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Synthesis and Reactions of 3-Methylcyclobutene

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The synthesis of 3-methylcyclobutene (XII) was accomplished by two different methods, one involving thermal decomposition of N,N-dimethyl-3-methylcyclobutylamine oxide and the other, base detosylation of *trans*-2-tosyloxy-1-methylcyclobutane. In the presence of a sodium–alumina catalyst, at 5°, XII yields an equilibrium mixture containing 1-methylcyclobutene (85.5%), methylenecyclobutane (14.5%), and XII (less than 0.02%). Thermal isomerization of XII proceeds between 160 and 250° giving stereospecifically *trans*-1,3-pentadiene as the sole product. Mechanistic aspects of the ring cleavage and some other reactions of XII are discussed.

In view of the extensive recent work[1] on small ring compounds, it is noteworthy that one of the simplest derivatives of cyclobutene, *i.e.*, 3-methylcyclobutene (XII), has not yet been synthesized. Probable formation of the compound has, however, been reported by the authors,[2] and more recently by Srinivasan.[3] The difficulty of obtaining monosubstituted cyclobutenes with the substituent in the 3-position is illustrated by the reported[4] failure of cyclobutene to undergo Ziegler bromination to an extent useful for preparative purposes.

Synthesis of XII is of particular interest for the study of the stability relationships of cyclic olefins having a four-membered ring. Recent experiments[5] have shown that XII is not produced in more than trace amounts during the base-catalyzed equilibrium isomerization of methylenecyclobutane and 1-methylcyclobutene. The formation of XII appeared, therefore, to be highly unfavorable energetically.

Another interesting aspect of the chemistry of cyclobutenes is thermal isomerization,[2,6,7] which results in the formation of an open-chain diene. In the case of XII, splitting of the ring at the biallylic position should yield 1,3-pentadiene and could conceivably be stereospecific,[7] giving only one of the two possible isomers.

Preparation of XII was accomplished by two different routes, one involving in its final step thermal decomposition of N,N-dimethyl-3-methylcyclobutylamine oxide (XI) and the other, base detosylation of *trans*-2-tosyloxy-1-methylcyclobutane (XIV).

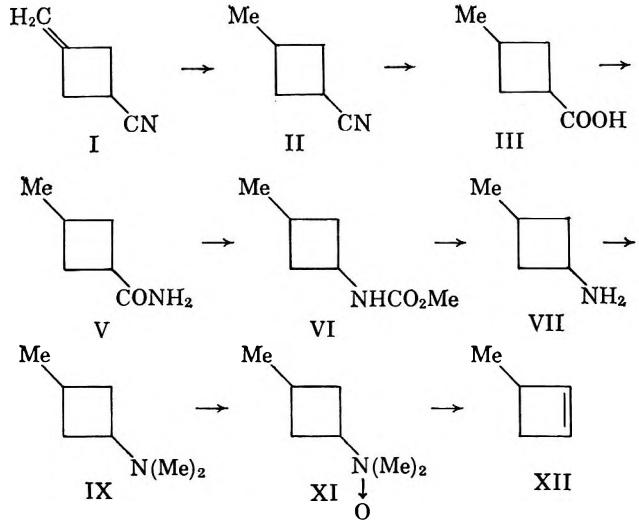
The scheme for the synthesis *via* the amine oxide is given in Chart I. 3-Methylcyclobutanecarboxylic acid (III) was prepared by cycloaddition of allene to acrylonitrile according to Cripps, *et al.*,[8] and selective hydrogenation of the resulting methylenecyclobutanecarbonitrile (I), followed by hydrolysis. Using the procedure of Kazanskii and Lukina,[9] the acid was converted into the amide (V). Hofmann reaction to obtain amine VII has to be carried out by first preparing[10] the urethane (VI), followed by hydrolysis with calcium hydroxide.[11] The amine (VII) was converted to the desired olefin *via* the amine oxide (XI) of the N,N-dimethyl derivative (IX). Decomposition of XI proceeds slowly at 130–135° with a yield of 88%. After washing with dilute hydrochloric acid to eliminate the dimethylhydroxylamine formed in the decomposition, the olefin was examined by gas chromatography and found to be 97% pure. No isomers of XII such as 1-methylcyclobutene or pentadiene were present in the product.

The structure of XII was proved by oxidation[12] to α-methylsuccinic acid, which was identified by conversion to the diphenacyl ester, m.p. 101–102° (lit.[13] m.p. 101–101.5°).

The structure was also confirmed by n.m.r. The spectrum showed (1) a doublet at 1.14 p.p.m. (J = 7 c.p.s.), due to the secondary methyl group; (2) a complex of lines between 1.9 and 2.9 p.p.m., assigned to the allylic protons; and (3) a closely spaced group of lines centered at 6.0 p.p.m., due to the vinylic protons.

(1) E. Vogel, *Angew. Chem.*, **72**, 4 (1960).
(2) J. Herling, J. Shabtai, and E. Gil-Av, *Bull. Res. Council Israel*, **11A**, 20 (1962).
(3) R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 4141 (1962).
(4) E. R. Buchman and D. R. Howton, *ibid.*, **70**, 3510 (1948).
(5) E. Gil-Av and J. Herling, *Tetrahedron Letters*, **No. 1**, 27 (1961).
(6) H. M. Frey, *Trans. Faraday Soc.*, **58**, 957 (1962).
(7) E. Vogel, *Ann.*, **615**, 14 (1958).
(8) H. N. Cripps, J. K. Williams, and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 2723 (1959).
(9) B. A. Kazanskii and M. Yu. Lukina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 47 (1951).
(10) *Cf.* E. S. Wallis and J. F. Lane, "Organic Reactions," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 289.
(11) E. Jeffreys, *Ber.*, **30**, 898 (1897); N. Zelinskii and J. Gutt, *ibid.*; **40**, 4744 (1907).
(12) E. von Rudloff, *Can. J. Chem.*, **34**, 1413 (1956).
(13) I. M. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. III, Eire and Spottiswoode, London, 1953, p. 509.

CHART I



The relative intensities of the three groups of lines were in the ratio 3:3:2, respectively.

It should be pointed out that on hydrogenation of the methylene group of I both the *cis*- and *trans*-3-methylcyclobutanecarbonitrile may be formed.[14] Hence compounds II–XI should be mixtures of two substances. Separation of such geometric isomers could not be achieved in all cases, even though gas chromatography with capillary columns was employed (see Analytical). Resolution into two distinct peaks was observed in the case of compounds VII, IX, and the methyl ester of III.

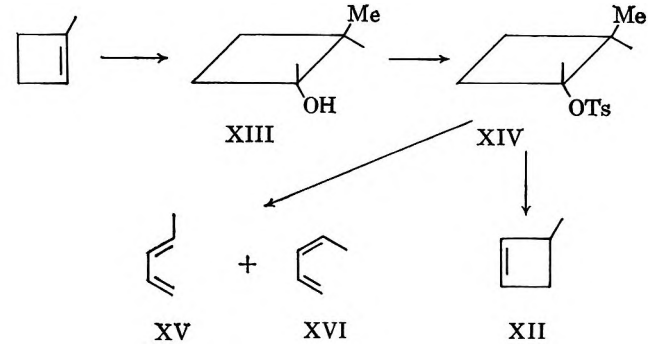
The second approach to XII is outlined in Chart II. It represents an extension of the recently developed method of Brown and Zweifel[15] for the synthesis of 3-alkylcyclenes to four-membered ring derivatives. According to Brown and Zweiel hydroboration of 1-methylcyclobutene should give practically pure *trans*-2-methylcyclobutanol (XIII). Gas chromatography on a capillary column of the alcohol obtained showed indeed a main peak representing 95% of the material. As found[15] in the case of corresponding, larger ring homologs, 3-methylcyclobutene is formed in the detosylation of XIV to the exclusion of any trace of 1-methylcyclobutene. On the other hand, ring opening also takes place yielding *trans*-1,3-pentadiene (XV), as well as a small amount of the *cis* isomer (XVI). This undesirable competing reaction can be reduced in importance by operating at 130–135°, at which temperature a product containing XII (53%), XV (40%), and XVI (7%) was obtained. At 150°, however, the yield of XII already drops to less than 10%. The presence of XII was established by gas chromatography (see Analytical), as well as by oxidation of the reaction mixture and isolation of α-methylsuccinic acid in the form of its diphenacyl ester.

Selective formation[15] of 3-methylcyclenes from the corresponding *trans*-2-tosyloxymethylcyclanes can be understood readily, for instance, in the case of the cyclohexane derivative, where the leaving groups are in the favorable *anti* position. However, in the four-membered ring compound XIV the relative disposition of the bonds involved in the reaction is less favorable for

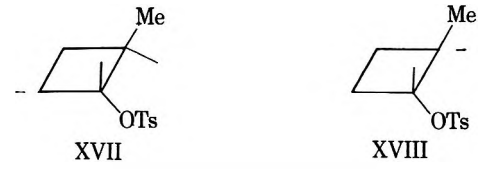
(14) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 3671 (1961).

(15) H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961).

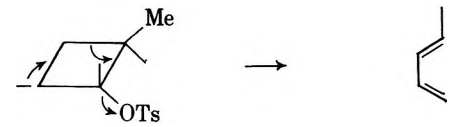
CHART II



E2 elimination. The detosylation of XIV could, therefore, proceed in part or entirely through a nonconcerted mechanism. An intermediate carbanion, such as XVII, arising by the action of the base (sodium isoamylate) on the substrate, will give XII on losing the tosyloxy group, but none of the isomeric 1-methylcyclobutene. It can be argued that the selectivity of the reaction by such a two-step mechanism is due to the higher stability of the secondary carbanion XVII and the lesser steric hindrance to its formation as compared with the alternative tertiary carbanion XVIII.



The competing ring-opening reaction leading to pentadiene may be regarded as a 1,4 elimination, which could equally proceed through the carbanion XVII.



Experiments were carried out with compound XII under the conditions of detosylation, but in the absence of sodium isoamylate. No reaction was observed even when the temperature was raised to 145° and the contact time prolonged up to 10 min. These results exclude the possibility that the 1,3-pentadienes arise by thermal splitting of XII, following detosylation.

As mentioned earlier, *cis*-1,3-pentadiene (XVI) is formed in unimportant amounts compared with the *trans* isomer (XV), ratio, ~1:6, although the former is thermodynamically more stable.[16] Since 1,3-pentadienes were found to isomerize slowly under the conditions of detosylation, it is probable that the small amount of XVI present is essentially a secondary product derived from XV. It thus appears that the ring opening proceeds stereospecifically, as also has been found to be the case for the thermal cleavage of XII (following). The absence of 1-methylcyclobutene and methylenecyclobutane in the product shows that XII does not isomerize under the conditions of detosylation.

Base-Catalyzed Isomerization of 3-Methylcyclobutene (XII).—It has been reported[5] previously that on equilibration of 1-methylcyclobutene and methylenecy-

(16) F. D. Rossini, "Physical Chemistry of the Hydrocarbons," A. Farkas, Ed., Academic Press, New York, N. Y., 1950, p. 425.

clobutane in the presence of a sodium–alumina catalyst[17] not more than a trace of XII was possibly formed. After XII became available, this observation was checked by approaching the equilibrium from this compound. The isomerization was carried out at 5° in pure 2,4-dimethylpentane as solvent, using the above-mentioned catalyst. The reaction was followed by gas chromatography, and it was found that XII is gradually transformed into its double bond isomers. After 5 hr. of reaction time the following constant composition was reached: 1-methylcyclobutene, 85.5%, methylenecyclobutane, 14.5%, and XII, <0.02%.

The difference in the stability of the two endocyclic isomers is in keeping with similar behavior of corresponding pairs of larger ring homologs. Thus, it has been found[18] that at 25° the ratio of the 1-methyl to the 3-methyl isomers is about 30 for the cyclohexene and about 60 for the cyclopentene derivatives. Qualitatively the higher stability of the 1-methyl compounds can be understood in terms of hyperconjugation and weaker nonbonded interaction with adjacent hydrogens. As ring size is decreased, one would also expect a lowering of the relative stability of the 3-methyl isomer due to increased nonbonded interactions of the methyl group. However, the magnitude of the effect observed in the four-membered ring series (ratio of 1-methylcyclobutene to XII > 4000:1) seems higher than would be normally expected on the basis of the preceding considerations.

Thermal Isomerization of 3-Methylcyclobutene (XII).—Compound XII was pyrolyzed at several temperatures between 140–250° in a flow system, and the products were examined by gas chromatography. It was found that *trans*-1,3-pentadiene is formed as the sole product in all experiments.[19] As seen in Table I, XII undergoes reaction to an appreciable extent (8.2%) already at 160° and a contact time of 30 sec. On the basis of available kinetic data,[20] it was calculated that cyclobutene itself will isomerize to the extent of less than 2% under these conditions. Further, isomerization to the corresponding diene is faster for XII than for 1-methylcyclobutene (Table I, footnote *c*).

TABLE I

THERMAL ISOMERIZATION[a] OF 3-METHYLCYCLOBUTENE[b,c] INTO *trans*-1,3-PENTADIENE

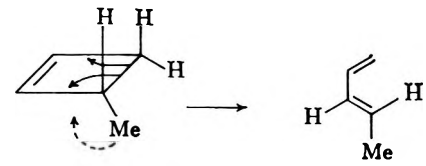
Temperature, °C.	Isomerization, %
140	None
160	8.2
180	55.0
200	90.7
250	100.0

[a] Contact time, 30 ± 2 sec. [b] A 10% solution of 3-methylcyclobutene in 2,4-dimethylpentane (>99% pure) was employed in the experiments; recovery was about 95%. [c] Under the same set of conditions 1-methylcyclobutene isomerizes into isoprene to the extent of 7.6% at 200° and 44.3% at 250°; *cis*-1,3-pentadiene remains unchanged at 250°.

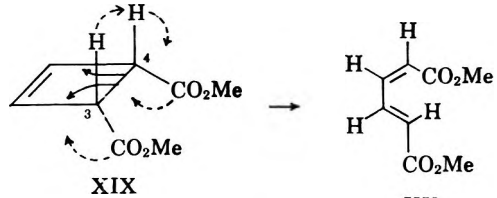
These results indicate that the methyl group in XII increases the ease of ring splitting at the biallylic position. This is in accord with the findings of Vogel,[7] who observed that introduction of allylic substituents in cyclobutene decreases the stability of the ring. It was reported,[7] for instance, that the dimethyl ester of *cis*-3,4-cyclobutenedicarboxylic acid is converted already at 120° to a mucconic acid ester.

The lower thermal stability of XII, as compared with cyclobutene, can be explained by increased Pitzer tension due to the methyl group in the 3-position. Further, if the ring opening at the C-3,C-4 bond proceeds through a transition state incorporating a biradical component,[21] it can be expected that the resonance stabilization of the activated complex is larger in the case of the substituted compound XII as compared with cyclobutene.[7]

The stereospecificity of the ring-opening reaction of XII, as expressed by the exclusive formation of *trans*-1,3-pentadiene, can be explained by preferred outward rotation of the relatively bulky methyl group in the splitting process. Such strain-relieving movement (marked with a dotted arrow) will lead to a *trans* configuration around the newly formed ($\Delta^{3,4}$) double bond in the open-chain product.



Vogel[7] has pointed out that pyrolysis of the dimethyl ester of *cis*-3,4-cyclobutenedicarboxylic acid (XIX) gives only one of the possible open-chain products, *i.e.*, the diester of *cis*-*trans*-mucconic acid (XX). This observation can likewise be explained by an oriented mode of relief from nonbonded interaction. The outward rotation of one of the ester groups, *e.g.*, at



XIX XX

the 3-carbon, causes a corresponding inward movement of the hydrogen at the same position. The repelling action of the latter hydrogen will then result in an outward movement of the vicinal hydrogen (at carbon 4) and in a corresponding inward rotation of the second ester group.

In extending this reasoning to *trans*-3,4-disubstituted cyclobutenes, it can be predicted that both substituents should turn outwards on ring opening.

Full support for the outlined mechanism is provided by the work of Criegee and Noll[22] on the pyrolysis at 200° of the *trans* and *cis* isomers of 1,2,3,4-tetramethylcyclobutene (XXI and XXIII, respectively). Both compounds are cleaved stereospecifically. As expected, XXI yields *cis,cis*-1,2,3,4-tetramethylbutadiene (XXII), while XXIII forms *cis,trans*-1,2,3,4-tetramethylbutadiene (XXIV).

(17) H. Pines and W. O. Haag, *J. Org. Chem.*, **23**, 328 (1958); W. O. Haag and H. Pines, *J. Am. Chem. Soc.*, **82**, 387 (1960).

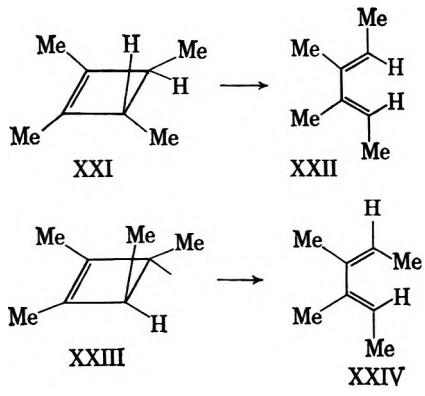
(18) J. Herling, Ph.D. thesis, Hebrew University, Jerusalem, 1961.

(19) This result supports the suggested[3] formation of XII by irradiation of 1,3-pentadiene.

(20) W. Cooper and W. D. Walters, *J. Am. Chem. Soc.*, **80**, 4220 (1958).

(21) C. T. Genaux, F. Kern, and W. D. Walters, *ibid.*, **75**, 6196 (1953).

(22) R. Criegee and K. Noll, *Ann.*, **627**, 1 (1959).



Bromination of 3-Methylcyclobutene (XII).—Compound XII absorbs 1 mole of bromine in carbon tetrachloride solution, giving $C_5H_8Br_2$. Gas chromatography on a capillary column showed the presence of two components in the ratio of 60:40. Since, normally, bromination proceeds by *trans* addition,[23] it can be assumed that the two compounds are 2-*cis*-3-*trans*-dibromomethylcyclobutane and 2-*trans*-3-*cis*-dibromomethylcyclobutane. Two minor peaks, representing about 2% of the total product, also were observed, indicating the possible occurrence of *cis* addition to a limited extent.

Experimental

3-Methylcyclobutanecarbonitrile (II).—A solution of allene (120 g., 3 moles) in toluene (60 ml.) reacted[8] with freshly distilled acrylonitrile (636 g., 12 moles) in a rocking bomb. The temperature was raised from −75° to 200° within 2 hr., resulting in a maximal autogenous pressure of about 3000 p.s.i. The total reaction time was 7 hr. The product was fractionated on a 20 cm. × 12 mm. column, packed with Dixon fillings to give 3-methylenecyclobutanecarbonitrile (I, 168 g., 60% yield), b.p. 66.5–67.5° (25 mm), $n^{25}D$ 1.4596; lit.[8] b.p. 64–65° (21 mm.), $n^{25}D$ 1.4595.

Nitrile I was selectively hydrogenated at 60 p.s.i., over a 10% palladium-on-charcoal catalyst in ethanol, to give compound II in practically quantitative yield. II of about 99% purity was obtained by distillation on the previous column, b.p. 66–67° (25 mm.), $n^{23}D$ 1.4265.

Anal. Calcd. for C_6H_9N: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.52; H, 9.63; N, 14.85.

3-Methylcyclobutanecarboxamide (V).—Compound II (140 g., 1.47 moles) was hydrolyzed by refluxing for 16 hr. with 20% aqueous sodium hydroxide (700 ml.). The product was acidified, saturated with sodium chloride, and continuously extracted with ether for 48 hr. The resulting 3-methylcyclobutanecarboxylic acid (III, 118 g., 70% yield) had b.p. 62–63° (0.5 mm.), $n^{25}D$ 1.4355; lit.[8] b.p. 108–108.5° (18 mm.), $n^{25}D$ 1.4351.

Thionyl chloride (48 g., 0.4 mole) and pyridine (0.1 ml.) were introduced into a flask and warmed at 55–60°. To this was added dropwise and with constant stirring acid III (42 g., 0.4 mole). After completing the addition, the liquid was heated on a water bath for 40 min. The 3-methylcyclobutanecarbonyl chloride (IV) obtained (44 g., 83% yield) had b.p. 147–148° (760 mm.), 74° (70 mm.), $n^{25}D$ 1.4425. The conversion of III to the chloride IV was checked by infrared spectroscopy which showed a shift[24] of the C=O frequency from 1715 cm.$^{-1}$ (in III) to 1798 cm.$^{-1}$ (in IV).

To a saturated solution of ammonia in dry ether (250 ml.), kept at −20°, was added with occasional shaking, a cold solution of chloride IV (20 g., 0.15 mole) in dry ether (40 ml.). After completing the addition, ammonia gas was passed through the reaction mixture for 15 min. The precipitate of 3-methylcyclobutanecarboxamide (V) was filtered, and recrystallized from acetone (14.5 g., 86% yield), m.p. 168°, lit.[9] m.p. 167°.

Methyl 3-Methylcyclobutylcarbamate (VI).—To a solution of V (11.3 g., 0.1 mole) in absolute methanol (65 g.), kept in a round-bottomed flask, was added a freshly prepared solution of sodium methoxide (4.6 g. of sodium in 115 g. of methanol). This was followed by the dropwise addition with constant stirring of bromine (16 g., 0.1 mole). The resulting solution was warmed for 10 min. on a water bath and, after cooling, brought to about pH 6 by adding glacial acetic acid. The solvent was removed and the methyl 3-methylcyclobutylcarbamate (VI) formed was extracted with ether, dried, and distilled (13.1 g., 92% yield), b.p. 63–64° (0.3 mm.), m.p. 26°, $n^{20}D$ 1.4550.

Anal. Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.45; H, 9.12; N, 9.78.

The structure of VI was confirmed by infrared spectroscopy. The CO absorption (amide I) band of the compound appears at 1725 cm.$^{-1}$, *i.e.*, in the frequency range characteristic of urethanes,[25] while the NH deformation (amide II) band appears, normally, at 1516 cm.$^{-1}$.

3-Methylcyclobutylamine (VII).—Urethane VI (14.3 g., 0.1 mole) was thoroughly mixed in a vibrating machine with freshly prepared, powdered calcium hydroxide (50 g.). The mixture was transferred to a round-bottomed flask, provided with a reflux condenser, and heated slowly in a metal bath up to a temperature of about 170°, at which point reflux started and the temperature of the mixture gradually dropped to 80–85°. The reflux was maintained for 30 min. and the amine produced was distilled and collected in a Dry Ice–acetone trap. At the end any residual amine was removed from the reaction flask at 25 mm. and collected in a liquid air trap. The product was distilled on the same column to separate the methanol, formed during the hydrolysis, from the 3-methylcyclobutylamine (VII, 6.1 g., 72% yield). Several batches of compound VII were united and redistilled to give a sample of more than 97% purity, as determined by gas chromatography, b.p. 99–100° (760 mm.), $n^{20}D$ 1.4310.

The two NH stretching absorption bands of VII appear in the vicinity of 3350 cm.$^{-1}$ (higher intensity) and 3500 cm.$^{-1}$ (lower intensity), while the NH deformation band appears, also normally,[26] at 1590 cm.$^{-1}$.

A small sample of VII was neutralized with 10% hydrochloric acid and the solution evaporated to dryness. The 3-methylcyclobutylamine hydrochloride (VIII) obtained was recrystallized from dry chloroform and washed with dry *n*-pentane, m.p. 166–167°.

Anal. Calcd. for $C_5H_{12}NCl$: C, 49.38; H, 9.95; N, 11.52; Cl, 29.16. Found: C, 49.43; H, 9.85; N, 11.30; Cl, 28.82.

N,N-Dimethyl-3-methylcyclobutylamine (IX).—Amine VII (8.5 g., 0.1 mole) was added dropwise to a 90% solution of formic acid (25.6 g., 0.5 mole) in a three-necked flask provided with a stirrer and a reflux condenser. To the resulting mixture was added a 37% solution of formaldehyde (22.5 ml., 0.3 mole) and the flask heated on a water bath until vigorous evolution of gas started. The flask was removed to allow the reaction to subside (20 min.) and then heated again at 95–100° for 8 hr. To the product was added 4 *N* hydrochloric acid (50 ml.) and the solution evaporated to dryness at 25 mm. The crystalline residue was dissolved in water and the amine liberated by the addition of aqueous sodium hydroxide and then extracted with ether. After removing the solvent, the N,N-dimethyl-3-methylcyclobutylamine (IX) was distilled on the same column (7.6 g., 67% yield), b.p. 111–112° (760 mm.), $n^{20}D$ 1.4194. The equivalent weight of IX, as determined by nonaqueous titration with perchloric acid, was 118 (theoretical, 113).

A small portion of IX was converted into N,N-dimethyl-3-methylcyclobutylamine hydrochloride (X) by the procedure given before. The compound, which was highly hygroscopic, was recrystallized from a mixture of dry chloroform and *n*-pentane and dried for a prolonged period.

Anal. Calcd. for $C_7H_{16}NCl$: C, 56.18; H, 10.78; N, 9.36; Cl, 23.68. Found: C, 55.90; H, 10.61; N, 9.49; Cl, 23.44.

N,N-Dimethyl-3-methylcyclobutylamine Oxide (XI).—To compound IX (5.1 g., 0.05 mole), dissolved in absolute methanol (30 ml.), was added 30% aqueous hydrogen peroxide (15 ml.) and the solution obtained was stirred at room temperature for 6 hr. An additional 8 ml. of the hydrogen peroxide was added and the stirring continued for another 18 hr., at which point a drop of the solution gave a negative test for free amine with phenol-

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

(24) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 125.

(25) Ref. 24, pp. 221–222.

(26) Ref. 24, p. 249.

phthalein. The excess of hydrogen peroxide was subsequently decomposed by stirring the solution for 24 hr. in the presence of a small amount of platinum black. The mixture was filtered and the filtrate concentrated at 35°, initially at 20 mm. and then at 1 mm. The N,N-dimethyl-3-methylcyclobutylamine oxide (XI, 5.4 g., 84% yield) was obtained completely dry by heating at 20 mm. and 100°. A small sample of XI was sublimed at 130° (20 mm.) to a white crystalline substance.

Anal. Calcd. for C_7H_5ON: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.69; H, 11.92; N, 10.84.

