boronophenylethynyl)pyridine in 7 ml. of water and 5 ml. of concentrated sulfuric acid was refluxed for 2.5 hr., cooled, diluted with 20 ml. of water, and made alkaline with concentrated ammonium hydroxide. Extraction with ether and recrystallization of the ether soluble material from pentane afforded 0.7411 g. (82%) of 2-phenacylpyridine, m.p. 57–58.5°, lit.[13] m.p. 59°. The oxime melted at 117–118°; for the oxime of 2-phenacylpyridine, lit.[13] m.p. 120°.

2-[β-Hydroxy-β-*o*-(boronophenyl)vinyl]pyridine and Derivatives.—A solution containing 0.5296 g. of compound I in 25 ml. of chloroethanol was warmed at 89° for 20 hr., concentrated at reduced pressure, and made just basic to litmus by addition of aqueous sodium hydroxide. The resulting precipitate was collected and dissolved in methanol. On acidification with hydrochloric acid and concentration of the solution a yellow, crystalline hydrochloride salt separated, m.p. 230–231°, 0.2132 g. The analysis of a sample dried at 65° (1 mm.) for 20 hr. corresponded to an anhydride of 2-(*o*-boronophenacyl)pyrdine hydrochloride.

Anal. Calcd. for $C_{13}H_{11}BClNO_3$: C, 60.2; H, 4.27; N, 5.40. Found: C, 60.9; H, 4.66; N, 5.39.

On heating in a refluxing solution of water (2 ml.) and concentrated sulfuric acid (2 ml.) for 2.5 hr., this compound (25.3 mg.) was converted to **2-phenacylpyridine**, m.p. 50–52°, which was

(10) R. L. Letsinger and J. D. Morrison, *J. Am. Chem. Soc.*, **85**, 2227 (1963).

(11) The procedure was patterned after the preparation of stilbazole described by B. D. Shaw and E. A. Wagstaff, *J. Chem. Soc.*, 77 (1933).

(12) Many of the aromatic B–N compounds have given low carbon analyses as a consequence of incomplete oxidation of carbon at the temperature used in the analytical train.

(13) G. Schering and L. Winterhalder, *Ann.*, **473**, 135 (1929).

Isolated in 78% yield (14 mg.) by addition of water to the solution, treatment of the solution with ammonium hydroxide, extraction of the precipitate with ether, and recrystallization from pentane of the solid obtained from the ether extract. The oxime prepared from this sample of phenacylpyridine melted at 115–117°.

2-[β-Hydroxy-β-(*o*-boronophenyl)vinyl]pyridine was obtained by addition of sodium hydroxide in 50% alcohol–water to the hydrochloride salt (0.2940 g.), evaporation of the solution to dryness, extraction of the resulting solid with chloroform, and evaporation of the extract. For further purification, the sample was dissolved in methanol and the solution was filtered and taken to dryness. The resulting pale yellow solid charred and decomposed without melting when heated in the range of 230°. The analysis of the material dried at room temperature corresponded to a dihydrate of compound II.

Anal. Calcd. for $C_{13}H_{12}BNO_3 \cdot 2H_2O$: C, 56.3; H, 5.82; N, 5.06. Found: C, 55.9; H, 5.90; N, 4.92.

After the sample had been heated at 65° (1 mm.) for 24 hr., the analysis agreed with that for 2-[β-hydroxy-β-(*o*-boronophenyl)vinyl]pyridine .

Anal. Calcd. for $C_{13}H_{12}BNO_3$: C, 64.7; H, 5.02; N, 5.81. Found: C, 64.5; H, 5.33; N, 5.99.

A semicarbazone derivative was obtained by warming a solution of 86 mg. of compound II, 0.2 g. of semicarbazide hydrochloride, and 0.3 g. of sodium acetate in 4 ml. of ethanol and 2 ml. of water for 15 min. When the solution was cooled, 60 mg. of the yellow crystalline semicarbazone derivative of compound II was obtained, m.p. 169–172°. The analytical sample was dried at 65° (1 mm.) for 8 hr.

Anal. Calcd. for $C_{14}H_{15}BN_4O_3$: C, 56.4; H, 5.07; N, 18.80. Found: C, 56.5; H, 4.88; N, 18.78.

Notes

Reduction of 1-Methyl-3-acylindole Derivatives with Lithium Aluminum Hydride[1]

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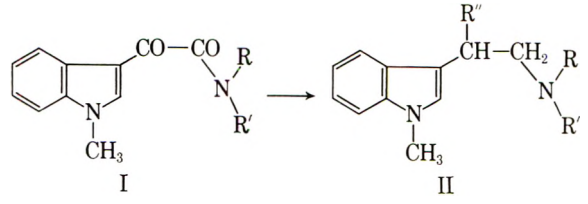
Received February 1, 1963

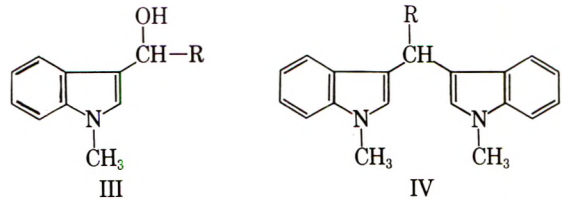
The application of lithium aluminum hydride to the reduction and cyclization of (2-3′-indolylethyl)- or (2-3′-indolyl-2-oxoethyl)pyridinium and isoquinolinium salts has been described in previous papers.[3] This note reports some results obtained in the *ind*-N-methyl series.[4]

The reduction of various 3-acylindoles with lithium aluminum hydride is a well authenticated[5] hydrogenolysis reaction, the 3-alkylindoles being readily obtained. With *ind*-N-methyl-3-acylindoles the reduction has been reported to stop at the intermediate alcohol stage and does not appear to be analogous to the reduction of a disubstituted vinylogous amide. Thus 1,N-dimethyl-3-indoleglyoxamide (I, R = CH_3; R′ = H) and lithium aluminum hydride gave the alcohol[6] II (R = CH_3; R′ = H; R″ = OH). However, conflicting reports have appeared, *e.g.*, the reduction of I (R = R′ = $-CH_2Ph$) with lithium aluminum hydride to give the oxygen-free product[7] II (R = R′ = $-CH_2Ph$; R″ = H); on the other hand, 1-methyl-3-indolylaldehydes have been shown[8] to undergo reduction to 1-methyl-3-hydroxymethyl indoles, in agreement with the former reaction. In attempts to effect the reductive cyclization of 1-[2-(1′-methyl-3′-indolyl)-2-oxoethyl]pyridinium derivatives, no clear-cut results could be obtained and it was decided to investigate the reduction of 1-methyl-3-acetylindole.



I II

Immediately after isolation in the usual way, the product from the lithium aluminum hydride reduction showed intense hydroxyl absorption in its infrared spectrum, indicating the presence of a predominant amount of structure III (R = CH_3). However, no derivative of the alcoholic function could be obtained and, on standing, the crude product developed an odor of acetaldehyde. This was of interest in view of the reported[8] decomposition of 1-methyl-3-hydroxymethylindole (III, R = H) to formaldehyde and the diindolylmethane IV (R = H). However, this decomposition pathway was not followed in the case of our 1-(1′-methyl-3′-indolyl)ethanol. On distillation or on boiling with water it underwent ready dehydration to 1-methyl-3-vinylindole, which immediately polymerized to poly-(1-methyl-3-vinylindole). There was no evidence of the formation of an appreciable amount of 1,1-di(1′-methyl-3′-indolyl)ethane (IV, R = CH_3), authentic



III IV

(1) Regarded as Part IV in the series: Synthetic Experiments Related to the Indole Alkaloids.

(2) Recipient of a C.S.I.R.O. Senior Postgraduate Studentship, 1961–1962.

(3) Part III: K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3066 (1963).

(4) This work was supported in part by PHS Grant H-6475 from the National Heart Institute, Public Health Service.

(5) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

(6) M. E. Speeter, U. S. Patent 2,815,734; *Chem. Abstr.*, **52**, 12923*f* (1958).

(7) A. Buzas, C. Hoffman, and G. Regnier, *Bull. soc. chim. France*, 643 (1950).

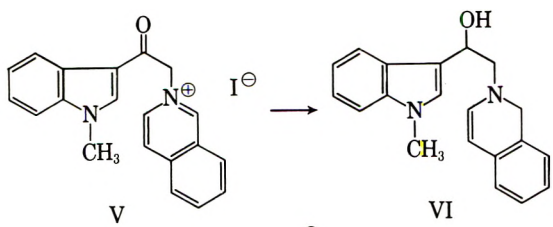
(8) E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).

samples of which were prepared by (1) methylation of 1,1-di(3′-indolyl)ethane, and (2) from 1-methylindole, paraldehyde, and zinc chloride. The poly(1-methyl-3-vinyl)indole structure was assigned on the basis of the following evidence. Analytical data established the empirical formula $(C_{11}H_{11}N)_n$, supported by complete absence of hydroxyl absorption in the infrared spectrum. The ultraviolet spectrum showed, in addition to the peak characteristic of 1-methylindole, a broad shoulder at 2670 Å.; 1-methyl-3-vinylindoles have been found[9] to exhibit maxima in the region of 2650 Å. The isolation of a small amount of acetaldehyde can be most simply attributed to a retroaldol type reaction, probably catalyzed by the alkali of the glass though we were unable to establish the conditions under which this was the major decomposition pathway.

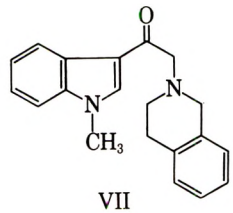
The conjugate base of the indole system must assist in the hydrogenolysis of the coordinated oxygen atom of the 3-ketone function and, as no conjugate base can be formed in the case of the 1-methylindole products, the reduction was next carried out in a system in which the carbon–oxygen bond was weakened by coordination with a stronger Lewis acid such as aluminum chloride. 1-Methyl-3-acetylindole was accordingly reduced with lithium aluminum hydride–aluminum chloride mixture and, as expected, 1-methyl-3-ethylindole was isolated in excellent yield.

Parallel results were also obtained with similar arylmethyl ketones such as 3,4-dimethoxyacetophenone. Reduction with lithium aluminum hydride gave 1-(3,4-dimethoxyphenyl)ethanol, which readily lost water on distillation forming 3,4-dimethoxystyrene, characterized as the dibromide. With lithium aluminum hydride and aluminum chloride, the course of the reaction was altered to yield 3,4-dimethoxyethylbenzene. This is analogous to the hydrogenolysis[10] of benzophenone to diphenylmethane, and acetophenone to ethylbenzene.

With this more definite knowledge of the behavior of 1-methyl-3-acetylindole toward lithium aluminum hydride, a series of reductions of the salt 2-[2-(1′-methyl-3′-indolyl)-2-oxoethyl]isoquinolinium iodide (V) was carried out. Despite repeated attempts using lithum aluminum hydride alone or mixed with aluminum chloride, no pure products could be isolated when tetrahydrofuran was used as the solvent. Spectral evidence indicated that in the majority of fractions at least partial reduction had occurred and it is likely that



V VI



VII

the large number of fractions formed is due to the many ways in which a highly reactive intermediate such as VI can undergo further reaction. The use of dioxane as solvent gave an intermediate reaction complex that was almost insoluble so that at no stage was the reaction mixture homogeneous. It is interesting that the main product isolated from this system was 2-[2-(1′-methyl-3′-indolyl)-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline (VII), besides unidentified oily fractions similar to those already mentioned. The identity of this product was indicated by analytical and spectral data. The infrared spectrum showed main absorption bands at 3100, 3020, 2911, 2805, and 1620 cm.$^{-1}$, and the ultraviolet spectrum showed the presence of a 1-methyl-3-acylindole chromophore[11] (λ_{max} 248, 306 mμ). The n.m.r. spectrum[12] was not complex, showing main peaks at 7.1 τ (N–CH_3), 6.26 and 6.23 τ (–CH_2– peaks), and aromatic protons. These results indicated that the 3-acylindole group had not undergone hydrogenolysis and that the pyridine ring system had been reduced to the tetrahydro stage. Confirmation was obtained by the synthesis of VII from the chloride of the salt V by reduction with Adam's catalyst in acetic acid solution. The failure of the 3-acylindole function to undergo hydrogenolysis in this reaction can be attributed to a large extent to the heterogeneous reaction medium.

The results obtained with these 1-methylindole compounds indicate the desirability of working with the unmethylated series. The cyclized products may then be readily converted into the methyl-substituted series with sodamide and methyl iodide in liquid ammonia.[13,14]

Experimental[15]

Reduction of 1-Methyl-3-acetylindole with Lithium Aluminum Hydride. Poly(1-methyl-3-vinylindole).—1-Methyl-3-acetylindole[16] (6.0 g., 0.03 mole) and a solution of lithium aluminum hydride (4.0 g., 0.11 mole) in dry tetrahydrofuran (300 ml.) were heated together under reflux for 4.5 hr. After decomposition of the reaction complex with water, the reaction mixture was extracted with ether and the ether solution dried (sodium sulfate). Removal of the solvent left a pale yellow oil (6 g.), ν_{OH} 3400 cm.$^{-1}$ (broad, very intense). Extraction of the crude product, which had an odor of acetaldehyde, with cold water and treatment of the aqueous extract with Brady's reagent gave a yellow precipitate of acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 168°, alone and when mixed with an authentic sample.[17] The infrared spectra of the two samples were superimposable.

The residue from the water extraction was divided into two portions. The first was boiled with water for 24 hr. and on cooling a brown solid, m.p. 70–80° was deposited. It showed no hydroxyl group absorption and was purified by dissolution in benzene and filtration through a column of neutral alumina.

(9) E. Leete, *J. Am. Chem. Soc.*, **82**, 6338 (1960).

(10) R. F. Nystron and C. R. A. Berger, *ibid.*, **80**, 2896 (1958).

(11) J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings, and A. Robertson, *J. Chem. Soc.*, 2227 (1957).

(12) The spectra were recorded from a Varian V-4302 dual purpose 60-Mc. n.m.r. spectrometer and chemical shift values are reported in τ units using tetramethylsilane (τ 10) as internal standard. We are indebted to Dr. T. Spotswood for his assistance in determining this spectrum.

(13) K. T. Potts and J. E. Saxton, *Org. Syn.*, **40**, 68 (1960).

(14) E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962).

(15) Evaporations were carried out under reduced pressure on the water bath and melting points were determined in capillaries. Ultraviolet spectra were recorded in ethanol solution, and petroleum ether refers to the fraction, b.p. 60–80°. Microanalyses are by the C.S.I.R.O. Microanalytical Service, Melbourne.

(16) Y. A. Baskakov and M. N. Melnikov, *Sb. Statei Obshchei Khim. Akad. Nauk SSSR*, **1**, 712 (1953); *Chem. Abstr.*, **49**, 1006*d* (1955).

(17) Prepared from an aqueous solution of acetaldehyde and Brady's reagent in the standard way.

Evaporation of the solvent gave a colorless glass which did not crystallize.

An attempt was made to distil the second portion under high vacuum. As the sample appeared to be reaching the boiling point, polymerization occurred with the formation of a brown glass. Purification was effected by filtration in benzene solution through a column of neutral alumina and the product finally isolated had an infrared spectrum identical with that of the product obtained by boiling with water for 24 hr. Poly(1-methyl-3-vinylindole) distilled (distillation bulb, free flame, 0.001 mm.) as a colorless glass.

Anal. Calcd. for $(C_{11}H_{11}N)_n$: C, 84.0; H, 7.1; N, 8.9. Found: C, 84.0; H, 6.9; N, 8.8.

Light absorption: λ_{max} 2290, 2670 (broad sh), 2930 Å. (log ϵ 4.76, 4.07, 4.18); λ_{min} 2530 Å. (log ϵ 3.92).

The infrared spectrum was similar to but not identical with that of 1,1-di-1′-methyl-3′-indolylethane.

1,1-Di(1′-methyl-3′-indolyl)ethane. A.—Sodium (46 mg.) was added to liquid ammonia (30 ml.) containing a crystal of ferric nitrate. To the stirred reaction mixture, 1,1-di-3′-indolylethane[18] (470 mg.) was added, followed 5 min. later by the dropwise addition of methyl iodide (300 mg.). After the ammonia had evaporated at room temperature, the product (520 mg., quantitative) was isolated as a pale yellow oil by the addition of water and extracted with three 50-ml. portions of ether. Purification was effected by passage in benzene through a small column of Woelm neutral alumina (activity I). The product, obtained as a colorless glass soluble in petroleum ether, could not be induced to crystallize. It had an infrared spectrum identical with that of the product prepared as in method B.

B.—1-Methylindole (6.0 g.), paraldehyde (1.2 g.), and zinc chloride (1.5 g.) were heated together on a steam bath for 4 hr. The resultant black tar was extracted with hot benzene (charcoal), and the solvent removed to yield the diindolylethane as a pale yellow glass (5.8 g., 87%). After purification as in method A, the product distilled (distillation bulb, free flame, 0.001 mm.) as a colorless glass.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.3; H, 7.0; N, 9.7. Found: C, 83.1; H, 6.9; N, 9.9.

Light absorption: λ_{max} 2290, 2940 Å. (log ϵ 4.70, 3.98); λ_{min} 2560 Å. (log ϵ 3.64).

Reduction of 1-Methyl-3-acetylindole with a Mixture of Lithium Aluminum Hydride and Aluminum Chloride.—A solution of 1-methyl-3-acetylindole (1.7 g., 0.01 mole) and aluminum chloride (2.68 g., 0.02 mole) in dry tetrahydrofuran (100 ml.) was added over 30 min. to a stirred solution of lithium aluminum hydride (0.4 g., 0.01 mole) and aluminum chloride (1.0 g., 0.0075 mole) in tetrahydrofuran (50 ml.). An immediate blue fluorescence was produced and the mixture was heated under gentle reflux for 4 hr. The complex was decomposed by treating the cooled solution with hydrated sodium sulfate, and then with water. The filtered solution was extracted with ether and dried (sodium sulfate). Evaporation of the solvent yielded 1.4 g. of a fluorescent liquid, showing no hydroxyl group absorption in its infrared spectrum. The oil (1.2 g.) was distilled and 1-methyl-3-ethylindole (1.0 g., 74%) was collected, b.p. 74–76° (0.3–0.4 mm.); $n^{20}D$ 1.5808 [lit.[19] b.p. 95–96° (0.6 mm.); $n^{20}D$ 1.5806, fluorescent oil]. The picrate, formed in ethanol, crystallized from a small volume of ethanol as long, red needles, m.p. 97–98° (lit.[19] m.p. 96–97°).

Reduction of 2-[2-(1′-Methyl-3′-indolyl)-2-oxoethyl]isoquinolinium Iodide with a Mixture of Lithium Aluminum Hydride and Aluminum Chloride in Dioxane Solution.—A suspension of the iodide (3.87 g., 0.009 mole) and aluminum chloride (2.4 g., 0.018 mole) in dioxane (100 ml.) was added over a period of 30 min. to a stirred solution of lithium aluminum hydride (0.8 g., 0.021 mole) and aluminum chloride (1.62 g., 0.012 mole) in dioxane (200 ml.). As stirring was continued for 5 hr. at 60–65° under nitrogen a yellow-brown gummy precipitate was formed. After reaction work-up as essentially previously described, the residual orange-brown, glassy residue was absorbed onto Woelm neutral alumina (activity IV, 90 g.). Elution with petroleum ether gave 440 mg. of a pale yellow oil which decomposed to a brown mass on exposure to air. The sample was not obtained crystalline nor could satisfactory derivatives be obtained. Its behavior was similar to that of the oils obtained when tetrahydrofuran was used as solvent. Development of the column with a 1:1 mixture of benzene–petroleum ether yielded 2-[2-(1′-methyl-3′-indolyl)-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline (0.73 g., 27%) which crystallized from benzene as fine, colorless needles, m.p. 162–164°. This product did not depress the melting point and had an infrared spectrum identical with that of an authentic specimen prepared in the next section.

Further elution with a 4:1 mixture of benzene–ether gave a brown oil (480 mg.) which could not be characterized.

Increasing the reaction time to 18 hr. did not alter the results appreciably from those obtained in the foregoing procedure.

Reduction of the isoquinoline salt in tetrahydrofuran solution with lithium aluminum hydride alone, or mixed with aluminum chloride, gave an unstable oily product which, even after exhaustive chromatography on alumina, could not be resolved into recognizable entities.

2-[2-(1′-Methyl-3′-indolyl)-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline.—2-[2-(1′-Methyl-3′-indolyl)-2-oxoethyl]isoquinoliniumiodide (500 mg.) dissolved in a mixture of ethanol (350 ml.) and water (180 ml.) was heated under reflux with silver chloride (*ca.* 4 g.) for 18 hr. The cooled solution was filtered and the solvent removed from the filtrate under reduced pressure. The residue was dissolved in a small volume of methanol (charcoal) and on addition of ether the chloride separated as clusters of cream needles, m.p. 277–281° dec. Platinum oxide (19 mg.) was suspended in acetic acid (10 ml.) and reduced with hydrogen. The chloride (27.1 mg.) was introduced and hydrogen (4.07 ml.) was absorbed over 30 min. (calculated absorption for the reduction of two double bonds, 3.90 ml./774 mm./17°). The catalyst was removed and, after evaporation to dryness, water was added to dissolve the residue whose solution was basified wth ammonium hydroxide and extracted with ether. 2-[2-(1′-Methyl-3′-indolyl)-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline crystallized from benzene as small colorless needles, m.p. 162–164°.

Anal. Calcd. for $C_{20}H_{20}N_2O$: C, 78.9; H, 6.6; N, 9.2. Found: C, 78.8; H, 6.6; N, 9.1.

Light absorption: λ_{max} 2470, 3030 Å. (log ϵ 4.29, 4.26); λ_{min} 2330, 2750 Å. (log ϵ 3.99, 4.04).

Reduction of 3,4-Dimethoxyacetophenone. A. With Lithium Aluminum Hydride.—The ketone (7.2 g., 0.04 mole) was added in small portions to a suspension of lithium aluminum hydride (2.5 g., 0.06 mole) in dry tetrahydrofuran (150 ml.) with marked effervescence occurring. After a 4-hr. reaction period, the reaction mixture was worked up as in the previous reductions. The crude product was a colorless liquid (6.6 g.) exhibiting strong hydroxyl absorption in its infrared spectrum and distilled at 118–120° (0.5 mm.). During the distillation dehydration occurred, as evidenced by a decrease in the hydroxyl group absorption intensity and the appearance of absorption bands at 1625 (s), 1440 (s), 987 (s), 1305 (m), and 1830 (w) cm.$^{-1}$ usually associated with a conjugated vinyl group. The distillate, consisting mainly of 3,4-dimethoxyvinylbenzene was treated with bromine and carbon tetrachloride and gave 3,4-dimethoxy-1-(1,2-dibromoethyl)benzene as clusters of colorless needles, m.p. 97–98°, on crystallization from petroleum ether (lit.[20] m.p. 98°). 3,4-Dimethoxyvinylbenzene polymerized to a colorless rubbery mass on standing in air.

B. With a Mixture of Lithium Aluminum Hydride and Aluminum Chloride.—A solution of 3,4-dimethoxyacetophenone (3.6 g., 0.02 mole) and aluminum chloride (5.4 g., 0.04 mole) in dry tetrahydrofuran (100 ml.) was added over 30 min. to a stirred solution of lithium aluminum hydride (0.8 g., 0.02 mole) and aluminum chloride (2.0 g., 0.015 mole) in tetrahydrofuran (50 ml.). After a 4-hr. reaction period, the reaction mixture was worked up as previously described and gave 3.2 g. of a colorless oil. The infrared spectrum indicated the presence of a small amount of hydroxyl-containing product. Distillation of 3 g. of the oil yielded 3,4-dimethoxyethylbenzene (2.6 g., 87%), b.p. 122–124° (15 mm.), containing a trace of 1-(3,4-dimethoxyphenyl)-1-hydroxyethane. Distillation from sodium produced a pure sample of the hydrocarbon, b.p. 122–124° (15 mm.) [lit.[21] b.p. 110–112° (9 mm.)].

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 72.3; H, 8.5; O, 19.3. Found: C, 72.3; H, 8.7; O, 19.1.

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(19) H. R. Snyder, E. Eliel, and R. E. Carnahan, *J. Am. Chem. Soc.*, **73**, 970 (1951).

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Acknowledgment.—The authors wish to express their thanks to Professor G. M. Badger for his interest and encouragement throughout this work.

Aromatic Cyclodehydration. LV.[1] Quaternizations with Chloroacetaldoxime

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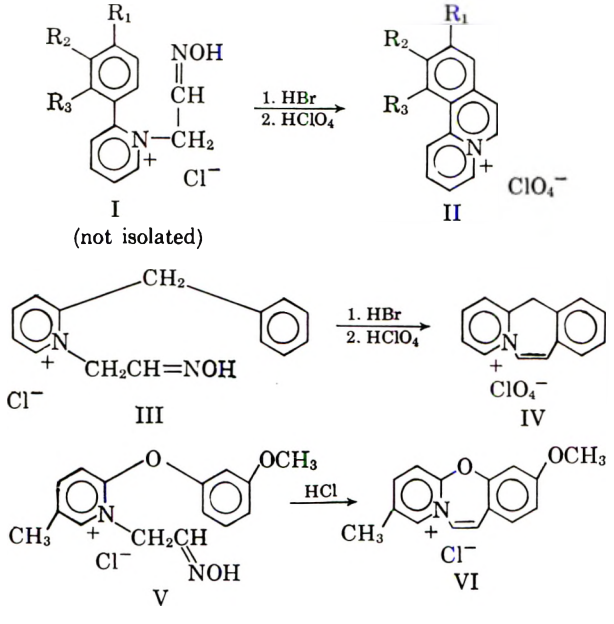
Received April 22, 1963

Previous attempts to obtain unsubstituted benzo[*a*]-quinolizinium salts[3] by the cyclodehydration method have been unsuccessful. It was found that chloro-, bromo-, and iodoacetals would not form quaternary salts with 2-phenylpyridine, while bromopyruvic acid afforded only the hydrobromide of the starting material.[4]

As the α-haloacetaldehydes exist predominantly as trimers or polymers, and therefore display low reactivity to quaternization, it was felt that an α-haloacetaldoxime might prove more reactive. The presence of a double bond in chloroacetaldoxime should activate the α-methylene group in the same manner as the olefin in allyl bromide or the carbonyl in bromoacetone. This activation by the carbon–nitrogen double bond in the oxime should facilitate the displacement of a halogen on the α-methylene group and permit quaternization with a tertiary amine. Our results confirm this hypothesis.

Quaternization of 2-phenylpyridine proceeded readily with chloroacetaldoxime in tetramethylene sulfone.



Cyclization with hydrobromic acid gave a mixed salt which on addition of perchloric acid was converted to benzo[*a*]quinolizinium perchlorate (II).[5] Similar procedures carried out with the three 2-tolylpyridines gave the expected methylbenzo[*a*]quinolizinium perchlorates (II, $R_1 = CH_3$; II, $R_2 = CH_3$; and II, $R_3 = CH_3$). Confirmation of cyclization in each case was given by the ultraviolet absorption spectrum of the product.

The low yield of 11-methylbenzo[*a*]quinolizinium perchlorate (12%) is apparently due to steric inhibition and is comparable to that of the 7,11-dimethyl analog (9%) reported previously.[6]

This method was successfully extended to include the preparation of the unsubstituted morphanthridizinium perchlorate[7] (IV) and a benz[*f*][1,3]oxazepinium chloride[8] (VI) having no substituent on the central nucleus.

Experimental

All analyses were carried out by Dr. Ing. A. Schoeller, Kronach, Germany. The melting points were determined in capillary tubes in a Mel Temp apparatus and are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol using 1-cm. quartz cells with a Cary Model 14 spectrophotometer. The asterisk (*) is used to denote a shoulder.

Chloroacetaldoxime.—To 40 g. of chloroacetaldehyde diethyl acetal (or the dimethyl acetal) was added a solution of 96 g. of hydroxylamine hydrochloride in 100 ml. of water and the mixture was stirred at room temperature for 72 hr. The resultant single phase solution was extracted continuously with ether in an ether extractor for 3 days. The ether extract was washed three times with water and dried over anhydrous calcium chloride. The ether was removed under vacuum (aspirator) at room temperature with slight warming to remove the final traces of solvent. The colorless oil which solidified in the refrigerator was sufficiently pure for the quaternization reactions; yield, 20 g. (85%). A sample on distillation had b.p. 64.5° (20 mm.), lit.[9] b.p. 61° (20 mm.).

Benzo[*a*]quinolizinium Perchlorate (II).—A solution containing 1 g. (0.0064 mole) of 2-phenylpyridine and 1 g. (0.011 mole) of chloroacetaldoxime in 3 ml. of dry tetramethylene sulfone was allowed to stand for 12 days in a stoppered flask at room temperature. The resultant dark viscous oil was triturated with ethyl acetate but could not be crystallized, nor could a solid perchlorate be formed by the addition of perchloric acid to a portion of it. The crude product was dissolved in 20 ml. of 48% hydrobromic acid and heated under reflux for 24 hr. The acid was removed under vacuum (aspirator) and the resultant mixed salt, isolated as a dark gum, was dissolved in 5 ml. of water. Addition of perchloric acid gave the perchlorate; yield 0.6 g. (35%), m.p. 195–196°. Crystallization from methanol (charcoal) afforded the pure product as colorless needles, m.p. 196–197° (lit.[3] m.p. 197°); λ_{max} (log ε), 217 (4.29), 222 (4.32), 237 (4.28), 256* (4.08), 269 (4.23), 278 (4.28), 323 (3.70), 337 (4.01), 354 mμ (4.14).

Anal. Calcd. for $C_{13}H_{10}ClNO_4$: C, 55.82; H, 3.79; N, 5.27. Found: C, 56.05; H, 3.72; N, 5.02.

Quaternization of 2-phenylpyridine with chloroacetaldoxime in refluxing acetone proved less satisfactory due to the greater decomposition encountered.

9-Methylbenzo[*a*]quinolizinium Perchlorate (II, $R_1 = CH_3$).—The quaternization of 2 g. of 2-(4-tolyl)pyridine by reaction with 2 g. of chloroacetaldoxime in dry tetramethylene sulfone was carried out over 6 days. Trituration with ethyl acetate, as previously described, gave a gum which was heated for 24 hr. under reflux with 20 ml. of hydrobromic acid. The perchlorate prepared as for II was crystallized (charcoal) from methanol; yield, 1.5 g. (45%); m.p. 227–229°. The analytical sample

(1) For the preceding communication of this series, see *J. Org. Chem.*, **28**, 3070 (1963).

(2) This research was supported by a research grant (CA-05509) of the National Cancer Institute of the National Institutes of Health.

(3) E. E. Glover and G. Jones [*J. Chem. Soc.*, 3021 (1958)] have reported the synthesis of benzo[*a*]quinolizinium perchlorate from 1-cyanoisoquinoline by a 4-step route. The present 2-step procedure, however, offers considerable advantage in its simplicity.

(4) L. E. Beavers, Ph.D. dissertation, Duke University, 1955.

(5) All R groups not otherwise specified are assumed to be hydrogen.

(6) C. K. Bradsher and K. B. Moser, *J. Am. Chem. Soc.*, **81**, 1941 (1959).

(7) K. B. Moser and C. K. Bradsher, *ibid.*, **81**, 2547 (1959).

(8) C. K. Bradsher, L. D. Quin, and R. E. LeBleu, *J. Org. Chem.*, **26**, 3273 (1961).

(9) H. Brintzinger and R. Titzmann, *Ber.*, **85**, 344 (1952).

prepared by recrystallization from methanol was obtained as colorless prisms, m.p. 231–232°; λ_{max} (log ϵ), 219* (4.33), 225 (4.40), 242 (4.33), 272 (4.38), 278* (4.35), 308* (3.76), 323 (3.83), 338 (4.11), 354 mμ (4.26).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.49; H, 4.43; N, 4.87.

The picrate crystallized from methanol as yellow needles, m.p. 177–178.5°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found: C, 56.60; H, 3.21; N, 13.38.

10(?)-Methylbenzo[*a*]quinolizinium Perchlorate (II, R_2 = CH_3).—This was prepared in a similar manner to its isomer (II) from 2 g. of 2-(3-tolyl)pyridine and 2 g. of chloroacetaldoxime. The perchlorate was crystallized from methanol (charcoal); yield 2 g. (61%), m.p. 221–224°. Recrystallization three times from methanol gave the analytical sample as colorless prisms, m.p. 231–232°; λ_{max} (log ϵ) 218* (4.25), 224 (4.32), 236* (4.36), 240 (4.37), 264 (4.17), 276* (4.20), 284 (4.30), 330 (3.63), 344 (3.94), 360 mμ (4.09).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 56.85; H, 4.12; N, 4.76.

The picrate crystallized from methanol as yellow needles, m.p. 210–215°, with previous softening.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found: C, 56.26; H, 3.71; N, 13.02.

11-Methylbenzo[*a*]quinolizinium Perchlorate (II, R_3 = CH_3).—Treatment of 1 g. of 2-(2-tolyl)pyridine with 1 g. of chloroacetaldoxime by the usual procedure over 12 days and heating the quaternization product under reflux for 65 hr. in 20 ml. of hydrobromic acid afforded 0.20 g. (12%) of tan colored crystals, isolated as the perchlorate. Recrystallization from methanol–ethyl acetate gave the product as light tan prisms, m.p. 209–210°; λ_{max} (log ϵ) 220 (4.62), 274 (4.69), 330 (3.77), 344 (3.97), 360 mμ (4.06).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.61; H, 4.35; N, 4.99.

The picrate crystallized from methanol as yellow needles, m.p. 184–185°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found: C, 56.87; H, 3.16; N, 13.36.

1-(2-Oximidoethyl)-2-benzylpyridinium Chloride (III).—A solution containing 2 g. (0.012 mole) of 2-benzylpyridine and 1.8 g. (0.019 mole) of chloroacetaldoxime in 3 ml. of dry tetramethylene sulfone was allowed to stand in a stoppered flask at room temperature. Quaternization proceeded rapidly and after 2 days the crystalline product was collected and recrystallized from methanol–ethyl acetate; yield, 2.2 g. (71%); m.p. 204–206°. Further recrystallization from methanol–ethyl acetate gave the pure compound as colorless prisms, m.p. 205–207°; λ_{max} (log ϵ) 204 (4.17), 264* (3.73), 268 (3.75), 274* mμ (3.70).

Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 63.99; H, 5.75; N, 10.65. Found: C, 64.18; H, 5.76; N, 10.95.

Morphanthridizinium Perchlorate (IV).—A solution of 2 g. (0.0074 mole) of the quaternary salt (III) in 20 ml. of 48% hydrobromic acid was heated under reflux for 40 hr. The acid was removed in the usual manner and the red-brown residue taken up in a small volume of water. Addition of perchloric acid gave the perchlorate which separated on cooling as a pale yellow microcrystalline material. Recrystallization from methanol–ethyl acetate afforded the pure product as colorless leaflets; yield, 1.6 g. (81%); m.p. 182–183°; λ_{max} (log ϵ), 225* (4.12), 282 (3.69), 318 mμ (3.83).

Anal. Calcd. for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 57.04; H, 4.21; N, 5.06.

5-Methyl-1-(oximidoethyl)-2-(3-methoxyphenoxy)pyridinium Chloride (V).—Quaternization of 1 g. of 5-methyl-2-(3-methoxyphenoxy)pyridine[5] with chloroacetaldoxime followed the usual procedure, and the mixture was allowed to react for 17 days. The solid obtained by trituration with ethyl acetate crystallized from methanol–ethyl acetate as colorless plates; yield, 0.77 g. (66%); m.p. 158–160°; λ_{max} (log ϵ), 222 (3.97), 253* (2.30), 275* (3.53), 281 (3.60), 303 (3.71), 315 * mμ (3.66).

Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$: C, 58.34; H, 5.55; N, 9.07. Found: C, 57.84; H, 5.53; N, 9.38.

The perchlorate crystallized from methanol–ethyl acetate as colorless prisms, m.p. 156–157°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_7$: C, 48.33; H, 4.60; N, 7.52. Found: C, 48.62; H, 4.48; N, 7.67.

3-Methoxy-8-methylpyrido[2,1-*b*]benz[*f*][1,3]oxazepinium Chloride (VI).—The quaternary salt (V) (0.5 g.) was cyclized by heating under reflux in concentrated hydrochloric acid for 24 hr. The acid was removed as usual and the residue recrystallized with difficulty from methanol–ethyl acetate to give a tan powder; yield, 0.25 g. (61%); m.p. 265° dec.; λ_{max} (log ϵ), 289 (3.70), 314 mμ (3.71).

Anal. Calcd. for $C_{15}H_{14}ClNO_2 \cdot 0.5\ H_2O$: C, 63.26; H, 5.23; N, 4.92. Found: C, 63.17; H, 5.58; N, 5.39.

Acknowledgment.—The authors wish to thank Dr. Charles K. Bradsher for his helpful suggestions and continued encouragement.

The Hoesch Condensation of Dihydro-β-tubanol with Benzyl Cyanides

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Received April 22, 1963

Several dimethylpyranoisoflavones, *e.g.*, jamaicin,[1] toxicarolisoflavone,[2] osajin,[3] and pomiferin,[3] have been isolated in recent years. However, the syntheses of these compounds have not been reported. This paper presents the Hoesch condensation of dihydro-β-tubanol with benzyl cyanides and the syntheses of 2,2-dimethyl-3,4-dihydropyranoisoflavones.

The Hoesch condensation of dihydro-β-tubanol (I)[4] with benzyl cyanide (II) afforded isomeric phenylacetyldihydro-β-tubanols, having m.p. 145–147 and 81–83°, respectively. On the basis of qualitative tests and spectral data, which are summarized in Table I, the former was found to be 8-phenylacetyldihydro-β-tubanol (III) and the latter to be the 6-phenylacetyl isomer IV. 6-Phenylacetyldihydro-β-tubanol thus obtained was converted into 2,2-dimethyl-3,4-dihydropyrano[5,6–7,8]isoflavone (V), m.p. 162–164°, according to the Späth–Venkataraman method.

2,4-Dimethoxybenzyl cyanide (VI) similarly reacted with I as described, affording 8-(2,4-dimethoxyphenylacetyl)dihydro-β-tubanol (VII), m.p. 117–118°, and 6-(2,4-dimethoxyphenylacetyl)dihydro-β-tubanol (VIII), m.p. 102–104°. According to the procedure mentioned previously the deoxybenzoin VIII was transformed into 2′,4′-dimethoxy-(2,2-dimethyl-3,4-dihydropyrano)[5,6–7,8]isoflavone (IX), m.p. 191–193°.

3,4-Methylenedioxybenzyl cyanide (X) and I gave 6-(3,4-methylenedioxyphenylacetyl)dihydro-β-tubanol (XI), m.p. 95–97°, and an unidentified compound $C_{18}H_{16}O_8$, m.p. 125–127°, under the Hoesch reaction conditions.

It is of interest to note that two 8-substituted dihydro-β-tubanols III and VII are soluble in aqueous alkali, whereas 6-substituted compounds IV, VIII, and XI are insoluble, in agreement with the general property of 2-hydroxydeoxybenzoins. In contrast to the 8-substituted dihydro-β-tubanols III and VII, the 6-substituted compounds IV, VIII, and XI showed an intense color

(1) O. A. Stamm, H. Schmid, and J. Büchi, *Helv. Chim. Acta*, **41**, 2006 (1958).

(2) S. H. Harper, *J. Chem. Soc.*, 1178 (1940).

(3) M. L. Wolfrom, W. D. Harris, G. F. Johnson, J. E. Mahan, S. M. Moffett, and B. Wildi, *J. Am. Chem. Soc.*, **68**, 406 (1946).

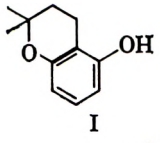
(4) R. Huls, *Bull. Classe Sci. Acad. Roy. Belg.*, **39**, 1064 (1953).

TABLE I

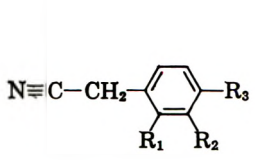
Compound no.	M.p., °C.	Reaction with 2,4-DNP	Solubility in 2 *N* NaOH	Color reaction with $FeCl_3$	$\nu_{C=O}$ in $CHCl_3$, $cm.^{-1}$	λ_{max} (ϵ) in EtOH, mμ
III	145–147	+	Soluble	Negative	1650	235 (12,800) 281 (13,600) 305 (9,600)
IV	81–83	+	Insoluble	Deep violet	1620	234 (13,600) 241 (11,600) s[a] 291 (18,200) 314 (10,700) s
V	162–164				1635	247 (33,100) 302 (24,800) 308 (24,200) s
VII	117–118	+	Soluble	Negative	1660[b]	278 (15.400) 305 (9,400) s
VIII	102–104	+	Insoluble	Deep violet	1615	285 (17.700) 314 (9,000) s
IX	191–193				1635	264 (27,100) 289 (24,100) 308 (21,200) s
XI	95–97	+	Insoluble	Deep violet	1620	289 (19,800) 315 (10,000) s

[a] Shoulder. [b] In Nujol.

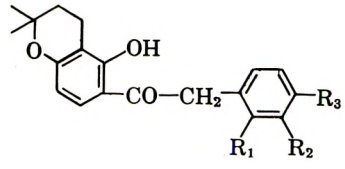
reaction with ferric chloride, indicating the influence of chelation. This is confirmed by the spectral data; *i.e.*, not only the carbonyl bands in the infrared but also the absorption maxima in the ultraviolet[5] of IV and VIII were shifted toward longer wave lengths than those observed for III and VII, respectively.



I



II, $R_1 = R_2 = R_3 = H$ III, $R_1 = R_2 = R_3 = H$
VI, $R_1 = R_3 = OMe$; $R_2 = H$ VII, $R_1 = R_3 = OMe$; $R_2 = H$
X, $R_1 = H$; $R_2, R_3 = -OCH_2O-$



IV, $R_1 = R_2 = R_3 = H$ V, $R_1 = R_2 = R_3 = H$
VIII, $R_1 = R_3 = OMe$; $R_2 = H$ IX, $R_1 = R_3 = OMe$; $R_2 = H$
XI, $R_1 = H$; $R_2, R_3 = -OCH_2O-$

Experimental

The Hoesch Reaction of Dihydro-β-tubanol with Benzyl Cyanide.—Into a solution of dihydro-β-tubanol (I) (0.8 g.) and benzyl cyanide (II) (0.8 g.) in a mixture of anhydrous ether (28 ml.) and chloroform (3 ml.) containing anhydrous zinc chloride (2.5 g.) was passed dry hydrogen chloride for 10 min. under ice-cooling, and the mixture was then allowed to stand at room temperature overnight. After removal of the upper ethereal layer by decantation and addition of water to the oily residue, the aqueous solution was heated on a water bath for 2 hr. An oily substance thus formed was extracted with ether, the ethereal solution was washed with 5% aqueous sodium hydroxide, and then the ether was evaporated. Upon crystallizing the residue from ether–pentane (1:1), 6-phenylacetyldihydro-β-tubanol (IV) (0.33 g.), m.p. 81–83°, was obtained.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.75; H, 6.93.

The sodium hydroxide solution described in the preceding preparation was acidified and extracted with ether. After removal of the ether, 8-phenylacetyldihydro-β-tubanol (III) was obtained as colorless prisms (0.28 g.), m.p. 145–147°, upon recrystallization from methanol.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.82; H, 6.82.

2,2-Dimethyl-3,4-dihydropyrano[5,6-7,8]isoflavone (V).—A solution of the deoxybenzoin (IV) (0.377 g.) in ethyl formate (20 ml.) was added dropwise to sodium powder (0.3 g.) under ice-cooling, and the mixture was kept in a refrigerator for 3 days. The reaction mixture was poured into ice-water and the excess ethyl formate was removed under reduced pressure. The product was extracted with chloroform, chromatographed with aluminum oxide (acid washed), eluted with benzene, and distilled *in vacuo* [b.p. 165–171° (0.02–0.012 mm.)]. The distillate was crystallized from 80% ethanol and colorless needles, m.p. 162–164°, were obtained.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.43; H, 5.92. Found: C, 78.52; H, 5.95.

The Hoesch Reaction of Dihydro-β-tubanol with 2,4-Dimethoxybenzyl Cyanide.—The Hoesch reaction of dihydro-β-tubanol (I) (0.8 g.) with 2,4-dimethoxybenzyl cyanide (VI) (1.2 g.) was carried out as described previously and isomeric deoxybenzoin derivatives were yielded. 6-(2,4-Dimethoxyphenylacetyl)dihydro-β-tubanol (VIII) (0.151 g.) showed m.p. 102–104° on recrystallization from 70% ethanol, and the 8-isomer (VII) (0.13 g.), m.p. 117–118°, from aqueous ethanol.

Anal. of VIII. Calcd. for $C_{21}H_{24}O_6$: C, 70.76; H, 6.79. Found: C, 70.98; H, 7.11.

Anal. of VII. Calcd. for $C_{21}H_{24}O_6$: C, 70.76; H, 6.79. Foound: C, 70.63; H, 6.92.

2′,4′-Dimethoxy-(2,2-dimethyl-3,4-dihydroyrano)[5,6-7,8]isoflavone (IX).—Cyclization of the deoxybenzoin (VIII) (0.15 g.) in ethyl formate (10 ml.) with sodium (1.15 g.) was carried out as mentioned, giving a solid substance. The product was refluxed in acetic acid (2 ml.) for 30 min.[6] After cooling, water was added dropwise until no more solid was formed. The solid was collected by filtration and was crystallized from ethanol, m.p. 191–193°.

Anal. Calcd. for $C_{22}H_{22}O_6$: C, 72.11; H, 6.05. Found: C, 71.88; H, 6.22.

The Hoesch Reaction of Dihydro-β-tubanol with 3,4-Methylenedioxybenzyl Cyanide.—The Hoesch reaction of dihydro-β-tubanol (I) (0.8 g.) with 3,4-methylenedioxybenzyl cyanide (X) (1.2 g.) was carried out by the usual method and yielded 6-(3,4-methylenedioxyphenylacetyl)dihydro-β-tubanol (XI) (0.23 g.)

(5) D. J. Cram and F. W. Cranz, *J. Am. Chem. Soc.*, **72**, 595 (1950).

(6) W. B. Whalley, *ibid.*, **75**, 1059 (1953).

from the alkali-insoluble part. It gave m.p. 95–97° on recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.66; H, 5.83.

A compound, m.p. 125–127°, was isolated from the alkali-soluble part.

Anal. Calcd. for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 60.09; H, 4.45.

The Mechanism of Dehydration of β,β-Diphenyl-β-hydroxypropiophenone[1]

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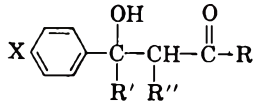
Received May 16, 1963

It previously has been demonstrated[3] that, depending on structure, two different mechanisms are available for the dehydration of β-hydroxy ketones. Thus, 4-phenyl-4-hydroxy-2-butanone (I),[3] 4-(*p*-nitrophenyl)-4-hydroxy-2-butanone (II)[3] and β-phenyl-β-hydroxypropiophenone (V)[4] undergo dehydration *via* a mechanism involving a rate-determining enolization step, while 4-(*p*-methoxyphenyl)-4-hydroxy-2-butanone (III)[3] and 4-(*p*-methoxyphenyl)-4-hydroxy-3-methyl-2-butanone (IV)[5] dehydrate *via* a carbonium ion mechanism. The change in mechanism is manifested by a different dependence of the rate on the acidity



I, R = CH_3 R′ = H; R″ = H; X = H
II, R = CH_3 R′ = H; R″ = H; X = NO_2
III, R = CH_3 R′ = H; R″ = H; X = OCH_3
IV, R = CH; R′ = H; R″ = CH_3; X = OCH_3
V, R = C_6H_5; R′ = H; R″ = H; X = H
VI, R = C_6H_5; R′ = C_6H_5; R″ = H; X = H

function H_0 (the carbonium ion mechanism is characterized by linear correlation with H_0 with slope greater than unity) and by different entropies of activation (the carbonium ion mechanism has a less negative entropy by a magnitude corresponding to the absence of involvement of water in the transition state).

It was of interest to study the effect that the introduction of a phenyl substituent on the β-position of V would have on the mechanism of the dehydration reaction. The stability of the 1,1-diphenylethyl cation is quite similar to that of the (*p*-methoxyphenyl)ethyl carbonium ion, as estimated from solvolytic data.[6] From the published results of Deno and co-workers[7–9] on arylcarbonium ion equilibria, it is evident that the two carbonium ions are formed, to the extent of 50% from their corresponding alcohols, at 72% and 65% sulfuric acid, respectively. On the basis of these stability estimates for the carbonium ions derived from III and VI, it was expected that the dehydration mechanism would change from the enolization mechanism found in V to a carbonium ion mechanism for β,β-diphenyl-β-hydroxypropiophenone (VI). We have, in fact, found this to be the case.

Rates of dehydration for VI were measured under conditions similar to those used previously. In order to facilitate solubility of VI in the reaction medium, we used a 5% dioxane–95% aqueous sulfuric acid medium. This solvent system has been shown[10] to be useful for H_0 comparisons, and the H_0 scale established in it. Even so it was necessary to carry out measurements with extremely dilute solutions of VI (about 10^{-6} *M*) using 10-cm. cells.

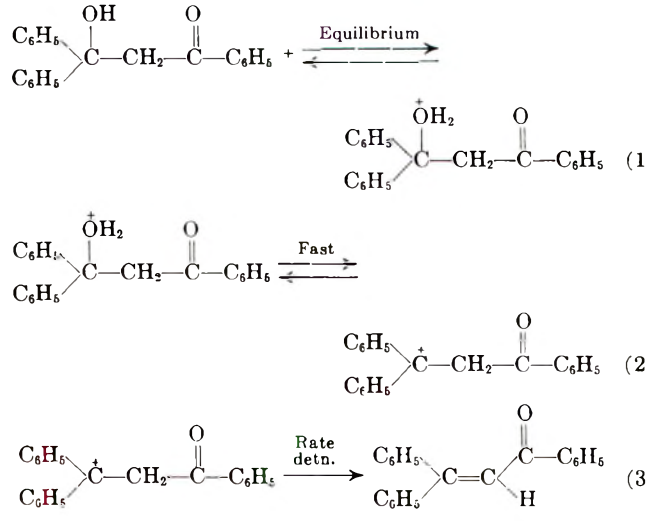
TABLE I

RATE OF DEHYDRATION OF β,β-DIPHENYL-β-HYDROXYPROPIOPHENONE IN 5% DIOXANE–95% AQUEOUS SULFURIC ACID

H_2SO_4, *M*	H_0	k, sec.$^{-1}$	log k + H
		(T = 25.00°)	
1.42	−0.45	1.54×10^{-1}	−5.26
2.56	−1.04	6.20×10^{-1}	−5.25
2.87[a]	−1.15	$8.50 \pm 0.10 \times 10^{-2}$[b]	−5.22
3.35	−1.42	1.80×10^{-4}	−5.17
3.94	−1.71	4.12×10^{-4}	−5.10
4.26	−1.87	7.0×10^{-4}	−5.03
4.84	−2.13	1.05×10^{-3}	−5.11
		(T = 45.00°)	
2.87[a]	−1.15	8.60×10^{-4}	

[a] $\Delta H^* = 21.2$ kcal.; $\Delta S^* = -10.9$ e.u. [b] Average of two runs.

The measured rates (Table I) show smooth correlation with the acidity function, the slope of log k *vs.* H_0 being 1.15. From the temperature coefficient of the rate the entropy of activation (at $H_0 = 0$) was determined. The value, −11, is similar to that obtained for other dehydration reactions proceeding *via* a carbonium ion mechanism.[3,11] These two facts provide a sound basis for suggesting that β,β-diphenyl-β-hydroxypropiophenone undergoes dehydration *via* the carbonium ion mechanism, namely, equations 1–3.



(1)

(2)

(3)

Further support for the conclusion that dehydration of VI is proceeding *via* the carbonium ion mechanism

(1) Carbonyl Reactions XXII: previous paper, D. S. Noyce and M.J. Jorgenson, *J. Am. Chem. Soc.*, **85**, 2427 (1963).
(2) National Institutes of Health Postdoctoral Fellow, 1959–1961.
(3) D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, **80**, 5539 (1958).
(4) D. S. Noyce, W. A. Pryor, and P. A. King, *ibid.*, **81**, 5423 (1959).
(5) D. S. Noyce and W. L. Reed, *ibid.*, **81**, 624 (1959).
(6) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).
(7) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.*, **77**, 3044 (1955).
(8) N. C. Deno, P. T. Groves, and G. Saines, *ibid.*, **81**, 5790 (1959).
(9) N. C. Deno, P. T. Groves, J. J. Jaruzelski and M. N. Lugasch, *ibid.*, **82**, 4719 (1960).
(10) D. S. Noyce and M. J. Jorgenson, *ibid.*, **83**, 2525 (1961).
(11) D. S. Noyce and C. A. Lane, *ibid.*, **84**, 1635 (1962).

comes from a consideration of the predicted rate for enolization of VI. The previously published data on the hydroxybutanones I, II, and III show clearly that the rate of enolization is not appreciably influenced by the electron-withdrawing or electron-donating groups in the benzene ring. Therefore, the inductive influence of the additional phenyl group in VI will be negligible.

Consideration of the possible steric influence on enolization suggest that the additional phenyl group will have a retarding effect. The rate of enolization (halogenation) of isovalerophenone is only one-third that of *n*-valerophenone,[12] a reflection of the change to a carbon skeleton branched at the β-carbon to the carbonyl group. Thus, these facts suggest that VI should undergo reaction no faster than V, and probably substantially more slowly, were enolization the rate controlling step for VI. In fact, VI undergoes dehydration from three to fifty times faster than V.

Inasmuch as the close energetic similarity of a benzhydryl cation and a *p*-methoxybenzyl cation suggested the desirability of the present study, it is of value to compare the rates of reaction of VI with III. Relevant data are summarized in Table II. The increase in the rate of dehydration, at an H_0 of -2, caused by the change to the carbonium ion mechanism, consists of a factor of 15 for the pair I, III and of a factor of 25 for the pair V, VI. The rate of dehydration of VI was found to be only one-third that of III. This decrease in rate may be attributed to either, or both, of the following causes. Estimates suggest a somewhat

TABLE II

RATES OF DEHYDRATION OF VARIOUS β-HYDROXY KETONES AT $H_0 = -2.0$

($T = 25.00°$)

Hydroxy ketone	log k, sec.$^{-1}$	Relative rate
I	−3.78	4.8
II	−3.78	4.8
III	−2.60	72
IV	−4.40	1.2
V	−4.46	1
VI	−3.06	25

lessened stability for the carbonium ion derived from VI compared to that originating from III. A further decrease in the rate of dehydration may be expected from consideration of the transition state of step 3 of the carbonium ion mechanism. The energy requirements of this step might well be increased in the reaction of VI, for two reasons. Due to electronic effects, the α-proton which is lost in the rate-determining step 3 is abstracted less rapidly in VI than in III[13]; the rate of proton loss is also likely to be reduced by the unfavorable *cis* interactions between a benzene ring and a benzoyl group developing in the transition state. Evidence for the presence of *cis* interactions in the product, β-phenylchalcone, has been obtained both from the ultraviolet spectrum[14] and from the measured basicity[15] of β-phenylchalcone. A similar reduction in rate, a factor of 60, is found in comparing the rates of dehydration of III and IV. Again a necessary *cis* interaction develops at the transition state.

(12) D. P. Evans, *J. Chem. Soc.*, 785 (1936); D. P. Evans and J. J. Gordon, *ibid.*, 1434 (1938).

(13) That the α-proton is less acidic when it is located alpha to a benzoyl group (as in VI) than when it is found alpha to an acetyl group (as in III) is evidenced by the lowered rate of dehydration *via* the enolization mechanism of the hydroxypropixphenone V from that of the corresponding hydroxybutanone I.

(14) W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **77**, 5134 (1955).

Experimental

β,β-Diphenyl-β-hydroxypropiophenone was prepared by a Grignard reaction of phenylmagnesium bromide on 1,3-diphenyl-1,3-propanedione as described by Vorländer, *et al.*[16]

Kinetic Measurements.—Preparation of optical solutions and spectral measurements were carried out as previously described.[10] All measurements were carried out in a thermostated compartment block. The ultraviolet spectrum of the solution after ten half-lives of reaction corresponded exactly to that of the product, β-phenylchalcone, at the same acid concentration; it was found to remain constant for an additional period of ten half-lives. No competing cleavage reaction was observed.

Acknowledgment.—Grateful acknowledgment is made for partial support of this work by a grant from the Petroleum Research Fund administered by the American Chemical Society, and for a grant from the National Science Foundation (G-13125).

(15) D. S. Noyce and M. J. Jorgenson, *ibid.*, **84**, 4312 (1962).

(16) D. Vorländer, J. Osterburg, and O. Meye, *Ber.*, **56**, 1138 (1923).

Transmission of Electronic Effects by the Acetylenic Group. Rates of Alkaline Hydrolysis of *m*- and *p*-Substituted Ethyl Phenylpropiolates

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Received March 29, 1963

Several pieces of evidence suggest that the acetylenic unit (–C≡C–) is a poorer transmittor of electronic effects than the *trans* ethylenic group (H>C=C<H). Resonance effects on the heats of hydrogenation of substituted acetylenes are slightly smaller than those in olefin hydrogenation,[22] thus suggesting that π bond interactions involving sp hybridized carbon are weaker than those of sp^2 carbon under these conditions. Similarly, ionization constants of 3-substituted propiolic acids,[26] rates of hydrolysis of the corresponding ethyl esters,[26] dipole moment measurements on substituted acetylenes,[26] and estimates of polarizibility[3] all confirm the same conclusion. Hammett ρ values of 0.41[4] and 0.69[5] have been reported for the ionization of phenylpropiolic acids in 50% ethanol. The value of 0.466 has been given for the ionization of cinnamic acids in water,[6] but this value is probably increased by 40–60% by a change to 50% ethanol (*cf.* benzoic acids[6]), and any comparison is equivocal. One definite anomaly is the reported[4] value of 1.91 for the saponification of a series of ethyl phenylpropiolates, which is nearly 50%

(1) Present address: Chemistry Department, University of Houston, Houston 4, Tex.

(2)(a) M. M. Kreevoy, *J. Am. Chem. Soc.*, **81**, 1608 (1959); (b) M. Charton, *J. Org. Chem.*, **26**, 735 (1961).

(3) H. Sinn, *Z. Elektrochem.*, **61**, 989 (1961); J. K. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, **57**, 3454 (1953).

(4) J. D. Roberts and R. A. Carboni, *ibid.*, **77**, 5554 (1955).

(5) I. Benghiat and E. I. Becker, *J. Org. Chem.*, **23**, 885 (1958).

(6) H. H. Jaffé, *Chem. Rev.*, **73**, 191 (1953).

larger than the corresponding value of 1.314[7] for cinnamate hydrolysis in the same solvent, 87.8% ethanol. This difference, only a small part of which can be due to the different temperatures (20° *vs.* 30°) of the two studies, has been attributed[4,8] to an especially large "field effect" through the linear system. There then remains an uncertainty as to which systems may reasonably be expected to show this large effect.

It is surprising that phenylpropiolic acid and ester series do not show abnormal σ-values. If, in fact, transmission of electronic effects from the phenyl ring to the functional group is largely a "field" or inductive effect, this should be reflected in σ-values which approach Taft's σ^0 based on benzene derivatives having nonconjugated side-chain functional groups.[9] This does not appear to be true in the preceding cases, nor in the shielding of acetylenic protons in the phenylacetylenes.[10] Rates of alkaline hydrolysis of the ethyl phenylpropiolates have, therefore, been redetermined on a more extensive series than previously studied.[4] A lower temperature (10°) and greater dilution have been used to permit more accurate determination of these fast rates (Table I).

TABLE I

RATES OF ALKALINE HYDROLYSIS OF ETHYL PHENYLPROPIOLATES[a] IN 87.8% ETHANOL AT 10°

Substituent	$k \times 10^2$ l. mole^{-1} sec.$^{-1}$
p-CH_3	1.19
H	1.61
p-F	2.08[b]
p-Cl	3.13
m-Cl	4.48
p-NO_2	12.0

[a] Prepared by the methods of M. S. Newman and S. H. Merrill, *J. Am. Chem. Soc.*, **77**, 5552 (1955). Initial [KOH] = 0.02 *M*, [RCOOEt] = 0.012 *M*. The kinetic method is that reported in ref. 7. [b] *Anal.* Calcd. for $C_{11}H_9O_2F$: C, 68.74; H, 4.72. Found: C, 69.02; H, 4.90.

About 20% of the *p*-nitro ester is diverted to an ester of much lower reactivity, probably the ethoxycinnamate. Nevertheless, it has been possible to obtain consistent rate constants corresponding with more than 90% of the desired reaction. *The value of ρ is 1.10.* Five of the points (excepting II) of the plot of log *k vs.* ordinary σ-values fall on a straight line with such precision that no deviation is detectable graphically. The unsubstituted compound falls slightly off this line. All points have been weighed equally in determining ρ; the average deviation from the best line is about 0.01 σ-unit. Making use of σ-values derived from the saponification of ethyl cinnamates in 87.8% ethanol[11] the average deviation in σ is only 0.005 unit, which indicates a close correspondence of the resonance-inductive balance in the two systems. While it would have been desirable to include additional compounds having "reliable" *meta* substituents[12] in this study, it was not found possible to obtain by published procedures samples of sufficient homogeneity to increase confidence in the determined value of ρ.

The earlier value of ρ for ethyl phenylpropiolate saponification, based on four points fitting with rather poor precision, appears to be in error.[13] *There is now no substantiated case in which the acetylenic unit transmits electronic effects better than, or, as well as, a trans ethylenic unit.*

Acknowledgment.—The author wishes to thank Dr. Jordan J. Bloomfield and Mr. Scott Cohen for furnishing several of the compounds.

(13) The new value of ρ appears to give a much improved fit of Miller's ρ–ρ relationship. (S. I. Miller, unpublished studies.)

(7) J. J. Bloomfield and R. Fuchs, *J. Org. Chem.*, **26**, 2991 (1961).
(8) R. E. Dessy and J.-Y. Kim, *J. Am. Chem. Soc.*, **83**, 1167 (1961).
(9) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).
(10) C. D. Cook and S. S. Danyluk, *Tetrahedron*, **19**, 177 (1963).
(11) K. Kindler, *Ber.*, **69**, 2792 (1936).
(12) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **81**, 5343 (1959).

Investigations in Heterocycles. XIV. 2- and 3-Azaoctahydroindolo[2,3*a*]quinolizines[1]

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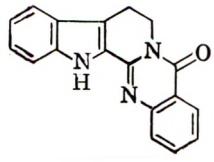
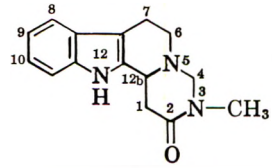
In a recent report[2] from our Laboratory, there was outlined the synthesis of a variety of tetracylic and pentacyclic indolo[2,3*a*]quinolizines related to naturally occurring substances. It was of particular interest to prepare tetracyclic indolo[2,3*a*]quinolizines containing a nitrogen atom in ring E, compounds bearing a formal resemblance to Rutecarpine (I). Thus, as previously described,[2] II was converted to its N-methyl amide III which was allowed to react with formaldehyde in refluxing ethyl alcohol with a trace of alkaline catalyst to afford 3-methyl-3-aza-1,2,3,4-6,7,12,12b-octahydro-2-oxoindolo[2,3*a*]quinolizine (IV). It was also pointed out at the time that condensation of III with a variety of aromatic aldehydes yielded the corresponding 4-aryl derivatives of IV.



I



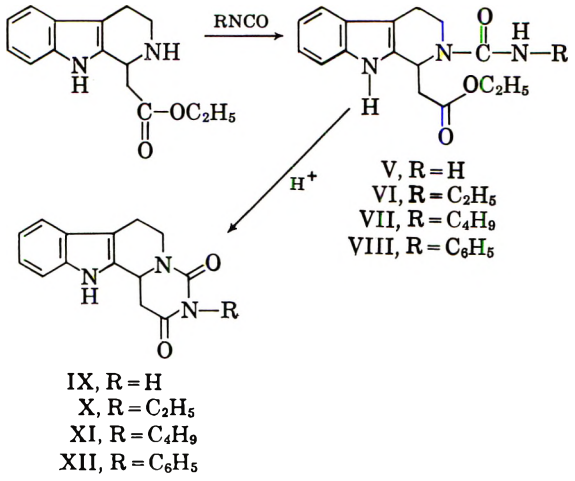
IV

It appeared now that a further extension to modifications of IV would be (a) the preparation of similar tetracyclic indoles with a keto group in position 4 and substituents other than a methyl group at the 3-aza position, and (b) the preparation of a 2-azaoctahydroindolo[2,3*a*]quinolizine. The synthesis of some of these compounds, as outlined in Scheme I, serves as the subject of this note.