3-Methylcyclobutene (XII).—The dried compound XI (5.2 g., 0.04 mole) was mixed with Pyrex beads (2-mm. diameter) and heated at 20-mm. pressure in a 50-ml. round-bottomed flask connected to a series of two traps, the first cooled with Dry Ice–acetone and the second with liquid air. The temperature was raised gradually to 130° at which point slow decomposition of the amine oxide takes place. As sublimation tends to compete with the decomposition, it was necessary to interrupt the reaction several times and scrape down any white crystalline material accumulated around the neck of the flask. Decomposition into volatile products was complete in 4 hr., care being taken to keep the temperature below 135°.

The liquid condensed in the traps was washed several times with cold 5% hydrochloric acid, then with ice-cold water and finally dried over anhydrous magnesium sulfate. The 3-methylcyclobutene (XII) so obtained (2.4 g., 88% yield) had $n^{20}D$ 1.4005. The boiling point of XII, as determined by extrapolation of gas chromatographic data on a 10% silicone column, was 32.0°; the retention volume of XII relative to 2,4-dimethylpentane, at 30°, on the same column, was 0.26.

Oxidation of 3-Methylcyclobutene (XII).—Compound XII (68 mg., 1 mmole) and potassium carbonate (150 mg.) were added to 100 ml. of aqueous 60% *t*-butyl alcohol and stirred at 0–2° for 30 hr. with 90 ml. of the oxidant[12] (containing 98.3 mmoles of $NaIO_4$ and 1.7 mmoles of $KMnO_4$ per liter of solution). The product was acidified with dilute sulfuric acid and, after reducing the excess oxidant, continuously extracted with ether. The extract was evaporated to dryness and the crude acid obtained (120 mg.) was examined by infrared spectroscopy. The spectrum was essentially identical with that of a pure sample of α-methylsuccinic acid. A 100-mg. sample of the acid was esterified[27] with phenacyl bromide to give the diphenacyl ester (198 mg., 73% yield), which after recrystallization from ethanol had m.p. 101–102°, lit.[13] m.p. 101–101.5°; the derivative when mixed with an authentic sample showed no melting point depression.

***trans*-2-Methylcyclobutanol (XIII).**—Pure 1-methylcyclobutene[28] (13.6 g., 0.2 mole) and tetrahydrofuran (130 g.) were placed in a three-necked flask, equipped with a condenser, a thermometer, and a sintered glass dispersion tube. The latter was connected to a diborane generator.[15] A solution of boron trifluoride etherate (43 g., 0.3 mole) in diglyme (40 ml.) was placed in the generator flask and a suspension of sodium borohydride (6.8 g., 0.18 mole) in diglyme (200 ml.) added dropwise. The hydroboration[15] was carried out at 0–1°, and the flask was then allowed to stand for 2 hr. at room temperature. Excess hydride was destroyed by the addition of water (20 ml.) and, subsequently, the organoborane was oxidized by first adding 3 *N* aqueous sodium hydroxide (30 ml.), followed by 30% hydrogen peroxide (30 ml.). The warm reaction mixture was stirred for 1 hr. and then continuously extracted with ether. The extract was washed, dried, and the solvent removed. The *trans*-2-methylcyclobutanol (XIII) obtained was distilled on the same column (13.8 g., 80% yield), b.p. 137–138° (760 mm.), 83–84° (100 mm.) $n^{25}D$ 1.4284.

Anal. Calcd. for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.56; H, 11.46.

Characteristically[29] for a cyclobutanol, the C–O stretching absorption of compound XIII appears at 1087 $cm.^{-1}$ (cyclobutanol, 1090 $cm.^{-1}$).

***trans*-2-Tosyloxy-1-methylcyclobutane (XIV).**—A solution of *p*-toluenesulfonyl chloride (20.9 g., 0.11 mole) in warm pyridine (10 g.) was introduced into a three-necked flask and cooled rapidly in an ice–water bath to obtain small crystals.[30] *trans*-2-Methylcyclobutanol (9 g., 0.105 mole) was then added dropwise and with constant stirring while keeping the reaction temperature below 20°. After completing the addition and allowing the mixture to stand for 18 hr. at room temperature, water (30 ml.) was added to the externally cooled flask. The liquid was neutralized with ice-cold 8% hydrochloric acid and the ester formed taken up in ether. The ether solution was washed, dried, and the solvent removed; the tosylate was then freed from any volatile impurities by warming at 100° (20 mm.). The slightly yellow *trans*-2-tosyloxy-1-methylcyclobutane (XIV) so obtained (17 g., 68% yield) had $n^{25}D$ 1.5150; it was prepared in slightly better yield (75%) by an alternative procedure.[31]

The infrared spectrum of XIV showed the following bands ($cm.^{-1}$) characteristic[32] for *p*-toluenesulfonates: 1610 (w), 1364 (s), 1191 (m), 1179 (s), 815 (m).

Detosylation of *trans*-2-Tosyloxy-1-methylcyclobutane (XIV).—The allglass apparatus employed for the elimination reaction consisted of a three-necked flask, provided with a thermometer, a dropping funnel, and a magnetic mixer, and connected to a series of two traps cooled in liquid air. Isoamyl alcohol (120 ml.) and diglyme (120 ml.), dried and freshly distilled over lithium aluminum hydride, were introduced into the flask, and to this was added sodium hydride (7.2 g., 0.3 mole, 50% suspension in oil). The mixture was brought with constant stirring to a temperature of 115°, at which point the tosylate XIV (8 g., 0.033 mole) was added dropwise to the flask and, subsequently, the temperature carefully raised to 135° (1 hr.). No condensate was observed in the traps below this temperature. The reaction mixture was kept at 135° for 3 hr. and the distillate collected (1.9 g., 84% yield) was examined by gas chromatography; it contained XII (53%), *trans*-1,3-pentadiene (40%), and *cis*-1,3-pentadiene (7%).

Catalytic Isomerization of 3-Methylcyclobutene (XII).—The apparatus, catalyst preparation, and isomerization procedure were essentially the same as described in previous work.[28] A 3-g. sample of pretreated[28] alumina (Alcoa, grade F-1, 100 mesh) and 0.5 g. of sodium were employed for the preparation of the catalyst in a 50-ml. three-necked flask, and to this was added XII (0.5 g.), dissolved in pure (Phillips, 99%) 2,4-dimethylpentane (8 g.). The mixture was stirred at 5° under nitrogen for 5 hr. and the product distilled at 20 mm. into a liquid air trap. The recovery was 92%. The product, as determined by gas chromatography, contained methylenecyclobutane (14.5%), 1-methylcyclobutene (85.5%), and XII (<0.02%).

Thermal Isomerization of 3-Methylcyclobutene (XII).—The decomposition experiments were carried out in a flow system which consisted essentially of a vertical 30 cm. × 1 cm. Pyrex tube, packed with Pyrex beads, 2 mm. in diameter; the tube was equipped with a constant rate dropping funnel and was connected to a series of coolers and traps. Heat was supplied by a well-insulated furnace and the temperature was measured with a thermocouple at points 5 cm. apart along the entire length of the tube. The isothermal zone (±3°) had a length of about 15 cm. Prior to every experiment the system was purged with dry nitrogen and the temperature adjusted and stabilized for a period of at least 2 hr. The flow of nitrogen was reduced to a minimum during the experiments.

Samples (1–2 ml.) of a 10% solution of 3-methylcyclobutene in 2,4-dimethylpentane (>99.0% pure) were employed in all runs. The same solvent and concentration were used in the comparative experiments with 1-methylcyclobutene and *cis*-1,3-pentadiene.

Bromination of 3-Methylcyclobutene (XII).—To a solution of XII (136 mg., 2 mmoles) in dry carbon tetrachloride, cooled at 0°, was added dropwise and with constant mixing a 5% solution of bromine in the same solvent until a yellow color persisted. The solvent was then removed by microdistillation. The remaining yellow 1,2-dibromo-3-methylcyclobutane (XV, 425 mg., 93% yield) had $n^{25}D$ 1.5210.

Anal. Calcd. for $C_5H_8Br_2$: C, 26.35; H, 3.54; Br, 70.12. Found: C, 26.06; H, 3.90; Br, 70.25.

Gas chromatographic examination of XV showed the presence of two components in the ratio of about 60:40. The retention volumes of the two compounds relative to *n*-pentane, at 96°, on a capillary column coated with polypropylene glycol were 3.2 and 4.3, respectively.

Analytical.—Olefin samples were analyzed by gas chromatography on a 2-m. column containing 30% silver nitrate–glycol

(27) *Cf.* R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 157.

(28) J. Shabtai and E. Gil-Av, *J. Org. Chem.*, **28**, 2893 (1963).

(29) Ref. 24, p. 109.

(30) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

(31) F. Drahowzal and D. Klamann, *Monatsh.*, **82**, 460 (1951).

(32) R. S. Tipson, *J. Am. Chem. Soc.*, **74**, 1354 (1952).

solution as the stationary phase.[33] The presence of XII in the detosylation product was confirmed by blending with a sample of the pure compound, obtained by the decomposition of XI. The blending technique was employed for identification purposes also in the case of the *cis*- and *trans*-1,3-pentadiene. The identity of the latter was further established by partial subtraction chromatography on a column containing chloromaleic anhydride.[34]

Geometric isomers of disubstituted cyclobutanes were separated on a capillary column, 150 ft. long and 0.01 in. wide, coated with squalane. 2-Methylcyclobutanol, as well as the dibromo derivatives of XII, was analyzed on a capillary column of the same dimensions, coated with polypropylene glycol.

A Varian A-60 spectrometer was employed for the measurement of the n.m.r. spectrum of XII, using carbon tetrachloride as a solvent and tetramethylsilane as the reference compound.

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(33) J. Shabtai, J. Herling, and E. Gil-Av, *J. Chromatog.*, **11**, 32 (1963).

(34) Y. Herzberg-Minzly and E. Gil-Av, *Bull. Res. Council Israel*, **10A**, 86 (1961); E. Gil-Av and Y. Herzberg-Minzly, *J. Chromatog.*, in press.

Jervine. XI. The Structure and Stereochemistry of Isojervine

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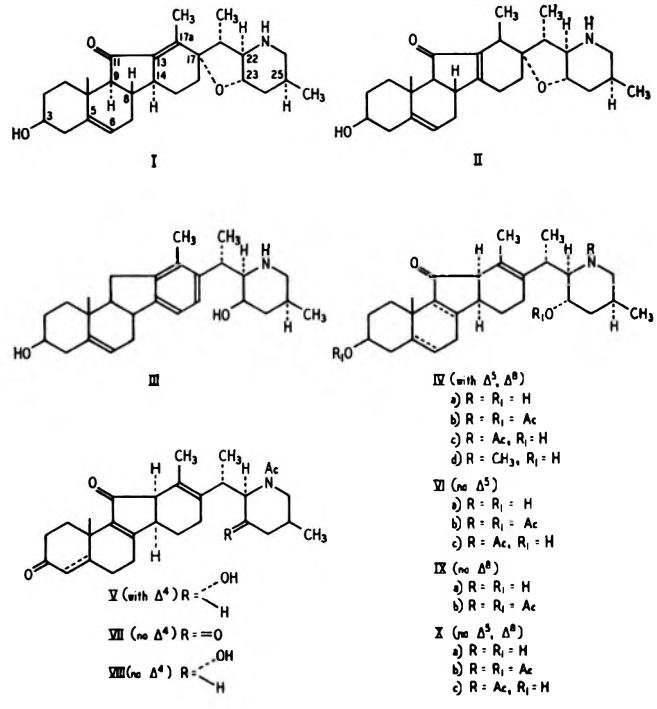
The structure of isojervine has been established as IVa by transformations which lead through its N-acetyl 5,6,8,9-tetrahydro derivative (Xc) and the latter's 17β,17aβ-oxide (XIa) to the enone (XIV) and thence to 5,6-dihydrojervisine 17-monoacetate (XIX) and to triacetyl-5,6-dihydro-11-ketoveratramine (XVII). The abnormal ultraviolet spectrum of isojervine is due to inhibition of resonance in the $\Delta^{8,9}$-11-keto system by the 5,6-double bond, an effect also exerted by the 4,5-double bond in N-acetyl-Δ^4-isojervone (V). Configurational assignments have been made for the asymmetric carbon atoms in rings C and D of isojervine, 5,6,8,9-tetrahydroisojervine, and the latter's derivatives, XI, XII, XIV, and XVIII.

In 1944, Jacobs and Craig[1] recorded the observation that the native veratrum alkaloid jervine, on treatment with hydrochloric acid or methanolic hydrogen chloride, is transformed into an isomer, isojervine, which markedly differs in its properties from the native alkaloid. Thus the hydrochloride and sulfate of isojervine are far more soluble in water or ethanol than the corresponding salts of jervine; in contrast to jervine the isomer is unstable to caustic alkali at room temperature (immediate formation of red pigment); in its ultraviolet absorption spectrum the high maximum at 250 mμ (ε 15,000) characteristic for jervine is replaced by strong end absorption showing only a shoulder of much lower ε (~3000) in that region, while the low intensity maximum at 360 mμ (ε ~60) is hypsochromically shifted to 330 mμ (ε ~250).[2] On short warming with acetic anhydride isojervine formed a N-acetyl derivative and, on more prolonged heating with this reagent, a triacetate.[2]

Concurrently with the investigation which led to the establishment in 1951 of structure I[3] for jervine, a limited amount of work on isojervine was carried out in this laboratory. The results, supplemented by more recent findings, have led us to assign to isojervine, structure IVa. In this paper we present the facts immediately relevant to the structure proof,[4] while other, more tangential aspects of the work will be presented in the following two papers of this series.

Isojervine conforming in its properties with the description of Jacobs and Craig[1] showed in its infrared spectrum a strong carbonyl band at 5.92 μ and a medium high band at 6.10 μ indicative of a conjugated C=C bond. In this respect isojervine resembles Δ^{13}-jervine (II)[5] which exhibits a corresponding band at 5.94 and



(1) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **155**, 565 (1944).

(2) W. A. Jacobs and C. F. Huebner, *ibid.*, **170**, 635 (1947).

(3) The stereochemical features of formula I derive from evidence adduced in the following papers: (a) C-17, C-23, ref. 9; (b) C-22:C-23, J. Sicher and M. Tichy, *Tetrahedron Letters*, **12**, 6 (1959); (c) C-25, S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.* (London), 512 (1961); (d) C-22:C-25, R. L. Augustine, *ibid.*, 1448 (1961); (e) C-8, C-9, C-14, H. Mitsuhashi and Y. Shimizu, *Tetrahedron Letters*, **21**, 777 (1961); *Tetrahedron*, **19**, 1027 (1963).

(4) A brief account of this phase of the work has been published [O. Wintersteiner and M. Moore, *Tetrahedron Letters*, **18**, 795 (1962)]. T. Masamune, M. Takasugi, H. Suzuki, S. Kawahar, M. Godha, and T. Irie [*Bull. Chem. Soc. Japan*, **35**, 1749 (1962)] and W. G. Dauben, W. W. Epstein, M. Tanabe, and B. Weinstein [*J. Org. Chem.*, **28**, 293 (1963)] have independently arrived at the same conclusion regarding the structure of isojervine. We are indebted to Professor Masamune and Professor Dauben for making available to us prepublication copies of their manuscripts.

The communication by R. Ikan and H. Conroy [*Bull. Res. Council Israel*, **11A**, 33 (April, 1962)] postulating the same structure is based almost entirely on our own data to which R. Ikan had access in 1960 through Professor Conroy, who has meanwhile informed us that he never authorized the use of these data and of his name for publication.

(5) B. M. Iselin and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 5318 (1955).

6.12 μ, rather than jervine (5.88, 6.16 μ).[6] Since isojervine, like jervine, is completely inert to ketone reagents, the keto group indicated by the infrared data must occupy its original position 11.

Isojervine triacetate (IVb) could be prepared in good yield either by the method of Jacobs and Huebner[2] or with acetic anhydride and pyridine. However, when the preparation of N-acetylisojervine we tried to take advantage of the selective N-acetylation in methanol which we have used routinely with jervine and its reduced derivatives,[7] the base was recovered unchanged. Since the secondary base veratramine (III) behaves in the same manner,[8] it could be assumed that the oxide ring of jervine has been opened with the establishment of a hydroxyl group at C-23, a supposition which later was rigidly proved by the conversion of isojervine to a known derivative of this alkaloid (*vide infra*). We have already reported[9] that N-acetylisojervine (IVc) can be readily obtained by treating N-acetyljervine with methanolic hydrogen chloride. The hitherto undescribed N-methylisojervine (IVd) could be prepared similarly from N-methyljervine.[10] These observations clearly ruled out participation of the nitrogen atom in the isomerization reaction.

The presence of the 5,6-double bond was established by Oppenauer oxidation of N-acetylisojervine to the strongly dextrorotatory N-acetylisojervone (V), $[\alpha]_D$ +199°; λ_{max} 230 mμ (ε 22,300), 331 (200). The new Δ^4-3-ketone chromophor is evidenced by λ_{max} 235 mμ (ε 16,500) of the curve obtained by subtraction of the isojervine curve from that of oxidation product.[11] The molecular rotation change accompanying the formation of the ketone has an abnormally high positive value (+806°), as is the case in the corresponding reaction of jervine (+742°) and of N-acetyl-11-ketoveratramine (+733°).[12]

Contrary to the experience of Jacobs and Huebner[2] we found that isojervine consumed hydrogen on catalytic reduction with platinum oxide in acetic acid as well as with palladium on charcoal in ethanol, and is thereby transformed into a 5,6-dihydro base (VIa) which differs from isojervine by showing typical α,β-unsaturated ketone absorption in the ultraviolet range, with maxima at 238 mμ (ε 9500) and 333 mμ (ε 210); furthermore the absorption curve, in contradistinction to those of jervine and Δ^{13}-jervine,[5] exhibited a minimum at 225 mμ with ε ~ 7000, a feature obviously referable to the absence of the 5,6-double bond. Strong bands at 5.92 and 6.15 μ are in evidence in the infrared spectrum. For the reasons given later we place the ethylenic bond of the α,β-unsaturated ketone chromophor thus clearly revealed in the 8,9-position. The base forms addition compounds with the common solvents and, hence, was characterized analytically as the triacetate VIb and as the N-acetyl derivative VIc, which is obtained most conveniently by catalytic reduction of N-acetylisojervine. Since 5,6-dihydroisojervine differs from isojervine by being stable to strong base, the latter derivative also could be prepared by O-deacetylation of the triacetate.

To make sure that it was the 5,6-double bond of isojervine which had been reduced in the formation of the dihydro derivatives, N-acetyl-5,6-dihydrojervine was oxidized with chromium trioxide in acetone.[13] The resulting 3,11,23-triketone (VII) (infrared bands at 5.84, 5.94, and 6.09 μ, no hydroxyl band) showed in its ultraviolet spectrum end absorption with a shoulder at 230 mμ (ε 11,500) which undoubtedly represents the 238-mμ band of the starting product VIc superimposed on the end absorption originating in the two new keto groups (N-acetyl-22,26-iminojervane-3,11,23-trione,[4] at 225 mμ, ε ~3000). Since VII was recovered unchanged after short refluxing in methanolic potassium hydroxide solution, it cannot be the Δ^5-unsaturated ketone.[13b] The marked negative molecular rotation shift accompanying the oxidation (−458°) parallels those for the formation of N-acetyldihydroveratramine-3,23-dione[8] and N-acetyl-22,26-iminojervane-3,11,23-trione[14] from the corresponding 3,23-diols (−425° and −256°, respectively).

N-Acetyl-Δ^4-isojervone (V) on catalytic reduction with palladium yielded in facile reaction N-acetyl-4,5-dihydroisojervone (VIII) exhibiting the ultraviolet spectrum typical of the 5,6-dihydro derivatives [λ_{max}^{alc} 237 mμ (ε 9690), 332 (186)]. Saturation of the 4,5-double bond in V has, therefore, the same normalizing effect on the isojervine chromophore as that of the 5,6-double bond in isojervine itself.

It is evident from the ultraviolet absorption data of the new isojervine derivatives described in the foregoing that the inhibition of resonance in the α,β-unsaturated ketone system of isojervine (IV) which must be responsible for its abnormal ultraviolet absorption characteristics still obtains in N-acetyl-Δ^4-isojervone (V), but that this restraint disappears when either the 5,6-double bond in IV or the 4,5-double bond in V is reduced. The disappearance of the spectral abnormality in the reaction IV → VI is paralleled by a similar phenomenon in the transition of simple compounds having a system such as that represented by rings B and C of IV, to their reduction products lacking the "opposed" isolated double bond (1-acetyl-1,4-cyclohexadiene,[15] 1,4-cyclohexadiene-1-carboxylic acid[16]).

Since this matter has already been briefly mentioned by us[4] and more fully discussed by Dauben, *et al.*,[4] we refrain from further elaborating on it here, except for making reference to a finding to these authors relating

(6) The C=C bands of isojervine and Δ^{12}-jervine are of considerably lower intensity than their carbonyl bands, while in jervine this relationship is reversed; *cf.* R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *ibid.*, **76**, 4013 (1954), and ref. 9.

(7) B. M. Iselin and O. Wintersteiner, *ibid.*, **76**, 5616 (1956).

(8) Ch. Tamm and O. Wintersteiner, *ibid.*, **74**, 3842 (1952).

(9) O. Wintersteiner and M. Moore, *ibid.*, **78**, 6193 (1956).

(10) K. Saito, H. Suginome, and M. Takaoto, *Bull. Chem. Soc. Japan*, **11**, 172 (1936).

(11) The absorption spectrum of N-acetyl-Δ^4-13,17a-dihydrojervone, the preparation of which is described in the Experimental section, exhibits the same characteristics (λ_{max} 234 mμ, ε 16,300). The marked hypsochromic shift from the position this band occupies in the spectrum of normal Δ^4-3-keto steroids (241 mμ) must be ascribed to the influence of the skeletal abnormality and/or of the 11-keto group, probably mostly of the latter, since this shift is not nearly so pronounced in the case of N-acetyl-Δ^4-veratraminone.

(12) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **75**, 4938 (1953).

(13)(a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(14) O. Wintersteiner, M. Moore, and B. M. Iselin, *J. Am. Chem. Soc.*, **76**, 5609 (1954).

(15) K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 52 (1946); E. A. Braude, E. R. H. Jones, F. Sondheimer, and J. B. Toogood, *ibid.*, 607 (1949).

(16) L. S. Emerson and J. Meinwald, *J. Org. Chem.*, **21**, 375 (1956).

to the absorption spectrum of Δ^4-isojervone which is at variance with our own.[17]

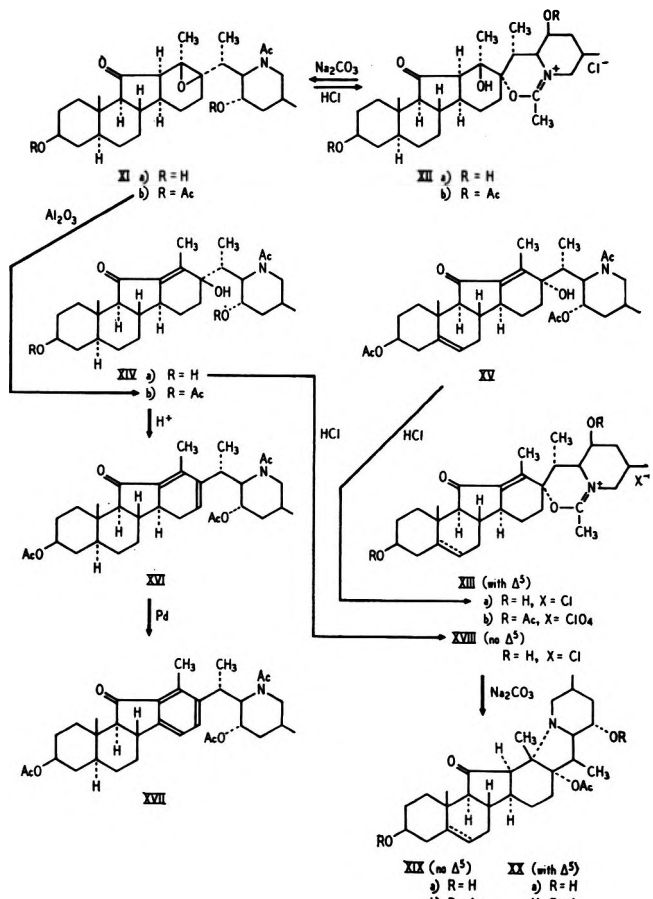
The 8,9-double bond in isojervine (IVa) and 5,6-dihydroisojervine (VIa) could be reduced with lithium in liquid ammonia. The resulting crystalline bases, 8,9-dihydroisojervine (IXa) and 5,6,8,9-tetrahydroisojervine (Xa), obtained in moderate yield only, were always contaminated with small amounts of the starting bases as evidenced by the survival, in low intensity, of the infrared bands at 5.92 and 6.10 (6.15) μ. These impurities could be removed for the most part by acetylation and chromatography of the triacetates (IXb and Xb). More satisfactory in regard to yield and purity of the product was the reduction of N-acetyl-5,6-dihydroisojervine (VIc) to N-acetyl-5,6,8,9-tetrahydroisojervine (Xc), which was needed for the conversions described later. The presence of a strong band at 5.78 (5.76) μ in the infrared spectra of the bases IXa and Xa and the N-acetyl derivative (Xc) showed that the 11-keto group is still situated in a five-membered ring C. The ultraviolet spectra of IXa and Xa and of their respective acetyl derivatives differ from that of tetrahydrojervine or 13,17a-dihydrojervine (λ_{max} 305 mμ, ϵ ~30) in that they showed two or three not too well-defined maxima in the 300–330-mμ region with higher than usual intensity [for instance Xc, 311 mμ (ϵ 168), 320 (159), 330 (100)]. The stereochemical significance of this abnormality, which is characteristic for certain types of β,γ-unsaturated ketones,[18] will be discussed later.

The presence of a third double bond in isojervine followed from the fact that N-acetyl-5,6,8,9-tetrahydroisojervine (Xc) reacted with 1 mole of perbenzoic acid with the formation of an oxide (XIa) the reactions and further transformations of which leave no doubt as to the location of this double bond in the 17,17a-position. Its ultraviolet spectrum no longer exhibited the abnormal features seen in that of the parent olefin Xc (only one poorly defined maximum at 305 mμ, ϵ 28). The acetylation product of XIa, the triacetate (XIb), could not be obtained in crystalline form. The reasons for assigning to the oxidic oxygen bonds the β configuration will become apparent later.

On short treatment at room temperature with one equivalent of hydrochloric acid in 90% methanol, the oxide XIa was transformed to the chloride of a quaternary base to which we ascribe the dihydrometoxazine structure XIIa in analogy to the quaternary base chloride (XIIIa) formed along with N-acetylisojervine from N-acetyljervine with methanolic hydrogen chloride.[9] The spectral properties of XIIa are consonant with this assignment [λ_{max}^{alc} 303 mμ (ϵ 71); λ_{max}^{Nujol} 3.00, 5.78 (11-keto group), 6.06 (>C=N$^+$<) μ]. The amorphous triacetate (XIIb) obtained from XIIa by acetylation with acetic anhydride was characterized only by rotation and infrared data.

The quaternary chloride (XIIa) reverted instantaneously to the parent oxide (XIa) on treatment with sodium carbonate in aqueous methanol. This suggests a concerted reaction accompanied by inversion at C-17, analogous to the formation of oxides from diaxial *trans* bromohydrins, and make it extremely likely that in XIIa the 17a-hydroxyl group and the ring oxygen attached to C-17 are both axial, and *trans* to each other.

Another but irreversible isomerization occurred when the amorphous oxide triacetate (XIb) was adsorbed on neutral alumina from benzene solution and then eluted with ether containing a little methanol. The resulting crystalline product contained a new, nonacetylatable hydroxyl group and a new double bond conjugated with the 11-keto group as evidenced by the ultraviolet spectrum [maxima at 261 mμ (ϵ 10,300) and 355 mμ (ϵ 120)]. For the reasons given farther on we formulated this substance as the 5,6-dihydro 17-epimer (XIVb) of a compound (XV) which we obtained 10 yr. ago in the sulfuric acid-catalyzed acetolysis of 3,N-diacetyljervine ["second acetolysis product," λ_{max}^{alc} 252 mμ (ϵ 14,000) and 355 (85)][12] and assign to the two compounds the configurations shown (side chain, α in XIVb and β in XV). We have no explanation for the abnormally high λ_{max} of the main band in the spec-



(17) Dauben, *et al.*,[4] claim that subtraction of the ultraviolet absorption curve of cholestenone from that of 23,N-diacetyl-Δ^4-isojervone (λ_{max} 232 mμ, ϵ 21,450) gives a curve exhibiting a residual maximum at 238 mμ (ϵ not given), thus "showing the presence of two separate chromophores" in this compound. The inference is that, contrary to our own conclusion from the similarity of the subtraction curve (N-acetyl-Δ^4-isojervone – N-acetyl-13,17a-dihydro-Δ^4-jervone) with the isojervine spectrum, the 4,5-double bond (or the whole ring A chromophore) of Δ^4-isojervone does *not* inhibit resonance in the $\Delta^{8,9}$-11-ketone grouping of this compound. We have, therefore, determined the curve obtained by subtraction of the cholestenone curve (λ_{max} 240 mμ, ϵ 17,000) from that of our N-acetyl-Δ^4-isojervone curve (λ_{max} 230 mμ, ϵ 23,000) in which all points on the wave-length scale were moved up by 2 mμ to make it more closely comparable to that of Dauben, *et al.*, with λ_{max} 232 mμ. The subtraction curve showed no sign of a maximum or even a shoulder at 238 mμ, and ϵ was only 4000 at this wave length. As it is most improbable that the curves of the N-acetyl and diacetyl derivatives of Δ^4-isojervone differ substantially from each other, we are forced to conclude that the claim of Dauben, *et al.*, referred to has no basis in fact.

(18)(a) R. C. Cookson and N. S. Wasiyar, *J. Chem. Soc.*, 2302 (1956); (b) H. Labhart and G. Wagnière, *Helv. Chim. Acta*, **42**, 2219 (1959); (c) C. A. Grob and A. Weiss, *ibid.*, **43**, 1390 (1960); (d) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962).

trum of XIVb and the low ϵ-value as compared with that of the 252-mμ band of XV.

On hydrolysis with alkali the enone triacetate (XIVb) merely suffered O-deacetylation to give the amorphous N-acetyl derivative (XIVa) exhibiting the same ultraviolet characteristics, whereas the acetolysis product (XV) is thereby transformed into jervisine 17-monoacetate (XXa).[9,12] It is interesting that XIVa cannot be obtained from N-acetyl-5,6,8,9-tetrahydroisojervine oxide (XIa) by adsorption on neutral alumina and elution with methanol–ether as is XIVb from the triacetate (XIb) of the oxide. Indeed, elution of the more polar XIa is effected already with benzene–ether, and merely results in the recovery of a more homogeneous product with a considerably higher melting point.

The structure of the enone (XIV) rests on unambiguous evidence derived from two different reaction sequences. The first of these starts with the dehydration of the 17-hydroxyl group of the triacetate (XIVb), which was effected by prolonged heating in dioxane containing maleic acid.[19] The resulting crystalline compound showed in its ultraviolet spectrum aside from shoulders at 227 mμ (ϵ 9000) and 260 (5300), a high maximum at 317 mμ (ϵ 10,500) comparable with that at 314 (7620) of cholesta-2,4-dien-6-one,[20] and hence must be the homoannular dienone (XVI). Conclusive proof for the correctness of this assignment and hence for the structure of the enone was adduced by dehydrogenating XVI with palladium in boiling cymene[21] to the known[22] triacetyl-5,6-dihydro-11-ketoveratramine (XVII).

The other reaction sequence by which the enone (XIV) was correlated with a compound of known structure preserves the asymmetry of C-17 and thus was instrumental in defining the configuration of this carbon atom in XIV. When the amorphous N-acetyl derivative of the enone (XIVa) was treated with one equivalent of hydrochloric acid in aqueous methanol, it was transformed into the chloride of a base, the ultraviolet spectrum of which resembled that of the quaternary base chloride (XIIIa) resulting from the treatment of N-acetyljervine with methanolic hydrogen chloride[9] in that it exhibited a high maximum at 243 mμ (ϵ 14,800). That this new base chloride from the enone (XIVa) was nothing else but the 5,6-dihydro derivative (XVIII) of the salt (XIIIa) followed from its conversion by sodium carbonate to a weak tertiary base which was identified as 5,6-dihydrojervisine 17-monoacetate (XIXa), as an identical product was obtained by catalytic reduction of the 5,6-double bond of jervisine 17-monoacetate (XXa), the basic rearrangement product formed from the chloride (XIIIa) with sodium carbonate. The identity of the base monoacetate from the salt (XVIII) with that obtained by reduction of jervisine 17-monoacetate (XXa) was confirmed by acetylation of the two specimens to the same triacetate (XIXb).

It will be recalled that the conversion of the amorphous enone (XIVa), in which the 3- and 23-hydroxyl groups are free, to the quaternary chloride (XVIII) was effected with one molar equivalent of hydrochloric acid in aqueous methanol. Strangely, similar treatment of the crystalline enone *triacetate* (XIVb) left this compound unchanged. That the 23-hydroxyl groups must be free before this reaction can proceed also would appear from the fact to be reported in the following paper that the conversion of a compound analogous to XIVb (with the 23-hydroxyl group acetylated) to the corresponding quaternary chloride of type XVIII could be brought about by excess hydrogen chloride in anhydrous methanol, conditions which also effect the loss of the 23-acetyl group.

It was of interest to ascertain how the fully acetylated enone (XV), which must differ from the enone (XIVb) by epimerism at C-17 (and the presence of the 5,6-double bond), would behave in this respect. That XV can be transformed into quaternary salts of type XVIII by acidic reagents was already clear from a study of the perchloric acid-catalyzed acetolysis of diacetyljervine in which it was shown that XV (as well as diacetyljervine) on treatment with acetic anhydride and acetic acid containing perchloric acid form the 3,23-dicetylated dihydrometoxazine perchlorate (XIIIb) in good yield.[12] We have now found that XV behaves like the enone (XIVb) in that it is not changed by aqueous methanolic 0.1 *N* hydrochloric acid, but with methanolic hydrogen chloride gave as expected the acetyl-free quaternary chloride (XIIIa), though in poor yield. There is no doubt then that these quaternary dihydrometoxazine salts are formed under acidic conditions from enones of type XIV, as well as from their 17-epimers, and that an inversion at C-17 must, therefore, occur in this reaction with one class of epimers but not with the other. The reasons for our belief that it is XIV and its congeners which react with inversion will be given subsequently.

Finally, reference should be made to an anomaly apparently at variance with the β,γ-unsaturated ketone structures assigned to 5,6-dihydroisojervine and 5,6,8,9-tetrahydroisojervine, namely, their failure to undergo isomerization, on treatment with strong alkali, to the corresponding α,β-($\Delta^{13,17a}$)-unsaturated ketones (*cf.* preparation of N-acetyl-5,6-dihydroisojervine from the triacetate). Since there was a remote possibility that the enolization of the 11-keto group towards C-13 was reversible, *i.e.*, that proton addition occurred at C-13 instead of at C-17, the ultraviolet spectra of N-acetyltetrahydroisojervine and of triacetyl-5,6-dihydroisojervine were measured in 1% methanolic potassium hydroxide solution kept under nitrogen. In the case of the tetrahydro compound the slow emergence of a maximum at 247 mμ, the intensity of which corresponded to ϵ 6900 after 24 hr. and became constant in about 5 days at ϵ 8450, was indeed observed under these conditions. Acidification with hydrochloric acid produced no change in the position and the intensity of this maximum either immediately or on standing. This observation was not follow up preparatively, but there cannot be much doubt that the α,β-unsaturated ketone with the double bond in the 13,17a-position was

(19) The use of maleic acid for this purpose goes back to an early attempt to aromatize ring D of the Δ^4-isojervone analog of XIVb by simultaneous dehydration and dehydrogenation; the latter reaction was to be effected by palladium in boiling dioxane with maleic acid serving as the hydrogen acceptor. However, only dehydration resulting in homoannular diene formation occurred. Since the yield of dehydration product was reasonably good also in the absence of palladium, the method was subsequently used routinely for the preparation of XVI and of its more unsaturated analogs described in the following paper.

(20) H. Reich, F. E. Walden, and R. W. Collins, *J. Org. Chem.*, **16**, 1953 (1951).

(21) D. Rosenthal, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **84**, 877 (1962).

(22) O. Wintersteiner and N. Hosansky, *ibid.*, **74**, 4474 (1952).

formed. The lower extinction coefficient as compared with that of jervine and the acetolysis product (XV) indicates that the reaction leads to an equilibrium at which the ratio of the two ketones is about 1:1.

In contrast, the spectrum of triacetyl-5,6-dihydroisojervine remained completely unchanged in the presence of alkali for a 24-hr. period. Alkali is, therefore, incapable of promoting the formation of the conjugated trienic system which would result from enolization of the keto group towards C-13 and on reketonization give the $\Delta^{8,9,13-17a}$-cross-conjugated dienone.

Stereochemistry.—There can be no doubt that the C-14 hydrogen atom in tetrahydroisojervine (X) must be α-oriented as it is in jervine,[3e] since both these compounds have been converted to jervisine derivatives (XX and XIX, respectively) by reactions which do not involve this carbon atom. Since the latter statement, as will be shown in the following paper of this series, applies also to 5,6-dihydrojervine and N-acetyl-Δ^4-isojervone, we believe, albeit with the reservations set forth in that paper, that these compounds and hence isojervine itself likewise have the 14α configuration.

The proposition that C-13 in tetrahydroisojervine (and in isojervine itself if the 14α configuration is accepted for this compound) likewise has the α configuration is based on the following evidence indicating that rings C and D are *cis* linked.

(1) The Dreiding models of both isojervine and tetrahydroisojervine show that the C/D system is far more strained in the 13β,14α-*trans* than in the 13α,14α-*cis* form.[23]

(2) The abnormal ultraviolet absorption characteristics of 8,9-dihydroisojervine (IXa) and 5,6,8,9-tetrahydroisojervine (Xa) and their acetylated derivatives (two or three maxima at 300–330 mμ, ϵ 100–260) are not seen in the spectra of other jervine or isojervine derivatives having an isolated 11-keto group (*e.g.*, 13,17a-dihydrojervine, jervisine, XI, XII, which show λ_{max} ~305 mμ with ϵ 30–70) and are, therefore, connected with the 17,17a-double bond. Similar characteristics (two to three maxima with ϵ-values from 100 to 800) are exhibited by a number of β,γ-unsaturated ketones[18] in which the C=O and C=C elements are noncoplanar and twisted against each other in such a fashion that the p-orbitals of the carbonyl and β-atoms can be assumed to overlap to a greater or lesser extent. The scale models of X shows that the 13α,14α isomer conforms with this description much better than the essentially flat 13β,14α-*trans* isomer.

(3) In 1954 we described an acetolysis product of diacetyltetrahydrojervine[14] which differs from triacetyltetrahydroisojervine only by having its single double bond in the 16,17- instead of the 17,17a-position. This strongly levorotatory compound is isomerized by alkali, with concurrent loss of the O-acetyl groups, to a dextrorotatory N-acetyl derivative which on reacetylation furnishes a likewise dextrorotatory isotriacetate. We recently have shown (n.m.r.) that the two isomers are 13-epimers, and from equilibrium studies on the two epimers and their respective 16,17-dihydro derivatives obtained convincing evidence permitting us to formulate the iso compound, which predominates in the equilibrium mixture in the ratio 3:1, as the 13β,14α-*trans* isomer, and the original acetolysis product as the 13α,14α-*cis* isomer.[24] The "opposed" 16,17-double bond, together with the β-oriented and hence quasi-equatorial 17a-methyl group, thus stabilizes the *trans* junction of rings C and D in the Δ^5-hydrinden-1-one system represented by these rings. This parallels the greater stability of *trans- vs. cis*-Δ^2-octalins.[25] Since, on the other hand, the double bond in Δ^1-octalins stabilizes the *cis vs.* the *trans* form,[25] it is reasonable to assume that this holds also for the comparable Δ^6-hydrindenone system of tetrahydroisojervine. True, N-acetyltetrahydroisojervine is not stable to alkali as it should be according to this postulate, but this is because the basic reagent promotes the shift of the double bond into conjugation with the 11-keto group. On the other hand, the fact that N-acetyl-5,6-dihydroisojervine (which does not undergo this isomerization) is, in contrast to the abovementioned 16,17-olefin, *not* epimerized at C-13 by alkali in its preparation from the triacetate may be interpreted as supporting the prior proposition that the 17,17a-double bond stabilizes the *cis* junction of rings C and D, and that isojervine, therefore, has the 13α,14α configuration.

The configurations of carbon atoms 8 and 9 in 8,9-dihydroisojervine (IX), 5,6,8,9-tetrahydroisojervine (X), and all compounds derived from the latter must be on the basis of the correlation of X with jervisine and veratramine, and likewise be the same as in jervine.[3e] The configurations of carbon atoms 22, 23, and 25[3b–d] follow, of course, from the correlation with veratramine. The configuration of C-20 has as yet not been established experimentally, but may be assumed to be the same as that in rubijervine and hence as in normal sterols since this alkaloid, which possesses a normal steroid skeleton, has been correlated with sarsasapogenin *via* 5β-solanidanol.[26]

There remain to be discussed the configurations assigned to C-17 and C-17a in the transformation products (XI, XII, and XIX) and to C-17 in the enone (XIV) and the quaternary base chloride (XVIII).

The postulate that the oxiran ring in the 17,17a-oxide (XI) and its congeners (paper XII in this series) is β-oriented is based on the following argument which also defines the configuration at C-17 of the enone (XIV). In a previous paper[9] it was proposed for good reasons that all the solvolysis products of jervine including enone XV (the 17-epimer of XIV otherwise differing from it only by the presence of the 5,6-double bond) and the dihydrometoxazine salts (XIIIa and b) correspond to the native alkaloids in regard to the configuration of C-17, and that this is the "natural" configuration with the side chain β-oriented. More direct evidence supporting this view is now at hand with the ultraviolet spectrum of XIV. While the spectra of jervine and XV are very similar [λ_{max} 250 mμ (ϵ 15,000), 252 (14,000)], that of XIV is markedly different [λ_{max}

(23) In the *cis* form of both compounds two conformations of ring D are possible, both of which resemble a distorted boat rather than a distorted half-chair in that the 13- and the 14-hydrogen atoms are both either quasi-equatorial or quasi-axial in respect to this ring. In the former C-14 and C-15 lie below the plane of carbon atoms 13, 17a, 17, and 16; in the latter, above that plane.

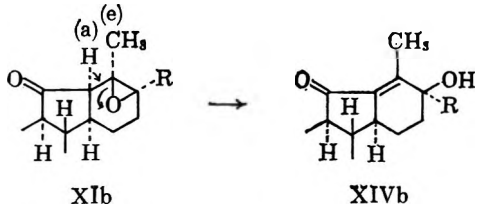
(24) O. Wintersteiner and M. Moore, to be published.

(25) D. A. H. Taylor, *Chem. Ind.* (London), 250, (1954); A. S. Dreiding, *ibid.*, 1419 (1954).

(26) F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945); Y. Sato and W. A. Jacobs, *ibid.*, **179**, 623 (1949).

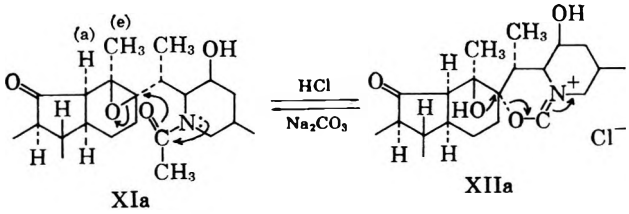
261 mμ (ε 10,300)] from that of jervine.[27] It may then be assumed with some confidence that XIV has the 17-hydroxyl group instead of the side chain β-oriented, and this means that its precursor XIb must be the 17β,-17aβ-oxide.

The alumina-catalyzed isomerization XIb → XIVb can then be visualized to proceed by the concerted mechanism shown below to which XI would be predisposed by the near coplanarity of the four reacting centers involved.[28]



XIb XIVb

The nucleophilic displacement of the oxide oxygen at C-17 by the N-acetyl oxygen in the facile formation of the dihydrometoxazine chloride (XIIa) from XIa with hydrochloric acid, as well as the equally facile reverse reaction induced by sodium carbonate, is undoubtedly concerted, so that XIIa must be formulated with the side chain β, and the linkage of the metoxazine oxygen with C-17 α as shown.

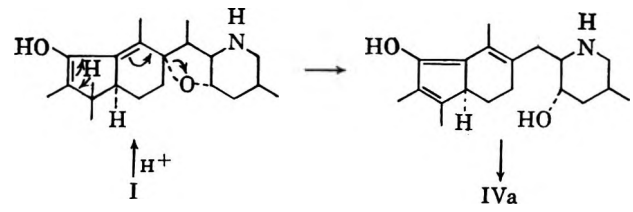


XIa XIIa

In regard to the cyclic quaternary base chloride (XVIII), this compound must have the C-17 stereochemistry depicted (side chain β), because (1) it is transformed by sodium carbonate instantaneously into 5,6-dihydrojervisine 17-monoacetate (XIXa), and (2) jervisine 17-monoacetate (XXa) has been obtained with stronger alkali directly from the enone (XV),[12] in which, as argued further earlier, the side chain is β-oriented. Therefore, it is in the acid-catalyzed reaction leading from the 5,6-dihydro-17-epimer of XV, enone XIV, to XVIII, and not in the analogous reaction XV → XIIIa, where inversion at C-17 must have occurred.

The C-13 and C-17a configurations shown in jervisine derivatives XIX and XX are admittedly postulates unsupported by experimental evidence. They have been chosen for no other reason than that the models of the other three stereoisomers show more unfavorable interactions (or one that is severely so) than that of XIX and that, in one case (the 13β-epimer of XIX), the model cannot be assembled unless ring D is made a boat. Although even in XIX there is a 1,3-diaxial relationship of the 18- and 21-methyl groups, these are tilted away from each other so that their separation in space is greater than it would be in a cyclohexane ring.

Mechanism of Formation of Isojervine.—We visualize the isomerization of jervine to isojervine to proceed by the mechanism depicted.



I IVa

The acid-catalyzed enolization towards C-9, which is assumed to initiate the reaction, would depend, as a prototropic change,[29] on the availability in high concentration of hydrogen ions (to form the conjugated acid at the carbonyl oxygen) and of chlorine ions (the "base" abstracting the 9α-proton), and hence would be expected to proceed only in ionizing solvents. This accords with the fact that the isomerization has so far been found to occur only when water[1] or methanol was used as the solvent, whereas in water-free media (acetic anhydride), acid catalysis merely results in the (acetolytic) cleavage of the oxygen–C-17 linkage in ring E. To reassure ourselves on this point, we have treated N-acetyljervine with hydrogen chloride in chloroform carefully freed from ethanol and moisture and found that, aside from a small amount of the quaternary chloride (XIII), only traces of N-acetylisojervine were formed, in spite of the fact that the reaction was allowed to proceed for as long as 20 hr.

Experimental

The melting points were taken in open Pyrex glass capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semimicrotube, with chloroform as the solvent, unless indicated otherwise. The ultraviolet spectra were measured in absolute ethanol in a Cary self-recording instrument Model 11 M. The infrared spectra were determined on Nujol mulls in the Perkin-Elmer double beam self-recording spectrophotometer Model 21. The characteristics of the infrared bands are expressed in the text as follows: (s), strong; (m), medium; (l), low; (vl), very low; (br), broad; (sh), shoulder. The analytical samples were dried at 110° (2 mm.) unless indicated otherwise.

Isojervine (IVa) was prepared from jervine with methanolic hydrogen chloride (room temperature, 1 hr.) as described by Jacobs and Craig.[1] In a typical experiment starting with 5 g. of jervine, 2.67 g. of the chloroform adduct, m.p. 140–149°, was obtained. Two recrystallizations from acetone of this material with an additional 400 mg. obtained from the mother liquor yielded the acetone compound, m.p. 105–112°, lit.[1] m.p. 105–112°. This preparation, as well as those from other runs, showed somewhat higher levorotation ($[\alpha]^{23}D$ −36 to 37° in 95% ethanol) than found by Jacobs and Craig (−32°). Contrary to the experience of these authors we could not remove the acetone by drying at 110° (2 mm.), 3 hr., weight loss of 7.1%.

(27) The scale models of the two "epimers" give no clue as to what these spectral differences may mean in spatial terms. If ring D is made a half-chair, there is no difference in the dihydral angles formed by the two 17-substituents with the plane of the adjacent α,β-unsaturated ketone systems, since not only C-14, C-13, C-17a, and C-17, but also C-16 lie in that plane. If, however, ring D is a boat, then the β-substituent likewise lies in that plane, while the α-substituent becomes truly axial. It is possible that the tendency of the bulky β-oriented side chain in XV to assume a more equatorial conformation might stabilize ring D in a form intermediate between half-chair and boat. The 17α-hydroxyl would then become more truly axial and apt to interact with the π-electrons at the C-terminal of the resonating system.

(28) One of the referees pointed out that the isomerization need not be initiated by base, but could be an acid-catalyzed reaction in which the alumina acts as a Lewis acid. In that event a carbonium ion mechanism would be operative which does not require a *trans*-diaxial relationship of the 13- and 17a-substituents, and hence α-orientation of the 13-hydrogen. While it is true that there is no proof for the concerted mechanism postulated, it must be pointed out that acid catalysis promotes the isomerization of XIb to the cyclic base salt (XIIb), not to the enone (XIVb).

(29) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., p. 553.

Anal. Calcd. for $C_{27}H_{39}O_3N \cdot C_3H_6O$ (483.7): C, 74.49; H, 9.38. Found: C, 74.33; H, 9.46.

The ultraviolet characteristics were identical with those reported by Jacobs and Huebner[2,30]; chloroform adduct, λ_{max}^{Nujol} 3.05 (m), 5.92 (s), 6.04 (vl), 6.11 (m) μ.

As noted by Jacobs and Huebner,[2] isojervine immediately produces a wine-red pigment when treated in alcoholic solution with alkali hydroxides. Little or no isojervine could be extracted from such solutions with chloroform after standing overnight and dilution with water.

The preparation of N-acetylisojervine (IVc) by isomerization of N-acetyljervine has been described in the preceding paper of this series[9]; m.p. 207–210° (lit.[2] m.p. 202–203°); $[\alpha]^{25}D$ +15° (*c* 0.930); ultraviolet spectrum identical with that of free base; λ_{max}^{Nujol} 3.00 (s), 5.92 (s), 6.14, 6.20 (doublet, s) μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.47; H, 8.84. Found: C, 74.31; H, 8.84.

Addition of alkali hydroxide (but not of ammonia or potassium carbonate) to a methanolic solution of N-acetylisojervine produced an intense cherry-red color which in time turned brown-red. In a preparative experiment a solution of 100 mg. in 6 ml. of 5% methanolic potassium hydroxide which had been allowed to stand overnight was concentrated, diluted with water, and extracted with chloroform. The extract was washed with 2 *N* hydrochloric acid and water, dried, and evaporated, yielding 35 mg. of a yellow gum. The acid phase after alkalinization yielded only 3 mg. of chloroform-extractable bases, while the original alkaline solution was found to contain substantial amounts (27 mg.) of chloroform-soluble acids. The balance appeared to consist of amphoteric products. Similar results were obtained when the potassium hydroxide concentration was reduced to 0.1 *N*. Under the latter conditions, N-acetyljervine was recovered in virtually quantitative yield in the neutral fraction.

The triacetate (**IVb**) was obtained from the base by acetylation with acetic anhydride and pyridine in the usual manner (room temperature, 20 hr.), m.p. 187–190°, unchanged after chromatography; $[\alpha]^{25}D$ +29° (*c* 0.988).

Anal. Calcd. for $C_{33}H_{45}O_6N$ (551.7): C, 71.84; H, 8.22. Found: C, 71.72; H, 7.87.

A specimen prepared in the same manner from N-acetylisojervine melted at 187–189° (no depression in mixture) and had $[\alpha]^{23}D$ +26°.

N-Methylisojervine (IVd).—N-Methyljervine[10] (m.p. 205–209°, $[\alpha]^{24}D$ −98°, 150 mg.) was dissolved in methanol (4 ml.) which had been saturated at 0° with gaseous hydrogen chloride. The solution was allowed to stand at room temperature for 1 hr. and was then worked up as in the preparation of isojervine.[1] The amorphous crude product (150 mg.), on recrystallization from 33% aqueous ethanol and then from methanol–ethyl acetate, yielded rods (38 mg.) melting with decomposition at 220–224°, $[\alpha]^{25}D$ 0° (c 0.45, ethanol). The ultraviolet spectrum was practically identical with that of isojervine; λ_{max}^{Nujol} 3.00 (m), 5.92 (s), 6.12 (m) μ. The analytical sample lost no weight on drying at 110° (2 mm.) for 3 hr.