Compound II proved very useful in these studies, since it readily underwent condensation with alkyl and aryl isocyanates in cyclohexane to form the corresponding urea derivatives which were converted to the 2,4-dioxo-3-substituted 3-azaoctahydroindolo[2,3*a*]quinolizine in refluxing ethyl alcohol containing small amounts

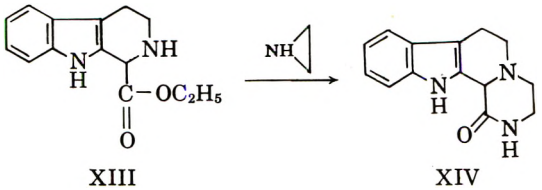
(1) This subject was discussed in part by G. deS. in a Symposium Lecture on the Chemistry of Nitrogen Heterocycles sponsored by the Medicinal Chemistry Division of the 141st National Meeting of the American Chemical Society, Washington, D. C., March 27, 1962.
(2) G. deStevens, H. Lukaszewski, M. Sklar, A. Halamandaris, and H. M. Blatter, *J. Org. Chem.*, **26**, 2457 (1962).

SCHEME I



of hydrogen chloride. The 3-unsubstituted aza compound IX was prepared by the interaction of the hydrochloride of II with potassium cyanate to form V, followed by ring closure as described. It is noteworthy that the infrared spectrum of V was unusually different in the carbonyl region from the other urea derivatives when measured in Nujol mull. Compound V gave a strong band at 1695 cm.$^{-1}$ for the ester absorption, whereas the absorption of esters VI–VIII was at 1722 cm.$^{-1}$. However, the ester carbonyl absorption of V in chloroform solution was shifted to 1725 cm.$^{-1}$. Thus, at least for the unsubstituted urea intermediate, there exists significant intermolecular hydrogen bonding. The conversion of V to IX gave a substance whose spectrum contained two strong bands in the carbonyl region, one at 1705 cm.$^{-1}$ and the other at 1685 cm.$^{-1}$, which was typical of these 2,4-dioxooctahydroindolo-[2,3a]quinolizines.

Another modification of ring D was concerned with the synthesis of a 2-azaoctahydroindolo[2,3*a*]quinolizine. This was accomplished in one step merely by allowing 1-carbethoxy-1,2,3,4-tetrahydro-β-carboline (XIII) to react with ethyleneimine in refluxing ethyl alcohol. Ultraviolet absorption data preclude the



XIII XIV

possibility that ring closure could have occurred on N_a since the major maximum for such substituted indole nitrogen compounds would be from 236–238 mμ.[3]

Several attempts were made to reduce the carbonyl group in XIV with lithium aluminum hydride to obtain a saturated ring D compound. However, this carbonyl proved to be very resistant to hydride reduction, and at best, only trace amounts of impure product were realized. Strong hydrogen bonding between N_a and the amide carbonyl, as illustrated with Dreiding models, offers a reasonable explanation for this lack of reactivity of the amide carbonyl.

(3) J. Pecher, R. H. Martin, N. Defay, M. Kaisin, J. Peeters, G. van Binst, N. Veryele, and F. Alderweireldt, *Tetrahedron Letters*, No. **8**, 270 (1961).

Experimental[4]

2-Carbamoyl-1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline (V).—1-Carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline hydrochloride[5] (2.7 g.) was dissolved in water warmed to 50°. This solution then was treated with 0.9 g. of potassium cyanate dissolved in 5 ml. of water, whereupon an immediate reaction occurred. A thick oil separated from solution. This oil was triturated well with distilled water and then taken up in ether. After drying the ether extract over sodium sulfate the drying salt was filtered off, and the filtrate was evaporated to dryness *in vacuo*. Trituration of the residue with ethyl alcohol resulted in the formation of a crystalline mass which was recrystallized from ethyl alcohol to yield a pure substance, m.p. 157–158°. Recrystallization of this substance from methyl alcohol gave a compound with identical chemical and physical properties. Infrared absorption in Nujol mull shows a strong band at 1695 cm.$^{-1}$ for the bonded ester group. In chloroform solution, this absorption band is shifted to 1725 cm.$^{-1}$. The carbamoyl absorption is evidenced at 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.65; H, 6.32; N, 13.90. Found: C, 63.35; H, 6.52; N, 13.70.

3-Aza-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3*a*]quinolizine (IX).—Two grams of V dissolved in 50 ml. of ethyl alcohol was treated with 10 ml. of ethyl alcohol saturated with hydrogen chloride, and the solution was refluxed on the steam bath for 4 hr. The solution was refrigerated overnight, and the resulting precipitate was collected on a filter. The light tan solid was recrystallized from excess ethyl alcohol to afford 1.1 g. of white crystals, which did not melt up to 350°. Infrared absorption in Nujol mull: 3300 (indole NH), 3150, and 3055 cm.$^{-1}$ (quinolizine NH); also strong absorptions at 1705 and 1685 cm.$^{-1}$ for 2,4-dioxoquinolizine grouping.

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.14; N, 16.46. Found: C, 65.62; H, 5.09; N, 16.35.

1-Carbethoxymethyl-2-ethylcarbamoyl-1,2,3,4-tetrahydro-β-carboline (IV).—A mixture of 2.6 g. (0.01 mole) of 1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline and 0.71 g. (0.01 mole) of ethyl isocyanate in 50 ml. of dry cyclohexane was heated at reflux temperature for 30 min. and chilled in an ice bath. The white precipitate which formed was collected and washed with a small amount of cyclohexane. Two recrystallizations from ethyl alcohol gave an 83% yield of white cubic crystals, m.p. 137°. Infrared absorption shows the principal band at 1722 cm.$^{-1}$ for ester group.

Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.03; H, 7.05; N, 12.60. Found: C, 64.88; H, 7.05; N, 12.39.

The following compounds were prepared in the same manner.

2-*n*-Butylcarbamoyl-1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline (VII), m.p. 131–133°, infrared absorption at 1720 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{20}H_{27}N_3O_3$: C, 67.21; H, 7.61; N, 11.76. Found: C, 67.34; H, 7.68; N, 11.54.

1-Carbethoxymethyl-2-phenylcarbamoyl-1,2,3,4-tetrahydro-β-carboline (VIII), m.p. 179–180°, infrared absorption at 1722 (ester carbonyl) and 1675 cm.$^{-1}$ (carbamoyl).

Anal. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.00; H, 6.14; N, 11.14. Found: C, 69.74; H, 6.17; N, 10.85.

The cyclization of compounds VI–VIII was carried out according to the previously described precedure for the preparation of IX. The compounds prepared are listed.

2,4-Dioxo-3-ethyl-3-aza-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3a]quinolizine (X), m.p. 184–185°.

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.81; H, 6.05. Found: C, 67.48; H, 6.01.

3-*n*-Butyl-3-aza-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3*a*]quinolizine (XI), m.p. 140–141°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.39; N, 13.49. Found: C, 69.25; H, 6.42; N, 13.24.

2,4-Dioxo-3-phenyl-3-aza-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3*a*]quinolizine (XII), m.p. 196–197°, infrared absorption in Nujol mull at 3300–3450 (broad), 1690, 1640, 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{17}N_3O_2 \cdot C_2H_5OH \cdot H_2O$: C, 66.82; H, 6.37; N, 10.51. Found: C, 66.82; H, 6.00; N, 10.51.

2-Aza-1,2,3,4,6,7,12,12b-octahydro-1-oxoindolo[2,3*a*]quinolizine (XIV).—Four grams of 1-carbethoxy-1,2,3,4-tetrahydro-β-

(4) All melting points reported herein are uncorrected.

(5) G. B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959).

carboline[6] and 0.040 g. of the hydrochloride salt of the above ester were dissolved in 25 ml. of refluxing ethyl alcohol. Ethyleneimine (0.67 g.) dissolved in 10 ml. of ethyl alcohol was added dropwise to the refluxing solution and this heating was continued for 24 hr. On chilling, this solution deposited light yellow crystals which were collected on a Büchner funnel, washed with ethyl alcohol, and then recrystallized from an excess of that solvent. One gram of pure product, m.p. 234–235° dec., was obtained. Infrared absorption shows a strong broad band at 3400 cm.$^{-1}$ (overlap of indole and amide NH) and a strong amide band at 1670 cm.$^{-1}$; $\lambda_{max}^{C_2H_5OH}$ 224 mμ (ε 36,190), 278 (39,340), 289 (6,360).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.26; N, 17.42. Found: C, 69.95; H, 6.29; N, 17.57.

Acknowledgment.—The authors extend their sincere thanks to Dr. E. Schlittler for his continuing interest. We are also indebted to Mr. L. Dorfman and his associates for the microanalytical and spectral data.

(6) F. J. Vejdelek, V. Treka, and M. Protiva, *J. Med. Pharm. Chem.*, **3**, 427 (1961).

A Synthesis of 6-Methyl-2-phenyl-5-azacycl[3.2.2]azine and Related Compounds[1,2]

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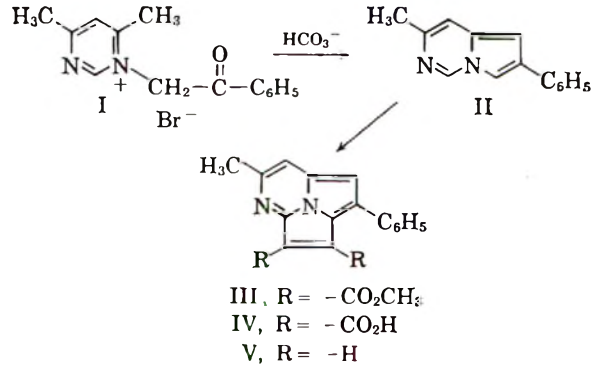
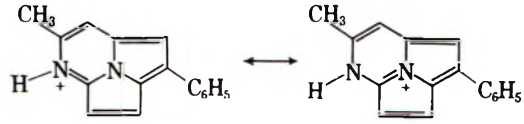
Received June 14, 1963

The reaction of pyrrocolines with dimethyl acetylenedicarboxylate,[3–5] an early example of a general procedure now known as the 1,3-dipolar addition reaction,[6] provides convenient access to cycl[3.2.2]azine and its various derivatives. Although the central nitrogen of cycl[3.2.2]azine is not basic, nitrogen atoms placed in the perimeter are basic and allow for the preparaton of the corresponding quaternary salts which are more suitable for physiological testing.[7] It was for this reason that work was initiated on the synthesis of 5-azacycl[3.2.2]azine derivatives. However, since then studies on the correlation of molecular orbital calculations with experimental data on the electronic spectra and basicity of the cyclazines has made it desirable to have additional examples with nitrogen in the periphery as an aid to evaluating the parameter to be assigned to nitrogen.[8,9]

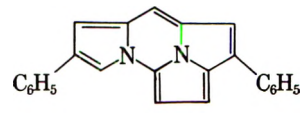
As starting material, 4,6-dimethylpyrimidine was converted in 97% yield to the corresponding quaternary bromide I using phenacyl bromide in benzene at room temperature. Cyclization by the Chichibabin procedure[10] gave 7-methyl-2-phenyl-6-azapyrrocoline(II) in 56% yield. Treatment of II with dimethyl acetylenedicarboxylate in the presence of a palladium-on-charcoal catalyst and toluene then led to the corresponding 5-azacycl[3.2.2]azine III in 28% yield. Hydrolysis of the diester with base proceeded essentially quantitatively to give the diacid IV. Finally, decarboxylation of the diacid using copper powder and aniline occurred smoothly in 78% yield to produce the desired 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (V).



As expected, 6-methyl-2-phenyl-5-azacycl[3.2.2]azine was readily soluble in aqueous acid. However, its ultraviolet and visible absorption spectrum showed an unexpected shift to longer wave lengths in the presence of acid. Thus, in neutral ethanol V showed maxima at 227 (4.26), 264 (4.54), 327 (4.34), and 452 mμ (log ε 3.59), whereas in 0.09 *M* hydrochloric acid maxima were observed at 227 (4.22), 268 (4.55), 366 (4.33), and 473 mμ (log ε 3.31). This shift becomes understandable, however, when it is considered that V, on protonation, is a resonance hybrid with contributing structures such as VI and VII.



In the original plan the presence of the methyl group at the 6-position of V was desired so that a second Chichibabin ring closure could be effected to give the interesting fused bispyrrocoline represented by VIII. Unfortunately, attempts to accomplish this ring closure were unsuccessful.



Experimental[11]

1-Phenacyl-4,6-dimethylpyridinium Bromide (I).—A solution of 11.0 g. of 4,6-dimethylpyrimidine and 21.0 g. of phenacyl bromide in 60 ml. of benzene was allowed to stand at room temperature for 10 days. The orange-yellow precipitate, which separated, was collected by filtration, washed with benzene, and air-dried. This gave 31.4 g. (97%) of product of sufficient purity for use in the next step. Recrystallization of the orange-yellow solid from absolute ethanol gave 23.0 g. (71%) of yellow crystals, m.p. 173° dec.

Anal. Calcd. for $C_{14}H_{15}N_2OBr$: C, 54.73; H, 4.92; N, 9.12; Br, 26.01. Found: C, 54.38; H, 4.95; N, 8.84; Br, 25.94.

7-Methyl-2-phenyl-6-azapyrrocoline (II).—To a stirred solution of 10.5 g. of the crude quaternary bromide I in a mixture of 50 ml. of ethanol and 350 ml. of water there was added a saturated

(1) Abstracted from the M.S. thesis of S. S. Kertelj, University of Oregon, 1963.

(2) Aided in part by the National Science Foundation and by the U. S. Army Research Office (Durham).

(3) J. C. Godfrey, *J. Org. Chem.*, **24**, 581 (1959).

(4) A. Galbraith, T. Small, and V. Boekelheide, *ibid.*, **24**, 582 (1959).

(5) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 453 (1961).

(6) R. Huisgen and A. Eckell, *Tetrahedron Letters*, **12**, 5 (1960); *cf.* R. Huisgen, "Theoretische Chemie und Organische Synthese," Festschrift der Zehnjahresfeier des Fond der Chemischen Industrie, Düsseldorf, Germany, 1960.

(7) V. Boekelheide and A. Miller, *J. Org. Chem.*, **26** 431 (1961).

(8) V. Boekelheide, F. Gerson, E. Heilbronner, and D. Meuche, *Helv. Chim. Acta*, in press.

(9) F. Gerson, E. Heilbronner, N. Joop, and H. Zimmermann, *ibid.*, in press.

(10) A. E. Chichibabin, *Ber.*, **59**, 2048 (1926).

(11) Microanalyses by Micro-Tech Laboratories and F. Pascher. Melting points are uncorrected.

aqueous solution prepared from 10 g. of potassium bicarbonate. The resulting orange-brown suspension was heated on a steam bath for 1 hr. and cooled, and the solid which separated was collected. This, after being washed thoroughly with water and then air-dried, was recrystallized from benzene to give 3.8 g. (56%) of yellow crystals, m.p. 180–190° dec. Treatment with charcoal in acetonitrile followed by an additional recrystallization from benzene yielded white crystals, m.p. 180–190° dec. The ultraviolet absorption spectrum of II in ethanol showed a maxima at 254 mμ (log ε 4.74) with a shoulder at 258 mμ (log ε 4.72).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.67; H, 5.86; N, 13.23.

3,4-Dicarbethoxy-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (III).—To a solution of 9.0 g. of 7-methyl-2-phenyl-6-azapyrrocoline (II) and 9.4 g. of dimethyl acetylenedicarboxylate in 540 ml. of toluene there was added 8.0 g. of a 5% palladium-on-charcoal catalyst, and the mixture was heated under reflux in a nitrogen atmosphere for 21 hr. After removal of the catalyst and solvent, the brown, gummy residue was taken up in benzene and passed over neutral alumina (800 g., grade III, Woelm). Following the initial eluate which contained 0.25 g. of II, the main fraction gave 4.15 g. (28%) of bright yellow crystals, m.p. 152–154°. A further recrystallization from ethyl acetate yielded yellow needles, m.p. 155–156°. The absorption spectrum of III in ethanol showed maxima at 242 (4.53), 266 (4.30), 336 (4.29), and 448 mμ (log ε 3.91).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.77; H, 4.75; N, 7.87.

3,4-Dicarboxy-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (IV).—A mixture of 150 mg. of III and 30 ml. of methanol saturated with potassium hydroxide was heated at 50° with stirring until complete solution resulted (30 min.), whereupon precipitation of the dipotassium salt of IV occurred. The mixture was heated for an additional 30 min. before collecting the precipitate by filtration. The solid precipitate was redissolved in a minimum amount of water, and the solution was acidified with concentrated hydrochloric acid. There separated 130 mg. (95%) of yellow crystals, m.p. 230–235°.

Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.20; H, 3.98; N, 8.58.

When the diacid IV was recrystallized from pyridine, the monopyridinium salt of IV separated as long, orange needles, m.p. 170° dec.

Anal. Calcd. for $C_{23}H_{17}N_3O_4$: C, 69.16; H, 4.29; N, 10.52. Found: C, 69.07; H, 4.42; N, 10.55.

6-Methyl-2-phenyl-5-azacycl[3.2.2]azine (V).—A mixture of 900 mg. of the crude diacid IV and 1.0 g. of copper powder in 250 ml. of aniline was boiled under reflux until evolution of carbon dioxide ceased. After removal of the catalyst and concentration under reduced pressure, the gummy residue was taken up in benzene and chromatographed over Florisil (300 g.). From the third fraction of eluate there was obtained 510 mg. (78%) of an orange-yellow solid, m.p. 135–140°. Recrystallization from an ether–pentane mixture (1:1) produced large, yellow-orange crystals, m.p. 145–147°. The n.m.r. spectrum in methylene chloride showed a proton signal for the methyl group at 7.18 τ. In concentrated sulfuric acid this signal was shifted to 6.77 τ with two smaller additional signals at 6.70 and 7.03 τ. The latter two signals are presumably due to protonation on carbon at the 1- and 4-positions.[5]

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.86; H, 5.28; N, 11.90.

Synthesis and Polymerization of 3-Azabicyclo[4.3.1]decan-4-one and 7,7-Dimethyl-2-azabicyclo[4.1.1]octan-3-one

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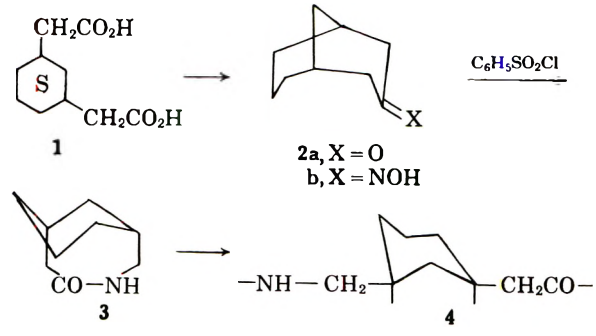
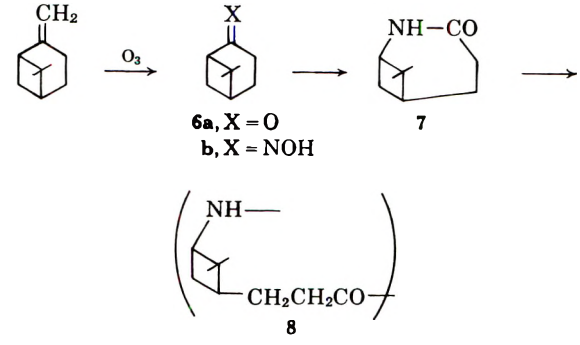
Received May 15, 1963

Cyclohexane-1,3-diacetic acid readily cyclized to bicyclo[3.3.1]nonan-3-one (**2a**) when heated with barium oxide. Hydroxylamine converted the ketone to the oxime **2b**, which underwent the Beckmann rearrangement to give the desired lactam, 3-azabicyclo[4.3.1]decan-4-one (**3**). Cyclohexane-1,4-diacetic acid, under conditions which readily cyclized the 1,3-isomer, gave no bicyclo[3.2.2]nonan-3-one (**5**). The ketone **2a** can exist in a stable two-chair conformation, while **5** would possess a strained boat form of the cyclohexane ring. This difference in conformation may account for the difference in ease of formation of the two ketones.



Nopinone (**6a**) recently has been made available[1] by ozonolysis of β-pinene. This preparation was repeated and the ketone was converted to the oxime **6b** and thence by Beckmann rearrangement to a crystalline lactam. The oxime is assigned the configuration with the hydroxyl group *anti* to the cyclobutane ring, since this configuration is sterically less strained than the *syn* form. Because of the *trans* nature of the rearrangement, the lactam is assigned the structure 7,7-dimethyl-2-azabicyclo[4.1.1]octan-3-one (**7**). This type of assignment, applied previously to other atom-bridged oximes and lactams,[2] was shown subsequently to be correct by degradation studies.[3]



Polymerizations.—The lactams were converted to polyamides by heating at 200–223° with 5% of 85% phosphoric acid as catalyst.[2,4] Lactam **3** polymerized much more readily than lactam **7**. Hydrogen crowding within the bridged rings is considered to be the destabilizing factor in these molecules which causes them to polymerize. Like many other polyamides possessing alicyclic rings in the polymer chain,[2,4] these polymers displayed quite high melting points; **4** melted at 297° and **8** at 358°.

Experimental

Cyclohexane-1,3- and 1,4-diacetic Acids.—Pure *m*-phenylenediacetic acid was not available but an approximately 1:1 mixture

(1) J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960).
(2) H. K. Hall, Jr., *ibid.*, **82**, 1209 (1960).
(3) R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, **26**, 1703 (1961).
(4) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **80**, 6412 (1958).

of *m*- and *p*-isomers (du Pont Electrochemicals Department RH-870) was on hand. A mixture of 315 g. of this acid, 520 ml. of ethanol, and 2.5 l. of benzene was brought to boiling and stirred for 1 hr. The mixture was chilled and filtered. There was recovered 117 g. of almost pure *p*-isomer, m.p. 255°, m.m.p. 255° on a heated bar (lit.[5] m.p. 244°). The filtrate was concentrated to a small volume. Ethanol, 1.2 l., was added and the mixture was saturated with hydrogen chloride gas. After 20 hr. it was distilled to give 217 g. of diethyl phenylenediacetates, b.p. 127–130° (1.1 mm.). Hydrogenation was performed over 3 g. of ruthenium dioxide in 250 ml. of ethanol at 135° and 1565 p.s.i. Hydrogen, 1.4 moles (54%), was absorbed. Rehydrogenation resulted in no further uptake. The product, 174.5 g., boiled at 115–133° (0.15 mm.). The infrared spectrum showed the presence of ester groups and absence of aromatic or unsaturated links. The diester, 70.0 g., was boiled under reflux for 5 hr. with 70 g. of sodium hydroxide, 200 ml. of ethanol, and 300 ml. of water. The ethanol was distilled, and the residue was cooled and acidified with 12 *N* hydrochloric acid. After 3 days, the precipitate was filtered, rinsed with water, and air dried to give 51.0 g. of mixed cyclohexane-1,3- and 1,4-diacetic acids, m.p. 130–132°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 59.7; H, 8.1.

Bicyclo[3.3.1]nonan-3-one (2a).—The mixture of cyclohexanediacetic acids, 26.0 g. (0.13 mole), was mixed with 50 ml. of acetic anhydride, and acetic acid was distilled over a 1-hr. period. The remainder was distilled through a Claisen head at 150 mm. using a pale blue flame. The distillate was taken up in 100 ml. of ether and washed with 100 ml. of water and with 150 ml. of 15% sodium carbonate solution. The aqueous layers were back extracted with 50 ml. of hexane. The organic layers were dried and the solvents were evaporated. Short-path distillation of the residue at 15 mm., followed by crystallization of the residue at −80° from hexane, gave 4.6 g. of an off-white solid. Sublimation at 140° (18 mm.) gave 4.06 g. (22.6%) of pure ketone, m.p. 180–182°. The use of barium oxide in place of acetic anhydride in the distillation gave a lower yield of the same ketone.

Anal. Calcd. for $C_9H_{14}O$: O, 11.6. Found: O, 11.7.

The carbonyl group absorption in the infrared spectrum[6] of this ketone was split into two bands at 1706 and 1717 cm.$^{-1}$. The 2,4-dinitrophenylhydrazone[7] melted at 208–209° after one recrystallization from ethanol–ethyl acetate.

Similarly, esterification of pure *p*-phenylenediacetic acid gave diethyl ester, m.p. 59–59.5° (lit.[5] m.p. 59–59.5°); hydrogenation gave the diethyl ester of cyclohexane-1,4-diacetic acid; and hydrolysis provided cyclohexane-1,4-diacetic acid, m.p. 164–165°, which was analyzed.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1. Found: C, 59.8; H, 8.2.

Distillation of the 1,4-diacid from barium oxide gave no ketonic product, proving that the ketone described above was derived from cyclohexane-1,3-diacetic acid.

Bicyclo[3.3.1]nonan-3-one Oxime (2b).—The crude oxime, b.p. 113–115° (1.0 mm.), 12.25 g., was obtained as described[2] from 12.79 g. (0.0925 mole) of ketone as a white solid in the receiver, m.p. 108–114°. Recrystallization from 30 ml. of hexane gave 10.10 g. (71.3%) of oxime, m.p. 108–109°.

Anal. Calcd. for $C_9H_{15}ON$: N, 9.14. Found: N (Dumas), 9.36.

3-Azabicyclo[4.3.1]decan-4-one (3).—The oxime **2b**, 9.92 g. (0.065 mole), led by Beckmann rearrangement[8] to a lactam which sublimed at 100–160° (0.45 mm.), 6.2 g. This was taken up in 25 ml. of hexane and crystallized at −80° to give 3.30 g. of white solid. Crop 2, 1.26 g., and crop 3, 0.98 g., were obtained by evaporation of the solvent and crystallization again at −80°. The combined yield was 55.9%.

Anal. Calcd. for $C_9H_{15}ON$: N, 9.14. Found: N, 8.84, (crop 1), 8.77 (crop 2), 8.73 (crop 3).

These fractions did not melt sharply but rather became semisolid at 80–120°. They were evidently polymerizing during the determination.

Nopinone Oxime (6b).—"Sulfate" β-pinene, from Hercules Powder Co., was established as 91% pure by vapor phase chromatography. It was ozonized as described by Meinwald and Gassman[1] to give nopinone, b.p. 92° (16 mm.), 99+% pure by v.p.c. The oxime was prepared as described.[2] Distillation of the oxime prepared from 38.2 g. of nopinone gave 40.1 g., b.p. 107° (1.5 mm.). It crystallized slowly and completely. Recrystallization from 20 ml. of heptane gave 33.2 g. oxime, m.p. 61.5–65.0°.

Anal. Calcd. for $C_9H_{15}ON$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.50, 70.46; H, 9.99, 10.06; N, 8.86, 8.97.

7,7-Dimethyl-2-azabicyclo[4.1.1]octan-3-one (7).—The Beckmann rearrangement of 23.1 g. of oxime was carried out using sodium hydroxide and benzenesulfonyl chloride.[8] The chloroform extract was concentrated and diluted with 800 ml. of ether. Flocculent material was filtered. The filtrate was concentrated and distilled at 0.3 mm. up to 130°. The distillate solidified in the receiver and considerable undistillable residue remained. After three sublimations and crystallization from 15 ml. of heptane, the lactam weighed 9.85 g. (42.6%) and melted at 111.0–113.0°.

Anal. Calcd. for $C_9H_{15}ON$: C, 70.6; H, 9.9; N, 9.14. Found: C, 70.5, 70.3; H, 9.9, 9.9; N, 8.91, 8.91.

The infrared spectrum was consistent with that of a lactam, although no 6.50-μ band was observed.

Polymerizations.—Lactam **3**, 1.50 g., was polymerized by heating with 1 drop of water and 1 drop of 85% phosphoric acid[2,4] in a sealed glass tube under nitrogen for 8.5 hr. at 223°. The polyamide **4** of *cis*-3-aminomethylcyclohexylacetic acid weighed 1.32 g. (88.0%) after washing with water and acetone. It melted at 297° and had an inherent viscosity in *m*-cresol of 0.21.

Lactam **7** was polymerized similarly by 5% of 85% phosphoric acid at 200° for 17 hr., and a 75% yield of product was obtained after methanol extraction. The polyamide **8** of *cis*-3-amino-2,2-dimethylcyclobutanepropionic acid melted at 358° and possessed an inherent viscosity of 0.62 in *m*-cresol. The use of less phosphoric acid for longer times led to lower molecular weight polymer, while the use of sodium hydride–acetic anhydride gave only dark oils.

Acknowledgment.—We are indebted to the following individuals and their associates: Mr. I. D. Plank and Mr. W. Childress and their associates for the microanalyses, Mr. H. E. Cupery for the hydrogenations, Mrs. Janet W. Willoughby and Mr. George Elechko for excellent technical assistance, and Dr. P. W. Morgan and Dr. R. G. Beaman for unfailing encouragement.

(5) T. Zincke and L. Klippert, *Ber.*, **9**, 1767 (1876).

(6) R. Zbinden and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **82**, 1215 (1960).

(7) R. L. Shriner and R. C. Fusion, "Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

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

Products from the Acetolysis of (−)-(S)-Bicyclo[2.2.2.]octyl-2 *p*-Bromobenzenesulfonate. A Reinvestigation[1]

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Received May 23, 1963

In a previous publication[2] it was reported that acetolysis of (−)-bicyclo[2.2.2]octyl-2 *p*-bromobenzenesulfonate resulted in a mixture of (+)-acetates which upon reduction with lithium aluminum hydride yielded a mixture of alcohols consisting of 65 ± 3% bicyclo[2.2.2]octanol-2 and 35 ± 3% of axial bicyclo[3.2.1]-octanol-2. The mixture was separated using preparative vapor phase chromatography, but only 4–6-mg. quantities of each component were isolated in a pure state, since the peaks overlapped considerably because

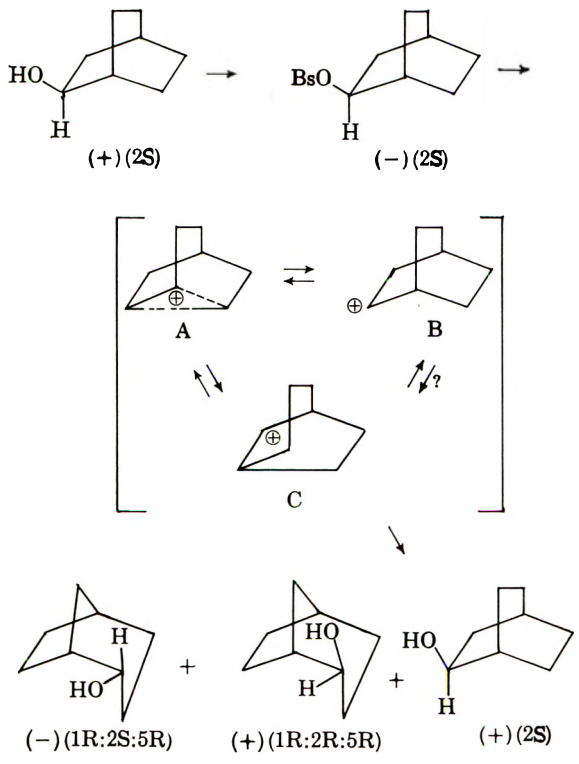
(1) This work was supported by research grant Cy-4065, National Institutes of Health, Public Health Service.

(2) H. M. Walborsky, M. E. Baum, and A. A. Youssef, *J. Am. Chem. Soc.*, **83**, 988 (1961).

of very similar retention times. Since only small amounts of material were available, the optical rotations of the alcohols were in doubt.

The preceding product analysis was repeated in order to obtain more accurate data. A sample of (+)-(*S*)-bicyclo[2.2.2]octanol-2, $[\alpha]^{25}D$ +5.7° (14.3% optical purity[3]) was converted to the *p*-bromobenzenesulfonate ester, m.p. 79.5–81.0°. In the previous work the brosylate was recrystallized, until m.p. 88–88.5° and a partial resolution may have been effected. In this work the brosylate, m.p. 79.5–81.0°, was subjected to acetolysis after it was shown not to be contaminated by unchanged alcohol. The acetolysis product, $[\alpha]^{28}D$ +0.82 ± 0.03°, was reduced with lithium aluminum hydride to yield a mixture of alcohols, $[\alpha]^{25}D$ +2.3 ± 0.2°. The alcohol mixture was analyzed by v.p.c. using a 150-ft. triscyanoethoxypropane Golay column. The mixture was shown to consist of 54.1% bicyclo[2.2.2]octanol-2, 43.0% axial bicyclo[3.2.1]octanol-2, 1.7% equatorial bicyclo[3.2.1]-octanol-2, and 1.2% of an unknown component.

Preparative v.p.c. yielded a sample of bicyclo[2.2.2]-octanol-2, $[\alpha]^{25}D$ +2.52°, which corresponds to 44% retention of activity. However, this sample was shown to contain 3% of equatorial bicyclo[3.2.1]-octanol-2 which should, if it retained optical activity, be levorotatory.[4] Using a minimum value,[5] $[\alpha]D$ 17.2°, for the rotation of equatorial alcohol and assuming complete retention of activity in going from bicyclo[2.2.2]octanol of 14.3% optical purity, the equatorial alcohol should have a rotation of −3.1°. Since it is present to the extent of 3% in the bicyclo[2.2.2]-octanol-2, it would have the effect of raising the rotation of solvolysis alcohol by 0.19°. Therefore the maximum amount of retention of activity and configuration would be 47%. In contrast to our earlier work[2] the axial bicyclo[3.2.1] alcohol isolated was shown to be dextrorotatory, $[\alpha]^{24}D$ 1.85°, and should be assigned the (1R:2R:5R) configuration[2] which is in agreement with the findings of Berson[3] on the relative configurations of (+)-axial and (−)-equatorial bicyclo-[3.2.1]octanol-2.



If solely an unsymmetrical nonclassical ion A were produced in the acetolysis of the brosylate, one would predict that the resulting products would not be racemized. On the other hand if the symmetrical classical ion B were initially formed, the expected stereochemical findings would be that of mainly racemization with some inversion of configuration.

The stereochemical findings in the acetolysis can be rationalized by postulating the initial formation of an optically active nonclassical ion A which may be converted to an optically active classical ion C. Reaction of A and C with solvent leads to the formation of optically active products. However, A and C may also be converted to the optically inactive classical ion B and this would then account for the observed racemization. It should be pointed out that if extensive 6–2 hydride shift occurred[6] then the observed racemization could be accounted for without resorting to the formation of the classical ions B and C.

An alternate explanation has been advanced by H. C. Brown[7] who argues that if the interconversion of classical ions B and C is extremely rapid ("windshield wiper effect") then attack by solvent would be favored from the side of the molecule that the brosylate anion departed from and this too, would result in retention of configuration.

Experimental

(−)-(*S*)-Bicyclo[2.2.2]octyl-2 *p*-Bromobenzenesulfonate.—To 6.3 g. of (+)-(*S*)-bicyclo[2.2.2]octanol-2,[8] $[\alpha]^{25}D$ +5.7° (chloroform, *c* 4.4), dissolved in 50 ml. of freshly dried and distilled pyridine was added at 0° 19.0 g. of *p*-bromobenzenesulfonyl chloride. The mixture was refrigerated at 0–5° for 60 hr. and then poured on ice and the precipitated material taken up in ether. The ether solution was filtered and dried and the ether removed *in vacuo* to yield 17.3 g. of brosylate, m.p. 79.5–81.0°, $[\alpha]^{29}D$ −0.2 ± 0.3° (AcOH, *c* 10.41). The infrared spectrum showed the absence of starting alcohol.

Acetolysis of (−)-(*S*)-Bicyclo[2.2.2]octyl *p*-Bromobenzenesulfonate.—The acetolysis was run as previously described[2] to yield 5.8 g. (70%) of the acetate mixture, b.p. 64.5° (3 mm.), $n^{23}D$ 1.4702, and $[\alpha]^{28}D$ +0.82 ± 0.02 (neat, 1 dm.).

The mixture of acetates (5.8 g.) was reduced with lithium aluminum hydride to yield 4.0 g. (92%) of the alcohol mixture, m.p. 200–206°, $[\alpha]^{28}D$ +2.3° ± 0.2° ($CHCl_3$, *c* 10.9). A chloroform solution of the alcohol mixture was analyzed by v.p.c. using a 150-ft. triscyanoethoxypropane Golay column. At a helium flow rate of 30 ml./min. and a column temperature of 57° the retention times of the alcohols, relative to chloroform, were found to be 17.3 min. for axial bicyclo[3.2.1]octanol-2 (43.0%), 19.4 min. for bicyclo[2.2.2]octanol-2 (54.1%), and 20.5 min. for equatorial bicyclo[3.2.1]octanol-2 (1.7%). A small amount of unknown impurity appeared at 12 min. (1.2%). The values in parentheses represent the per cent composition as determined by measuring the areas under the peaks.

Repetitive v.p.c. using a 15 ft. × 3/8 in. 20% DEGS on 60/80 Chromosorb-W column[9] and a column temperature of 150°

(3) J. A. Berson and D. Willner, *J. Am. Chem. Soc.*, **84**, 675 (1962); J. A. Berson and P. Reynolds-Warnhoff, *ibid.*, **84**, 683 (1962).

(4) The levorotation is based on the observation[3] that (−)-equatorial and (+)-axial bicyclo[3.2.1]octanol-2 are epimers.

(5) This value was reported to us by Professor J. Berson.

(6) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

(7) H. C. Brown, "The Transition State," Special Publication No. 16, Chemical Society, London, 1962; P. S. Skell and R. J. Maxwell, *J. Am. Chem. Soc.*, **84**, 3963 (1962).

(8) H. M. Walborsky and A. E. Young, *J. Org. Chem.*, **27**, 2261 (1962).

(9) We wish to acknowledge the assistance of Dr. E. Taft in carrying out this separation.

yielded 44 mg. of bicyclo[2.2.2]octanol-2, $[\alpha]^{25}D$ + 2.52° ($CHCl_3$, *c* 4.4), which was shown by analytical v.p.c. to contain 3% of equatorial bicyclo[3.2.1]octanol-2 and 56 mg. of pure axial bicyclo[3.2.1]octanol-2, $[\alpha]^{25}D$ +1.85° ($CHCl_3$, *c* 5.6).

Acknowledgment.—We are indebted to Professor J. A. Berson for many valuable and stimulating discussions.

Nuclear Magnetic Resonance Identification of Substitutional Isomers in Chelated Polycyclic Aromatic Systems[1]

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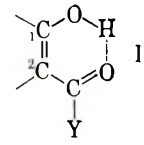
Received June 10, 1963

Some time ago we made a study of chemical shifts in chelated phenols which contain the structure I, where Y = –H, $-CH_3$, and $-OCH_3$, and from the results obtained[3] it seems likely that magnetic resonance methods may be useful in distinguishing between isomers of phenols with chelating substituents. The arguments which we will employ can easily be extended to other systems. The results exhibit two aspects by means of which the isomers may be distinguished on the basis of their high-resolution proton magnetic resonance spectra.

A. From the –OH Proton Chemical Shift.—In aromatic systems, the shift of a chelated –OH proton relative to the –OH peak in the corresponding parent phenol is quite large. We have found that this chemical shift is a linear function of the bond order of bond C-1=C-2, with the slope depending somewhat upon the substituent Y.[3] Therefore, the –OH proton shift in an unknown structure establishes whether or not the –OH group is *ortho* to substituent Y. If it is, the shift determines also the approximate bond order between the two carbons of the aromatic nucleus to which the –OH and –Y groups are attached. In turn, since approximate bond orders are known, and differ considerably for the various bonds in many aromatic systems, the bond order inferred from the –OH proton shift gives the location of the chelated structure in the molecule.

B. From the Chemical Shift of the Protons in Y.—A large part of the chemical shift of a proton, which is situated near an aromatic system, arises from the π-electronic ring currents induced in the aromatic system when the molecule is placed in a magnetic field.[4,5] It is this effect which leads to the other method of assigning the substituent position in polynuclear aromatic systems.

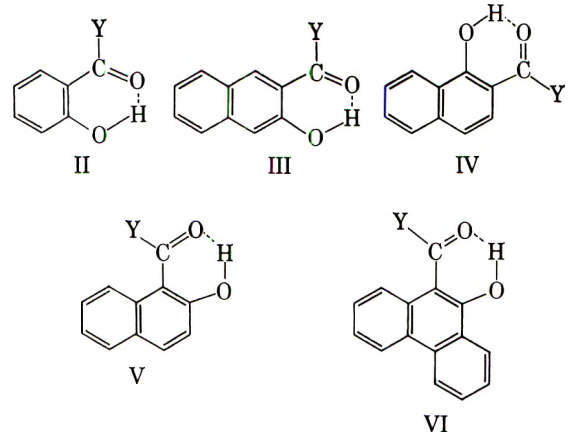


I

Method A is straightforward, direct, and requires little amplification.[3] Method B we will discuss in more detail. To a first approximation, the π-electron currents induced in each six-membered ring can be replaced by an elementary dipole situated at the center of the ring. Each dipole exerts a secondary magnetic field at Y, which is inversely proportional to the third power of the distance between the dipole and Y. This secondary field is in the same direction as the applied magnetic field, provided Y lies in the same plane as the aromatic system. If Y does not lie in this plane, then the effective field is reduced until, eventually, the applied field may be opposed by the secondary field. The maximum opposition to the applied field occurs when Y lies on the perpendicular drawn through the center of the dipole.

It is quite easy to show[4,5] that when Y does lie in the same plane as the aromatic system, then each secondary field causes a chemical shift of about $27.58/r^3$ parts per million if *r*, the distance from the protons or other magnetic nuclei in Y to the π-electronic dipole, is expressed in angstrom units. Hence, if the dimensions of the molecule are known, the approximate relative chemical shifts of Y may be predicted for a series of similar compounds. These predicted shifts will be only approximately correct, because the π-electron systems are perturbed to different extents by interaction with the substituents, and this interaction, in its turn, modifies the diamagnetic circulations induced in the substituents. However, these effects are less important than the geometrical considerations outlined above, and they do not affect the qualitative arguments that are used.

The ring current shifts will be modified by solvent interactions, and so our arguments apply to solutions in which the solvent interactions are either negligible or very similar for the solutes in question.



With this qualification, one predicts that the downfield, ring-current shifts in compounds of types II to VI of the Y = H proton absorption peaks should be about 0.175 p.p.m. on going from I to III, somewhat less on going from II to IV, and about 0.55 p.p.m. on going from II and III to V and VI. These predictions

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Also, this work was supported by the Office of Naval Research.

(2) Chemistry Department, The University, Glasgow, Scotland.

(3) A. L. Porte, H. S. Gutowsky, and I. M. Hunsberger, *J. Am. Chem. Soc.*, **82**, 5057 (1960).

(4) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956).

(5) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co. Inc., New York, N. Y., 1959.

are in reasonable agreement with the observed shifts which in τ units are

	II	III	V	VI
Y = H	0.04	−0.09	−0.71	−0.57

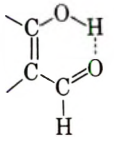
Here, negative values are downfield with respect to positive. These, and the other measurements given later, were made on dilute solutions in tetrachloride using cyclohexane as an internal reference.[3] The shifts were converted to the tetramethylsilane τ-scale by using a τ-value of 8.51 for cyclohexane.

In the case of the corresponding ketones, Y = CH_3, prediction of the ring current shifts is complicated by rotation about the C–CH_3 bond, but similar principles hold. The relative chemical shifts, however, will be smaller within this series than in the case of the aldehydes, because the protons of the –CH_3 group are further away from the elementary induced dipoles, and they do not lie in the same plane as the aromatic system. The observed shifts of the –CH_3 absorption peaks in τ units are

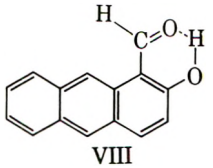
	II	III	IV	V	VI
Y = CH_3	7.35	7.21	7.23	7.14	7.19

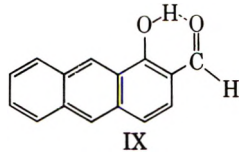
in qualitative agreement with the above arguments.

As an example of the use of these methods in structural determination, consider the position to be assigned to the –CYO groups in an hydroxyanthraldehyde (A) and in an hydroxyanthryl methyl ketone (B) which melt at 167 and 116°, respectively. In the case of the hydroxyanthraldehyde, chemical evidence[6,7] showed that the –OH group was at the 2-position, but it was not known whether the aldehyde group was at the 1- or the 3-position. The –OH proton line of A occurs at τ −3.64. This position is about 8.75 p.p.m. downfield from that expected[3] for the –OH position in either 1-hydroxy, or 2-hydroxyanthracene ($\tau \cong 5.1$) and is at the position expected for the chelated system VII


VIII

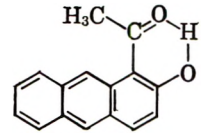
in which the mobile bond order of the C=C bond is 0.745.[3] Hence, it follows that the –OH and aldehyde groups are chelated and that the chelated system must span the 1–2 bond in the anthracene nucleus. It can not span the 2–3 position; *i.e.*, A is either VIII or IX on the basis of the –OH proton shift alone. Combining the –OH proton shift and chemical evidence, we find VIII to be the correct structure.


VIII


IX

The ring current effects enable us to confirm that VIII is the correct structure. The observed position of the –CHO absorption peak, at a τ-value of −0.87, is in the range predicted for structure VIII. For structure IX, the –CHO τ-value is predicted to be about −0.1, which differs so greatly from experiment that VIII must be the correct structure. This conclusion supports a structural determination based upon chemical arguments.[6,7]

In a similar way, the –OH and –CH_3 chemical shifts, with τ-values of −4.37 and 7.18 p.p.m., respectively, indicate[3] that B is X. In this case, the arguments based upon the –CH_3 group proton shift are not conclusive and the isomeric form with –OH and –$COCH_3$ groups interchanged was eliminated primarily by chemical evidence[6,7] as to the –OH position.


X

Experimental

The samples and experimental procedure, with one exception, were the same in these experiments as described in an earlier report.[3] The exception is the hydroxyanthraldehyde (A), the synthesis of which has been described elsewhere.[6,7] Furthermore, we are indebted to Professor I. Moyer Hunsberger for furnishing the samples and giving us some helpful comments on the manuscript.

(6) J. L. Ferrari and I. M. Hunsberger, *J. Org. Chem.*, **25**, 485 (1960).
(7) J. L. Ferrari, Ph.D. thesis, Fordham University, 1962.

trans-5-Cyclodecenone[1]

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Received May 6, 1963

Although studies of medium carbocycles (C_{8-11}) have yielded interesting information on interactions of functional groups with transannular double bonds,[2] the synthetic inaccessibility of the simplest systems has hindered a dissection of the nature of such interactions. One of the most promising methods of generating the exemplary 5-cyclononenyl and 5-cyclodecenyl systems is the fragmentation of appropriately substituted hydrindane and decalin precursors,[3] two further examples of which we report herewith for the stereospecific synthesis of *trans*-5-cyclodecenone (**4**).[2c]

Allylic alcohol **2**[4] prepared *via* photosensitized oxygenation of Δ^9-octalin,[4a] was converted to a mixture[5] of 1,10-decalindiols (**3a**) in 78% yield by the standard procedure using diborane.[6] The oily mixture of

(1) This investigation was supported by a Frederick Gardner Cottrell grant from Research Corporation and by Public Health Service Research Grant GM 09759 from the Division of General Medical Sciences, U. S. Public Health Service.

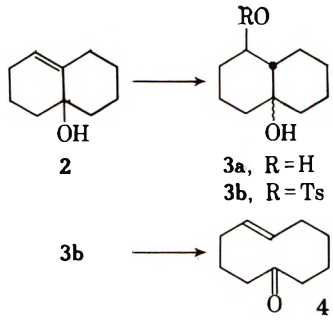
(2)(a) See J. Sicher, *Progr. Stereochem.*, **3**, 202 (1962), for a review and leading references. Later references include (b) A. C. Cope, S. Moon, and P. E. Peterson, *J. Am. Chem. Soc.*, **84**, 1935 (1962), and (c) H. L. Goering, *et al.*, *ibid.*, **83**, 3507, 3511 (1961).

(3) P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961); E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **85**, 362 (1963).

(4) (a) G. O. Schenck and K. Schulte-Elte, *Ann.*, **618**, 185 (1958); (b) S. Dev, *J. Indian Chem. Soc.*, **34**, 121 (1957).

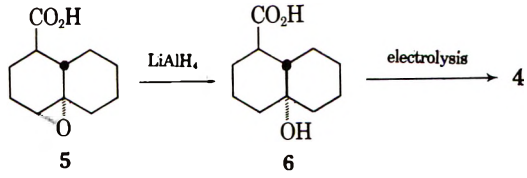
(5) Unpublished work has resulted in the separation of two crystalline *p*-nitrobenzoates of the oily diol mixture in yields of 50 and 20%.

(6) H. C. Brown, *et al.*, *J. Am. Chem. Soc.*, **80**, 1552 (1958); **81**, 6428 (1959); and **84**, 183 (1962).



diols was monotosylated and the crystalline mixture of monotosylates (**3b**) fragmented by treatment with potassium *t*-butoxide in *t*-butyl alcohol.[7] The distilled product (82% based on diol) was identified as *trans*-5-cyclodecenone from infrared and capillary vapor phase chromatographic data,[8] the latter indicating a purity of 97% and, therefore, 62% over-all yield of **4** from **2**. Using literature yields[4a,9] for the preparation of **2** from β-naphthol, it is calculated that **4** is available from β-naphthol by this reported sequence in an over-all yield of 22%.

We also have observed the formation of *trans*-5-cyclodecenone from electrolytic fragmentation of a type commented on recently.[10] Epoxide **5**, of established stereochemistry,[11] was reduced to γ-hydroxy acid **6** with lithium aluminum hydride. Fragmentation of **6** was realized under arbitrary (and presumably nonideal) conditions. A methanol solution in a non-



compartmented cell was subjected to 40 volts applied to two immersed platinum electrodes. Short-path distillation of the neutral product yielded a volatile material (80% based on unrecovered acid), the infrared spectrum of which differed little from that of authentic[8] **4**. Comparison with the spectrum of authentic *cis*-5-cyclodecenone showed, by the absence of absorption at 14.2 μ, that an undetectable amount (less than 5%) of the *cis* isomer was present, a result consistent with stereospecificity of the fragmentation and subsequent nonisomerization of the double bond. Assay of **4** in the distillate was effected by capillary v.p.c. (55%) and semicarbazone formation (56%). Several attempts to separate pure **4** from the remaining unidentified multicomponent 45% by chromatography on alumina and silica gel were unsuccessful (lack of separation combined with decomposition on the columns) and were not pursued when the sequence **2** → **4** was developed.

(7) *Cf.* R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957).

(8) Authentic samples were generously supplied by Professor H. L. Goering.

(9) W. P. Campbell and C. G. Harris, *J. Am. Chem. Soc.*, **63**, 2721 (1941).

(10) E. J. Corey, *et al.*, *ibid.*, **81**, 1743 (1959); **82**, 2645 (1960).

(11) V. F. Kucherov, *et al.*, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 559 (1956); 367 (1958); 673 (1959); *Chem. Abstr.*, **51**, 1929 (1957); **52**, 12813 (1958); and **54**, 442 (1960).

Experimental[12]

The published[4a] procedure for the preparation of **2** was modified slightly as recorded herewith.

10-Hydroperoxy-Δ$^{1(9)}$-octalin (1).[4a]—A mixture of octalins[9] (100 g. of *ca.* 70% Δ^{9}) in 1000 ml. of isopropyl alcohol containing 5 g. of rose bengal was irradiated with a Hanovia Type L lamp, using a Vycor immersion well and Corex sleeve.[13] By using a diaphragm pump,[14] oxygen was bubbled rapidly through the system while maintaining a closed system, thus enabling gas consumption to be measured volumetrically.[15] The rate of uptake fell from an initial value of 166 to 26 ml. per minute after 2 hr. at which time 11.37 l. (60%) had been absorbed and the reaction was stopped.[16] The solvent was evaporated at room temperature, hexane and Filter Cel added to the residue, and the resulting suspension filtered. Concentration and cooling (−20°) of the red hexane solution yielded 24.2 g. (19%) of **1**, m.p. 55–59° (lit. m.p. 59–60°).

Δ$^{1(9)}$-10-Octalol (2).[4a] **A.**—To a solution of 59.2 g. of **1**, m.p. 49–60°, in 300 ml. of refluxing cyclohexene[17] was added dropwise 50 ml. of hydrazine hydrate. Heating was continued until gas evolution ceased. After cooling, the cyclohexene solution was washed well with water and then dried. Evaporation of solvent yielded 52.5 g. (98%) of crude **2**, m.p. 70–80° (lit.[4a] 87–88°), crystallization of which from ether at −20° gave 32.4 g., m.p. 84–85.5°, and further crops from the filtrate.

B.—A cyclohexene solution of evaporated mother liquors (*ca.* 210 g.) from crystallization of **1** was similarly reduced with hydrazine hydrate. After removal of the solvent the crude product was distilled at oil pump pressure and unchanged octalins (83 g., b.p. *ca.* 40°) separated from **2** (77 g., b.p. *ca.* 70°). The crude **2** solidified in the receiver, m.p. 41–75°, and could be purified by crystallization from ether or 2-methylbutane at −20°.

Hydroboration of Δ$^{1(9)}$-10-Octalol.—Diborane, generated by dropwise addition of a solution of 34.2 g. (0.90 mole) sodium borohydride in 650 ml. of diglyme to a mixture of 227 ml. (1.8 mole) of boron trifluoride etherate and 100 ml. of diglyme, was passed, with a stream of nitrogen, through a solution of 32.4 g. (0.213 mole) of **2**, m.p. 84–85.5°, in 100 ml. of tetrahydrofuran. Sodium hydroxide solution (56 ml. of 3 *N*) was then added dropwise with stirring followed by dropwise addition of 20.5 ml. of 30% hydrogen peroxide with cooling and stirring. After stirring overnight at room temperature, the water layer was saturated with potassium carbonate, separated, and extracted several times with tetrahydrofuran. The combined organic solutions were washed with saturated sodium chloride solution, treated with a small amount of 10% palladium on charcoal, and dried. Evaporation of solvent yielded a residue of 33.6 g. which was distilled, giving 24.7 g. (78%) of an oily mixture of 1,10-decalindiols (**3a**), b.p. 103° (0.2 mm.).

***trans*-5-Cyclodecenone (4).**—A solution of 0.989 g. (5.8 mmoles) of distilled **3a** and 1.438 g. (7.5 mmoles) of tosyl chloride in 10 ml. of dry pyridine was stirred at 0° for 9 hr. Water was added (a small amount followed by excess after 5 min.) and the mixture extracted with ether. The combined ether solutions were extracted with dilute acid, washed with salt solution, and dried. Evaporation of the solvent yielded 2.56 g. of crystalline residue (still containing some solvent), a portion of which, 1.87 g., was dissolved in 45 ml. of *t*-butyl alcohol. To this solution was added 12 ml. of 1 *N* potassium *t*-butoxide in *t*-butyl alcohol and the mixture maintained at 35° for 45 min. (a white precipitate formed immediately after mixing). Addition of water and extraction with ether gave, after further work-up, 0.650 g. of a yellow oil, 0.589 g. of which was subjected to short-path distillation; bath temperature, 45–65° (0.1 mm.); yield, 0.483 g. (82%);

(12) Melting points are uncorrected. Analytical data were recorded using a Perkin-Elmer Infracord spectrophotometer, Model 137, a Cary spectrophotometer, Model 11, and a Perkin-Elmer vapor phase fractometer, Model 154D, with flame ionization detection and disk integration.

(13) Engelhard Hanovia, Inc., Newark, N. J.

(14) Fisher Scientific Co., 1-092-10.

(15) The apparatus was basically the same as described by G. O. Schenck, K. G. Kinkel, and H. J. Mertens, *Ann.*, **584**, 125 (1953), without automatic leveling and recording.

(16) Δ^{9}-Octalin is reported to be oxygenated 25 times as fast as the Δ$^{1(9)}$-octalin, which is also present in the octalin mixture: G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).

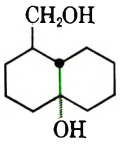
(17) Cyclohexene was used as solvent to prevent the reduction of **2** by any diimide formed; for references to diimide reductions see E. E. van Tamelen and R. J. Timmons, *J. Am. Chem. Soc.*, **84**, 1067 (1962).

$n^{24}D$ 1.4957 (lit.[18] for **4**, $n^{24}D$ 1.4982); λ_{max}^{neat} 5.88 and 10.2 μ; no indication of *cis* isomer at 14.2 μ. Capillary v.p.c. on a 150-ft. Ucon Polar column at 169° showed 97% of a single component with retention time the same as authentic[8] **4** (20.8 min.), and 3% of a minor component (21.2 min.).

10α-Hydroxy-*trans*-decalin-1β-carboxylic Acid (6).—To a solution of 2.00 g. (10.2 mmoles) of epoxide **5**,[11] m.p. 132.5–133.5°, in 50 ml. of ether was added 0.589 g. (15.5 mmoles) of lithium aluminum hydride. Work-up, after stirring for 3 hr. at room temperature, gave 1.42 g. (70%) of crude acid **6**, m.p. 119–125°, and 0.546 g. of neutral material. An analytical sample of **6** was obtained from the crude acid after four recrystallizations from chloroform, m.p. 133–134.5°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 66.67; H, 9.09. Found: C, 66.96; H, 9.39.

Crystallization on a larger scale presented a problem as no satisfactory solvent was found. A single stage, high-yield purification to material of m.p. 127–130° could be effected with ether as solvent but the melting point could not be raised by further crystallization.



7

The neutral fraction yielded analytically pure diol **7**, m.p. 114–115°, on crystallization from ether.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 71.92; H, 11.06.

Electrolysis of 6.—To a 300-ml. beaker fitted with a cold-finger spiral condenser and two platinum electrodes separated by 2–3 mm., each 5 cm.^{2}, was added a solution of 4.76 g. of crude[19] **6**, m.p. 119–125°, in 150 ml. of boiled methanol. A nitrogen atmosphere was maintained over the solution throughout the electrolysis. Sufficient sodium hydride was added to produce a current of *ca.* 0.5 amp. at constant applied voltage, 41 v. The current was stopped after the passage of 2.2 times the theoretical amount,[20] the methanol evaporated, and the residue worked up normally. Recovered crystalline **6** amounted to 0.37 g. (7%); the remainder was a neutral oil, 3.37 g. (92%, based on loss of carbon dioxide), which was subjected to short-path distillation. The yield of clear colorless liquid was 2.70 g. (80%); bath temperature, 85–110° (0.3 mm.); λ_{max}^{neat} 5.88 and 10.2 μ (no absorption at 14.2 μ). V.p.c. of the distilled product (168° on a 150-ft. capillary column with a Ucon Polar coating) showed the presence of the following components[21] (retention time in minutes, area): 1.8, 6%; 18.0, 7%; 22.3, 55%; 25.1, 7%; 39.5, 4%; 54.7, 4%. Treatment of 81 mg. of the distillate with a solution of 65 mg. of semicarbazide hydrochloride and 90 mg. of sodium acetate in 0.8 of ml. water, 20 min. at 70° and 48 hr. at room temperature, gave white crystals of the semicarbazone which were filtered from the solution and dried, 63 mg. (56%), m.p. 176–178°. Recrystallization from acetonitrile raised the m.p. to 182–183° (authentic[8] m.p. 183–184°, m.m.p. 182–183°); ultraviolet spectrum superimposable on that of authentic semicarbazone, $\lambda_{max}^{95\%\ EtOH}$ 232 mμ (ε 11,000).

(18) E. M. Kosower, W. D. Closson, H. L. Goering, and J. C. Gross, *J. Am. Chem. Soc.*, **83**, 2013 (1961).

(19) Similar results were obtained using purified **6** on a smaller scale.

(20) The approximate quantity of electricity required to give high conversion without overelectrolysing was determined in trial runs.

(21) Numerous minor peaks, each less than 3%, constituted the remaining 17%.

cis- and *trans*-1,2,3-Tricyanocyclopropanes

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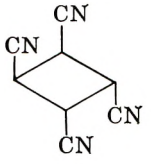
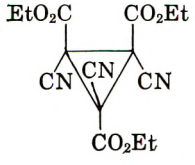
Received July 8, 1963

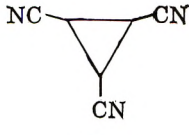
In 1958, Sadeh and Berger[1] reportedly obtained tetracyanocyclobutane (I) while attempting to synthesize ethyl cyanoacetoxyacetate from ethyl bromocyanoacetate and potassium acetate. The properties of their product were in no way similar to those of the solid state photodimer of fumaronitrile which we have shown has structure I.[2] However, it did not appear unreasonable that Sadeh and Berger's product might actually be the "all-*trans*" isomer of I in view of the possibility for thermodynamic equilibration under the reaction conditions. A structure proof was, therefore, undertaken.



I



II



IIIa, *cis*
b, *trans*

An initial literature survey revealed that, in 1900, Errera and Perciabosco[3] had obtained *trans*-1,2,3-tricyano-1,2,3-tricarbethoxycyclopropane (II)[4] on treating the anion of ethyl cyanoacetate with bromine. Subsequent hydrolysis of II with cold, dilute barium hydroxide afforded small amounts of a substance whose elemental analysis was consistent with that expected for a 1,2,3-tricyanocyclopropane (III). In view of the similarity of the reaction conditions and reagents employed by the two groups, it seemed reasonable that Sadeh and Berger's product, in reality, might be either *cis*- or *trans*-1,2,3-tricyanocyclopropane.

Preliminary investigations on a sample of Sadeh and Berger's nitrile[5] indicated that indeed it was a 1,2,3-tricyanocyclopropane and not a tetracyanocyclobutane. The infrared spectrum of the nitrile has a strong absorption band at 3063 cm.$^{-1}$ which may be attributed to the cyclopropyl C–H stretching[6] as well as a doublet at 2261 and 2278 cm.$^{-1}$ in the characteristic region for nitriles.[6] Hydrolysis with aqueous sodium hydroxide and subsequent esterification with diazomethane provided a material whose infrared and n.m.r. spectra are identical to those of an authentic sample of *trans*-1,2,3-tricarbomethoxycyclopropane.[7] The stereochemistry of the original nitrile, of course, cannot be inferred from these results.

It is noteworthy, that in our attempts to reproduce Sadeh and Berger's experiments, we obtained not one but two products (in a 1.2:1 ratio) which could be separated by chromatography on neutral alumina. Although infrared spectra of the two compounds possessed features in common, they were not identical. The major product (m.p. 201°) was identical in all respects with Sadeh and Berger's nitrile. The elemental analyses and ebullioscopic molecular weight determina-

(1) T. Sadeh and A. Berger, *Bull. Res. Council Israel*, **7A**, 98 (1958).

(2) G. W. Griffin, J. E. Basinski, and L. I. Peterson, *J. Am. Chem. Soc.*, **84**, 1012 (1962).

(3) G. Errera and F. Perciabosco, *Chem. Ber.*, **33**, 2976 (1900).

(4) The infrared and n.m.r. spectra of II confirm Errera and Perciabosco's structural assignment. The stereochemistry was clearly established as *trans* from the n.m.r. spectrum which shows two equivalent and one nonequivalent ethyl groups.

(5) We wish to thank Dr. T. Sadeh for samples of his nitrile (*cis*-1,2,3-tricyanocyclopropane) and *trans*-1,2,3-tricarbethoxy-1,2,3-tricyanocyclopropane for purposes of comparison.

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958.

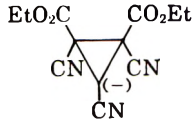
(7) Prepared according to the method of E. Buchner, *Chem. Ber.*, **21**, 2637 (1888).

tions for both nitriles are compatible with tricyanocyclopropane structures. The mass spectra of the two compounds exhibit a parent peak at *m/e* 117 as expected, and all of the major fragment peaks are easily interpreted assuming cyclopropyl structures.[8] The minor product (m.p. 191.5–192.5°) was shown to be the isomeric tricyanocyclopropane by basic hydrolysis and subsequent esterification to *trans*-1,2,3-tricarbomethoxycyclopropane. The n.m.r. spectrum of the minor product determined in acetonitrile exhibits resonance characteristic of an AB_2 multiplet, centered at τ 7.10. In contrast, the n.m.r. spectrum of Sadeh and Berger's compound (also determined in acetonitrile) shows only one peak at τ 7.28. The combined chemical and spectral data unequivocally identifies Sadeh and Berger's product as *cis*-1,2,3-tricyanocyclopropane (IIIa). The accompanying minor product must then possess the isomeric *trans*-1,2,3-tricyanocyclopropane structure IIIb.