Anal. Calcd. for $C_{28}H_{41}O_3N$ (439.6): C, 76.49; H, 9.40. Found: C, 76.35; H, 9.48.

N-Methylisojervine gave an orange color on treatment with methanolic potassium hydroxide.

N-Acetyl-Δ^4-isojerv-3-one (V).—N-Acetylisojervine (1.00 g.) was dissolved in dry benzene (20 ml.) and dry acetone (30 ml.). Aluminum *t*-butylate (4 g.) in benzene (40 ml.) was added, and the mixture was boiled under reflux for 21 hr. After chilling and decomposition of the reagent with cold 1 *N* sulfuric acid the product was recovered by repeated extraction with benzene. The extract was washed successively with dilute sulfuric acid, sodium bicarbonate solution, and water, dried, and freed from solvent *in vacuo*. Since the crystalline product obtained from the residue with acetone appeared to be a mixture, the total material (705 mg.) was subjected to treatment with Girard's reagent T (750 mg.) and separated into ketonic and nonketonic fractions in the usual manner. From the nonketonic fraction 158 mg. of starting material, m.p. 199–202°, was recovered. The ketonic fraction (325 mg.) extracted from the acidified (pH 1) aqueous phase with chloroform yielded on crystallization from ethyl acetate square platelets (252 mg.) melting at 234–239°. On further recrystallization from methanol–ethyl acetate the melting point became constant at 239–241.5°; $[\alpha]^{25}D$ +199° (c 0.983); λ_{max}^{alc} 230 mμ (ϵ 22,300), 331 (198); λ_{max}^{Nujol} 3.00 (m), 5.96 (s), (sh, l), 6.16 (sh, m), 6.22 (s) μ.

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.80; H, 8.44. Found: C, 74.89; H, 8.35.

When a small sample of V was dissolved in 5% methanolic potassium hydroxide, a pink color developed immediately which turned deep blue on warming.

5,6-Dihydroisojervine (VIa).—Isojervine acetonate (983 mg.) was dissolved in benzene (50 ml.) and the solution was brought to dryness to remove the acetone. After two repetitions of the procedure the residue was dissolved in absolute ethanol (20 ml.), and the solution added to a prehydrogenated suspension of 5% palladium-on-charcoal catalyst (1.0 g.) in ethanol (8 ml.). Shaking under hydrogen was continued till the uptake stopped after 2.75 hr. at 56 ml. (calcd. for 1 molar equiv., 50.8 ml.). After filtering off the catalyst the solution was brought to dryness, and the residue (small plates) recrystallized first from aqueous methanol (needles, m.p. 144–147°, 798 mg.) and then from ethyl acetate; (m.p. 155–157°, unchanged after drying at 110° (2 mm.); weight loss, 1.9%; $[\alpha]^{23}D$ −23° (*c* 0.506, 95% ethanol).

Anal. Calcd. for $C_{27}H_{41}O_3N \cdot {}^1/_2H_2O$ (436.6): C, 74.27; H, 9.70. Found: C, 74.76; H, 9.47.

Prolonged drying at 137° (2 mm.) of the crystals obtained from ethyl acetate, acetone, or chloroform usually raised the melting point to the range 170–176°. Samples dried in this manner, although they gave analyses somewhat too high in carbon, were used for the spectral measurements; λ_{max}^{alc} 238 mμ (ϵ 9500), 333 (210) λ_{min}^{alc} 224 (6980); λ_{max}^{Nujol} 2.95 (sh, s), 3.15 (s), 5.92 (s), 6.15 (s) μ.

In our early experiments the hydrogenation was carried out with prereduced platinum dioxide catalyst in glacial acetic acid. Although the uptake usually exceeded 2 moles, only the dihydro base of the properties described before could be isolated, albeit in somewhat lower yield.

For the preparation of the triacetate (**VIb**), a solution of the base (71 mg.) in 1:1 acetic anhydride–pyridine (2 ml.) was allowed to stand overnight, and then worked up in the usual way. The crystalline product (104 mg.) was recrystallized from aqueous ethanol and then twice from ethyl acetate, from which it formed needles melting at 209–211°; $[\alpha]^{20}D$ +37.5° (*c* 1.05); λ_{max}^{alc} 238 mμ (ϵ 10,300), 332 (135); λ_{max}^{Nujol} 5.76 (s), 5.92 (s), 6.12 (s), 8.08 (s) μ.

Anal. Calcd. for $C_{33}H_{47}O_6N$ (553.7): C, 71.58; H, 8.56. Found: C, 71.77; H, 8.41.

A product with nearly identical properties [m.p. 208–210°, $[\alpha]^{21}D$ +35.7°; λ_{max}^{alc} 238 mμ (ϵ 9000), 332 (143)] was obtained by catalytic hydrogenation with palladium–charcoal in ethanol of triacetylisojervine (IVb). The catalytic reduction of the latter with platinum oxide in acetic acid likewise led to VIb, in this case in good yield since the uptake was confined to 1 mole. The infrared spectra of all three specimens were identical.

Similarly, hydrogenation of N-acetylisojervine (IVc) in ethanol with palladium black afforded **N-acetyl-5,6-dihydroisojervine (VIc)** in satisfactory yield. Thus, 3.035 g. of IVc, after taking up in 2.75 hr. 180 ml. of hydrogen (calcd., 159 ml.), gave 1.71 g. of twice recrystallized VIc as plates from ethyl acetate; m.p. 183–185°; $[\alpha]^{22}D$ +30.6° (*c* 0.782); λ_{max}^{alc} 238 mμ (ϵ 9400), 333 (207); λ_{max}^{Nujol} 3.03 (s), 5.95 (s), 6.11 (s), 6.22 (s) μ.

Anal. Calcd. for $C_{29}H_{43}O_4N$ (469.6): C, 74.16; H, 9.23. Found: C, 74.21; H, 9.14.

On acetylation in pyridine the compound was nearly quantitatively transformed to the triacetate (VIb). Conversely, pure VIc was recovered after one recrystallization from the product obtained by refluxing a solution of VIb in 5% methanolic potassium hydroxide for 0.5 hr.

Triketone VII from N-Acetyl-5,6-dihydroisojervine (VIc).—A solution prepared by diluting 0.50 ml. of the chromic acid reagent, specified by Djerassi, *et al.*[13b] (26.72 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid diluted with water to 100 ml.), to 10 ml. with reagent grade acetone was added dropwise from a buret to compound VIc (119 mg., 0.253 mmole) dissolved in pure dioxane (8 ml.). After addition of 4.20 ml. (0.61 matom of oxygen) the solution was allowed to stand for 10 min., treated with a few drops of 95% ethanol, and brought to dryness *in vacuo*. The residue was taken up in chloroform; the latter was washed with bicarbonate solution and water, dried, and evaporated. The residue was recrystallized thrice from ethyl acetate–hexane, yielding rosettes of needles; m.p. 185–187°; $[\alpha]^{22}D$ −67°

(30) A measurement carried out in 1951 at the University of Manchester with a Unicum SP-500 instrument showed the absence of maxima in the 200–220-mμ region. The ϵ-values were 6100, 8200, and 9900 at 220, 210, and 203 mμ, respectively. We wish to express our sincere thanks to Dr. H. B. Henbest and Dr. G. W. Wood for making available to us these data.

(c 0.488); the ultraviolet absorption curve exhibited a shoulder at 230 mμ (ε 11,500), a maximum at 305 (285), and shoulders at 323 and 335 (228, 150); λ_{max}^{Nujol} 5.85 (s), 5.95 (s), 6.10 (s), no band at ~3.0 μ.

Anal. Calcd. for $C_{29}H_{39}O_4N$ (465.6): C, 74.80; H, 8.44. Found: C, 74.89; H, 8.56.

The triketone was recovered unchanged after refluxing in 0.1 *N* methanolic potassium hydroxide solution for 5 min.[13b] (melting point infrared spectrum). The shoulder at 230 mμ in the ultraviolet spectrum was, however, somewhat increased in height (ε 13,200), possibly due to contamination of the starting material with the Δ^5-unsaturated compound corresponding to VIc.

N-Acetyl-4,5-dihydroisojerv-3-one (VIII).—N-Acetyl-Δ^4-isojervone (V, 120 mg.) was hydrogenated in pure ethanol (17 ml.) with palladium–charcoal (130 mg.) as the catalyst. The uptake of hydrogen gas stopped after 10 min. with 7.1 ml. of gas consumed (calcd. 6.3 ml.). The residue from the filtered solution was recrystallized twice from ethyl acetate, from which it formed small plates (85 mg.) melting at 216–218°; $[\alpha]^{21}D$ +37°; λ_{max}^{alc} 237 mμ (ε 9700), 332 (186); λ_{min}^{alc} 225 mμ (ε 9100); λ_{max}^{Nujol} 3.01 (s), 5.84 (s), 5.95 (s), 6.22 (s) μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.48; H, 8.84. Found: C, 74.78; H, 8.87.

8,9-Dihydroisojervine (IXa).—Isojervine acetonate (984 mg.) was freed from acetone by distillation with benzene as previously described. The sample, dissolved in tetrahydrofuran (25 ml.), was added slowly with mechanical stirring to a solution of lithium metal (240 mg.) in liquid ammonia (100 ml.) kept at acetone–solid carbon dioxide temperature and protected from outside moisture. After 1.3 hr. ammonium chloride (3 g.) was added in portions, and the ammonia was allowed to evaporate at room temperature. The reduced material, isolated by extraction with chloroform, was dissolved in warm ethanol, from which it deposited as small plates on addition of water to the point of incipient turbidity (534 mg.), m.p. 123–127°, after recrystallization 127–130°. Since the base formed a sparingly soluble chloroformate the rotation had to be measured in ethanol: $[\alpha]^{20}D$ −16.5° (*c* 0.792). The ultraviolet spectrum showed only end absorption (ε 3360 at 220 mμ) and a plateau between 310 and 323 mμ (ε 195); λ_{max}^{Nujol} 3.07 (ms, br) 5.78 (ms), 5.90 (l), 6.12 (vl) μ. The presence of a small amount of unreduced isojervine, indicated by the survival of the 5.90-μ band, also revealed itself in the gradual development of a faint pink color on alkalinization of an ethanolic solution.

The analyses, carried out on material dried at 100° (drying at 110° caused decomposition), gave varying results, generally on the low side for both carbon and hydrogen.

For the preparation of the triacetate (**IXb**) 259 mg. of the base were acetylated in the usual manner. The crude product was dissolved in 1:1 benzene–hexane and chromatographed on alumina (Woelm, almost neutral, activity grade I). Most of the material (185 mg.) was recovered in crystalline form in the fractions eluted with the above solvent mixture. It was recrystallized to constant melting point (156–160°, 159–161° after drying) from acetone–hexane and then hexane alone; $[\alpha]^{22}D$ +49° (c 0.860); λ_{max}^{alc} 310 mμ (ε 270), 320 (265); λ_{max}^{Nujol} 5.76 (sh, s), 5.80 (vs), 5.92 (vl), 6.10 (s), 8.03 (s) μ.

Anal. Calcd. for $C_{33}H_{47}O_6N$ (553.7): C, 71.58; H, 8.56. Found: C, 71.54; H, 8.89.

5,6,8,9-Tetrahydroisojervine (Xa).—5,6-Dihydroisojervine (VIa, 149 mg.) was reduced with lithium (40 mg.) in liquid ammonia as described above for isojervine. The partly crystalline reduction product was recrystallized three times from aqueous ethanol, yielding 54 mg. of small rods; m.p. 147–149°; $[\alpha]^{21}D$ +20.4° (*c* 0.961, ethanol); the ultraviolet spectrum showed shoulders at 230 mμ (ε ~2300) and 332 (145) and maxima at 310 (223) and 320 (221); λ_{max}^{Nujol} 2.91 (s), 3.10 (s, br), 5.78 (s), 5.90 (ml), 6.12 (ml) μ.

Anal. Calcd. for $C_{27}H_{43}O_3N \cdot {}^1/_2C_2H_5OH$ (452.7): C, 74.29; H, 10.25. Found: C, 74.58; H, 9.93.

Since the spectral data indicated contamination with about 20% starting material, the experiment was repeated but with the difference that more lithium metal was added at intervals along with the solution containing the substance. This caused the blue color of the reaction mixture to persist for 1.5 hr. However, the spectral properties of the final product were not appreciably different from those of the first specimen.

The triacetate (**Xb**), obtained in good yield without chromatography, melted at 173–175° after three recrystallizations from hexane, $[\alpha]^{22}D$ +63° (*c* 0.894). While the ultraviolet spectrum no longer exhibited the shoulder at 230 mμ, the infrared spectrum showed, aside from the bands at 5.78 (br) and 6.12 (s) μ, still a low band at 5.94 μ indicating contamination with the triacetate (VIb).

Anal. Calcd. for $C_{33}H_{49}O_6N$ (555.7): C, 71.32; H, 8.89. Found: C, 71.75; H, 8.99.

N-Acetyl-5,6,7,8-tetrahydroisojervine (Xc).—A solution of N-acetyl-5,6-dihydroisojervine (458 mg.) in dry tetrahydrofuran (30 ml.) was added dropwise with magnetic stirring and under anhydrous conditions to a solution of lithium (221 mg.) in liquid ammonia (200 ml.) cooled in a bath of acetone–solid carbon dioxide. After 1 hr., ammonium chloride (2 g.) was added slowly and then the ammonia was allowed to evaporate at room temperature. Water was added and the product was isolated by extraction with chloroform which was then washed with hydrochloric acid and water. The residue of the dried chloroform phase was crystallized twice from ethyl acetate, yielding 257 mg. of platelets which melted at 225–228°; $[\alpha]^{20}D$ +53° (*c* 0.818); λ_{max}^{alc} 311 mμ (ε 169), 322 (153), 331 (107); λ_{max}^{Nujol} 2.95 (m), 3.09 (m), 5.76 (s), 5.91 (l), 6.20 (s), 7.92 (m) μ.

Anal. Calcd. for $C_{29}H_{45}O_4N$ (471.7): C, 73.84; H, 9.62. Found: C, 73.95; H, 9.27.

N-Acetyl-5,6,8,9-tetrahydroisojervine 17,17a-Oxide (XIa).—N-Acetyl-5,6,8,9-tetrahydroisojervine (209 mg., 0.44 mmole) was treated with perbenzoic acid (0.690 mmole) in chloroform (50 ml.) at 4° for 48 hr., after which time 1.06 molar equiv. of the reagent had been consumed. The solution, diluted with an equal volume of chloroform, was washed with sodium bicarbonate and water. The glassy residue (253.3 mg.) from the dried and evaporated chloroform solution was twice crystallized from ethyl acetate yielding rods (109 mg.) melting at 195.5–198.5°. The melting point was raised to 231–235° by stirring a chloroform solution of the oxide with Woelm neutral alumina for 20 min., transferring to a chromatographic tube, and eluting with chloroform; $[\alpha]^{20}D$ −22° (*c* 0.617); λ_{sh}^{alc} 235 mμ (ε 1020); λ_{max}^{alc} 305–310 mμ (ε 22); λ_{max}^{Nujol} 3.00 (m), 5.78 (s), 5.93 (l), 6.20 (s), 7.98 (m) μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$ (487.7): C, 71.42; H, 9.30. Found: C, 71.26; H, 9.32.

The **triacetate (XIb)** prepared from XIa in the usual manner with anhydrous pyridine and acetic anhydride could not be crystallized; $[\alpha]^{20}D$ −9.4° (*c* 0.682); λ_{max}^{Nujol} 5.75 (s), 6.08 (m), 8.05 (s) μ.

Dihydrometoxazine Chloride (XIIa) from Oxide XIa.—N-Acetyl-5,6,8,9-tetrahydroisojervine 17,17a-oxide (XIa, 40 mg.) was dissolved in 90% methanol (5 ml.) and treated with 0.1 *N* hydrochloric acid (1 ml.). After 0.75 hr. at room temperature, the reaction mixture was evaporated to dryness *in vacuo* and the residue was twice crystallized from methanol and ethyl acetate, yielding needles (33 mg.) which melted at 197.5–201°; $[\alpha]^{21}D$ +59° (*c* 0.760, absolute ethanol); λ_{max}^{alc} 303 mμ (ε 71); λ_{max}^{Nujol} 3.00 (s), 5.78 (s), 6.06 (s) μ.

Anal. Calcd. for $C_{29}H_{46}O_5NCl \cdot 2CH_3COOC_2H_5$ (700.3): C, 63.45; H, 8.95. Found: C, 62.99; H, 8.95.

A solution of the chloride (12.6 mg.) in 1 ml. of methanol was shaken while being treated dropwise with 5% sodium bicarbonate solution (1.5 ml.). After the addition of water the reaction mixture was extracted with chloroform, the extract was washed with water and dried over sodium sulfate. Crystallization of the residue (7 mg.) from methanol–ethyl acetate yielded plates which were identified as the oxide XIa by the melting point (196°, undepressed in mixture with XIa) and the infrared spectrum.

Quaternary Dihydrometoxazine Chloride (XIIIa) from "Second Acetolysis Product" (XV).—The "second acetolysis product" from diacetyljervine[12] (7.8 mg.) was dissolved in methanol (1 ml.) which had been saturated with hydrochloric acid at 0°. After 20 min. at room temperature, the reaction mixture was evaporated to dryness *in vacuo*. The residue crystallized from methanol–ethyl acetate yielding 2 mg. of the salt (XV); λ_{max}^{alc} 243 mμ (ε 13,300). The infrared spectrum (potassium bromide) was identical with that of a reference sample.[9]

"Enone" 3,23,N-Triacetate (XIVb).—The 17,17a-oxide of triacetyl-5,6,8,9-tetrahydroisojervine (XIb, 564 mg.) was dissolved in benzene (75 ml.) and stirred with Woelm neutral alumina, grade I (22.6 g.), for 0.5 hr. The mixture was transferred into a chromatographic tube and the alumina column was washed first with benzene and then with ether; both these solvents eluted only minute amounts of amorphous substances. The main fraction (460 mg.), eluted with ether containing 2% of methanol,

was crystallized from ethyl acetate yielding rods (334 mg.); m.p. 222–223°; $[\alpha]^{20}D$ +48° (*c* 0.618); λ_{max}^{alc} 261 mμ (ε 10,300), 355 (120); λ_{max}^{Nujol} 2.79 (l), 5.76 (s), 5.80 (s), 5.85 (m), 6.03 (s), 6.11 (m), 7.96 (s) μ.

Anal. Calcd. for $C_{33}H_{49}O_7N$ (571.7): C, 69.32; H, 8.64. Found: C, 69.50; H, 8.55.

The **N-acetylenone (XIVa)**, which could not be prepared by treating N-acetyl-5,6,7,8-tetrahydroisojervine 17,17a-oxide with neutral alumina, was obtained by hydrolyzing the triacetylenone (XIVb) with 5% methanolic potassium hydroxide overnight. The product could not be crystallized; λ_{max}^{alc} 258 mμ (ε 8975), 335–355 (98); λ_{max}^{Nujol} 2.96 (m), 5.83 (m), 6.14 (s), 7.95 (m) μ.

Dehydration Product (XVI) from Enone Triacetate (XIVb).—A solution of enone triacetate (56.6 mg.) and maleic acid (107.6 mg.) in dioxane (5 ml.) was refluxed under nitrogen for 15 hr. and was then evaporated to a sirup *in vacuo*. The washed and dried chloroform extract yielded an amorphous residue (57 mg.) from which by chromatography on Woelm neutral alumina, grade I, there was obtained in the ether (10%)–benzene (90%) eluates the dehydration product, (XVI 34 mg.). Two crystallizations from ethyl acetate–hexane yielded needles (15 mg.) melting at 186.5–191°; λ_{sh}^{alc} 227 mμ (ε 9000), 260 (5300); λ_{max}^{alc} 317 mμ (ε 10,480); λ_{max}^{Nujol} 5.75 (s), 5.90 (m), 6.09 (s), 6.36 (l), 8.03 (s) μ

Anal. Calcd. for $C_{33}H_{47}O_6N$ (553.7): C, 71.58; H, 8.56. Found: C, 71.29; H, 8.31.

5,6-Dihydro-11-ketoveratramine Triacetate (XVII) from XVI.—A solution of the dehydration product, (XVI 14 mg.) in *p*-cymene (1.5 ml.) to which 10% palladium on carbon (15 mg.) had been added was stirred and heated at reflux temperature in a nitrogen atmosphere for 2 hr. After the removal of the catalyst by filtration, the cymene was evaporated *in vacuo* and the residue was crystallized twice from ethyl acetate–hexane. The small needles thus obtained (6.1 mg.) melted at 242–245°; $[\alpha]^{20}D$ +56° (*c* 0.406) (lit.[22] m.p. 242–245°; $[\alpha]D$ +57.5°); λ_{max}^{alc} 212 mμ (ε 3650), 251 (10,800), 300 (1870). The infrared spectrum was identical with that of an authentic specimen.[22]

Dihydrometoxazine Chloride (XVIII) from N-Acetylenone (XIVa).—To a solution of N-acetylenone (298 mg.) in methanol (24 ml.) 0.1 *N* hydrochloric acid (8 ml.) was added. After 1.5 hr., the mixture was evaporated to dryness *in vacuo* and the residue on crystallization from methanol–ethyl acetate yielded very small rods (116.4 mg.) melting at 219–222°; $[\alpha]^{20}D$ +14° (*c* 0.939, 95% ethanol); λ_{max}^{alc} 243 mμ (ε 14,800), plateau 306–318 (630); λ_{max}^{Nujol} 3.00 (sh), 3.09 (m), 5.79 (m), 6.08 (s), 8.00 (l) μ.

Anal. Calcd. for $C_{29}H_{44}O_4NCl$ (506.1): C, 68.82; H, 8.76; Cl, 7.01. Found: C, 68.69; H, 8.67; Cl, 6.97.

5,6-Dihydrojervisine 17-Monoacetate (XIXa). A. From Dihydrometoxazine Chloride (XVIII).—To a solution of the chloride (XVIII, 41 mg.) in methanol (5.5 ml.) a 2 *N* aqueous solution of sodium carbonate (5.5 ml.) was added slowly. The reaction mixture was diluted with water and extracted twice with ether (20 ml.). The residue from the washed and dried ether phase was twice crystallized from ethyl acetate–hexane, yielding 24 mg. of small rods which melted at 276–278°; $[\alpha]^{21}D$ −61° (*c* 0.7141); λ_{sh}^{alc} 235 mμ (ε 537); λ_{max}^{Nujol} 2.85 (l), 5.75 (s) μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$ (487.7): C, 71.42; H, 9.30. Found: C, 71.64; H, 9.01.

B. From Jervisine 17-Monoacetate.—Jervisine 17-monoacetate (100 mg.) was hydrogenated with prereduced PtO_2 (93 mg.) in glacial acetic acid (10 ml.). When 1 mole equiv. of hydrogen had been consumed the uptake came to a standstill. The crude reduction product was twice recrystallized from ethyl acetate–hexane yielding rectangular plates melting at 275–278°; $[\alpha]^{21}D$ −61° (*c* 0.742); λ_{sh}^{alc} 235 mμ (ε 331). The infrared spectrum was identical with that of the previous specimen.

The triacetate (XIXb) obtained from the monoacetate prepared according to A by acetylation with acetic anhydride and pyridine crystallized from hexane in small blocks melting at 187–189°; $[\alpha]^{21}D$ −73.0 (*c* 0.535); λ_{max}^{Nujol} 5.72 (sh), 5.76 (s), 8.00 (s) μ.

Anal. Calcd. for $C_{33}H_{49}O_7N$ (571.7): C, 69.32; H, 8.64. Found: C, 69.35; H, 8.49.

The specimen prepared from the monoacetate B showed identical properties, inclusive of the infrared spectrum.

N-Acetyl-13,17a-dihydro-Δ⁴-jerv-3-one.—A solution of N-acetyldihydrojervine,[2] m.p. 260–262° (118 mg.), and aluminum *t*-butoxide (500 mg.) in dry toluene (9 ml.) and acetone (1 ml.) was boiled under reflux for 5.5 hr. The solvents were removed *in vacuo*, and the residue was distributed between 1 *N* sulfuric acid and chloroform. After separation of the layers and extraction of the aqueous phase with another portion of chloroform the extract was washed with 1 *N* sulfuric acid, aqueous bicarbonate, and water. The residue from the dried extract was treated with Girard's reagent T and separated into nonketonic and ketonic fractions in the usual manner, except that the former fraction was extracted from the aqueous phase with benzene and the latter fraction with chloroform. The ketonic material (88 mg.) was dissolved in benzene and chromatographed on alumina. The crystalline material eluted with 1:9 ether–benzene (48 mg.) was recrystallized from ethyl acetate–hexane, from which it formed plates melting at 204–206°; $[\alpha]^{21}D$ +100° (*c* 0.762); λ_{max}^{alc} 234 mμ (ε 16,400), 295 (132); λ_{max}^{Nujol} 2.88 (l), 5.79 (s), 6.00, 6.05 (s, doublet), 6.19 (l) μ.

Anal. Calcd. for $C_{29}H_{41}O_4N$ (467.6): C, 74.47; H, 8.84. Found: C, 74.75; H, 8.59.

Acknowledgment.—The authors are indebted to Mr. Joseph Alicino and his associates for the microanalyses and to Dr. Nettie H. Coy and her colleagues for the ultraviolet and infrared measurements.

Jervine. XII. Transformation Products of 5,6-Dihydroisojervine and N-Acetyl-Δ⁴-isojerv-3-one

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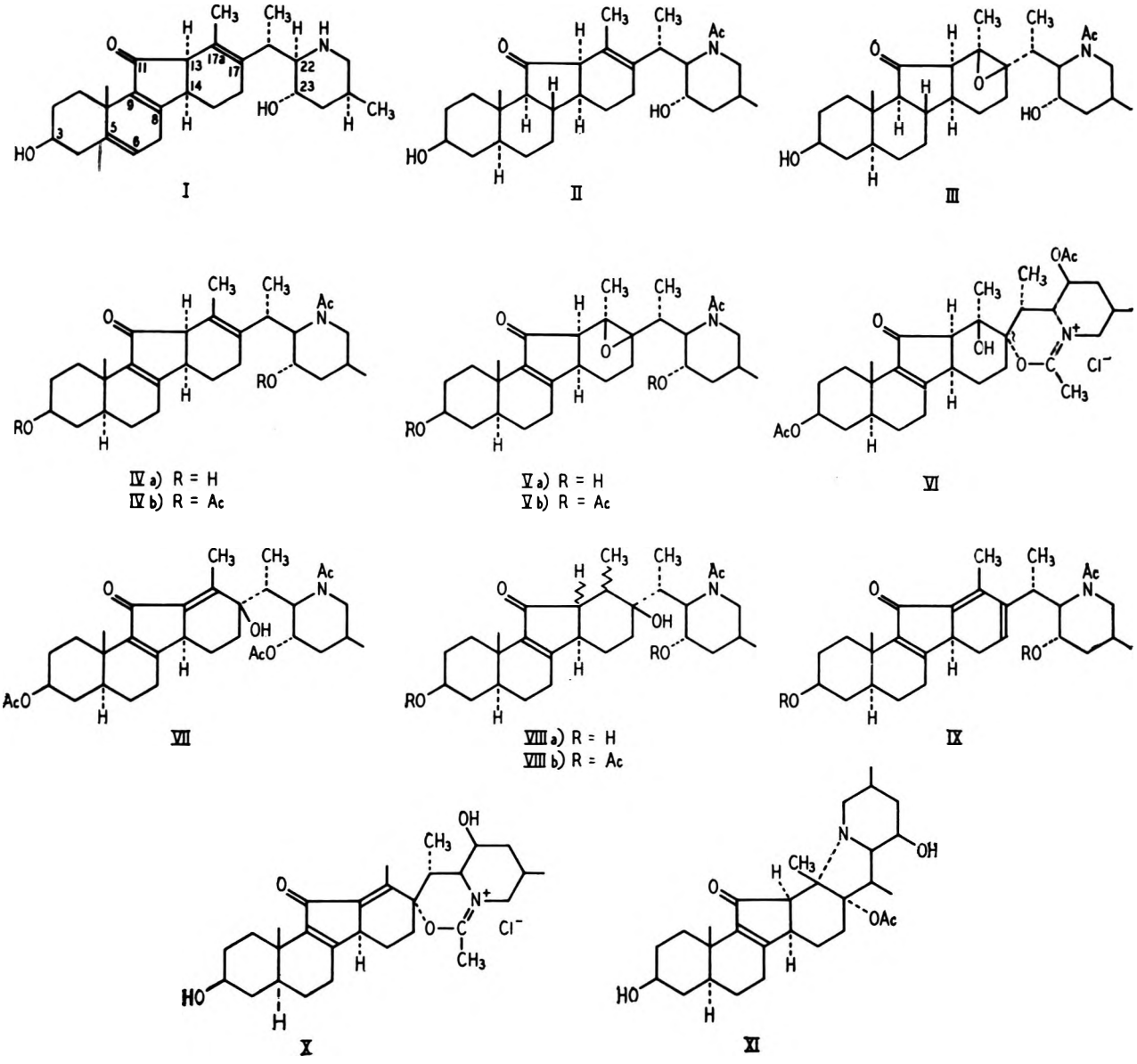
Transformations paralleling those previously performed on N-acetyl-5,6,8,9-tetrahydroisojervine (II) have been carried out on N-acetyl- and triacetyl-5,6-dihydroisojervine (IVa and b) and on N-acetyl-Δ⁴-isojerv-3-one (XII). The results, aside from lending additional support to structure I for isojervine, render it likely that no inversion of carbon atom 14 has occurred during the reduction of the 8,9-double bond in the preparation of the tetrahydro derivative, *i.e.*, that both compounds have the 14α configuration.

The preceding paper of this series[1] delineates the structure proof for isojervine (I) which was brought about by relating N-acetyl-5,6,8,9-tetrahydroisojervine (II) *via* the latter's 17,17a-oxide (III) to known derivatives of jervine, namely, triacetyl-5,6-dihydro-11-ketoveratramine and jervisine 17-monoacetate. Similar transformations *via* epoxides of type III had been performed prior to that work[1] with N-acetyl- and triacetyl-5,6-dihydroisojervine (IVa and b) and with N-acetyl-Δ⁴-isojerv-3-one (XII) as the starting materials and, while these were instrumental for recognizing I as the correct structure, it became clear later that conclusive proof

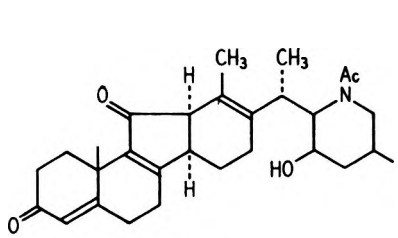
(1) O. Wintersteiner and M. Moore, *J. Org. Chem.*, **29**, 262 (1964); preliminary publication, *Tetrahedron Letters*, **18**, 795 (1962).



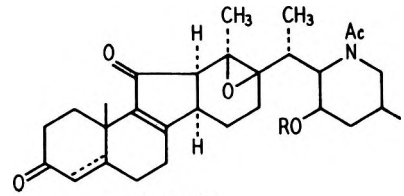
would be attainable only by carrying through these sequences in the tetrahydro series. Nevertheless the parallel results obtained in the 5,6-dihydro- and Δ^4-isojervone series and reported in this paper constitute important subsidiary evidence for structure I and are also essential to one of the points in the stereochemical argument.

The preparation of 5,6-dihydroisojervine and its acetylated derivatives has been described.[1] Its 3,23,N-triacetate (IVb) readily reacted with 1 mole of perbenzoic acid to yield the crystalline 17,17a-oxide (Vb) which still showed the ultraviolet characteristics of IVb [λ_{max}^{alc} 237 mμ (ϵ 11,420), 316 (70)], except that the minimum at 225 mμ was shifted to 217 mμ (lack of contribution of 17,17a-double bond). Alternatively, this compound could be prepared by epoxidation of N-acetyl-5,6-dihydroisojervine (IVa) and acetylation of the resulting likewise crystalline oxide (Va). The oxide (Vb) was transformed with dilute ethanolic hydrochloric acid into the cyclic quaternary base chloride (VI), the new hydroxyl group of which (infrared band at 2.86 μ) was resistant to acetylation. On treatment with sodium bicarbonate in methanol the salt reverted to the oxide (Vb).

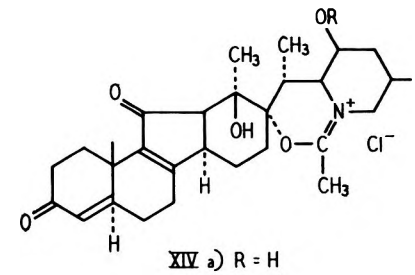
When the oxide triacetate (Vb) was adsorbed from benzene solution on neutral alumina and then chromatographed in the usual manner, no elution could be effected until some methanol (2%) was added to the last eluent (ether). This paralleled the behavior observed with the 17,17a-oxide derived from triacetyltetrahydroisojervine.[1] As in the latter case, the oxide ring had been opened with the formation of a hydroxyl group at C-17, and of an olefinic bond conjugated with the 11-keto group, as evidenced by λ_{max} 273 mμ (ϵ 11,300) of the crystalline product obtained in 90% yield in this reaction. The substance accordingly must be the cross-conjugated dienone (VII) corresponding to the 13,17a-en-11-one obtained in the tetrahydro series.[1] While the 13,17a-double bond of the latter is resistant to catalytic hydrogenation, it is sufficiently activated in the dienone (VII) to add hydrogen quite rapidly in the presence of palladium–charcoal. The resulting 8,9-en-11-one (VIIIb) was amorphous, but with alkali gave the crystalline N-acetyl derivative (VIIIa). The fact that the hydrogenation product exhibits the ultraviolet absorption spectrum characteristic for 5,6-dihydroisojervine [λ_{max} 238 mμ (ϵ 10,300)] constitutes conclusive



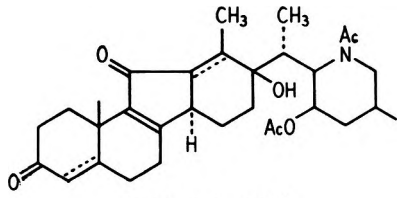
XII



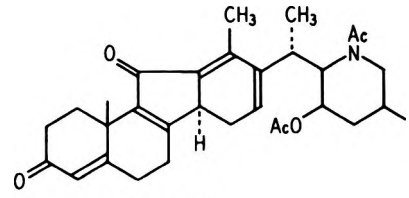
XIII (with Δ^4)
a) R = H
b) R = Ac
XIX (without Δ^4); R = Ac



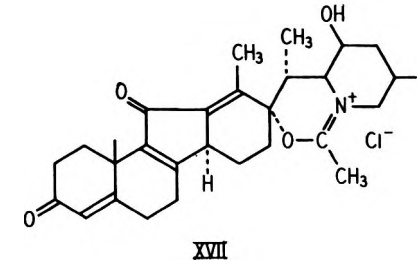
XIV a) R = H
b) R = Ac



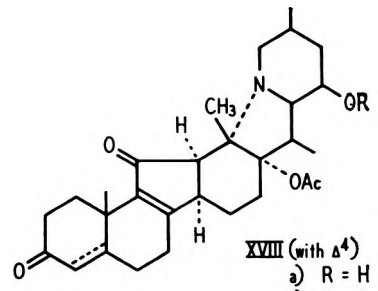
XV (with Δ^4, $\Delta^{13\text{-}17a}$)
XX (without Δ^4, $\Delta^{13\text{-}17a}$)



XVI



XVII



XVIII (with Δ^4)
a) R = H
b) R = Ac
XXI (without Δ^4)
R = H

proof for the 8,9-position of the "second" double bond of isojervine.

On prolonged boiling of a solution of the dienone (VII) in dioxane containing maleic acid[1] the 17-hydroxyl group was eliminated by dehydration, as evidenced by the ultraviolet characteristics [λ_{max} 325 mμ (ϵ 6600), and inflection at 233 (3800) and 294 (4500)] of the resulting trienone (IX). The dehydrogenation of ring D with palladium, which in the tetrahydro series had led to triacetyl-5,6-dihydro-11-ketoveratramine,[1] was not carried out on this compound, because the indenone which should have been formed was not known.

Short treatment of the dienone (VII) with methanolic hydrogen chloride at room temperature afforded, with loss of the 3- and 23-acetyl groups, the dihydrometoxazine base chloride (X).[2] The hypsochromic shift of the main ultraviolet maximum attending the analogous transformation of the enone of the tetrahydro series referred to before,[1] and of the "second acetolysis product" obtained in the sulfuric acid-catalyzed acetolysis of diacetyljervine[3] also was observed in the present case; as in the spectrum of X this maximum is located at 254 mμ.

As all the cyclic quaternary salts of this type, X was instantaneously isomerized on treatment with sodium carbonate to a crystalline weak tertiary base structurally related to jervisine[4,1] which in this case must be 5,6-dihydro-8,9-dehydrojervisine 17-monoacetate (XI). Its ultraviolet absorption spectrum showed that the chromophor present was that of 5,6-dihydroisojervine [λ_{max} 238 mμ (ϵ 8250)] as expected.

The same series of reactions was carried out with N-acetyl-Δ^4-isojervone (XII)[1] as the starting material. Its 17,17a-oxide (XIIIa) was amorphous, but on acetylation yielded a crystalline 23,N-diacetyl derivative (XIIIb). The ultraviolet spectrum of this compound is virtually the same as that of the parent diketone (XII) and, since the latter is a composite of the absorption curves of isojervine and 13,17a-dihydro-Δ^4-jervone (the latter representing the ring A chromophor contribution only),[1] it was clear that the "third" double bond of isojervine (the position of which was then unknown) was not connected in any way with the latter's abnormal ultraviolet characteristics.

The oxides (XIIIa and XIIIb) were transformed on short treatment with dilute hydrochloric acid to the crystalline cyclic quaternary base chlorides (XIVa and XIVb, respectively), of which the latter also could be obtained by acetylation of the former. The reaction XIIIb → XIVb was readily reversed when an aqueous solution of the salt was alkalinized with sodium carbonate.

The 23,N-diacetyl oxide (XIIIb) could be isomerized with neutral alumina in the usual manner to the enone-dienone (XV), the ultraviolet spectrum of which exhibited a high maximum at 235 mμ (ϵ 22,500) and an inflection at 268 (14,700), which originate, respectively,

(2) As pointed out in paper XI[1] this conversion cannot be effected, as in the similar reaction Vb → VI, with dilute ethanolic hydrochloric acid, since it depends, for reasons as yet obscure, on the prior or simultaneous removal of the 23-acetyl group.

(3) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **75**, 4938 (1953).

(4) O. Wintersteiner and M. Moore, *ibid.*, **78**, 6193 (1956).

in the enone and dienone chromophors. The absorption curve obtained by subtracting from the curve of XV that of N-acetyl-13,17a-dihydro-Δ^4-jervone shows a maximum at 275 mμ (ϵ 11,800), very similar to that in the absorption curve of the dienone (VII) derived from 5,6-dihydroisojervine [273 mμ (ϵ 11,300)]. It is clear from this that the inhibition of resonance produced in the $\Delta^{8,9}$-11-ketone system by the 4,5-double bond of Δ^4-isojervone is no longer operative when the conjugation in this system is extended by the additional double bond in the 13,17a-position.

In the ultraviolet spectrum of the dehydration product of XV, the enone–trienone XVI, the trienone chromophor gives rise to a maximum at 328 mμ (ϵ 9650) corresponding to the maximum at 325 mμ in that of the trienone (IX) of the 5,6-dihydro series. Treatment of XV with methanolic hydrochloric acid afforded the acetyl-free dihydrometoxazine chloride (XVII) analogous to the chloride (X) of the 5,6-dihydro series. The high maximum at 247 mμ (ϵ 25,300) in the ultraviolet spectrum of this compound is obviously a composite of the 254-mμ maximum characteristic for the dienone–dihydrometoxazine grouping in X and of the ring A, α,β-unsaturated keto group maximum at 235 mμ. The jervisine derivative (XVIIIa) obtained from XVII with sodium carbonate was amorphous, but could be obtained in crystalline form as the hydrochloride.[5] The acetylation product of XVIIIa, the 17,23-diacetate (XVIIIb), was likewise crystalline. These compounds contain the same two chromophors as the starting product, N-acetyl-Δ^4-isojervone (XII), and hence their spectra should show the same abnormality (lack of activity of spectra of separate chromophors) as that of XII. This was indeed the case, as, except for a slight bathochromic shift in the position of the main maximum and somewhat higher extinction coefficients [λ_{max} 231–232 mμ (ϵ ~22,000–24,000)], the spectra of the jervisine derivatives (XVIIIa and b) are identical with that of XII.

That saturation of the 4,5-double bond in N-acetyl-Δ^4-isojervone brings out the normal ultraviolet characteristics of the ring C chromophor as they are seen in 5,6-dihydroisojervine [λ_{max} 238 mμ (ϵ ~10,000)] has been reported.[1] This spectral change also occurred when this double bond was reduced catalytically in some of the transformation products of XII described before. The reduction products thus obtained were (1) the amorphous 23,N-diacetyl-4,5-dihydroisojervone 17,17a-oxide (XIX), by reduction of the oxide (XIIIb) (a product with an identical infrared spectrum was obtained by epoxidation with perbenzoic acid of N-acetyl-4,5-dihydroisojervone[1] followed by acetylation; these two reactions were originally carried out to make sure that the "third" double bond of isojervine did not shift under the influence of the palladium catalyst); (2) 23,N-diacetyl-4,5,13,17a-tetrahydro-17β-hydroxyisojervone (XX), amorphous, by catalytic reduction (uptake 2 moles of hydrogen) of the enone–dienone (XV); and (3) the 4,5-dihydro derivative (XXI, amorphous) of the 8,9-dehydro-Δ^4-jervisine-3-one 17-monoacetate (XVIIIa).

(5) As was reported in paper IV of this series (ref. 3) we were unable to prepare stable salts (hydrochloride or perchlorate) from jervisine 17-monoacetate itself. The divergent behavior of XVIIIa cannot be due to a difference in base strength, as the titration curves of both bases are practically identical.

The reasons for assigning the configurations shown in the formulas to carbon atoms 13, 14, 17, and 17a, whenever these are asymmetric, have been given in the preceding paper of this series.[1] As was mentioned there and in our preliminary communication[1] the assignment to C-14 in isojervine of the "natural" α configuration rests on the fact that not only 5,6,8,9-tetrahydroisojervine but also 5,6-dihydroisojervine and Δ^4-isojervone could be transformed into jervisine derivatives. Stated in full the argument runs as follows: As has been shown by Mitsuhasi and Shimizu,[6] the configurations of C-9, C-8, and C-14 in jervine are the same as in normal steroids (α, β, α, respectively), and this must be true also of jervisine which is obtained from jervine by reactions which do not involve these carbon atoms. Since the latter statement also applies to the conversion of N-acetyl-5,6,8,9-tetrahydroisojervine to 5,6-dihydrojervisine 17-monoacetate,[1] this isojervine derivative, too, must have the α configuration at C-14. On the other hand, it could not be *a priori* assumed that this holds also for isojervine itself and those of its derivatives which still possess the 8,9-double bond, because the possibility of an inversion at this vinylogous position consequent to the reduction of this double bond with lithium in liquid ammonia[1] cannot be entirely discounted (for the reason that such an inversion may lead to the thermodynamically more stable (α,α) *cis* linkage of rings C and D in case C-14 was β, and C-13 α, in isojervine). We believe that this possibility can be excluded for the following reasons.

First, in that case, all the transformation products of 5,6-dihydroisojervine and of N-acetyl-Δ^4-isojervone described in this paper inclusive of the final jervisine derivatives would have to differ from those of tetrahydroisojervine by epimerism at C-14 and, in view of the completely parallel results in all three series in regard to the reactions observed and yields obtained, particularly in the extremely facile last step yielding the jervisines, this does not seem very likely.[7]

Unfortunately, correlating 5,6-dihydrojervisine-17-monoacetate (the compound derived from tetrahydroisojervine) experimentally with XI (from 5,6-dihydroisojervine) would not resolve this uncertainty, because this could be achieved only by reduction of the 8,9-double bond of XI with lithium and ammonia, the very reaction which introduces this uncertainty. There is, however, suggestive evidence from a quite analogous case indicating that this reaction does not affect the configuration of C-14: 3β-Hydroxy-11-keto-Δ^8-22a-spirostene acetate (or propionate), a 14α-steroid, is reduced by lithium and ammonia to the corresponding nonacylated spirostane with the normal 8β, 9α, and 14α configurations,[8] in spite of the fact that it is the *unstable*

(6) H. Mitsuhasi and Y. Shimizu, *Tetrahedron Letters*, 777 (1961).

(7) One of the referees who was reluctant to go along with this reasoning suggested that the addition of the nitrogen atom to the 13,17a-double bond of the jervisine precursors (X and XVII) need not even result in the same configuration at C-17a as in jervisine itself if these compounds should have the 14β configuration. To counter this argument we can only point to the very similar values for the 18-methyl signals in the n.m.r. spectra of the three jervisine derivatives in question (5,6-dihydrojervisine 17-monoacetate, 8.65; XI, 8.63; XVIIIa, 8.61 τ), although it is, of course, not certain that the anisotropy effects of the 11-keto group and the 17α-acetoxy group, if operative at all, would differ sufficiently in the two 17a-epimeric forms to produce greater shifts than those observed for XI and XVIIIa.

(8) E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda, and M. Tishler, *J. Am. Chem. Soc.*, **74**, 2696 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *ibid.*, **74**, 2696 (1952).

14-epimer, since it is isomerized by strong alkali to the 14β-spirostene.[9] If with the corresponding compound, in our case N-acetyl-5,6-dihydroisojervine, inversion at C-14 should nevertheless have occurred during the reduction to the tetrahydro derivative, it would by virtue of this event have to be the unstable 14-epimer. The fact, however, is that it remained unchanged on treatment with boiling methanolic potassium hydroxide solution. It is, therefore, highly probable that isojervine, 5,6-dihydroisojervine, 8,9-dihydroisojervine, and tetrahydroisojervine all have the 14α configuration which is also that in jervine.

Experimental

The melting points were taken in open Pyrex glass capillaries and are corrected for stem exposure. The rotation measurements were carried out in a 1-dm. semimicrotube, with chloroform as the solvent, unless indicated otherwise. The ultraviolet spectra were measured in absolute ethanol in a Cary self-recording instrument Model 11 M. The infrared spectra were determined on Nujol mulls in the Perkins-Elmer double beam self-recording spectrophotometer Model 21. The characteristics of the infrared bands are expressed in the text as follows: (s), strong; (m), medium; (l), low; (vl), very low; (br), broad; (sh), shoulder. The analytical samples were dried at 110° (2 mm.) unless indicated otherwise.

N-Acetyl-5,6-dihydroisojervine 17,17a-Oxide (Va).—N-Acetyl-5,6-dihydroisojervine (257 mg., 0.547 mmole) was dissolved in chloroform (50 ml.) containing perbenzoic acid (0.84 mmole). The solution was kept at 4° for 46 hr., when, as was determined by titration of small aliquots at intervals, 0.953 equiv. of the acid had been consumed. After addition of more chloroform, the solution was washed with sodium bicarbonate solution and water, dried, and evaporated. The residue was recrystallized three times from ethyl acetate, yielding about 100 mg. of rods; m.p. 177–179°; $[\alpha]^{21}D$ +28° (*c* 0.998); λ_{max}^{alc} 237 mμ (ε 10,690), 319 (67); λ_{max}^{Nujol} 2.91 (s), 3.04) (sh, s), 5.93 (s), 6.15 (sh, s), 6.20 (s) μ.

Anal. Calcd. for $C_{29}H_{43}O_5N$ (485.6): C, 71.72; H, 8.93. Found: C, 72.00; H, 8.84.

Triacetyl-5,6-dihydroisojervine 17,17a-Oxide (Vb).—This compound was prepared from triacetyl-5,6-dihydroisojervine (8.962 g., 16.25 mmoles) with perbenzoic acid (24 mmoles) in the manner described before for Va. The crude product crystallized from aqueous ethanol in small rod (6.7 g.) melting at 172–174°.

A slightly higher melting specimen (m.p. 174–175°) showing identical infrared characteristics was obtained by acetylation in pyridine and acetic anhydride of the N-acetyl derivative (Va); $[\alpha]^{20}D$ +40.5° (*c* 0.859); λ_{max}^{alc} 237 mμ (ε 11,420), 316 (70); λ_{min}^{alc} 217 mμ (ε 7700); λ_{max}^{Nujol} 2.80 (s), 5.93 (s), 6.11 (s), 8.08 (s) μ.

Anal. Calcd. for $C_{33}H_{47}O_7N$ (569.7): C, 69.57; H, 8.32. Found: C, 69.83; H, 8.14.

3,23-Diacetyldihydrometoxazine Chloride (VI) from Vb.—A solution of the epoxide (Vb, 50 mg., 0.088 mmole) in 80% aqueous methanol (8 ml.) containing 0.9 mg. of 0.1 *N* hydrochloric acid was allowed to stand for 1 hr., and then evaporated to dryness *in vacuo*. The residue crystallized from methanol–ethyl acetate in small rods (51 mg.) which after recrystallization melted at 197–199°; $[\alpha]^{22}D$ +101° (0.635); λ_{max}^{alc} 237 mμ (ε 10,000), 315 (56); λ_{max}^{Nujol} 2.86 (m), 3.04 (s), 5.73 (m, s), 5.79 (s), 5.95 (s), 6.14 (s) 8.04 (s) μ. The strong band at 6.14 μ must represent the combined contribution of the conjugated double bond and of the grouping —O—C=N⁺< as does the band at 6.10 μ of the dihydrometoxazine salt (X).[4]

The analysis of a sample (a) dried at 110° showed that the salt contained 1 mole of water of crystallization which, however, could be removed by drying at 137° (sample b).

Anal. Calcd. for $C_{33}H_{48}O_7HCl \cdot H_2O$ (624.2): C, 63.50; H, 8.07; for $C_{33}H_{48}O_7NCl$ (606.2): C, 65.39; H, 7.98. Found for sample a: C, 63.41; H, 8.12; neut. equiv. ($HClO_4$ titration in acetic acid in presence of mercuric acetate), 612. Found for sample b: C, 65.47; H, 7.98.

(9) C. Djerassi, W. Frick, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 3496 (1953).

The salt was recovered unchanged after treatment with acetic anhydride and pyridine overnight.

For the back conversion to the epoxide (Vb) a solution of the salt (17 mg.) in methanol (1 ml.) was added dropwise to 2 ml. of a cold 5% sodium bicarbonate solution (the product obtained with sodium carbonate proved to be more difficult to purify). After a short standing and dilution with more water the product was recovered by extraction with chloroform (11 mg.) and twice recrystallized from aqueous methanol. The crystals (m.p. 172–174°) did not depress the melting point of the epoxide (Vb) and exhibited the same infrared spectrum.

Dienone VII from Vb.—A solution of triacetyl-5,6-dihydroisojervine 17,17a-oxide (2.13 g.) in benzene (60 ml.) was stirred with Woelm neutral alumina (63 g.) for 25 min. The mixture was transferred to a chromatographic tube and eluted first with benzene, then ether, and finally with ether containing 2% methanol, the first portion of which contained 1.768 g. of the crude dienone. After one crystallization there remained 1.089 g. of small rods; m.p. 205–207°; $[\alpha]^{20}D$ +155° (*c* 0.794); λ_{max}^{alc} 273 mμ (ε 11,300), shoulder 337 (476); λ_{max}^{Nujol} 2.90 (l), 5.78 (vs), 5.95 (l, sh), 6.02 and 6.11 (s), 6.24 (ms), 7.99 and 8.10 (vs), 9.78 (s), 10.51 (m) μ.

Anal. Calcd. for $C_{33}H_{47}O_7N$ (569.7): C, 69.57; H, 8.32; $3COCH_3$, 22.66. Found: C, 69.51; H, 8.13; $COCH_3$, 17.16.

13,17a-Dihydro Derivative of VII (Triacetate VIIIb).—When a solution of the dienone (VII, 202 mg.) in absolute ethanol (20 ml.) was shaken with hydrogen in the presence of 5% palladium on charcoal (200 mg.), 1 molar equiv. of hydrogen was consumed in 25 min. After the removal of the catalyst and solvent, the noncrystalline residue was lyophilized from benzene; $[\alpha]^{20}D$ +85.0° (*c* 0.581); λ_{max}^{alc} 238 mμ (ε 10,350), 318 (81); λ_{max}^{Nujol} 2.92–3.01 (l, br), 5.78 (vs), 5.95 (s), 6.10 (s, sh) and 6.19 (s), 8.04 (vs), 9.68 (s), 10.49 (m) μ.