A probable intermediate in the formation of the isomeric tricyanocyclopropanes from ethyl bromocyanoacetate is 1,2,3-tricarbethoxy-1,2,3-tricyanocyclopropane (II). Subsequent hydrolysis and decarboxylation would lead to the observed products. That this is indeed a plausible route was demonstrated by subjecting *trans*-1,2,3-tricarbethoxy-1,2,3-tricyanocyclopropane to the reaction conditions. The triester II smoothly underwent hydrolysis and decarboxylation in 95% ethanol solution containing potassium acetate. The products were exclusively *cis*- and *trans*-1,2,3-tricyanocyclopropane, formed in a 1.35:1 ratio, respectively.

The decarboxylation reaction is clearly kinetically controlled. Each of the isomeric trinitriles IIIa and IIIb was found to be stable under the reaction conditions; however, isomerization of *cis*-1,2,3-tricyanocyclopropane to the thermodynamically more stable *trans* isomer was achieved with potassium *t*-butoxide in *t*-butyl alcohol.

An attractive mechanism for the decarboxylation of II to afford predominately the *cis* nitrile IIIa involves the preferential attack of the proton donor from the less hindered side of the intermediate cyanoanion IV.[9]



IV

After initial loss of a molecule of carbon dioxide and subsequent acquisition of a proton, the side possessing the hydrogen atom becomes the less hindered side in the two ensuing decarboxylation steps.

This reaction offers a direct route to the *cis*-1,2,3-trisubstituted cyclopropane series.[10] The utility of 1,2,3-trisubstituted cyclopropanes as precursors for the unknown trimethylenecyclopropane is currently being investigated.

(8) We are indebted to Dr. T. Aczel and the Mass Spectral Group of the Research and Development Division of the Humble Oil and Refining Company, Baytown Texas, for the mass spectral data.

(9) A similar explanation was advanced to explain the predominant formation of the more sterically crowded isomer on decarboxylation of either of the two half esters of *cis*-2,5-dimethylcyclopentane dicarboxylic acid: see M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 358.

(10) Recently Ettlinger has reported the synthesis of the first member of this series, *cis*-1,2,3-tricarboxycyclopropane and its corresponding methyl ester: see M. G. Ettlinger and J. Kagen, *Chem. Ind.* (London), 1574 (1962).

Experimental

Preparation of the *cis* and *trans* 1,2,3,-Tricyanocyclopropanes (IIIa and IIIb).—These compounds were prepared by essentially the same procedure employed by Sadeh and Berger.[1] Ethyl bromocyanoacetate [10.0 g., 0.052 mole, b.p. 135° (40 mm.)], prepared according to the method of Errera and Perciabosco,[3] was added dropwise to a stirred solution of 5.5 g. (0.056 mole) of potassium acetate in 50 ml. of 95% ethanol. The reaction temperature was maintained at 20° during the course of the addition and the resulting deep red reaction mixture was stirred overnight. The solvent was then removed under vacuum, and the product was separated from potassium acetate by extraction with 30 ml. of cold acetonitrile. Subsequent removal of the solvent under reduced pressure gave a mixture of the isomeric tricyanocyclopropanes whose n.m.r. spectrum, determined in acetonitrile, showed a *cis* to *trans* ratio of 2.1:1. The crude mixture was separated by chromatography on neutral alumina. Since the tricyanocyclopropanes are insoluble in nonpolar solvents, the solid mixture was intimately ground with an equal volume of alumina and placed in a narrow band on top of the prepacked column. The solvents used for elution were benzene, ethyl acetate, and methanol in the order of increasing polarity. *trans*-1,2,3-Tricyanocyclopropane (IIIb) (280 mg., m.p. 191.5–192.5°) was eluted in a benzene–ethyl acetate fraction. The *cis* isomer IIIa (360 mg., m.p. 199–200°) was obtained from an ethyl acetate–methanol fraction. The total yield of the tricyanocyclopropanes was 32%. Both compounds were recrystallized from aqueous ethanol.

Anal. (IIIa). Calcd. for $C_6H_3N_3$: C, 61.53; H, 2.58; N, 35.89; mol. wt., 117. Found: C, 61.79; H, 2.45; N, 35.71; mol. wt., 121 (ebullioscopic with 2-butanone as the solvent).

Anal. (IIIb). Calcd. for $C_6H_3N_3$: C, 61.53; H, 2.58; N, 35.89; mol. wt., 117. Found: C, 61.72; H, 2.56; N, 36.13; mol. wt., 120 (ebullioscopic with 2-butanone as the solvent).

Preparation of the *cis*- and *trans*-1,2,3-Tricyanocyclopropanes (IIIa and IIIb) from *trans*-1,2,3-Tricyano-1,2,3-tricarbethoxycyclopropane (II).—*trans*-1,2,3-Tricyano-1,2,3-tricarbethoxycyclopropane (6.1 g., 0.018 mole, m.p. 123–124°), prepared according to the method of Sadeh and Berger,[1] was dissolved with stirring in a solution of 2.65 g. (0.028 mole) of potassium acetate in 200 ml. of 95% ethanol. Stirring was continued overnight at 20°. After removal of all volatile solvents, the product was extracted from the residual potassium acetate with 30 ml. of cold acetonitrile. Evaporation of the acetonitrile gave 2.1 g. (99%) of a mixture of *cis*- and *trans*-1,2,3-tricyanocyclopropanes in a 1.35:1 ratio, respectively. The ratio was again determined from the n.m.r. spectrum of the mixture. The infrared spectrum of the crude reaction mixture showed absorption due only to the two isomeric trinitriles IIIa and IIIb. The pure compounds where isolated by alumina chromatography as in the preceding case.

Conversion of the Isomeric Tricyanocyclopropanes (IIIa and IIIb) to *trans*-1,2,3-Tricarbomethoxycyclopropane.—*cis*-1,2,3-Tricyanocyclopropane (IIIa) (0.075 g. 0.64 mmole, m.p. 199–200°) was added to a solution of 0.30 g. (7.5 mmoles) of sodium hydroxide in 25 ml. of water. The reaction mixture was heated under reflux overnight and subsequently acidified with hydrochloric acid. The volatile solvents were removed under vacuum and the resulting solid was esterified with diazomethane in benzene. After removal of the benzene under vacuum, the desired product was extracted from the residual sodium chloride with carbon tetrachloride. The n.m.r. and infrared spectra of the reaction product in carbon tetrachloride were identical in all respects with those for an authentic sample of *trans*-1,2,3-tricarbomethoxycyclopropane.[7] The melting point of the triester after recrystallization from aqueous methanol was 56–57° (lit.[7] m.p. 61°).

Similarly, the *trans* isomer IIIb (m.p. 191.5–192.5°) also was converted to *trans*-1,2,3-tricarbomethoxycyclopropane.

Acknowledgment.—We are indebted to the Army Research Office (Durham) for financial support of this work.

1,5-Dimethyl-2-oxo-3-pyrrolidineglyoxylic Acid

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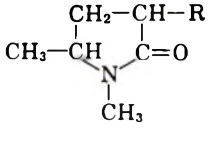
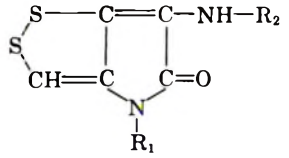
Received March 8, 1963

Our general interest in substituted 2-pyrrolidones (I) stemmed from earlier studies on their derivation (*i.e.*, Ia) from the antibiotic Thiolutin (IIa)[1,2] and by synthesis.[3,4] The ability of the pyrrolidine ring to accommodate multiple exocyclic double bonds was investigated further through the preparation of 1,5-dimethyl-2-oxo-3-pyrrolidineglyoxylic acid (Id) and several of its derivatives. Although enol character (positive ferric chloride test) had been previously noted[5] for ethyl 2-oxo-3-pyrrolidineglyoxylate, it remained to be seen whether enol quality carried over to N-substituted variants, such as Id. Discussion of this study, together with pertinent experimental details, are presented in this Note.



I

R
(a) —NH—$COCH_3$
(b) —H
(c) —$COCO_2CH_2CH_3$
(d) —$COCO_2H$
(e) —$COCO_2CH_3$



II

R_1	R_2
(a) CH_3—	—$COCH_3$
(b) CH_3—	—$COCH_2CH_3$
(c) CH_3—	—$COCH(CH_3)_2$
(d) H—	—$COCH_3$

Reductive methylamination of levulinic acid in methanol solution with palladium-on-charcoal catalyst afforded crystalline 4-N-methylaminovaleric acid,[6] m.p. 160–161°, which when fused gave known[7,8] liquid 1,5-dimethyl-2-pyrrolidone (Ib); λ_{max}^{film} 5.94 μ. Reaction of Ib with diethyl oxalate and ethanolic sodium ethoxide furnished crude ethyl 1,5-dimethyl-2-oxo-pyrrolidineglyoxylate (Ic) (λ_{max}^{film} 5.88, 6.02 μ, positive ferric chloride test) which was converted without purification[9] to crystalline 1,5-dimethyl-2-oxo-pyrrolidineglyoxylic acid (Id), m.p. 139.5–140.5°. Methanol–sulfuric acid treatment of the free acid afforded its crystalline methyl ester Ie, m.p. 58–59°, which after reaction with acetic anhydride–sulfuric acid gave crystalline methyl ester enol-acetate IIIa, m.p. 92–93°. Pertinent infrared data on IIIa and its precursors are listed and assigned in Table I. Although only enolic forms are evident in all cases, a small amount of the ketonic form could have escaped detection in each of the possible systems: IIIb ⇋ Ie and IIIc ⇋ Id.[10]

Experimental[11]

4-N-Methylaminovaleric Acid[6,12].—To a stirred, chilled (5°) suspension of 5 g. of 5% palladium-on-charcoal in 100 ml. of a 1.67 *M* ethanolic levulinic acid solution was added dropwise 100 ml. of 4.2 *M* ethanolic methylamine solution. Hydrogenation was then conducted in a stainless steel bomb (480-ml. capacity) at 1200 p.s.i. at 66° for 2 hr. After cooling and removing the catalyst by filtration, the solution was evaporated to dryness. Trituration of the residue with ether afforded 14 g. (64%) of crystalline product, m.p. 154–156° (the analytical sample, from ethanol–ether, melted at 160–161°).

Anal. Calcd. for $C_6H_{13}NO_2$ (131.17): C, 54.94; H, 9.99; N, 10.68. Found: C, 54.93; N, 10.03; N, 10.23.

1,5-Dimethyl-2-pyrrolidone (Ib).[7]—Heat was gradually applied to a distilling flask containing 25 g. (0.19 mole) of the amino acid until the contents melted (160°) and evolution of water vapor was complete (1 hr.). The resulting product was then distilled [b.p. 94–95° (17.5–18 mm.)] to afford 18.1 g. (84.5%) of a liquid, $n^{25}D$ 1.4638. Redistillation, after drying over magnesium sulfate, gave 14.5 g. (67.6%) of a colorless liquid, b.p. 95° (18 mm.); $n^{25}D$ 1.4644 [lit. $n^{25}D$ 1.4611; b.p. 84–86° (13 mm.); b.p. 102–104° (27 mm.)[7]; b.p. 215–217° (743 mm.)[8]].

Anal. Calcd. for $C_6H_{11}NO$ (113.16): C, 63.68; H, 9.80. Found: C, 63.39; H, 9.93.

1,5-Dimethyl-2-oxo-3-pyrrolidineglyoxylic Acid.—To a solution of sodium ethoxide (2.02 g. of sodium in 40 ml. of ethanol) was added a mixture of 10 g. (0.0885 mole) of Ib and 13.2 g. (0.0904 mole) of diethyl oxalate. The reaction was kept at 60° (60 mm.) until the distillation of ethanol was virtually complete (3 hr.). The residue was treated with 25 ml. of water, and the resulting alkaline solution was kept at 25°. After 30 min., the solution was acidified with 15 ml. of 6 *N* hydrochloric acid which afforded 7.5 g. of crude acid. The recrystallized sample, from carbon tetrachloride, weighed 3.8 g. (23%) and melted at 139.5–140.5°.

Anal. Calcd. for $C_8H_{11}NO_4$ (185.18): C, 51.88; H, 5.99; N, 7.57. Found: C, 51.78; H, 5.92; N, 7.43.

Methyl 1,5-Dimethyl-2-oxo-3-pyrrolidineglyoxylate.—To a methanolic solution of 1.85 g. (0.01 mole) of 1,5-dimethyl-2-oxo-3-pyrrolidineglyoxylic acid was added 0.04 ml. of concentrated sulfuric acid. After 16 hr. at 25°, the methanol was removed by vacuum distillation. A solution of most of the residue in 20 ml. of ether was decanted from remaining insoluble sulfuric acid and was neutralized further with sodium bicarbonate. Vacuum distillation of the ether afforded 1.61 g. (80%) of crystalline resi-

(1) W. D. Celmer, F. W. Tanner, Jr., M. Harfenist, T. M. Lees, and I. A. Solomons, *J. Am. Chem. Soc.*, **74**, 6304 (1952).

(2) W. D. Celmer and I. A. Solomons, *ibid.*, **77**, 2861 (1955).

(3) Related antibiotics include aureothricin (IIb), *cf.* ref. 2; isobutyropyrrothine (IIc), *cf.* W. D. Celmer and I. A. Solomons, *Antibiot. Ann.*, 622, (1953–1954), and also D. S. Bhate, R. K. Hulyalkar, and S. K. Menon *Experientia*, **16**, 504 (1960); holomycin (IId), *cf.* L. Ettlinger, E. Gäumann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, and H. Zähner, *Helv. Chim Acta*, **42**, 563 (1959). Total synthesis of the II-type antibiotics has been accomplished by two independent routes: U. Schmidt and F. Geiger, *Angew. Chem. Intern. Ed. Engl.*, **1**, 265 (1962); G. Buchi and G. Lukas, *J. Am. Chem. Soc.*, **85**, 647 (1963).

(4) For a recent report on 4-substituted-2-pyrrolidones, see F. C. Uhle, *J. Org. Chem.*, **27**, 4081 (1962).

(5) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1523 (1937).

(6) This compound (IV) also served as starting material for an alternate synthesis of the previously described (ref. 2) 2-amino-4-N-methylaminovaleric acid (V); W. D. Celmer and I. A. Solomons, unpublished experiments. The following reaction sequence (standard procedures) was employed: IV → N-benzoylation → esterification (Et) → ethoxylation → decarbonylation → nitrosation → reductive acetylation → hydrolysis → V. This route was less satisfactory than the scheme reported previously which involved initial preparation of Ia followed by hydrochloric acid hydrolysis.

(7) For a direct synthesis of Ib from levulinic acid employing aqueous methylamine and Raney nickel-catalyzed hydrogenation see R. L. Frank, W. R. Schmitz, and B. Zeidman, *Org. Syn.*, **27**, 28 (1947).

(8) L. Senfter and J. Tafel, *Chem. Ber.*, **27**, 2313 (1894).

(9) Most of the yield loss occurred over the ethoxylation step; no advantage was gained by isolating the intermediate product Ic. For the preparation of the related ethyl 1-methyl-2-oxo-3-pyrrolidineglyoxylate (24%) and its hydrolysis to the free acid (85%), see L. W. Masch and R. Peterson, *Arzneimittel-Forsch.*, **9**, 715 (1959).

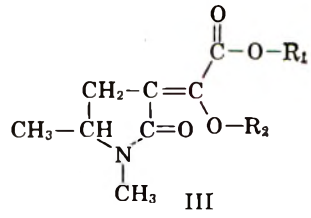
(10) It is assumed that the same principle applies to the ethyl ester Ic which was not extensively studied (*cf.* ref 9).

(11) Melting points are reported as determined on a Kofler hot stage.

(12) Free 4-N-methylaminovaleric acid (zwitterionic form) is recovered despite exposure to excess methylamine (presumably because of greater basicity of the secondary amine); hence portrayal of the methylamine salt of 4-N-methylaminovaleric acid is incorrect (*cf.* ref. 7).

TABLE I

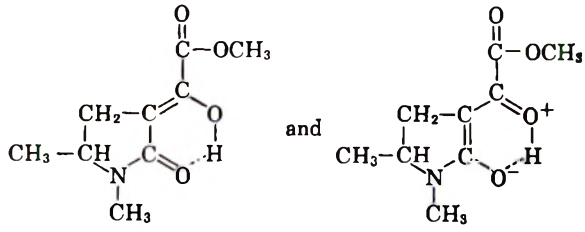
INFRARED SPECTRA AT 2–6 μ[a]



III

Compound	R_1	R_2		λ_{max} (c 2.5, chloroform) μ	(cm.$^{-1}$)	Assignments[b]	Ref.
IIIa	CH_3—	—$COCH_3$	Shoulder	6.00–6.03	(1667–1665)	>C=C<	
				5.93	(1686)	Lactam C=O	
			Sharp	5.78	(1730)	Conjugated ester C=O	
			Sharp	5.65	(1770)	Enol acetate C=O	
				3.41	(2933)	C–H	
IIIb	CH_3—	—H	Shoulder	6.04–6.07	(1656–1647)	>C=C<	*c*
				6.01	(1664)	H-bonded lactam	*d*
			Sharp	5.79	(1727)	Conjugated ester C=O	*e*
				3.43	(2924)	C–H	
			Diffuse	2.8–3.2	(3571–3125)	Bonded OH	*f*
IIIc	H—	—H		5.98	(1672)	Lactam C=O	*g*
			Sharp	5.87	(1704)	Monomeric, conjugated carboxyl C=O	*h, i, j*
			Doublet	3.42, 3.48	(2924, 2874)	Unmasked C–H	*h*
			Very sharp	3.00	(3333)	Unbonded OH	*h, f*

[a] A Baird double beam spectrometer, Model AB, was employed. [b] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958. [c] A similar occurrence of shoulder absorption on the long wave-length side of the lactam C=O λ_{max} in IIIa (containing unequivocal C=C) is consistent with this ethylenic assignment. [d] This lactam C=O λ_{max} occurs at a substantially longer wave length than that exhibited by lactam in IIIa. Factors such as H-bonding or conjugation are well known to shift carbonyl absorption in a bathochromic manner (*i.e.*, to lower frequency). "Ordinary" H-bondings result in slight downward shifts (less than 10 cm.$^{-1}$) whereas resonance stabilized H-bondings, associated with so-called "conjugate chelate" systems, give rise to substantially lower C=O frequencies (60- to 90-cm.$^{-1}$ shifts for affected esters); *cf.* I. M. Hunsberger, R. Ketcham, and H. S. Gutowsky, *J. Am. Chem. Soc.*, **74**, 4839 (1952); L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4487 (1954). A $\Delta\nu$ (C=O, lactam) value of 23 cm.$^{-1}$ (expression of Hunsberger, *et al.*) is observed here which, although lower than the standard $\Delta\nu$ (C=O, ester) range of values, may be typical of conjugate chelate lactam systems for which a norm is yet to be established. Resonance stabilization of IIIb would presumably occur between the forms



We are indebted to a referee for calling our attention to lack of precedent for this type of conjugate chelate. [e] The striking similarity of this λ_{max} to its counterpart in IIIa, both in position and quality (band width at half maximum intensity), supports formulation IIIb; absorption at a lower wave length expected of form Ie is not detected; *cf.* methyl pyruvate λ_{max} 5.72 μ, ref. *b*. [f] This diffuse absorption (significantly also observed in ester film spectra) is consistent with resonance-stabilized formulations; *cf.* ref. *d;* ref. *b*, p. 96. [g] Sparsity of appropriate reference compounds makes any estimate of possible $\Delta\nu$ (C=O, lactam) here extremely tenuous; *cf.* ref. *d* and p. 214 in ref. *b*. [h] The sharp hydroxyl and unmasked C—H absorption define this acid as monomeric. The observed carboxyl C=O λ_{max} is definitely in the conjugated region; hence, formulation IIIc is preferred. Monomeric, unconjugated form Id would be expected to manifest carboxyl C=O λ_{max} near 5.60 μ where, in fact, no absorption is observed; *cf.* M. L. Josien, M. Jousset-Dubien, and J. Vizet, *Bull. soc. chim. France*, **5**, 1148 (1957). [i] Comments on the infrared spectrum of pyruvic acid by Bellamy (*cf.* p. 141 in ref. *b*) called to our attention by a referee are misleading since the data cited, single λ_{max} 5.73 μ, obviously refer to the dimeric form (commonly observed in film spectra). A number of α-keto acids in addition to pyruvic acid can be measured as their monomeric form in carbon tetrachloride or chloroform solution; *cf.* Josien, *et al.*, ref. *h*. We and others (P. A. Leermakers, personal communication) have noted three carbonyl bands exhibited by phenylglyoxylic acid in chloroform solution which are attributed to the presence of both monomeric and dimeric forms. [j] Monomeric enolic qualities (*cf.* ref. *h* and *i*) persist in the solid state judging from an infrared spectrum obtained, on a crystalline suspension in Nujol; λ_{max} at 3.00, 5.90, 6.00 μ.

due, m.p. 52–55°. The analytical sample from hexane melted at 58–59°.

Anal. Calcd. for $C_9H_{13}NO_4$ (199.20): C, 54.26; H, 6.58. Found: C, 54.28; H, 6.54.

Methyl α-Acetoxy-1,5-dimethyl-2-oxo-$\Delta^{3,\alpha}$-pyrrolidineacetate.—To a solution of 600 mg. (0.03 mole) of the methyl ester in 15 ml. of acetic anhydride was added 0.01 ml. of concentrated sulfuric acid. After 16 hr. at 25° the solution was vacuum distilled. The residue was triturated with 10 ml. of ether and the decanted solution was evaporated to give 542 mg. (75%) of crystalline residue, m.p. 92–93°.

Anal. Calcd. for $C_{11}H_{15}NO_5$ (241.24): C, 54.76; H, 6.27. Found: C, 54.63; H, 6.39.

Acknowledgment.—The authors are indebted to Dr. J. A. Means and Mr. T. J. Toolan for microanalyses, and to Mr. G. D. Hess (deceased) for infrared spectral determinations.

Synthesis and Characterization of Some Toluides of o-Phthalic Acid

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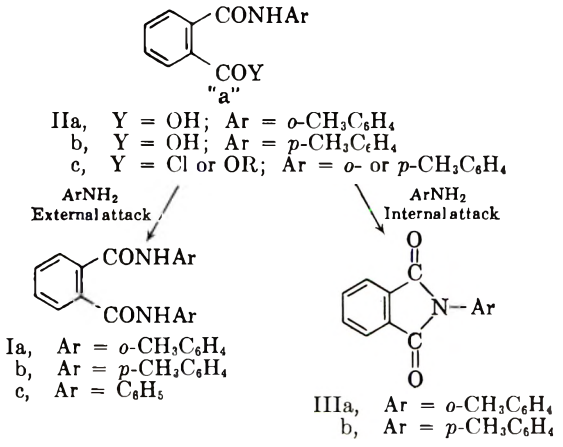
Received May 6, 1963

For some time *o*- and *p*-toluides have served as useful derivatives of carboxylic acids, and routine methods for the preparation of these compounds have been developed.[1] Many dicarboxylic acids have been converted to ditoluides[2] even though yields have often been low due to incomplete reaction and consequent contamination by monotoluides and/or concurrent reaction to yield imides. Indeed, in at least one case, that of *o*-phthalic acid, attempts to prepare ditoluides[2d,3] have resulted only in formation of the corresponding imides.

Usual methods for the preparation of ditoluides involve the attack of the appropriate toluidine on either the diacid[2b,3a] or a derivative of the diacid such as a diacyl chloride,[2a,3b] a diester,[2c] or a diazide.[2e] The failure of these methods to yield any of the di-*o*- and di-*p*-toluides of *o*-phthalic acid (Ia and Ib) can be rationalized on the basis of the assumption that the monotoluide II is an intermediate product in all such reactions. Ditoluide formation would require external attack by the appropriate toluidine on carbon "a" of II. However, if the amide nitrogen of II were sufficiently nucleophilic, the N-substituted phthalimide III would be formed by internal attack. The toluidine present would serve as a useful basic catalyst. Tingle and Rolker[4] have shown that only internal attack occurs when the monotoluide–monoacids, IIa and IIb, are allowed to react with the toluidines; *i.e.*, the products produced, in nearly quantitative yields, are the imides, IIIa and b. Since the intermediate monotoluide resulting from use of *o*-phthalic acid derivatives (IIc) would possess a more electrophilic carbon "a" than IIa or b, attack on IIc by any nucleophile should be more facile than the analogous attack on IIa or IIb; hence, the imide, III, should form more easily when IIc is the intermediate, but I would not be an expected product.



Success of syntheses for Ia and Ib appears to be dependent upon using a system in which external attack is heavily favored over internal attack. This prerequisite can be met if the external attacking agent is highly nucleophilic, thus rendering internal attack on carbon "a" of II by the less nucleophilic amide nitrogen ineffectual as a competing reaction. That intermediate nucleophilicity in the external attacking reagent is insufficient to result in ditoluide formation has already been demonstrated. Bodroux,[2d] using Grignard type reagents of the toluidines, $CH_3C_6H_4NHMgI$,[5] and diethyl oxalate, obtained good yields of the ditoluides of oxalic acid. Analogous reactions with diethyl phthalate failed to yield any of Ia or Ib.

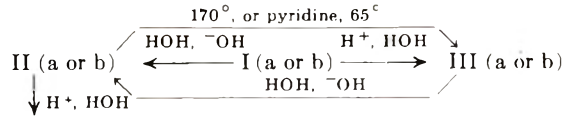
We though it probable that the sodium salts of *o*- and *p*-toluidine would be sufficiently strong nucleophiles to exclude internal attack and allow formation of Ia and Ib. Apparently, sodium salts of amines have been little used although Hjelt[6] prepared the dianilide of succinic acid by heating a mixture of aniline, sodium, and diethyl succinate, a process which presumably involved the sodium salt of aniline. The application of a modification of Hjelt's synthesis to the present problem was successful. The sodium salts of the toluidines were prepared from sodium metal and the amines; reaction of the sodium toluides with diethyl phthalate resulted directly in high yields of Ia and Ib.

Syntheses of Ia and Ib were also carried out by using sodium ethoxide rather than sodium to obtain the intermediate sodium toluides. Undoubtedly the equilibrium in this reaction lies far to the left. However, consumption of the sodium toluide by diethyl phthalate renders the reaction feasible. This situation is a familiar one; it is reminiscent, *e.g.*, of the production and consumption of anions in the Claisen condensation.[7]

$$ArNH_2 + NaOC_2H_5 \rightleftharpoons ArNHNa + C_2H_5OH$$

It seemed desirable to demonstrate that these synthetic methods could be used to produce a known N,N′-diarylamide of *o*-phthalic acid. The dianilide IIc is one of few known compounds of this type.[8] The product obtained using the present methods was shown to be identical with that produced by earlier methods.[1,8a]

Relationships among Ia and Ib, IIa and IIb, and IIIa and IIIb were investigated in order to provide structure proof for the ditoluides. Reactions carried out may be briefly summarized.



o-Phthalic acid

(1) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 198, 200.

(2) (a) C. R. Barnicoat, *J. Chem. Soc.*, 2926 (1927); (b) P. F. Frankland and A. Slator, *ibid.*, **33**, 1349 (1903); (c) A. Reissert and A. More, *Ber.*, **39**, 3301 (1906); (d) M. F. Bodroux, *Compt. rend.*, **142**, 401 (1906); (e) T. Curtius, *J. prakt. Chem.*, [2] **91**, 10 (1915).

(3) (a) E. Froehlich, *Ber.*, **17**, 2679 (1884); (b) M. Kuhara, *Am. Chem. J.*, **9**, 52 (1887); M. Kuhara and S. Komatsu, *Chem. Zentr. I*, 1509 (1911).

(4) J. R. Tingle and H. F. Rolker, *J. Am. Chem. Soc.*, **30**, 1882 (1908).

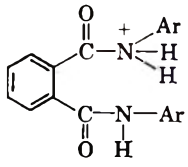
(5) In view of recent work concerning the structure of Grignard reagents [E. C. Ashby and W. E. Becker, *ibid.*, **85**, 118 (1963)] this structure may require modification.

(6) E. Hjelt, "Jahresbericht über die Fortschritte der Chemie," F. Vieweg and Son, Braunschweig, Germany, 1887, p. 1536.

(7) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 334, and references therein.

(8) (a) M. Rogow, *Ber.*, **30**, 1442 (1897); (b) F. L. Dunlap and F. W. Cummers, *J. Am. Chem. Soc.*, **25**, 612 (1903).

Base-catalyzed hydrolysis of Ia or Ib with 20% aqueous sodium hydroxide at reflux resulted in formation of the known compounds,[4] IIa or IIb, as expected; the monotoluide–monoacids were obtained first as sodium salts which were stable under the reaction conditions. Hydrolysis of Ia or Ib in the presence of 5 *N* hydrochloric acid yielded the corresponding known imides,[4] IIIa and IIIb. Formation of the imides under the conditions used probably involved the protonated amides IV.[9] These reactions are being further investigated. We have confirmed the earlier work[4] concerning the interconversions of IIa and IIb and IIIa and IIIb and have established that *o*-phthalic acid is the product of acid-catalyzed hydrolysis of IIa or IIb.



IV

Solid state infrared spectra of Ia, Ib, Ic, and IIa have been examined. Certain absorption peaks important to structure determination are given in Table I; all peaks occur in expected regions.[10]

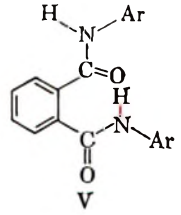
TABLE I

ABSORPTION MAXIMA (cm.$^{-1}$)

Assignment	Ia	Ib	Ic	IIa
Bonded NH	3210 (vs)	3200 (vs)	3190 (vs)	3240 (s)
	3190 (m)	3240 (vs)	3200 (vs)	
			3240 (vs)	
Carboxyl CO				1670 (vs)
Amide I CO	1635 (vs)[a]	1635 (vs)[a]	1635 (vs)[a]	1626 (vs)
CH out-of-plane deformation	739–750 (vs)[b]	739 (m)	752 (vs)	739 (vs)
		815 (vs)	760 (vs)	

[a] Wave number given is that of sharp, strong peak; shoulders also occur in this region. [b] At least two peaks occur in this area, one at 750 and one at 745 cm.$^{-1}$; the latter is broad and is probably a doublet.

The presence of more than one bonded NH band, as well as the suggestion of multiplicity in the carbonyl region, in the spectra of Ia, Ib, and Ic may be attributed to the existence of rotational isomers.[10] Since IIa shows NH absorption at 3240 cm.$^{-1}$ which is almost certainly due to chelation, and since this band is missing in the spectrum of Ia but present in the spectra of Ib and Ic, the *trans–trans*-rotational isomer, V, may



V

quite possibly be an important conformer for Ib and Ic. That chelation is important in Ib is also indicated by its melting point which is *ca.* 27° lower than that of Ia.

(9) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 205.

Further evidence for the structure of Ia was obtained by integration of its n.m.r. spectrum. Six methyl hydrogen atoms accounted for a sharp peak at 2.25 δ. Twelve aromatic hydrogen atoms gave rise to multiple peaks centered at 7.10 and 7.65 δ; the former aromatic multiplet had an area corresponding to eight hydrogen atoms, the latter an area corresponding to four hydrogen atoms. Two exchangeable hydrogen atoms attached to nitrogen resulted in a peak at 8.22 δ. Exchangeability of these hydrogen atoms was shown by running spectra in both deuteriochloroform and deuterium oxide.

Experimental[11]

Materials.—Aniline, *o*-toluidine, *p*-toluidine, and diethyl phthalate were obtained from Eastman Kodak Company and purified by standard methods. The amines were repurified immediately prior to use.

Di-*o*-toluide of *o*-Phthalic Acid (Ia). Method A.—*o*-Toluidine (32.1 g., 0.3 mole) was heated with sodium (4.60 g., 0.2 g.-atom) at 150° in an atmosphere of nitrogen for 1 hr. To the cooled reaction mixture were added absolute ethanol (10 ml.) and diethyl phthalate (22.2 g., 0.1 mole). The mixture was stirred at 75° for 1 hr. and filtered while hot. Cooling to room temperature resulted in deposition of a white crystalline solid which was recrystallized from ethanol to yield 25.0 g. (73%) of Ia, m.p., 209.0–209.5°.

Method B.—*o*-Toluidine (2.68 g., 0.020 mole) was added dropwise to a stirred solution of sodium ethoxide (0.46 g., 0.020 g.-atom of sodium in 10 ml. of absolute ethanol) protected from atmospheric moisture; over a period of 5 min. the temperature was raised sufficiently to bring about reflux. Diethyl phthalate (2.22 g., 0.01 mole) was added in one portion after the mixture had refluxed for 10 min. Heating and stirring were continued for 30 hr. after which the reaction mixture was filtered while hot and concentrated on a rotary evaporator to approximately half volume. Cooling resulted in deposition of Ia which, when recrystallized from ethanol, melted at 209.0–209.5° and weighed 2.7 g. (78%).

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81; N, 8.14. Found: C, 76.72; H, 5.59; N, 8.14.

Di-*p*-toluide of *o*-Phthalic Acid (Ib).—Methods used for the preparation of Ib were completely analogous to those described for Ia. Reaction mixtures were treated with water after hot filtration and cooling in order to facilitate precipitation of Ib. Recrystallization from benzene yielded colorless needles, m.p. 181–182° (55% yield *via* method A, 65% *via* method B).

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81; N, 8.14. Found: C, 76.70; H, 5.76; N, 7.99.

Dianilide of *o*-Phthalic Acid (Ic).—Application of method A or method B to the synthesis of Ic yielded a white crystalline solid which, after recrystallization from ethanol, melted at 230–231° (lit.[8a] 231–232°). Yields ranged from 60–70%. Ic produced in this manner was shown by undepressed mixture melting point and identical infrared spectrum to be identical with Ic resulting from earlier methods of synthesis.[1,8a]

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86. Found: C, 75.91; H, 5.00; N, 8.97.

Monotoluides of *o*-Phthalic Acid (IIa and IIb). Base-Catalyzed Hydrolysis of Ia and Ib.—Treatment of either Ia or Ib (3.44 g., 0.01 mole) with 20% aqueous sodium hydroxide at reflux for 3 hr. followed by acidification with 8 *N* hydrochloric acid resulted in formation of IIa or IIb. Both monotoluide–monoacids were recrystallized from ethanol to yield, in each case, 2.2 g. (86%) of purified material. IIa melted at 168.5–169.5° (lit.[4] 166–167°) and had a neutralization equivalent of 255 ± 2 (calcd. 255); IIb melted at 160.0–160.5° (lit.[4] 160°).

(11) Melting points were taken on a Büchi melting point apparatus calibrated against standard substances. Infrared spectra were determined in potassium bromide pellets (1–2 mg. of sample/400 mg. of KBr) on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance spectra were determined by Varian Applications Laboratory, Palo Alto, Calif., using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Elemental analyses were performed by Clark Microanalytical Laboratories, Urbana, Ill., or by the authors.

When heated above their melting points or with pyridine at 65°, both IIa and IIb were converted to the corresponding imides, as previously reported.[4]

N-Tolyl Phthalimides (IIIa and IIIb). Acid-Catalyzed Hydrolysis of Ia and Ib.—Hydrolysis of either Ia or Ib (3.44 g., 0.01 mole) with 5 *N* hydrochloric acid (10 ml., 0.05 mole) at reflux for 3 hr. resulted in high yields (2.0 g., 84%, from Ia; 1.9 g., 80%, from Ib) of the corresponding phthalimides, IIIa and IIIb. IIIa had a melting point of 182.5–183.0° (lit.[3] 182°), undepressed by admixture with an authentic sample prepared by a usual method[3a]; IIIb melted at 201–202° (lit.[4] 201–202°).

As previously reported,[4] IIIa and IIIb were converted to IIa and IIb, respectively, when heated on a steam cone for 1 hr. with 10% sodium hydroxide.

Acid-Catalyzed Hydrolysis of IIa and IIb.—Hydrolysis of IIa or IIb (2.55 g., 0.01 mole) with excess 5 *N* hydrochloric acid on a steam bath for 15 min. resulted in formation of *o*-phthalic acid (1.4 g., 84% in both cases). The product was identified by its infrared spectrum which was identical with that of an authentic sample.

Acknowledgment.—The authors wish to thank the Research Corporation for financial support of this work.

F^{19} Nuclear Magnetic Resonance Spectra of Some Benzotrifluorides

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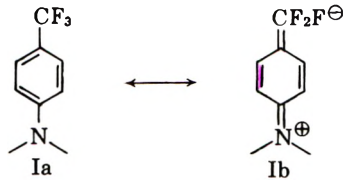
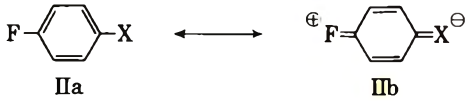
Received March 21, 1963

The electronic effect of the trifluoromethyl group attached to an aromatic ring and the dipole moment of *p*-dimethylaminobenzotrifluoride have been discussed in terms of resonance forms Ia,b.[1] If forms such as



Ia Ib

Ib are important, this effect might be reflected in the F^{19} n.m.r. spectrum. Taft, *et al.*,[2] have interpreted the F^{19} chemical shifts in various substituted fluorobenzenes as evidence for contributing forms IIa,b.



IIa IIb

To see if n.m.r. spectroscopy could be used to detect interactions exemplified by form Ib (negative hyperconjugation), we examined the benzotrifluorides collected in Table I.

Table I shows clearly that n.m.r. spectroscopy does distinguish between the *p*-aminobenzotrifluorides and all other compounds listed. In the same solvent there is little change in the spectra until the *p*-aminobenzotrifluorides are encountered. In methanol, for example,

(1) J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Am. Chem. Soc.*, **72**, 408 (1950).

(2) R. W. Taft, Jr., R. E. Glick, I. C. Lewis, I. Fox, and S. Ehrenson, *ibid.*, **82**, 756 (1960).

TABLE I

F^{19} N.M.R. SPECTRA OF BENZOTRIFLUORIDES

	Cyclohexane[a] ϕ^{*b}	Methanol[a] ϕ^{*b}
Benzotrifluoride	64.1	62.7
m-Nitrobenzotrifluoride	64.2	63.1
p-Nitrobenzotrifluoride	64.5	63.2
m-Aminobenzotrifluoride	63.9	62.9
m-Dimethylaminobenzotrifluoride	63.7	62.6
p-Aminobenzotrifluoride	62.2	61.2
p-Dimethylaminobenzotrifluoride	62.0	60.8

[a] Approximately 5% solutions by volume. [b] B. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

the ϕ^* values of *p*-nitrobenzotrifluoride and *m*-dimethylaminobenzotrifluoride differ by only 0.6 unit, whereas those of *m*-dimethylaminobenzotrifluoride and *p*-aminobenzotrifluoride differ by 1.4 units. The difference between *m*-dimethylaminobenzotrifluoride and *p*-dimethylaminobenzotrifluoride is even greater (1.8 units). A similar trend is shown by the values obtained in cyclohexane.

Resonance exemplified by Ia,b, which has been invoked to account for the high dipole moment of *p*-dimethylaminobenzotrifluoride,[1] also may be responsible for the unusual F^{19} n.m.r. spectra displayed by *p*-amino and *p*-dimethylaminobenzotrifluoride. Interestingly, Gutowsky, *et al.*,[3] who have compared the F^{19} n.m.r. spectra of several substituted benzotrifluorides and fluorobenzenes, observed that substituents affect the aromatic fluorine and trifluoromethyl fluorine resonances in an opposite manner.

Experimental

The *para* substituted benzotrifluorides in Table I and *m*-dimethylaminobenzotrifluoride were prepared according to directions given in ref. 1. The remaining compounds were purchased from Columbia Organic Chemicals Company, Columbia, South Carolina, or from Aldrich Chemical Company, Milwaukee, Wisconsin. N.m.r. spectra were obtained with a Varian Associates, Model V-3000-B, high resolution spectrometer using a 40-Mc. probe at 28°. Samples were measured with trichlorofluoromethane as internal standard by counting sideband frequencies. The CF_3 peaks were sharp and symmetrical in all cases.

Acknowledgment.—This research was carried out under Army Ordnance Contract Da-01-021 ORD-11878. We are grateful to Mr. Kirt Keller for technical assistance and to Mrs. Carolyn Haney for n.m.r. spectra.

(3) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *ibid.*, **74**, 4809 (1952).

Proton Nuclear Magnetic Resonance Analysis of Some Acylmetallocenes

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Received May 10, 1963

A gradual deshielding of the cyclopentadienyl ring protons in the metallocene series proceeding from ferrocene to ruthenocene to osmocene has been noted by

TABLE I

H¹ N.M.R. SPECTRA OF SOME ACYLMETALLOCENES

	Metallocene	Chemical shifts at ring positions, τ,[a] and multiplicity[b] C_5H_5 ring	α	β	Line separation in the apparent triplets, J, c.p.s.[a]
I	Ferrocene	5.86 (s)	...	...	...
II	Ruthenocene	5.45 (s)	...	...	...
III	Osmocene	5.30 (s)	...	...	...
IV	Acetylferrocene	5.82 (s)	5.23 (t)	5.51 (t)	1.90
V	Acetylruthenocene	5.42 (s)	4.91 (t)	5.23 (t)	1.80
VI	Acetylosmocene	5.21 (s)	4.77 (t)	5.06 (t)	1.65
VII	1,1′-Diacetylferrocene	...	5.23 (t)	5.49 (t)	1.91
VIII	1,1′-Diacetylruthenocene	...	4.88 (t)	5.19 (t)	1.82
IX	1,1′-Diacetylosmocene[c]	...	4.73 (t)	5.03 (t)	1.67
X	Benzoylferrocene	5.81 (s)	5.10 (t)	5.43 (t)	1.91
XI	Benzoylruthenocene	5.39 (s)	4.82 (t)	5.16 (t)	1.80
XII	Benzoylosmocene	5.18 (s)	4.68 (t)	4.99 (t)	1.65
XIII	1,1′-Dibenzoylferrocene	...	5.08 (t)	5.43 (t)	1.93
XIV	1,1′-Dibenzoylruthenocene	...	4.76 (t)	5.12 (t)	1.82
XV	1,2-Dibenzoylruthenocene	5.23 (s)	4.83 (d)	5.07 (t)	2.50

[a] Values given were measured on an expanded (50 c.p.s.) scale and are estimated to be accurate to within ±0.02 unit. [b] s = singlet d = doublet, t = apparent triplet (except for XV, in which a true triplet is observed). [c] The ratio of intensities of the α, β, and acety protons (7.91 τ) is 4:4:6. The presence of very weak singlets at 5.12 and 7.68 τ is probably due to a minor amount of a homoannular diacetylosmocene.

several investigators.[1-3] We have undertaken the n.m.r. analysis of several mono- and diacylmetallocenes in order to examine the generality of these observations, to compare quantitatively the $\Delta\tau$-values for each set of acylmetallocenes, and to obtain information regarding the coupling interactions of acylmetallocene ring protons as a function of the metal.

The nuclear magnetic resonance spectra of the acylmetallocenes are summarized in Table I, together with the n.m.r. constants of the parent metallocenes. Analysis of the data by comparison of related structures and, within the groups, of pertinent portions of the molecules, indicates a linear relationship of remarkable consistency.

The presence of both the acetyl and the benzoyl group in the metallocene molecule is reflected by a deshielding of not only the hydrogens alpha and beta to the acyl group, but also by a consistent, although smaller, deshielding of the nonsubstituted ring. As indicated by Pople[4] and by Jackman,[5] the diamagnetic anisotropy of the carbonyl group effects positive shielding in conical regions above and below the plane of the double bond and negative shielding (deshielding) elsewhere. A coplanarity of the carbonyl group with the cyclopentadienyl ring thus leads to a deshielding of the protons of the same ring, and, depending on the shape and dimensions of the positive shielding cone of the carbonyl group, to a deshielding or shielding of the unsubstituted ring hydrogens. If there were no rotation of the rings around the center axis, more than one signal would result from the protons of the unsubstituted ring. The presence of only one signal in the second ring of IV–VI and X–XII is consistent with earlier evidence for an essentially free rotation of the rings in ferrocene.[6] The observed singlet in the n.m.r. spectra of monoacylmetallocenes thus represents an averaged frequency of the unsubstituted ring protons. The small, but consistent, low field shifts[7] can be due to several factors. The unsubstituted ring could lie in the negative zone of the carbonyl cone so that the deshielding effect is dominating. Inductive deactivation across the metal atom might also contribute to the observed trend.[8]

In comparison with the monoacetylmetallocenes, the monobenzoyl derivatives X–XII showed a more enhanced effect on the relative chemical shifts. Such an enhancement in the deshielding of the protons alpha and beta to the acyl group was anticipated due to the presence of the additional deshielding effect of the phenyl ring. The strong negative shift is indicative of the coplanarity of the cyclopentadienyl and phenyl rings with the carbonyl group.

Parallel with the effect on the unsubstituted ring is the strong deshielding by the acyl groups on the α- and β-hydrogens of the substituted cyclopentadienyl ring. Both the α- and β-protons have the appearance of well resolved triplets.[9] The more deshielded protons were assigned as being alpha to the acyl group on the basis of the effect of the acetyl group on ring protons in the benzene series[10] and on the basis of the analysis of 1,2-dibenzoylruthenocene (*vide infra*). The deshielding effect of the carbonyl group is thus felt to a lesser extent in the more distant β-position than in the adjacent α-position. Such a difference between the effect on the α- and β-protons parallels analogous cases in benzene substituted by carbonyl and nitro groups. The

(1) T. J. Curphey, J. O. Santer, M. Rosenblum, and J. H. Richards, *J. Am. Chem. Soc.*, **82**, 5249 (1960).

(2) G. Fraenkel, R. E. Carter, A. McLachlan, and J. H. Richards, *ibid.*, **82**, 5846 (1960).

(3) D. E. Bublitz, W. E. McEwen, and J. Kleinberg, *ibid.*, **84**, 1845 (1962).

(4) J. A. Pople, *Proc. Roy. Soc.* (London), **A239**, 541, 550 (1957).

(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 121–125.

(6) M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).

(7) The observation that the protons of the unsubstituted cyclopentadienyl ring in monoacetylferrocene appear at a higher field than those of ferrocene when the spectrum is determined in benzene solution [K. L. Rinehart, Jr., D. E. Bublitz, and D. H. Gustafson, *ibid.*, **86**, 970 (1963)] is in accord with recent findings of R. E. Klinck and J. B. Stothers [*Can. J. Chem.*, **40**, 2329 (1962)]. The phenomenon of increased shielding in benzene solution is interpreted by the latter authors as being caused by a specific solute-solvent interaction of preferred geometry.

(8) For a review and discussion of interannular electronic effects in ferrocene, see M. D. Rausch, *ibid.*, in press.

(9) Although these triplets are themselves not symmetrical, there is a plane of symmetry between them, in accordance with an A_2B_2 system.

(10) See ref. 5, p. 63.

difference in the frequency between the α- and β-protons in the acetylmetallocene series, 0.28–0.32 p.p.m., is in the same order as the frequency difference between the *ortho* and *meta* protons in acetophenone (0.36 p.p.m.). Similarly, in the benzoylmetallocene series, the difference between the α- and β-frequencies is 0.31–0.34 p.p.m.

The extent of deshielding of the α- and β-protons in acetylmetallocenes, with respect to the parent metallocene, is also found to match closely the deshielding encountered in the benzene series. A comparison of the $\Delta\tau$ values with the extent of deshielding of the *ortho* and *meta* hydrogens in acetophenone (with respect to the proton resonance of benzene)[10] indicates a close coincidence. The $\Delta\tau$ values of -0.63 and -0.27 p.p.m. for the *ortho* and *meta* hydrogens in acetophenone are thus matched with corresponding -0.63 and -0.35 p.p.m. values for the α- and β-protons, respectively, in acetylferrocene. A similar set of values is also obtained from the frequencies of acetylruthenocene (-0.54 and -0.22 p.p.m.) and acetylosmocene (-0.53 and -0.24 p.p.m.). The $\Delta\tau$-values for the α- and β-protons in 1,1′-diacetylmetallocenes exhibit a similar relationship, the constants being -0.63 and -0.37 p.p.m. in the ferrocene, -0.57 and -0.26 p.p.m. in the ruthenocene, and -0.57 and -0.27 p.p.m. in the osmocene derivatives.

In the benzoylmetallocene series, an added deshielding due to the phenyl group should be expected. Indeed, the replacement of a methyl by a phenyl group in the acylmetallocenes causes an additional deshielding of the α-protons by 0.13 and 0.09 p.p.m. in the ferrocene and ruthenocene series, and of the β-protons by 0.08 and 0.07 p.p.m. in this series. The corresponding figures in the 1,1′-dibenzoyl series are 0.15 and 0.12 p.p.m. for the α-protons and 0.06 and 0.07 p.p.m. for the β-protons. The deshielding effect of the replacement of the methyl by a phenyl group in these acylmetallocenes can be compared to the known deshielding of the cyclopentadienyl protons by a phenyl substituent attached directly to the ring. The β-protons in *p*-nitrophenylferrocene, for example, are deshielded by 0.4 τ with respect to ferrocene.[11]

The consistent behavior of the α, β, and unsubstituted ring protons with respect to the acetyl and benzoyl substituents is also matched by the regularity in the variation of the proton frequencies with respect to changing the metal. A presentation of this data in the form of a diagram is given in Fig. 1, where the proton frequencies (in τ) are given for metallocenes containing either iron, ruthenium or osmium central atoms. Every series examined shows a gradual deshielding of *all* the corresponding ring protons proceeding from the ferrocene to the ruthenocene and osmocene derivatives. All of the series also indicate a larger difference between the proton frequencies of the ferrocene and ruthenocene derivatives than between the latter and the osmocene analogs. The order of decreased shielding of the ring protons parallels qualitatively the order of decreasing reactivities in electrophilic substitution reactions of the ferrocene, ruthenocene, and osmocene triad,[12] and parallels further the order of increasing reactivity of the ring protons toward *n*-butyllithium.[12]

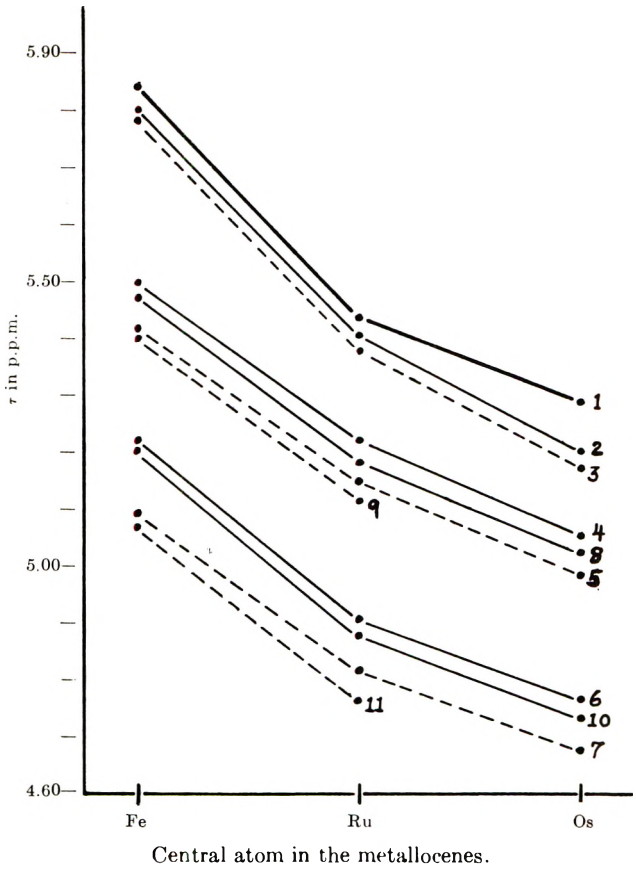

Fig. 1.—Variation of the proton frequencies in the n.m.r. spectra of acylmetallocenes: (1) H in metallocenes; (2) H′ in monoacetylmetallocenes; (3) H′ in monobenzoylmetallocenes; (4) H_β in monoacetylmetallocenes; (5) H_β in monobenzoylmetallocenes; (6) H_α in monoacetylmetallocenes; (7) H_α in monobenzoylmetallocenes; (8) H_β in 1,1′-diacetylmetallocenes; (9) H_β in 1,1′-dibenzoylmetallocenes; (10) H_α in 1,1′-diacetylmetallocenes; (11) H_α in 1,1′-dibenzoylmetallocenes.

A relationship in which a similar trend is reflected is obtained from a comparison of the line separation in the apparent triplets with the changing of the metal atom. The differences, although small, are nevertheless reproducible and probably indicate that the coupling between the ring protons in acylmetallocenes decreases from the iron to the ruthenium to the osmium derivatives. Contrary to the differences in the chemical shifts, however, the decrease in the line separation in the apparent triplets between the ruthenocenes (1.80 cp.s.) and osmocenes (1.65 c.p.s.) is somewhat greater than between the ferrocenes (1.90 c.p.s.) and ruthenocenes.[13]

The position and shape of the resonance lines permit the assignment of structures to isomers in substituted metallocenes. For example, the isolation of a dibenzoylruthenocene, m.p. 141.8–142.4°, from the benzoylation of ruthenocene was shown by infrared analysis to be a homoannular dibenzoylruthenocene, although the position of the benzoyl groups within the

(11) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High-Resolution N.M.R. Spectra Catalog," Spectrum No. 321, Varian Associates, Palo Alto, Calif.

(12) M. D. Rausch, E. O. Fischer, and H. Grubert, *J. Am. Chem. Soc.*, **82**, 76 (1960).

(13) Coincidentally, a similar sequence is found in the in-plane bending modes of the ring hydrogens of the metallocene triad, where the ruthenocene frequency (1001 cm.$^{-1}$) is closer to the ferrocene mode (1002 cm.$^{-1}$) than to the osmocene mode (995 cm.$^{-1}$) [ref. 12; E. R. Lippincott and R. D. Nelson, *J. Chem. Phys.*, **21**, 1307 (1953); *J. Am. Chem. Soc.*, **55**, 4990 (1955); *Spectrochim. Acta*, **10**, 307 (1958)].

substituted ring was not determined.[3,14] The n.m.r. spectrum of this product indicates three kinds of cyclopentadienyl ring protons by the presence of three frequencies at 4.83, 5.07, and 5.23 τ with intensities of 2.0:1.0:5.0. The lines represent a doublet, a triplet, and a singlet, respectively, with J = 2.5 c.p.s. The frequency of the doublet matches closely the value for the α-protons in benzoylruthenocene (4.82 τ), and the frequency of the triplet is close to that of the β-protons in benzoyl- (5.16 τ) and 1,1′-dibenzoylruthenocene (5.12 τ). A 1,2-dibenzoyl structure is thus indicated for the isomer with m.p. 141.8–142.4°. For 1,3-dibenzoylruthenocene, a low field triplet and a higher field doublet near 4.76–4.83 τ with an intensity ratio of 1:2 may be anticipated, in addition to a frequency for the unsubstituted ring hydrogens at about 5.2 τ.[15]

The identification of the homoannular dibenzoylruthenocene as the 1,2-isomer lends some support to the prediction, based on molecular orbital calculations,[16,17] that in electrophilic substitution reactions of ferrocene derivatives bearing electron-withdrawing groups, the 2-position is somewhat favored over the 3-position. By contrast, the descriptive resonance treatment indicates the 3-position as the preferential site of attack. The identification of homoannular diacetylferrocene as the 1,2-isomer[6,16] is thus paralleled by the isolation and identification of 1,2-dibenzoylruthenocene, and both support the molecular orbital prediction concerning site reactivities in monoacylmetallocene derivatives. The support for this interpretation is rendered even stronger when one considers the increased bulkiness of the benzoyl substituent.

The occurrence of well resolved and well separated lines in the n.m.r. spectra of various metallocene derivatives designate these compounds as suitable substrates for the study of substituent effects on the ring protons. The simplicity of the spectra allows the study of substituents and the assignment of modes in cases where the analogous operations in benzenoid systems are rendered difficult due to the multiplicity of lines resulting from long-range interactions.

Experimental

1,1′-Diacetylosmocene was isolated from the reaction of osmocene with a large molar excess of acetic anhydride and phosphoric acid. The general procedure of Hill and Richards was used,[18] except that the reaction was made on a fourfold larger scale. Chromatography of the reaction product from such a run, using benzene and benzene–ethyl ether mixtures on alumina, produced 0.050 g. of osmocene, m.p. 227–228°, 1.64 g. of acetylosmocene (91%), m.p. 130.5–131.5° (lit.[18] m.p. 129.5–130°), and 2.0 mg. of a yellow crystalline solid. The latter was recrystallized from *n*-heptane to produce 1.6 mg. (0.1%) of 1,1′-diacetylosmocene, m.p. 148–152°. The n.m.r. spectrum of this product in deuteriochloroform solution is consistent with the proposed formulation (see Table I).

Homoannular dibenzoylruthenocene was generously supplied by Prof. W. E. McEwen. All other metallocenes used in this study were analytically pure samples and were prepared by methods reported in the literature.[12,18]

N.m.r. spectra were determined on a Varian Model A-60 spectrometer as 10% (weight to volume) solutions in deuteriochloroform. In several comparative spectra in which the sample concentrations were varied from 5 to 10%, no effect due to dilution could be detected.

(14) D. E. Bublitz, J. Kleinberg, and W. E. McEwen, *Chem. Ind.* (London), 936 (1960).

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The Synthesis of a Glucosamine–Asparagine Compound. Benzyl N^2-Carbobenzyloxy-*N*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-L-asparaginate[1]

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Received May 6, 1963

In the course of the study of the link between the carbohydrate and protein parts of egg albumin, a glycosylamine type of linkage has been proposed by Johansen, Marshall, and Neuberger[3] and by Nuenke and Cunningham.[4] The carbon at position 1 of 2-acetamido-2-deoxy-D-glucose (*N*-acetyl-D-glucosamine) would be linked to the amide group of asparagine. Such a structure also has been suggested by other investigators[5] for egg albumin and seems also to agree with the experimental data obtained in the study of γ-globulins.[6,7] It recently has been proposed for the linkage of the carbohydrate part to the protein part of the α_1-acid glycoprotein of human plasma.[8,9]

As a part of the study carried out on the structure of the carbohydrate component of the α_1-acid glycoprotein of human plasma,[10] the synthesis of a glucosamine–asparagine compound, possessing the above-proposed structure, namely benzyl N^2-carbobenzyloxy-*N*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-L-asparaginate (VIII), was undertaken.

A first approach was an attempt to condense L-aspartic acid with a benzylidene derivative of D-glucosamine: a β-D-glucosylamide compound of D-glucose and L-aspartic acid has been first obtained by

(1) Amino Sugars XXXVI. This is publication No. 340 of the Robert W. Lovett Memorial Group for the Study of Crippling Diseases, Harvard Medical School at the Massachusetts General Hospital. This investigation has been supported by research grants from the American Cancer Society (Institutional Grant 42-B) and from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, United States Public Health Service (Grant A-3564-C1). Preliminary reports describing this work have been presented at the International Colloquium on Glycoproteins and on the Biochemistry of Connective Tissue in Normal and Pathological States, Paris, June, 1962, and before the Division of Carbohydrate Chemistry at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) Department of Organic Chemistry, The University, Bristol, England.

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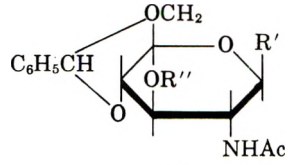
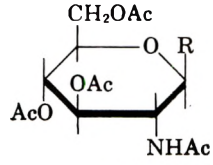
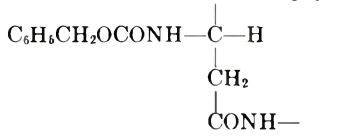


	R′	R″
I	OH	H
II	NH_2	H
III	NHAc	H
IV	NHAc	Ac



	R
V	NH_2
VI	N_3
VII	$NHCOC_6H_5$
VIII	$COOCH_2C_6H_5$



Coutsogeorgopoulos and Zervas,[11] who condensed 4,6-*O*-benzylidene-α-D-glucopyranose with ammonia to give 4,6-*O*-benzylidene-β-D-glucosylamine, which was in turn condensed with 1-benzyl-*N*-carbobenzyloxy-L-aspartate. In the present investigation, 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucose (I) was condensed in the same way, but for a prolonged period of time, with ammonia in dry methanol. No crystalline glycosylamine II could, however, be isolated, but the presence of II could be ascertained, since *N*-acetylation and total acetylation afforded in low yields crystalline 1,2-diacetamido-4,6-*O*-benzylidene-1,2-dideoxy-β-D-glucopyranose (III) and 1,2-diacetamido-3-*O*-acetyl-4,6-*O*-benzylidene-1,2-dideoxy-β-D-glucopyranose (IV), respectively. No crystalline material could be isolated from the condensation of impure II with 1-benzyl-*N*-carbobenzyloxy-L-aspartate.

In order to condense aspartic acid with a pure glycosylamine, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine (V) was prepared. The intermediate azide VI had been previously obtained by Micheel and Wulff[12] by acetylation of the 2-amino-2-deoxy-β-D-glucopyranosyl azide synthesized by Bertho and Révész.[13] In the present investigation, a shorter route was used in which 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide, prepared according to Inouye, *et al.*,[14] was condensed directly with silver azide according to the method of Bertho and Révész.[13] Reduction of VI gave the crystalline glycosylamine V, which was further characterized by preparation of the 1-benzamido derivative VII.

Condensation of V with 1-benzyl-*N*-carbobenzyloxy-L-aspartate in the presence of dicyclohexylcarbodiimide[15] or *N*-ethyl-5-phenylisoxazolium-3′-sulfonate[16] gave only very small amounts of a homogeneous crystalline product. Thus the use of another derivative was considered and 1-benzyl-*N*-carbobenzyloxy-L-aspartyl chloride[17] was condensed with V, giving VIII in a 28% yield. The use of an acyl chloride for the preparation of an *N*-acylglycosylamine has been previously reported by Baddiley, *et al.*[18] After this work had been completed, the condensation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine with 1-benzyl-*N*-carbobenzyloxy-L-aspartate by Marks and Neuberger[19] came to our attention, and we were informed by Dr. Neuberger of the synthesis of VIII using the carbodiimide method. Since the removal of the *O*-acetyl groups of VIII[20] may cause partial migration of the glycosylamine residue from position 4 to position 1 of aspartic acid, no attempt was made to prepare the de-*O*-acetylated derivative of compound VIII.

Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro- or micro- (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph Photoelectric Polarimeter Attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Chromatograms were made with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950; 60–200 mesh), which was used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluants was hexane, benzene or chloroform, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 50–100. The proportion of weight of substance in grams to volume of fraction of eluent in milliliters was 1 to 100. The ratio of diameter to length of the column was 1 to 20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen. The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

2-Acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosylamine (II).—A solution of 0.24 g. of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose (I), prepared according to the method of Roth and Pigman,[21] in dry methanol (30 ml.) was saturated at 0° with ammonia gas, and heated in a sealed tube at 60–70° for 4 days. After cooling, the excess of ammonia was removed from the solution with nitrogen. The yellow solution was decolorized by filtration through a pad of Darco G-60 and Celite, and concentrated to dryness, yielding 0.25 g. of sirup. This material could not be crystallized, and attempts to purify it by silica gel chromatography were unsuccessful. It was, therefore, used without further purification. When the reaction was attempted for a shorter time, most of the starting material was recovered unchanged.

1,2-Diacetamido-4,6-*O*-benzylidene-1,2-dideoxy-β-D-glucopyranose (III).—A solution of 0.2 g. of II in 2 ml. of methanol containing 0.2 ml. of acetic anhydride was allowed to stand at room temperature for 24 hr. The product crystallized from the solution yielding 0.04 g. of needles. It was recrystallized from a mixture of dimethyl sulfoxide and methanol, $[\alpha]^{26}D$ +16° (*c* 1.07, in dimethyl sulfoxide). It did not melt below 385° though some decomposition took place above 300°.

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Anal. Calcd. for $C_{17}H_{22}N_2O_8$: C, 58.28; H, 6.28; N, 8.00. Found: C, 58.17; H, 6.36; N, 8.11.