Anal. Calcd. for $C_{33}H_{49}O_7N$ (571.7): C, 69.32; H, 8.64. Found: C, 69.11; H, 8.46.

The N-acetyl derivative (VIIIa) was prepared by hydrolyzing the triacetate was 5% methanolic potassium hydroxide at room temperature overnight. The product crystallized from methanol–ethyl acetate as needles melting at 266–268°; $[\alpha]^{21}D$ −3.8° (*c* 0.617); λ_{max}^{alc} 239 mμ (ε 10,630), 290 (9326); λ_{max}^{Nujol} 3.00–3.15 (m, br), 5.95 (s), 6.08 (s), 6.20 (vs), 8.03 (m), 9.53 (m), 10.52 (ml) μ.

Anal. Calcd. for $C_{29}H_{45}O_5N$ (487.7): C, 71.42; H, 9.30. Found: C, 71.44; H, 8.92.

Dehydration Product IX of VII ($\Delta^{8,13-17a,16-17}$-trien-11-one).—A solution of the dienone (VII, 114 mg.) and maleic acid (218 mg.) in dioxane (10 ml.) was boiled under reflux in a nitrogen atmosphere for 16 hr., and then evaporated under nitrogen to a sirup which was dissolved in chloroform and washed with sodium bicarbonate solution and water. The residue from the chloroform phase (111 mg.) crystallized as small rods from ethyl acetate–hexane and after four crystallizations melted at 207–209°; λ_{max}^{alc} 325 mμ (ε 6600), 294 (4550), shoulder 233 (3785); λ_{max}^{Nujol} 5.75 (s), 6.03 (s), 6.10 (s), 6.20 (m), 6.39 (ml), 8.05 (s), 9.77 (ms), 11.06 (ml) μ.

Anal. Calcd. Calcd. for $C_{33}H_{45}O_6N$ (551.7): C, 71.84; H, 8.22. Found: C, 71.89; H, 8.14.

Dihydrometoxazine Chloride (X) from VII.—The dienone (VII, 649 mg.) was dissolved in 9 *N* methanolic hydrochloric acid (30 ml.). After 20 min. standing at room temperature, the solution was evaporated to dryness *in vacuo*. Water was added, and the reaction mixture was again evaporated to dryness. The residue was crystallized twice from methanol–ethyl acetate, yielding 140 mg. of m.p. 225–228°; $[\alpha]^{24}D$ +153° (*c* 0.603, 95% ethanol); λ_{max}^{alc} 254 mμ (ε 14,760), 338 (1430); λ_{max}^{Nujol} 3.04 and 3.12 (s), 5.93 (s), 6.10 and 6.19 (s), 9.58 (s), 11.08 (s), 11.29 (m) μ.

Anal. Calcd. for $C_{29}H_{42}O_4NCl$ (504.1): C, 69.09; H, 8.40. Found: C, 69.16; H, 8.27.

5,6-Dihydro-8,9-dehydrojervisine 17-Monoacetate (XI).—A solution of the chloride (X, 123 mg.) in methanol (15 ml.) was treated with 2 *N* sodium carbonate (17 ml.) and then diluted with water (50 ml.). The residue (97 mg.) from the washed and dried ether extract crystallized as small needles from ethyl acetate. After two recrystallizations from ether–hexane the base (49 mg.) melted at 155–158°; $[\alpha]^{21}D$ +28° (*c* 1.026); λ_{max}^{alc} 237 mμ (ε 8500); λ_{max}^{Nujol} 3.03 (m), 5.76 (ms), 5.81 (s), 8.00 (s), 9.62 (s) μ.

Anal. Calcd. for $C_{29}H_{43}O_5N$ (485.6): C, 71.71; H, 8.93. Found: C, 71.67; H, 8.98.

Potentiometric titration in 50% ethanol with 0.015 *N* hydrochloric acid showed that the compound is a very weak base with $pK_a \sim 3$.

N-Acetyl-Δ^4-isojerv-3-one 17,17a-Oxide (XIIIa).—N-Acetyl-Δ^4-isojervone (3.01 g., 6.47 mmoles) was treated with perbenzoic acid (8 mmoles) in chloroform (300 ml.) for 27 hr., after which time 1.00 molar equiv. of the reagent had been consumed. The solution was washed with sodium bicarbonate solution and water, dried, and freed from solvent *in vacuo*, yielding an amorphous product which could not be induced to crystallize. The sample for the analysis and spectral measurements was dried at 56° (2 mm.); weight loss, 4.8%; λ_{max}^{alc} 230 mμ (ε 21,500), 315 (275); λ_{max}^{Nujol} 2.94 (l), 5.90, 5.96, and 6.08 (triplet, s), 6.15 (sh, s) μ.

Anal. Calcd. for $C_{29}H_{39}O_5N$ (481.6): C, 72.32; H, 8.18. Found: C, 72.02; H, 7.93.

23,N-Diacetyl-Δ^4-isojerv-3-one 17,17a-Oxide (XIIIb).—The epoxide XIIIa (1.4 g.) was treated with acetic anhydride (17 ml.) and pyridine (34 ml.) for 20 hr. at room temperature. The product, isolated in the usual manner by extraction with chloroform, crystallized from a small volume of methanol (660 mg., m.p. 170–172°). The crystalline fraction was recrystallized from methanol–ether and then from acetone–ether, and melted at 181–182°; $[\alpha]^{21}D$ +198° (c 0.850); λ_{max}^{alc} 233 mμ (ε 21,200), 318 (115); λ_{max}^{Nujol} 5.79 (ms), 5.92 (s), 6.02 (s), 6.11 (s), 8.04 (s) μ.

Anal. Calcd. for $C_{31}H_{41}O_6N$ (523.7): C, 71.10; H, 7.87. Found: C, 71.32; H, 7.70.

Dihydrometoxazine Chloride (XIVa) from XIIIa.—The amorphous epoxide (XIIIa, 1.141 g., 2.37 mmoles) was dissolved in ethanol (100 ml.), and 0.1 *N* hydrochloric acid (25 ml.) and water (75 ml.) were added. After 0.75 hr. the solution was concentrated to a small volume *in vacuo*. The resulting crystals (588 mg.) were recrystallized from methanol ethanol, yielding 368 mg. of needles melting at 237–238°. Additional amounts of already pure material (345 mg.) were obtained from the two mother liquors; $[\alpha]^{21}D$ +294° (c 0.929, water); λ_{max}^{alc} 229 mμ (ε 23,800), 315 (109); λ_{max}^{Nujol} 3.02 (sh, ms) 3.09 (s), 5.92 (s), 6.04 (s), 6.19 (m) μ.

Anal. Calcd. for $C_{29}H_{40}O_5NCl$ (518.1): C, 67.22; H, 7.78; Cl, 6.84. Found: C, 67.32; H, 7.62; Cl, 6.61; neut. equiv. ($HClO_4$ titration in acetic acid in presence of mercuric acetate), 530.

No acetyl was demonstrable by the Kuhn–Roth method. On titration of the salt in water solution (pH 3.3) the pH rose to 9.0 after the addition of 0.1 equiv. of alkali and then to 10.2 at half-neutralization, only 0.5 units lower the water blank curve at this point. On standing for 10 min. the pH dropped by 1 unit, indicating slow back conversion to the epoxide. In contrast, in the titration of the dihydrometoxazine salts of type X this phenomenon occurred already at pH 7.7 after the addition of the first drops of alkali (rearrangement to weakly basic jervisine derivatives).[4]

For the preparation of the **23-acetyl base chloride (XIVb)** a suspension of XIVa (80 mg.) in acetic anhydride (2 ml.) and pyridine (4 ml.) was shaken mechanically overnight. The clear, pale yellow solution was taken to dryness, and the residue was recrystallized twice from methanol–ethyl acetate. Small rods (42 mg.) were obtained; they were hygroscopic, m.p. 162–165°, and 167–169°, after drying to constant weight at 110° (2 mm.); weight loss, 13%; $[\alpha]^{21}D$ of dry material +244° (c 0.832); λ_{max}^{alc} 299 mμ (ε 23,500), 308 (196); λ_{max}^{Nujol} 5.75 (m), 5.90 (s), 6.05 (vs, br), 8.11 (s) μ.

Anal. Calcd. for $C_{31}H_{42}O_6NCl$ (560.1): C, 66.47; H, 7.56. Found: C, 66.22; H, 7.68.

An identical product (m.p. 167–168°) was obtained in good yield (86 mg.) when the epoxide (XIIIb, 100 mg.) was treated with 1 equiv. of hydrochloric acid as described earlier for the reaction XIIIa → XIVa.

For the back conversion of the chloride (XIVb) to the epoxide (XIIIb) an aqueous solution of the salt (20 mg.) was added dropwise to 2 *N* sodium carbonate solution with shaking. The product was recovered by extraction with ether and crystallized from aqueous methanol (12 mg., m.p. 177–182°). The identity with XIIIb was confirmed by the mixture melting point, the spectral data, and analysis (Found: C, 71.31; H, 7.90.).

Enone–Dienone XV from XIIIb.—23,N-Diacetyl-Δ^4-isojervone 17,17a-oxide (907 mg.) was chromatographed in the usual manner on a column of Woelm neutral alumina (277 g.). The fractions eluted with benzene, benzene–ether, and ether were negligible. The enone–dienone (830 mg.) was eluted by ether containing 2% methanol and after recrystallization from acetone–methanol melted at 202–204.5°; $[\alpha]^{21}D$ +305°; λ_{max}^{alc} 235 mμ (ε 22,550); λ_{sh}^{alc} 268 mμ (ε 14,740), 360 (276); λ_{max}^{Nujol} 2.90 (ml), 3.03 (l), 5.78 (ms), 5.85 (s), 6.00 (vs), 6.07 (s), 6.19 (s), 8.00 (s), 9.79 (m), 10.42 and 10.60 (m), 11.52 (l), 13.92 (l) μ.

Anal. Calcd. for $C_{31}H_{41}O_6N$ (523.7): C, 71.10; H, 7.87; $2COCH_3$, 16.44. Found: C, 70.83; H, 8.15; $COCH_3$, 14.51.

Dehydration Product XVI of Enone–Trienone XV.—A solution of the enone–dienone (100 mg.) and maleic acid (201 mg.) in dioxane (10 ml.) was boiled under reflux in an atmosphere of nitrogen for 16 hr. After removal of the solvent *in vacuo*, the residue was taken up in chloroform and washed with sodium bicarbonate solution and water. The crude product from the dried chloroform phase was twice crystallized from ethyl acetone–hexane, yielding 46 mg., melting at 187–190°; $[\alpha]^{22}D$ +257° (c 0.797); λ_{max}^{alc} 233 mμ (ε 19,900), 328 (9650); λ_{max}^{Nujol} 5.74 (ms), 5.99 (s), 6.10 (s), 6.13 (s,sh)., 6.34 (ml), 8.10 (s), 9.77 (m), 10.50 (ml), 11.04 (l) μ.

Anal. Calcd. for $C_{31}H_{39}O_5N$ (505.6): C, 73.63; H, 7.77. Found: C, 73.43; H, 7.92.

Dihydrometoxazine Chloride (XVII) from XV.—The enone–dienone (600 mg.) was dissolved in methanol (5 ml.) which had been saturated with hydrogen chloride at 0°. After 0.5 hr. at room temperature, the reaction mixture was evaporated to dryness *in vacuo*. Water was added and the mixture was again evaporated to dryness. The residue, crystallized from methanol–ethyl acetate, gave material melting at 202–206°; $[\alpha]^{20}D$ +245° (c 0.886, 95% ethanol); λ_{max}^{alc} 247 mμ (ε 25,300), 372 (259); λ_{max}^{Nujol} 2.97 (m), 312 (m), 5.95 (s), 6.13 (s), 9.72 (l), 11.52 (l) μ.

Anal. Calcd. for $C_{29}H_{35}O_4NCl \cdot H_2O$ (518.1): C, 67.22; H, 7.78. Found: C, 67.27; H, 7.76.

8,9-Dehydro-Δ^4-jervisin-3-one 17-Monoacetate (XVIIIa) from XVII.—The chloride (XVII, 262 mg.) was dissolved in methanol (30 ml.), and 2 *N* sodium carbonate solution (35 ml.) was added dropwise with stirring. A heavy precipitate was formed, and the solution immediately assumed a deep purple color which quickly faded. After the addition of water (100 ml.) the mixture was extracted twice with ether (100 ml.). The glassy residue (238 mg.) from the washed and dried ether phase could not be crystallized; $[\alpha]^{21}D$ +176° (c 0.801); λ_{max}^{alc} 232 mμ (ε 21,250) 399 (192); λ_{sh}^{alc} 320 mμ (ε 234); λ_{max}^{Nujol} 2.91 (ml), 5.78 (s), 5.91 and 599 (s), 6.16 (ml), 8.01 (s), 9.60 and 9.77 (m) μ.

Anal. Calcd. for $C_{29}H_{39}O_5N$ (481.6): C, 72.32 H, 8.16. Found: C, 71.48; H, 8.12, neut. equiv. ($HClO_4$ titration), 484.

The hydrochloride salt prepared by treating an ethanol solution of the jervisine base with 2 equiv. of aqueous hydrochloric acid and evaporating to dryness crystallized with 1 mole of ethyl acetate from methanol–ethyl acetate as needles which melted at 169–172° with decomposition; λ_{max}^{alc} 232 mμ (ε 24,900); λ_{max}^{Nujol} 3.04 (l), 5.78 (m), 5.90 (m), 6.01 (ms), 6.19 (l), 8.05 (ms) μ.

Anal. Calcd. for $C_{29}H_{40}O_5NCl + CH_3COOC_2H_5$ (606.2): C, 65.39; H, 7.98; Cl, 5.85. Found: C, 65.63; H, 7.68; Cl, 6.00.

The 17,23-Diacetylated jervisine base (XVIIIb) was obtained by acetylating the monoacetate (93 mg.) with anhydrous pyridine (4 ml.) and acetic anhydride (2 ml.) at room temperature overnight. The reaction mixture was worked up in the usual manner and yielded a residue which crystallized from methanol as small plates; m.p. 215–216° dec.; $[\alpha]^{20}D$ +156° (c 0.8911); λ_{max}^{alc} 231 mμ (ε 23,750), shoulder 315 (103); λ_{max}^{Nujol} 5.79 (vs), 5.92 and 5.99 (s), 6.10 (ml), 6.17 (ml), 8.05 (vs), 9.62 (m, sh), 9.76 (m), 11.56 (m), 14.15 (l) μ.

Anal. Calcd. for $C_{31}H_{41}O_6N$ (523.6): C, 71.10; H, 7.87. Found: C, 71.01; H, 7.86.

4,5-Dihydro Derivative XIX of 23,N-Diacetyl-Δ^4-isojerv-3-one 17,17a-Oxide (XIIIb).—The epoxide (XIIIb, 60 mg.) was subjected to catalytic hydrogenation in ethanol (2 ml.) in the presence of palladium–charcoal (62 mg.). Hydrogen uptake stopped after 5 min. with 3.4 ml. consumed (calcd. for 1 mole, 2.84 ml.). The product could not be obtained in crystalline form. It was readily soluble in 2 *N* hydrochloric acid and then gave a positive test with Mayer's reagent (conversion to dihydrometoxazine chloride of type XIVb). The ultraviolet characteristics [λ_{max}^{alc} 238 mμ (ε 10,570), sh 320 (70)] were virtually identical with those of epoxides Va and Vb particularly in that the minimum was situated at 218 mμ (ε 7400) instead of at 228 mμ as in 5,6-dihydro-

isojervine triacetate IVb (lack of contribution of 17,17a-double bond); λ_{max}^{Nujol} 5.79 (s), 5.86 (s), 5.93 (s), 6.11 (s), 8.08 (s) μ. For analysis the material was lyophilized from benzene and dried at 56° (2 mm.) for 3 hr.

Anal. Calcd. for $C_{31}H_{43}O_6N$ (527.7): C, 70.83; H, 8.25. Found: C, 70.44; H, 8.02.

Material exhibiting a completely identical infrared spectrum was obtained from the crystalline 4,5-dihydro derivative[1] of N-acetyl-Δ^4-isojervone (XII) by treatment with perbenzoic acid and subsequent acetylation.

4,5,13,17a-Tetrahydro Derivative XX of Enone–Dienone of XV.—A solution of the enone–dienone (101 mg.) in absolute ethanol (14 ml.) was shaken in a hydrogen atmosphere with 5% palladium on charcoal (105 mg.), and 2 equiv. of hydrogen were consumed in 40 min. After the removal of the solvent and the catalyst, the residue which could not be crystallized was lyophilized from benzene; λ_{max}^{alc} 238 mμ (ϵ 9180); λ_{sh}^{alc} 317 mμ (ϵ 74); λ_{max}^{Nujol} 2.95 (m, br), 5.78 (s, sh), 5.85 and 5.93 (s), 6.17 (s, br), 8.08 (s, br), 9.77 (ms), 10.45 (m, br) μ.

Anal. Calcd. for $C_{31}H_{45}O_6N$ (527.68): C, 70.56; H, 8.60. Found: C, 69.85; H, 8.57.

4,5-Dihydrojervisine Base XXI from XVIIIa.—When a solution of the jervisine base 17-monoacetate (51.1 mg.) in absolute ethanol (6 ml.) was hydrogenated in the presence of 5% palladium on charcoal (54 mg.), 1 molar equiv. of hydrogen was consumed in 10 min. The residue, after the filtration and evaporation of the ethanol, could not be crystallized and hence was lyophilized from benzene; λ_{max}^{alc} 237 mμ (ϵ 9140); λ_{sh}^{alc} 325 mμ (ϵ 64); λ_{max}^{Nujol} 2.90 (ml), 5.79, 5.85, and 5.91 (s), 8.00 (s) μ.

Acknowledgment.—The authors are indebted to Mr. J. F. Alicino and his associates for the microanalyses and to Dr. N. Coy and her associates for the spectral determinations reported in this paper.

The Photochemical Reactions of Alkyl Phenylglyoxalates in Alcohols[1]

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The primary and secondary alkyl esters of phenylglyoxalic acid undergo a photochemical reaction in alcohols in which the phenylglyoxalate is reduced to the mandelate ester of the solvent alcohol and the alcohol moiety of the phenylglyoxalate ester is oxidized. A mechanism involving an intramolecular hydrogen abstraction reaction in the photochemically excited phenylglyoxalate ester is suggested to account for the products of these reactions.

The photochemically induced reactions of aryl ketones in various solvents generally result in reductive dimerization of the aryl ketone to a 1,2-diol and an oxidation of the solvent.[3] A familiar example of such a reaction is the photochemical reduction of benzophenone in 2-propanol, a reaction which yields benzpinacol (I) as the reduction product of the aryl ketone and acetone as the oxidation product of the solvent.

$$C_6H_5CC_6H_5 + CH_3CHCH_3 \xrightarrow{h\nu} \underset{\mathbf{I}}{(C_6H_5)_2COH\,(C_6H_5)_2COH} + CH_3CCH_3 \quad (1)$$

The mechanism of this reaction has been proposed and involves the following sequence of reactions.[3,4]

$$C_6H_5CC_6H_5 \xrightarrow{h\nu} [C_6H_5CC_6H_5]^* \longrightarrow \underset{\mathbf{A}\cdot}{C_6H_5\dot{C}C_6H_5} \quad (2)$$

$$A\cdot + CH_3CHCH_3 \longrightarrow \underset{\mathbf{B}\cdot}{C_6H_5CC_6H_5} + \underset{\mathbf{C}\cdot}{CH_3\dot{C}CH_3} \quad (3)$$

$$C\cdot + C_6H_5CC_6H_5 \longrightarrow CH_3CCH_3 + B\cdot \quad (4)$$

$$2B\cdot \longrightarrow I \quad (5)$$

The alkyl esters of phenylglyoxalic acid can be reduced photochemically to the corresponding alkyl esters of α,α'-diphenyltartaric acid presumably by the same mechanistic path shown in eq. 2–5. Thus, at ambient temperatures (about 30°), diethyl α,α'-diphenyltartrate (II) and 2-butanone were found to be the major products obtained from the reaction of ethyl phenylglyoxalate in 2-butanol induced by sunlight.

$$2C_6H_5CCO_2C_2H_5 + CH_3CHC_2H_5 \xrightarrow{h\nu} \underset{C_6H_5C(OH)CO_2C_2H_5}{\overset{C_6H_5C(OH)CO_2C_2H_5}{|}} + CH_3CC_2H_5 \quad (6)$$

We have found that the photochemical reductions of primary and secondary alkyl phenylglyoxalates in alcohols follow a different and quite unique course at somewhat higher temperatures. The alkyl phenylglyoxalate is reduced to the mandelate ester of the alcohol in which the reaction is performed and the original alcohol moiety of the phenylglyoxalate ester is oxidized. For example, illuminating a solution consisting of cyclohexyl phenylglyoxalate in ethanol at 40° yielded equivalent amounts of ethyl mandelate (III) and cyclohexanone as the major reaction products.

$$\underset{0.022\ \text{mole}}{C_6H_5CCO_2C_6H_{11}} + C_2H_5OH \xrightarrow{h\nu} \underset{\substack{0.018\ \text{mole}\\ \mathbf{III}}}{C_6H_5CHCO_2C_2H_5} + \underset{0.019\ \text{mole}}{C_6H_{10}O} \quad (7)$$

No detectable amounts of either ethyl phenylglyoxalate or cyclohexyl mandelate could be found on gas chromatographic analysis of the reaction mixture. At this temperature, only 16% of the cyclohexyl phenylglyoxalate was converted to the dimeric reduction product, dicyclohexyl α,α'-diphenyltartrate.

(1) This work was supported in part by a research grant (A-5620) from the National Institutes of Health.

(2) National Science Foundation Cooperative Fellow, 1962–1963.

(3) *Cf.* A. Schoenberg and A. Mustafa, *Chem. Rev.*, **40**, 181 (1947); W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Am. Chem. Soc.*, **83**, 2789 (1961); G. S. Hammond, W. P. Baker, and W. M. Moore, *ibid.*, **83**, 2797 (1961).

(4) J. N. Pitts, Jr., R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Rectenwald, and R. B. Martin, *ibid.*, **81**, 1068 (1959).

TABLE I

PHOTOCHEMICAL REACTIONS OF ALKYL PHENYLGLYOXALATES IN ALCOHOLIC SOLUTIONS AT 78°

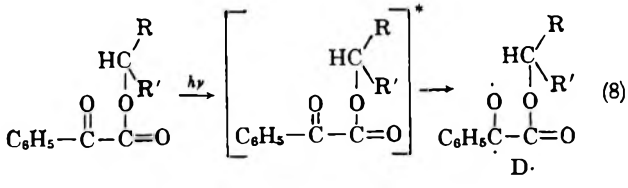
Phenylglyoxalate	Solvent alcohol	Products
(1) Ethyl phenylglyoxalate	2-Butanol	2-Butyl mandelate[a]
(2) Ethyl phenylglyoxalate	Cyclohexanol	Cyclohexyl mandelate[b,a]
(3) Ethyl phenylglyoxalate	*l*-Menthol	*l*-Menthyl mandelate[c,a]
(4) 2-Propyl phenylglyoxalate (0.007 mole)	Ethanol	Ethyl mandelate (0.003 mole) + acetone (0.003 mole)
(5) 2-Hexyl phenylglyoxalate	Ethanol	Ethyl mandelate + 2-hexanone
(6) Cyclohexyl phenylglyoxalate[d] (0.022 mole)	Ethanol	Ethyl mandelate (0.018 mole) + cyclohexanone (0.019 mole)
(7) 2-Octyl phenylglyoxalate	Ethanol	Ethyl mandelate + 2-octanone
(8) 2-Octyl phenylglyoxalate	2-Butanol	2-Butyl mandelate + 2-octanone

[a] No attempt was made to isolate the acetaldehyde in these reactions. [b] M.p. 56–58°. [c] M.p. 81–82°. [d] Performed at 40°.

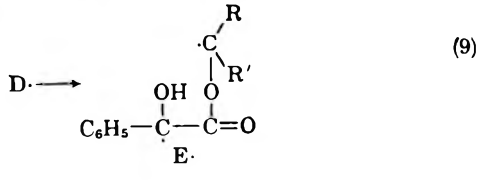
Illuminating ethyl phenylglyoxalate in cyclohexanol yielded cyclohexyl mandelate and no detectable amounts of either ethyl mandelate or cyclohexyl phenylglyoxalate. In another reaction in which a quantitative determination of the products was made, the photochemical reduction of 2-propyl phenylglyoxalate in ethanol at 78° yielded ethyl mandelate and acetone in equivalent amounts. Esters of phenylglyoxalic acid that were reduced to esters of mandelic acid in alcohols with the accompanying exchange of the alcohol moieties are shown in Table I.

Only in the case of the 2-octyl phenylglyoxalate was any detectable amount of ester exchange occurring prior to the photochemical reduction noted. This was evident from the appearance of 2-octanol in the reaction mixtures of the 2-octyl phenylglyoxalate reactions. In all cases, the mandelate ester found was that of the alcohol in which the photochemical reduction was performed. Although there was some oxidation of the solvent alcohol due to the formation of the dimeric reduction product, the alcohol portion of the phenylglyoxalate used was always oxidized to a greater extent and, in those reactions in which it was quantitatively determined, in an amount equivalent to the mandelate ester formed.

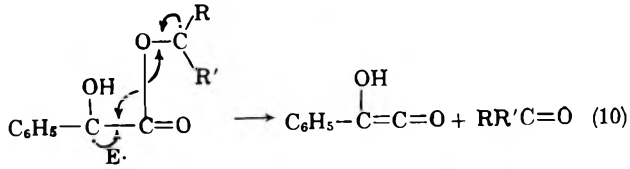
A mechanism for these photochemically induced reduction reactions with the accompanying exchange of the alcohol moieties which is consistent with our observations is shown in the following equations.



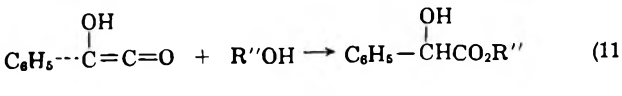
(8)



(9)



(10)



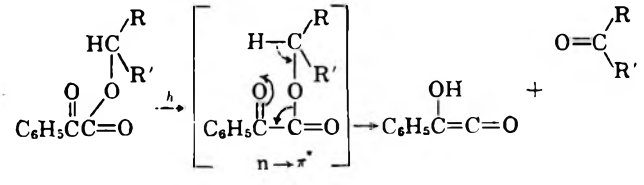
(11)

The photolytic excitation of the alkyl phenylglyoxalate to the triplet diradical D· by way of the n → π* excited state as shown in reaction 8 is similar to that proposed for the photochemical reactions of other aryl ketones. The oxygen part of the diradical D· is suitably positioned to abstract a hydrogen atom from the alcohol portion of the ester as shown in the intramolecular reaction 9 producing the diradical E·. Such intramolecular hydrogen atom abstractions have been reported to occur when the conformational aspects of the diradical are suitable.[5] By the appropriate shifting of electrons in the manner shown in eq. 10, the diradical E· can fragment to the oxidation product of the alcohol portion of the ester and to the enol of phenylglyoxal.[6] This enol is a ketene and might be expected to react faster with the solvent alcohol to form an ester of mandelic acid (eq. 10) than to ketonize to phenylglyoxal. We found no phenylglyoxal in any of our reaction mixtures. The consequence of this sequence of reactions is that the original alcohol portion of the phenylglyoxalate ester is oxidized and the only mandelate ester formed must be that of the alcohol used as the solvent. Further, the amounts of the oxidized alcohol moiety of the starting phenylglyoxalate and the mandelate ester formed should be equivalent.

The formation of acetaldehyde and carbon monoxide in both the direct and benzophenone-sensitized photolyses of ethyl pyruvate reported by Hammond, Leermakers, and Turro[7] could proceed in a manner similar to that proposed here for the alkyl phenylglyoxalates. In this case, the benzophenone-sensitized reaction must involve the triplet state. A mechanism involving an intramolecular hydrogen abstraction reaction was suggested by Leermakers and Vesley[8] to explain the for-

(5) N. C. Yang and D. H. Yang, *J. Am. Chem. Soc.*, **80**, 2913 (1958); N. C. Yang and C. Rivas, *ibid.*, **83**, 2213 (1961); W. H. Urry and D. J. Trecker, *ibid.*, **84**, 118 (1962).

(6) It has been suggested that the ketene intermediate could arise from a one-step fragmentation of the initial n → π* excited state in the manner shown in the following equation.



This path certainly cannot be excluded. However, in view of the marked effect of temperature on the course of the reaction, the intramolecular hydrogen abstraction reaction by the triplet shown in eq. 9 may accommodate the facts somewhat better.

(7) G. S. Hammond, P. A. Leermakers, and N. J. Turro, *J. Am. Chem. Soc.*, **83**, 2395 (1961).

(8) P. A. Leermakers and G. F. Vesley, *J. Org. Chem.*, **28**, 1161 (1963).

mation of carbon dioxide and acetoin from the photolysis of pyruvic acid.

The observation that the dimeric reduction products are formed at lower temperatures and the mandelate esters at higher temperatures deserves further comment. The formation of the dimeric reduction product requires an intermolecular hydrogen abstraction from the solvent alcohol by the oxygen moiety of the diradical D·, whereas an intramolecular hydrogen abstraction from the alkyl portion of the phenylglyoxalate ester is required by the proposed mechanism for the formation of the mandelate ester. The reactivity of the α-hydrogen of the solvent alcohol toward abstraction could very likely be greater than that of the α-hydrogen of ester. If such is the case, an increase in temperature would be expected to increase the rate of the slower reaction, namely the intramolecular hydrogen abstraction, more markedly and thereby favor the formation of the mandelate ester.

Experimental

The phenylglyoxalic acid required for the preparation of the esters was prepared by the permanganate oxidation of mandelic acid.[9] The following esters were prepared by the reaction of the phenylglyoxalic acid and the appropriate alcohol in the presence of sulfuric acid.

2-Propyl phenylglyoxalate had b.p. 97° at 2 mm.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.92; H, 6.80.

2-Butyl phenylglyoxalate had b.p. 127–130° at 5 mm.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 70.17; H, 7.03.

2-Hexyl phenylglyoxalate had b.p. 121° at 2 mm.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.76; H, 7.76. Found: C, 72.14; H, 8.02.

2-Octyl phenylglyoxalate had b.p. 142° at 2 mm.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.26; H, 8.79. Found: C, 73.19; H, 8.92.

Cyclohexyl phenylglyoxalate had b.p. 167° at 5 mm.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.41; H, 6.95. Found: C, 72.43; H, 7.07.

The alcohols used were commercial materials and redistilled when necessary.

Reaction of Ethyl Phenylglyoxalate and 2-Butanol.—Ethyl phenylglyoxalate (2.5 g., 0.014 mole) was dissolved in 2-butanol (8.0 g., 0.11 mole). The solution was sealed in a Pyrex tube and exposed to the sun for a period of 2 days at ambient temperatures (about 30°). At the end of the illumination, the tube was cooled at 0° for 6 hr. and 1.03 g. (0.0029 mole) of the solid dimeric reduction product, diethyl α,α′-diphenyltartrate, which had m.p. 118–120° from petroleum ether (b.p. 35–60°), crystallized from the solution. Gas chromatographic analysis of the reaction mixture indicated the presence of 2-butanone and only a trace of acetaldehyde.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.04; H, 6.15. Found: C, 67.7; H, 6.21.

(9) B. B. Corson, R. A. Dodge, S. E. Harris, and R. K. Hazen, "Organic Syntheses" Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 241.

Photochemical Reaction of Cyclohexyl Phenylglyoxalate and Ethanol.—A solution consisting of 5.0 g. (0.022 mole) of cyclohexyl phenylglyoxalate in 10 g. of ethanol was illuminated for 16 hr. at 40° with a 275-w. Sylvania sun lamp. Gas chromatographic analysis of the reaction mixture showed that cyclohexanone and ethyl mandelate were formed. No gas chromatographic peaks with retention times the same as those of authentic samples of either cyclohexanol or ethyl phenylglyoxalate were found. Quantitative determination of the amounts of cyclohexanone (1.8 g., 0.019 mole) and ethyl mandelate (3.05 g., 0.018 mole) by gas chromatography was made by using a weighed portion of the reaction mixture with a weighed amount of an internal standard. On standing overnight at about 0°, dicyclohexyl α,α′-diphenyltartrate (0.8 g., 0.0017 mole) crystallized from the solution. After several recrystallizations from petroleum ether, the material melted at 132–133°.

Anal. Calcd. for $C_{28}H_{34}O_6$: C, 72.10; H, 7.30. Found: C, 72.40; H, 7.30.

The infrared spectrum showed the presence of both a hydroxy group (2.92 μ) and a carbonyl (5.79 μ). The n.m.r. spectrum showed three types of protons, those of the cyclohexyl groups (centered at 2.52 p.p.m.), those of the phenyl groups (centered at 7.45 p.p.m.), and those of the hydroxy groups (centered at 5.01 p.p.m.). The integrated peak areas were consistent with these assignments.

Reaction of 2-Propyl Phenylglyoxalate and Ethanol.—A reaction mixture consisting of 1.3 g. (0.007 mole) of 2-propyl phenylglyoxalate in 3.3 g. of ethanol was illuminated with a sun lamp at 78° for 16 hr. At the end of this period, the amounts of acetone (0.17 g., 0.003 mole) and ethyl mandelate (0.40 g., 0.0028 mole) formed were determined by gas chromatography using a weighed portion of the reaction mixture with a weighed amount of *t*-butyl alcohol as an internal standard.

Photochemical Reactions of Alkyl Phenylglyoxalates with Alcohols.—The alkyl phenylglyoxalate was in each case dissolved in a better than 2:1 molar excess of the indicated alcohol. The solution was placed in a Pyrex tube and immersed in an alcohol vapor bath (78°) and illuminated for several hours with a 275-w. Sylvania sun lamp. The products of the reaction were determined qualitatively by gas chromatography. In each case, the reaction mixture gave a chromatographic peak with a retention time identical with that of the mandelate ester of the alcohol in which the reaction was performed. In no case were any detectable amounts of the mandelate ester of the alcohol moiety of the starting phenylglyoxal detected. Cyclohexyl mandelate was isolated from the reaction of ethyl phenylglyoxalate in cyclohexanol, m.p. 56–58°, after recrystallization from petroleum ether.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.08; H, 7.98.

l-Menthyl mandelate was isolated from the reaction of ethyl phenylglyoxalate in *l*-menthol, m.p. 82°, lit.[10] m.p. 84–85°. The infrared spectrum of the material was identical with that of an authentic sample.

The ketones formed in the reactions of the secondary alkyl phenylglyoxalates were qualitatively determined by their gas chromatographic retention times which were identical in each case with those of authentic samples. In the reaction of 2-octyl phenylglyoxalate in 2-butanol, the 2-octanone formed was isolated by distillation under vacuum and the 2,4-dinitrophenylhydrazone prepared, m.p. 56.5–58°, lit.[11] m.p. 58°.

(10) A. McKenzie, *J. Chem. Soc.*, **85**, 384 (1904).

(11) 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.

Reactions of Nitrogen Dioxide with Organic Halogen Compounds. I. Synthesis of Fluoro Aldehydrols and Fluoro Ketols from Fluoro Alcohols

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Contribution No. 867 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware

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Long-chain fluoro aldehydrols, free of the corresponding fluorocarboxylic acids, can be prepared conveniently and in good yield by passing a mixture of a primary fluoro alcohol, nitric oxide, and air over an inert surface heated at 300–400°. In similar manner, oxidation of the secondary fluoro alcohol, 1H,3H,5H-octafluoro-3-pentanol (**13**), by nitrogen dioxide at 400° gives the corresponding fluoro ketone hydrate (**14**). 1H,9H-Hexadecafluoro-1,1-nonandiol (**3b**), a typical fluoro aldehydrol prepared by this method, reacts with conventional carbonyl reagents, such as sodium bisulfite, hydroxylamine hydrochloride, and semicarbazide hydrochloride, to yield unusually stable derivatives of the fluoro aldehyde. The aldehydrol (**3b**) reacts with 2 moles of benzonitrile in sulfuric acid to give 1H,9H-1,1-bis(benzamido)hexadecafluorononane (**12**). Action of fuming nitric acid on the fluoro aldoxime (**9**) derived from **3b** affords a bis(fluoroalkyl)furoxan (**10**) in 50% yield, a reaction which may involve intermediacy of a 1-nitroso-1-nitrofluoroalkane (**11**).

Nitrogen dioxide and its dimer, dinitrogen tetroxide,[1] are known to undergo a wide variety of reactions with organic compounds, giving products that might be classified as arising primarily by processes of addition, substitution, or oxidation. For example, the facile addition of dinitrogen tetroxide to olefins[2] and acetylenes[3] in solvents has been studied thoroughly and found to afford *vic*-dinitro alkanes, nitro nitrites, nitro nitrates, dinitro olefins, etc. Substitution reactions, exemplified by the nitration of aliphatic and aromatic hydrocarbons[4] and the nitrosation and nitration of amines and alcohols,[5] also have been examined by a number of workers. Oxidation of organic compounds by dinitrogen tetroxide has, however, received relatively scant attention[6] in spite of the fact that this type of reaction is probably the oldest of the three. Indeed, it was not until Levy and Scaife[2] found how to minimize the oxidation reactions of nitrogen dioxide that research on the chemistry of this compound began to advance significantly.

The work described in this and the following two papers was undertaken in view of the relative resistance toward oxidative degradation of organic compounds containing a high proportion of halogen. In particular, this paper reports the selective oxidation of several primary fluoro alcohols[7] and one secondary fluoro alcohol by nitrogen dioxide at high temperatures. Oxidation of primary fluoro alcohols with nitrogen dioxide at 300–400° in a hot tube has been found to be a convenient source of hydrated fluoro aldehydes, *i.e.*, fluoro aldehydrols.[8]

In 1955 Field and Grundy[9] reported that substituted benzyl alcohols are converted at 0–25° to the corresponding aldehydes in 91–98% yields by equimolar amounts of dry dinitrogen tetroxide dissolved in chloroform. This type of reaction appeared, for all practical purposes, to be limited to benzylic alcohols. Thus, a year later Langenbeck and Richter[10] demonstrated the oxidation of primary alkanols and diols to the corresponding mono- and dicarboxylic acids with dinitrogen tetroxide in inert solvents at −10 to 18°. Kinetic analysis of these reactions indicated that aldehydes were not formed as intermediates and 2-phenylethanol and 3-phenylpropanol were oxidized to the corresponding aldehydes in only 14% and trace yield, respectively.

Results

The fluoro alcohol, 1H,1H,5H-octafluoro-1-pentanol, was recovered unchanged after treatment for 3 days at room temperature with excess dinitrogen tetroxide dissolved in methylene chloride.[11] However, 1H,-1H,9H-hexadecafluoro-1-nonanol (**1b**) was oxidized by nitrogen dioxide (2 moles) at 110° in an autoclave

(1) Dinitrogen tetroxide exists in equilibrium with the free radical, nitrogen dioxide, but the latter predominates at higher temperatures. At 27° the tetroxide is about 20% dissociated; at about 140° dissociation is complete. *Cf.* P. Gray and A. D. Yoffe, *Chem. Rev.*, **55**, 1069 (1955), for a review of the structure, reactivity, and physical properties of the nitrogen dioxide–dinitrogen tetroxide system.

(2) For example, N. Levy and C. W. Scaife, *J. Chem. Soc.*, 1093 (1946); H. Baldock, N. Levy, and C. W. Scaife, *ibid.*, 2627 (1949); H. Shechter and F. Conrad, *J. Am. Chem. Soc.*, **75**, 5620 (1953); H. Shechter, J. J. Gardikes, and A. H. Pagano, *ibid.*, **81**, 5420 (1959); J. L. Riebsomer, *Chem. Rev.*, **36**, 157 (1945); T. E. Stevens, *J. Chem. Soc.*, **81**, 3593 (1959).

(3) See, for example, H. H. Schlubach and W. Rott, *Ann.*, **594**, 59 (1955); J. P. Freeman and W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 1712 (1957); K. N. Campbell, J. Shavel, and B. K. Campbell, *ibid.*, **75**, 2400 (1953).

(4) The nitration of aliphatic and aromatic compounds by the oxides of nitrogen is reviewed by A. V. Topchiev, "Nitration of Hydrocarbons," Pergamon Press Ltd., London, 1959, p. 226 ff.

(5) E. H. White and W. R. Feldman, *J. Am. Chem. Soc.*, **79**, 5832 (1957); M. Anabor, *ibid.*, **76**, 3603 (1954); C. C. Addison, N. Hodges, and J. C. Sheldon, *Chem Ind.* (London), 1338 (1953); *cf.* also ref. 4.

(6) A recent example of the use of dinitrogen tetroxide as a useful oxidizing reagent in organic chemistry is the oxidation of alkyl sulfides of sulfoxides without further oxidation to sulfones [C. C. Addison and J. C. Sheldon, *J. Chem. Soc.*, 2705 (1956)]. Oxidation of negatively substituted quinols to *p*-benzoquinones by mixed nitrogen oxides, predominantly dinitrogen tetroxide, has been described by A. G. Brook [*ibid.*, 5040 (1952)] and by K. Wallenfels [*Angew. Chem.*, **68**, 142 (1961)].

(7) The primary α,α,ω-trihydrofluoroalkanols described in this paper are available in developmental quantities from the Organic Chemicals Department, E. I. du Pont de Nemours and Co., Wilmington 98, Del.

(8) A. L. Henne, R. L. Pelley, and R. M. Alm report that efforts to prepare trifluoroacetaldehyde by oxidation of trifluoroethanol failed using "conventional" reagents, *e.g.* sodium dichromate in sulfuric acid [*J. Am. Chem. Soc.*, **72**, 3370 (1950)]. H. Shechter and F. Conrad report that the oxidation of 1,1,1-trifluoropropane with nitric acid in the presence of oxygen at about 450° affords trifluoroacetaldehyde in small (20–40%) yield (*ibid.*, 3371). D. R. Husted and A. H. Albrecht [U. S. Patent 2,568,500 (1951)] and M. Braid [U. S. Patent 2,852,569 (1958)] describe the preparation of fluoro aldehydrols by reduction of fluorocarboxylic acids with lithium aluminum hydride. N. O. Brace describes the preparation of α,α ω-trihydroperfluoroaliphatic hemiacetals of ω-hydroperfluoro aliphatic aldehydes by photochlorination of α,α,ω-trihydroperfluoro alcohols [U. S. Patent 2,842,601 (1958) and *J. Org. Chem.*, **26**, 4005 (1961)]. Pyrolysis of the hemiacetals affords the ω-hydrofluoroaliphatic aldehydes. R. N. Haszeldine claims the preparation of R_fCH_2CHO by catalytic hydrogenation of the vinyl ethers, $R_fCH{=}CHOR$ [Canadian Patent 618,346 (1961)] M. Braid and F. Lawlor claim the oxidation of trifluoroethanol to trifluoroacetic acid and/or trifluoroacetaldehyde with oxygen or a peroxy compound in the presence of certain heavy metal oxides [U. S. Patent 3,038 936 (1962)].

(9) B. O. Field and J. Grundy, *J. Chem. Soc.*, 1110 (1955); *cf.* also J. B. Cohen and H. T. Calvert, *ibid.*, **71**, 1050 (1897).

(10) W. Langenbeck and M. Richter, *Ber.*, **89**, 202 (1956).

(11) This experiment was carried out by Dr. D. W. Wiley, Central Research Department, E. I. du Pont de Nemours and Co., Inc.

TABLE I

OXIDATION OF PRIMARY FLUORO ALCOHOLS TO FLUORO ALDEHYDROLS BY NO_2

Fluoro alcohol, $H(CF_2)_nCH_2OH$ n =	Temp. of hot tube, °C.	Alcohol, g./hr	NO, ml./sec.	Air, ml./sec.	Organic material balance, %[a]	Purity of crude aldehydrol, %[b]	Conversion to aldehydrol, %	M.p. of crude product, °C.
6	375	13	2.5	2.5	55			58–60
6	300	10	1.9	4.2	65	50–60	33–39	60–63
8	230	10	2.8	4.2		low	low	45–50
8	275	7	2.8	4.2	74		71	90–92
8	280	10	5.5	8.3	72	83	60	92–93
8	300	10	2.5	4.0	91	93	85	79–83; 80–84
8	304	16	5.5	8.3	95	50	47	73–76
8	318	20	5.5	8.3	93	50	46	
8	325	10	5.5	8.3	44		39	90–92
8	338	20	6.5	8.3	83	83	69	
10	320	17	5.5	8.3	92	40	37	86–95

[a] After evaporation of gaseous products at room temperature. [b] In most instances estimated by carbonyl analysis (*cf.* ref. 14).

over a period of 10 hr. to give, as the major product, 9H-hexadecafluorononanoic acid (**2**) in 69% yield.

$$\underset{\textbf{1b}}{H(CF_2)_8CH_2OH} \xrightarrow{NO_2} \underset{\textbf{2}}{H(CF_2)_8CO_2H}$$

At significantly lower temperatures, with shorter reaction times or with equimolar quantities of nitrogen dioxide, conversions to the carboxylic acid diminished and recovery of unchanged fluoro alcohol increased.

Turning to the hot-tube reaction technique, we found that fluoro aldehydrols could be obtained conveniently, quickly, and in good yields by passing a mixture of excess nitric oxide,[12,13] air,[13] and a primary fluoro alcohol through a Pyrex tube packed with glass or quartz chips and heated at 300–400°.

$$\underset{\textbf{1}}{H(CF_2)_nCH_2OH} \xrightarrow{NO_2} \underset{\textbf{3}}{H(CF_2)_nCH(OH)_2}$$

1	3
1a, n = 6	3a, n = 6
b, n = 8	b, n = 8
c, n = 10	c, n = 10

This technique proved especially convenient for the preparation of long-chain fluoro aldehydrols which are nonhygroscopic solids at room temperature; they could be collected and separated from gaseous coproducts simply by permitting them to condense on the walls of an air-cooled condenser attached to the exit of the reaction tube. In the largest single run, carried out over a period of 32 hr. of continuous operation, 7.7 kg. of the C_9 fluoro alcohol (**1b**) was passed through a 6.5-cm. diameter Pyrex tube partially filled with 600 ml. of quartz chips and maintained at 380 ± 10°. Nitric oxide and air were passed through the tube, each at a rate of 7 ml./sec. This gave 6.6 kg. of crude 1H,9H-hexadecafluoro-1,1-nonanediol (**3b**), estimated by gas chromatography and titrimetric carbonyl analysis[14] to be 70 ± 3% pure aldehydrol. A single crystallization from benzene gave the aldehydrol in 96% purity and in 57% conversion. Additional runs on a smaller scale (10–100 g.) gave fluoro aldehydrols **3a**, **3b**, and **3c** from the corresponding alcohols in conversions ranging from 33 to 85%. These runs are summarized in Table I.

Gas chromatographic analysis of a typical batch of crude aldehydrol **3b** indicated the virtual absence (less than 0.1%) of the corresponding fluorocarboxylic acid (**2**). This observation was at first quite surprising in view of the fact, mentioned earlier, that action of nitrogen dioxide on the primary fluoro alcohol (**1b**) in an autoclave at a lower temperature gives primarily the corresponding fluorocarboxylic acid (**2**). Subsequent experiments showed, however, that the acid **2**, even if it were formed[15] as a by-product of the oxidation, would not survive the conditions of the hot-tube reaction. Thus, when acid **2** was passed through a packed tube heated at 350°, together with nitric oxide–air, it underwent complete conversion to a mixture composed primarily of gaseous products accompanied by a small amount (5–10% by weight) of volatile liquid.[15]

Mechanism of Oxidation.—A study of the mechanism of the oxidation of fluoro alcohols to fluoro aldehydrols has not been undertaken. The known chemistry of nitrogen dioxide does, however, suggest a reasonable reaction scheme.

Nitrogen dioxide, because of its free-radical character, is prone, especially at high temperatures, to abstract hydrogen from an organic molecule leaving an alkyl radical.[16] Combination of another molecule of nitrogen dioxide with the radical so produced can occur with formation of either a nitro or a relatively unstable nitrite compound.[16] Abstraction of a hydrogen atom from the methylene group of a primary fluoro alcohol would give rise to the radical represented by structure **4** in eq. 1. Combination of this radical with nitrogen

(12) To facilitate metering, a mixture of (excess) nitric oxide and air was used rather than pure nitrogen dioxide (b.p. 21°). The gases were mixed in a chamber outside the reaction tube to ensure complete reaction since the rate of this reaction is known to decrease with increasing temperature [M. Bodenstein, *et al.*, *Z. physik. Chem.* [Leipzig], **100**, 87, 106 (1922)].

(13) No oxidation of the fluoro alcohols was observed when they were passed through a reaction tube at 400° with either nitric oxide or air alone.

(14) S. Siggia, "Quantitative Organic Analysis," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, p. 28.

(15) The gaseous products from the degradation of fluorocarboxylic acid **2** were not identified. Infrared analysis of the volatile liquid obtained indicated that it was a mixture of ω-H–α-nitroperfluoro alkanes similar to those described in the next part of this series [*J. Org. Chem.*, **29**, 284 (1964)]. Since the gaseous or liquid products from the hot-tube degradation of acid **2** were neither sought nor found among the products from the hot-tube oxidation of fluoro alcohol **1b**, no evidence exists for the formation (and degradation) of acid **2** during the hot-tube oxidation of fluoroalcohol **1b** to fluoro aldehydrol **3b**. Nevertheless, in view of the autoclave experiments, this seems more likely to us than the alternative possibility that the fluoro alcohol (**1b**) and the fluoro aldehydrol (**3b**) are completely resistant toward oxidation of fluorocarboxylic acid **2** in the presence of nitrogen dioxide in a hot tube at 300–400°. Formation of fluorocarboxylic acids and their degradation to volatile products, as side reactions in the hot-tube synthesis of fluoro aldehydrols, would, furthermore, account for the low material balance of nongaseous organic products generally found in these hot-tube syntheses (Table I).

(16) P. Gray and A. D. Yoffe, *Chem. Rev.*, **55**, 1091, 1102 (1955).

$$R_fCH_2OH + NO_2 \longrightarrow R_f\dot{C}HOH + HNO_2 \quad (1)$$
(4)

$$2HNO_2 \longrightarrow H_2O + NO + NO_2 \quad (2)$$

$$R_f\dot{C}HOH \xrightarrow{NO_2} R_fCH(ONO)OH \text{ or } R_fCH(NO_2)OH \quad (3)$$
(4) (5) (6)

dioxide in the manner depicted by eq. 3 would afford an α-hydroxynitrite (**5**) or an α-hydroxynitro (**6**) intermediate.

Decomposition of the nitrite (**5**) by homolytic O–N bond fission[17] would give a radical species **7** which, by abstracting a hydrogen atom from another molecule of

$$R_fCH(ONO)OH \longrightarrow R_fCH(O\cdot)OH + NO \quad (4)$$
(5) (7)

fluoro alcohol, would regenerate another radical **4** and afford a molecule of fluoro aldehydrol (eq. 5). Decomposition of the nitrocarbinol (**6**) would be expected

$$R_fCH(O\cdot)OH + R_fCH_2OH \longrightarrow R_f\dot{C}HOH + R_fCH(OH)_2 \quad (5$$
(7) (4)

to afford fluoroaldehyde and, ultimately, by combination with water (from eq. 2), fluoro aldehydrol.

$$R_fCH(NO_2)OH \xrightarrow{-HNO_2} R_fCHO \xrightarrow{H_2O} R_fCH(OH)_2$$
(6)

Vapor Pressure of Fluoro Aldehydrols.—Although, as expected, the melting points of the three fluoro aldehydrols **3a, 3b,** and **3c** exceed those of the corresponding fluoro alcohols[18] **1a, 1b,** and **1c,** so also do their apparent vapor pressures. Table II compares the vapor pressures of the C_9 fluoro alcohol (**1b**) and the fluoro aldehydrol (**3b**) as measured in a Sickle cell over a range of temperatures. Gas chromatography substantiates the unusual volatility of the fluoro aldehydrols relative to the fluoro alcohols. Figure 1 shows a plot of the log of retention times *vs.* chain length of the three fluoro

TABLE II

VAPOR PRESSURES OF 1H,9H-HEXADECAFLUORO-1,1-NONANEDIOL (**3b**) AND 1H,1H,9H-HEXADECAFLUORO-1-NONANOL (**1b**)

Temp., °C.	Vapor pressures, mm. of Hg—Fluoro aldehydrol **3b**	Fluoro alcohol **1b**
25	<1	<1
50	7	<1
60	12	
70	32	3
80	71	8
90	143	12
100	225	21
110	350	33
120	489	49
130	668	

(17) Literature dealing with the homolytic decomposition of nitrites is surveyed by P. Gray, P. Rothbone, and A. Williams, *J. Chem. Soc.*, 3932 (1960), and by A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 48 (1962).