1,2-Diacetamido-3-*O*-acetyl-4,6-*O*-benzylidene-1,2-dideoxy-β-D-glucopyranose (IV).—A solution of 0.12 g. of II in a mixture of 0.6 ml. of pyridine and 0.2 ml. of acetic anhydride was allowed to stand for 24 hr. at room temperature. Water (2 drops) was added, the mixture was allowed to stand a further 5 min., and it was then poured into ice–water (70 ml.). The precipitate was filtered, washed with much water, and dissolved in chloroform. The solution, after drying, was treated with Darco G-60 and Celite and concentrated. The product (0.027 g.) crystallized into needles, and was recrystallized from a mixture of methanol and chloroform. The sample did not melt below 365°, though some decomposition took place above 300°.

Anal. Calcd. for $C_{19}H_{24}N_2O_7$: C, 58.15; H, 6.17; N, 7.14. Found: C, 58.06; H, 6.23; N, 7.40.

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl Azide (VI).—A freshly prepared, dried solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide, prepared from 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucopyranose according to Inouye, *et al.*,[14] (*ca.* 1 g.), in 20 ml. of chloroform was added to a suspension of silver azide in chloroform. The suspension had been prepared by mixing aqueous solutions of sodium azide (0.45 g.) and silver nitrate (1.1 g.) and washing the precipitate by decantation with water, ethanol, ether, and chloroform. The mixture was refluxed for 30 min., then it was filtered and the filtrate concentrated to dryness. The residue crystallized readily, and recrystallization from a mixture of chloroform and ether afforded 0.62 g. (68%) of needles with the same properties as those described by Micheel and Wulff.[12]

2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine (V).—A solution of 2.87 g. of azide VI in 25 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure for 4 hr. in the presence of 0.28 g. of Adams' platinum oxide catalyst. After removal of the catalyst by filtration through a Darco G-60 Celite pad, the filtrate was concentrated to dryness. The residue was crystallized from a mixture of ethyl acetate and pentane, yielding 0.8 g. (30%) of needles, m.p. 225–230° dec.; $[\alpha]^{28}D$ −5.2° (c 1.27, in chloroform).

Anal. Calcd. for $C_{14}H_{22}N_2O_8$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.52; H, 6.51; N, 7.97.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-benzamido-1,2-dideoxy-β-D-glucopyranose (VII).—A solution of 0.5 g. of V in 3 ml. of pyridine containing 0.3 ml. of benzoyl chloride was allowed to stand at room temperature for 3 days. After the addition of 1 drop of water, the mixture was left for a short time, and then it was poured into ice–water (75 ml.) and extracted with chloroform. The extract was washed with cold dilute hydrochloric acid, then with aqueous cadmium chloride, aqueous sodium bicarbonate, and water. The solution was dried over sodium sulfate and was concentrated to dryness. The residue was crystallized from a mixture of ethyl acetate and pentane yielding 0.173 g. (27%), m.p. 250.5–251.5°; $[\alpha]^{26}D$ −14° (c 1.10, in chloroform).

Anal. Calcd. for $C_{21}H_{26}N_2O_9$: C, 55.99; H, 5.82; N, 6.22. Found: C, 55.98; H, 5.89; N, 6.36.

Benzyl *N*²-Carbobenzyloxy-*N*-(2-acetamido-3,4,6-tri-*O*-acetyl 2-deoxy-β-D-glucopyranosyl)-L-asparaginate (VIII).—1-Benzyl-*N* carbobenzyloxy-L-aspartyl chloride was prepared according to the method of Bergmann, *et al.*,[17] after purification of 1-benzyl *N*-carbobenzyloxy-L-aspartate according to LeQuesne and Young.[19,22]

The glucosylamine V (0.57 g.) was added to a solution of 0.76 g. of the acid chloride in 5 ml. of dry pyridine and the mixture was allowed to stand at room temperature for 3 days. The mixture was diluted with chloroform, and the resulting solution was washed with cold *N* sulfuric acid and water, then dried over sodium sulfate, and concentrated to dryness. The residue, dissolved in benzene, was purified by chromatography on silica gel. Elution with a mixture of ether and ethyl acetate (1:1) afforded VIII as a colorless sirup (0.32 g., 28.5%), which crystallized in fine needles from a mixture of chloroform and ether, m.p. 214–217° dec.; $[\alpha]^{25}D$ +28° (c 1.41, in chloroform).

Anal. Calcd. for $C_{33}H_{39}N_3O_{13}$: C, 57.80; H, 5.73; N, 6.13. Found: C, 57.89; H, 5.87; N, 6.19.

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A Convenient Preparation of 1,2-Mono-*O*-isopropylidene-α-D-glucofuranose[1]

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Received May 10, 1963

In connection with a series of reactions to introduce new heteroatoms into the D-glucose ring, a convenient method was developed for the preparation of monoacetone D-glucose, 1,2-mono-*O*-isopropylidene-α-D-glucofuranose.

Monoacetone D-glucose is a useful compound for the preparation of numerous D-glucose derivatives. It is usually prepared from diacetone D-glucose, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, by preferential hydrolysis of the more acid labile 5,6-isopropylidene group. Previous methods[2-8] have been rather long and require pH control, neutralization, filtration, and evaporation of large quantities of solvent before the first crop of crude crystals are obtained. The present method is shorter and avoids some of the manipulations required in other procedures.

The 5,6-isopropylidene group of diacetone D-glucose is hydrolyzed in 77% aqueous acetic acid and the solution completely evaporated to produce a quantitative yield of monoacetone D-glucose, free of D-glucose and diacetone D-glucose. It is suitable for direct use in many sugar reactions but may be purified by one crystallization from ethyl acetate. Isolation of almost pure crystalline monoacetone D-glucose from the hydrolysis mixture is attributed to its insolubility in 77% aqueous acetic acid. Scale-up of the preparation from 5 g. to 500 g. can be done without reduction in yield or loss of purity.

Experimental

Purity of monoacetone D-glucose preparations was determined by thin layer chromatography on 1 × 3 in. silica gel G-coated[9] microscope slides, irrigated with ethyl acetate and chloroform. Plates were sprayed with a dilute solution of sulfuric acid in ethanol and charred at 100° until permanent spots appeared. Further chromatographic identification of the components was performed on Whatman No. 1 filter paper at 25° with irrigants (A) ethyl acetate–pyridine–water (10:4:3 v./v.) and (B) 1-butanol–ethanol–water (40:11:19 v./v.). The spray indicator was (C) permanganate–periodate.

Preparation of 1,2-Mono-*O*-isopropylidene-α-D-glucofuranose.—Diacetone D-glucose (5 g.) was dissolved at 25° in a solution containing 10 ml. of acetic acid and 3 ml. of water. This solution was poured into a shallow evaporating dish and allowed to evaporate slowly in a hood at 25°. Within a few hours the entire mixture crystallized as a mass of crystalline monoacetone D-glucose. This was broken up with a spatula and recrystallized or allowed to air dry. Thin layer chromatography revealed no contamination from either the starting material or from D-glucose.

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(9) Brinkmann Instruments, Inc., Great Neck, Long Island, N. Y.

Paper chromatograms developed in irrigants A and B and sprayed with indicator C revealed monoacetone D-glucose as the only sugar derivative; yield, 100%; m.p. 159–160°, undepressed when admixed with authentic sample; $[\alpha]^{25}D$ −12.3 (c 6.5, in water).

Pure monoacetone D-glucose was obtained by dissolving the undried crystalline mass obtained above in 100 ml. of warm ethyl acetate. Incompletely dried monoacetone D-glucose preparations dissolve rapidly in a minimum of ethyl acetate, whereas thoroughly dried preparations are difficult to solvate. Cooling the ethyl acetate solution to 0° gave a pure white crystalline product in 90% yield; m.p. 161°; $[\alpha]^{25}D$ −11.6 (c 2.5, in water).

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl Bromide Hydrobromide[1]

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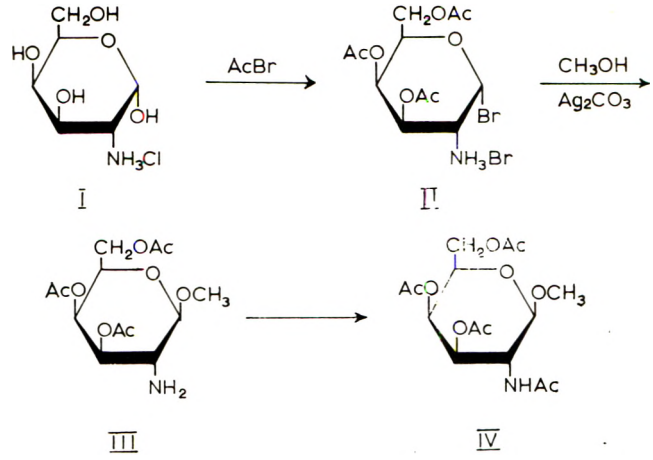
Received May 6, 1963

Peracylated glycosyl halides are valuable intermediates in a wide range of syntheses,[2] but such derivatives of the 2-amino-2-deoxy sugars suffer from two important limitations as general intermediates in synthesis. It is difficult or impossible to remove the *N*-acyl blocking group after a coupling reaction has been effected, with, for example, the peracetylated or perbenzoylated derivatives, and a 2-acetamido or 2-benzamido derivative results. Even labile *N*-substituents may be difficult to remove when sensitive functions are introduced at C-1.[3] The second complicating factor arises from the readiness with which a 2-acylamido group interacts with the C-1 glycosyl halide function, to give oxazoline[4] or oxazolidine[5] type derivatives.[6]

In the 2-amino-2-deoxy-D-galactose series, the fully acetylated halides, 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl bromide,[7] and chloride[8] have been reported; the present work describes the synthesis of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl bromide hydrobromide (II), a glycosyl halide derivative in which the amino group is unsubstituted. By analogy with the corresponding known[9] D-glucose derivative, compound II should undergo a wide range of reactions leading to β-D-galactopyranosyl derivatives with an unsubstituted amino group at C-2.

The D-glucose analog of II is prepared[9] by heating 2-amino-2-deoxy-D-glucose hydrochloride with acetyl bromide at 70°, a procedure which is an adaptation of



the seldom-used[3,4] method of Colley[10] for preparation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride. The reaction is capricious, but under carefully controlled conditions[11] good yields of the aminoglycosyl halide are obtainable. When applied to 2-amino-2-deoxy-α-D-galactose hydrochloride (I) under the conditions of Wolfrom and Shen Han[11] for the D-glucose analog, a dark red crystalline product, exhibiting a poor analysis for II, was obtained in modest yield; at lower temperatures reaction was incomplete, even at extended reaction times. Conditions were established, with heating at 55°, where about 60% of the starting material underwent reaction, to give the desired glycosyl bromide II as a crystalline product with acceptable purity without further recrystallization. The yields based upon material reacted, varied between 65 and 90%, the run described (76%) being typical. The unchanged starting material could be recovered by filtration and recycled in the reaction. Product II appeared stable for at least several weeks, if stored in a desiccator, and the stored material showed no change in its infrared spectrum. The observed molecular rotation value of +71,200° is indicative of the α-D anomeric configuration.

Compound II was treated with methanol in the presence of silver carbonate to give methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranoside (III) as a sirup. Acetylation of III hydrobromide gave the known[7] crystalline methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranoside (IV); this establishes that II reacts with alcohols to give glycosides of the β-D configuration.

Experimental[12]

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl Bromide Hydrobromide (II).—A modification of the procedure

(1) Supported by Contract No. DA-49-193-MD-2143 (Research Foundation Project 1187) from the Walter Reed Army Institute of Research, Washington, D. C. The opinions expressed in this article are those of the authors, and not necessarily those of the sponsoring agency.

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(11) M. L. Wolfrom and T. M. Shen Han, *J. Org. Chem.*, **26**, 2145 (1961).

(12) Melting points were determined with a Fisher-Johns apparatus and correspond to corrected melting point. Specific rotations were determined with a 4-dm. polarimeter tube, and optical rotatory dispersion measurements were taken with a Rudolph Model 260/655/850/810-614 recording spectropolarimeter. Infrared spectra were determined with a Perkin-Elmer Infracord infrared spectrophotometer. The potassium bromide pellets were pressed from a finely ground mixture of the dried sample with dry analytical grade potassium bromide. Elemental microanalyses were made by W. N. Rond. X-Ray powder diffraction data: interplanar spacing, Å., CuKα radiation; relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. Strongest lines are numbered in order of intensity (1, strongest); double numbers indicate approximately equal intensities. Thin layer chromatographic data refer to separations made with silica gel G (E. Merck, Darmstadt, Germany) activated at 100°. Zones were detected with concentrated sulfuric acid.

used for the D-*gluco* analog[9,11] was used. 2-Amino-2-deoxy-α-D-galactose hydrochloride[13] (I, 1.00 g.) was placed in a 25-ml. Erlenmeyer flask equipped with a Teflon-covered stirring bar and a drying tube, acetyl bromide (2.5 g., 5 mole equiv.) was added, and the vigorously stirred mixture was heated slowly during 30 min. to 55° (oil bath temperature). This temperature was maintained for 1 hr., during which time the mixture became red and slowly solidified. At this point the flask was cooled and was connected to a water pump aspirator through a series of four 8-in. U-tubes containing soda lime. After all the acid vapors were absorbed (about 3 hr.), the residue was extracted with dry methylene chloride, the undissolved residue removed by filtration, and the filtrate decolorized with activated carbon. Dry ether was added to the solution to the point of incipient crystallization, and the mixture was refrigerated overnight to give II as pink plates, yield 900 mg. or 76% (range 65–90%) based on the amount of I which had undergone reaction, m.p. 144–148° dec., $[\alpha]^{23}D$ +160 ± 2° (*c* 0.7, chloroform); specific optical rotatory dispersion curve (*c* 0.34, 26°) +100 (700), +157 (600), +231 (500), +463 (400), +574° (350 mμ); λ_{max}^{KBr} 5.74 vs (OAc), 6.11 w, 6.70 m (NH_3^+), 7.34 m (CH_3C), 11.80 w (equatorial H at C-1), 13.45 μ w (C–Br?); X-ray powder diffraction data[12]: 12.96 vs (2), 8.76 w, 8.04 w, 6.03 vs (1,1), 5.31 w, 4.33 vs (1,1), 4.15 m, 4.04 s, 3.93 s, 3.58 w, 3.02 vs (3), 2.87 s. Recrystallization from methylene chloride and ether gave a less colored product, but the melting point and specific rotation did not change significantly.

Anal. Calcd. for $C_{12}H_{19}Br_2NO_7$: C, 32.09; H, 4.26; Br, 35.56; N, 3.12. Found: C, 32.01; H, 4.44; Br, 35.37; N, 3.12.

The methylene chloride-insoluble material was dissolved in aqueous ethanol (decolorizing carbon), and recovered by evaporation; yield, 400 mg. This material was treated with acetyl bromide as already described, and a further quantity of II was isolated, in similar yield.

When higher reaction temperatures were employed, the amount of methylene chloride-insoluble material remaining diminished, and was negligible when the reaction temperature was raised to 70°. However, under these more vigorous conditions, the product was deep red in color, and required several recrystallizations for acceptable purity. Reaction at room temperature for extended periods gave very little product. Efficient stirring was essential for success of the reaction.

The bromo sugar II underwent no decomposition when stored in a desiccator for 6 weeks. The infrared spectrum of II was very similar to that exhibited by the D-*gluco* analog.

A crude product, m.p. 161°, considered to contain II, has been prepared by another route,[14] but no analytical or other physical data were given.

Methyl 3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranoside (III).—A solution of the bromo sugar II (500 mg.) in dry methanol (5 ml.) was shaken overnight with an excess of dry silver carbonate and finely ground Drierite.[15] The mixture was filtered through Celite,[16] and the filtrate evaporated to a colorless sirup which failed to crystallize. The product gave a positive ninhydrin reaction, migrated as a single zone (R_f = 0.75) on thin layer chromatograms with 8:1:1 benzene–methanol–pyridine as developer, and did not reduce Fehling solution.

Conversion of the product to the hydrobromide salt with an equivalent of hydrogen bromide in methanol, followed by evaporation, gave a hygroscopic sirup, λ_{max}^{KBr} 2.97 s (NH), 5.73 vs (OAc), 6.12 w, 6.63 μ w (NH_3^+). The product was not obtained crystalline.

Methyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranoside (IV).—The sirupy hydrobromide product from the preceding preparation was dissolved in a cold mixture of dry pyridine (5 ml.) and acetic anhydride (2.5 ml.), and left for 3 hr. at room temperature. The mixture was poured into water, and the product was extracted with chloroform. The extract was washed with water, and the final traces of pyridine were removed by shaking the extract with aqueous cadmium chloride solution. The cadmium chloride–pyridine complex was filtered, and the dried extract evaporated to a crystalline residue. Recrystallization from methanol gave IV as large prisms; yield 200 mg. (55% calculated on II), m.p. 212–216°. A further recrystallization gave analytically pure product; m.p. 215–217°, $[\alpha]^{23}D$ −15 ± 1° (*c* 1.5, chloroform); λ_{max}^{KBr} 3.03 m (NH), 5.70 s (OAc), 6.03 s, 6.40 m (NHAc), 7.28 m (CH_3C), 11.13 μ w (axial H at C-1); X-ray powder diffraction data[12]: 13.27 s, 7.97 vs (1,1), 7.38 vs (3), 6.92 m, 6.15 vs (2), 5.5 w, 4.93 s, 4.57 m, 4.37 m, 4.15 m, 3.95 vs (1,1), 3.75 s.

Anal. Calcd. for $C_{15}H_{23}NO_8$: C, 49.84; H, 6.42; N, 3.87. Found: C, 50.09; H, 6.44; N, 3.91.

The following constants have been recorded[7] for this compound, prepared by a different procedure: m.p. 216–217°, $[\alpha]^{23}D$ −17 ± 1° (*c* 1.84, chloroform).

The Chromous Chloride Reduction of Ergosterol Epidioxide[1]

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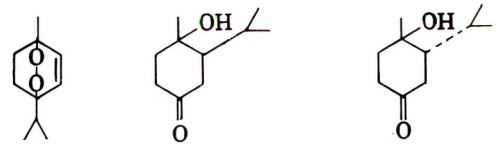
Received June 24, 1963

The reduction of ascaridole (I) with ferrous ion is reported to yield,[2] besides ascaridole glycol, a mixture of two stereoisomeric hydroxy ketones II and III.



I II III

Formation of the isomeric ketones is thought to arise by one electron transfer from ferrous ion to the oxide bridge, generating a tertiary alkoxy radical. The alkoxy radical fragments to an α,β-unsaturated cyclohexenone and an isopropyl radical, followed by isopropyl radical attack on the β-carbon of the cyclohexenone. Further electron and proton acquisitions yield the observed products II and III.

To establish whether one-electron reduction by a metal ion on ergosteryl acetate epidioxide (IV) would follow a similar reaction course and generate a steroidal *t*-alkoxy radical, the reduction of IV was studied.

Treatment of epidioxide IV with chromous chloride[3] in ethanolic hydrochloric acid resulted in rapid reduction. Chromatography of the materials formed yielded ergosteryl acetate (V), a dimeric substance, $C_{60}H_{90}O_4$ (VI), and the hydroxy acetate (VII), all formed in equal yields of about 30%.

The structures are assigned as follows. The dimer VI showed no selective ultraviolet absorption. Saponification of the dimer diacetate yielded a diol which differed from the well known bisergostatrienol (IX),[4] the product of photodimerization of ergosterol. The n.m.r. spectrum of the dimer VI indicated vinyl proton absorp-

(13) A product of Pfanstiehl Laboratories, Waukegan, Ill. The authors thank Dr. D. G. Doherty, of Oak Ridge National Laboratory, Oak Ridge, Tenn., for a gift of this material.

(14) K. Onodera and T. Komano, *J. Org. Chem.*, **26**, 3932 (1961).

(15) Anhydrous calcium sulfate, a product of W. A. Hammond Drierite Co., Xenia, Ohio.

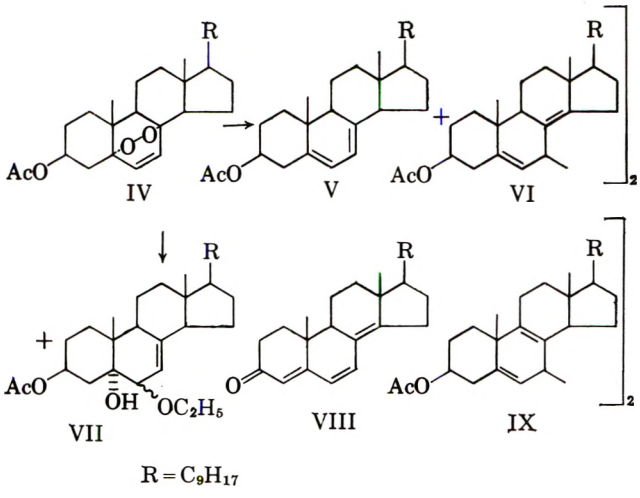
(16) Celite, a siliceous filter-aid, product of the Johns-Manville Co., N. Y.

(1) This work was supported by Public Health Service Research Grant AM-05183 from the National Institute of Arthritis and Metabolic Diseases.

(2) D. Brown, B. T. Davis, T. G. Halsall, and A. R. Hands, *J. Chem. Soc.*, 4492 (1962).

(3) J. Kochi, *J. Am. Chem. Soc.*, **84**, 1193 (1961), has reported that the chromous ion reduction of tertiary alkyl hydroperoxides affords products of *t*-alkoxy radical fragmentation and the corresponding tertiary alcohols.

(4) A. Windaus and P. Borgeaud, *Ann.*, **460**, 235 (1928).



$R = C_9H_{17}$

tion at 4.77 τ, broad C-3 proton absorption characteristic of protons adjacent to an acetoxyl function at 5.3 τ, and a broad band at 6.83 τ. These protons appear in a relative intensity ratio of 3:1:1.[5]

Oxidation of the dimeric diol with chromium trioxide in pyridine or under the Oppenauer conditions resulted in fission of the dimer to the monomeric ergostatetraenone (VIII).[6]

Based on these data, we assign the structure VI to the dimer, a Δ^{14} double bond isomer of bisergostatrienol.

The hydroxy acetate VII exhibited in the infrared a pair of bands for an acetate carbonyl at 5.80 and 5.85 μ which Henbest has shown to be characteristic of 5α-hydroxy 3β-acetates.[7] The presence of the ethoxyl group in VII was revealed by the characteristic n.m.r. bands with a methylene quartet at 6.43 τ. The vinyl proton region of the n.m.r. was also in accord with the Δ^7 unsaturation (4.85 τ), with a relative intensity of 3 (C_7–C_{22}–C_{23}).

Oxidation of the hydroxy acetate VII with chromic acid yielded the corresponding C-6 ketone, which has been prepared previously by dichromate oxidation of ergosteryl acetate.[8]

Formation of the reduction products V, VI, and VII can be explained by assuming the initial formation of an intermediate 5α,8α-diol by reduction of the epidioxide.[9]

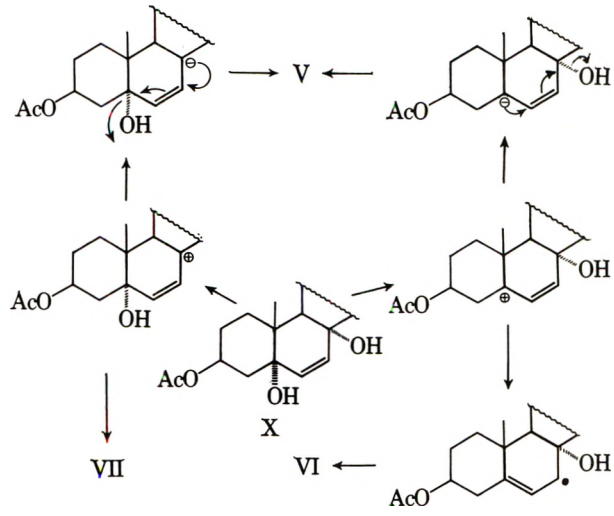
To verify this assumption, the reduction of the 5α,8α-diol X with chromous chloride was next studied. The diol was prepared in an independent manner by zinc and alkali treatment of ergosterol epidioxide.[10]

The results of the reduction of the diol were identical with those of the epidioxide and afforded the same three reduction products, all in yields of approximately 30%.

The mode of formation of the reduction products can now be accounted for by postulating the initial acid-catalyzed formation of either of the allylic carbonium ions at C-5 or C-8 from the diol.[11] Reaction of the allylic carbonium ion at C-7 with the ethanol medium accounts for the formation of the ethoxy derivative VII.[12]

Electron acquisition by the C-5 carbonium ion from chromous ion leads to an allylic radical, which couples and forms the dimer through C-7.[13] Further dehydration of the remaining C-8 α-ols toward the proton at C-14 affords the observed dimeric compound VI.

The origin of the ergosterol acetate from the chromous chloride reduction of its 5,8-epidioxide can be visualized as arising from either the C-5 or C-8 carbonium ion by a two-electron acquisition from the reducing agent. This intermediate anion expels either the C-5 or C-8 hydroxyl group to form the homoannular diene ergosterol.



Experimental[14]

Reduction of Ergosteryl Acetate Epidioxide with Chromous Chloride.—An acidic, ethanol solution (1200 ml.) of chromium trichloride (312 g. of chromic chloride, 1280 ml. of ethanol, and 275 ml. of concentrated hydrochloric acid) was percolated through granular (20-mesh) zinc; the blue chromous solution generated in this manner was passed directly into a stirring solution of 10.2 g. of ergosteryl acetate epidioxide in 675 ml. of tetrahydrofuran and 675 ml. of ethanol under a carbon dioxide atmosphere. A precipitate formed before the addition of chromous reagent had been completed. The blue-green mixture was stirred at room temperature under a carbon dioxide atmosphere for 4 hr. It was then poured into 2 l. of water, filtered, and washed with water. The solid was dried, dissolved in a minimum of benzene, and chromatographed on 300 g. of Florisil. The first two benzene fractions (250 ml. each) eluted 2.61 g. of ergosteryl acetate.

(5) For comparative purposes the n.m.r. spectrum of bisergostatrienol acetate (IX) showed vinyl proton absorption (C-6, C-22, C-23) at 4.83 τ, the C-3 protons at 5.3 τ, and the C-7 protons at 7.0 τ in the ratio of 3:1:1.

(6) D. H. R. Barton and T. Brunn, *J. Chem. Soc.*, 2728 (1951). The mechanism of fragmentation of the dimer to the monomeric ketone is unknown. The thermal fission of bisergostatrienol to neoergosterol is a related process. It is of interest to note that oxidation of bisergostatrienol under Oppenauer conditions also yielded a small but detectable amount of the same ergostatetraenone.

(7) H. B. Henbest, G. D. Meakins, and T. I. Wrigley, *ibid.*, 2633 (1958).

(8) M. Fieser, A. Quilico, A. Nickon, W. E. Rosen, E. J. Tarlton, and L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 4066 (1953).

(9) In ref. 2, Kochi has demonstrated that the chromous ion reduction of *t*-alkyl hydroperoxides affords a large proportion of *t*-alcohol formed by bimolecular reduction of the intermediate *t*-alkoxy radical.

(10) A. Windaus and O. Linsert, *Ann.*, **465**, 148 (1928).

(11) R. B. Clayton, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 2015 (1953), have shown that 5α,8α-diols dehydrate readily under mild acidic conditions to Δ^7 unsaturated compounds.

(12) In addition to the ethoxy derivative VII, a smaller quantity of product arising from reaction of the ion with water to yield the corresponding C-6 alcohol was isolated. This is described in the Experimental section.

(13) The coupling of carbonium ions to dimers in the presence of chromous chloride has been observed by J. B. Conant, L. F. Small, and B. S. Taylor, *J. Am. Chem. Soc.*, **47**, 1959 (1925), and more recently by C. E. Castro, *ibid.*, **83**, 3262 (1961). The stereochemistry of the dimer at C-7–C-7′ is not known.

(14) Melting points were taken on a Fisher-Johns melting point apparatus. A Perkin-Elmer Infracord was used to obtain the infrared spectra. Ultraviolet absorption data were obtained from a Beckman Model DB spectrophotometer. Rotations were determined in chloroform at 1% concentrations unless otherwise stated.

The next benzene fractions (1500 ml. total) contained 1.89 g. of solid that crystallized from methylene chloride–ethanol, m.p. 204–208°, $[\alpha]^{25}D$ −95°, λ^{Nujol} 5.75 and 5.80 μ (OCCH$_3$), for VI.

Anal. Calcd. for $C_{60}H_{90}O_4$: C, 82.32; H, 10.36; mol. wt., 875.5. Found: C, 82.56; H, 10.12; mol. wt., 876.

Elution was continued with 10% ether in benzene (1000 ml.) and 2.36 g. of 3β-acetoxy-6-ethoxy-7(8),22-ergostadien-5α-ol was obtained. After crystallization from methylene chloride–ethanol, the sample VII melted at 167–168°. Further crystallization gave an analytical sample, m.p. 174–175°, $[\alpha]^{26}D$ −95°, λ^{Nujol} 2.91 (–OH), 5.80 and 5.89 μ (–OC–CH$_3$).

Anal. Calcd. for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.90; H, 10.20.

When 750 mg. of the chromatographic fraction of VI was crystallized from ether, 90 mg. of colorless crystalline material (m.p., 225–260°) was obtained. Further crystallization gave an analytical sample, m.p. 259–263°, $[\alpha]^{26}D$ −49° (0.75%).

The analyses was calculated as 3β-acetoxy-7(8),22-ergostadiene-5α-6β-diol.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 75.94; H, 10.19.

Acetylation of 35 mg. of this C-6 alcohol with acetic anhydride in pyridine yielded 25 mg. of the 3,6-diacetate which, after trituration with methanol, melted at 165–166°, $[\alpha]^{24}D$ −129°; lit.[8] m.p. 171°, $[\alpha]D$ −146°.

Oxidation of 3β-Acetoxy-6-ethoxy-7(8),22-ergostadien-5α-ol.—A solution of 200 mg. of the steroid in 40 ml. of acetone was treated dropwise, at room temperature, with Jones chromium trioxide solution until a slight excess was present. The mixture was filtered through Celite, and the volume of the filtrate was reduced to approximately one-half under reduced pressure; it was then poured into ice–water (200 ml.). The precipitate was filtered and washed with water. After crystallization from methylene chloride–ethanol, the 3β-acetoxy-7(8),22-ergostadien-5α-ol-6-one melted at 253–259°, λ_{max}^{ether} 240 mμ (12,000). Another recrystallization raised the melting point to 261–263°, $[\alpha]^{25}D$ −1° [lit.[8] m.p. 269°, $[\alpha]D$ ±0, $\lambda_{max}^{ethanol}$ 248 (12,900)].

Hydrolysis of the Dimer VI.—The dimer VI with aqueous potassium hydroxide in methanol dioxane (1:1) yielded a diol, after crystallization from acetone, m.p. 191–193°, λ^{Nujol} 2.9 μ (OH), $[\alpha]^{26}D$ −258° (pyridine); reported[3] for bisergostatrienol, m.p. 202–203°, $[\alpha]^{16}D$ −209 (pyridine). A mixture melting point determination showed m.p. 181–190°.

Oxidation of the Dimer VI. A.—A solution of 200 mg. of the diol prepared from VI in 20 ml. of pyridine was added to a mixture of anhydrous chromium trioxide (300 mg.) and 10 ml. of pyridine. The mixture was allowed to stand at room temperature for 18 hr. It was poured into ice–water, and sodium bisulfite was added to decompose excess chromium trioxide. Hydrochloric acid was added until the solution was slightly acidic and the precipitate was filtered and washed with water. The yellow solid (132 mg.) was dissolved in a minimum amount of benzene and chromatographed on 6 g. of acid-washed alumina (Merck). Benzene (65 ml.) eluted 56 mg. of 4,6,8(14),22-ergostatetraen-3-one, m.p. 108–113°, $\lambda_{max}^{ethanol}$ 350 mμ (24,500), $[\alpha]^{25}D$ +526°; lit.[7] m.p. 114–115°, $[\alpha]^{35}D$ +590, $\lambda_{max}^{ethanol}$ 348 mμ (26,500).

B.—To 200 mg. of VI in 10 ml. of benzene and 10 ml. of acetone was added 1.8 g. of aluminum *t*-butoxide. After refluxing the mixture for 6 hr. under a nitrogen atmosphere, 10 ml. of a 1:1 mixture of acetone–benzene was added. After 13 hr. of refluxing, an additional 1.0 g. of aluminum *t*-butoxide and 10 ml. of acetone–benzene (1:1) was added. After refluxing for 23 more hr., the solution was cooled and 25 ml. of benzene was added. The mixture was poured into a cold dilute solution of sulfuric acid and Rochelles salt. The benzene layer was separated, and a benzene extract (50 ml.) of the aqueous layer was added. The benzene was washed with two 100-ml. portions of water and with saturated salt solution (50 ml.). It was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to leave a yellow oil weighing approximately 500 mg. The oil was dissolved in a minimum amount of benzene and filtered through a column of Florisil (4 g.). A benzene wash (25 ml.) yielded 420 mg. of a yellow-brown oil. This oil was then redissolved in benzene and chromatographed on 12 g. of Florisil. Benzene (160 ml.) eluted 332 mg. of a multicomponent oil. Methylene chloride (150 ml.) eluted 70 mg. of 4,6,8(14),22-ergostatetraen-3-one of an estimated 80% purity by its ultraviolet spectrum. The infrared spectrum and thin layer chromatography showed this material to be identical with that prepared *via* the chromium oxide–pyridine oxidation.

Reduction of 3β-Acetoxy-6,22-ergostadiene-5α,8α-diol (X) with Chromous Chloride.—The triol corresponding to X was obtained by the method of Windaus and Linsert[10] and acetylated with pyridine and acetic anhydride to yield X. A solution of 1.51 g. of X in 150 ml. of tetrahydrofuran and 150 ml. of ethanol was treated with 180 ml. of chromous chloride reagent in a manner identical with that employed for the reduction of the epidioxide IV. A colorless solid (1.37 g.) obtained by this procedure was chromatographed on 45 g. of Florisil. The first two benzene fractions (50 ml. each) eluted 451 mg. of ergosteryl acetate. The next three benzene fractions totalling 220 ml. eluted 354 mg. of the dimer diacetate VI. Elution with ether (100 ml.) afforded 515 mg. of the hydroxy acetate VII. The physical and spectral characteristics of the products obtained from this reduction were identical in all respects with the compounds obtained from the reduction of ergosteryl acetate epidioxide.

The Reactions of Nortricyclyl and Dehydronorbornyl Chloride with Sodium

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Received March 5, 1963

An interest in whether α-elimination would occur in the reaction of nortricyclyl chloride with sodium, since β-elimination is prevented by Bredt's rule, prompted the investigation reported here.

Nortricyclyl chloride (I) reacts with sodium in decane at 85–90° to produce a 19–20% yield of C_7 hydrocarbons, isolated directly from the reaction mixture by vacuum distillation. Vapor phase chromatographic and infrared analysis of this volatile hydrocarbon mixture demonstrated that there were four components present: nortricyclene (II), 71%; norbornene (III), 10%; and two additional C_7H_{10} hydrocarbons, 5.9%, 13.1%. The ultraviolet and infrared spectra indicated that the structures of these two hydrocarbons must be reasonably limited to 3-vinylcyclopentene (IV) and 4-vinylcyclopentene (V). The 13.1% component showed only end absorption in the ultraviolet (ϵ_{210} 250), while the infrared spectrum indicated a vinyl double bond (ν_{max} 905, 992, 1638 cm.$^{-1}$)[2] and a cyclopentene double bond (ν_{max} 1610 cm.$^{-1}$).[3] The spectra of the 5.9% component were very similar (end absorption, ϵ_{210} 1774; ν_{max} 910, 990, 1608, and 1635 cm.$^{-1}$). The n.m.r. spectrum of this minor component exhibits complex multiplet absorption centered at 4.38 (3.0 H), 5.04 (1.8 H), and 6.70 τ (0.9 H) and a complex absorption region, 7.50–8.50 τ (4.0 H), while the major (13.1%) component shows complex multiplet absorption centered at 4.16 and 4.39 (3.1 H), 5.08 (2.0 H), and a complex absorption region 6.93–8.10 τ (4.9 H). In both cases the internal olefinic absorption near 4.38

(1) National Defense Act Fellow, 1959–1962.

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, Chap. 3.

(3) R. N. Jones and C. Sandorfy, "Technique of Organic Chemistry. Volume IX. Chemical Applications of Spectroscopy," W. West, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 371.

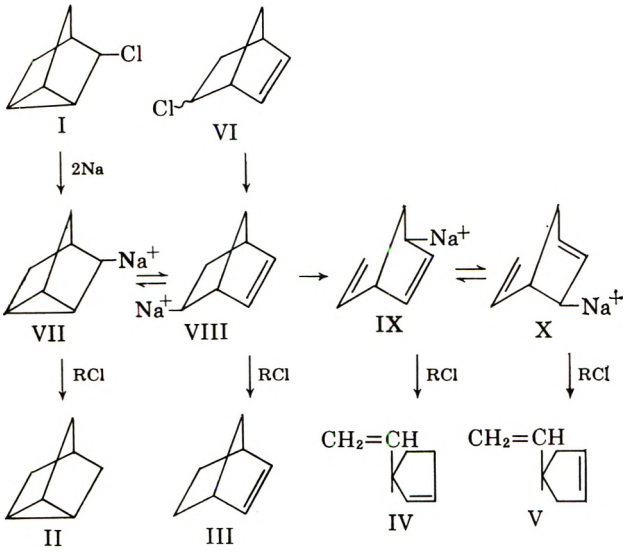
TABLE I

RCl	Reaction temperature,[a] °C.	Yield, %	II, %	III, %	IV, %	V, %	Norbornadiene, %
I	85–90 (133)	19.2	71.0	10.0	5.9	13.1	...
VI	85–90 (133)	27.1	64.0	13.0	7.5	13.5	2.0

[a] Temperature of oil bath. The figure in parentheses is maximum temperature reached inside the reaction flask due to the exothermic nature of the reaction.

τ and the terminal methylene near 5.04 τ are consistent with 3- and 4-vinylcyclopentene structures.[4]

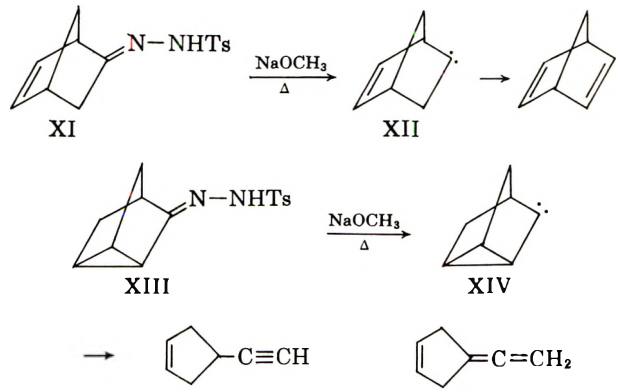
A choice may be made between the two possibilities, since in the spectrum of the minor (5.9%) component the single proton absorption at 6.70 τ appears at an appropriate position for a C–H alpha to two double bonds. This is supported by the fact that the methylene absorption region extends further upfield in the spectrum of the minor component—a reflection of the fact that one of the methylenes in the minor component is beta to the double bonds, while both methylenes in the major component are alpha.[4a] Thus, the minor component may be assigned structure IV, the major component V. Additional confirmation of the basic skeletal structure was obtained by hydrogenation of a



mixture of IV and V. The only product obtained was the known ethylcyclopentane.

When dehydronorbornyl chloride (VI) (50% *endo*, 50% *exo*) was allowed to react with sodium, using the same reaction conditions, a 27% yield of C_7 hydrocarbons was obtained. The composition of this volatile fraction (Table I) was very similar to that obtained from nortricyclyl chloride.

With the exception of the small amount of norbornadiene formed in the dehydronorbornyl chloride reaction, all the C_7 hydrocarbons formed are C_7H_{10} hydrocarbons and would not be expected to arise by way of a bivalent carbon precursor. The two bivalent carbon intermediates anticipated (XII and XIV) have been generated by decomposition of *p*-toluenesulfonylhydrazones XI and XIII. Decomposition of XI with sodium methoxide in bis(2-ethoxyethyl) ether at



180° resulted in a 25% yield of norbornadiene as the only C_7 hydrocarbon. Thus, the small amount of norbornadiene generated in the dehydronorbornyl chloride reaction may arise by either α- or β-elimination. Cristol and Harrington[5] have shown that decomposition of XIII with sodium methoxide in bis(2-methoxyethyl) ether at 160°, also results in a C_7H_8 hydrocarbon fraction: a 19% yield of a mixture of 4-ethynylcyclopentene (69%) and 4-vinylidenecyclopentene (29%). Evidence is presented which suggests that the 4-vinylidenecyclopentene arises as a result of base-catalyzed isomerization of 4-ethynylcyclopentene.

The similarity in skeletal structure of 4-ethynylcyclopentene to 3- and 4-vinylcyclopentene raised the possibility that 4-ethynylcyclopentene may possibly be a precursor of the vinylcyclopentenes. This possibility was tested by repeating the nortricyclyl chloride–sodium reaction and isolating the C_7 hydrocarbon fraction after neutralization of the reaction mixture with methyl alcohol. Small amounts of 4-vinylidenecyclopentene (0.6%) and 4-ethynylcyclopentene (2%) appeared to be present. A second experiment carried out with a mixture of nortricyclyl chloride (1.00 g.) and 4-ethynylcyclopentene (97 mg.), using identical reaction conditions, resulted in a 47% recovery of ethynylcyclopentene. Thus perhaps 4–5% 4-ethynylcyclopentene was originally formed in the nortricyclyl chloride–sodium reaction. However, the difference between the amount presumably generated and the amount isolated would not appear sufficient to explain vinylcyclopentene formation by way of an ethynylcyclopentene intermediate.

Since the C_7 hydrocarbon products are formed in very similar percentage compositions from both nortricyclyl and dehydronorbornyl chloride, it seems reasonable to suggest a common reaction pathway. Nortricyclene and norbornene may be pictured as arising *via* an equilibrium of homoallylic carbanions VII and VIII.[6] The dehydronorbornyl carbanion may rearrange through a shift of the pair of electrons at C-5 to form a double bond (C-5, C-6) and release

(4)(a) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, pp. 51–62; (b) the olefinic proton absorption regions in both spectra are quite similar to the olefinic proton absorption region of 4-vinylcyclohexene: N. S. Bhacca, L. F. Johnson and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 210.

(5) S. J. Cristol and J. K. Harrington, *J. Org. Chem.*, **28**, 1413 (1963).

(6) A similar homoallylic carbanion rearrangement has been observed by G. Wittig and E. Hahn, *Angew. Chem.*, **72**, 781 (1960).

of the electron pair bonding C-6 and C-1 to form allylic carbanions IX and X, which in turn may then proceed to product hydrocarbons IV and V. The rearrangement of VIII to IX is similar to the mechanism suggested for the cleavage of dehydronorcamphor with sodium amide.[7]

The experimental results presented do not rule out representation of the reactions in terms of mesomeric homoallylic and mesomeric allylic carbanions. Furthermore, a second mechanistic possibility is that the rearrangments occur *via* free radical intermediates, analogous to carbanions VII, VIII, IX, and X, which could be generated by a one electron transfer reaction of alkyl chloride and sodium.

Although it is unlikely that nortricyclene, norbornene, and the vinylcyclopentenes were generated *via* carbene intermediates, neutralization of the carbanions VII, VIII, IX, and X may occur by abstraction of an α-proton from I or VI. Since only trace amounts of C_7H_8 products (norbornadiene, 4-ethynylcyclopentene, and 4-vinylidenecyclopentene) were detected, the electrophilic carbene intermediate produced by α-elimination presumably adds to an alkylsodium to form a C_{14}-carbanion (after proton abstraction, a Wurtz hydrocarbon product[8]) more rapidly than it rearranges.[9]

Experimental[10]

Reaction of Nortricyclyl Chloride with Sodium.—A solution of 10 g. (0.078 mole) of nortricyclyl chloride in 10 ml. of redistilled *n*-decane was added, dropwise, with stirring, to a mixture of 1.80 g. (0.078 g.-atom) of freshly cut sodium pieces and 15 ml. of redistilled *n*-decane. The reaction was carried out at 85–90° (oil bath temperature) and under an atmosphere of nitrogen. After all the chloride had been added, stirring was continued for 1 hr. at 85–90°. An independent measurement using the conditions as described revealed that the temperature inside the reaction flask rose to a maximum of 133° during a 12-min. period from the time the chloride addition was begun, then fell back to the oil bath temperature.

After the stirring period was completed, the reaction mixture was subjected to vacuum distillation; the reaction flask was heated until decane (b.p. 63°, 20 mm.) reached the thermometer in the distillation head. The C_7 products (1.43 g., 19.2%) collected in the Dry Ice trap. Vapor phase chromatographic analysis on a 2-m. DC-200 silicone oil column (Perkin-Elmer column CX) demonstrated that this mixture consisted of 71.0% nortricyclene, 10.0% norbornene, and a 19.0% peak representing both 3- and 4-vinylcyclopentene. Nortricyclene and norbornene were separated and identified by comparison of their infrared spectra with a published spectrum of nortricyclene[11] and with the spectrum of an authentic sample of norbornene. The vinylcyclopentenes were also isolated by v.p.c.

Anal. Calcd. for C_7H_{10}: C, 89.29; H, 10.71. Found: C, 89.15; H, 10.65.

Subsequent v.p.c. on a 1-m. 40% phenylacetonitrile–silver nitrate (saturated at 90°) on firebrick column resolved the two vinylcyclopentene isomers to give 69% (13.1% of the total C_7 hydrocarbons) 4-vinylcyclopentene and 31% (5.9% of total) 3-vinylcyclopentene. A 0.78-g. mixture of the vinylcyclopentenes, isolated by v.p.c. on a 2-m. DC 200 silicone oil column was hydrogenated in ether over a 10% palladium-on-charcoal catalyst. The only product, separated from the solvent by v.p.c. was identified as ethylcyclopentane by comparison of its infrared spectrum with a published spectrum.[12]

The reaction of nortricyclyl chloride with sodium was repeated using one-half quantities, an oil bath temperature of 85–95° and otherwise identical reaction conditions. After the stirring period was completed, the reaction mixture was neutralized with methanol. The organic layer was washed several times with water and dried over anhydrous magnesium sulfate. Vapor phase chromatographic analysis (on a 3-m. DC-200 column) of a 2.46-g. fraction (b.p. 30–61° at 20 mm.) indicated the formation of 431 mg. (12%) of a four-component mixture: 84.8% nortricyclene, 5.2% norbornene, 9.4% 3- and 4-vinylcyclopentene, and 0.6% 4-vinylidenecyclopentene (identified by retention time comparison with an authentic sample). Since it was not possible to resolve 4-ethynylcyclopentene and norbornene simply by v.p.c., infrared analysis was used to detect 4-ethynylcyclopentene. The absorption at 3360 cm.$^{-1}$ indicated that as much as 2% of 4-ethynylcyclopentene was present in the C_7 hydrocarbon fraction.

Reaction of Nortricyclyl Chloride and 4-Ethynylcyclopentene with Sodium.—A solution of nortricyclyl chloride (1.00 g.) and 97 mg. of 4-ethynylcyclopentene in 420 mg. of a hydrocarbon mixture (23.2% of 4-ethynylcyclopentene, 8.2% 4-vinylidenecyclopentene, and 68.6% of pentane) in 2 ml. of *n*-decane was added to 180 mg. of sodium in 2 ml. of *n*-decane with stirring, under nitrogen, using an oil bath temperature of 85–95°. The remaining procedure was identical with the nortricyclyl chloride–sodium reaction in which the C_7 hydrocarbons were isolated after neutralization with methanol. Vapor phase chromatographic and infrared analysis showed that the 720 mg. fraction obtained (b.p. 30–50° at 20 mm.) contained a total of 162 mg. of C_7 hydrocarbons which included 46 mg. of ethynylcyclopentene (a 47% recovery).

Reaction of Dehydronorbornyl Chloride with Sodium.—The procedure for this reaction was identical with that described for nortricyclyl chloride in which the C_7 hydrocarbons were isolated directly from the reaction mixture by vacuum distillation. The dehydronorbornyl chloride used was a 50/50 mixture of the *exo* and *endo* isomers. A 27.1% yield of C_7 hydrocarbons was obtained. Vapor phase chromatographic analysis on a 2-m. DC 200 silicone–oil column and a 1-m. 40% phenylacetonitrile–silver nitrate (saturated at 90°) on firebrick column showed that the C_7-hydrocarbon composition was 64.0% nortricyclene, 13.0% norbornene, 7.5% 3-vinylcyclopentene, 13.5% 4-vinylcyclopentene, and 2.0% norbornadiene. Norbornadiene had the same retention time as the vinylcyclopentenes on the silicone–oil column, but was completely separated on the silver nitrate column.

Dehydronorcamphor *p*-Toluenesulfonylhydrazone.—A solution of 15.0 g. (0.139 mole) of dehydronorcamphor, prepared by the procedure of Cristol and Freeman[7] involving the Oppenauer oxidation of dehydronorborneol, and 25.95 g. (0.139 mole) of *p*-toluenesulfonylhydrazine in 225 ml. of 95% ethanol and 45 ml. of 6 *N* hydrochloric acid was heated at an oil bath temperature of 45–50° for 1 hr. After cooling to room temperature, the crystalline product was filtered and washed with petroleum ether. The filtrate was allowed to cool overnight in the refrigerator and a second crop of crystals was collected. The total yield amounted to 27.40 g. (71.4%) and had m.p. 177–181° dec. Recrystallization from 95% ethanol gave 16.90 g. with m.p. 183–184° dec. An analytical sample had m.p. 185–188° dec.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.84; H, 5.84. Found: C, 60.78; H, 5.91.

Carbenoid Decomposition of Dehydronorcamphor *p*-Toluenesulfonylhydrazone.—The method of Friedman and Shechter[13] was adapted to the decomposition of this particular hydrazone. In a 500-ml. three-necked flask, fitted with nitrogen inlet tube, mechanical stirrer, and Claisen distillation head, was placed 250 ml. of bis(2-ethoxyethyl) ether, which had been distilled from sodium, and 3.70 g. (0.0685 mole) of solid sodium methoxide, weighed and transferred in a nitrogen atmosphere. To this mixture was added 8.44 g. (0.0305 mole) of dehydronorcamphor *p*-toluenesulfonylhydrazone, and the system was flushed with nitrogen. The reaction mixture was heated with stirring to 180–183°. Distilling material was collected in a flask which was attached to the Claisen head by an adapter. The flask was im-

(7) S. J. Cristol and P. K. Freeman, *J. Am. Chem. Soc.*, **83**, 4427 (1961).

(8) The Wurtz hydrocarbons were not investigated.

(9) G. L. Closs, *J. Am. Chem. Soc.*, **84**, 809 (1962), has reported that chlorocarbene, generated by addition of methylene chloride to a mixture of *n*-butyllithium and olefin, adds to the olefin to produce only trace quantities of chlorocyclopropane. It seems clear that the low yields are due to the competing addition of the electrophilic carbene to *n*-butyllithium.

(10) Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(11) K. Alder, H. K. Schafer, H. Esser, H. Krieger, and R. Reubke, *Ann.*, **593**, 23 (1955).

(12) S. F. Sadtler, "Sadtler Standard Spectra, Midget Edition," S. F. Sadtler and Son, Philadelphia, Pa., 1957, Spectrum No. 11829.

(13) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959); **82**, 1002 (1960).

mersed in a Dry Ice bath and protected from atmospheric moisture with a calcium chloride drying tube. The reaction mixture was heated at 180–183° for 1 hr., at which time the flask was cooled down. A vacuum pump was attached and further material was distilled into the collection flask at 1–2 mm. until the solvent began to distil. The distillate, analyzed by v.p.c. on a 2-m. polypropylene glycol column (Perkin-Elmer column RX), contained only methanol, norbornadiene, and bis(2-ethoxyethyl) ether. Calculations, utilizing Eastman's formula,[14] gave 0.71 g. (25.3%) of norbornadiene. The norbornadiene generated in this reaction was isolated and identified by comparison of its infrared spectrum with that of an authentic sample.

Acknowledgment.—The authors gratefully acknowledge the support of this research by the National Science Foundation (NSF-G13511), and wish to express their appreciation to Dr. Donald P. Hollis and Varian Associates, Palo Alto, California, for the n.m.r. spectra.

(14) R. H. Eastman, *J. Am. Chem. Soc.*, **79**, 4243 (1957).

Reaction of α,ω-Dienes with Diisobutylaluminum Hydride

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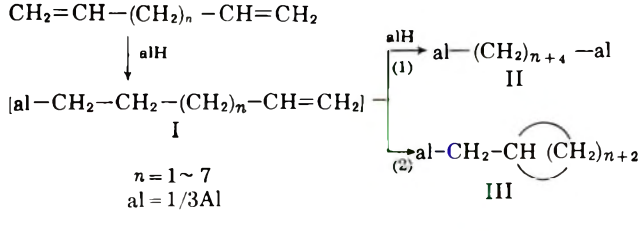
Received April 22, 1963

It is expected that organoaluminum compounds having two aluminum atoms attached to both ends of the polymethylene chain can be prepared by addition of aluminum hydride to an α,ω-diene. Ziegler[1] reported, however, that 1,5-hexadiene and diisobutylaluminum hydride gave methylenecyclopentane and a cyclopentylmethylaluminum compound, but not the expected 1,6-dialuminohexane derivative. It also was reported that 2,5-dimethyl-1,5-hexadiene easily cyclized to a five-membered ring compound.

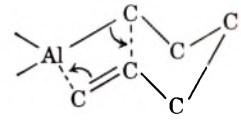
In this type of cyclization, the chain length of the α,ω-diene seems to be a most important factor. In order to clarify the effect of the chain length on the reaction product, we have investigated the reaction between diisobutylaluminum hydride and α,ω-dienes having carbon numbers from five to eleven.

The reaction was carried out by heating a mixture of the α,ω-diene and diisobutylaluminum hydride in a 1:2 molar ratio at 70° for sixteen hours. Two products, II and III, were obtained, but no ω-alkenylaluminum compound (I) was detected (see Table I).



It is clear from the table that the ratio of *n*-alkane to methylcycloalkane varies widely depending on the chain length of the starting diene. The reaction of 1,4-pentadiene resulted in an exclusive formation of 1,5-dialuminopentane derivative and no four-membered ring compound was formed. 1,5-Hexadiene gave predominantly the cyclopentylmethylaluminum derivative (97.6%). On the other hand, 1,6-heptadiene was found to form almost quantitatively the 1,7-dialuminoheptane derivative with a minor amount (0.9%) of the cyclohexylmethylaluminum derivative. The higher dienes gave exclusively the α,ω-dialuminoalkane compounds. Formation of the six-membered ring is very difficult in contrast to the ease of five-membered ring formation.

Reactions 1 and 2 are competitive and reaction 2 would proceed, as shown by formula IV, through the intramolecular addition reaction of the ω-alkenylaluminum compound produced by the addition of one mole of diisobutylaluminum hydride to α,ω-diene.



IV

Under the same reaction conditions, the intermolecular addition reaction of trialkylaluminum to α-olefin was found to be very slow. For example, the reaction of triethylaluminum with 1-hexene (molar ratio 1:1, 70°, 16 hr.) gives an addition compound in only 1% yield. The easy ring closure of 1,5-hexadiene to the five-membered ring compound suggests that the intramolecular addition of the 5-hexenylaluminum derivative is facilitated by the cyclic intermediate in which the carbon–aluminum bond is favorably located to attack the terminal double bond as shown in the preceding formula. On the other hand, difficulty in the six-membered ring formation shows that the steric requirement of the 6-heptenylaluminum derivative is less favorable for this type of attack.

This decisive effect of the chain length of an α,ω-diene on the reaction product indicates that the intramolecular addition reaction of an ω-alkenylaluminum compound is extremely sensitive to steric factor.

The 1,7-dialuminoheptane derivative has considerable stability at a higher temperature. At 125° a small portion of the compound cyclized to the cyclohexylmethylaluminum derivative. This ring closure seems to proceed through the reverse reaction of 1.

Experimental

Diisobutylaluminum Hydride.—The hydride was prepared by the pyrolysis of distilled triisobutylaluminum under a purified nitrogen atmosphere.[2] At the end of the pyrolysis, temperature and pressure were kept at 130° (3 mm.) until evolution of isobutylene ceased.

1,4-Pentadiene.—The previously described apparatus and method[3] were used to give 78% of 1,4-pentadiene from 205 g. (1.1 moles) of 1,5-diacetoxypentane. It was purified by digestion over sodium and repeated distillations through a Widmer column, b.p. 26.0–26.5°,[4] n^{20}D 1.3889.

1,5-Hexadiene.—The diene was prepared from allyl bromide and magnesium in ethyl ether. Purification was effected by distillation over sodium, followed by preparative gas chromatogra-

(1) K. Ziegler, "Organometallic Chemistry," H. Zeiss, Ed., Reinhold Publishing Corp., New York, N. Y., 1960, p. 234.

(2) K. Ziegler, H. G. Gellert, H. Lehmkuhl, W. Pfohl, and K. Zosel, *Ann.*, **629**, 1 (1960).

(3) R. E. Benson and B. C. McKusick, *Org. Syn.*, **38**, 78 (1958).

(4) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.*, **58**, 146 (1936).

TABLE I

REACTION OF α,ω-DIENES WITH DIISOBUTYLALUMINUM HYDRIDE

α,ω-Diene	Mole	$(i\text{-Bu})_2AlH$(mole)	Hydrolyzed products (composition, %)	
			n-Alkane	Methylcycloalkane
1,4-Pentadiene	0.03	0.063	*n*-Pentane (100)	.....
1,5-Hexadiene	0.02	0.042	*n*-Hexane (2.4)	Methylcyclopentane (97.6)
1,6-Heptadiene	0.02	0.042	*n*-Heptane (99.1)	Methylcyclohexane (0.9)
1,7-Octadiene	0.02	0.042	*n*-Octane (100)	.....
1,8-Nonadiene	0.03	0.063	*n*-Nonane (100)	.....
1,9-Decadiene	0.03	0.063	*n*-Decane (100)	.....
1,10-Undecadiene	0.03	0.063	*n*-Undecane (100)	.....

phy using a Beckman Megachrom instrument equipped with an Apiezon "L" column, $n^{20}D$ 1.4043.[5]

1,6-Heptadiene.—The procedure used by Marvel and Stille[6] was followed. Reduction of 97.2 g. (0.45 mole) of diethyl pimelate with a solution of 36 g. (0.9 mole) of lithium aluminum hydride in 1400 ml. of ethyl ether yielded 31 g. (53%) of 1,7-heptanediol, b.p. 125–127° (3.5 mm.). The diol (61 g., 0.46 mole) was acetylated with acetyl chloride in ethyl ether, yielding 89 g. (90%) of 1,7-diacetoxyheptane, b.p. 99–100° (0.6 mm.). Using the same apparatus as described for the preparation of 1,4-pentadiene, this acetate was subjected to pyrolysis at 500° with an addition rate of 1 ml./min. to yield 18 g. (45%) of 1,7-heptadiene, b.p. 90–93°. It was purified by distillation over sodium, followed by preparative gas chromatography, $n^{20}D$ 1.4148.[7]

1,7-Octadiene.—The diene (b.p. 115–121°)[8] was digested over sodium, redistilled and purified by preparative gas chromatography, $n^{20}D$ 1.4220.

1,8-Nonadiene.—Diethyl azelate was the starting ester for the preparation of 1,9-nonanediol. Pyrolysis of 162 g. (0.66 mole) of 1,9-diacetoxynonane[8] gave 60% of 1,8-nonadiene, b.p. 120–143°. After digestion over sodium and distillation through a Widmer column, it boiled at 142–143°, $n^{20}D$ 1.4289.[8]

1,9-Decadiene.—Pyrolysis of 87 g. (0.34 mole) of 1,10-diacetoxydecane was carried out at 500° with an addition rate of 2 ml./min., yielding 25 g. (53%) of 1,9-decadiene. The diene was digested over sodium and redistilled through a Widmer column, b.p. 164–165°, $n^{20}D$ 1.4318.[8]

1,10-Undecadiene.—The previously described method[9] was used to give diene of b.p. 86.5–87.5° (31 mm.), $n^{20}D$ 1.4354.

Purity of the prepared dienes, determined by vapor phase chromatography on an 8-ft. squalane column, was found to be 99.9% or higher.

Reaction between α,ω-Dienes and Diisobutylaluminum Hydride.—α,ω-Diene and diisobutylaluminum hydride in a 1:2.1 molar ratio were added to a glass tube flushed with nitrogen. After sealing, the glass tube was kept in an oil bath at 70° for 16 hr. The reaction products from 1,6-heptadiene, 1,7-octadiene, 1,8-nonadiene, 1,9-decadiene, and 1,10-undecadiene were viscous at a room temperature. Those from 1,4-pentadiene and 1,5-hexadiene were not viscous. The products from 1,4-pentadiene and 1,6-heptadiene were diluted with 10 ml. of *n*-hexane. The products from the other dienes were diluted with 10 ml. of *n*-heptane. The diluted products were decomposed by successive addition of 2.5 ml. of ethanol, 1 ml. of water, and 25 ml. of 6 *N* hydrochloric acid. The organic layer was washed twice with water and dried over sodium sulfate. The hydrocarbon produced by the hydrolysis was separated by the gas chromatographic technique. *n*-Pentane, *n*-hexane, methylcyclopentane, *n*-heptane, *n*-octane, *n*-nonane, *n*-decane, and *n*-undecane were identified by comparing their gas chromatographic retention times and infrared spectra with authentic samples. Methylcyclohexane was identified by comparison of its retention time with an authentic sample. The composition of the products was determined from the peak area of gas chromatogram.

Stability of 1,7-Dialumino-heptane Compound.—A mixture of 1.9 g. (0.02 mole) of 1,6-heptadiene and 6.0 g. (0.042 mole) of diisobutylaluminum hydride was at first heated under the same conditions as described previously (16 hr., 70°), and then for an additional 13 hr. at 125°. The reaction mixture was hydrolyzed as in the aforementioned method. The hydrolyzed product consisted of 91.5% of *n*-heptane and 8.5% of methylcyclohexane. Thus the additional heating at the higher temperature (125°) increased the yield of methylcyclohexane by 7.6%. Methylcyclohexane was separated by gas chromatographic technique and its infrared spectrum was identical with that of an authentic sample.

(5) F. Cortese, *J. Am. Chem. Soc.*, **51**, 2266 (1929).
(6) C. S. Marvel and J. K. Stille, *ibid.*, **80**, 1740 (1958).
(7) A. L. Henne and K. W. Greenlee, *ibid.*, **65**, 2020 (1943).
(8) C. S. Marvel and W. E. Garrison, *ibid.*, **81**, 4737 (1959).
(9) J. N. Reformatsky, E. Grischkewitsch-Frochimowsky, and A. Semenzow, *Ber.*, **44**, 1885 (1911).

Ferrocenes. VI. Oxidation in Friedel–Crafts Reactions[1,2]

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Received May 20, 1963

During an investigation toward the synthesis of difunctional ferrocenes, a number of attempted Friedel–Crafts reactions under nitrogen resulted in significant oxidation of ferrocene to ferricinium ion.

Although over thirty publications and patents describe Friedel–Crafts reactions on ferrocene with some thirty-five different acyl chlorides, only one was found in which the yield of ferrocene was reported from reduction of the purple aqueous layer obtained upon hydrolysis. In this instance, the reaction of chloroacetyl chloride, aluminum chloride, and ferrocene under conditions chosen for monosubstitution gave 32% ferrocene upon reduction of the aqueous layer.[3] Oxidation can be assumed to be small when hydrolysis produced an aqueous layer that was pale blue[4,5] or when yields of expected products exceeded 90%.[6,7]

Like chloroacetyl chloride, dichloro- and trichloroacetyl chlorides with aluminum chloride were found to oxidize ferrocene significantly; reduction of the purple aqueous layers gave ferrocene in 47 and 48% yields, respectively. Similarly, terephthaloyl, *p*-nitrobenzoyl, and ethyl oxalyl chlorides gave ferricinium ion in 57, 47, and 64% yields. The high per cent of oxidation with ethyl oxalyl chloride suggests that the failure

(1) Presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961.
(2) This investigation was conducted under Air Force Contract AF 33(616)-7214, monitored by the Aeronautical Systems Division, Wright-Patterson Air Force Base, Ohio.
(3) K. Schlögl, *Monatsh. Chem.*, **88**, 601 (1957). The organic layer yielded 12% chloroacetylferrocene and 16% unreacted ferrocene.
(4) M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, **80**, 5443 (1958).
(5) M. D. Rausch and L. E. Coleman, *J. Org. Chem.*, **23**, 107 (1958).
(6) M. D. Rausch, M. Vogel, and H. Rosenberg, *ibid.*, **22**, 903 (1957).
(7) E. L. DeYoung, *ibid.*, **26**, 1312 (1961).

of oxalyl chloride to undergo a normal Friedel–Crafts reaction on ferrocene[8] may be due to oxidation.

It is commonly accepted by chemists in the ferrocene field that oxidized products from Friedel–Crafts reactions arise as a result of inadvertent exposure of reaction mixtures to moisture and oxygen.[9] While this may be true in instances of 5% oxidation or less, it is unlikely that this is the case with major oxidations unless a catalytic effect exists that varies greatly with the acyl halide. We found oxidation to be insignificant with *p*-fluorobenzoyl chloride, benzoyl chloride,[6] and *n*-butyryl chloride.[10]

A more attractive interpretation for significant oxidations is that the acylium ion that is formed from the acyl chloride and aluminum chloride may remove an electron from the ferrocene system in competition with acylation, and that the former reaction to give ferricinium ion is a major one if the acylium ion is sufficiently positive. All of the mentioned oxidizing acyl chlorides have electron-withdrawing groups adjacent to the chlorocarbonyl group and should produce an acylium ion more electron deficient than that of a simple acyl halide. With the limited data, however, the delineation between oxidizing and nonoxidizing acyl chlorides is not clear-cut. Thus, while terephthaloyl chloride caused 57% oxidation, *o*-carbomethoxybenzoyl chloride gave 83% monoacylated ferrocene.[11]

$$C_{10}H_{10}Fe \xrightarrow[\text{(b) } H_2O]{\text{(a) RCOCl, } AlCl_3} (C_{10}H_{10}Fe)^+ \quad 37\text{–}64\%$$

R = *p*-$ClCOC_6H_4$–, *p*-$NO_2C_6H_4$–, Cl_3C–, Cl_2CH–, and C_2H_5OOC–

Major oxidation was also encountered when chloroacetal was added to ferrocene and aluminum chloride. Reduction of the aqueous layer gave 37% ferrocene and about 20% ferrocenyl compounds, while the organic layer returned 19% ferrocene and about 15% of a crude ferrocene, m.p. 14–21°. Here, the probable intermediate carbonium ion was bound to two electron-withdrawing groups ($ClCH_2C^+HOCH_2CH_3$) and should be unusually electron deficient. Under different conditions, triphenylmethylcarbonium ion also oxidized ferrocene.[12] While chloroacetal gave both substituted and unsubstituted ferricinium ions, the acyl chlorides gave only the latter, in accord with the failure of acylferrocenes to form isolatable ferricinium derivatives.[13]

The oxidations might appear to be related to the recently reported[14,15] degradation of ferrocene by aluminum chloride, in which oxidation was postulated by Goldberg as an intermediate step.[16] However, electron-rich ferrocene in the latter case was apparently attacked by electron-poor aluminum chloride and in the former case by electron-poor acylium ions. With the differences in attacking species, the results were also different: disruption of iron-cyclopentadienyl bonding *vs.* removal of an electron from the ferrocene system. Goldberg's assumption that oxidation was a step in the degradation required a second assumption that enough air and moisture were inadvertently introduced to bring about the oxidation.[15] If such were the case, a fair amount of ferricinium ion should be present at work-up, but the results, at least at lower temperatures, were not significantly altered by omitting the reduction of the aqueous layer prior to isolation.[17] If oxidation is not an intermediate step—and it seems unnecessary in view of the strong attraction of aluminum chloride for π-electrons—then the degradation reaction is of interest here only as a potential side reaction.

In this regard, it would seem important to prepare the acyl chloride–aluminum chloride complex first rather than to allow ferrocene to come in contact with the aluminum chloride. This procedure was not always followed, however, and in practice the order of addition was not critical. Thus, addition of ferrocene to the Perrier complex from dichloroacetyl chloride gave 47% ferricinium ion, and addition of aluminum chloride to a mixture of ferrocene and trichloroacetyl chloride yielded 37–48% ferricinium ion.

The organic layers from the oxidation reactions were in general examined only to the point at which it was evident that the reactions were unsuitable for preparation of heteroannularly disubstituted ferrocenes in quantity.

Experimental

Reactions of Ferrocene and Aluminum Chloride with Terephthaloyl, *p*-Nitrobenzoyl, and Dichloroacetyl Chlorides.—These reactions are typified by the following example with terephthaloyl chloride. To 30.5 g. (0.15 mole) of terephthaloyl chloride in 100 ml. of dry methylene chloride under nitrogen in an ice bath was added 20.0 g. (0.15 mole) of aluminum chloride in five portions during a 30-min. period. The mixture was stirred in the ice bath while 9.3 g. (0.05 mole) of ferrocene in 50 ml. of dry methylene chloride was added during a 2-hr. period. After the mixture was stirred overnight, it was poured into 100 ml. of methanol, stirred 30 min., and added to 250 ml. of water. The water layer was extracted once with chloroform and treated with zinc dust until the purple had disappeared. Filtration of the aqueous mixture, extraction of the solids with chloroform, and evaporation of the dried extract left 5.34 g. (57%) of ferrocene, identified by infrared comparison.

With *p*-nitrobenzoyl chloride, 47% of the ferrocene was recovered by reduction of the aqueous layer.

With dichloroacetyl chloride at a reactants ratio of 2:5:5 instead of 1:3:3, reduction of the aqueous layer gave material amounting to 47% of the starting ferrocene; the infrared spectrum showed two medium carbonyl bands not present in the spectrum of ferrocene. No methanol was used in the work-up. When boron trifluoride was the catalyst at a reaction time of 3.5 hr. at ice-bath temperature, 16% ferrocene was isolated from the aqueous layer and 62% ferrocene from the organic layer.

Reactions of Ferrocene and Aluminum Chloride with Trichloroacetyl Chloride and with Ethyl Oxalyl Chloride.—To a solution of 3.72 g. (0.02 mole) of ferrocene and 5.6 ml. (0.05 mole) of trichloroacetyl chloride in 40 ml. of dry methylene chloride at

(8) In one instance it was reported that no reaction took place, and this would appear to be the case if the aqueous layer were routinely reduced prior to isolation [R. Riemschneider and D. Helm, *Chem. Ber.*, **89**, 155 (1956)]. In another instance, 0.5% diferrocenyl ketone was isolated [S. I. Goldberg, *J. Org. Chem.*, **25**, 482 (1960)].

(9) Two referees took this view of a shorter version of the present work.

(10) M. Vogel, M. Rausch, and H. Rosenberg, *J. Org. Chem.*, **22**, 1016 (1957).

(11) A. N. Nesmeyanov, N. A. Vol'kenau, and V. D. Vilchevskaya, *Dokl. Akad. Nauk SSSR*, **118**, 512 (1958).

(12) M. F. Hawthorne, *J. Org. Chem.*, **21**, 363 (1956).

(13) R. B. Woodward, M. Rosenblum, and M. C. Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).

(14) S. G. Cottis and Harold Rosenberg in "Conference on High Temperature Polymer and Fluid Research," Technical Documentary Report No. ASD-TDR-62-372, August, 1962, p. 637.

(15) S. I. Goldberg, *J. Am. Chem. Soc.*, **84**, 3022 (1962).

(16) Goldberg referred to the work of Rosenblum and Santer that concerned the complex $(C_{10}H_{10}Fe \cdot HAlCl_4)_n$. This complex yielded ferrocene upon hydrolysis and not ferricinium ion [*J. Am. Chem. Soc.*, **81**, 5517 (1959)].

(17) H. Rosenberg, private communication.

−30° was added 6.66 g. (0.05 mole) of aluminum chloride in three portions during a 5-min. period. After 2 hr. below −20°, the mixture was poured into ice water and stirred 5 min. The organic layer was extracted three times with water and the extracts and water layer combined. Treatment of the aqueous solution with zinc dust and subsequent extraction with chloroform gave 1.37 g. (37%) of ferrocene (infrared comparison).

A similar reaction with ethyl oxalyl chloride gave 64% ferrocene (infrared comparison) upon reduction of the aqueous layer.

Reaction of Ferrocene and Aluminum Chloride with Chloroacetal.—Chloroacetal (15.3 g.; 0.1 mole) was added dropwise during an 80-min. period to 9.3 g. (0.05 mole) of ferrocene and 13.3 g. (0.10 mole) of aluminum chloride in 65 ml. of ethylene dichloride under nitrogen at −20°. After 30 min., the mixture was warmed to −5°, added to ice, and the aqueous layer extracted with chloroform. After removal of solvent from the combined organic layers, the residue (5.92 g.) was extracted with 120 ml. of petroleum ether (b.p. 30–60°) in 20-ml. portions and each portion added to 180 g. of alumina and eluted with petroleum ether to give 1.75 g. (19%) of ferrocene. Continued elution with the usual solvents removed distinct fractions (oils), the infrared spectra of which suggested that the ferrocenes present were monosubstituted. Reduction of the aqueous layer with zinc dust, extraction with chloroform, and removal of solvent left moist solid, which when extracted with methanol left 3.04 g. (33%) of crude ferrocene. Removal of methanol and chromatography of the residue (2.73 g.) gave 4% ferrocene and 1.65 g. of solid, m.p. 14–21°, the infrared spectrum of which showed strong bands at 9 and 10 μ (a monosubstituted ferrocene).

1,1′-Bis(*p*-fluorobenzoyl)ferrocene.—A mixture of 37.1 g. (0.263 mole) of *p*-fluorobenzoic acid and 48 ml. (0.658 mole) of thionyl chloride in 25 ml. of benzene was refluxed 7 hr. Volatile material was removed *in vacuo*, 90 ml. of dry methylene chloride was added, and the solution was treated with 31.1 g. (0.233 mole) of powdered anhydrous aluminum chloride. To the mixture in an ice bath was then added dropwise a solution of 17.3 g. (0.093 mole) of ferrocene in 90 ml. of methylene chloride during a 1.5-hr. period, and the mixture was stirred overnight at room temperature. The solution was poured onto ice, stirred 4 hr., and the aqueous phase washed with chloroform. The organic phases were combined, washed twice with water and once with 5% sodium hydroxide solution, dried, and evaporated *in vacuo*. Crystallization of the residue from 150 ml. of toluene yielded 30.4 g. (76%) of 1,1′-bis(*p*-fluorobenzoyl)ferrocene, m.p. 129–130.5°; λ_{max} (log ϵ) 472 (2.83), 350 (3.29), 250 mμ (4.28).

Anal. Calcd. for $C_{24}H_{16}F_2FeO_2$: C, 67.00; H, 3.75; Fe, 12.98. Found: C, 66.95; H, 3.86; Fe, 13.63.

1,1′-Bis(*n*-butyryl)ferrocene.—The reaction of *n*-butyryl chloride, aluminum chloride, and ferrocene was carried out by the method employed by Vogel, *et al.*, for the preparation of 1,1′-dicaprylylferrocene.[10] 1,1′-Dibutyrylferrocene, m.p. 73.0–74.5°, was obtained in 77% yield; lit.[18] m.p. 74–75°.

Acknowledgment.—We are grateful to Mr. Richard Thivierge for technical assistance.

(18) A. N. Nesmeyanov and N. A. Vol'kenau, *Dokl. Akad. Nauk SSSR*, **107**, 262 (1956).

o-Nitrosobenzamide. A Possible Intermediate in the von Richter Reaction

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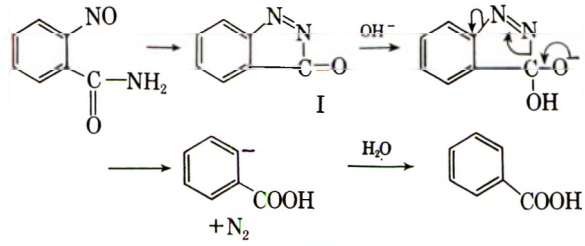
Received May 29, 1963

The previously unknown *o*-nitrosobenzamide has been synthesized and its behavior under the conditions of the von Richter reaction studied; the conditions of the von Richter reaction employed were those established by the research of Bunnett and his group.[1] This work was undertaken because of our interest in the peroxy acid oxidations of aromatic amines[2] and of nitrosobenzenes,[3] and because *o*-nitrosobenzamide has been implicated as an intermediate in the von Richter reaction.[4]

o-Nitrosobenzamide was obtained in excellent yield by oxidizing *o*-aminobenzamide with peroxyacetic acid in ethanolic medium at *ca.* 0°. These conditions previously have been shown[2] to favor the formation of nitrosobenzenes as the chief products of the peroxyacetic acid oxidation of aromatic amines. The amido group in the present substrate did not cause any complications. Its indifference to peroxyacetic acid was foreseen on mechanistic grounds[2] and by analogy with the peroxyacetic acid oxidation of nicotinamide to nicotinamide N-oxide in 82% yield.[5] The elemental and spectral analyses of the reaction product confirmed it to be the desired nitrosobenzamide.[2,6]

A recently proposed mechanism for the von Richter reaction[4] requires that *o*-nitrosobenzamide should give benzoic acid and nitrogen gas according to the following reaction sequence.



When *o*-nitrosobenzamide was treated with cyanide ion or hydroxide ion in aqueous ethanolic medium at 150°, the von Richter reaction conditions,[1] benzoic acid was formed with evolution of nitrogen gas as predicted by the Rosenblum mechanism.[4] The yield of isolated benzoic acid was 20% with cyanide ion and 45% with hydroxide ion. The reported yields of benzoic acids from the von Richter reaction range between 10 and 40%.[1] The isolated product melted at 122° and its ultraviolet spectrum in water was superimposable with that of an authentic sample of benzoic acid.

A transient red color appeared immediately upon addition of base to the aqueous ethanolic solutions of *o*-nitrosobenzamide. This color may be attributable to the formation of 3-indazolone, the intermediate I. The preparation of I (in solution) by independent synthesis and its hydrolysis to benzoic acid and nitrogen gas has been reported recently.[7] The solutions of I in acetonitrile were reported to have deep red color.[7]

Experimental

Materials.—*o*-Aminobenzamide (Matheson Coleman and Bell, practical grade) was purified by treatment with decolorizing

(1) (a) J. F. Bunnett, J. F. Cormack, and F. C. McKay, *J. Org. Chem.*, **15**, 481 (1950); (b) J. F. Bunnett, M. M. Rauhut, D. Knutson, and G. E. Bussell, *J. Am. Chem. Soc.*, **76**, 5755 (1954); (c) J. F. Bunnett and M. M. Rauhut, *J. Org. Chem.*, **21**, 934 (1956).

(2) K. M. Ibne-Rasa and J. O. Edwards, *J. Am. Chem. Soc.*, **84**, 763 (1962).

(3) K. M. Ibne-Rasa, C. G. Lauro, and J. O. Edwards, *ibid.*, **85**, 1165 (1963).

(4) M. Rosenblum, *ibid.*, **82**, 3796 (1960).

(5) E. C. Taylor, Jr., and A. J. Crovetti, *Org. Syn.*, **37**, 63 (1957).

(6) K. Nakamoto and R. E. Rundle, *J. Am. Chem. Soc.*, **78**, 1113 (1956).

(7) E. F. Ullman and E. A. Bartkus, *Chem. Ind.* (London), 93 (1962).

charcoal and recrystallization from ethanol to m.p. 109–111°; lit.[8] m.p. 109–111.5°. Commercial peroxyacetic acid solutions, generously donated by BECCO, were used.

Preparation of *o*-Nitrosobenzamide.—To absolute ethanol (40 ml.), previously saturated with anhydrous sodium acetate, was added ~40% peroxyacetic acid (20 ml.). The mixture was centrifuged and the supernatant liquid cooled to 0°. To the cooled solution was added a solution of *o*-aminobenzamide (1.4 g.) in ethanol (20 ml.), and the reaction mixture was allowed to stand for about 1 hr. The solution was then evaporated at room temperature (reduced pressure) to lower volume (about 15 ml.); the precipitated solid was removed by filtration, and washed first with cold ethanol (−10°) and then with ether. The product (1.3 g., 85%) was a pale green solid, m.p. 220° dec. It was stored at −10° in the absence of light until used. Absorption (in ethanol): λ_{max} at 750 (1.40; 0.01 *M* solution), 310 (3.67), and 285 mμ (log ε 3.71). Selected infrared maxima (KBr): 6.7 and 7.9 μ.

Anal. Calcd. for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66. Found: C, 56.51; H, 4.25; N, 18.36. The elemental analysis was done by Dr. S. M. Nagy at Massachusetts Institute of Technology.

Reaction of *o*-Nitrosobenzamide with Cyanide Ion.—*o*-Nitrosobenzamide (2.0 g.) was heated with an equivalent amount of potassium cyanide (or sodium hydroxide) in 60 ml. of 50% aqueous ethanol in a sealed tube at 140–160° for 1.25 hr. The resulting brownish solution was acidified with hydrochloric acid and repeatedly treated with decolorizing charcoal until colorless. The clear solution was then made basic, evaporated to near dryness, and acidified with hydrochloric acid, and the resulting precipitate was removed by filtration. This precipitate was then sublimed once and the yellowish sublimate recrystallized from water. The resulting benzoic acid melted at 122°. Its ultraviolet spectrum in aqueous medium was identical with that of an authentic sample of benzoic acid, and it did not depress the melting point of authentic benzoic acid. The yield of the isolated product was 20% with cyanide ion and 40% with hydroxide ion. The reaction was accompanied by the evolution of a gas, which was dried with liquid nitrogen and then shown to be nitrogen by mass spectral analysis.

Acknowledgment.—The authors wish to thank Professors J. F. Bunnett and J. O. Edwards for their kind interest in this work. Professor Bunnett directed our attention to ref. 4. This work was supported in part by the U. S. Atomic Energy Commission, Contract 1983. The gas analysis was performed at Harvard University through the courtesy of Dr. G. O. Dudek.

(8) I. M. Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1934, p. 37.

Amines Derived from Dihalopropenes. V.[1a] Reaction of 2-Haloallylamines with Various Bases[1b]

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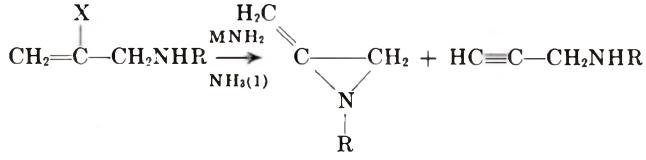
Received May 20, 1963

An N-alkylallenimine III is obtained as the main product from the reaction of an N-(2-bromoallyl)-alkylamine I with sodium amide in liquid ammonia,[2,3] but the only discernible product from the reaction of N-(2-chloroallyl)ethylamine (IIa, R = C_2H_5) with potassium amide in liquid ammonia was N-ethylpropargylamine (IVa, R = C_2H_5). In order to determine if the course of the reaction of an N-(2-haloallyl)alkylamine with amide in liquid ammonia was influenced by the alkyl metal cation,[4] we examined the reactions of the N-(2-haloallyl)ethylamines with the common alkali metal amides in liquid ammonia. Reactions were carried out on a small scale, and the yields and product compositions were determined by gas–liquid partition chromatography (g.l.p.c.).



I, X = Br
II, X = Cl

III IV

We observed no significant difference in the yields or product compositions from reactions of N-(2-bromoallyl)ethylamine (Ia, R = C_2H_5) with lithium amide, sodium amide, and potassium amide. Using a constant amide–Ia mole ratio of 1.2, which Pollard and Parcell found gave optimum yields of allenimines from N-(2-bromoallyl)alkylamines,[2] initial Ia concentrations of 0.25 and 0.5 *M*, and reaction times of 4.5 to 5 hr., imine–amine mixtures consisting of 75–82% N-ethylallenimine (IIIa, R = C_2H_5) were obtained in yields of 48–62%. As the 2,3-dibromopropene used for the preparation of Ia and other N-(2-bromoallyl)alkylamines contained less than 1.5% of the isomeric 1,3-dibromopropenes,[5] we could estimate that the Ia contained less than 2% of the isomeric N-(3-bromoallyl) ethylamines, which yield only the propargylamine under the reaction conditions used for allenimine formation.[6] Thus, most of the IVa was formed from dehydrobromination of Ia.

The product compositions obtained from all reactions of N-(2-chloroallyl)ethylamine (IIa) with any of the three alkali metal amides were identical and consisted of <1% IIIa and >99% IVa. Under the same reaction conditions used for Ia, treatment of IIa at an initial concentration of 0.5 *M* with potassium amide gave yields of 50–56% based on IIa, while use of lithium amide or sodium amide gave yields of 20–29%. When the amide–IIa ratio was increased to more than 2, yields of IVa from reactions of potassium amide with IIa at an initial concentration of 0.4 *M* were increased to over 80%. Comparable yields were also obtained using sodium amide, but reaction times of 9–10 hr. were required instead of 5 hours.

Reactions of N-(2-bromoallyl)methylamine, N-(2-bromoallyl)isopropylamine, and N-(2-bromoallyl)-hexylamine were carried out on a preparative scale with 0.8–1.5 moles of the amine using sodium amide–I ratios of 1.2. These reactions gave 46–70% yields of mixtures of three to four parts of the corresponding

(1) (a) Part IV: A. T. Bottini, V. Dev, and M. Stewart, *J. Org. Chem.*, **28**, 156 (1963); (b) acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research; (c) American Chemical Society Petroleum Research Fund Fellow, 1961.

(2) C. B. Pollard and R. F. Parrell, *J. Am. Chem. Soc.*, **73**, 2925 (1951).

(3) A. T. Bottini and J. D. Roberts, *ibid.*, **79**, 1462 (1957).

(4) See W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **24**, 416 (1959).

(5) Treatment of the 2,3-dibromopropene with lithium aluminum hydride in ether gave a mixture of 1- and 2-bromopropenes that was 98.8% 2-bromopropene as determined by g.l.p.c. See L. F. Hatch, P. D. Gardner, and R. E. Gilberg, *J. Am. Chem. Soc.*, **81**, 5943 (1959), for an earlier application of a method similar to that used by us.

(6) A. T. Bottini, B. J. King, and J. M. Lucas, *J. Org. Chem.*, **27**, 3688 (1962).

TABLE I

PHYSICAL AND ANALYTICAL DATA OF 2-HALOALLYLAMINES AND ALLENIMINES

Compound	R	B.p., °C. (mm.)	$n^{25}D$	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	t-C_4H_9	103–105 (90)	1.4671	43.76	7.34	7.29	43.71	7.17	7.06
I	n-C_6H_{13}	122–124 (24)	1.4715	49.10	8.24	6.36	48.96	7.87	5.97
II	t-C_4H_9	61–62 (26)	1.4431	56.93	9.55	...	56.81	9.66	...
III	CH_3	52.2–52.6 (760)	1.4380	[a]	...	...	...	...	...
III	t-C_4H_9	113–115 (760)	1.4350	75.62	11.78	12.60	75.26	11.69	12.55

[a] Because of the volatility of this compound, a satisfactory elemental analysis was not obtained. A study of the n.m.r. spectrum of N-methylallenimine has been reported by A. Lowenstein, J. F. Neueer, and J. D. Roberts, *J. Am. Chem. Soc.*, **82**, 3599 (1960).

allenimine and one part of the corresponding propargylamine. Treatment of N-(2-bromoallyl)-*t*-butylamine (Ib, R = *t*-C_4H_9) under conditions optimum for formation of other allenimines from other N-(2-bromoallyl)-alkylamines gave a 45% yield of a mixture containing 32% N-*t*-butylallenimine (IIIb, R = *t*-C_4H_9) and 68% N-*t*-butylpropargylamine (IVb, R = *t*-C_4H_9). A number of small scale reactions were carried out using Ib at an initial concentration of 0.4 *M* and sodium amide–Ib mole ratios ranging from 1.4 to 2.0. An amide–Ib mole ratio of 1.6 to 1.8 appeared to be optimum, and three preparative scale reactions using a mole ratio of 1.7 gave 62–68% yields of products consisting of 35–45% IIIb and 55–65% IVb.

N-Isopropylpropargylamine[7a] and N-*t*-butylpropargylamine (IVb)[7b] were isolated in yields of 82% and 87%, respectively, from reactions of 0.55 mole of N-(2-chloroallyl)-isopropylamine[7a] and 0.8 mole of N-(2-chloroallyl)-*t*-butylamine with 2.1 equivalents of sodium amide. Products from these reactions contained less than 1% of the allenimine as estimated by g.l.p.c.

Several observations incidental to this work should also be noted. Treatment of either I or II with sodium amide, lithium aluminum hydride, and methylmagnesium bromide in ether at 35° proved to be unsatisfactory methods of preparation for either III or IV. Surprisingly, Ia was found to undergo significant dehydrobromination to IVa in liquid ammonia when treated with coarsely powdered sodium hydroxide.

Experimental[8]

Preparation of N-(2-Haloallyl)alkylamines, N-Alkylallenimines, and N-Alkylpropargylamines.—Appropriate modifications of the procedure described for the preparation of N-(2-bromoallyl)-*n*-propylamine,[9] which is a slight modification of the procedure of Pollard and Parcell[2] for the preparation of N-(2-bromoallyl)-alkylamines from water-soluble primary amines, were used for the preparation of the N-(2-haloallyl)alkylamines except N-(2-bromoallyl)methylamine and N-(2-bromoallyl)-*n*-hexylamine. Yields ranged from 68–84%.

N-(2-Bromoallyl)-*n*-hexylamine (283 g.) was obtained in 66% yield by use of a modification of Pollard and Parcell's procedure[2] for the preparation of N-(2-bromoallyl)alkylamines from water-insoluble primary amines. Isopropyl ether was used as solvent in place of ethyl ether, and the reaction mixture was stirred mechanically.

Addition with stirring over a period of 220 min. of 600 g. (3.0 moles) of 2,3-dibromopropene to 2000 g. of 40% by weight aqueous methylamine (25.8 moles) in a 5-l. flask equipped with a Dry Ice condenser charged with an ice–salt mixture gave 283 g. (63%) of N-(2-bromoallyl)methylamine, b.p. 66–68° (90 mm.), $n^{25}D$ 1.4858, lit.[10] b.p. 135°, and 54 g. (13%) of methyl bis(2-bromoallyl)amine, b.p. 93–95° (7 mm.), $n^{25}D$ 1.5236, lit.[10] b.p. 100–102° (14 mm.).

With the exception that commercial sodium amide was usually used in place of freshly prepared sodium amide, Pollard and Parcell's procedure[2] was used for the preparation of allenimines from N-(2-bromoallyl)alkylamines. The use of toluene in place of ether was found to simplify the isolation of N-methylallenimine. Allenimines that were >99.5% pure as indicated by g.l.p.c. were obtained from distillations through a 1000 × 13 mm. column packed with glass helices and equipped with a total reflux head.

Preparations of N-alkylpropargylamines from N-(2-chloroallyl)alkylamines were carried out in the same manner as preparations of N-alkylallenimines from N-(2-bromoallyl)alkylamines except reaction times were 10 hr. or longer and the sodium amide–N-(2-chloroallyl)alkylamine mole ratio was 2.1. Initial sodium amide concentrations were 0.8 *M*.

Boiling points, refractive indices, and elemental analyses of new compounds are given in Table I.

Analytical Method.—Solutions containing 19–78% N-ethylallenimine (IIIa) by weight were prepared using IIIa and N-ethylpropargylamine (IVa) that were >99.5% pure. Each of these solutions was diluted with ether to give a series of solutions containing 64.2–99.1% ether by weight, and g.l.p. chromatograms were taken of 5 μl. samples of all solutions at 120° with a helium flow rate of 90 ml./min. The retention times (t_r) in sec. measured from the air peak were 50, 215, and 330 for ether, IIIa, and IVa, respectively. A linear plot with a slope of unity was obtained when the weight fraction of IIIa was plotted against $H_{IIIa}/(H_{IIIa} + H_{IVa})$ where H_{IIIa} and H_{IVa} are the peak heights of the bands due to IIIa and IVa, respectively. Data obtained for all solutions (0–99.1% ether by weight) fitted the plot, and no value of $H_{IIIa}/(H_{IIIa} + H_{IVa})$ was obtained that was different from the weight-fraction of IIIa by more than 2%. The accuracy of the analytical method was not affected by the addition to the solutions of N-(2-bromoallyl)ethylamine, t_r = 1550 sec., or N-(2-chloroallyl)ethylamine, t_r = 845 sec., or by variation of the sample size from 2 to 10 μl.[11] For solutions containing 90.8–99.1% ether by weight, the sum of the weight fractions of IIIa and IVa was equal to (2.4 ± 0.2) $(H_{IIIa} + H_{IVa})/(H_{IIIa} + H_{IVa} + H_e)$, where H_e is the normalized height of the ether band.

Description of a typical small scale reaction and analysis follows. A slurry of potassium amide was prepared by the addition of 2.38 g. of potassium to 100 ml. of ammonia and 12 mg. of anhydrous ferric chloride contained in a 250-ml. flask equipped with a sealed mechanical stirrer and Dry Ice condenser protected with a tube containing soda lime. N-(2-Bromoallyl)ethylamine (Ia, 8.2 g.) was added to the stirred slurry from a syringe in 2 min. After 4.5 hr., the Dry Ice had been allowed to evaporate, and the condenser was charged with an ice–salt mixture. Ether (50 ml.) and water (50 ml.) were added cautiously in that order. The ammonia was allowed to evaporate, the phases were separated, and the aqueous solution was extracted with 30 ml. of ether. The ether extracts were combined and dried with sodium

(7) These compounds are prepared more conveniently by the reaction of propargyl bromide with excess alkylamine: (a) J. J. D'Amico, M. W. Harman, and R. H. Cooper, *J. Am. Chem. Soc.*, **79**, 5270 (1957); (b) J. J. D'Amico, U. S. Patent 2,943,079 (June 28, 1960); *Chem. Abstr.*, **54**, 25,943 (1960).

(8) Boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. Gas–liquid partition chromatograms were obtained using a 2-m. column packed with nonyl phthalate on firebrick in a Model 1 Chromat-O-Flex, Loe Engineering Co., Pasadena, Calif. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif., and Drs. Weiler and Strauss, Oxford, England.

(9) A. T. Bottini and R. E. Olsen, *J. Am. Chem. Soc.*, **84**, 195 (1962).

(10) J. V. Braun, M. Kühn, and J. Weismantel, *Ann.*, **449**, 249 (1926).

(11) A standard curve for analysis of mixture of N-*t*-butylallenimine (IIIb, t_r = 465 sec.) and N-*t*-butylpropargylamine (IVb, t_r = 640 sec.) was also prepared from data obtained in a similar manner. The plot of weight fraction of IIIb *vs.* $H_{IIIb}/(H_{IIIb} + H_{IVb})$ was also linear with a slope of unity.

hydroxide. The average values of $(H_{IIIa} + H_{IVa})/(H_{IIIa} + H_{IVa} + H_c)$ and $H_{IIIa}/(H_{IIIa} + H_{IVa})$ in 3 g.l.p. chromatograms of the ether solution, which weighed 54 g., were $(1.84 \pm 0.08)\ 10^{-2}$ and 0.77 ± 0.01, respectively, indicating that the conversion was 58% and that the product was 77% IIIa and 23% IVa.

Miscellaneous Reactions of N-(2-Haloallyl)ethylamines with Various Bases.—Treatment of 8.2 g. of N-(2-bromoallyl)ethylamine (Ia) with 2 g. of sodium amide in 100 ml. of ether at 25° for 5 hr. and room temperature for 24 hr., gave a 29% conversion to IVa. No IIIa was detected by means of g.l.p.c. A 6.0-g. sample of N-(2-chloroallyl)ethylamine (IIa) was treated in the same manner. No indication of the presence of IIIa or IVa in the ether solution was obtained by g.l.p.c.

Treatment of 36 g. of Ia with 300 ml. of *N*-methylmagnesium bromide in ether at reflux for 4 hr. and at room temperature for 16 hr., gave a 10% yield of a mixture of 24% IIIa and 76% IVa. Formation of IIIa and IVa was confirmed by means of infrared spectroscopy, and 29 g. (80%) of Ia was recovered. N-(2-Chloroallyl)isopropylamine (35 g.) was treated in the same manner. Traces of the corresponding III and IV (~90% IV), estimated as <0.5 g. (<2%), were detected by g.l.p.c.

Compound Ia (36.0 g.) was treated with 2.8 g. of lithium aluminum hydride in 300 ml. of ether at reflux for 2.5 hr. The mixture had darkened considerably after 1 hr. The mixture was allowed to stand overnight, and 10 ml. of water was added cautiously with stirring. After 1 hr., the ether solution was decanted from the dark precipitate and dried with sodium hydroxide. Presence of <0.6 g. (<4%) of IIIa and IVa consisting of more than 90% IIIa was detected by means of g.l.p.c. Only 18.5 g. (51%) of Ia was recovered. Compound IIa (18.0 g.) was also treated with 2.8 g. of lithium aluminum hydride in the same manner. No trace of either IIIa or IVa was detected in the concentrated ether solution from the reaction.

A mixture prepared from 4.0 g. of coarsely powdered sodium hydroxide, 8.2 g. of Ia, and 100 ml. of liquid ammonia was stirred at reflux for 10 hr. Ether (50 ml.) was added to the stirred mixture, and the ammonia was allowed to evaporate. Formation of 1.0 g. (24%) of IVa was detected by means of g.l.p.c.; formation of IVa was confirmed by means of infrared spectroscopy.

Dihalomalonaldehydes

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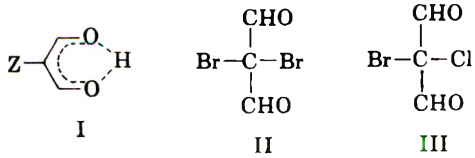
Contribution No. 879 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware

Received June 3, 1963

There are numerous examples of monosubstituted malonaldehydes,[1] depicted best by the "pseudoaromatic" structure I. By contrast, disubstituted malonaldehydes devoid of this "aromaticity" are little known. While acetals of dibromomalonaldehyde[2] and dimethylmalonaldehyde[3] have been reported, they were prepared indirectly and, until recently,[4] could not be converted to the free dialdehydes. This paper reports the first synthesis of negatively disubstituted malonaldehydes, dibromomalonaldehyde (II), and bromochloromalonaldehyde (III).



I II III

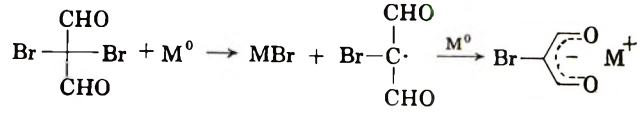
Both of these compounds were prepared by the action of the appropriate halogen on the sodium salt of bromomalonaldehyde, under scrupulously anhydrous conditions.[5]

Dibromomalonaldehyde was obtained in better yields and was studied in more detail. It is readily soluble in common organic solvents; in water or aqueous tetrahydrofuran it dissolves with the formation of an isolable hydrate. Aqueous solutions of dibromomalonaldehyde can be titrated with base, the hydrate being cleaved to formic acid and dibromoacetaldehyde.

Dibromomalonaldehyde exhibits surprising thermal stability, remaining unchanged when refluxed at its boiling point (186°) for two hours. Even under such drastic conditions as passage over quartz chips at 390 and 450°, 50 and 40%, respectively, of the starting material is recovered.

In contrast to the thermal stability of dibromomalonaldehyde is its high sensitivity to radicals. When solutions of dibromomalonaldehyde (in benzene or carbon tetrachloride) are exposed to light or azo initiators, a rapid and complex reaction ensues; hydrogen bromide is evolved, and bromomalonaldehyde precipitates as an isolable product. When the reaction is allowed to proceed further, a complex mixture of acid bromides is obtained. It is noteworthy that bromomalonaldehyde by itself does not react under those conditions, nor does dibromomalonaldehyde in the absence of a solvent.

Dibromomalonaldehyde reacts with metals or metal carbonyls, presumably *via* two one-electron transfers, and yielded the metal salt of bromomalonaldehyde.



The bromomalonaldehyde radical gave no evidence of coupling in any of the preceding reactions; in fact, the most pronounced characteristic of dibromomalonaldehyde (or bromomalonaldehyde radical) is its tendency to revert to the aromaticity of bromomalonaldehyde anion, as a metal or proton chelate. In almost all reactions tried, including pyrolysis of anhydrous bromomalonaldehyde salts, bromomalonaldehyde could be sublimed out of the reaction mixture.

(1) (a) Z = R or Ar [Z. Arnold and F. Sorm, *Collection Czech. Chem. Commun.*, **23**, 452 (1958)]; (b) Z = –CN [S. Trofimenko (unpublished results)]; (c) Z = –CHO [Z. Arnold and J. Zemlicka, *Collection Czech. Chem. Commun.*, **25**, 1318 (1958)]; (d) Z = $-NO_2$ [H. B. Hill, *Ber.*, **15**, 1906 (1882); *Am. Chem. J.*, **22**, 89 (1899)]; (e) Z = –COOR [L. Panizzi, *Gazz. chim. ital.*, **76**, 56 (1946)]; (f) Z = Br [M. J. Grard, *Compt. rend.*, **190**, 187 (1930); *Ann.*, **13**, 336 (1930)]; (g) Z = Cl [W. Diekmann, *Ber.*, **37**, 4638 (1904)]; (h) Z = OH (reductone) [T. Reichstein and R. Oppenauer, *Helv. Chim. Acta*, **16**, 988 (1933)]; (i) Z = –CRO [Z. Arnold and A. Holy, *Collection Czech. Chem. Commun.*, **28**, 869 (1963)].

(2) S. M. McElvain and L. R. Morris, *J. Am. Chem. Soc.*, **73**, 206 (1957).

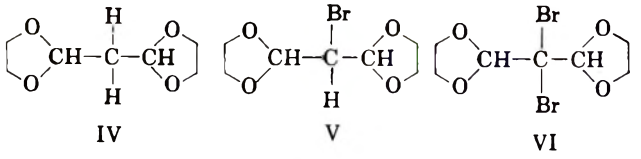
(3) K. C. Brannock, *J. Org. Chem.*, **25**, 258 (1960).

(4) After this work has been completed, a report of the successful hydrolysis of dimethylmalonaldehyde tetraethyl acetal appeared: L. A. Yanovskaya, B. A. Rudenko, V. F. Kucherov, R. N. Stepanova, and J. A. Kogan, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2189 (1962).

(5) The question whether direct C-halogenation or O-halogenation, followed by some secondary process, takes place, remains open; only O-acylation has been reported for malonaldehydes [T. V. Protopopova and A. P. Skoldinov, *Zh. Obshch. Khim.*, **28**, 240 (1958); Z. Arnold and J. Zemlicka, *Collection Czech. Chem. Commun.*, **25**, 1318 (1960)].

Dibromomalonaldehyde gives the usual aldehyde reactions. Spectral data (infrared, ultraviolet, n.m.r.) are also in accord with the assigned structure.

The effect of the two bromine atoms makes the acetalization of dibromomalonaldehyde difficult; on the other hand, the cyclic acetal VI is very resistant to hydrolysis, more so than the analogous acetals IV and V. Nuclear magnetic resonance peaks of the dioxolane portion in IV and V fall close to those reported for 2,2′-bis-1,3-dioxolane[6]; in the case of VI a substantial shift to lower τ is observed.



IV V VI

Experimental

Bromomalonaldehyde.—1,1,3-Trimethoxy-3-ethoxypropane[7] (1127 g., 6.33 moles) was stirred with 1127 ml. of water and 45 ml. of concentrated hydrochloric acid until a homogeneous solution resulted. Bromine (1021 g., 6.33 moles) was added slowly to the stirred and cooled (below 35°) solution. After the addition was complete, the clear yellow solution was concentrated at reduced pressure and temperatures not exceeding 70° to yield a thick slurry. Filtration gave slightly yellowish crystals that were washed with cold 50% ethanol and dried in a vacuum desiccator. The yield was 616 g. (65%), m.p. 155° dec.; lit.[1f] m.p. 148°; Ultraviolet: λ_{max}^{EtOH} 248 mμ, log ε 4.16. (Note: The contact of metal with the product is to be avoided, as it induces decomposition.)

Sodium Salt of Bromomalonaldehyde.—The sodium salt was prepared by treating bromomalonaldehyde with an equivalent amount of aqueous sodium hydroxide. The solution was concentrated *in vacuo* and diluted with much acetone. Shiny crystals of the solvated salt separated; they lost their luster on preliminary drying at room temperature and were then dried *in vacuo* at 80° until the –OH band in the infrared disappeared; Ultraviolet: $\lambda_{max}^{H_2O}$ 277, log ε 4.38. N.m.r. (D_2O), 5.31 τ (singlet.

For larger runs, the water was removed by azeotropic distillation with benzene. Yields ranged from 60 to 78%. The salt darkens from 180–310° without melting.

Dibromomalonaldehyde (II).—Dry sodium salt of bromomalonaldehyde (118 g., 0.682 mole) was stirred in 700 ml. of carbon tetrachloride. Bromine was added slowly to the cooled solution (20–30°) until the red color persisted. The suspension was stirred for another 10 min. at room temperature, then filtered, and the cake washed with three 100-ml. portions of carbon tetrachloride. The organic phases were combined, dried with magnesium sulfate and filtered, and the solvent was removed at reduced pressure. Distillation of the residue on a spinning-band column gave 119 g. (76%) of dibromomalonaldehyde, b.p. 55° (9 mm.), $n^{20}D$ 1.5492.

Anal. Calcd. for $C_3H_2Br_2O_2$: C, 15.7; H, 0.9; Br, 69.5; mol. wt., 230. Found: C, 16.2; H, 1.1; Br, 70.4; mol. wt., 210 (cryoscopic in benzene).

Infrared: 3.50, 5.75, 7.40, 9.14, 10.13, 10.7 (w), and 11.7 (w) μ. Ultraviolet: λ_{max} 261 mμ, ε 64. n.m.r.: singlet at τ 0.275.

Dibromomalonaldehyde stores well at room temperature provided moisture is scrupulously excluded.

Bromochloromalonaldehyde (III).—When chlorine was substituted for bromine in the reaction, bromochloromalonaldehyde, b.p. 38 (9 mm.), $n^{20}D$ 1.5245, was obtained in 32% yield (considerable losses due to volatility occurred during solvent removal).

Anal. Calcd. for C_3H_2BrCl: C, 19.4; H, 1.08. Found: C, 18.9; H, 1.26.

Infrared is the same as that of II except for a band at 12.7 μ instead of 11.7 μ.

The Hydrate of Dibromomalonaldehyde.—To a solution of dibromomalonaldehyde in tetrahydrofuran was added an excess of water, and the solution was stirred at room temperature for 2 hr. It was then evaporated *in vacuo* yielding a white solid. It could be recrystallized from water (rhombic plates) but melted unsharply (95–110°). It gave the 2,4-dinitrophenylhydrazine derivative of dibromomalonaldehyde.

The infrared spectrum of the solid had characteristic bands at 2.95, 3.10, 7.6, 9.08, 9.25, 9.60, 10.02, 10.68, and 12.16 μ.

Titration of Dibromomalonaldehyde.—Two dibromomalonaldehyde samples (4.5 and 4.8 mmoles, respectively) were each stirred in 15 ml. of water until solution resulted and were titrated with 0.1 *N* sodium hydroxide to phenolphthalein end point. The samples consumed 4.6 and 4.8 mmoles of base, respectively.

Addition of excess 2,4-dinitrophenylhydrazine reagent yielded the derivative of glyoxal in 96% yield, known to be formed from dihaloacetaldehyde.[8]

Pyrolysis of Dibromomalonaldehyde.—Dibromomalonaldehyde was pyrolyzed by being passed dropwise through a 30-cm. tube packed with quartz chips and maintained at the appropriate temperature by means of an electric furnace. The products were swept with nitrogen into a −80° trap. At 450°, 40% of dibromomalonaldehyde was recovered; at 390°, 50% dibromomalonaldehyde and 29% bromomalonaldehyde was obtained.

Free Radical Reactions of Dibromomalonaldehyde. A.—Dibromomalonaldehyde was refluxed in a small amount of benzene with azobisisobutyronitrile. Hydrogen bromide was evolved and after about 10 min. solid started separating. It was identified as bromomalonaldehyde by comparison with an authentic sample.

B.—Dibromomalonaldehyde was dissolved in benzene and exposed to sunlight. Within a few minutes hydrogen bromide was evolved and bromomalonaldehyde started precipitating. If the bromomalonaldehyde was not removed and the irradiation continued, the solid went back into solution and a strongly acidic sirup was obtained on evaporation of solvent. The same behavior was observed when a sunlamp was used as the light source and carbon tetrachloride as the solvent.

No reaction took place when pure dibromomalonaldehyde was irradiated. Upon dilution with benzene the reaction promptly commenced and proceeded as before.

C.—A 1.71-g. sample of nickel carbonyl was added to a solution of 2.30 g. of dibromomalonaldehyde in 5 ml. of benzene. After stirring for 3 hr. at room temperature there was obtained 3.0 g. of a hygroscopic solid. It gave positive ferric chloride and 2,4-dinitrophenylhydrazine tests and yielded bromomalonaldehyde upon acidification and sublimation.

Similar results were obtained upon refluxing dibromomalonaldehyde in xylene with molecular silver.

Malonaldehyde Bisethylene Acetal (IV).—1,1,3-Trimethoxy-3-ethoxypropane (178 g., 1.0 mole) was mixed in a 1-l. flask with redistilled ethylene glycol (140 g., 2.2 moles), 10 drops of sulfuric acid was added, and the mixture was heated in an oil bath at 140°. The alcohol was distilled slowly through a helices-packed column. After about 2 hr. the distillation almost ceased. The pot residue was mixed with 600 ml. of dilute potassium carbonate solution and extracted with six 200-ml. portions of ether. After drying and removal of ether, there was obtained 102 g. (64%) of a crude oil. Distillation gave a pure fraction, b.p. 85°, (1 mm.), which solidified. Recrystallization from ether–ligroin gave crystals, m.p. 42–43°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 52.5; H, 7.55. Found: C, 52.8; H, 7.72.

The n.m.r. spectrum showed three kinds of protons in a 1:4:1 ratio resolved as triplet, A_2B_2 multiplet, and triplet, centered at 5.00, 6.07, and 8.02 τ, respectively (J = 5.5).

Bromomalonaldehyde Bisethylene Acetal.—Bromomalonaldehyde (134 g., 0.89 mole) was mixed with ethylene glycol (110 g., 1.78 moles) and 350 ml. of benzene. The mixture was stirred and refluxed, and the water was collected in a separator. When water separation ceased, the solution was cooled, 50 ml. of ether was added, and the organic phase extracted with dilute base and then with water. Drying of the organic layer gave, after solvent removal, 150 g. (70%) of an oil. It was distilled

(6) E. Caspi, T. A. Wittstruck, and D. M. Piatak, *J. Org. Chem.*, **27**, 3183 (1962).

(7) Available from Kay-Fries Chemicals, Inc., 180 Madison Ave., New York 16, N. Y. Other 1,1,3,3-tetraalkoxypropanes gave comparable results.

(8) F. D. Chattaway and L. H. Farinholt, *J. Chem. Soc.*, 96 (1930).

on a spinning-band column, b.p. 100–104° (1 mm.); yield, 128 g. (60%).

Anal. Calcd. for $C_7H_{11}BrO_4$: C, 35.1; H, 4.54; Br, 33.4. Found: C, 35.4; H, 4.66; Br, 33.0.

The infrared spectrum contains bands at 3.30, 3.40, 6.75, 7.27, 7.98, 8.12, 8.25, 8.65 (vs), 8.90, 9.30, 9.5 (broad), 10.0, 10.50 (broad), 11.25, and 12.95 μ.

The n.m.r. spectrum consists of a doublet and a narrow A_2B_2 multiplet with an area ratio (by integration) of 2:9, indicating coincidence of the central hydrogen with the methylene groups.

Dibromomalonaldehyde Bisethylene Acetal (VI).—Dibromomalonaldehyde (32 g., 0.139 mole) was refluxed in 200 ml. of benzene with ethylene glycol (18.1 g., 0.291 mole) and sulfuric acid (5 drops). Water was removed continuously. After refluxing overnight, 4.2 ml. of water had been collected. The solution was washed with dilute alkali, the organic layer dried, and the solvent removed.

The residual sirup was distilled *in vacuo*. A viscous oil distilled that contained –OH and carbonyl bands. The pot residue solidified and was recrystallized from carbon tetrachloride, yielding 2.6 g. (6%) of VI, m.p. 70–75°. Two recrystallizations from hexane raised the m.p. to 81–82°.

Anal. Calcd. for $C_7H_{10}Br_2O_4$: C, 26.4; H, 3.14; Br, 50.3. Found: C, 26.9; H, 3.24; Br, 49.7.

The n.m.r. spectrum consisted of a singlet at 4.72 τ and a narrow A_2B_2 multiplet centered at 5.81 τ with an area ratio of 1:4.

Hydrolysis Rates of Acetals IV, V and VI.—Samples of IV, V, and VI were dissolved in minimum amounts of ethanol and treated with 2,4-dinitrophenylhydrazine reagent. Derivative formation, as evidenced by precipitation of a colored solid (which later redissolved in the case of VI) took place in about 30 sec. with compounds IV and V. The acetal VI required about 12 hr. for derivative formation.

Effect of Solvent Composition on the Kinetics of the Cyanoethylation of Methanol

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Received April 18, 1963

In previous work,[1] the kinetics and mechanism of the alkali metal alkoxide-catalyzed nucleophilic addition of alcohols to acrylonitrile in alcoholic solvents were studied; the rate equation obtained was $R = k[\text{acrylonitrile}][CH_3O^-]$. We have investigated further the cyanoethylation of methanol in solvent mixtures of methanol and aprotic solvents such as dimethylformamide (DMF) and dioxane. Dipolar solvents were found to change the nucleophilicity order of nucleophiles in bimolecular substitutions.[2] Rates of nucleophilic substitution reactions in which anions participate were found to be accelerated by a factor of 10^5–10^7 or more[3,4] on passing from protic to dipolar aprotic solvents[5]; this phenomenon was used with great advantage in the syntheses of many compounds.[5] It was presumed that this solvent effect must be due largely to the greater reactivity of anions poorly solvated, relative to the transition states of their reactions in dipolar aprotic solvents.[5] A similar solvent effect is to be expected in the case of cyanoethylation and related addition reactions, involving a nucleophilic attack of anions on acidic double bonds. Very little is known at present in this field; thus, the rate of addition of *p*-toluene thiolate to phenylacetylene in ethanol–dimethylformamide mixtures was found to increase greatly in the presence of high dimethylformamide concentrations.[6]

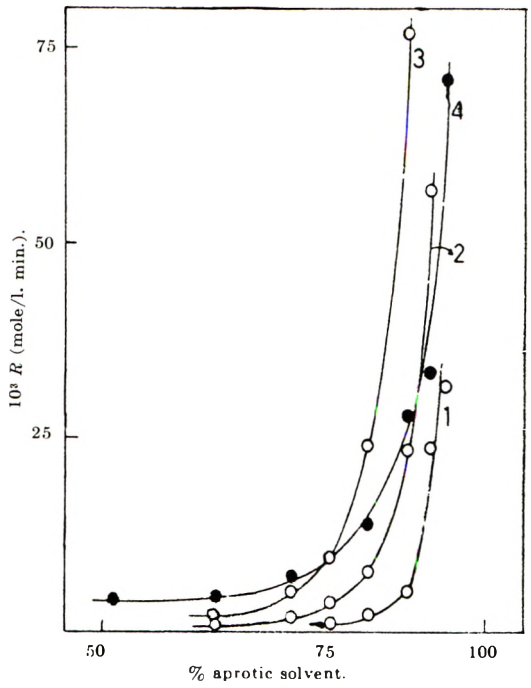

Fig. 1.—Plots of per cent aprotic solvent in the mixed methanol–aprotic solvent against initial rate (mole/l. min.) in methanol–dimethylformamide mixed solvent: (1) at 0°; (2) at 15°; (3) at 25°; (4) methanol–dioxane mixed solvent at 20°.

Results and Discussion

The kinetics of the cyanoethylation of methanol was studied in mixtures of methanol–dimethylformamide, at various temperatures, using lithium methoxide as basic catalyst, and in methanol–dioxane mixtures at 20° using potassium methoxide. Rates of reaction were calculated from the initial slopes of conversion *vs.* time plots. The rate increased progressively with decrease in the proportion of methanol in the mixed solvents (Fig. 1). A very great increase in rate was noticed in the range of low methanol concentrations, which in the case of methanol–dioxane mixtures obviously cannot be attributed solely to the effect of lowering of the dielectric constant on the rate of reaction between an ion and a neutral molecule.[7] In the case of methanol (ϵ 34)[8] and dimethylformamide (ϵ 37.6)[9] mixtures, the increase in rate has but little to do with change in the dielectric constant.

In all cases the rate of reaction was first order in acrylonitrile. First-order rate constants were calculated from the linear plots of log $[\text{acrylonitrile}]_t$ *vs.* time (Tables I, II). The rate of reaction was also approximately first order in catalyst; its value was 1.2

(1) B.-A. Feit and A. Zilkha, *J. Org. Chem.*, **28**, 406 (1963).

(2) S. Winstein, L. G. Savedoff, S. G. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Letters*, No. **9**, 24 (1960).

(3) J. Miller and A. J. Parker, *J. Am. Chem. Soc.*, **83**, 117 (1961); A. J. Parker, *J. Chem. Soc.*, 1328 (1961).

(4) D. J. Cram, B. Rickborn, C. A. Kingsburg, and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 3678 (1961).

(5) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(6) W. E. Truce and R. F. Heine, *J. Am. Chem. Soc.*, **81**, 592 (1959).

(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 135.

(8) H. L. Schlafer and W. Schaffernicht, *Angew. Chem.*, **72**, 618 (1960).

(9) S. Olive, *Makromol. Chem.*, **42**, 251 (1961).

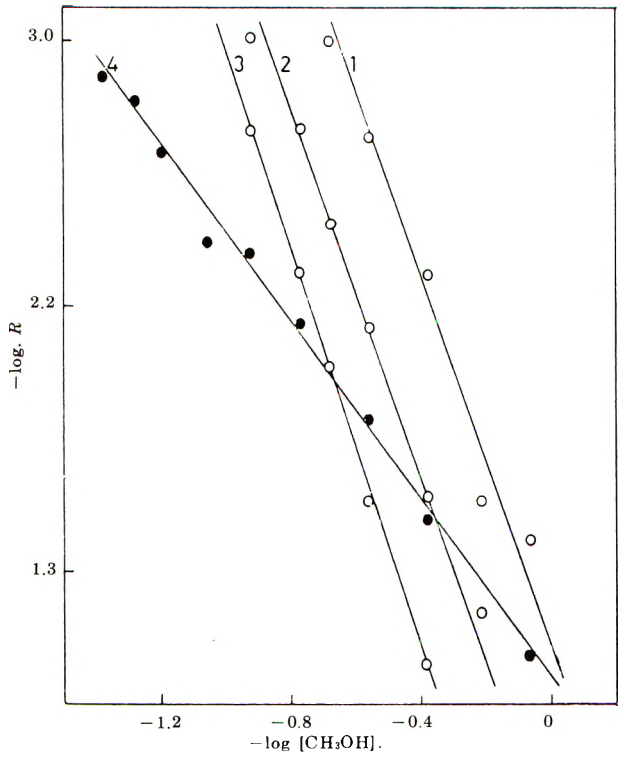

Fig. 2.—Order plots of logarithm of methanol concentration against logarithm of initial rate in methanol–dimethylformamide mixed solvent: (1) at 0°, slope −2.75; (2) at 15°, slope −2.75; (3) at 25°, slope −2.97; (4) methanol–dioxane mixed solvent at 20°, slope −1.33.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE CYANOETHYLATION OF METHANOL IN DMF–METHANOL MIXTURES[a]

DMF, % by volume	10^3k_1 (min.$^{-1}$) at 0°	10^3k_1 (min.$^{-1}$) at 15°	10^3k_1 (min.$^{-1}$) at 25°
50	...	...	1.23
65	...	1.80	3.70
75	...	4.16	11.41
80	1.84	9.47	22.26
85	4.61	19.39	56.66
90[b]	10.80	64.36	187.75
93	50.83	164.29	...
95[c]	109.01	...	...

[a] Experimental conditions: initial concentration of acrylonitrile, 0.506 mole/l.; of lithium methoxide, 3.333 × 10^{-4} mole/l. Rate measurements were carried out as previously described.[1] [b] Under otherwise constant conditions, 10^3k_1 (min.$^{-1}$) values at various base concentrations, 10^4[CH_3OLi], shown in parentheses (moles/liter) were: 8.75 (0.83), 33.45 (1.67), 64.36 (3.33), 115.00 (5.00), 163.09 (6.67). [c] At low equivalent concentrations of methanol, polymerization of excess acrylonitrile occurs. See B.-A. Feit and A. Zilkha, *J. Appl. Polymer Sci.*, **7**, 287 (1963).

in the case of methanol–dimethylformamide solvent (containing 90% by volume of dimethylformamide) at 15°, and 1.1 in the case of methanol–dioxane (93% dioxane) at 20°. Negative values were found for the order of reaction in methanol (Fig. 2). In methanol–dimethylformamide mixtures, the order in methanol was approximately −3 at all three reaction temperatures, whereas in methanol–dioxane mixtures it was −1.3. It might well be assumed, therefore, that methanol itself participates in the reaction, for example, by solvation of the methoxide anions. An equilibrium involving free methoxide anions and solvated ones, the former being much more reactive, may exist: CH_3O^-·n-$CH_3OH \rightleftharpoons CH_3O^- + n$-$CH_3OH$. Such an equilibrium followed by a rate determining nucleophilic attack[1] may be responsible for the negative order in methanol.

TABLE II

FIRST-ORDER RATE CONSTANTS FOR THE CYANOETHYLATION OF METHANOL IN DIOXANE–METHANOL MIXTURES[a]

Dioxane, % by volume	10^3k_1 (min.$^{-1}$) at 20°	Dioxane, % by volume	10^3k_1 (min.$^{-1}$) at 20°
0	2.31	75	15.81
20.7	3.57	85	29.27
34.5	5.11	90	56.61
51.7	8.42	93[b]	123.21
65	10.22	95	281.75

[a] Experimental conditions: initial concentration of acrylonitrile, 0.506 mole/l.; of potassium methoxide 6.720 × 10^{-3} mole/l. [b] Under otherwise constant conditions 10^3k_1 (min.$^{-1}$) values at base concentrations, 10^4[CH_3OK], shown in parentheses (moles/liter) were: 9.50 (8.33), 33.81 (20.00).

$$RO^- + CH_2{=}CH{-}CN \longrightarrow ROCH_2{-}\bar{C}H{-}CN$$

Support for the above can be found from the work of Cram, *et al.*,[4] on the sodium methoxide-catalyzed H–D exchange, where the reaction was 10^9 times faster in dimethyl sulfoxide than in methanol, due to a strong solvation of methoxide anions in methanol by hydrogen bonds, and a very poor one in dimethyl sulfoxide. Cavell and Speed[10] found a large increase in the rate of the isotopic exchange reaction of radioactive iodine with butyl iodide in mixed methanol–acetonitrile (ϵ 36) solvent, with increasing acetonitrile proportion. They too suggested that the existence of the equilibrium, $I^-{\cdot}CH_3OH \rightleftharpoons I^- + CH_3OH$, and the much greater reactivity of the free I^- as compared to the solvated one is responsible for this increase in rate.

The results of the present work offer possibilities for the shortening of reaction time and for obtaining higher yields in suitable nucleophilic additions.

(10) E. A. S. Cavell and J. A. Speed, *J. Chem. Soc.*, 1453 (1960); 226 (1961).

Oxidation of Thiols by Dimethyl Sulfoxide

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Received May 24, 1963

Various oxidizing agents such as nitric acid, hydrogen peroxide, oxygen, and potassium ferricyanide have been employed for the conversion of thiols to disulfides. However, most of these reagents are also capable of reacting with other oxidizable sites such as aldehyde and amino groups.

We wish to report a convenient laboratory synthesis of disulfides from the corresponding thiols by selective oxidation of the latter with dimethyl sulfoxide.

While most oxidizable functional groups are quite stable to dimethyl sulfoxide, there are several reports in the literature of its use as a unique oxidizing agent, for example, in the conversion of α-bromo ketones to gly-

TABLE I

Thiol used			Corresponding disulfides obtained						
				Crude product, yields and purity				Recrystallized product	
No.	Name	Purity, %	Name	Yield, by wt., %	Disulfide by analysis, %	(-SH), %	M.p., °C.	Obsd. m.p., °C.	Lit. m.p., °C.
1	Benzenethiol	100	Diphenyl disulfide	100	94.5	0.00	61–62	62–63	61
2	α-Toluenethiol	100	Dibenzyl disulfide	100	96.5	1.39	71–72	71–72	71–72
3	*o*-Aminobenzenethiol	100	Di-2-aminophenyl disulfide	80	[a]	14.8	91–92	94–95	93
4	*p*-Chloro-α-toluenethiol	100	Di-*p*-chlorobenzyl disulfide	97	96.8	0.45	53–55	56–57	58–59
5	*p*-Bromo-α-toluenethiol	99.6	Di-*p*-bromophenyl disulfide	100	95	0.04	92–95	95–96	93.8
6	*p*-Chlorobenzenethiol	99.7	Di-*p*-chlorophenyl disulfide	100	96.5	0.00	69–73	73–74	71.5
7	Mercaptoacetic acid	96.1	Dithiodiglycolic acid	100	92.0	0.63		105–108	107–108
8	3-Mercaptopropionic acid	99.9	3,3′-Dithiodipropionic acid	96	93.8	2.63	156–157	156–158	155
9	Pentachlorobenzenethiol	Tech.	Dipentachlorophenyl disulfide	80		4.60	223–227	235–237	229 and 235–237
10	1-Butanethiol	Tech.	Di-*n*-butyl disulfide	86	92.3	0.46	90[b] (3.7 mm.)	90.5[b] (3.7 mm.)	110–113[b] (15 mm.)
11	2-Diethylaminoethanethiol, HCl	98.3	2,2′-Diethylaminodiethyl disulfide, 2HCl	100	91.4	7.6	221–222	221–222	220–221

[a] End point not detectable due to color. [b] Boiling point.

oxals,[1] later modified for the conversion of alkyl halides and tosylates to their corresponding aldehydes.[2] In addition a number of higher molecular weight sulfides were found to undergo oxygen exchange with dimethyl sulfoxide to produce the corresponding sulfoxide.[3]

In their work on the bromination of amines and phenols in dimethyl sulfoxide Fletcher, *et al.*,[4] mention that increasing amounts of 48% hydrogen bromide with *p*-chlorothiophenol in dimethyl sulfoxide gave a crystalline product presumed to be the corresponding disulfide. There appears to be no further investigation of this finding. On the other hand, it is known that hydrogen sulfide can be oxidized to sulfur and water with dimethyl sulfoxide.[5]

In the present work it was found that when a thiol was dissolved in an excess of dimethyl sulfoxide and stirred for a maximum of eight hours at temperatures varying from 80–90°, the corresponding disulfides were obtained in excellent yield and purity. The present procedure is attractive not only for its simplicity and general applicability, but also because the dimethyl sulfoxide plays a double role of oxidizing agent and solvent.

In order to establish the oxidative function of dimethyl sulfoxide, several experiments using benzenethiol and α-toluenethiol were carried out under a nitrogen atmosphere. In both cases the yields of disulfide were identical with those obtained in Table I where air had not been excluded from the reaction. In addition the by-product of the reaction, dimethyl sulfide, was isolated and identified by its infrared spectrum. It should be mentioned that dimethyl sulfide could be reconverted to dimethyl sulfoxide by catalytic air oxidation in a larger scale process.

(1) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).
(2) N. Kornblum, W. J. Jones, and G. J. Anderson, *ibid.*, **81**, 4113 (1959); H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).
(3) S. Searles, Jr., and H. R. Hays, *ibid.*, **23**, 2028 (1958).
(4) T. L. Fletcher, M. J. Namkung, and H. L. Pan, *Chem. Ind.* (London), 660 (1957).
(5) N. Kharasch, "Organic Sulfur Compounds," Pergamon Press, New York, N. Y., 1961, p. 174.

Experimental

General Procedure.—The apparatus consisted of an erlenmeyer flask fitted with an Agit-Therm Magnet stirrer, a water condenser, and a thermometer hung from the top of the condenser.

The thiol (0.1 mole) was dissolved in 50 g. of dimethyl sulfoxide. The resulting solution was stirred for 8 hr. at 80–90°. After that period of time the product solution was decolorized with charcoal and allowed to cool to room temperature. Further details are indicated in Table I.

For the isolation and purification of the disulfides the following three procedures were employed.

Procedure A for Solid Disulfides Insoluble in Water.—Examples are 1, 2, 3, 4, 5, 6, and 8 in Table I. The product solution was poured into a tenfold volume of ice–water and after 3-hr. standing, the precipitated disulfide was collected by filtration, washed three or four times with water, and dried under vacuum.

Procedure B for Disulfides Soluble in Water.—An example is 7 in Table I. The excess of the dimethyl sulfoxide was removed from the product solution by distillation under vacuum (3 mm.). In some instances, complete removal of dimethyl sulfoxide using this procedure was difficult and crystallization of the disulfides was inhibited.

Procedure C for Disulfides Forming a Separate Layer.—Examples are 9, 10 and 11 in Table I. The disulfide layer was collected in a separatory funnel, diluted with ethyl ether, and washed three or four times with water. The ethereal solution was dried over anhydrous sodium sulfate, the ether evaporated, and the product dried in a vacuum desiccator. In the case of example 9, the bispentachlorophenyl disulfide precipitated from dimethyl sulfoxide and was collected and washed with acetone. In the case of example 11, the product was partially soluble in dimethyl sulfoxide. The insoluble product was collected by filtration and the remainder precipitated by addition of ether. The combined precipitates were washed with ether and dried.

Purification.—Solid disulfides were recrystallized from ethyl alcohol–water, or ethyl acetate–benzene systems. Liquid disulfides were distilled under vacuum.

The yields and purity of the crude disulfides were determined by weight and analytical methods.[6,7] Their disulfide and thiol contents were determined and the results are shown in Table I, along with melting points of the crude and purified disulfides.

Oxidation of Benzenethiol.—Two-tenths of a mole of benzenethiol was dissolved in 100 ml. of dimethyl sulfoxide and the solution was maintained at 85 ± 1°. Samples were removed at various intervals and analyzed for thiol and disulfide content.[6,7] The following conversions of thiol to disulfide were found: 85% after 30 min., 92.4% after 1 hr., 96.7% after 2 hr., 98.3% after 4 hr., and 98.9% after 6 hr.

Oxidation of Benzenethiol in the Absence of Air.—A 250-ml. three-necked flask was equipped with a magnetic stirrer, thermometer, a nitrogen gas inlet tube, and an outlet to a trap cooled in Dry Ice. The flask was charged with 11 g. (0.1 mole) of benzenethiol and 50 ml. of dimethyl sulfoxide under a blanket of nitrogen and the solution was heated with stirring at 80° for 18 hr. with a continuous flow of nitrogen through the system. The disulfide isolated in almost theoretical yield by procedure A weighed 10.8 g. and melted at 61–62°.

The liquid condensed in the Dry Ice trap separated in two layers. The upper one proved to be the expected dimethyl sulfide by infrared spectrum and boiling point; the lower layer was mainly water.

Similar results were obtained when the experiment was carried out with α-toluenethiol with the by-products being identified as dimethyl sulfide and water. The disulfide was obtained in 88% yield with m.p. 71–72°.

(6) S. Siggia and R. L. Edsberg, *Anal. Chem.*, **20**, 938 (1948).

(7) J. W. Kimball, R. L. Kramer, and E. E. Reid, *J. Am. Chem. Soc.*, **43**, 1199 (1921).

The Jacobsen Rearrangement of 6-Methyl-7-propyltetralin[1]

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Received May 28, 1963

The Jacobsen rearrangement of 6-methyl-7-propyltetralin was initially investigated by Smith and Lo[2] who reported that a low yield (25%) of 6-methyl-5-propyltetralin was obtained. This result quite apparently was a surprise to the authors since they commented at some length on the mode of formation of this product. Clearly this is a result of considerable mechanistic implication. The starting material contains four alkyl substituents on the benzene ring which are *effectively all nonequivalent*. However, the differences among these four groups are quite subtle, particularly with respect to the *a priori* migratory aptitudes of the two alicyclic groups a and b. If A alone is the product either the propyl group migrates to C-1 or a migrates to C-4 or both occur. Since the product obtained is not the thermodynamically most stable one, it is appropriate to ask that the mechanism explain why the propyl group and/or a can migrate while the methyl and/or b cannot. This entirely unexpected migratory specificity prompted our interest in this case.

We have prepared a sample of 6-methyl-7-propyltetralin according to the procedure of Smith and Lo.[2] The hydrocarbon obtained in this way is impure and careful fractionation showed that it contained at least four other hydrocarbons. A sample of the purified 6-methyl-7-propyltetralin which was homogeneous as shown by gas partition chromatography analysis was subjected to the Jacobsen rearrangement. The hydrocarbon product was isolated in 28–30% yield and was shown to contain at least eleven substances. We have identified by comparison g.p.c. analysis five of these as 6-methyltetralin, 6-propyltetralin, starting material, 6-methyl-5-propyltetralin, and 5-methyl-6-propyltetralin. These latter two make up the major portion of the hydrocarbon product isolated, and are present in equivalent amounts. Thus, whatever the combination of migrating groups may be, it is now clear that we can derive no information about migratory preference from this experiment.

In the course of the synthesis of the starting material and of comparison samples of 6-methyl-5-propyl- and 5-methyl-6-propyltetralins we have had occasion to examine the products of partial reduction of several naphthalenes substituted in one ring. The reduction of β-methylnaphthalene gave 80% 6-methyltetralin, 10% of 2-methyltetralin, and 10% of methyldecalins. Similarly the reduction of 1-methyl-2-propylnaphthalene and of 1-propyl-2-methylnaphthalene gave about 70% of the product with the hydrogen added to the nonsubstituted ring. These results are in good accord with the findings of Hipsher and Wise,[3] though they used copper chromite while we employed Raney nickel.

Experimental

6-Methyltetralin.—2-Methylnaphthalene was reduced over Raney nickel according to the procedure of Fieser and Jones.[4] The product, b.p. 226–227°, $n^{20}D$ 1.5350, was obtained in 70% yield. G.p.c. at 200° on a 6-ft. Carbowax 1500 column showed this to be a mixture containing an 8:1:1 ratio of two tetralins and isomeric decalins, respectively. Fractional distillation on a 30-in. Podbielniak Heli-Grid semimicro column gave a product, b.p. 130° (48 mm.), $n^{19}D$ 1.5341, $\bar{\nu}$ 800, 825 cm.$^{-1}$, 97% pure by g.p.c.

6-Methyl-7-propionyltetralin.—Samples of 6-methyltetralin (prepared as described above or by Clemmensen reduction of 7-methyl-1-tetralone[5]) were acylated according to the procedure of Smith and Lo.[2] The ketone was obtained as a clear oil, b.p. 150° (1.25 mm.), $n^{23}D$ 1.5490–1.5510, in 70–84% yield, showing on g.p.c. analysis a broad peak partially separated into two peaks, but not sufficiently resolved to permit estimation of amounts of the components.

6-Methyl-7-propyltetralin.—Clemmensen reduction of 6-methyl-7-propionyltetralin as described by Smith and Lo[2] gave in 85–92% yield an oil, b.p. 94–99° (0.8 mm.), $n^{20}D$ 1.5188–1.5284. This material showed two nearly resolved peaks using g.p.c., showing approximately a 5:1 ratio. The hydrocarbon was carefully fractionated on a Podbielniak Mini-Cal column to give 16 fractions. Fractions 11–16, b.p. 124° (6 mm.), $n^{20}D$ 1.5294–1.5295, $\bar{\nu}$ 865 cm.$^{-1}$ (m), were uniform as indicated by g.p.c.

Rearrangement of 6-Methyl-7-propyltetralin.—A 21.0-g. (0.11 mole) sample of the pure hydrocarbon was mixed with 125 ml. of concentrated sulfuric acid and rearranged as described by Smith and Lo.[2] Hydrolysis of the product with superheated steam at

(1) Grateful acknowledgment is made to the Atomic Energy Commission (AEC AT (45-1) 352) and the general research grants of Oregon State University for partial financial support of this work. David Lini is indebted to the National Science Foundation for support as an NSF Undergraduate Research Participant during the summer of 1960.

(2) L. I. Smith and C. P. Lo, *J. Am. Chem. Soc.*, **70**, 2209 (1948).

(3) H. F. Hipsher and P. H. Wise, *ibid.*, **76**, 1747 (1954).

(4) L. F. Fieser and R. N. Jones, *ibid.*, **60**, 1940 (1938).

(5) E. de B. Barnett and F. G. Saunders, *J. Chem. Soc.*, 434 (1933).

155° gave 6.7 g. (32%) of a light oil, b.p. 60–66° (0.2 mm.), $n^{20}D$ 1.5443. Analysis by g.p.c. showed 11 peaks. Two peaks, retention times 52.5 and 61.0 min., respectively, made up 90–95% of the total. These were identified by internal comparison as 6-methyl-5-propyltetralin and 5-methyl-6-propyltetralin, respectively.

6-Methyl-5-propyltetralin.—A sample (2.0 g.) of 2-methyl-1-propylnaphthalene[6] was hydrogenated at 1100 p.s.i. and 130° in absolute ethanol over Raney nickel. After 12 hr. the hydrogen uptake had virtually ceased. The product was found to consist of two major components and eight minor components by g.p.c. analysis. The largest component, retention time 54.0 min., was purified by g.p.c. and the infrared spectrum showed strong absorption bands at 1600, 1500, and 810 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{20}$: C, 89.30; H, 10.70. Found: C, 89.02; H, 10.62.

6-Propyltetralin.—Tetralin was converted to 6-propionyltetralin and the ketone reduced according to the procedure of Smith and Lo.[2] The 6-propyltetralin, b.p. 61–63° (0.3 mm.), was obtained in 54% yield over-all, and gave a single peak on g.p.c. analysis.

2-Propylnaphthalene.—A mixture of 15.5 g. of 6-propyltetralin and 0.8 g. of 5% palladium on charcoal was heated for 5 hr. at 300° while a slow stream of nitrogen was passed over the reaction mixture. The product isolated by distillation, b.p. 62° (0.1 mm.), was obtained in 80% yield. A boiling point of 130° (12 mm.) is reported.[7] The substance gave a single peak on g.p.c. analysis.

1-Chloromethyl-2-propylnaphthalene.—A mixture of 12 g. (0.07 mole) of 2-propylnaphthalene, 6.5 g. of paraformaldehyde, 18 g. of glacial acetic acid, 12 g. of 85% phosphoric acid, and 65 g. of concentrated hydrochloric acid was stirred vigorously while being heated for 5 hr. on a steam bath. The reaction mixture was diluted with water and extracted with ether. The product boiled at 98–100° (0.025 mm.), $n^{21}D$ 1.6053, 9.3 g. (60%).

Anal. Calcd. for $C_{14}H_{15}Cl$: C, 76.88; H, 6.91. Found: C, 77.17; H, 7.14.

1-Methyl-2-propylnaphthalene.—Nine grams (0.041 mole) of the previous chloromethylation product was treated with hydrogen at 34-p.s.i. initial pressure and 0.6 g. of palladium on charcoal in acetone. The product was isolated by distillation, b.p. 78° (0.3 mm.), $n^{25}D$ 1.5915, in 55–60% yield; lit.[8] $n^{25}D$ 1.5928.

5-Methyl-6-propyltetralin.—A solution containing 1.56 g. of 1-methyl-2-propylnaphthalene in 15 ml. of absolute ethanol was hydrogenated at 130° and 1050 p.s.i. over W-4 Raney nickel.[9] The product was isolated in the normal manner and g.p.c. analysis showed 10 peaks, the major one constituting about 66% of the total. The material responsible for this peak was isolated by repetitive g.p.c., and showed $\bar{\nu}$ 810 cm.$^{-1}$. The amount isolated was insufficient for analysis.

Gas Chromatography.—All the hydrocarbons were analyzed on a Model 154C Perkin-Elmer vapor fractometer using a 6 ft. × 0.25 in. 5% Ucon Polar on Chromosorb column at 200° with helium as carrier gas. The following retention times are representative though the actual times varied about ± 3% in various runs: 6-methyl-7-propyltetralin, 46 min.; 5-methyl-6-propyltetralin, 60 min.; 6-methyl-5-propyltetralin, 54 min.; 1-methyl-2-propylnaphthalene, 102 min. The 6-methyl-7-propionyltetralin was analyzed on an 8 ft. × 0.25 in. 5% Ucon Polar column at 220°.

(6) E. N. Marvell, A. V. Logan, B. E. Christensen, P. Roberti, and M. Cook, *J. Org. Chem.*, **24**, 224 (1959).

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An Extention of the Gomberg–Bachmann Pinacol Synthesis

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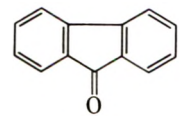
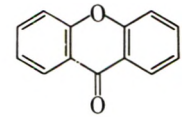
Received June 28, 1963

In 1927, Gomberg and Bachmann described the use of a magnesium–magnesium iodide mixture to reduce aromatic ketones to the corresponding pinacols.[2] This technique provided nearly quantitative yields, even in cases such as the reduction of fluorenone (I) and xanthone (II), where the corresponding pinacols

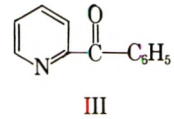


I

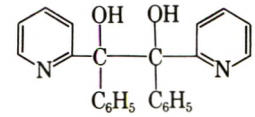


II

had not been obtainable by alternative methods. An apparent limitation of this reaction was noted, however, by Kegelman and Brown, who found that phenyl 2-, 3-, and 4-pyridyl ketones formed insoluble complexes with the magnesium halide.[3] These complexes gave only unchanged starting materials upon hydrolysis. In the case of phenyl 2-pyridyl ketone (III), a 14% yield of the desired pinacol, IV, was obtained by the use of sodium amalgam in aqueous alcohol. We wish to report the successful conversion of III to IV in better than twice this yield by a simple modification of the original Gomberg–Bachmann technique.



III



IV

In our initial investigations of this reduction, we obtained negative results similar to those of Kegelman and Brown. A yellow insoluble complex was formed which on hydrolysis yielded the original ketone. With an increased ratio of magnesium iodide to phenyl 2-pyridyl ketone, however, the yellow complex changed to a green precipitate which, on hydrolysis, gave a 38% yield of the pinacol IV.

The need for double the usual amount of magnesium iodide may be explained by assuming that the first half-mole serves to coordinate with the nitrogen of the pyridyl ketone, and that a second half-mole then serves to bring about the actual reduction.

Although we have not studied other examples of this reduction, it would appear that this simple expedient will allow the magnesium–magnesium iodide reductive dimerization to be applied to a wide variety of nitrogen-containing heterocyclic ketones.

Experimental[4]

α,α-Di-2-pyridylhydrobenzoin (IV).—To 5 g. of powdered magnesium (0.21 g.-atom) in 35 ml. of ether and 50 ml. of benzene was added with shaking 14 g. (0.055 mole) of iodine in portions to keep the solution boiling. After complete addition, the mixture was shaken until the liquid was practically colorless. To this mixture was added 18.3 g. (0.1 mole) of phenyl 2-pyridyl ketone dissolved in 30 ml. of benzene. A green precipitate separated which on shaking slowly turned to a yellow solid. The mixture was shaken and heated on a water bath for 1 hr., but no visible change occurred. A small portion of the mixture was withdrawn and hydrolyzed with water. The benzene–ether layer was dried and then evaporated to dryness to give a pale yellow solid, m.p.

(1) William S. Merrell Co. Fellow, 1951–1953; The Norwich Pharmacal Co., Norwich, N. Y.

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

(3) M. R. Kegelman and E. V. Brown, *ibid.*, **75**, 4649 (1953).

(4) Melting points are corrected.

< 40°, picrate m.p. 123° (phenyl 2-pyridyl ketone picrate[5] m.p. 128–129°). To the mixture was added an additional quantity of magnesium and magnesium iodide (prepared from 5 g. of magnesium and 14 g. of iodine) and on shaking, the yellow precipitate changed to a green precipitate. The mixture was refluxed on a water bath for 4 hr. and then allowed to stand at room temperature for 1 week after which time no visible change had taken place. The mixture was added to water and the benzene–ether layer separated. The water layer was washed several times with ether and the benzene–ether solution combined with the ether washings and dried over magnesium sulfate. Distillation of the solution yielded an orange oily solid which on washing with ethanol yielded 7.0 g. (38%), m.p. 139–140°, of white solid. The filtrate on evaporation yielded 4.3 g. of phenyl 2-pyridyl ketone. The white solid was recrystallized twice from ethyl acetate to constant m.p. 141–142° (lit.[3,6] m.p. 129–130°).

Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47. Found: C, 78.40; H, 5.39.

Acknowledgment.—The authors thank Dr. Jerrold Meinwald for a critical discussion of this manuscript.

(5) P. C. Teague, *J. Am. Chem. Soc.*, **69**, 714 (1947).

(6) The different melting points can be attributed to purity or to steric differences since *dl* and *meso* forms are possible.

Ring Expansion and Electron Transfer in the Cleavage of 2,2′-Diphenyl-2,2′-biindan-1,1′,3,3′-tetrone with Base[1]

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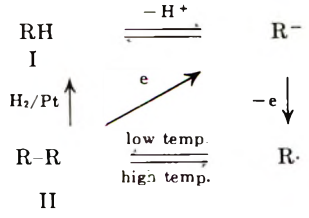
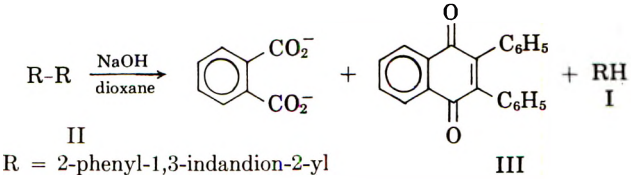
Received May 6, 1963

An article from this laboratory[3] reported the isolation of a dehydro dimer of 2-phenyl-1,3-indandione (I) as a minor product in the phenylation of I with diphenyliodonium chloride[4] or acetate[3] in *t*-butyl alcohol in the presence of sodium *t*-butoxide, the major product (85–93%) being 2,2-diphenyl-1,3-indandione. Although this dehydro dimer was obtained previously by other workers,[5] its mode of formation allowed formulations other than the proposed symmetrical C–C structure. New evidence[6] has confirmed the structure of this dehydro dimer as 2,2′-diphenyl-2,2′-biindan-1,1′,3,3′-tetrone (II). Also reported[6] were the synthesis of II by oxidation of 2-phenyl-1,3-indandione (I) in base, the homolytic and reductive cleavage of II, and its thermal rearrangement.[7]

The present work reports a new, heterolytic cleavage of II by sodium methoxide or sodium hydroxide and proposes a mechanism for the formation of the observed products.



Results.—Dehydro dimer II was cleaved to 2,3-diphenyl-1,4-naphthoquinone[8,9] (III, 76%), sodium phthalate, and 2-phenyl-1,3-indandione (I) when boiled with 1 *N* sodium hydroxide in dioxane. A hot methanolic solution of II containing sodium methoxide gave III, I, and methyl phthalate. The identity of the quinone III was proven by its melting point and infrared spectrum and by its conversion to 2,3-diphenylnaphthalene-1,4-diol diacetate[10] and to 2,3-epoxy-2,3-dihydro-2,3-diphenyl-1,4-naphthoquinone.[11]



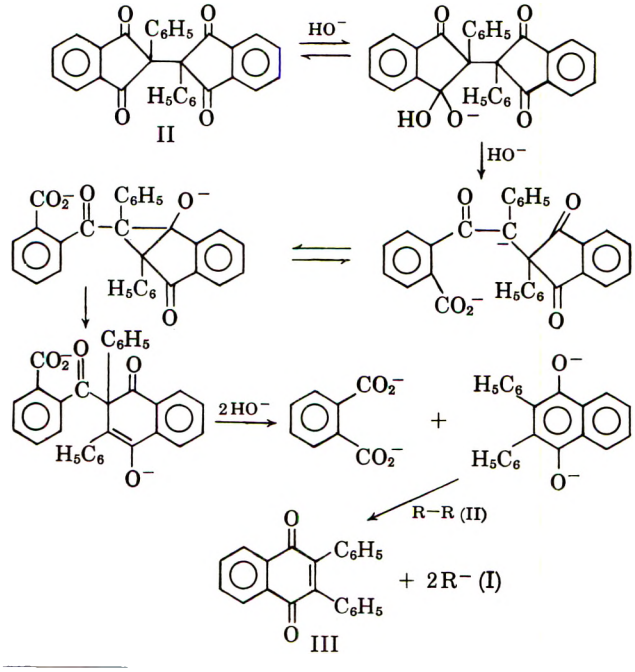
R = 2-phenyl-1,3-indandion-2-yl

While the sequence by which the dehydro dimer II is cleaved to give the 2,3-diphenyl-1,4-naphthoquinone and I is not fully established, it probably includes the formation of the dianion of the hydroquinone of III as an intermediate; indeed, 2,3-diphenylnaphthalene-1,4-diol[8] was isolated from the reaction in small quantities.

Proposed Mechanism for Ring Expansion.—A possible formulation of the cleavage of II by hydroxide ion is shown in Scheme I; the cleavage with methoxide ion can be interpreted analogously.

SCHEME I

PROPOSED MECHANISM FOR THE ALKALINE CLEAVAGE OF 2,2′-DIPHENYL-2,2′-BIINDAN-1,1′,3,3′-TETRONE



(1) This article is taken from the doctoral dissertation of Suzanne A. Galton, submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Chemistry).

(2) Eastman Kodak Co. Fellow, 1961–1962; Texaco Co. Fellow, 1963.

(3) F. M. Beringer, S. A. Galton, and S. J. Huang, *J. Am. Chem. Soc.*, **84**, 2919 (1962).

(4) F. M. Beringer, E. J. Geering, M. Mausner, and I. Kuntz, *J. Phys. Chem.*, **60**, 141 (1956).

(5) (a) F. Nathanson, *Ber.*, **26**, 2576 (1893); (b) D. Radulescu and F. Barbulescu, *Bull. soc. chim. Romania*, **20**, 29 (1938); *Chem. Zentr. I*, 1830 (1940).

(6) F. M. Beringer, S. A. Galton, and S. J. Huang, *Tetrahedron*, **19**, 809 (1963).

(7) The rearrangement was first reported by J. Rigaudy and P. Auburn, *Compt. rend.*, **254**, 2372 (1962).

(8) R. Weiss and K. Bloch, *Monatsh.*, **63**, 39 (1933).

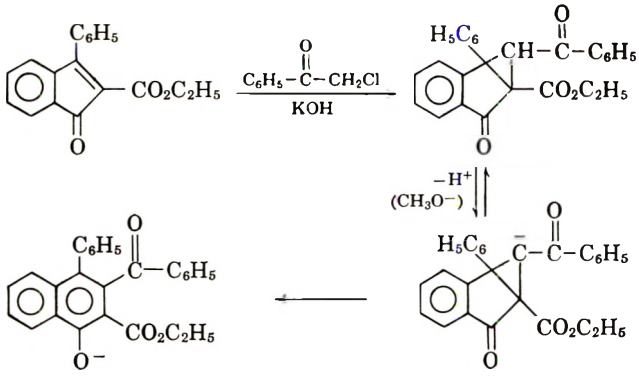
(9) H. M. Crawford, *J. Am. Chem. Soc.*, **70**, 1081 (1948).

(10) C. F. H. Allen, A. Bell, J. H. Clark, and J. E. Jones, *ibid.*, **66**, 1617 (1944).

(11) M. M. Shemyakin, D. A. Bochvar, and L. A. Shchukina, *J. Gen. Chem. USSR* (Eng. Transl.), **22**, 505 (1952); *Chem. Abstr.*, **47**, 2741*f* (1953).

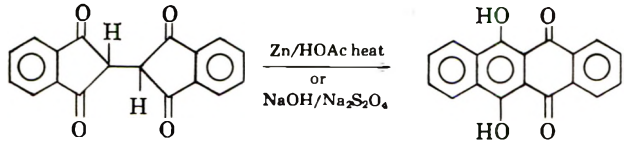
SCHEME II

AROMATIZATION OF A BENZO[3.1.0]BICYCLOHEXENONE (KOELSCH[12])



A related formation of a hydroxynaphthalene from a [3.1.0]bicyclohexanone under similar conditions was recently reported by Koelsch[12] and is formulated as Scheme II.

Another related ring expansion is that of 2,2′-biindan-1,1′3,3′-tetrone in the presence of zinc dust in acetic acid, or of sodium hydrosulfite (sodium dithionite) in aqueous alkali to form a dihydroxynaphthacenequinone.[13,14]



Reductive Cleavage of II.—The reductive cleavage of II to the anion of I has been effected by sodium in dioxane or liquid ammonia and by benzophenone ketyl.[6] It was also reported that in these reductions the quinone III was also formed in small amounts, possibly due to the presence of some hydroxide, alkoxide, or amide ions. In the present study the proposed reductive cleavage of II by the intermediate dianion of 2,3-diphenylnaphthalene-1,4-diol is supported by a separate experiment.

The quinone III was catalytically reduced to its hydroquinone, which in turn was converted to the dianion by sodium hydride in a dioxane solution. On addition of II to this solution and acidification, I (29%) was obtained along with unchanged II (61%). The dianion of the hydroquinone was easily reoxidized to III.

Experimental[15]

2,2′-Diphenyl-2,2′-biindan-1,1′,3,3′-tetrone (II).—The dehydro dimer II used in this study was prepared by oxidation of the anion of 2-phenyl-1,3- indandione (I) by iodine, according to the previously reported procedure.[6]

Cleavage of II by Aqueous Base.—A solution of 15.0 g. (34.0 mmoles) of II in 150 ml. of dioxane and 150 ml. of 1 *N* sodium hydroxide was refluxed overnight under nitrogen and then concentrated to about 50 ml. by distillation. A solution of the residue in 900 ml. of water was cooled in ice, and the yellow precipitate was collected. Extraction of the red filtrate with methylene chloride gave, on evaporation of the solvent, more yellow solid. The combined yield was 8.0 g. (25.7 mmoles, 76%) of impure **2,3-diphenyl-1,4-naphthoquinone** (III), m.p. 130–135°. The infrared spectrum of this impure quinone showed a hydroxyl band in the 3500-cm.$^{-1}$ region in addition to the expected[16] carbonyl band at 1665 cm.$^{-1}$.

When this impure quinone was dissolved in boiling ethanol, the small amount of colorless 2,3-diphenylnaphthalene-1,4-diol[17] which did not dissolve was collected, m.p. 200–224° (red melt); lit.[8] m.p. 236–243°, after softening at 220°.

It was not possible to remove this hydroquinone completely by recrystallization from ethanol. However, when oxygen was bubbled through a boiling solution of the mixture in ethanol for about 30 min., the color changed from a red-orange to a bright yellow and pure **2,3-diphenyl-1,4-naphthoquinone**, m.p. 140–141°, was isolated. Another recrystallization followed by sublimation at 140° (0.1 mm.) raised the melting point slightly, to 141–141.5°; lit.[9] m.p. 140–142°.

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55; mol. wt., 310.3. Found: C, 85.00; H, 4.60; mol. wt., 318.

The ultraviolet spectrum had one band, λ_{max}^{EtOH} 250 mμ (ϵ_{max} 27,000), and showed a broad shoulder with its maximum at 310 mμ.

The red aqueous phase from the cleavage was cooled, acidified, and filtered. The light tan solid was washed with water and dried to yield 2.0 g. (9 mmoles, 13%) of **2-phenyl-1,3-indandione**,[17] m.p. 145–147°; lit.[3] m.p. 149°.

The filtrate was further cooled to give as a white precipitate 2.88 g. (17.4 mmoles, 51%) of **phthalic acid**,[17] m.p. 204–205° dec.; lit.[18] m.p. 206–208° dec.

Cleavage of II with Sodium Methoxide.—To a solution of 4.6 g. (0.2 g.-atom) of sodium in 500 ml. of methanol, there was added with stirring 17.68 g. (40 mmoles) of II. The clear red solution was refluxed under nitrogen for 20 hr. and then concentrated to 50 ml. by distillation of the solvent. The residue was diluted with methylene chloride and extracted once with 0.1 *N* sodium hydroxide and twice with water. The red aqueous phase after acidification with hydrochloric acid, extraction with methylene chloride, and evaporation of the solvent, yielded a light orange crystalline residue. This on trituration with hexane–ether gave 5.56 g. (25 mmoles, 31%) of **2-phenyl-1,3-indandione** (I),[17] m.p. 141–143°.

The neutral yellow methylene chloride layer was concentrated to a thick oil, which was then dissolved in benzene and chromatographed on a 325-g. silica gel column. The column was eluted successively with hexane, benzene, methylene chloride, ether, and methanol. The benzene fraction on evaporation of the solvent and trituration of the residue with ether yielded 2.15 g. (4.85 mmoles, 12%) of II,[17] m.p. 210–213°. From the methylene chloride fraction 5.16 g. (16.6 mmoles, 41.5%) of **2,3-diphenyl-1,4-naphthoquinone** (III),[17] m.p. 139–140°, was isolated. One recrystallization from ethanol raised the melting point to 141–142°. The ether fraction on evaporation of the solvent gave 3.5 g. (18 mmoles, 45%) of **methyl phthalate**.[17]

When the reaction was run with one equivalent of sodium methoxide, 13% of I, 11% of II, 22% of III, and 38% of methyl phthalate were obtained.

2,3-Diphenylnaphthalene-1,4-diol and Its Diacetate.—When 200 mg. of 2,3-diphenyl-1,4-naphthoquinone was reduced under Clemmensen conditions (amalgamated zinc, concentrated hydrochloric acid, toluene), white shiny flakes formed in the toluene layer in 2 or 3 min. The white flakes were collected and recrystallized from benzene to yield 100 mg. of **2,3-diphenylnaphthalene-1,4-diol**, m.p. 205–225° (red melt); lit.[8] m.p. 236–243°, after softening at 220°.

The infrared spectrum of this compound was identical with that of the hydroquinone obtained in the previous reaction, showing a strong hydroxyl band at 3500 cm.$^{-1}$ and no carbonyl band at 1665 cm.$^{-1}$. No satisfactory analysis was obtained because of susceptibility to air oxidation. For this reason the acetoxy derivative was prepared.

(12) C. F. Koelsch, *J. Org. Chem.*, **26**, 1003 (1961).

(13) (a) C. Dufraisse, *Bull. soc. chim. France*, [5] **3**, 1880 (1936); (b) G. Wanag, *Ber.*, **70**, 274 (1937).

(14) A. Schönberg and R. Moubasher, *J. Chem. Soc.*, 212 (1949).

(15) Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Infrared spectra were taken on a Perkin-Elmer double beam recording spectrophotometer, Model 21, and a Perkin-Elmer Infracord spectrophotometer, Model 137. Ultraviolet spectra were taken on a Cary Model 11 recording spectrophotometer. Melting points were taken in capillary tubes and were corrected.

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., J. Wiley and Sons, Inc., New York, N. Y., 1958.

(17) The infrared spectrum was superimposable on that of an authentic sample.

(18) "Handbook of Chemistry and Physics," 44th Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1963.

To a solution of 1 g. of 2,3-diphenyl-1,4-naphthoquinone in 30 ml. of glacial acetic acid, 1 g. of powdered zinc and 5 ml. of concentrated hydrochloric acid were added. The mixture was boiled until the solution became colorless (5–10 min.) and a white solid separated. The mixture was then cooled, diluted with 200 ml. water, and extracted with methylene chloride. To the dried extract there were added immediately 1 ml. of pyridine and 1 ml. of acetyl chloride with cooling. The pale yellow solution was evaporated to dryness, and the residue was triturated with ethanol. The white crystals of **2,3-diphenylnaphthalene-1,4-diol diacetate** were collected and recrystallized from ethanol to yield 350 mg. of product, m.p. 199–200°, unchanged by further crystallization; lit.[10] m.p. 200–202°; ultraviolet spectrum: λ_{max}^{EtOH} 219 (ϵ 45,600) and 232 mμ (45,000).

Anal. Calcd. for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.69; H, 5.06.

2,3-Epoxy-2,3-dihydro-2,3-diphenyl-1,4-naphthoquinone.—To a hot solution of 1 g. (3.2 mmoles) of 2,3-diphenyl-1,4-naphthoquinone in 25 ml. of ethanol there were added 3 ml. of 30% hydrogen peroxide and 5 ml. of 10% aqueous sodium carbonate. The solution turned deep red and then colorless. After heating for 5 min., a solid separated. The mixture was cooled, diluted with 100 ml. of water and filtered. Two recrystallizations of the precipitate from ethanol yielded 720 mg. (2.2 mmoles, 69%) of **2,3-epoxy-2,3-dihydro-2,3-diphenyl-1,4-naphthoquinone**, m.p. 159–160°; lit.[11] m.p. 155–166°; ultraviolet spectrum: λ_{max}^{EtOH} 235 mμ (ϵ_{max} 37,200).

Anal. Calcd. for $C_{22}H_{14}O_3$: C, 80.97; H, 4.32. Found: C, 81.08; H, 4.35.

Reductive Cleavage of II with the Dianion of 2,3-Diphenylnaphthalene-1,4-diol.—A solution of 1.0 g. (3.2 mmoles) of 2,3-diphenyl-1,4-naphthoquinone (III) in 50 ml. of dioxane was hydrogenated for 30 min. at 50 lb./in.^{2} using 0.5 g. of platinum oxide as catalyst. After removal of the catalyst the solution was added to a suspension of 300 mg. (6.4 mmoles) of sodium hydride (51.6% in mineral oil) in 50 ml. of dioxane with stirring under nitrogen. After the evolution of gas ceased, a light brown-yellow solution was obtained. To this solution there was added with stirring a solution of 1.414 g. (3.2 mmoles) of II in 50 ml. of dioxane. The red solution was stirred at room temperature overnight and concentrated to a thick sirup. This was diluted with methylene chloride and extracted once with 0.1 *N* sodium hydroxide and once with water. The yellow organic phase was concentrated to a gum, which on trituration with methanol gave 1.88 g. of a yellow solid containing 0.87 g. (1.95 mmoles, 61%) of unchanged II and 1.0 g. (100%) of **2,3-diphenyl-1,4-naphthoquinone**. The concentrations of these two substances in the mixture were determined by ultraviolet spectroscopy from the optical density at 231 mμ of a solution in ethanol.

The red aqueous phase after acidification and extraction with methylene chloride gave 0.41 g. (1.84 mmoles, 29%) of **2-phenyl-1,3-indandione**.[17]

The Photochemical Conversion of Phenyl Isocyanate and Diphenyldiazomethane to 2,2-Diphenylindoxyl

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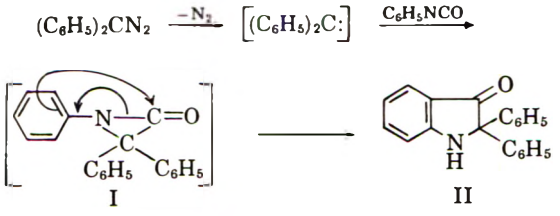
Received July 29, 1963

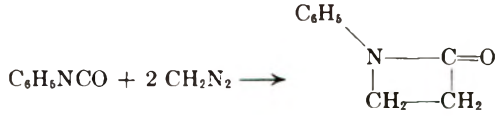
We have found that phenyl isocyanate and diphenyldiazomethane react under the influence of ultraviolet light to afford 2,2-diphenylindoxyl.[1] This reaction appears to be the first example of the addition of a carbene to an isocyanate and the first photoinitiated reaction of an isocyanate. In addition, each reactant is converted individually into a characteristic irradiation product; that is, diphenyldiazomethane produces benzophone azine[2] and phenyl isocyanate gives the cyclic dimer 1,3-diphenyluretedione.[3]

The formation of 2,2-diphenylindoxyl can be explained by assuming that the photo-generated carbene from diphenyldiazomethane adds to the phenyl isocyanate to produce an α-lactam I which then collapses to the indoxyl II.



Recently[1] this same α-lactam I was proposed as an intermediate in the reaction of α-chloro-α,α'-diphenylacetanilide with sodium hydride; in that case also 2,2-diphenylindoxyl (II) was the principal product.

In two earlier communications from this laboratory[4,5] the nonphotochemical reaction of diazomethane with phenyl isocyanate was reported to give a β-lactam (that of N-phenyl-β-alanine). At that time it was suggested[5] as one possible mechanism that first one molecule of diazomethane reacted with one molecule of phenyl isocyanate to give an intermediate α-lactam, which on subsequent reaction with a second molecule of diazomethane formed the β-lactam.



Staudinger stated[6] that diphenyldiazomethane does not react with phenyl isocyanate. Our present experiments confirm the absence of a detectable change on simple mixing of the reagents; heating decomposes diphenyldiazomethane to benzophenone azine. Irradiation, however, initiates a rapid reaction.

Experimental

Irradiation of Phenyl Isocyanate and Diphenyldiazomethane.—A solution of diphenyldiazomethane (1.2 g., 6.2 mmoles) in phenyl isocyanate (3.5 g., 29.6 mmoles) was irradiated[7] in a quartz tube with occasional cooling. After 6 hr. 115 ml. of nitrogen (25°) had been evolved and the deep violet color of diphenyldiazomethane had disappeared. The excess phenyl isocyanate was evaporated at room temperature and the residue was chromatographed over silicic acid (Mallinckrodt, 100 mesh). Elution with *n*-pentane–benzene yielded **benzophenone azine** (356 mg., m.p. 162–163°). Benzene eluted **1,3-diphenyluretedione** (53 mg., m.p. 174–175°); both were characterized by comparison with samples prepared by known methods.[2,3] Elution with benzene–ether (97:3) afforded 312 mg., m.p. 212–213° (after recrystallization from ether–petroleum ether), of **2,2-diphenylindoxyl**. Identification was made by mixture melting point and comparison of infrared and ultraviolet spectra with an authentic sample.[1] The molecular weight (mass spectrometric) was 285 (calcd. for $C_{20}H_{15}NO$: 285). Continued elution with benzene–ether gave a viscous red oil in which the probable pres-

(1) J. C. Sheehan and J. W. Frankenfeld, *J. Am. Chem. Soc.*, **83**, 4792 (1961).

(2) T. Curtius and F. Rauterberg, *J. prakt. Chem.*, [2] **44**, 200 (1891).

(3) L. C. Raiford and H. B. Freyermuth, *J. Org. Chem.*, **8**, 230 (1943).

(4) J. C. Sheehan and P. T. Izzo, *J. Am. Chem. Soc.*, **70**, 1985 (1948).

(5) J. C. Sheehan and P. T. Izzo, *ibid.*, **71**, 4059 (1949).

(6) H. Staudinger, E. Anthes, and F. Pfenninger, *Ber.*, **49**, 1928 (1916).

(7) The irradiation was carried out from a distance of 12–15 cm. with a 140-w. Hanovia Utility Model high-pressure quartz mercury-vapor arc lamp, which transmits the complete ultraviolet spectrum.

ence of 1,3-diphenyloxindole[1] was detected by thin layer chromatography (silica gel G and aluminum oxide G in four different solvent systems: 97% benzene–3% ether, 99% benzene–1% ethyl acetate, 99% benzene–1% dioxane, and 99% benzene–1% methanol).

However, two other products,[1] which are derivable from the α-lactam I, namely 1-keto-2,3-diphenylisoindole and 3,3-diphenyloxindole, could not be found.

Acknowledgment.—I. L. gratefully acknowledges financial support from Public Health Predoctoral Fellowship GPM-11,445-C2. We are indebted to Professor K. Biemann and Dr. W. Richter for the mass spectra.

The Synthesis of Naphtho[2,1-*a*]perylene and Dibenzo[*ae*]perylene[1,2]

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Received May 14, 1963

Many papers attest to the fact that a causal relationship very likely exists between air pollution and respiratory diseases including lung cancer.[6] A relationship between polynuclear aromatic hydrocarbons found in certain polluted air and lung cancer is also suggested.[7] Continuing our work in this area,[8] we were concerned with the dehydrogenation of 7-(1-naphthyl)benz[*a*]anthracene (I). This compound, on catalytic intramolecular dehydrogenation, might lead to dibenzo[*ae*]perylene (II) and/or naphtho[2,1-*a*]perylene (III). When I was dehydrogenated with aluminum chloride and stannic chloride, only one perylene derivative was found. In order to establish the structure of the product, which was either II or III, we undertook an unequivocal synthesis of naphtho[2,1-*a*]perylene (III).

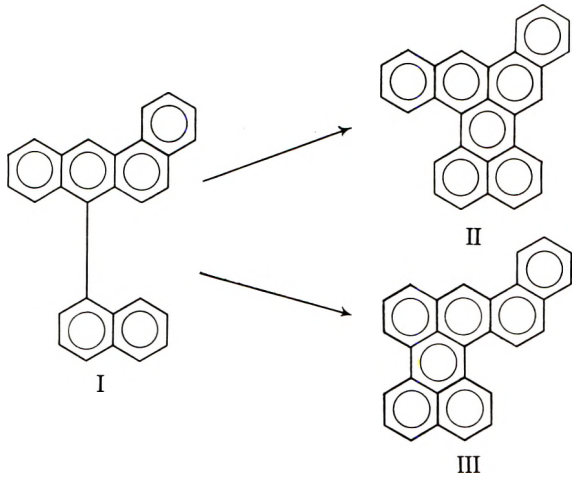
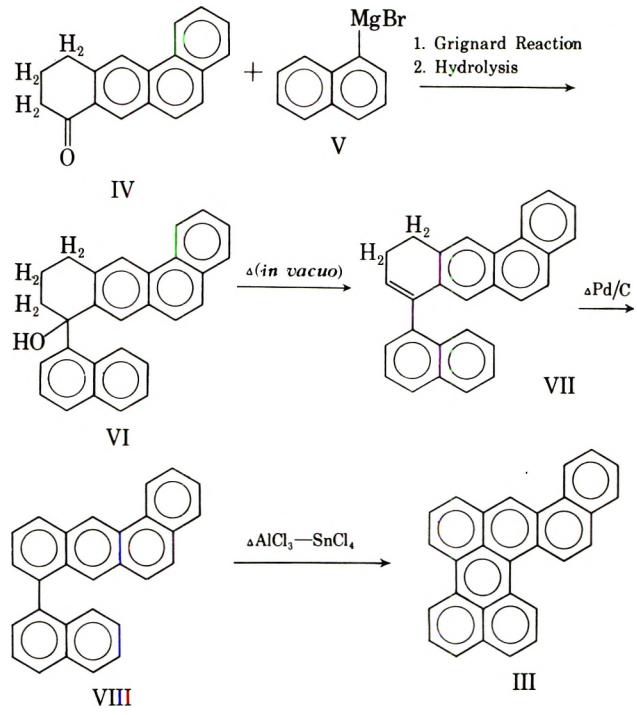


CHART I



On the basis of similar experiments,[9] it seemed that if we could prepare 8-(1-naphthyl)benz[*a*]anthracene (VIII), an unequivocal dehydrogenation to III might be achieved. The reactions shown in Chart I were undertaken to this end. A four-step reaction sequence was used to prepare 8-keto-8,9,10,11-tetrahydrobenz[*a*]anthracene (IV).[10] The action of 1-naphthylmagnesium bromide on this ketone followed by hydrolysis afforded a mixture of 8-(1-naphthyl)-8-hydroxy-8,9,10,11-tetrahydrobenz[*a*]anthracene (VI) in a 22% yield and the dehydrated product, 8-(1-naphthyl)-10,11-dihydrobenz[*a*]anthracene (VII) in 13% yield. Satisfactory analytical data could not be obtained on the carbinol VI due to its easy dehydration on crystallization. The carbinol was converted quantitatively to the dehydration product 8-(1-naphthyl)-10,11-dihydrobenz[*a*]anthracene (VII) when it was heated *in vacuo*. VII on dehydrogenation with a palladium-on-charcoal catalyst in boiling *p*-cymene gave 8-(1-naphthyl)benz[*a*]anthracene (VIII) in 83% yield.

Many known dehydrogenation agents and reaction procedures[8] were used in an attempt to convert VIII to naphtho[2,1-*a*]perylene (III); heating with sulfur, with selenium, with palladium on carbon; vapor phase dehydrogenation at 430° on asbestos; fusion with sodium chloride and aluminum chloride[11]; pyrolysis at 700°; aluminum chloride in boiling benzene[8];

(1) The nomenclature used in this paper is that presented in the "Definitive Rules for Nomenclature of Organic Chemistry," *J. Am. Chem. Soc.*, **82**, 5545 (1960).

(2) Presented before the Division of Organic Chemistry at the Combined Southeastern-Southwestern Regional Meeting of the American Chemical Society, New Orleans, La., December, 1961.

(3) Chemistry Department, Villanova University, Villanova, Pa.

(4) This paper has been taken from the Doctorate thesis of Walter W. Zajac, Jr., and the Masters thesis of Louis G. Mahone presented to the Virginia Polytechnic Institute in 1959 and 1961, respectively.

(5) This investigation was supported by a research grant (AP-88) from the Division of Air Pollution, Bureau of State Services, Public Health Service.

(6) M. Katz, *Occupational Health Rev.*, **14**, 3 (1962); M. O. Amdur, *New Engl. J. Med.*, **266**, 555 (1962); W. McDermott, *Sci. Am.*, **205**, 49 (1961); M. R. Purvis, S. Miller, and R. Ehrlich, *J. Infect. Diseases*, **109**, 238 (1961); *Japan. Heart J.*, **2**, 180 (1961); J. Cuthbert, *Public Health* (London), **74**, 123 (1960); E. Gorham, *Med. Officer* (London), **101**, 178 (1959).

(7) E. L. Wynder, F. R. Lemon, and I. J. Bross, *Cancer*, **12**, 1016 (1959); P. Stocks, *Brit. J. Cancer*, **14**, 397 (1960); L. Kreyberg, *ibid.*, **13**, 618 (1959); H. L. Falk, P. Kotin, and A. Miller, *Intern. J. Air Pollution*, **2**, 201 (1960).

(8) F. A. Vingiello and W. W. Zajac, Jr., *J. Org. Chem.*, **26**, 2228 (1961).

(9) See, for example, M. Orchin and R. Friedel, *J. Am. Chem. Soc.*, **68**, 573 (1946); P. G. Copeland, R. E. Dean, and D. McNeil, *J. Chem. Soc.*, 1689 (1960); E. Clar and M. Zander, *ibid.*, 1861 (1958).

(10) J. Cook, *ibid.*, 1592 (1933).

(11) A. Zincke and E. Ziegler, *Ber.*, **74**, 115 (1951).

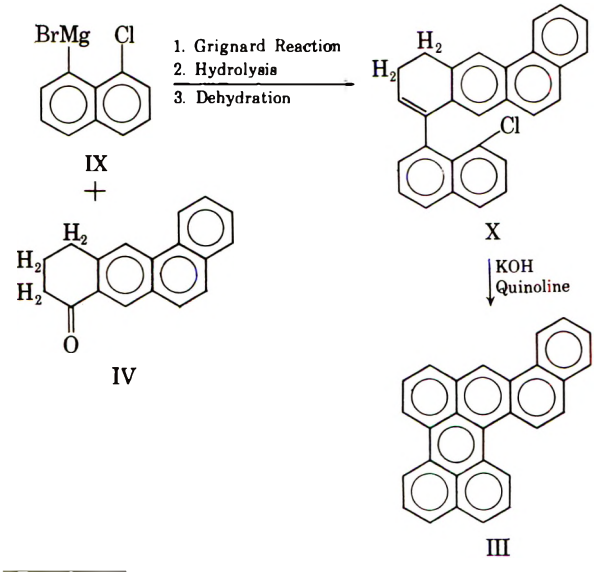
and aluminum bromide in boiling benzene—all failed to yield any of the desired product III. Finally, cyclodehydrogenation of VIII with stannic chloride and aluminum chloride in boiling benzene for five minutes gave a 40% yield of naphtho[2,1-*a*]perylene. A comparison of the ultraviolet and infrared spectra with known benzoperylenes and dibenzoperylenes revealed a similarity in type. A 2,4,7-trinitrofluorenone adduct (TNF) was formed and this gave a satisfactory analysis for a 1:1 adduct.

A comparison of the properties of the naphtho[2,1-*a*]perylene (III) with the product obtained by the dehydrogenation of 7-(1-naphthyl)benz[*a*]anthracene revealed many strong differences and therefore we believe this latter compound is dibenzo[*ae*]perylene (II). It is interesting to note that both calculated localization energies[12] and frontier electron densities[13] for benz[*a*]anthracene suggest that position 8 is more susceptible than position 6 to electrophilic attack. Since I gives II and not III, it may be that under the conditions of the experiment the attack on the benz[*a*]anthracene moiety is not electrophilic in nature; indeed, the mechanism may not be ionic.

In view of the modest yield achieved in the conversion of VIII to III, and because such a powerful catalyst as stannic chloride and aluminum chloride had to be used, another route to III was sought. Clar[14] has effected the cyclodehydrochlorination of 1-chloro-9,10-di-1-naphthylanthracene to 7-(1-naphthyl)benz[*a*]perylene with potassium hydroxide and quinoline. It occurred to us that we might pattern an experiment after Clar's[14] and prepare III using a milder catalyst than the stannic chloride–aluminum chloride mixture. With this idea in mind, we prepared 8-[1-(8-chloronaphthyl)]-10,11-dihydrobenz[*a*]anthracene (X) as shown in Chart II. 1-Bromo-8-chloronaphthalene was prepared from naphthalene in four steps according to the method of Fieser and Seligman.[15] The Grignard reagent IX was prepared and allowed to react with the ketone IV to give, after dehydration, 8-[1-(8-chloronaphthyl)]-10,11-dihydrobenz[*a*]anthracene (X). No attempt was made to isolate the carbinol which is presumably an intermediate in the preparation of X because of the known instability of a similar compound VI. The action of potassium hydroxide and quinoline upon compound X gave a 36% yield of naphtho[2,1-*a*]perylene (III). On treatment with palladium on carbon, X gave a 52% yield of VIII and a 2% yield of III. Naphtho[2,1-*a*]perylene formed a 1:1 adduct with TNF.

A III sample, submitted for carcinogenicity testing,[16] revealed the compound to be a potent carcinogen.

CHART II



Experimental[17-19]

8-(1-Naphthyl)-8-hydroxy-8,9,10,11-tetrahydrobenz[*a*]anthracene (VI) with Partial Dehydration.—A Grignard reagent was prepared in ether from 2.74 g. (0.113 g.-atom) of magnesium and 23.4 g. (0.113 mole) of 1-bromonaphthalene. The ether was distilled while 200 ml. of anhydrous benzene was added slowly. The Grignard reagent was then cooled and 20.5 g. (0.0833 mole) of 8-keto-8,9,10,11-tetrahydrobenz[*a*]anthracene[10] was added in four portions during a period of 10 min. The clear solution which resulted was stirred at room temperature for 21 hr. The solution was cooled and decomposed with cold 20% ammonium chloride solution. The organic layer was separated and concentrated until *ca.* 50 ml. of solution remained. Treatment with hot ethanol followed by cooling gave 6.7 g. (22%) of the carbinol VI, m.p. 215–223°. The filtrate was concentrated, to remove the benzene, and *ca.* 500 ml. of ethanol was added. The solid was recrystallized from 10% benzene–ethanol and gave 3.8 g. (13%) of the dehydrated carbinol, 8-(1-naphthyl)-10,11-dihydrobenz[*a*]anthracene, m.p. 257–258°.

8-(1-Naphthyl)-10,11-dihydrobenz[*a*]anthracene (VII).—A sample of 1.00 g. of 8-(1-naphthyl)-8-hydroxy-8,9,10,11-tetrahydrobenz[*a*]anthracene was heated for 12 hr. in a drying pistol at 180° (1.0 mm.). There was obtained 0.95 g. (100%) of 8-(1-naphthyl)-10,11-dihydrobenz[*a*]anthracene (VII), m.p. 257–258°. Recrystallization of this sample from a benzene–ethanol mixture gave colorless plates, m.p. 260–261°.

Anal. Calcd. for $C_{28}H_{20}$: C, 94.34; H, 5.66. Found: C, 94.28; H, 5.62.

8-(1-Naphthyl)benz[*a*]anthracene (VIII).—A mixture of 1.12 g. (0.00314 mole) of 8-(1-naphthyl)-10,11-dihydrobenz[*a*]anthracene, 0.88 g. of 10% palladium on charcoal, and 115 ml. of *p*-cymene was heated under reflux for 12 hr. The hot mixture was filtered and the solution evaporated under reduced pressure. The solid obtained was recrystallized from a benzene–ethanol mixture. There was obtained 0.92 g. (83%) of 8-(1-naphthyl)-benz[*a*]anthracene, m.p. 241–242°.

Anal. Calcd. for $C_{28}H_{18}$: C, 94.87; H, 5.13. Found: C, 94.84; H, 5.47.

Naphtho[2,1-*a*]perylene (III).[20]—A mixture of 0.50 g. of stannic chloride, 0.60 g. of anhydrous aluminum chloride, and 50 ml. of anhydrous benzene was heated on a steam bath. To this was added 0.50 g. (0.0014 mole) of 8-(1-naphthyl)benz[*a*]anthracene in 25 ml. of hot benzene. The mixture was heated under reflux for 5 min., then cooled to room temperature and decomposed with 100 ml. of dilute hydrochloric acid. The organic layer was separated, washed with water, dried over anhydrous calcium sulfate, and concentrated to *ca.* 5 ml. Treatment with 100 ml. of ethanol gave 0.20 g. (40%) of III, m.p. 201–203°. The material was recrystallized from 10% benzene–ethanol giving red needles, m.p. 203–204°.

(12) M. J. S. Dewar, *J. Am. Chem. Soc.*, **74**, 3357 (1952).

(13) K. Fukui, T. Yonezawa, C. Nagata, and H. Shinyu, *J. Chem. Phys.*, **22**, 1433 (1954).

(14) E. Clar, W. Kelly, D. Stewart, and J. Wright, *J. Chem. Soc.*, 2652 (1956).

(15) L. F. Fieser and A. Seligman, *J. Am. Chem. Soc.*, **61**, 136 (1939).

(16) Private communication from Dr. Paul Kotin, Chief, Carcinogenesis Studies Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md. Compound II was not prepared in sufficient quantities for carcinogenicity testing. An adequate amount is now being prepared and will be tested.

(17) Unless otherwise indicated all melting points were taken on a Fisher-Johns melting point block and are corrected.

(18) (a) All the analyses were carried out by Geller Laboratories, Bardonia, N. Y., except those which were performed by (b) Galbraith Laboratories, Knoxville, Tenn.

(19) All procedures involving naphtho[2,1-*a*]perylene, dibenzo[*ae*]perylene, and their derivatives were carried out with a minimum of exposure to light.

(20) This experiment was performed by Mr. Jose Yanez.

Anal. Calcd. for $C_{28}H_{16}$: C, 95.42; H, 4.59. Found[18b]: C, 95.24; H, 4.72.

The compound dissolved in concentrated sulfuric acid giving a green color which turned blue on prolonged standing.

8-[1-(8-Chloronaphthyl)]-10,11-dihydrobenz[*a*]anthracene (X).—A Grignard reagent was prepared in ether from 9.0 g. (0.037 mole) of 1-bromo-8-chloronaphthalene[15] and 0.95 g. (0.039 g.-atom) of magnesium. The reaction mixture was stirred and heated under reflux for 24 hr. Anhydrous benzene was added as needed to keep the Grignard reagent from crystallizing too much. The ether was distilled and benzene was added to bring the volume to *ca.* 100 ml. In one portion, 9.1 g. (0.037 mole) of 8-keto-8,9,10,11-tetrahydrobenz[*a*]anthracene was added and the solution was heated under reflux for 24 hr. The solution was cooled, decomposed with cold 20% ammonium chloride solution, and extracted with ether. The organic layer was separated, washed with water, dried over anhydrous calcium sulfate, and concentrated to *ca.* 20 ml. The oil was crystallized using acetone, giving 3.5 g. of solid, m.p. 219–220°. The solid was vacuum sublimed at 210° (0.6 mm.) and then recrystallized from 20% benzene–ethanol giving 3.4 g. (23%) of X as colorless needles, m.p. 222–223°. Recrystallization from 1:1 benzene–petroleum ether (30–60°) gave colorless needles, m.p. 225–226°.

Anal. Calcd. for $C_{28}H_{19}Cl$: C, 86.03; H, 4.90; Cl, 9.07. Found: C, 85.63; H, 4.89; Cl, 8.95.

Cyclization of 8-[1-(8-Chloronaphthyl)]-10,11-dihydrobenz[*a*]-anthracene (X). A. *Via* Potassium Hydroxide and Quinoline.—A mixture of 0.50 g. (0.0013 mole) of X, 10.0 g. of potassium hydroxide, and 15 ml. of quinoline was heated under reflux for 30 min. The mixture was cooled, decomposed with cold dilute hydrochloric acid, and extracted with ether. The organic layer was filtered. The filtrate was washed with dilute hydrochloric acid, then water, and finally dried over anhydrous calcium sulfate. The solid, crude naphtho[2,1-*a*]perylene was dissolved in benzene and combined with the ether extract. This solution was then concentrated to *ca.* 5 ml. and chromatographed[21] on alumina[22] using petroleum ether[23] as the eluant. A blue fluorescent[24] band appeared, followed by a red band with a green-yellow fluorescence.[24] Concentration and recrystallization of the first band, after elution, gave 0.06 g. of starting material. The red band was eluted, concentrated, and crystallized. The yield was 0.17 g. (36%) of naphtho[2,1-*a*]perylene, m.p. 201.5–203.5°.

B. *Via* **Palladium on Charcoal.**—A mixture of 0.50 g. (0.0012 mole) of X and 0.10 g. of 10% palladium on charcoal was heated at 310° for 15 min. and then at 350° for 1 hr. The mixture was worked up and chromatographed as described under A. There was obtained 0.26 g. (52%) of compound VIII and 0.11 g. (2%) of III, m.p. 202–203°.

TNF Adduct of Naphtho[2,1-*a*]perylene (III).—A solution of 0.12 g. (0.00034 mole) of naphtho[2,1-*a*]perylene in 40 ml. of hot 10% benzene–ethanol was added to a hot solution of 0.10 g. of 2,4,7-trinitrofluorenone in 40 ml. of 10% benzene–ethanol. On cooling, a black precipitate appeared, 0.10 g. (47%), which on recrystallization from 10% benzene–ethanol gave fine black needles, m.p. 222–223°.

Anal. Calcd. for $C_{41}H_{23}O_6N_3$: C, 73.76; H, 3.17; N, 6.29. Found: C, 73.52; H, 3.44; N, 6.30.

Dibenzo[*ae*]perylene (II).—A mixture of 0.50 g. of 7-(1-naphthyl)benz[*a*]anthracene[25] and 0.5 g. of powdered anhydrous aluminum chloride and 0.5 g. of fuming stannic chloride in 50 ml. of dry benzene was heated in a steam bath for 30 min. The deep red solution was allowed to cool to room temperature and was then decomposed with 100 ml. of 10% hydrochloric acid. The green fluorescent organic layer was separated and the aqueous layer was extracted twice with 50-ml. portions of benzene. The combined benzene extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was distilled until only *ca.* 10 ml. remained. This solution was chromatographed.[19,21] Two bands appeared on the column, a colorless blue fluorescent band and a red-orange band. The first band was eluted with petroleum ether[23] and discarded. The second band was removed with benzene and the resultant solution concentrated to give red crystals of dibenzo[*ae*]perylene (II), 0.24 g. (48%), m.p. 183–186°.

An analytical sample was prepared by recrystallization of the hydrocarbon from benzene, m.p. 188–189°.

Anal. Calcd. for $C_{28}H_{16}$: C, 95.42; H, 4.28. Found[18b]: C, 95.72; H, 4.37.

The hydrocarbon dissolved in concentrated sulfuric acid giving a Prussian blue color which changed to brown on standing.

TNF Adduct of Dibenzo[*ae*]perylene.[26]—A hot saturated solution of 0.12 g. of dibenzo[*ae*]perylene in benzene was mixed with a hot saturated solution of 0.4 g. of 2,4,7-trinitrofluorenone in ethanol. A brown solid formed immediately, 0.21 g. (quantitative). Four recrystallizations from benzene gave a brown, granular solid, m.p. 253–254°.

Anal. Calcd. for $C_{41}H_{21}N_3O_7$: C, 73.75; H, 3.17; N, 6.30. Found[18b]: C, 73.51; H, 3.61; N, 6.19.

(21) The column used throughout this investigation was 18 × 370 mm.

(22) Fisher's adsorption alumina, 80–200 mesh.

(23) The petroleum ether used as an eluent had a 30–60° boiling point range.

(24) Fluorescent under ultraviolet radiation with a Blak-ray ultraviolet long wave lamp (3660 Å.) as the source.

(25) F. A. Vingiello, A. Borkovec, and W. W. Zajac, Jr., *J. Am. Chem. Soc.*, **80**, 1714 (1958).

(26) This experiment was performed by Mr. Leo Ojakaar.

α-Hydroxy Acid Amides. A Convenient Synthesis

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Received June 24, 1963

Using a procedure patterned after the one described for the preparation of α-amino acid amides,[1] a variety of cyanohydrins have been converted in reasonable yield to the corresponding α-hydroxy acid amides. This reaction probably proceeds similarly[1]; an intermediate imido ester salt is formed which, upon heating, eliminates alkyl chloride to produce the desired amide. With the possible exception of a recently reported preparation of α-hydroxyphenylacetamide[2] this report apparently is the first record of an application of the Pinner amide synthesis[3] to the synthesis of α-hydroxy acid amides.

$$\mathrm{RCHCN} + \mathrm{R'OH} + \mathrm{HCl} \longrightarrow \underset{\mathrm{OH}}{\mathrm{RCHCN}}$$

$$\underset{\mathrm{OH}}{\overset{\mathrm{NH\cdot HCl}}{\overset{\|}{\mathrm{RCHCOR'}}}} \longrightarrow \underset{\mathrm{OH}}{\overset{\mathrm{O}}{\overset{\|}{\mathrm{RCHCNH_2}}}} + \mathrm{R'Cl}$$

The best yields of amides were generally obtained by allowing the cyanohydrin to react with isopropyl alcohol saturated with hydrogen chloride. Evaporation of the solvent followed by pyrolysis of the imido ester salt and subsequent distillation produced the hydroxy amide in yields as high as 80%. Alternatively, the synthesis was performed in an inert solvent such as xylene, employing a slight excess over equivalent quantities of an alcohol. After a suitable reaction time with hydrogen chloride, the reaction mixture was heated under reflux to decompose the imido ester salt and the product recovered by a filtration of the cooled mixture. The combined versatility of these two procedures was sufficient to allow the preparation of the various α-hydroxy amides tabulated in Table I.

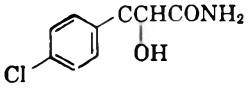
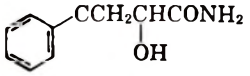
(1) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 798 (1962).

(2) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961), ref. 329.

(3) Refer to S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **73**, 2233 (1951), for pertinent references.

TABLE I

α-HYDROXY ACID AMIDES

Amide	M.p., °C.	Lit. m.p., °C.	Method[a]	% yield
$CH_3CHCONH_2$ (OH)	74–75	74[b]	B	59
$CH_3CH_2CHCONH_2$ (OH)	104–105	105[c]	A	55
$(CH_3)_2CCONH_2$ (OH)	97–99	96–98[d]	B	80
$(CH_3)_2CHCHCONH_2$ (OH)	102–104	104[e]	B	78
$CH_3CH_2CCONH_2$ (CH_3, OH)	68–69	160[f]	B	56
$(CH_3)_2CHCH_2CHCONH_2$ (OH)	81–82	51–52[g]	A	79
$CH_3CH_2CHCHCONH_2$ (CH_3, OH)	49–56[h]		B	70
$CH_3(CH_2)_5CHCONH_2$ (OH)	151–152	150[i]	B	44[l]
	124–125	122–123[j]	A	45
	110–112	111–112[k]	A	71

[a] Method A: inert solvent with equivalent quantities of alcohol. Method B: alcohol used as a solvent. [b] J. Wislicenus, *Ann.*, **133**, 257 (1865). [c] H. Bredereck, R. Gompper, and G. Theilig, *Ber.*, **87**, 537 (1954). [d] G. Ciamician and P. Silber, *ibid.*, **38**, 1671 (1905). [e] A. Lipp, *Ann.*, **205**, 1 (1880). [f] G. Ciamician and P. Silber, *Ber.*, **47**, 1806 (1914). *Anal.* Calcd. for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.27; H, 9.73; N, 11.94. [g] P. Nicolle, *Bull. soc. chim. France*, [4] **39**, 55 (1926). *Anal.* Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.13; H, 9.68; N, 10.75. [h] An obvious mixture of isomers. *Anal.* Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.16; H, 10.03; N, 10.63. [i] E. Erlenmeyer and O. Sigel, *Ann.*, **177**, 102 (1875). [j] H. G. Rule, *J. Chem. Soc.*, **113**, 3 (1918). [k] A. McKenzie, G. Martin, and H. G. Rule, *ibid.*, **105**, 1583 (1914). [l] Recrystallized yield.

Some ammonium chloride (up to 15%) was always formed during the reaction sequence and limited attempts were made to overcome its formation. Since this salt formation is most likely the result of alcoholysis of the imido ester, a brief study of the effect of various alcohols on the formation of ammonium chloride was conducted. Contrary to the striking effects of "subtle" changes in alcohol structure observed in the related synthesis of α-amino acid amides[2], little difference in the course of the reaction was noted when 2-propanol, 2-butanol, and 3-pentanol were employed as solvents.

Those α-hydroxy acid amides analogous to the essential α-amino acids valine, leucine, and phenylalanine were evaluated for their ability to replace them nutritionally in a mouse diet. As expected, complete replacement was observed.

Experimental[4]

2-Hydroxy-3-phenylpropionamide. Procedure A.—A mixture of 649 g. (4.41 moles) of phenylacetaldehyde cyanohydrin, 210 g. (4.57 moles) of ethanol, and 2.6 l. of dry benzene (dry xylene was used in all other cases) was saturated with anhydrous hydrogen chloride (358 g.) at 25°. The mixture was stirred for 20 hr. at 25° and then heated under reflux for 6 hr. During this time the product precipitated and was collected after cooling the mixture to 10°. A total of 586 g. of light yellow crystalline product was obtained, m.p. 107–112° and was found to contain 6% ammonium chloride as calculated from a chloride analysis. The product was crystallized from 3 l. of benzene containing 450 ml. of ethanol to give 450 g. (62%) of colorless crystals, m.p. 110–112°.

2-Hydroxy-3-methylbutyramide. Procedure B.—A solution of 500 g. (5.06 moles) of isobutyraldehyde cyanohydrin in 3 l. of isopropyl alcohol was saturated with anhydrous hydrogen chloride at 25–30°. The mixture was stirred at 25° for 20 hr. and then excess alcohol and hydrogen chloride were removed by evaporation under reduced pressure. The remaining residue was heated slowly to 170° under 20–50-mm. pressure and then cooled to room temperature. Two liters of ethanol was added and the ammonium chloride present was removed by a filtration (11 g.). Evaporation of the ethanol followed by distillation of the residue gave 461 g. (78%) of colorless distillate, b.p. 145–150° (2 mm.) m.p. 93–98°. Crystallization from an isopropyl ether–ethanol mixture raised the melting point to 102–104°.

Acknowledgment.—The authors wish to thank C. R. McClure for able assistance and Q. Quick and his associates for microanalyses and spectral data.

(4) Melting points are corrected.

The Brominating Properties of Tetramethylammonium Tribromide[1a]

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Received June 7, 1963

Organic ammonium perbromides are considered mild brominating agents. Pyridinium bromide perbromide was introduced by Djerassi and Scholz for the bromination of keto steroids and has since been used widely in place of bromine, which occasionally causes undesired substitution or oxidation reactions.[2] Unlike N-bromosuccinimide (NBS), it lacks the ability to perform allylic bromination. Marquet and coworkers preferred phenyltrimethylammonium perbromide (PTAP) to pyridinium bromide perbromide because of the greater stability of the former.[3] With this reagent they were able to brominate ketones and 1,3-dioxolanes, without affecting isolated ethylenic double bonds, present in the same molecule. Its mild brominating characteristic and specificity were shown in the reaction with 2-acetyl-6-methoxynaphthalene. In tetrahydrofuran 2-bromoacetyl-6-methoxynaphthalene was obtained, while in acetic acid a 1:1 mixture of this bromoacetyl compound and the nuclear substituted derivative, 2-acetyl-5-bromo-6-methoxynaphthalene was formed. Although NBS is considered a specific reagent for allylic bromination,[4] it can bro-

(1) (a) Taken in part from the M.S. thesis of J. Weiss, Bar Ilan University, 1963; (b) Weizmann Institute of Science, Rehovoth, Israel.

(2) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **70**, 417 (1948); P. C. Merker and J. A. Vona, *J. Chem. Educ.*, **26**, 613 (1949); J. A. Vona and P. C. Merker, *J. Org. Chem.*, **14**, 1048 (1949); N. B. Lorette, T. B. Gage, and S. H. Wender, *ibid.*, **16**, 930 (1951).

(3) A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlock, C. Onannes, and J. Jacques, *Bull. soc. chim. France*, 1822 (1961); A. Marquet and J. Jacques, *ibid.*, 90 (1962).

(4) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

TABLE I

BROMINATION BY MEANS OF TETRAMETHYLAMMONIUM TRIBROMIDE

Starting material	Method A: Product	Time, hr.	M.p. or b.p. (mm.), °C.	Yield, %	Method B: Product	Time, min.	M.p. or b.p. (mm.), °C.	Yield, %
Toluene	Benzyl bromide[a]		194–198[b] (760)	59	*p*-Bromotoluene[a,c]		184–186[d] (760)	72
Fluorene	9-Bromofluorene	5	104[e]	70	2-Bromofluorene	30	112–113[f]	82
1-Methylnaphthalene	1-Bromomethylnaphthalene	24[g]	55–56[h]	57	2-Bromo-1-methylnaphthalene	20	35–37[i]	65
2-Methylnaphthalene	2-Bromomethylnaphthalene	8	54–55[j]	62	1-Bromo-2-methylnaphthalene	20	112–115[k] (2)	72
2-Acetyl-6-methoxynaphthalene	2-Bromoacetyl-6-methoxynaphthalene	3	110–110.5[l]	70	2-Acetyl-5-bromo-6-methoxynaphthalene	10	126–127[m]	50
Cyclohexene	1,2-Dibromocyclohexane[n]		134–136[o] (40)	86	1,2-Dibromocyclohexane[n]	10	134–136[o] (40)	78

[a] This reaction is described separately in the Experimental section. [b] Lit.[15] b.p. 198°. [c] When the reaction was performed as described in method B in the presence of catalytic amounts of ferric chloride, benzyl bromide was obtained in 50% yield. [d] Lit.[16] b.p. 184°. [e] Lit. m.p. 104° [Elsevier's "Encyclopaedia of Organic Chemistry," Vol. 13, Elsevier Publishing Co., Inc., New York, 1948, p 41]. [f] Lit. m.p. 113° [*ibid.*, p. 92]. [g] The orange tribromide did not disappear completely. [h] Lit. m.p. 56° [ref. 15, p. 343]. [i] Lit.[9] m.p. 35°; picrate m.p. 104–106°, lit.[9] m.p. 105–106°. [j] Lit. m.p. 56°. Hexamine complex m.p. 159°, lit. m.p. 160° [F. Mayer and A. Sieglitz, *Ber.*, **55**, 1835 (1922)]. [k] $n^{20}D$ 1.6493, picrate m.p. 113–114°. Lit. b.p. 117–118° (2 mm.), $n^{20}D$ 1.6484, picrate m.p. 114.7–115.1° [M. S. Newman and A. I. Kosak, *J. Org. Chem.*, **14**, 375 (1949)]. [l] Lit. m.p. 110–111°, pyridinium salt m.p. 240–241°, lit. m.p. 241° [A. Marquet and J. Jacques, *Tetrahedron Letters*, **9**, 24 (1959)]. [m] Lit. m.p. 126–127° [H. A. Weidlich and M. Meyer-Delius, *Ber.*, **72**, 1941 (1939)]. [n] The reaction was started by adding slowly a solution of cyclohexene in the corresponding solvent to the solution or the suspension of the tribromide and was performed at room temperature. [o] Lit. b.p. 145–146° (100 mm.) [ref. 15, Vol. II, p. 79]; $n^{20}D$ 1.5507, lit.[11] $n^{20}D$ 1.5516.

minate, in the presence of equimolar amounts of certain metal chlorides, the nucleus of benzene and of toluene.[5]

Previous to the work of Marquet, one of the present authors suggested that a mixture of tetramethylammonium perbromides (Me_4NBr_x; x = 5.1–6.2) could be used for the convenient preparation of dibromopropanol from allyl alcohol.[6] In the present investigation we have studied the brominating properties of tetramethylammonium tribromide[7] (TMAT, Me_4NBr_3), preferring this solid compound to the previously mentioned liquid mixture of the polybromides. The stable and easily prepared tribromide is an orange solid, melting at 118–118.5°, containing 50.9% of active bromine and like phenyltrimethylammonium perbromide (PTAP), is also a mild brominating agent. While each of these tribromides gives only 2-bromoacetyl-6-methoxynaphthalene, when used in nonpolar solvents, only TMAT gives the nuclear brominated derivative (2-acetyl-5-bromo-6-methoxynaphthalene) as the sole product in acetic acid.

Subsequently we investigated the effect of this reagent on several aromatic hydrocarbons which could undergo either nuclear or benzylic bromination. The direction of the substitution could be controlled by varying the nature of the reaction medium. These results are summarized in Table I. In benzene solution containing benzoyl peroxide, toluene, fluorene, and 1- and 2-methylnaphthalenes undergo benzylic bromination. In acetic acid solution, even in the absence of a catalyst, regular aromatic substitution takes place. It is interesting to note the unusual orientation of the bromine in the product obtained from the reaction of this reagent with 1-methylnaphthalene in acetic acid. In contrast with bromine, which gives 1-methyl-4-bromonaphthalene,[8] we obtained the 2-bromo derivative.[9] The bromination of toluene with this reagent in acetic acid is anomalous; in the absence of a catalyst, benzyl bromide is formed, while in the presence of an equimolar amount of ferric chloride *p*-bromotoluene is obtained. Cyclohexene was used as a model compound for comparing the brominating properties of TMAT with those of NBS. The latter affords 3-bromocyclohexene in 80–90% yield[10]; in the presence of alkylammonium halides the yield of this product is markedly reduced and an appreciable amount of the addition product, 1,2-dibromocyclohexane, is isolated.[11] In contrast TMAT, in benzene in the absence of a catalyst, afforded only the addition product in 80% yield. Varying the solvent did not affect the nature of the product, even in the presence of benzoyl peroxide.

The results of this investigation would indicate that this brominating agent is highly dissociated in polar solvents like acetic acid.[12] The liberated bromine molecule undergoes the usual heterolytic fission in ionic reactions, like the aromatic substitution observed in this investigation. In nonpolar solvents (for example, benzene) and in the presence of free-radical initiators, the complex presumably undergoes homolytic fission to perform free-radical reactions, like benzylic substitution. This convenient, versatile reagent resembles bromine in its ability to perform ionic addition and substitution reactions, as well as NBS in performing free-radical substitution under mild conditions.

Experimental[13]

The starting materials were obtained from regular commercial sources and were purified by recrystallization or distillation when necessary. TMAT was prepared from tetramethylammonium bromide and bromine in acetic acid in an 87% yield, as described by Chattaway and Hoyle.[7] 2-Acetyl-6-methoxynaphthalene was prepared by acetylation of 2-methoxynaphthal-

(5) H. Schmid, *Helv. Chim. Acta*, **29**, 1144 (1946).

(6) L. Farkas and O. Schächter, *J. Am. Chem. Soc.*, **71**, 2252 (1949).

(7) F. D. Chattaway and G. Hoyle, *J. Chem. Soc.*, **123**, 654 (1923).

(8) F. Mayer and A. Sieglitz, *Ber.*, **55**, 1835 (1922).

(9) This compound is usually prepared from the diazotized 2-amino-1-methylnaphthalene [V. Veselý, F. Šturša, H. Olejniček, and E. Rein, *Chem. Abstr.*, **24**, 3008 (1930)].

(10) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 80 (1942).

(11) E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952).

(12) The brown color of the solution of TMAT in acetic acid is reminiscent of that of a solution of bromine in acetic acid. To repress this dissociation, the presence of an excess of bromine is required when the reagent is prepared in acetic acid.

(13) The boiling and melting points are uncorrected.

ene according to the procedure described by Robinson and Ryldon.[14]

The identities of the reaction products were confirmed by their inability to depress the melting points of authentic samples. The yields in Table I refer to compounds whose boiling points or melting points are given in the same table.

Method A.—To a solution of 0.01 mole of starting material in 20 ml. of benzene containing a catalytic amount of benzoyl peroxide, was added 0.01 mole of TMAT. The mixture was stirred at room temperature for the specified reaction period, which was determined by the disappearance of the tribromide and the cessation of hydrogen bromide evolution. The colorless tetramethylammonium bromide was dissolved by adding water. The organic layer was separated, washed with water and aqueous sodium carbonate in succession, dried over sodium sulfate, and the solvent removed. The reaction product was isolated by recrystallization, distillation, or by both procedures.

Method B.—A solution of 0.01 mole of the starting material and 0.01 mole of TMAT in 30 ml. of acetic acid was refluxed for the specified reaction time until the bromide color disappeared and no more hydrogen bromide was evolved. The cold reaction mixture was poured into water to dissolve the precipitated tetramethylammonium bromide, and the aqueous solution was then extracted with ether. The organic layer was treated, and the product isolated, as described in method A.

Benzyl Bromide.—A mixture of 0.921 g. (0.01 mole) of toluene, 6.27 g. (0.02 mole) of TMAT, and a trace of benzoyl peroxide was heated under reflux for 15 min. The cold reaction mixture was treated as described in method B to yield 1.00 g. (59%), b.p. 194–198° (lit.[15] b.p. 198°).

Benzoic acid was obtained on oxidation of the reaction product with potassium permanganate in aqueous sodium carbonate solution at reflux temperature.

***p*-Bromotoluene.**—A mixture of toluene (35 ml.), anhydrous ferric chloride (13.85 g.), and TMAT (21.55 g.) was stirred at 60° for 6 hr. The mixture was poured into water and extracted with ether. The organic layer was washed with dilute hydrochloric acid, followed by sodium carbonate solution. After removing the solvent, the residue was fractionated to afford 7.12 g. (72% yield), b.p. 184–186° (lit.[16] b.p 184°).

Oxidation of the reaction product with dilute nitric acid gave *p*-bromobenzoic acid.

Acknowledgment.—The authors are indebted to Prof. I. A. Kaye from Brooklyn College, Brooklyn, New York, for helpful discussions in the preparation of the manuscript.

(14) R. Robinson and H. N. Ryldon, *J. Chem. Soc.*, 1394 (1939).

(15) I. Heilbron, "Dictionary of Organic Compounds," Vol. I, Eyre and Spottiswoode, London, 1953, p. 271.

(16) Ref. 15, p. 374.

The Reaction of Secondary Amines with Formaldehyde

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Received May 23, 1963

The reaction of secondary amines with formaldehyde can lead to two products: aminomethylols (I) and methylenebisamines (II).[1] Although many examples of II

$$R_2NH + HCHO \longrightarrow \underset{\text{I}}{R_2NCH_2OH} \xrightarrow{R_2NH} \underset{\text{II}}{R_2NCH_2NR_2} + H_2O$$

have been reported, only a few examples of I have been isolated. Usually the methylols are unstable and form none of the derivatives of alcohols or amines.[2]

(1) E. C. Wagner, *J. Org. Chem.*, **19**, 1862 (1954).

Since aminomethylols have never been isolated in these reactions, and only weak evidence has been presented for their existence,[3] we wished to learn if they indeed exist in any significant amount in this reaction. Our evidence suggests that in the cases studied the methylenebisamine is the predominant product.

We used the following approach. One mole of formaldehyde was added to two moles of amine and the temperature rise ΔT_1 measured in a simple Nernst type calorimeter.[4] A second mole of formaldehyde was then added to this mixture and ΔT_2 measured. The data presented in Table I are corrected for heats of dilution of amine in water. Since alleged preparations of aminomethylols were reported at 0–5°,[2,3,5,6] we made determinations at that temperature and at room temperature. The ΔT_1 and ΔT_2 values are readily explained by considering the equilibria involved.

$$R_2NH + HCHO \rightleftharpoons R_2NCH_2OH \xrightleftharpoons{R_2NH} R_2NCH_2NR_2 + H_2O$$

On addition of the first equivalent of formaldehyde, equilibrium is established. If the equilibrium greatly favors the aminomethylol, then there is still one equivalent of amine left to react with the second equivalent of formaldehyde. The addition of this second portion of formaldehyde, then, results in a ΔT_2 which is nearly equal to ΔT_1. If, however, the equilibrium greatly favors the methylenebisamine, then there is no unchanged amine left to react with the second portion of formaldehyde and $\Delta T_1 > \Delta T_2$. If there is no aminomethylol at equilibrium after addition of the first portion of formaldehyde, ΔT_2 is zero except for heat of dilution of formaldehyde, which in these experiments can only account for temperature rises of less than 0.05.[7]

The data of Table I indicate that in most cases equilibrium favors the methylenebisamine at both temperatures. Moreover, in nearly all the cases studied the ratio $\Delta T_1/\Delta T_2$ (Table I) was greater at 30° than at 5°. This is explained by the greater stability of methylene bisamines over aminomethylols.

Two of the compounds which exhibited low ratios of $\Delta T_1/\Delta T_2$ are N-ethylethanolamine and diethanolamine which form the oxazolidine on reaction with formaldehyde.

$$RNHCH_2CH_2CH + HCHO \longrightarrow RN\begin{array}{l}CH_2\\ \diagup\quad\diagdown\\ O\\ \diagdown\quad\diagup\\ CH_2CH_2\end{array} + H_2O$$

(2) K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

(3) E. R. Alexander and E. J. Underhill *J. Am. Chem. Soc.*, **71**, 4014 (1949). The only evidence heretofore that aminomethylols are present at equilibrium was offered by these authors who stated that the dimethylaminomethylol which they prepared had only a weak infrared band in the OH region. We have examined the infrared spectrum of dimethylaminoethanol which has a strong OH band. This compound, because of a greater possibility of intramolecular hydrogen bonding, should have a weaker absorption in this region. This leads us to believe that the concentration of dimethylaminomethylol was probably small in the reference cited.

(4) J. M. Sturdevant, "Calorimetry, Technique of Organic Chemistry," Vol. I (1), 3rd Ed., A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 572.

(5) M. Zief and J. P. Mason *J. Org. Chem.*, **8**, 1 (1943).

(6) H. G. Johnson, *J. Am. Chem. Soc.*, **68**, 12 (1946).

(7) J. F. Walker, "Formaldehyde," Reinhold Publishing Corp., New York, N. Y., 1953, p. 90.

TABLE I[a]

ΔT[b] FOR THE REACTION OF FORMALDEHYDE WITH R_2NH[c]

Amine	5° ΔT_1	5° ΔT_2	30° ΔT_1	30° ΔT_2	References[d]
Morpholine	2.12	0.50	1.54	−0.02	*e,f*
Dibutylamine	0.93	0.45	0.83	0.26	*g*
N-Ethylethanolamine	0.33	0.17	0.56	0.16	New compound
Piperidine	1.29	0.67	1.06	0.26	*c*
Diallylamine	1.23	0.07	1.28	0.07	*h*
Dibenzylamine	0.28	0.05	0.52	−0.05	*i*
Diethanolamine	0.81	0.31	0.45	0.23	*j*
Diethylamine	1.07	0.10	0.83	0.07	*k*

[a] Due to the high concentrations used and the resulting large errors due to large solute–solute interactions and to differences in the specific heat of the contents of the calorimeter, these data are probably of limited value as true thermochemical quantities. [b] The standard deviation is 0.17°. [c] See ref. 6. [d] References to the reaction with formaldehyde. [e] See ref. 5. [f] U. S. Patent 2,388,058 (October 30, 1945). [g] H. Brintzinger and B. Hesse, *Kolloid-Z.*, **111**, 156 (1948). [h] N. Lewis, Ph.D. thesis, University of Florida, 1951. [i] S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949). [j] See ref. 8. [k] L. Henry, *Bull. acad. roy. med. Belg.*, [3] **26**, 200 (1893); **29**, 355 (1895).

We found that these compounds formed readily under the conditions of our experiments.

Dibenzylamine is the only other amine which does not exhibit a large difference between ΔT_1 and ΔT_2. The low values of ΔT_1 for this compound made it impossible to decide whether this compound forms predominantly the methylenebisamine or the aminomethylol.

Experimental

Materials.—The chemicals used and their sources or methods of purification are stated. All distillations were through a 20-in. column packed with nichrome wire. Temperatures are uncorrected.

Formaldehyde, Merck and Co., C.P. 37% aqueous solution, standardized by the sodium sulfite method[7]; morpholine, b.p. 128.5° (760 mm.); dibutylamine, b.p. 159–160° (760 mm.); N-ethylethanolamine, b.p. 166–166.5° (760 mm.); piperidine, b.p. 106° (760 mm.); diallylamine, b.p. 109° (760 mm.); dibenzylamine, Eastman "White Label," used as received; diethanolamine, b.p. 132–135° (3.0–3.2 mm.); diethylamine, b.p. 55.5° (760 mm.).

Apparatus.—The calorimeter consisted of a 1-l. dewar flask fitted with a Beckmann differential thermometer, mechanical stirrer, and 2.5 × 14 cm. thin-walled copper test tube. The test tube was fitted with a thermometer, and glass loop stirrer through a rubber stopper, and was held in place in the dewar flask by a large rubber stopper. Water, 750 ml., was used as the calorimeter fluid. The pure amine was added to the copper tube through a funnel which was replaced with a long stem buret for slow addition of the aqueous 37% formaldehyde. The latter was added at such a rate that the temperature of the reaction mixture remained always near the bath temperature. In the low temperature runs the entire calorimeter was immersed in an ice–water bath to minimize heat loss. The temperature changes, ΔT_1, were corrected for external heat gain by preparing plots of time *vs.* temperature for the low temperature runs. To correct for heat of dilution, runs were made in which the formaldehyde was replaced by equivalent amounts of water.

3-(β-Hydroxyethyl)oxazolidine[8] was distilled from the benzene extract of an equimolar mixture of diethanolamine and formalin after it had stood for several hours, b.p. 93°(4.7 mm.), $n^{30}D$ 1.4753; lit.[8] b.p. 68°(0.5 mm.), $n^{25}D$ 1.4775.

3-Ethyloxazolidine was prepared by the same procedure as for 3-(β-hydroxyethyl)oxazolidine, b.p. 122°, $n^{22}D$ 1.4322.

Anal. Calcd. for $C_5H_{11}NO$: C, 59.4; H, 11.0; N, 13.9. Found: C, 59.0; H, 11.9; N, 13.2.

(8) Miles Laboratories, Inc., British Patent 839,289 (June 30, 1960).

The Synthesis of Secondary and Tertiary Amines by Borohydride Reduction[1]

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RECEIVED JUNE 7, 1963

The preparation of secondary amines by the reduction of Schiff bases with lithium aluminum hydride or with borohydrides has been well established in earlier literature.[3] This note concerns the generality of the synthesis of secondary and tertiary amines by the action of sodium borohydride at 0° on the neutral aqueous solutions of amine salts and carbonyl compounds; reactions of this type were first reported for a special case (the preparation of dimethylamino acids) by Biemann and co-workers.[4] The process is advantageous, since it occurs rapidly without prior isolation of the Schiff bases, and even occurs in some instances where the equilibrium for the formation of the Schiff base is too unfavorable to permit its ready isolation. This synthesis, unlike previous catalytic reductions of Schiff bases formed *in situ*, may be used in the preparation of amines containing nitro or other groups sensitive to catalytic hydrogenation.

The formation of N^6-isopropyllysine[5] from lysine and acetone under various experimental conditions is reported in Table I. The primary α-amino acids could be easily identified with ninhydrin after paper chromatography. The reaction also gave N^2,N^6-diisopropyl-

(1) Supported by National Institutes of Health Research Grant GM-04712 to Professor F. H. Westheimer, whose help is gratefully acknowledged.

(2) National Institutes of Health Postdoctoral Fellow, 1960–1963; Department of Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Md.

(3) J. H. Billman and J. W. McDowell, *J. Org. Chem.*, **27**, 2640 (1962), and earlier papers of this series.

(4) K. Biemann, "Mass Spectrometry Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 358.

(5) The separation of "modified" lysine (probably N^6-isopropyllysine) has been reported by H. Fasold, G. Gundlach, and F. Turba, *Biochem. Z.*, **334**, 255 (1961), from the hydrolyzate of borohydride reduced chymotrypsin to which acetone had been added to destroy excess borohydride. The isolation of N^6-isopropyllysine from a reduction with very low concentrations of acetone and borohydride has been achieved in these laboratories by Dr. B. Zerner and Dr. F. H. Westheimer with acetoacetate decarboxylase; the compound was identified by an independent synthesis.[10]

TABLE I

Acetone,[a] *M*	$NaBH_4$, *M* total	pH	Yield[b] of N^6-isopropyllysine, %
2.4[c]	0.4[d]	4.1–4.7	4
2.4[c]	0.9[d]	4.1–4.7	15
2.4[c]	1.8[d]	4.1–4.7	34
2.4[c]	3.6[d]	4.1–4.7	46
2.4[c]	7.2[d]	4.1–4.7	50
0.6[c]	2.1[d]	4.1–4.7	8
1.1[c]	2.0[d]	4.1–4.7	26
4.1[c]	1.5[d]	4.1–4.7	53
2.4[e]	1.8[d]	6.1 (initial)	6
2.4[f]	1.8[f]	6.3–6.7	55
2.4[g]	1.8[g]	11	20

[a] Lysine 0.4 *M*, 0°. [b] Yield estimated from ninhydrin colors; see Experimental. [c] Sodium acetate buffer 4.2 *M*. [d] Solid added in small amounts over 10 min. [e] Sodium phosphate buffer 4.2 *M*. [f] Imidazolium chloride buffer 4.2 *M*. Boron hydride added in 10 min., allowed to react 10 min. more. [g] In water, pH 11 established by borohydride and sodium borate. Borohydride added at once, and allowed to react for 30 min.

lysine which was isolated in very low yield as the methyl ester dihydrobromide. As indicated in Table I, the yield of N^6-isopropyllysine is relatively insensitive to pH, but increases with increasing concentrations of borohydride and of the carbonyl compound.

Probably the Schiff base salt or tertiary iminium salt, formed from the reactants,[6] is actually reduced by BH_4^-; this hypothesis[7] may account for the rapid reduction under relatively acidic conditions, as compared to the relatively slow reduction of isolated Schiff bases.[3] Simple calculations reveal that the reduction of Schiff base salts must be several orders of magnitude faster than the reduction of acetone, which is pH independent.[8] And of course, acid-catalyzed decomposition of the borohydride[9] competes with the reduction.

The following additional amines were prepared: N-isopropylalanine methyl ester, N-benzylaniline, N-isopropylaniline, N-isopropylbutylamine, and N-ethylpiperidine. Paper chromatographic evidence was obtained for the reductive coupling of the N^6-amino group of lysine with acetaldehyde, benzaldehyde, and cyclohexanone to form the ethyl, diethyl, benzyl, and cyclohexyl derivatives. The reaction is most successful with reactive carbonyls and primary amines, since acetophenone and benzophenone apparently failed to form lysine derivatives, and piperidine failed to react with cyclohexanone or acetone, although it did form N-ethylpiperidine in the reaction with acetaldehyde.

Experimental

All melting points unless otherwise noted were taken with the Fisher-Johns apparatus and are corrected. Confirmatory evidence for the structures of the products was obtained from infrared spectra.

N^6-Isopropyllysine Methyl Ester Dihydrobromide.—N^2-Carbobenzyloxy-L-lysine (Cyclo Chemical Co., 1.72 g., 6.14 mmoles), 5 ml. of glacial acetic acid, 2.5 g., of sodium acetate trihydrate, 10 ml. of water, and 5 ml. of acetone were placed in a stirred vessel at 0°. Sodium borohydride (4 g.) was added in 30-mg. lots over a 30-min. period, interrupted by the addition of 5 ml. more of acetone after the first 15 min. The final pH was 7. The mixture was evaporated to dryness *in vacuo* at 100°, taken up in methanol (100 ml.), saturated with dry hydrogen bromide, and allowed to stand 12 hr. at room temperature. The hydrogen bromide and methanol simultaneously esterified the amino acid and removed the carbobenzyloxy group. The mixture was made alkaline, and the amine extracted with ether and washed. The dihydrobromide was obtained by adding methanol and hydrogen bromide to the ether solution and evaporating to dryness. The product was recrystallized from methanol–ether; yield, 1.22 g. (55%); m.p. 156.5–157.5°.

Anal. Calcd. for $C_{10}H_{24}O_2N_2Br_2$: Br, 43.89. Found: Br, 43.11.

N^6-Isopropyllysine methyl ester dihydrobromide had been synthesized previously by Dr. Burt Zerner.[10] The melting point, mixture melting point, and infrared spectrum of the compound prepared by the two methods are identical. Acid hydrolysis of the ester gave N^6-isopropyllysine, which, on ascending paper chromatography with Whatman No. 1 paper and the system 1-propanol 550, water 300, and ammonium hydroxide 100, gave a single spot after treatment with ninhydrin[11] with an R_f of 0.63. Similar reactions with lysine were analyzed by paper chromatography (Table I): the only ninhydrin positive spots found corresponded to lysine (R_f 0.46) and N^6-isopropyllysine. The yield of product reported in Table I was determined as follows: the two ninhydrin positive spots were cut out and eluted with 5:1 acetone–ammonia. The absorbance at 575 mμ of the eluates was determined, and the per cent yield was taken as the absorbance of the product eluate divided by that of the total eluates. Comparison of the total absorbance of aliquots before and after the reaction indicated that most of the starting lysine was accounted for as lysine and N^6-isopropyllysine.

In similar experiments acetaldehyde gave two ninhydrin positive derivatives of lysine, a major product with R_f 0.63, and a minor one of R_f 0.69. These are presumably the N^6-ethyl and N^6,N^6-diethyllysine. (N^2-alkyllysines do not give the purple ninhydrin color.) Cyclohexanone and benzaldehyde each gave only a single derivative with R_f 0.79 and 0.75, respectively. Acetophenone and benzophenone gave only the spot corresponding to lysine.

N^2,N^6-Diisopropyllysine Methyl Ester Dihydrobromide.—This preparation was similar to but on a larger initial scale than that of the N^6-derivative described previously, with L-lysine hydrochloride, 3.65 g. (20 mmoles), in place of N^2-carbobenzyloxylysine, and the other reagents in proportion. The product was crystallized from ether–methanol–hydrogen bromide, yield 0.32 g. (4%), m.p. 186.5–188.5°. Proton n.m.r. at 60 Mc. of the salt (previously exchanged with deuterioxide) in deuterioxide revealed the methyls of the two isopropyls (split with J = 6 c.p.s.) nearly coincident at $-\delta$ = 1.40 p.p.m. (tetramethylsilane external standard) and the ester methyl at $-\delta$ = 3.95 p.p.m., with proper ratios of the peak areas of all the protons.

Anal. Calcd. for $C_{13}H_{30}O_2N_2Br_2$: Br, 39.35. Found: Br, 39.37.

N-Isopropylalanine Methyl Ester Hydrobromide.—Identical to the synthesis of N^6-isopropyllysine methyl ester, with DL-alanine 0.9 g. (10 mmoles) as the amine. The product, 0.52 g. (23%) had m.p. 150–151.7°.

Anal. Calcd. for $C_7H_{16}NO_2Br$: Br, 35.34. Found: Br, 35.38.

N-Isopropylbutylamine.—Sodium borohydride (2 g.) was added in 30-mg. portions over a 10-min. period to a stirred solution of *n*-butylamine (1 ml., 10.1 mmoles), sodium acetate trihydrate (2.7 g.), acetic acid (8.4 ml.), acetone (5 ml.), and water (25 ml.), at 0°. The mixture was made alkaline and the product was extracted with ether, washed, and crystallized as the hydrochloride. The yield was 0.96 g. (63%), m.p. 197–197.8°, lit.[12] 195–196°.

N-Isopropylaniline.—The procedure was similar to the preparation of N-isopropylbutylamine, with aniline as amine, and eth-

(6) This is analogous to other carbonyl amine condensation: J. B. Conant and P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932); E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962).

(7) This mechanism was suggested by Professor F. H. Westheimer. An example of the reduction of a Schiff base salt by borohydride in a complex molecule is given in the synthesis of reserpine by R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstad, *Tetrahedron*, **2**, 1 (1958).

(8) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).

(9) R. E. Davis and C. G. Swain, *ibid.*, **82**, 5949 (1960).

(10) This synthesis was achieved by alkylation of N^2-carbobenzyloxylysine with isopropyl bromide, esterification, and removal of the carbobenzyloxy group with methanol and hydrogen bromide, and crystallization of N^6-isopropyllysine methyl ester dihydrobromide from chloroform. N^6-Isopropyllysine was obtained from the ester by acid hydrolysis.

(11) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., Revised, D. C. Heath and Co., Boston, Mass., 1957, p. 136.

(12) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).

anol (6 ml.) added to dissolve the aniline. The yield of amine was 1.35 g. (91%). Benzamide had m.p. 62–65°, lit.[13] 63–65°.

N-Benzylaniline.—The method was similar to the previous with aniline and benzaldehyde (5 ml.), and ethanol (20 ml.). The yield was 1.67 g., (83%), m.p. 36–37.2°, lit.[14] 37–38°.

N-Ethylpiperidine.—The method was similar to the previous with piperidine, 1.0 ml. (10.1 mmoles), and acetaldehyde (10 ml.). The borohydride was added over 30 min.; half of the acetaldehyde was added at the beginning, and the remainder after 15 min. The product was crystallized as the hydrochloride. The yield was 0.81 g. (53%) m.p. (evacuated capillary, uncor.) 225–227°, lit.[15] 225°. The picrate was also prepared, m.p. 165–167.5°, lit.[16] 167–168°. Corresponding synthetic attempts with acetone and cyclohexanone in place of acetaldehyde gave no detectable tertiary amine.

(13) W. S. Emerson and C. A. Uraneck, *J. Am. Chem. Soc.*, **63**, 749 (1941).
(14) K. Brand, *Ber.*, **42**, 3460 (1909).
(15) R. Lukes and J. Pliml, *Chem. Listy*, **50**, 557 (1956).
(16) R. Dulou, E. Elkik, and A. Veillard, *Bull. soc. chim. France*, 967 (1960).

The Reduction of Esters with Sodium Borohydride[1]

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Received July 17, 1963

It is generally accepted that sodium borohydride, a powerful reducing agent for aldehydes and ketones, will not reduce carboxylic esters. However, cases are reported in the literature in which reduction of esters to primary alcohols has been observed, and Schenker[3] has included many of these in his excellent review on the uses of complex borohydrides in organic chemistry. Also, instances of reduction of lactones and carbon–carbon double bonds, generally resistant to sodium borohydride, are given. Many of the compounds which undergo such "abnormal" reduction contain neighboring functional groups,[4] and Schenker implies that these groups may, in some way, take part in the reductions, although no suggestion is made as to the mechanism of this effect. We have now found that esters of simple heterocyclic, aromatic, and aliphatic acids are reduced to varying degrees by a large excess of sodium borohydride in methanol. Thus, it is evident that esters are not resistant to reduction by sodium borohydride, although the rate of reduction is much slower than for aldehydes and ketones.

For synthetic purposes, we were interested in preparing 3-(4′-pyrimidyl)-1-propanol.[5] Lithium aluminum hydride reduction of methyl 3-(4′-pyrimidyl)-propenoate or the corresponding saturated ester was complicated by simultaneous reduction of the pyrimidine ring. Therefore, in view of the suggestive reports cited, reduction of the unsaturated ester by sodium borohydride was attempted. A 77% yield of the desired propanol was obtained from the reduction carried out in methanol with a tenfold excess of sodium borohydride.

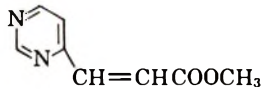
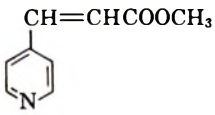
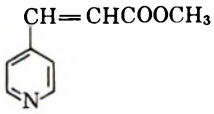
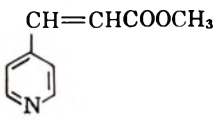
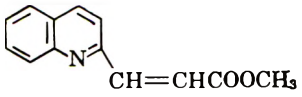
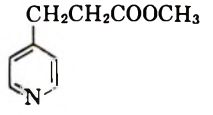
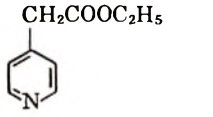
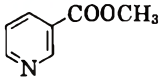
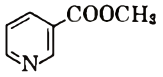
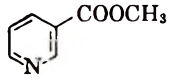
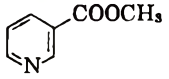
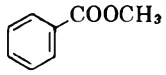
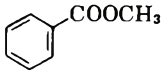
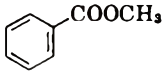
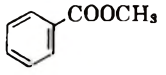
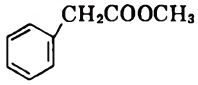
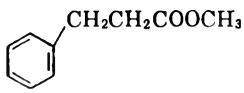
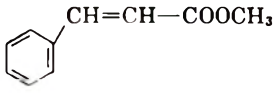
The reductions of several other unsaturated esters were then investigated, and the results are presented in Table I. The 3-(4′-pyridyl)propenoate, reduced with a tenfold excess of borohydride, behaved similarly to the pyrimidyl compound, giving mostly the saturated alcohol along with small amounts of the saturated ester and the unsaturated alcohol. With lesser amounts of reducing agent, larger amounts of saturated ester, unsaturated alcohol, and recovered starting material were obtained. The 3-(2′-quinolyl)propenoate, with a 16-fold excess of borohydride, surprisingly gave a mixture of products, although it might have been expected to be analogous to the pyridyl and pyrimidyl compounds. Methyl cinnamate and methyl 2-nonenoate also gave mixtures of reduction products and unaffected ester on treatment with a tenfold excess of reducing agent.

The reduction of several other esters with excess borohydride then was investigated, giving the results shown in Table I. The pyridine esters, methyl 4-pyridinepropanoate, ethyl 4-pyridineacetate, and methyl nicotinate, were reduced in high yields to the corresponding alcohols by a 20-fold excess of sodium borohydride in methanol. When less borohydride was used for the reduction of methyl nicotinate, some ester was recovered. Analogous phenyl esters, methyl hydrocinnamate, methyl phenylacetate, and methyl benzoate, also were substantially reduced by a 20-fold excess of borohydride, but not as cleanly as the pyridine esters, 10 to 15% of the ester being recovered. With lesser amounts of borohydride, methyl benzoate followed the same trend as methyl nicotinate, but in each corresponding case, less reduction was observed with the benzoate. One aliphatic ester, methyl nonanoate, was examined, and it was reduced to a lesser extent than the pyridine or phenyl esters, 57% of the ester being recovered.

From these results, it is obvious that no special structural features are necessary for reduction of esters by sodium borohydride to occur at least to some extent. However, such features may, indeed, enhance the reactivity in some manner, as is evident in going from aliphatic to phenyl to pyridine esters, and by the fact that many of the esters previously reported as being reduced contain proximate keto and hydroxyl groups.[3,4] Clearly, the solvent has an influence on the rate of reduction, as Chaikin and Brown[6] found that ethyl butyrate or ethyl phenylacetate, when heated with a suspension of sodium borohydride in dioxane or diethyl carbitol for one hour, showed no evidence of reduction. It was observed[7] that a mixture of ethyl benzoate and sodium borohydride in isopropyl alcohol lost but 12% of the available active hydrogen in six hours at 75°, and a similar mixture in diglyme lost less than 10% of the available hydrogen in twenty-four hours at 75°. In agreement with this behavior of esters is the fact that aldehydes and ketones are also reduced more slowly in these solvents than in

(1) Supported in part by the U. S. Army Research Office, Durham, N. C.
(2) Miller Research Fellow.
(3) E. Schenker, *Angew. Chem.*, **73**, 81 (1961).
(4) *E.g.*, V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.*, **81**, 1456 (1959), and J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963), for the borohydride reduction of some keto and hydroxy esters to diols.
(5) This has been successfully converted to 6-azapyrrocoline [$\lambda_{max}^{CH_2OH}$ 229 mμ (ε 30,100), 272 (7000), 283 (7800), 345 (900)]. Details will be reported in a forthcoming publication.
(6) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).
(7) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *ibid.*, **75**, 6209 (1955).

TABLE I PRODUCTS FROM THE REDUCTION OF ESTERS WITH SODIUM BOROHYDRIDE

Ester	Moles $NaBH_4$ / Mole ester	Product composition, % Satd. ester	Unsatd. ester	Satd. alcohol	Unsatd. alcohol	Satd. alcohol, yield, %
	10			100		77
	10	1		91	8	74
	5	10		54	36	
	2	34	36	8	22	
	16	22	7	34	37	
	10			100		90
	10			100		93
	10	2		98		81
	5	19		81		
	2.5	52		48		
	1	85		15		
	10	15		85		75
	5	68		32		
	2.5	87		13		
	1	97		3		
	10	15		85		73
	10	10		90		72
	10	13	55	15	17	
$CH_3(CH_2)_5CH{=}CH{-}COOCH_3$	10	35	30	15	20	
$CH_3(CH_2)_7COOCH_3$	10	57		43		

water, methanol, or ethanol.[7] Reduction of the double bond in the unsaturated esters is also noteworthy.

Thus, in some cases where it is desirable not to use a stronger reducing agent, a large excess of sodium borohydride in methanol may serve quite effectively to reduce saturated or unsaturated esters to saturated alcohols. When a ketone or an aldehyde is to be reduced in the presence of an ester function, care should be taken to avoid a large excess of borohydride and elevated temperatures if partial reduction of the ester is to be avoided.

Experimental

Sodium Borohydride.—The sodium borohydride used was obtained from Metal Hydrides, Inc., Beverly, Mass., Lot. No. 191-1, rated purity, 98 plus %. Spectrographic analysis indicated the following: Li, not detectable; K, 0.01%; Ca and Si, traces.

Esters.—The heterocyclic unsaturated esters were prepared by esterification of the appropriate acids with methanol and hydrochloric acid, the acids having been prepared[8] by condensation of the appropriate methyl heterocycle with chloral and hydrolysis of the product with alkali. Methyl 3-(4′-pyridyl)propanoate was prepared from the saturated acid obtained by hydrogenation of the unsaturated acid. The other esters were obtained from stock or prepared by esterification of the appropriate acid. All the esters [except methyl 3-(4′-pyrimidyl)propenoate, which see] are known compounds, and structures and purity were confirmed by n.m.r. spectroscopy.

Reductions.—All the reductions were done in a similar manner. A weighed amount of the ester was dissolved in methanol and added to a weighed amount of sodium borohydride. When the initial vigorous reaction had subsided, the mixture was heated under reflux for 1–2 hr. The solution was cooled, an equal volume of water was added, and some of the methanol was removed on a rotary evaporator. The aqueous solution was extracted with five 50-ml. portions of chloroform, the combined extracts were dried over sodium sulfate, and the chloroform was removed on the rotary evaporator at 30 to 40°. A portion of the product was dissolved in carbon tetrachloride or deuteriochloroform, and its n.m.r. spectrum was determined with a Varian A-60 spectrometer. Peak assignments were made by comparison with the spectra of the expected products where available or by analogy with similar compounds. The per cent of each product in the mixture was calculated from the integral of the spectrum. The reduction products from methyl cinnamate and methyl 2-nonenoate gave n.m.r. spectra which were too complex to allow calculation of the composition, but vapor phase chromatography (carried out on a 0.25-in. Ucon polar column at 210° for the methyl cinnamate reduction product and at 185° for the methyl 2-nonenoate reduction product), in conjunction with the n.m.r. data, allowed calculation of the per cents. The values given in Table I are probably accurate to within a few per cent.

3-(4′-Pyrimidyl)-1-propanol.—3-(4′-Pyrimidyl)propenoic acid[8] was esterified by treatment at room temperature with methanolic hydrochloric acid for 3 days. Concentration of the reaction mixture, addition of aqueous sodium bicarbonate, extraction into chloroform, evaporation of the chloroform, and crystallization of the residue from cyclohexane gave **methyl 3-(4′-pyrimidyl)-propenoate** in 71% yield, m.p. 86–88°.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.8; H, 5.1; N, 16.8.

The ester was reduced and the product was isolated by the standard procedure as described. Short-path distillation at 90° (50 μ) gave **3-(4′-pyrimidyl)-1-propanol** as a clear, slightly viscous oil; ultraviolet absorption, $\lambda_{max}^{CH_3OH}$ 245 mμ (ϵ 2950), 270 (330); n.m.r. absorption (in deuteriochloroform), C-2′ H, δ 9.50 (s); C-6′ H, 9.00 (d); C-5′ H, 7.67 (d); C-3 H_2, 4.05 (t); C-1 H_2, 3.28 (t); C-2 H_2, 2.42 (m).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 60.8; H, 7.3; N, 20.3. Found: C, 60.6; H, 7.1; N, 20.1.

(8) R. G. Jones, E. C. Kornfield, and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950).

Optically Active Benzylamine-α-d[1]

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Received January 30, 1963

As part of a study of optically active benzyl-α-d compounds,[3-5] we prepared the corresponding amine. Since we contemplate no further work with this material in the near future, we report herein the preparation and properties of optically active benzylamine-α-d. The preparation followed our previous stereospecific preparations of 2-octylamine and 1-aminobutane-1-d[6]; namely, conversion of the alcohol to an arenesulfonate, displacement by sodium azide, and reduction of the product azide with lithium aluminum hydride. By this procedure, alcohol having $[\alpha]D$ −0.215° gave a 54% over-all yield of crude amine which, on purification, had $[\alpha]D$ +0.24°. The reactions involve a single inversion of configuration; hence, amine and alcohol of the same sign of rotation have the same configuration.

The degree of optical purity of the amine relative to the alcohol was checked by the method of Snyder and Brewster.[7] The benzylamine-α-d was converted to the N,N-dimethylamine with formic acid and formaldehyde and thence to the trimethylammonium acetate by treatment successively with methyl iodide, silver oxide, and acetic acid. Pyrolysis of the quaternary acetate gave benzyl-α-d acetate which was reduced with lithium aluminum hydride to benzyl-α-d alcohol having $[\alpha]D$ −0.180°. Snyder and Brewster used a similar sequence to convert α-phenethylamine to α-phenethyl acetate with essentially complete inversion of configuration. In our over-all conversion of benzyl-α-d alcohol to amine and back to alcohol, there occurred 18% racemization.

We suspect that most, if not all, of this racemization occurred in the first step, the preparation of benzyl-α-d tosylate. During the Schotten–Bauman procedure used, any reaction of the aqueous sodium hydroxide with the benzyl-α-d tosylate formed would generate alcohol of inverted configuration and would result in tosylate having lower optical purity than the starting alcohol; hence, this method is not recommended for stereochemical studies. The benzyl-α-d tosylates used in our other studies were prepared in dry pyridine in which this problem does not occur.[4,5]

Experimental

(+)-Benzylamine-α-d.—A solution of 50 ml. of 25% sodium hydroxide was added over a period of 1.5 hr. to a stirred mixture of 21 g. of benzyl-α-d alcohol,[3] $\alpha^{25}D$ −0.860 ± 0.004°, α^{25}_{5463} −1.044 ± 0.007° (l 4), and 29 g. of *p*-toluene sulfonyl chloride,

(1) Stereochemistry of the Primary Carbon. XII. This research was supported in part by a grant from the Petroleum Research Fund.

(2) Monsanto Chemical Company Fellow, 1956–1957.

(3) A. Streitwieser, Jr., and J. R. Wolfe, Jr., *J. Am. Chem. Soc.*, **79**, 903 (1957).

(4) A. Streitwieser, Jr., and J. R. Wolfe, Jr., *ibid.*, **81**, 4912 (1959).

(5) A. Streitwieser, Jr., J. R. Wolfe, Jr., and W. D. Schaeffer, *Tetrahedron*, **6**, 338 (1959).

(6) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **78**, 5597 (1956).

(7) H. Snyder and J. Brewster, *ibid.*, **71**, 291 (1949).

maintained at 5°. An additional 29 g. of *p*-toluene sulfonyl chloride and 50 ml. of 25% sodium hydroxide were added during 1.5 hr. After additional stirring for 3 hr. at 5°, the mixture was poured into water and filtered. The solid product was dissolved in ether, dried with potassium carbonate, reprecipitated by cooling with Dry Ice, and centrifuged. Residual solvent was evaporated and the product was crystallized from benzene–hexane at low temperature. Yields by this procedure were about 70%. (Note: During one such run, the product polymerized spontaneously while being stored overnight in the refrigerator during recrystallization.)

The resulting benzyl-α-*d* tosylate was added to a solution of 20 g. of sodium azide in 58 ml. of water and 260 ml. of methanol and maintained at 60° for 1 day. The mixture was diluted with water and extracted with ether. The washed and dried ether solution was treated with 10 g. of lithium aluminum hydride in the usual manner. The reaction mixture was decomposed with water and the washed and dried ether solution was distilled giving 11.7 g. (54%) of amine, b.p. 72–95° (10–11 mm.), contaminated by some benzyl alcohol (infrared).

The combined product from two such runs was dissolved in dilute hydrochloric acid and washed with ether. The aqueous solution was made basic with sodium hydroxide and extracted with ether. The dried extract was distilled and the residue was fractionated giving two fractions: fraction 1, b.p. 79.5–81° (17 mm.), 9.6 g., $\alpha^{25}D$ 0.940 ± 0.006°, α^{25}_{5463} 1.087 ± 0.003° (*l* 4); fraction 2, b.p. 81–83° (18–19 mm.), 9.5 g., $\alpha^{25}D$ 0.941 ± 0.005° α^{25}_{5463} 1.105 ± 0.011° (*l* 4). The combined product had $n^{25}D$ 1.5404; freshly fractionated benzylamine had $n^{25}D$ 1.5410.

(−)-Benzyl-α-*d* Alcohol from (+)-Benzylamine-α-*d*.—A mixture of 9.8 g. of the benzylamine-α-*d*, 26.2 g. of 88% formic acid and 25.7 g. of 37% formalin was heated at 95–100° until a vigorous evolution of gas commenced. The flask was removed from the oil bath and when the reaction subsided, 25.7 g. of the formalin and 26.2 g. of 88% formic acid were added and the mixture was refluxed for 8 hr. After cooling, 75 ml. of 4 *N* hydrochloric acid was added and the mixture was evaporated *in vacuo* to a thick sirup. The mixture was diluted with water, made basic with sodium hydroxide, and extracted with ether. Evaporation of the solvent left a pale yellow liquid which was difficult to distil because of excessive foaming; hence, the crude product was stirred with 30 g. of methyl iodide and 90 ml. of ether for 2 hr. in an ice bath and 14 hr. at room temperature. The trimethylbenzyl-α-*d*-ammonium iodide was filtered, washed with ether, and dried *in vacuo*; yield, 22.7 g. (90% from amine).

A solution of this product in 250 ml. of water was treated with a suspension of silver oxide in 125 ml. of water prepared from 68 g. of silver nitrate.[8] After stirring for 8 hr., the mixture was filtered with Filter-aid and the solid was washed with water. To the combined aqueous solutions was added 69 g. of glacial acetic acid. The mixture was evaporated to a thick sirup which was distilled *in vacuo*. The distillate was dissolved in ether, washed, dried and distilled, yielding 7.5 g. (55% from amine) of benzyl-α-*d* acetate, b.p. 98–99° (10–11 mm.), identified by the infrared spectrum. Reduction in the usual way with lithium aluminum hydride gave benzyl-α-*d* alcohol, $\alpha^{27}D$ −0.355 ± 0.004°, α^{25}_{5463} −0.431 ± 0.004° (*l* 2). The alcohol was converted to the hydrogen phthalate, recrystallized from benzene–cyclohexane and again reduced to alcohol with lithium aluminum hydride giving benzyl-α-*d* alcohol, b.p. 92–94° (7–8 mm.), $\alpha^{25}D$ −0.352 ± 0.005°, α^{25}_{5463} −0.418 ± 0.012° (*l* 2).

(8) H. Rapoport, *J. Org. Chem.*, **13**, 714 (1948).

Organosilicon and Tin Alkylthiols

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Received July 1, 1963

Only a few organometallic alkylthiols have been described previously. Marvel and Cripps[1] prepared bismethylbis(propyl-3-thiol)silane by saponification of the respective thiolacetate. Later[2] several additional silicon-containing thiols were synthesized by this method. Noller and Post[3] prepared methylthioltrimethylsilane by alkaline hydrolysis of its isothiouronium bromide; Cooper[4] and Schmidt and Wieber[5] described the synthesis of methylthiolsiloxanes from chloromethylsiloxanes and potassium hydrosulfide. Only one publication[6] has become known describing the direct addition of hydrogen sulfide to unsaturated organosilanes at high temperatures and under pressure. However, the principal reaction products were organosilicon sulfides. Organosilicon alkylthiols were only identified as by-products in yields below 10%.

No organotin alkylthiols are reported in the literature. Noltes and van der Kerk[7] attempted the synthesis of propyl-3-thioltriphenyltin by the addition of triphenyltin hydride to allyl mercaptan, but obtained propene, H_2S, and bis(triphenyltin)sulfide instead. And Seyferth[8] observed only cleavage of vinyltin compounds by mercaptans as well as other electrophilic reagents.

This note describes the synthesis of the first reported organotin alkylthiols by two different routes and a new method for the preparation of organosilicon alkylthiols. These methods consist of either radiation-induced free-radical ("anti-Markovnikov") addition of hydrogen sulfide to olefinic unsaturated organometallic compounds at Dry Ice bath temperatures, or free-radical addition of thiolacetic acid at or below room temperature, followed by alkaline hydrolysis. The alkylthiols obtained by both methods were identical as demonstrated with tributylallyltin in the following example.

$$(C_4H_9)_3SnCH_2CH{=}CH_2 \xrightarrow[(-70^\circ)]{H_2S} (C_4H_9)_3SnCH_2CH_2CH_2SH \quad \text{VII}$$

$$\xrightarrow{CH_3CO\cdot SH} (C_4H_9)_3SnCH_2CH_2CH_2S\cdot CO\cdot CH_3 \quad \text{IX} \xleftarrow{OH^-}$$

A quartz mercury vapor lamp was the most effective source of radiation, especially if used in connection with the quartz reactor described in the Experimental reaction. Considerably lower yields were obtained in Vycor flasks and also with long wave ultraviolet light.

The primary mercaptan structure was unequivocally confirmed by 60-Mc. n.m.r. spectra.[9]

Main by-product of the hydrogen sulfide addition was sulfide, which—as shown by independent experiments—was formed by the following reaction.

$$(C_4H_9)_3Sn(CH_2)_3SH + CH_2{=}CH\cdot CH_2Sn(C_4H_9)_3 \xrightarrow{h\nu} [(C_4H_9)_3Sn(CH_2)_3]_2S$$

In order to suppress this side reaction a larger excess of hydrogen sulfide was employed. The use of low-boiling aliphatic hydrocarbon diluents influenced favor-

(1) C. S. Marvel and H. N. Cripps, *J. Polymer Sci.*, **9**, 53 (1952).

(2) V. F. Mironov and N. A. Pogonkina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 85 (1959).

(3) D. C. Noller and H. W. Post, *J. Org. Chem.*, **17**, 1393 (1952).

(4) G. D. Cooper, *J. Am. Chem. Soc.*, **76**, 2500 (1954).

(5) M. Schmidt and M. Wieber, *Ber.*, **94**, 1426 (1961).

(6) A. Zappel, German Patent 1,000,817 (1957), to Bayer Leverkusen.

(7) J. G. Noltes and G. J. M. van der Kerk, *Chem. Ind.* (London), 294 (1959).

(8) D. Seyferth, *J. Am. Chem. Soc.*, **79**, 2133 (1957).

(9) Determined by Varian Associates, in deuteriochloroform–tetramethylsilane.

TABLE I
COMPOUNDS PREPARED

	Compound	B.p., °C. (mm.)	$n^{25}D$	Sulfur, % Calcd.	Sulfur, % Found	Metal, % Calcd.	Metal, % Found	Infrared SH frequency
I	$Me_3Si(CH_2)_2SH$[2]	40 (18) 143 (760)	1.4515	23.9	23.75	20.8	19.9	3.94
II	$(Me_3SiCH_2CH_2)_2S$	39 (0.05) 268 (760)	1.4620	13.75	13.70	24.05	23.85	
III	$Me_3Si(CH_2)_3SH$[2]	53 (16) 164 (760)	1.4538	21.65	21.60	18.95	18.64	3.94
IV	$(Me_3SiCH_2CH_2CH_2)_2S$	46 (0.05) 66 (0.5)	1.4621	12.24	12.25	21.41	21.19	
V	$(Me_3SiCH_2CH_2)_2SO_2$	123 (m.p.)		12.02	11.96	21.08	20.95	
VI	$Bu_3Sn(CH_2)_2SH$	70–80 dec. (0.2)	1.5068	9.10	8.73	33.76	33.9	(3.75) 3.80 (3.89)
VII	$Bu_3Sn(CH_2)_3SH$	91 (0.1)	1.5025	8.78	8.72	32.62	33.40	(3.76) 3.80 (3.90)
VIII	$Bu_3Sn(CH_2)_2S{\cdot}CO{\cdot}CH_3$	115 (0.2)	1.5006	8.18	8.14	30.20	30.20	
IX	$Bu_3Sn(CH_2)_3SCO{\cdot}CH_3$	120 (0.3)	1.4982	7.89	7.76	29.12	28.95	

ably the yield of mercaptan. The yields of ethyl-2-thiolsilicon and -tin compounds by hydrogen sulfide addition to the corresponding trialkylvinyl compounds were lower than those of propyl-3-thiol derivatives, although no cleavage of vinyl groups was observed. All compounds described were sufficiently stable to be distilled with the exception of ethyl-2-thioltributyltin, which decomposed at 70° (0.2 mm.).

The addition of thiolacetic acid to allyl- and vinyltributyltin proceeded with remarkable ease. Mixing at 0° in the presence of long wave ultraviolet light resulted in excellent yields of 3-(tributyltin)propyl thiolacetate and 2-(tributyltin)ethyl thiolacetate, respectively, which were both distillable. No cleavage of vinyl groups was observed. Since also the saponification of these thiol esters to the corresponding thiols proceeded easily and in good yields this latter procedure is the method of choice for organotin alkylthiols.

Experimental

General Procedure. Hydrogen Sulfide Addition.—The addition of hydrogen sulfide was studied in two different reactors. Low yields were obtained if a Vycor flask was used rotating in a Dry Ice bath and if the mixture of liquid hydrogen sulfide and vinyl- or allyltrialkylmetal was irradiated by a ultraviolet lamp. Better yields were obtained in a reactor constructed as follows. A double-wall quartz well, open at the top, was inserted into the center-neck of a graduated reaction flask. The reaction flask was equipped with a gas inlet tube leading to the bottom and an outlet at the top leading to a hydrogen sulfide scrubber. This flask—with the inserted quartz well and charged with the olefinic unsaturated compound, catalyst and solvent—was immersed in a Dry Ice bath. Hydrogen sulfide was then distilled into the flask through the gas inlet tube to the desired level. A 100-w. Hanovia (8A-1) quartz mercury vapor lamp was switched on and introduced into the quartz well. Heat transfer was minimized by a high vacuum between the walls of the double-wall quartz well.

Addition of Thiolacetic Acid.—In all cases this reaction was achieved in good yields between 0–25° by using a simple Vycor flask. As radiation source a long wave ultraviolet lamp or even an ordinary 100-w. bulb was sufficient, which was used during the controlled addition of thiolacetic acid to the vinyl- or allyltin or silicon compounds.

Propyl-3-thioltrimethylsilane (III).—The graduated reactor was charged with a mixture of 57 g. (0.5 mole) of allyltrimethylsilane, 1.5 g. of ethyl acetate (catalyst), and 60 ml. of pentane. It was cooled to −70° in a Dry Ice bath and hydrogen sulfide was distilled into this mixture until its volume had increased by approximately 40 ml. The ignited Hanovia quartz light was then inserted into the open center well, and the reaction mixture was irradiated for 2 hr. By removing the Dry Ice bath the excess of hydrogen sulfide was slowly evaporated into a sodium hydroxide scrubber. Pentane was removed by distillation at atmospheric pressure. Seventy-three grams of a colorless liquid remained which contained about 19% sulfur. The pure reaction product (55 g., 74.4%) was isolated by two fractionations through a 20-in. Vigreux column; b.p. 52–53° (16 mm.).

Anal. Calcd. for $C_6H_{16}SSi$: C, 48.62; H, 10.76; S, 21.65; 18.95. Found: C, 49.01; H, 10.23; S, Si, 21.60; Si, 18.64.

Bis(3-trimethylsilylpropyl) Sulfide (IV).—The combined pot residues of the two distillations were distilled at 0.05 mm. Pure colorless sulfide (14.5 g., 19.2%) boiled at 46–47°.

Anal. See Table I.

Ethyl-2-thioltrimethylsilane (I).—In the graduated quartz reactor, immersed in a Dry Ice bath, 50 g. (0.5 mole) of vinyltrimethylsilane, 40 ml. of liquid hydrogen sulfide, and 1 g. of ethyl acetate were irradiated with the Hanovia quartz lamp for a period of 2.5 hr. The excess hydrogen sulfide was then distilled into a scrubber by slowly raising the temperature in the reactor to 20°. In the reactor remained 65 g. of a clear, colorless oil, which was purified by two fractional distillations through a 20-in. Vigreux column; b.p. 40–41° (18 mm.); yield, 14 g. (21%).

Bis(3-trimethylsilylethyl) Sulfide (II).—The combined pot residues of the preceding distillations were distilled at 0.05 mm. Pure, colorless sulfide (23.5 g.) distilled at 39–40°.

Bis(2-trimethylsilylethyl) Sulfone (V).—This compound was prepared by oxidizing 23.3 g. (0.1 mole) of II, dissolved in 180 ml. of anhydrous acetic acid, with a 50% excess (38 g.) of 30% hydrogen peroxide in 2 hr. at 50–60°. Upon storage in the refrigerator 18.5 g. (71%) of pure sulfone crystallized (m.p. 122–123°). An additional 4 g. was obtained by concentrating the mother liquor *in vacuo*.

Propyl-3-thioltri-*n*-butyltin (VII). By Direct Addition of Hydrogen Sulfide.—About 20 ml. of liquid hydrogen sulfide was distilled into the mixture of 30 g. of allyltri-*n*-butyltin, 50 ml. of pentane, and 1 ml. of acetone. The mixture in the quartz reactor was irradiated for 2 hr. with a Hanovia mercury lamp at −70°. Then the excess of hydrogen sulfide and pentane was removed, and the reaction product was purified by high vacuum distillation through a 5-in. Vigreux column (see Table I).

3-(Tri-*n*-butyltin)propyl Thiolacetate (IX). By Addition of Thiolacetic Acid.—To 160 g. (0.5 mole) of allyltri-*n*-butyltin was added with stirring and outside ice-cooling 46 g. (0.59 mole) of distilled thiolacetic acid.[10] At 0–10° the agitated mixture was irradiated with ultraviolet light for 2 hr. Then the small excess of thiolacetic acid was removed by distillation. The remaining clear, colorless oil was distilled at reduced pressure, the main fraction (87%) boiling at 120° (0.2 mm.). The infrared spectrum of this compound has a strong carbonyl band at 1675 $cm.^{-1}$.

(10) Stauffer Chemical Co.

Saponification.—In 25 ml. of ethanol was dissolved 20 g. (0.05 mole) of IX. The solution of 2.5 g. of potassium hydroxide in 5 ml. of water and 25 ml. of ethanol was added with agitation at room temperature. The clear solution was heated for 3 hr. at 50°. During this time two phases formed. The lower, oily phase was separated at room temperature, taken up in ether, washed with water, and dried over sodium sulfate. Ether was evaporated, and the remaining colorless oil was purified by high vacuum distillation. VII was obtained in 78% yield (14.2 g.).

A Hammett Study of Hydrogen Abstraction from Substituted Allylbenzenes

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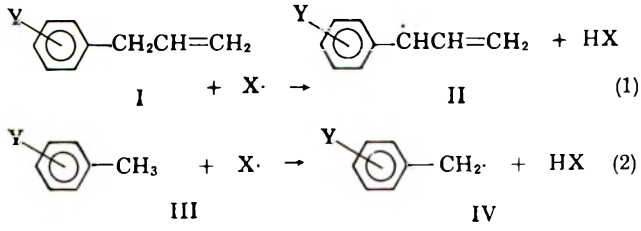
Received June 14, 1963

This study is a comparison of the polar effects operating in the abstraction of a hydrogen atom from a series of substituted allylbenzenes (reaction 1) and the more extensively investigated abstraction of a hydrogen atom from substituted toluenes (reaction 2).[2-7] The greater stability of the α-vinylbenzyl radical (II) compared to the benzyl radical (IV) would be expected to compress the activation energy scale for reaction 1 compared to reaction 2, and thereby decrease the effect of a polar substituent on reaction rate in the case of the allylbenzenes. In order to determine the extent to which this effect is reflected in the magnitude of the Hammett ρ-value for reaction 1 as compared to reaction 2, reaction constants have been determined for abstraction of a hydrogen atom from allylbenzenes by the trichloromethyl radical, generated from bromotrichloromethane, and by the bromine atom, generated from N-bromosuccinimide.[8]



Experimental

Materials.—The substituted allylbenzenes were all prepared by the coupling reaction of allyl bromide with an aryl Grignard reagent. The procedural details and properties of these compounds are reported elsewhere.[10] The N-bromosuccinimide was purified by recrystallization from petroleum ether (80°–100°), m.p. 179°. Chlorobenzene was purified by shaking with three portions of sulfuric acid, once with water, three times with 5% sodium bicarbonate, again with water, drying successively over calcium chloride, calcium sulfate, and phosphorus pentoxide, and distilling, b.p. 130–130.5°. Merck, Reagent carbon tetrachloride was used without further purification.

Products.—A mixture of 17.3 g. (0.147 mole) of allylbenzene, 26.1 g. (0.146 mole) of N-bromosuccinimide, and 100 ml. of carbon tetrachloride under nitrogen was refluxed for 24 hr. while being irradiated by a 275-w. General Electric sun lamp directed through the side of the reaction flask. At the end of this time the solution was cooled, whereupon 13.65 g. (94%) of succinimide, m.p. 124.5–126.5° (lit.[11a] 125–126°), separated. Solvent was removed from the liquid filtrate by distillation at reduced pressure, and the residue distilled through a Vigreux column, giving 25.8 g. (89%) of a liquid identified as cinnamyl bromide, b.p. 120–124° (30 mm.), m.p. 29° (lit.[11b] 31°). Vapor phase chromatography on a diethylene glycol succinate column indicated only one component, and the infrared spectrum was devoid of any absorption bands which would be characteristic of the possible isomeric product, phenylvinylcarbinyl bromide.

These results confirm the contention that the dominant reaction of an olefin with N-bromosuccinimide is allylic hydrogen abstraction and not addition to the double bond, and justifies the assumption in the kinetic studies that olefin disappears only by hydrogen abstraction without significant competition by addition.

Procedure for Kinetic Runs Using N-Bromosuccinimide.—Equimolar quantities of two allylbenzenes, N-bromosuccinimide and chlorobenzene (present as an inert internal standard for v.p.c. analysis) were sealed under a nitrogen in small Pyrex ampoules and placed in a horizontal position just beneath the surface of an oil bath maintained at 69.5 ± 0.2° and irradiated by a General Electric 275-w. sun lamp placed 19 cm. from the surfaces until anywhere from 45 to 70% of the total number of moles of allylbenzenes present had been consumed. An irradiation time of about 5 to 5.5 hr. was employed. After the ampoules had cooled, they were opened, the liquid portion decanted from undissolved solids, and analyses conducted by v.p.c. on a 6-ft. 10% diethylene glycol succinate column. *p*-Dimethylamino-, *p*-methoxy-, *p*-phenyl-, *m*-methoxy-, *p*-chloro-, and *m*-chloroallylbenzene were run in competition with the unsubstituted allylbenzene, whereas *p*-methyl-, *m*-methyl-, *p*-fluoro-, *p*-trifluoromethyl- and *m*-trifluoromethylallylbenzene were run against *m*-chloroallylbenzene to give better separation on v.p.c., and therefore better analytical results. The ratio of rate constants relative to the unsubstituted compound was then calculated from the expression

$$\frac{k_X}{k_0} = \frac{k_X}{k_{m\text{-Cl}}} \times \frac{k_{m\text{-Cl}}}{k_0}$$

where k_X is the rate constant for the substituted allylbenzene in question, k_0 the rate constant for the unsubstituted allylbenzene and $k_{m\text{-Cl}}$ the rate constant for *m*-chloroallylbenzene.

Determination of k_x/k_0.—The rate of hydrogen abstraction from the substituted compound relative to the unsubstituted compound was calculated from the expression

$$\frac{k_X}{k_0} = \frac{\log X_0/X_f}{\log U_0/U_f}$$

where X_0 and U_0 are the number of moles initially present of substituted and unsubstituted allylbenzene, respectively, and X_f and U_f are the number of moles present at the end of the irradiation period. The ratios X_0/X_f and U_0/U_f were determined by v.p.c. analysis from the expression

$$\frac{X_0}{X_f} = \frac{(\text{area under X peak}/\text{area under } C_6H_5Cl \text{ peak})_{\text{initially}}}{(\text{area under X peak}/\text{area under } C_6H_5Cl \text{ peak})_{\text{finally}}}$$

and the analogous one for the unsubstituted olefin. Areas were determined with the aid of a disk integrator.

Procedure for Kinetic Runs Using Bromotrichloromethane.—The experiments from which reactivity ratios for hydrogen abstraction by the trichloromethyl radical were determined are described elsewhere.[10] The results are included in this note for

(1) Petroleum Research Fund Predoctoral Fellow, 1961–1962 and 1962–1963.

(2) C. Walling and B. Miller, *J. Am. Chem. Soc.*, **79**, 4181 (1957).

(3) E. C. Kooyman, R. Van Helden, and A. F. Bickel, *Konikl. Ned. Akad. Wetenshap. Proc. Ser. B*, **56**, 75 (1953).

(4) R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 354 (1963).

(5) C. Walling and B. Jacknow, *ibid.*, **82**, 6113 (1960).

(6) G. A. Russell, *ibid.*, **78**, 1047 (1956).

(7) E. S. Huyser, *ibid.*, **82**, 394 (1960).

(8) Recent studies[4,9] have demonstrated that the bromine atom is the hydrogen abstracting species in benzylic brominations involving N-bromosuccinimide, and not the N-succinimidyl radical as had been originally believed.[2]

(9) G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Am. Chem. Soc.*, **85**, 365 (1963).

(10) M. M. Martin and G. J. Gleicher, *ibid.*, in press.

(11) (a) I. Heilbron, "Dictionary of Organic Compounds," Vol. 4, Oxford University Press, London, England, 1953, p. 384; (b) Vol. 1, p. 364.

the sake of completeness and comparison with the studies using N-bromosuccinimide.

Calculations.—The Hammett ρ-values were calculated from least squares slopes of the lines resulting from plots of log k_X/k_0 *vs.* σ^+ or *vs.* σ^0. The expected errors in ρ and the correlation coefficients were calculated by standard statistical methods.[12]

Relative Reactivity of Allylbenzene and Toluene toward N-Bromosuccinimide.—The procedure and calculations were the same as those employed to study relative reactivities of the various allylbenzenes.

Results and Discussion

In Table I are presented the relative rates of hydrogen abstraction from allylbenzenes by bromine atoms and trichlormethyl radicals. From the data in this Table it is possible to calculate reaction constants, that is ρ-values, for these reactions. The ρ-values, obtained by calculating the slopes of the regression lines resulting from plots of log k_X/k_0 *vs.* σ^+ or σ^0 are presented in Tables II and III. In the reaction with N-bromosuccinimide, the allylbenzenes were studied at a lower temperature than the toluenes (69.5° compared with 80°), whereas in the reaction with bromotrichloromethane, the allylbenzenes were studied at a higher temperature than the toluenes (69.5° compared with 50°). Since the magnitude of a ρ-value varies inversely with temperature below the isokinetic temperature, the ρ-values for the two systems in their reactions with N-bromosuccinimide would be further apart if studied at the same temperature than they are at the temperatures indicated in Table II, whereas for the reaction with bromotrichloromethane, the ρ-values would be nearer to each other in magnitude when studies at the same temperature, then they are at the temperatures indicated in Table III. Making allowances for the differences in temperatures at which these studies have been conducted, it would appear that hydrogen abstraction reactions from allylbenzenes have Hammett ρ-values of the order of one half to one-third as great in magnitude as those for abstraction from toluenes by the same radical.

TABLE I

RELATIVE RATES OF ABSTRACTION OF A HYDROGEN ATOM FROM SUBSTITUTED ALLYLBENZENES BY A BROMINE ATOM AND A TRICHLOROMETHYL RADICAL AT 69.5°

Substituent	σ^{0a}	σ^{+b}	k_X/k_0 (Br·)	k_X/k_0 (Cl_3C·)[c]
p-$(CH_3)_2N$	−0.44	−1.700	20.9 ± 0.07[d]	
p-CH_3O	−0.16	−0.778	3.23 ± 0.20	1.46 ± 0.07[d]
p-CH_3	−0.15	−0.311	1.89 ± 0.04	1.42 ± 0.03
p-C_6H_5	0.00	−0.179	1.70 ± 0.03	1.02 ± 0.08
p-F	+0.17	−0.073	1.08 ± 0.02	0.94 ± 0.03
m-CH_3	−0.07	−0.060	1.29 ± 0.13	1.15 ± 0.04
H	0.00	0.000	1.000	1.000
m-CH_3O	+0.13	+0.047	1.02 ± 0.01	0.82 ± 0.01
p-Cl	+0.27	+0.114	0.78 ± 0.05	0.78 ± 0.05
m-Cl	+0.37	+0.339	0.50 ± 0.06	0.60 ± 0.01
m-CF_3	+0.42[e]	+0.562	0.40 ± 0.01	0.54 ± 0.02
p-CF_3	+0.55[e]	+0.612	0.36 ± 0.01	0.47 ± 0.01

[a] R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960). [b] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958). [c] See ref. 10. [d] Average deviation. [e] σ^0 values are not available for m- and p-CF_3, but for strongly electron-withdrawing groups, $\sigma \approx \sigma^0$. The values indicated are σ values; J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 72.

(12) W. J. Gore, "Statistical Methods for Chemical Experimentation," Interscience Publishers, Inc., New York, N. Y., 1952, Chap. 6.

TABLE II

ρ-VALUES FOR THE REACTIONS, Br· + $C_6H_5CH_2R$ ⟶ HBr + $C_6H_5\dot{C}HR$

R	Temp., °C.	$\rho^{a}(r^{b})$
$CH{=}CH_2$	69.5	−0.76 ± 0.03 (−0.99)
H[c]	80.0	−1.39 ± 0.03 (−0.99)

[a] Calculated using σ^+. [b] Correlation coefficient. [c] ref. 4.

TABLE III

ρ-VALUES FOR THE REACTIONS, Cl_3C· + $C_6H_5CH_2R$ ⟶ $HCCl_3$ + $C_6H_5\dot{C}HR$

R	Temp., °C.	$\rho^{a}(r^{b})$	$\rho^{c}(r^{b})$
$CH{=}CH_2$	69.5	−0.39 ± 0.03 (−0.94)	−0.58 ± 0.03 (−0.99)
H[d]	50.0	−1.46	−1.72 (−0.99)

[a] Calculated using σ^+. [b] Correlation coefficient. [c] Calculated using σ^0. [d] See ref. 7.

It was also found that allylbenzenes is 17.5 ± 1.1 times as reactive toward hydrogen abstraction by the bromine atom as toluene at 69.5°, reflecting the stabilizing effect of the α-vinyl group. Comparing this figure with data recently published by Russell, Deboer, and Desmond,[9] it would appear that a hydrogen atom is more easily abstracted by a bromine atom from allylbenzene than from diphenylmethane. This is probably a consequence of the greater difficulty with which coplanarity is approached by the two phenyl groups of the diphenylmethyl radical compared to the phenyl group and vinyl group of the α-vinylbenzyl radical.

Acknowledgment.—It is a pleasure to thank the Donors of the Petroleum Research Fund for a grant (PRF-603A) which financed the greater part of this work.

Derivatives of 2-Benzyl-1-indanone. Competing Alicyclic and Aromatic Monobromination

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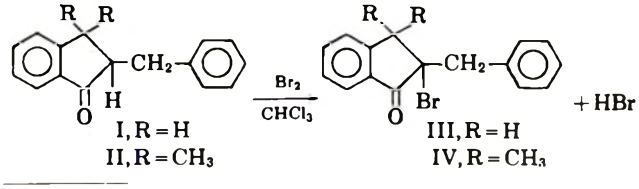
Received June 10, 1963

It has been shown previously that treatment of 2-benzyl-1-indanone (I) or 2-benzyl-3,3-dimethyl-1-indanone (II) with an equimolar quantity of bromine in chloroform leads to an excellent yield of the corresponding 2-bromo-2-benzyl-1-indanone.[2,3] The product controlling factor is the activating influence of the carbonyl group.



I, R = H
II, R = CH_3
III, R = H
IV, R = CH_3

(1) To whom communications concerning this paper should be addressed.
(2) N. H. Cromwell and R. P. Ayer, *J. Am. Chem. Soc.*, **82**, 133 (1960).
(3) B. D. Pearson, R. P. Ayer, and N. H. Cromwell, *J. Org. Chem.*, **27**, 3038 (1962).

Condensation of *p*-dimethylaminobenzaldehyde with 1-indanone and quantitative hydrogenation of the 2-(*p*-dimethylaminobenzal)-1-indanone (V) at atmospheric pressure yielded 2-(*p*-dimethylaminobenzyl)-1-indanone (VI). In VI, in addition to the activated 2-position, the two aromatic hydrogens *ortho* to the *p*-dimethylamino group are also expected to be replaceable.

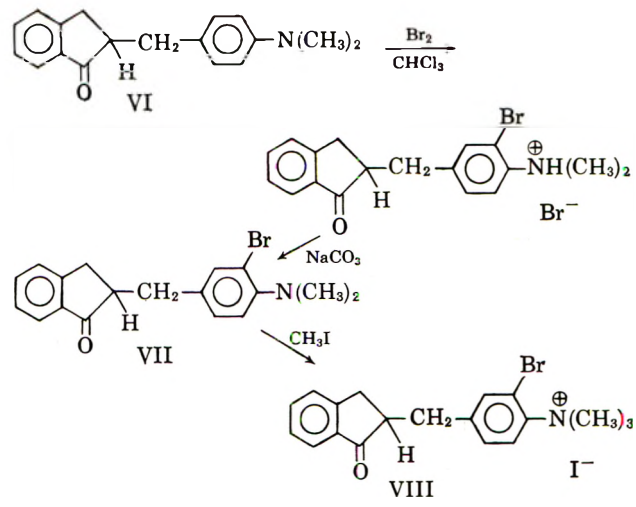
Bromination of IV produces a compound (VII) with analysis for a monobrominated derivative but which gives no reaction with piperidine in acetonitrile under conditions more rigorous than those in which 2-bromo-2-benzyl-1-indanone (III) gives a 100% yield of 2-benzal-1-indanone.[4] Similarly, conversion of VII to its methiodide (VIII) followed by attempted reaction of VIII with excess bromide ion in acetonitrile gave no reaction under conditions in which III gives 100% acid formation and at least a 90% yield of 2-benzal-1-indanone.

If the monobromoindanone VII was 2-bromo-2-(*p*-dimethylaminobenzyl)-1-indanone then the results would indicate that relative to the parent compound III, both electron-supplying ($-NMe_2$) and electron-withdrawing ($-N^+Me_3$) groups introduced into the *para* position of the benzyl group cause an enormous reduction in the rate of exocyclic dehydrobromination reactions. It is clear that the bromine has been introduced other than into the 2-position and into a position where it is immune from attack by nucleophilic reagents. The results point to aromatic bromination, and this is confirmed by consideration of proton magnetic resonance spectra.

In deuteriochloroform, 2-benzyl-1-indanone (I) and 2-(*p*-dimethylaminobenzyl)-1-indanone (VI), both give a complex splitting pattern in the region 6.5–7.8 τ due to five protons, the two methylene protons in the 3-position, the tertiary proton in the 2-position, and the two *exo* benzylic methylene protons. Bromination of I in the 2-position, to give III, leads to isolation of the two methylene groups and a much simpler splitting pattern, arising only from nonequivalence of protons within the methylene groupings.

Bromination of VI leads to VII in which the splitting pattern in the region 6.5–7.8 τ is unaltered. Major changes are, however, produced in the pattern of the aromatic protons, which now integrate for only seven protons showing that aromatic bromination has taken place. Two doublets at 3.35 and 2.90 τ (J = 8 c.p.s.) arising from two superimposed AB systems of aromatic protons in the *para* substituted benzyl group of VI are absent after bromination, and, in particular, no peaks due to aromatic protons are observed above 3.1 τ. It is clear that the activating influence exerted upon the aromatic hydrogens *ortho* to the *p*-dimethylamino group is sufficient to divert the bromination away from the carbonyl activated 2-position. (See col. 2.)

Proton Magnetic Resonance Spectra in Trifluoroacetic Acid.—Dimethylamino derivatives are protonated in trifluoroacetic acid, and the spectra are different in character from those observed in deuteriochloroform. The signal due to the six methyl protons is split by the proton on the nitrogen, and the protons of the benzyl aromatic ring are subjected to a very different substituent shielding effect. No signal corresponding to the quaternary ammonium proton could be detected.



The dimethylanilinium ion gives a signal corresponding to six methyl protons at 6.52 τ (J = 5 c.p.s.) and a fairly sharp signal corresponding to all five aromatic protons at 2.35 τ. 2-(*p*-Dimethylaminobenzyl)-1-indanone (VI) has absorption due to six methyl protons at 6.51 τ (J = 5 c.p.s.) and several peaks of moderate intensity in the range 2.0–2.7 τ with superimposed one sharp and intense peak, corresponding to four benzylic aromatic protons, at 2.38 τ. The monobromination product VII has absorption due to six methyl protons at 6.46 τ (J = 5 c.p.s.) and several aromatic peaks of moderate intensity in the range 2.0–2.6 τ. The shift of the methyl proton signal and the disappearance of the sharp and intense signal in the aromatic region upon monobromination is consistent with formulation as 2-(*m*-bromo-*p*-dimethylaminobenzyl)-1-indanone (VII).

The methiodide of VII (VIII) gives several peaks of moderate intensity in the range 2.0–2.7 τ and a sharp peak corresponding to the nine methyl protons at 6.00 τ.

For VI, VII, and VIII in addition to the peaks mentioned previously a complex splitting pattern arising from five nonaromatic protons was observed in the range 6.2–7.2 τ.

Proton Magnetic Resonance Spectra of Aromatic Protons in Methanol.—In methanol 2-(*p*-dimethylaminobenzyl)-1-indanone (VI) gives several moderately intense peaks corresponding to four indanone aromatic protons in the region 2.2–2.8 τ and two doublets (J_{AB} = 8 c.p.s.) corresponding to two protons *ortho* and two protons *meta* to the dimethylamino group at 3.37 and 2.95 τ. In the presence of 0.2 M hydrobromic acid the doublets disappear, and, consistent with the spectrum in trifluoroacetic acid, a new sharp and intense peak occurs at 2.58 τ, superimposed upon a background of moderately intense peaks in the region 2.2–2.7 τ.

2-(*m*-Bromo-*p*-dimethylaminobenzyl)-1-indanone (VII) gives a complex system of peaks in the region 2.1–3.1 τ which in the presence of 0.2 M hydrobromic acid gives a differing pattern of moderately intense peaks in the region 2.0–2.7 τ. The methiodide of VII (VIII) gives a doublet (J = 8 c.p.s.) corresponding to one proton at 2.04 τ and peaks corresponding to six other protons in the region 2.2–2.8 τ.

(4) G. A. Coppens, D. N. Kevill, and N. H. Cromwell, unpublished results.

Experimental[5]

2-(*p*-Dimethylaminobenzal)-1-indanone (V).—To an ice-cooled solution of 7.94 g. (0.0600 mole) of 1-indanone dissolved in 20 ml. of ethanol was added slowly an ice-cooled solution of 0.34 g. of potassium hydroxide (0.0060 mole) and 8.95 g. (0.0600 mole) of *p*-dimethylaminobenzaldehyde in 50 ml. of ethanol. The mixture was allowed to stand overnight in a refrigerator. Filtration and washing with ethanol gave 15.0 g. (99% yield) of yellow crystals, m.p. 161–162°. After recrystallization from dioxane, it had m.p. 164–165°; λ_{max} 271, 431 mμ (ε 17,400, 36,600); $\nu_{C=O}$ 1698 vs (1690 vs in acetonitrile), $\nu_{C=C}$ 1629 m, ν_{Ar} 1605 cm.$^{-1}$ vs.

The proton magnetic resonance spectrum in deuteriochloroform shows six methyl protons at 7.05 τ, two methylene protons (split by 2 c.p.s.) at 6.13 τ, two equivalent aromatic protons (*ortho* to the dimethylamino group and split by two equivalent protons *meta* to this grouping; J = 8 c.p.s.) at 3.37 τ, peaks corresponding to five aromatic and one vinyl proton in the range 2.3–2.9 τ, and the aromatic proton beta to the carbon group (split by the γ proton; J = 7 c.p.s.) at 2.15 τ.

Anal. Calcd. for $C_{18}H_{17}ON$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.32; H, 6.50; N, 5.26.

2-(*p*-Nitrobenzal)-1-indanone.—The same procedure as for V was followed, but using 9.07 g. (0.0600 mole) of *p*-nitrobenzaldehyde. Obtained was 12.8 g. (80% yield) of pale yellow crystals, m.p. 228–230°. Recrystallization from glacial acetic acid gave long pale yellow needles which were washed with petroleum ether and ether, m.p. 251–252°; λ_{max} 321 mμ; $\nu_{C=O}$ 1692 cm.$^{-1}$ (KBr pellet and LiF optics).

Anal. Calcd. for $C_{16}H_{11}O_3N$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.22; H, 4.14; N, 5.41.

2-(*p*-Dimethylaminobenzyl)-1-indanone (VI).—To a solution of 9.0 g. of 2-(*p*-dimethylaminobenzal) 1 indanone (V) in 900 ml. of dioxane was added 0.9 g. of 10% palladium on charcoal. The mixture was heated to 45–50° and quantitative hydrogenation carried out at atmospheric pressure. The solution was filtered and evaporated to dryness to give gray-brown crystals. Recrystallization from ethanol gave 6.4 g. (70% yield) of almost colorless crystals, m.p. 77–79°. Several additional recrystallizations raised the m.p. to 79–80°; λ_{max} 249, 293 mμ (ε 32,000, 6,700); $\nu_{C=O}$ 1715 vs (1710 cm.$^{-1}$ vs in acetonitrile), ν_{Ar} 1619 cm.$^{-1}$ s.

The p.m.r. spectrum in deuteriochloroform shows a sharp peak corresponding to six methyl protons at 7.12 τ, several peaks corresponding to five protons in the range 6.5–7.8 τ, two protons *ortho* and two protons *meta* to the dimethylamino group (constituting two superimposed AB systems; J_{AB} = 8 c.p.s.) at 3.35 and 2.90 τ, respectively, peaks corresponding to three aromatic protons in the range 2.4–2.9 τ, and the aromatic proton beta to the carbonyl group at 2.27 τ (J = 7 c.p.s.).

Anal. Calcd. for $C_{18}H_{19}ON$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.53; H, 7.28; N, 5.34.

2-(*m*-Bromo-*p*-dimethylaminobenzyl)-1-indanone (VII).—To a solution of 21.2 g. (0.0800 mole) of 2-(*p*-dimethylaminobenzyl)-1-indanone (VI) in 75 ml. of chloroform was added over a period of 1 hr. with stirring and in the presence of sunlight, a solution of 12.8 g. (0.0800 mole) of bromine in 25 ml. of chloroform. After standing for an additional 30 min. the solution was evaporated and the product recrystallized from ethanol to give 25.8 g. (76% yield) of the hydrobromide of VII. This product, m.p. 123°, was hygroscopic and gave an instantaneous precipitate with alcoholic silver nitrate; λ_{max} 246, 287 mμ (ε 19,800, 4800); $\nu_{C=O}$ 1712 cm.$^{-1}$ vs (in acetonitrile).

Extraction of 10 g. of the hydrobromide by 150 ml. of 5% aqueous sodium carbonate and 100 ml. of ether, washing the ether layer, drying over anhydrous magnesium sulfate, and evaporation gave 7.5 g. (81% yield) of crude VII. Recrystallization from ether–petroleum ether gave pure VII, m.p. 71–72°; λ_{max} 247, 289 mμ (ε 30,500, 8100); $\nu_{C=O}$ 1719 vs, ν_{Ar} 1614 cm.$^{-1}$ m.

The p.m.r. spectrum in deuteriochloroform shows a sharp peak corresponding to six methyl protons at 7.22 τ, several peaks corresponding to five protons in the range 6.5–7.8 τ, a complex series of peaks corresponding to six aromatic protons in the range 2.4–3.1 τ, and the signal from the aromatic proton beta to the carbonyl at 2.23 τ (J = 7 c.p.s.).

Anal. Calcd. for $C_{18}H_{18}ONBr$: C, 62.80; H, 5.27; N, 4.07. Br, 23.22. Found: C, 62.99; H, 5.35; N, 4.17; Br, 23.01.

An acetonitrile solution 0.01 *M* in VII and 0.03 *M* in piperidine, maintained in sealed bulbs at 91.9°, underwent no reaction as measured either by reduction in base concentration or by increase in bromide ion concentration[6] during a period of 30 hr.

2-(*m*-Bromo-*p*-dimethylaminobenzyl)-1-indanone Methiodide (VIII).—A mixture of 20 ml. of ethanol, 15 ml. of methyl iodide, and 7.0 g. of 2-(*m*-bromo-*p*-dimethylaminobenzyl)-1-indanone (VII) was maintained in a sealed tube at 60° for 15 hr. and then allowed to stand at room temperature for 2 days. Ether extraction left 2.8 g. (28% yield) of crude VIII. Recrystallization from ethanol gave pure VIII, m.p. 152–153°; λ_{max} 242, 295 mμ (ε 25,700, 4700).

Anal. Calcd. for $C_{19}H_{21}ONBrI$: C, 46.92; H, 4.35; N, 2.88; Br + I, 42.54. Found: C, 47.01; H, 4.45; N, 2.92; Br + I, 42.70.

Neither an acetonitrile solution 0.0082 *M* in VIII nor an acetonitrile solution 0.0041 *M* in VIII and 0.0239 *M* in tetraethylammonium bromide developed any acidity[6] during 3 days in sealed bulbs at 91.9°.

Acknowledgment.—This work was supported in part by Grant No. G-14469, National Science Foundation.

(5) Melting points were read with a calibrated thermometer. Infrared spectra were measured with a Perkin-Elmer Model 21 double beam recording instrument employing, unless otherwise stated, sodium chloride optics and matched sodium chloride cells with carbon tetrachloride solutions. The ultraviolet spectra were determined with a Cary Model 11-MS recording spectrophotometer using reagent grade methanol solutions. The proton magnetic resonance spectra were obtained with a Varian A-60 instrument *using a trace of tetramethylsilane (τ 10.00) as internal reference.*

(6) Acid–base titrations in acetone using Lacmoid, i.e., resorcinol blue, as indicator. Bromide titrations by potentiometric titration in acidified acetone against aqueous silver nitrate.

A Convenient Method for Utilizing the Allyl Grignard Reagent

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Received April 11, 1963

It is the purpose of this paper to point out and emphasize a convenient synthetic technique which has been known for a number of years but has been overlooked and even discouraged. The method of utilizing the allyl Grignard reagent reported here has been referred to as the Barbier–Grignard procedure.[1] In this procedure the organomagnesium compound is not formed as an intermediate in the presence of an excess of carbonyl compound as Barbier[2a,3,4] did, nor is the functional addend withheld until the preparation of the Grignard reagent is complete. Rather a solution of the alkyl halide and the functional addend is added to the magnesium metal to which a small amount of allyl halide has been added to start the reaction; there is no large excess of carbonyl compound present at any time. The application of the Barbier–Grignard procedure to allylic halides has been employed periodic-

(1) H. R. Henze, B. B. Allen, and W. B. Leslie, *J. Org. Chem.*, **7**, 326 (1942).

(2) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, (a) p. 3; (b) p. 27; (c) p. 143.

(3) G. H. Richter, "Textbook of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 170.

(4) P. Barbier, *Compt. rend.*, **128**, 110 (1899).

ally,[5-10] but the method has never been emphasized nor has the apparent generality of the reaction been appreciated. The Barbier–Grignard procedure appears to have been used routinely whenever the allyl Grignard reagent was desired before Gilman[11] discovered the technique required to make successfully allylmagnesium bromide. Since this discovery, it has been more common to make the allyl Grignard reagent in a separate step, especially in the light of studies such as Henze's.[1]

Recently the author has had occasion to use the Barbier–Grignard method successfully in a number of cases; some of them are verifications of reported cases and several are new examples. In the preparation[11] of the very useful allyl Grignard reagent, its coupling with allyl halide is avoided by slowly adding the allyl halide in very dilute solution to a large excess of magnesium. Some of these disadvantages are overcome by forming the ether-insoluble allylmagnesium chloride.[2b] In the present method the allyl Grignard is formed only as a transient intermediate, thus obviating the need for dilute solution and a large excess of magnesium and allowing the fast addition of the reagents to the magnesium. In most cases, addition can be as rapid as the vigor of the reaction will allow. The yields are generally high and in many cases are higher than those reported in the two step procedure. It is emphasized, however, that it was *found critical to the success of this method to start the reaction with a small amount of allyl halide in ether before beginning the addition of allyl halide and functional addend.* An unawareness of this technique probably accounts for the preference for the two-step procedure by workers such as Henze[1] and Bacon and Farmer.[12] The success of this reaction seems to depend on the fact that the allylic Grignard reacts with the carbonyl compound at a much higher rate than it reacts with the allylic halide.

In a recent volume of *Organic Syntheses* there is a report[15] of the synthesis of 1,5-hexadien-3-ol by the standard two-step procedure, preparation of allylmagnesium bromide followed by reaction with acrolein. Table I compares this report with the same preparation carried out by the simultaneous addition of allyl bromide and acrolein and points out the advantages in time and materials of the latter method.

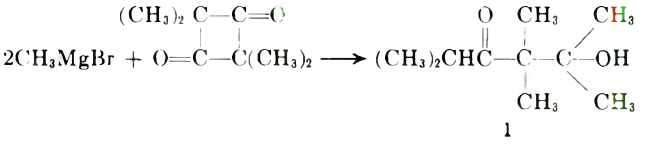
In addition, the reaction has been carried out using allyl bromide or chloride with a number of different functional addends. These results are summarized in Table II.

TABLE I

TWO-STEP *vs.* ONE-STEP PREPARATION OF 1,5-HEXADIEN-3-OL

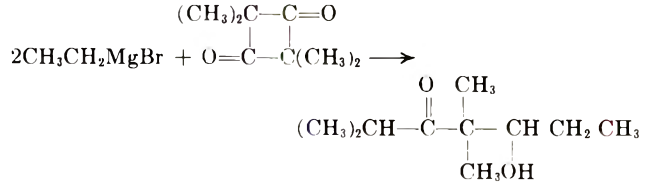
	Two-step[15]	One-step
G.-atoms of Mg	6.28	2.9
Moles of allyl bromide	2.90	2.5
Moles of acrolein	1.86	2.0
Total volume of ether	2960 ml.	900 ml.
Total time of addition of reagents	6 hr.	3 hr.
Boiling point	62–65° (50 mm.)	38–39° (11 mm.)
$n^{25}D$	1.4440	1.4450
Yield	57–59%	66%

The reaction with tetramethyl-1,3-cyclobutanedione appears worthy of comment. Erickson and Kitchens[16] reported that methyl Grignard reacted with tetramethyl-1,3-cyclobutanedione to form an open chain diadduct **1**.

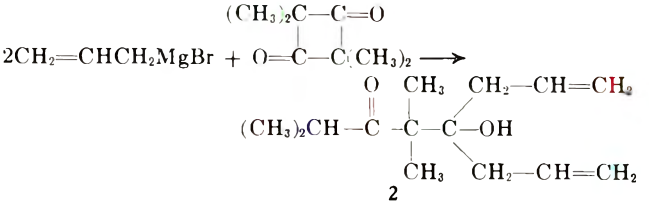


1

The ethyl Grignard formed only a reduced open chain monoadduct.

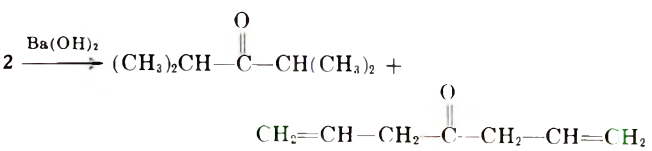


Allyl Grignard reacted with tetramethyl-1,3-cyclobutanedione under the conditions reported in this paper to form an open chain diadduct.



2

The fact that a diallyl rather than monoallyl adduct was formed was suggested by a boiling point more consistent with a C_{14} keto alcohol than with a C_{11} keto alcohol. The proton magnetic resonance (p.m.r.) spectrum of the product showed two allyl groups per four methyl groups and, therefore, confirmed that two moles of allyl Grignard had added to one mole of tetramethyl-1,3-cyclobutanedione. The p.m.r. spectrum also showed one hydroxyl per two allyl groups and an isopropyl group; thus the structure **2** analogous to structure **1** was indicated. The structure **2** was proven by carrying out the cleavage reaction reported by Erickson and Kitchens[16] for this type of compound.



(5) W. Jaworsky, *Ber.*, **42**, 435 (1909).

(6) F. G. Fischer, *ibid.*, **76**, 735 (1943).

(7) I. N. Nazrov and I. I. Zaretskaya, *J. Gen. Chem. USSR*, **27**, 693 (1957).

(8) N. A. Milas and A. McAlevy, *J. Am. Chem. Soc.*, **57**, 580 (1935); R. T. Arnold and E. C. Coyner, *ibid.*, **66**, 1542 (1944); N. G. Gaylord and E. I. Becker, *J. Org. Chem.*, **15**, 305 (1950).

(9) I. Matzurevich, *J. Russ. Phys. Chem. Soc.*, **43**, 973 (1911); *Chem. Abstr.*, **6**, 480 (1912).

(10) R. Ya. Levina and D. M. Trakhtenburg, *J. Gen. Chem. USSR*, **6**, 764 (1936); *Chem. Abstr.*, **30**, 6338 (1936).

(11) H. Gilman and J. H. McGlumphy, *Bull. soc. chim. France*, **43**, 1322 (1928).

(12) R. G. R. Bacon and E. H. Farmer, *J. Chem. Soc.*, 1065 (1937). These authors were unable to prepare 2-methyl-4-penten-2-ol using the Barbier–Grignard procedure as reported by Jaworsky[5] and instead used the two-step method. Fischer[6] successfully repeated Jaworsky's preparation. DuPont[13] at at first repeated Bacon and Farmer's preparation but subsequently[14] found Fischer's method superior.

(13) G. DuPont and M. Darmon, *Bull. soc. chim. France*, 240 (1954).

(14) G. DuPont, R. Dulou, and G. Christen, *ibid.*, 820 (1954).

(15) J. C. H. Hwa and H. Sims, *Org. Syn.*, **41**, 49 (1961).

(16) J. L. E. Erickson and G. C. Kitchens, *J. Am. Chem. Soc.*, **68**, 492 (1946).

TABLE II

ALLYLIC CARBINOLS PREPARED BY THE BARBIER–GRIGNARD PROCEDURE

Allyl halide[a] (moles)	Magnesium, g.-atoms	Functional addend (moles)	Ether, ml.	Addition time, hr.	Product	Yield, %	Properties B.p., °C.	Mm.	$n^{25}D$
B (2.5)	2.9	Acrolein (2.0)	900	3	1,5-Hexadien-3-ol	66	38–39[b]	11	1.4450[b]
B (2.23)	2.26	Acetone (2.0)	800	2	2-Methyl-4-penten-2-ol[c1]	74[d]	117.0–117.3[e]	Atm.	1.4246[e]
C (2.25)	2.26	Methyl isopropyl ketone (2.0)	800	3.5	2,3-Dimethyl-5-hexen-3-ol	70	56–58[f]	16	1.4411
B (1.12)	1.07	Cyclohexanone (1.02)	600	1.3[g]	1-Allylcyclohexanol[c2]	48	70–72[h]	8	1.4761[h]
B (1.65)	1.7	Ethyl carbonate (0.5)	600	0.8	Triallylcarbinol	70	68–70[i]	8	1.4685[i]
C (1.37)	2.14	Ethylene oxide (1.3)	650	4[j]	4-Pentenol	72	134–136[k]	Atm.	1.4288[k]
B (0.21)	0.214	Ethylene oxide (0.2)	60	0.5[l]	4-Pentenol	41	132–136[k]	Atm.	1.4320[k]
B (1.24)	1.44	1,2,5,6-Tetrahydrobenzaldehyde (1.0)	400	1.7	α-Allyl-3-cyclohexene-1-methanol[c3]	72	109–111[m]	16	1.4922[m]
C (0.55)	0.56	Ethyl formate[n] (0.25)	265	1.2	Diallylcarbinol[o]	52	51–52[p]	13	1.4479
B (1.25)	1.44	Tetramethyl-1,3-cyclobutanedione (0.5)	500	2	5-Allyl-5-hydroxy-2,4,4-trimethyl-7-octen-3-one (2)[q]	61	81–84	0.35	1.4723

[a] B = allyl bromide; C = allyl chloride. [b] Ref. 15 reports b.p. 62–65° (50 mm.), $n^{25}D$ 1.4440. [c] Previously made using the Barbier–Grignard procedure. Yields: (1) 39% (ref. 5), 70–75% (ref. 6), 70% (ref. 14); (2) 81% (ref. 9), 31% (ref. 10); (3) 85% (ref. 7). [d] Crude yield 82%, b.p. 103–115°, $n^{25}D$ 1.4242. [e] Ref. 1 reports b.p. 118.0–118.2°, $n^{2c}D$ 1.4263. [f] S. B. Schryver, *J. Chem. Soc.*, **63**, 1327 (1893), reports b.p. 151–153°. [g] Refluxed for 5 hr. after addition of reactants. [h] Ref. 10 reports b.p. 69–71° (5 mm.), $n^{22}D$ 1.476. [i] B. N. Dashkevich, I. V. Smolanska, and Yu. Yu. Tsmur, *Nauch. Zap., Uzhgorodsk. Gos. Univ.*, **22**, 81 (1957); *Chem. Abstr.*, **54**, 14100*f* (1960), report b.p. 72–73° (16 mm.), $n^{20}D$ 1.4650. [j] The reaction was terminated before the addition of reagents was complete because a nonstirrable gel formed. Dilution with ether did not help. The amounts of reactants shown are those actually added. [k] L. A. Brooks and H. R. Snyder, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 698, report b.p. 134–137°; L. E. Schniepp and H. H. Geller, *J. Am. Chem. Soc.*, **67**, 54 (1945), report b.p. 139–140°, $n^{25}D$ 1.4270. [l] A stirrable reaction mixture was observed throughout. [m] Ref. 7 reports b.p. 96–97° (7 mm.), $n^{20}D$ 1.4940. [n] Purified by the method of G. H. Coleman and D. Craig, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 179. [o] 3,5-Dinitrobenzoate, m.p. 61–62°; J. L. Everett and G. A. R. Kon, *J. Chem. Soc.*, 3131 (1950), report m.p. 62–63°. As in an analogous reaction, Coleman and Craig, footnote *n*, the diallylcarbinol was contaminated with a carbonyl containing impurity. Ten grams were purified by the method of Coleman and Craig to give 7.2 g. of carbonyl free diallyl carbinol, b.p. 50.5–51° (12 mm.), $n^{25}D$ 1.4490. [p] Everett and Kon, footnote *o*, report b.p. 49–51° (16 mm.). [q] *Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 74.95; H, 10.78. Found: C, 74.83, 75.06; H, 10.71, 10.89. In addition, 23 g. of lower boiling material was obtained. This was shown (p.m.r.) to consist of diisopropyl ketone and diallyl ketone in approximately equivalent amounts.

Diisopropyl ketone and diallyl ketone (contaminated with some allyl propenyl ketone) were isolated in 83% yield each. It is interesting to note that the rather simple ketone, diallyl ketone, has not previously been reported. Its structure follows from its reduction to the known diallyl carbinol and from its completely consistent p.m.r. spectrum. The p.m.r. and ultraviolet spectra of the yellow diallyl ketone suggested that about 10% of the diallyl ketone had rearranged to allyl propenyl ketone during the course of its preparation and isolation. This was not unexpected, since it is reported[7] that ethyl allyl ketone isomerizes to ethyl propenyl ketone merely upon fractionation (130°). However, it was observed that 2 could also be cleaved thermally *without* base catalysis. The cleavage was slower, but the yields were substantially the same and the diallyl ketone so obtained was colorless and found to contain at most traces of the rearranged ketone. Thus, not surprisingly, the rearrangement of diallyl ketone to allyl propenyl ketone appears to be base-catalyzed.

The Barbier–Grignard method has been shown to be a convenient method for utilizing the allyl Grignard reagent, but it is probably also applicable to Grignard reactions not involving allyl halides. In fact, as long ago as 1911, Davies and Kipping[17] reported the successful application of the Barbier–Grignard method to benzyl and ethyl halides. They also pointed out the need for first starting the reaction with a small amount of the halide. Benzyl halide can be thought of as being rather analogous to allyl halide, but the success with ethyl halide suggests the technique may have general application in the Grignard reaction. Indeed it would seem that the work of Davies and Kipping has never received the attention it merits.

(17) H. Davies and F. S. Kipping, *J. Chem. Soc.*, **99**, 296 (1911).

Experimental[18]

Allylic Carbinols by the Barbier–Grignard Procedure, General Method.—A solution of a few grams of allyl bromide or chloride and a few crystals of iodine in about 30% of the ether to be used was added to the magnesium turnings in a flask which had been flamed and purged with nitrogen. When the allyl halide was reacting smoothly with the magnesium, addition of a solution to the rest of the allyl halide and the functional addend in ether was started. Addition was carred out at a rate to maintain gentle reflux of the ether while cooling with ice–water. The reaction mixture was refluxed for 1–2 hr. after the addition was complete. The product was isolated by the method commonly used[2c] for Grignard reactions and after removal of the ether the crude product was distilled through a 6-in. vacuum jacketed Vigreux column fitted with a variable take-off head. The quantities employed, the yields, and the properties of the allylic carbinols prepared are summarized in Table II.

Starting the Reaction.—A solution of a few crystals of iodine and 2 g. of allyl bromide in 50 ml. of ether was added to 14 g. of magnesium. Reaction set in with virtually no induction and a solution of 29 g. of acetone and 65 g. of allyl bromide in 150 ml. of ether was then added smoothly. In a parallel reaction a solution of a few crystals of iodine in 50 ml. of ether was added to 14 g. of magnesium. The iodine color dispersed almost immediately, but on addition of about 20 ml. of a solution of 29 g. of acetone and 67 g. of allyl bromide in 150 ml. of ether, no reaction could be induced even after refluxing for 1.5 hr. The reaction was started by adding small portions of an approximately 1 *M* ethereal solu-

(18) Melting points and boiling points are uncorrected. Starting materials were commercial reagent chemicals used without further purification unless otherwise indicated. Analyses are by Huffman Microanalytical Laboratories, Wheatridge, Colo.

tion of ethylmagnesium bromide. About 35 ml., or approximately enough to react with the acetone present, was added before a self-sustaining reaction set in. The remainder of the acetone–allyl bromide solution was then added without further difficulty.

Structure of 5-Allyl-5-hydroxy-2,4,4-trimethyl-7-octen-3-one (2).—A mixture of 22.7 g. of **2** and 0.2 g. of $Ba(OH)_2$ was heated in a 125–140° oil bath at a pressure of 20 mm. Distillate, b.p. 43–50° (20 mm.), was collected as it formed; 21.1 g. was collected in 90 min. Fractionation of 30.7 g. of such pyrolysate through a spinning-band column at 20 mm. gave (1) 13.6 g., 31–32°, $n^{25}D$ 1.3992; (2) 3.0 g., 36–51°, $n^{25}D$ 1.4410; and (3) 10.5 g., 51–53°, $n^{25}D$ 1.4421. Fractions 2 and 3 were yellow. Fraction 1 was identified as diisopropyl ketone by its characteristic p.m.r. spectrum, fraction 2 by p.m.r. analysis contained 8% diisopropyl ketone, 69% diallyl ketone, and 23% allyl propenyl ketone, and fraction 3 similarly contained 1% diisopropyl ketone, 91% diallyl ketone, and 8% allyl propenyl ketone. Fraction 3 showed a λ_{max} 225 mμ (isooctane); this is consistent with the presence of allyl propenyl ketone rather than dipropenyl ketone since the latter is reported[19] to have a λ_{max} 245, 251 mμ.

Fraction 3 did not give a sharp melting 2,4-dinitrophenylhydrazone or semicarbazone. However, treatment of 3 g. of fraction 3 with 0.5 g. of lithium aluminum hydride in 20 ml. of ether yielded 1.9 g. of diallyl carbinol, b.p. 53–54° (14 mm.), $n^{25}D$ 1.4490, 3,5-dinitrobenzoate m.p. 60.5–61.5°, m.m.p. 60–61.5° with an authentic sample. The infrared spectrum of this diallyl carbinol was identical with a spectrum of the material independently prepared (see Table II).

It was found that **2** would cleave thermally without base-catalysis, but somewhat more slowly. Compound **2**, 11.2 g., was heated in a 130–160° oil bath at a pressure of 15 mm. and distillate, 10.0 g., was collected at 40–65° over a period of 5 hr. Fractionation through the spinning-band column at 15 mm. gave (4) 4.8 g., 24–25°, $n^{25}D$ 1.3982; (5) 0.8 g., 37–46°, $n^{25}D$ 1.4362; and (6) 3.5 g., 46–47°, $n^{25}D$ 1.4420. All fractions were colorless but fractions 5 and 6 yellowed on storage in soft glass containers. By p.m.r. analysis fraction 4 was substantially pure diisopropyl ketone; fractions 5 contained 13% diisopropyl ketone, 84% diallyl ketone, and 3% allyl propenyl ketone; and fraction 6 appeared to be better than 99% diallyl ketone and contained only traces of diisopropyl and allyl propenyl ketone. The λ_{max} at 225 mμ was absent in the ultraviolet spectrum of fraction 6.

Anal. of fraction 6. Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 75.86, 76.04; H, 9.18, 9.24.

A 2,4-dinitrophenylhydrazone of fraction 6 was readily obtained, dark red platelets, m.p. 133–135°, from ethanol.

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.78, 53.91; H, 5.47, 5.31; N, 19.48, 19.18.

Acknowledgment.—The author wishes to thank Dr. J. C. Westfahl for the determination and interpretation of the p.m.r. spectra and Dr. F. W. Shaver and Dr. J. C. Westfahl for many helpful discussions.

(19) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2078 (1951).

Rates and Relative Rates of Chloro- and Iododesilylation. Evidence for a Four-Center Transition State

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Received July 8, 1963

Recently, the mechanisms of cleavage of carbon–metalloid bonds have received considerable attention.[1-3] The major uncertainty in the description of the activated complex for these reactions involves the significance to be ascribed to four-center interactions. As an approach to this problem we have evaluated the effectiveness of iodine monochloride and chlorine as reagents for desilylation of phenyltrimethylsilane.

The reaction between phenyltrimethylsilane and iodine monochloride in dry acetic acid at 25° yields iodobenzene and hexamethyldisiloxane as the only detectable products in greater than 90% yield.

Observations obtained in a typical kinetic experiment are presented in Table I.

The failure of second- or third-order rate laws to accommodate the data, Table I, and the observations of other kinetic studies[4] of iodination suggested the effective concentration of iodine monochloride was reduced by complex formation.

$$ICl + Cl^- \overset{K}{\rightleftharpoons} ICl_2^-$$

Rate law based on this equilibrium and a second-order rate-determining reaction between iodine monochloride and phenyltrimethylsilane is the following.

$$ICl + PhSiMe_3 \xrightarrow{k} \text{products}$$

$$\frac{-d[ICl]}{dt} = \frac{k[PhSiMe_3][ICl]}{1 + K[Cl^-]} \qquad (1)$$

where [ICl] is the titrimetric concentration. The calculated second-order rate constants, k, reported in Tables I and II are based on the known value, K = 250 l. mole^{-1}, for the equilibrium constant in acetic acid at 25°.[4] As illustrated in Table I, this rate law provides a good fit of the kinetic observations.[5]

Chlorodetrimethylsilylation by chlorine in 1.5% aqueous acetic acid at 25° was previously examined by Eaborn and Webster.[6] They report the reaction kinetics are satisfied by a second-order rate equation, but their typical data reveal the observed second-order rate constant decreases through the course of an experiment from an initial value of 5.3×10^{-2} to 2.8×10^{-2} l. mole^{-1} sec.$^{-1}$ at 85% reaction. In this study, dry acetic acid was adopted as the solvent for the reaction. It was found that the reaction obeyed second-order kinetics to 70–80% completion. The rate constant observed, 1.57×10^{-2} l. mole^{-1} sec.$^{-1}$, is somewhat less than reported by Eaborn and Webster. Presumably, the removal of water contributes to the reduction of the reaction velocity.[7]

Rate constants for iododesilylation and chlorodesilylation as determined in a series of independent experiments with different samples of phenyltrimethylsilane, iodine monochloride, and chlorine are summarized in Table II.

Comparison of the second-order rate constants indicates chlorodesilylation is eightfold less rapid than iododesilylation under identical conditions.[8] This finding contrasts sharply with the rate ratios observed

(1) R. E. Dessy and F. Paulik, *J. Chem. Educ.*, **40**, 185 (1963).

(2) C. Eaborn and D. E. Webster, *J. Chem. Soc.*, 179 (1960); R. W. Bott, C. Eaborn, and J. A. Water, *ibid.*, 681 (1963).

(3) C. Eaborn and D. W. Steward, *Proc. Chem. Soc.*, 59 (1963).

(4) L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **79**, 1412 (1957).

(5) The corresponding third-order rate equation, second-order in iodine monochloride with inhibition by chloride ions, does not accommodate the results.

(6) C. E. Eaborn and D. E. Webster, *J. Chem. Soc.*, 4449 (1957).

(7) L. M. Stock and A. Himoe, *J. Am. Chem. Soc.*, **83**, 1937 (1961).

TABLE I

KINETIC OBSERVATIONS AND DERIVED RATE CONSTANTS FOR IODODETRIMETHYLSILYLATION WITH IODINE MONOCHLORIDE IN ACETIC ACID AT 25°

Observations				Rate constants		
Time, sec.	Titer[a]	[ICl], M	[PhSiMe3], M	k_2,[b] l. mole^{-1} sec.$^{-1}$	k_3,[c] l.^{2} mole^{-2} sec.$^{-1}$	k,[d] l. mole^{-1} sec.$^{-1}$
0.0		0.0216	0.0890			
21	5.355	.0174	.0848	0.119	6.13	0.149
76	4.155	.0135	.0809	.073	4.34	.125
150	3.20	.0104	.0778	.059	4.06	.137
212	2.755	.0089	.0763	.051	3.86	.141
297	2.350	.0076	.0750	.043	3.61	.133
414	1.925	.0062	.0736	.038	3.56	.139

[a] Milliliters of 0.0342 N $Na_2S_2O_3$ required for 5-ml. aliquot. [b] Second-order rate constant. [c] Third-order rate constant, first-order in silane, second-order in iodine monochloride. [d] Second-order rate constant calculated on the basis of equation 1.

TABLE II

RATE CONSTANTS FOR IODODETRIMETHYLSILYLATION (ICl) AND CHLORODETRIMETHYLSILYLATION (Cl_2) IN ACETIC ACID AT 25°[c]

Initial concentration, M			Second-order rate constants, l. mole^{-1} sec.$^{-1}$	
[PhSiMe3]	[ICl]	[Cl2]	k[a]	10^2k_2
0.178	0.0216		0.135 ± 0.005	
.178	.00866		.109 ± 0.009	
.100	.0232		.123 ± 0.003	
.089	.0216		.137 ± 0.005	
.0820		0.0397		1.63 ± 0.02
.0954		.0192		1.53 ± 0.06
.0968		.00875		1.54 ± 0.06

[a] Equation 1.

TABLE III

RELATIVE RATES FOR THE SUBSTITUTION OF SILANE AND BENZENE DERIVATIVES

Substrate	Relative rate	
Toluene[a, b]	k_{Cl2}/k_{Br2}	200
Phenyltrimethylsilane[c, d]	k_{Cl2}/k_{Br2}	1.7 ± 0.4
p-Chlorophenyltrimethylsilane[c, d]	k_{Cl2}/k_{Br2}	2.7 ± 0.5
Toluene[e, f]	k_{Cl2}/k_{ICl}	200
Phenyltrimethylsilane[g]	k_{Cl2}/k_{ICl}	0.13 ± 0.02

[a] In aqueous acetic acid solvents, reaction of mixed second- and third-order for bromination but second-order for chlorination. [b] See ref. 9. [c] In acetic acid with 1.5% water, reaction of mixed second- and third-order for bromination, but second-order for chlorination. [d] See ref. 6. [e] In trifluoroacetic acid at 25°, reaction is second-order for both iodination and chlorination. [f] See ref. 4, 10. [g] In acetic acid at 25°, second-order rate constants compared.

for electrophilic substitution in benzene. Some pertinent data are summarized in Table III.

Comparisons of the reactivity of the halogens are often complicated by uncertainties in the order of the reactions. The problem is evident for noncatalytic bromination and chlorination in acetic acid media, Table III. It is certain, nevertheless, that chlorine is a much better electrophile than bromine with benzene derivatives.[9] The large difference in the electrophilic reactivity of these halogens is appreciably reduced with phenyltrimethylsilane as a reference substrate. This fact has been most reasonably interpreted to be a consequence of the decreased selectivity of the more nucleophilic silane.[6]

The iodination of benzenes and its derivatives by iodine monochloride is far less rapid than the rates for noncatalytic bromination or chlorination. Because of the slowness of this reaction only a few kinetic observations have been reported. The large relative rate, k_{Cl_2}/k_{ICl} 200, found for the reactions with toluene in trifluoroacetic acid is presumably typical. This relative rate should decrease with the less selective phenyltrimethylsilane as a reference substrate. However, if selectivity effects are dominant the value must remain greater than one. The relative rate for chloro- and iododesilylation, 0.13, indicates other influences are more significant than selective properties of the substrate.

The large variation in the effectiveness of iodine monochloride relative to chlorine in reactions with C–H and C–Si bonds suggests the transition states for the reactions are quite dissimilar. For the C–H bond, the available information for iodination favors the view that the reaction proceeds through an activated complex which approaches the character of a benzenonium ion. This model is inadequate for iododesilylation. The relative rate variation and the polarizability of iodine monochloride prompts the suggestion that iododesilylation occurs with an important additional interaction between silicon and chlorine in a four-center transition state.[1,3] Four-center processes for other desilylations by dipolar or polarizable reagents in nondissociating solvents may be expected to be significant.

Experimental

Materials.—Phenyltrimethylsilane was prepared by the reaction of phenyl Grignard reagent with chlorotrimethylsilane and by the reaction of methyl Grignard reagent with phenyltrichlorosilane. Each product was carefully fractionated to yield material homogeneous to vapor phase chromatography, $n^{26}D$ 1.4880. Iodine monochloride was prepared from the elements and purified by fractionation, b.p. 103–105° at atmospheric pressure. This reagent was prepared and distilled just prior to each kinetic experiment. Chlorine (Matheson, 99.5%) was used without further purification. Acetic acid (Baker and Adamson reagent grade) was distilled in a column packed with glass helices in a dry atmosphere. Other reagents were employed as commercially available.

Kinetic Measurements.—The reaction rates were followed by conventional iodometric procedures.[7] Typical results and a summary of typical observations are reported in Tables I and II.

Reaction Products.—An examination of the products of the reaction was carried out by vapor phase chromatographic analysis. Comparison of the ratios of areas, chlorobenzene to residual phenyltrimethylsilane and iodobenzene to residual phenyltrimethylsilane indicated the reactions to be virtually quantitative.

(8) Competitive experiments indicated the relative rate k_{Cl2}/k_{ICl} to be 0.22. The competitive method, however, is not a valid technique for the assessment of the relative rate in this case because of the importance of complexation of ICl as ICl_2^-, the presumed formation of ICl_3, a chlorinating agent, and the possible catalysis of chlorination by ICl. In view of these difficulties the value determined in the competition experiments is useful only as a confirmation of the lesser reactivity of chlorine.

(9) See P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," Butterworths Scientific Publications, London, 1959, Chap. 9.

(10) A. Himoe and L. M. Stock, unpublished results.

TABLE IV.—COMPETITIVE EXPERIMENTS OF ICl AND Cl_2 FOR PHENYLTRIMETHYLSILANE IN ACETIC ACID AT 25°

Concentration, $10^3 M$						
$[PhSiMe_3]_i$	$[Cl_2]_i$	$[ICl]_i$	$[HCl]_f$	$[PhI]_f$	Reaction, %	k_{Cl_2}/k_{ICl}
16.9	69.2	74.6	6.6	5.5	39.1	0.23
12.7	51.9	112	8.8	8.0	69.0	0.21
12.7	104	56	5.1	3.5	40.0	0.21

The response of the detector to the halobenzene and phenyltrimethylsilane was shown to be in accord with the molar concentrations of these substances by the analysis of known mixtures. Chlorobenzene was not detected among the products of the iododesilylation reaction.

Competitive Measurements.—Several competitive experiments were performed to achieve a confirmation of the greater reactivity of iodine monochloride (see ref. 8). An attempt was made to avoid the inhibition of the iododesilylation reaction by hydrogen chloride through the adoption of a short reaction time (about 100 seconds). This approach, however, was not successful. It is pertinent to recognize that a 10% increase in the amount of iodobenzene produced would yield relative rate data in good agreement with the kinetic observations. The results of three experiments are summarized in Table IV.

Acknowledgment.—It is a pleasure to acknowledge the partial support of the Petroleum Research Fund administered by the American Chemical Society.

The Isolation of a New Diterpene Acid

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Recieved May 6, 1963

A bicyclic diterpene acid has been isolated from the acid fraction of slash pine oleoresin (*Pinus elliotti*). This new acid, termed elliotinoic acid, was isolated by partition chromatography on a silicic acid column by the method described by Loeblich, Baldwin, and Lawrence.[2] Elliotinoic acid collected from the silicic acid column was found to be essentially pure. Several batches of slash pine oleoresin and rosin were examined and elliotinoic acid was present in all samples and was the only acid eluted in fractions 16–21. Elliotinoic acid accounts for about 5% of the acid fraction of slash pine oleoresin. The new acid resisted all efforts to crystallize it and was quite sensitive to oxidation.

Elliotinoic acid was reduced with lithium aluminum hydride to the previously reported elliotinol.[3,4] On analysis by gas–liquid chromatography, elliotinol prepared by the lithium aluminum hydride reduction of elliotinoic acid and a sample of elliotinol isolated from the neutral fraction of slash pine oleoresin were found to have the same emergence time on a silicone (SE-30) column and on mixing in equal parts only one peak was obtained. The infrared spectra, optical rotation, and melting points of the two samples of elliotinol were identical. A mixture melting point of the two samples showed no depression. The elliotinyl *p*-nitrobenzoate derivative prepared from the two samples of elliotinol had identical infrared spectra, optical rotation, and melting points, alone and when mixed.

Elliotinoic acid and elliotinol are present in about equal amounts and together account for about 10% of the slash pine oleoresin. These two compounds are the first bicyclic diterpenes isolated from the oleoresin of the slash pine.

(1) Part of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) V. M. Loeblich, *et al*, *J. Am. Chem. Soc.*, **77**, 2823 (1955).

(3) E. McC. Roberts and R. V. Lawrence, Abstracts of Papers, 131st National Meeting of the American Chemical Society, Miami, Fla., April, 1957, p. 21-O.

(4) M. Tsutsui and E. A. Tsutsui, *Chem. Rev.*, **59**, 1046 (1959).

Experimental

Isolation of Elliotinoic Acid from Rosin.—A sample containing 2.50 g. of WW slash rosin in 10 ml. of isooctane was put on a silicic acid column.[2] Fractions (100-ml.) were collected and an aliquot of each was titrated. Elliotinoic acid was eluted in fractions 16–21. These fractions were combined, washed with water, and dried. The solvent was removed under reduced pressure and the dry residue dissolved in isooctane. A sodium hydroxide solution (3 *N*) was added dropwise with constant stirring until there was no further salt precipitation. The sodium elliotinate was filtered and dried under reduced pressure. Snow white plates of sodium elliotinate (0.12 g.) were recrystallized from hot water until the melting point, ultraviolet absorption, and optical rotation were constant: m.p. 387–389° (sealed evacuated tube); $\lambda_{max}^{alcohol}$ 233 mμ (ε 27,500); $[\alpha]^{25}D$ +42° (*c* 0.5, in alcohol).

Anal. Calcd. for $C_{20}H_{29}O_2Na$: C, 74.1; H, 9.0; Na, 7.1; neut. equiv., 324. Found: C, 74.2; H, 8.9; Na, 7.0; neut. equiv., 320.

Sodium elliotinate (0.10 g.) was suspended in ether and acidified with 3 *N* phosphoric acid. The ether solution was washed neutral, dried, and the ether removed. The residue (0.08 g.) was sublimed onto a cold finger at 120° (5 μ). The sublimate was a clear colorless oil; $[\alpha]^{25}D$ +40° (*c* 1.0, in alcohol); $\lambda_{max}^{alcohol}$ 232 mμ (ε 28,900); neut. equiv., 302.

Preparation of Elliotinol from Elliotinoic Acid. A.—An ether solution containing 0.10 g. of sodium elliotinate was added slowly to an excess of lithium aluminum hydride solution. The mixture was allowed to stand overnight and water was added to destroy the excess lithium aluminum hydride. The solution was filtered and the solvent removed under reduced pressure. The oily residue was subiimed at 140° (10 μ) onto a cold finger. The alcohol crystallized in long needles on the bottom of the cold finger; m.p. 14–15°; $\lambda_{max}^{alcohol}$ 232 mμ (ε 20,600); $[\alpha]^{25}D$ +14° (*c* 2.0, in alcohol).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.4; H, 10.9.

B.—Elliotinyl *p*-nitrobenzoate (2.30 g.), prepared from slash pine neutrals,[3] was saponified by refluxing in alcoholic potassium hydroxide. Water was added and the elliotinol extracted with ether. The ether was removed under reduced pressure to leave a yellow viscous oil (1.29 g.). A pentane solution of the oil was put through a short column of silicic acid to give 0.89 g. of a colorless viscous oil. Vacuum sublimation of this oil onto a cold finger gave pure elliotinol with infrared spectrum, optical rotation, and melting point (alone and mixture) identical with the alcohol prepared from elliotinoic acid.

Preparation of Elliotinyl *p*-Nitrobenzoate. A.—A dry pyridine (4 ml.) solution of 0.55 g. of the alcohol obtained by the lithium aluminum hydride reduction of elliotinoic acid was stirred at room temperature with *p*-nitrobenzoyl chloride for 6 hr. The resulting solution was poured over crushed ice and the water decanted. The yellow gummy precipitate crystallized from boiling 95% ethanol; m.p. 116–121°. Two crystallizations from 95% ethanol gave the pure ester; m.p. 128–130°; $[\alpha]^{25}D$ +74° (*c* 2.0 in alcohol).

Anal. Calcd. for $C_{27}H_{35}O_4N$: C, 74.1; H, 8.0. Found: C, 73.9; H, 8.0.

B.—Slash rosin neutrals (2.3 g.) in 7.0 ml. of pyridine on stirring with *p*-nitrobenzoyl chloride gave 0.63 g. of crude elliotinyl *p*-nitrobenzoate, m.p. 116–122°. Two recrystallizations from 95% ethanol gave 0.45 g. of the pure ester whose infrared spectrum, optical rotation, and melting point (alone and mixture) were identical with the ester of the alcohol prepared by the reduction of elliotinoic acid.