(18) The fluoro alcohols **1a**, **1b**, and **1c** are reported to melt at −14°, 69°, and 102°, respectively [D. R. Baer, *Ind. Eng. Chem.*, **51**, 829 (1959)]. The corresponding fluoro aldehydrols **3a**, **3b**, and **3c** melt at 67°, 95–96° (or 105–107°, *cf.* Experimental), and 113–114°, respectively.

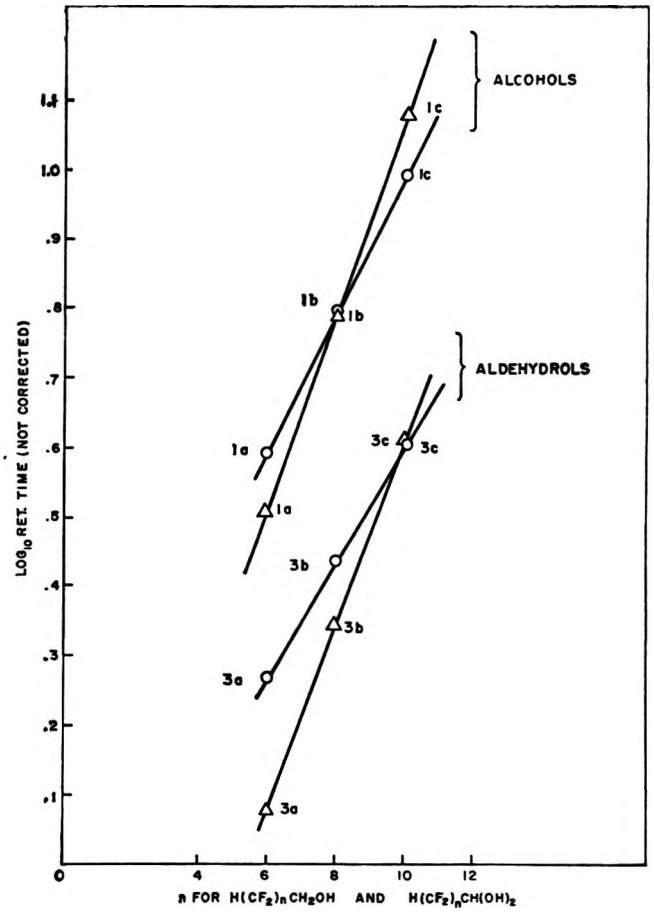

Fig. 1.—Column packings (see ref. 19): Δ, 20% tetrakis-(1H,1H,5H-octafluoropentyl and 1H,1H,7H-dodecafluoroheptyl)-pyromellitate in "Columpak" (Fisher Scientific); O, 25% Dow Corning high vacuum grease on 60–80-mesh "Celite."

alcohols and the corresponding fluoro aldehydrols on polar and nonpolar columns[19] operated at 175°. It is clear that, for given chain lengths, the fluoro alcohols have a significantly greater retention time than the corresponding fluoro aldehydrols. This is interpreted to be a consequence of the fact that the order of elution of closely related compounds from nonpolar columns is generally in the order of decreasing vapor pressures.[20] The unexpectedly high vapor pressures of the fluoro aldehydrols may be due to their partial dissociation into water and relatively volatile fluoro aldehydes.

Reactions of Fluoro Aldehydrols.—Relatively few derivatives of fluoro aldehydes or fluoro aldehydrols are reported in the literature. We have observed that, at least for the long-chain fluoro aldehydrol (**3b**), solid carbonyl derivatives are easily prepared directly from the *gem* diol without first resorting to a dehydration step. For example, a water–methanol solution of the aldehydrol (**3b**) and sodium bisulfite rapidly deposits a sparingly soluble bisulfite adduct (**8**). Somewhat surprisingly, this salt is recovered unchanged after

(19) A Perkin-Elmer vapor fractometer, Model 154-B, was employed using helium as the carrier gas at an inlet pressure of 10 p.s.i. and a flow rate of 35 ml./min. Column packing designated "nonpolar" was 25% Dow Corning high vacuum grease on 60–80-mesh "Celite" and was 2 m. in length. Packing designated "polar" was 20% tetrakis(1H,1H,5H-octafluoropentyl and 1H,1H,7H-dodecafluoroheptyl)pyromellitate on "Columnpak" (Fisher Scientific) and was also 2 m. in length. Samples were injected as solutions in acetone into a preheater at 14°.

(20) *Cf.* for example, F. H. Pollard and C. J. Hardy, in D. H. Desty "Vapour Phase Chromatography," Academic Press, Inc., New York, N. Y., 1957, p. 115.

$H(CF_2)_8CHSO_3Na$ (8) $H(CF_2)_8CH{=}NOH$ (9)

treatment for 1 hr. with boiling 10% aqueous hydrochloric acid. The aldoxime (**9**), prepared from the reaction of excess hydroxylamine hydrochloride with the aldehydrol (**3b**) in water–methanol, likewise shows unusual stability. It is recovered unchanged after treatment for 1 hr. with 85% sulfuric acid or for 12 hr. in boiling benzene with excess phosphorus pentachloride, reagents which generally bring about the Beckmann rearrangement of aliphatic or aromatic oxides.[21]

Aldoxime **9** appears to be predominantly, or totally, of one configuration for its proton magnetic resonance spectrum exhibits only one triplet peak ascribable to hydrogen on the doubly bonded carbon.[22]

Oxidation of aldoxime **9** with fuming (90%) nitric acid gives the bisfluoroalkylfuroxan (**10**) in 50% yield.[23] A relatively dense liquid, **10** (d^{30}_4 1.89), solidifying at 29°, exhibits the typical infrared[24] and ultraviolet[25] absorption spectra characteristic of furoxans. Its hydrogen n.m.r. spectrum consists of a single triplet (J = 51 c.p.s.) at τ 3.25. The most striking feature of the reaction affording this furoxan is a transient, but clearly visible, blue color that pervades the organic phase of the reaction mixture for 10–15 min. Kornblum[26] in his study of the reactions of sodium nitrite with organic halide compounds offers evidence for formation of (blue) pseudonitroles and nitrolic acids as intermediates. The latter apparently decompose with loss of nitrous acid to give nitrile oxides which dimerize to furoxans.[27] Addition of nitronium ion[28] to aldoxime **9** would produce a colored pseudonitrole (**11a**).

$$H(CF_2)_8CH{=}NOH \xrightarrow{HNO_3} H(CF_2)_8C(NO_2){=}NOH$$

(9 → 10)

$$H(CF_2)_8CH{=}NOH + NO_2 \longrightarrow H(CF_2)_8CH(NO_2)NO \rightleftharpoons H(CF_2)_8C(NO_2){=}NOH$$

(9 → 11a ⇌ 11b)

Decomposition of the pseudonitrole (**11a**), probably by way of its tautomer the colorless nitrolic acid (**11b**), would, by analogy to the Kornblum mechanism, give a fluoroalkylnitrile oxide and then, by dimerization, the bisfluoroalkylfuroxane (**10**). From one oxidation of the

$$11 \xrightarrow{-HNO_2} H(CF_2)_8C{\equiv}N \longrightarrow 10$$

aldehydrol (**3b**) with nitric acid, 9H-hexadecafluorononanoic acid (**2**) was isolated in about 15% yield. This acid may have originated from intermediate **11** since nitrolic acids are known to decompose into carboxylic acids.[26]

One experiment was carried out to determine whether a product formally derived from the *gem* diol group of **3b** could be prepared. Two moles of benzonitrile were indeed found to react with 1 mole of diol **3b** in the presence of fuming sulfuric acid to give the dibenzamido derivative (**12**).

$$H(CF_2)_8CH(OH)_2 + 2C_6H_5CN \longrightarrow H(CF_2)_8CH(NHCOC_6H_5)_2$$

(3b → 12)

Fluoro Ketone Hydrates.—Secondary fluoro alcohols can be oxidized to fluoro ketone hydrates by nitrogen dioxide. Thus, when 1H,3H,5H-octafluoro-3-pentanol (**13**) together with nitric oxide and air were passed through a Pyrex tube packed with quartz chips heated at 400°, 1H,5H-octafluoro-3,3-pentanediol (**14**)

$$HCF_2CF_2CH(OH)CF_2CF_2H \longrightarrow HCF_2CF_2C(OH)_2CF_2CF_2H$$

(13 → 14)

was obtained in 54% conversion, based on gas chromatography. Since the diol (**14**) also can be prepared in good yield by oxidation of the alcohol (**13**) with chromic acid,[29] further study of the oxidation of this and other secondary fluoro alcohols with nitrogen dioxide has not been pursued.

Experimental[30]

Oxidation of Primary Fluoro Alcohols.[31]—Table I summarizes the conditions used for oxidizing three fluoro alcohols[7] to fluoro aldehydrols. No efforts have been made to find optimum conditions for these oxidations. The following describes one experiment in detail.

1H,1H,9H-Hexadecafluoro-1-nonanol (20 g., 0.047 mole) was added dropwise[32] over a 2-hr. period to a Pyrex glass tube (about 50 cm. long and 4-cm. inside diameter) partly filled with 300 ml. of quartz chips (6–14 mesh) and heated at 300° while nitric oxide (2.5 cc./sec.) and air (4.0 cc./sec.) were metered into the tube.[12] Attached in series to the bottom of the reaction tube were an air condenser, about 2.5 cm. in diameter and 50 cm. long, and a two-necked round-bottom flask immersed in a solid carbon dioxide–acetone cooling bath. When addition of the alcohol had been completed, 13 g. of a white solid, m.p. 80–84°, was scraped from the walls of the air condenser and 5.5 g. of a slightly moist solid, m.p. 79–83°, was isolated from the cold trap after evaporation of the volatile components. The higher melting solid, 1H,9H-hexadecafluoro-1,1-nonanediol (**3b**), was analyzed without purification.

Anal. Calcd. for $C_9H_4F_{16}O_2$: C, 24.1; H, 0.90; F, 67.7; mol. wt., 449. Found: C, 24.4; H, 1.28; F, 67.0; mol. wt. (ebullioscopic in acetone), 460, 460.

(21) The resistance of this fluoro aldoxime to rearrangement might be ascribed to the effect of the electron-attracting fluoroalkyl group in inhibiting the required direction of heterolysis of the N–O bond (*cf.* for example, E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 618 ff).

(22) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 374.

(23) L. W. Kissinger, W. E. McQuistion, and M. Schwartz have described the synthesis of bisperfluoroalkylfuroxans by reaction of dinitrogen tetroxide with diazo compounds of the type R_fCHN_2 ("Symposium on Nitro Aliphatic Chemistry," Purdue University, Lafayette, Ind., May 26, 1961).

(24) N. E. Boyer, G. M. Czerniak, H. S. Gurowsky, and H. R. Snyder, *J. Am. Chem. Soc.*, **77**, 4238 (1955).

(25) J. N. Boyer, V. Toggweiler, and G. A. Stoner, *ibid.*, **79**, 1748 (1958).

(26) N. Kornblum, R. K. Blackwood, and D. D. Mooberry, *ibid.*, **78**, 1501 (1956); N. Kornblum and V. M. Weaver, *ibid.*, **80**, 4333 (1958).

(27) J. H. Boyer and H. Alul [*ibid.*, **81**, 4237 (1959)] invoke nitrolic acid and nitrile oxide intermediates in the reaction of benzaldoxime with dinitrogen tetroxide to give diphenylfuroxan.

(28) Nitronium ion is a well-authenticated species and is known in many nitrations with nitric acid to be the attacking electrophile. *Cf.*, for example, E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 419 ff.

(29) Unpublished work of Dr. D. C. England, Central Research Department, E. I. du Pont de Nemours and Co., Inc.

(30) Melting points are uncorrected.

(31) R. M. Scribner, U. S. Patent 2,980,738 (1961). A process for preparing fluoro ketone hydrates by oxidation of secondary fluoro alcohols with nitrogen dioxide also is described.

(32) Solid fluoro alcohols were kept molten for dropwise addition by heating the dropping funnel with an infrared lamp.

Combination of the two portions of crude aldehydrol and reaction with hydroxylamine hydrochloride in methanol followed by titration of the hydrogen chloride liberated[14] showed that it averaged 93% purity. Recrystallization of 8 g. of the crude aldehydrol from 40 ml. of benzene gave 2.8 g. of a waxy, amorphous solid melting at 95–96°. Concentration of the mother liquor to 20 ml. gave an additional crop of white solid (0.3 g.) melting at 105–107°. Brace also has observed the melting points of the two forms of the aldehyde hydrate prepared by a different method[8] to be 95–96° and 105–106°,[33] respectively. Reaction of crude 1H,9H-hexadecafluoro-1,1-nonanediol with a water–ethanol solution of 2,4-dinitrophenylhydrazine in 6 *N* sulfuric acid gave a 2,4-dinitrophenylhydrazone, m.p. 122°.[33] In like manner, 1H,11H-eicosafluoro-1,1-undecanediol, m.p. 113–114°, gave a 2,4-dinitrophenylhydrazone melting at 141–143°.[33]

1H,9H-Hexadecafluorononanol Oxime (9).—Hydroxylamine hydrochloride (15 g., 0.2 mole) dissolved in 15 ml. of water was added to 23 g. (0.05 mole) of 1H,9H-hexadecafluorononane-1,1-diol (m.p. 90–94°) in 70 ml. of methanol. The clear solution was allowed to stand at room temperature for 4 hr. and then heated at reflux for 15–20 min. Methanol was removed under vacuum, and the residual oil was poured into water and extracted with two 150-ml. portions of ether. The ether extract was washed with water and dried over magnesium sulfate. Fractional distillation through an 8-in. spinning-band column gave 22.6 g. of oxime, b.p. 95° (9 mm.), m.p. 42.0–42.5°.

Anal. Calcd. for $C_9H_3F_{16}NO$: C, 24.3; H, 0.67; N, 3.14. Found: C, 24.5; H, 0.72; N, 2.67.

The proton magnetic resonance spectrum[34] of the oxime consisted of a singlet at $\tau -1.19$ (NOH), a triplet (J = 51 c.p.s.) at 3.32 split further into triplets (J = 5 c.p.s.) (HCF_2CF_2–), and an overlapping triplet (J = 8 c.p.s.) at 2.32 (–CF_2CH=N–). Infrared analysis (potassium bromide) showed a strong band at 3.0 (λ_{OH}) and a very weak band at 6.05 μ ($\lambda_{C=N}$).

3,4-Bis(8H-hexadecafluoro)-1,2,5-oxadiazole N-Oxide (10).—Ten grams (0.023 mole) of the C_9 fluoro aldehyde oxime was added in small portions to 35 ml. of vigorously stirred 90% fuming nitric acid. The temperature of the mixture gradually rose from 26 to 42° and a transient, dark blue color appeared. Stirring was continued for 20 min. after addition was completed. The colorless mixture was poured into 100 g. of ice, and the water was extracted with two 75-ml. portions of ether. The combined ether extracts were washed with four 25-ml. portions of 5% sodium hydroxide and then with water. Evaporation of the ether gave 8.7 g. of a light yellow semisolid that on distillation through a single-plate, short-pass column gave 6.4 g. (65%) of the furoxan. Redistillation through a 6-in. spinning-band column gave an analytical sample, b.p. 125° (0.5 mm.), that on cooling in Dry Ice solidified to an amorphous solid, m.p. 29°, d^{30}_4 1.89.

Anal. Calcd. for $C_{18}H_2F_{32}N_2O_2$: C, 24.4; H, 0.23; F, 68.6; N, 3.16; mol. wt., 886. Found: C, 24.6; H, 0.34; F, 68.4; N, 3.04; mol. wt. (f.p., benzene), 990.

The p.m.r. spectrum of this compound consisted of a single triplet (J = 51 c.p.s.) centered at τ 3.25 split further into triplets (J = 5 c.p.s.). The infrared absorption spectrum, in essential agreement with spectra reported by Boyer, *et al.*,[24] for furoxans, showed bands at 6.05 ($\lambda_{C=N}$), 6.80, and 7.12 ($\lambda_{ON \rightarrow O}$), 7.50 ($\lambda_{N-O}$), 9.70 ($\lambda_{\text{furoxan ring system}}$), and 11.55 μ ($\lambda_{\text{furoxan ring}}$). Ultraviolet absorption (ethyl alcohol) was at a maximum at 266 mμ (ϵ_{max} 3910), which agrees with the range 255–285 mμ assigned by Boyer, *et al.*,[25] to furoxans.

1H,9H-1,1-Dibenzamidohexadecafluorononane (12).—To 2.85 g. (6.3 mmoles) of $H(CF_2)_8CH(OH)_2$ in 50 ml. of concentrated sulfuric acid and 50 ml. of fuming sulfuric acid was added 1.4 g. (13.6 mmoles) of benzonitrile. The mixture was stirred at room temperature for 1 hr. and poured into 500 g. of ice. Extraction of the aqueous solution with three 150-ml. portions of ether gave, on evaporation of the ether, 1.9 g. of white solid (46% yield), m.p. 217–218°, after two crystallizations from ethyl acetate.

Anal. Calcd. for $C_{23}H_{14}F_{16}N_2O_2$: C, 42.3; H, 2.14; N, 4.28. Found: C, 42.2; H, 2.23; N, 4.41.

The infrared spectrum was consistent with the assigned structure, showing bands at 3.0 (λ_{NH}), at 5.59 ($\lambda_{\text{secondary amide I}}$), and at 6.45 μ ($\lambda_{\text{secondary amide II}}$).

1H,9H-1-Hydroxyhexadecafluoro-1-nonanesulfonic Acid Sodium Salt (8).—To a filtered solution of 50 g. (0.35 mole) of sodium bisulfite in 200 ml. of water and 200 ml. of methanol was added with vigorous stirring and all at once 20 g. (0.045 mole) of the aldehydrol (**3b**). Immediately after dissolution of the aldehydrol a precipitate appeared. The resulting slurry was heated gently on a steam cone for about 15 min., cooled, and filtered. The white solid remaining after washing the filter cake with three 50-ml. portions of cold water, three 50-ml. portions of alcohol, and finally with generous amounts of ether weighed 17.4 g. (74%) and was analytically pure bisulfite adduct. It did not melt up to 300°.

Anal. Calcd. for $C_9H_3F_{16}NaO_4S$: S, 5.98. Found: S, 5.84.

The infrared spectrum exhibited a strong band at 3.10 (hydroxyl), a moderately strong band at 7.25, and a strong band at 8.35 μ; the latter two bands may be associated with the sulfonate group.[35]

1H,9H-Hexadecafluorononanal Semicarbazone.—An aqueous solution of semicarbazide hydrochloride was added to a solution of 4.5 g. (0.01 mole) of the aldehydrol (**3b**) in ethanol, and water and ethanol were added as necessary to make the mixture homogeneous. The mixture was heated on a steam cone for 30 min. and then stored at room temperature overnight. Collection by filtration of the crystals that appeared and recrystallization from benzene gave 3.4 g. (71%) of the semicarbazone as silvery white plates, m.p. 154–155°.

Anal. Calcd. for $C_{10}H_5F_{16}N_3O$: C, 24.7; H, 1.03; N, 8.62. Found: C, 24.9; H, 1.32; N, 9.03.

The infrared absorption spectrum of this compound (in potassium bromide) showed moderately strong bands at 5.84, 6.00, 6.15, and 6.25 μ. The ultraviolet absorption spectrum showed λ_{max}^{EtOH} 243 mμ (ϵ 15,000). The p.m.r. spectrum[34] consisted of a broad complex multiplet (NH, NH_2) centered 128 c.p.s. to low field from tetramethylsilane and having a total area 1.5 times the total area of the remaining peaks. The latter peaks, resembling the corresponding peaks for oxime 9, consisted of a triplet (J = 51 c.p.s.) centered at τ 3.17 split further into triplets (J = 5 c.p.s.) and an overlapping set of triplets (J = 8 c.p.s.) centered at 2.48.

Acknowledgment.—Mrs. Adah B. Richmond measured and correlated gas chromatography data. Dr. R. E. Benson made many helpful suggestions during the preparation of this paper.

(33) N. O. Brace, Ref. 8 and unpublished experiments.

(34) The n.m.r. spectra were taken with a Varian Associates 60-Mc. high resolution spectrometer. Solutions in deuterioacetone were used with tetramethylsilane as an internal standard.

(35) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

Reactions of Nitrogen Dioxide with Organic Halogen Compounds. II.[1] Synthesis of Nitrofluoro Alkanes from Fluorocarboxylic Acids

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Fluorocarboxylic acids react with nitrogen dioxide at elevated temperatures to give 1-nitrofluoro alkanes in small yields (5–30%).

Silver salts of fluorocarboxylic acids readily undergo the Hunsdiecker reaction[2] with halogens, at temperatures generally below 100°, to afford fluoroalkyl halides in excellent yields. Analogous to this is the reaction of perfluorocarboxylic acids, rather than their silver salts, with bromine at high temperatures[3] to give perfluoroalkyl halides.

$$C_2F_5CO_2H + Br_2 \xrightarrow[80\%]{350^\circ} C_2F_5Br + CO_2 + HBr$$

Silver perfluorobutyrate has been reported by Banus[4] to react with nitrogen dioxide in a sealed tube at 200° to afford a small yield of what is probably 1-nitroperfluoropropane, although no evidence for the structure of the product was given. Silver trifluoroacetate was found by Haszeldine and Jander[5] to react in the cold with nitrosyl chloride to form what was apparently trifluoroacetyl nitrite, decomposition of which by gentle heating gave a mixture of nitroso- and nitrotrifluoromethane. Superficially, at least,[6] both of these reactions appear similar to the Hunsdiecker reaction.

The reaction is carried out conveniently by heating a mixture of a fluorocarboxylic acid and excess nitrogen dioxide in an autoclave for several hours at 150–200°. Table I lists 1-nitrofluoro alkanes that have been prepared in this manner.

Passage of fluorocarboxylic acids and a mixture of nitric oxide (excess) and air through a reaction tube packed with glass helices and heated at 300° also produces 1-nitrofluoro alkanes,[1] but yields tend to be smaller, and the procedure is less convenient compared to the autoclave method.

Assignment of structure to these nitro compounds is based primarily on infrared spectroscopic evidence. Whereas simple nitro paraffins generally exhibit asymmetric and symmetric stretching vibrations at 6.38–6.49 and 7.26–7.45 μ, respectively, a powerful electron-withdrawing group attached directly to the nitro group shifts these bands to shorter and longer wave lengths, respectively.[7] Haszeldine,[8] for example, reports that 2-chlorotetrafluoro-1-nitroethane shows strong absorption bands at 6.18 and 7.85 μ. This is in good agreement with the band positions observed for our 1-nitrofluoro alkanes (Table II). To distinguish further our compounds from the isomeric nitrites (or nitrates), our compounds were shown to be unaffected by prolonged shaking with concentrated sulfuric acid or with 5% aqueous sodium hydroxide.

TABLE I

PREPARATION OF 1-NITROFLUORO ALKANES FROM FLUOROCARBOXYLIC ACIDS

Acid	Moles NO_2 per mole of acid	Temp., °C.	Time, hr.	Product	Yield, %	B.p., °C.[a]	Analysis, % N Calcd.	Analysis, % N Found
CF_3CO_2H	6	200	6	CF_3NO_2[b]	30[c]			
$ClCFHCF_2CO_2H$[d]	3	180	4	$ClCFH–CF_2NO_2$[e]	5	63–64	8.72	8.57
$H(CF_2)_4CO_2H$	5	160	6	$H(CF_2)_4NO_2$	30	80	5.67	5.48
$H(CF_2)_6CO_2H$	8	160	6	$H(CF_2)_6NO_2$	15	111	4.08	3.99
$F_3C(CF_2)_6CO_2H$	7	150	2	$F_3C(CF_2)_6NO_2$	10–15	121–122	3.38	2.99

[a] Ref. 13. [b] Identified by mass spectroscopic analysis and by comparison with the infrared spectrum reported by Haszeldine and Jander (ref. 5). [c] Approximate yield based on mass spectroscopy. [d] D. C. England, R. V. Lindsey, L. R. Melby, *J. Am. Chem. Soc.*, **80**, 6442 (1952). [e] The vapors of this nitro compound are extremely irritating to the nostrils.

Now, completing the two sets of analogies, we have found that fluorocarboxylic acids themselves react with nitrogen dioxide at elevated temperatures to give nitrofluoroalkanes in small yields.

$$RCF_2CO_2H \xrightarrow{NO_2} RCF_2NO_2 + CO_2$$

Although the reaction of fluorocarboxylic acids with nitrogen dioxide is undoubtedly quite complex, formation of 1-nitrofluoro alkanes can be rationalized, at least superficially, by the following radical reactions, exemplified by 7*H*-dodecafluoroheptanoic acid. Although eq. 1 implies nothing about the mechanism of formation of fluoroalkyl radical, there is ample ground

$$H(CF_2)_5CF_2CO_2H \xrightarrow{NO_2} H(CF_2)_5CF_2\cdot \qquad (1)$$

$$H(CF_2)_5CF_2\cdot + NO_2 \longrightarrow H(CF_2)_5CF_2NO_2 \qquad (2)$$

(1) Part I in this series, *J. Org. Chem.*, **29**, 279 (1964).

(2) R. G. Johnson and R. K. Ingham, *Chem. Rev.*, **56**, 250 (1956); C. V. Wilson, *Org. Reactions*, **11**, 332 (1957).

(3) J. D. LaZerte, W. H. Pearlson, and E. A. Kouck, U. S. Patent 2,647,933 (1953). Fluorine, however, reacts with perfluorocarboxylic acids at approximately 25° to give perfluoroacyl hypofluorites. *Cf.* G. H. Cady and K. B. Kellogg, *J. Am. Chem. Soc.*, **75**, 2501 (1953), and A. Meneffee and G. H. Cady, *ibid.*, **76**, 2020 (1954).

(4) J. Banus, *J. Chem. Soc.*, 3755 (1953). The preparation of $C_3F_7NO_2$ by irradiation of C_3F_7I and nitrogen dioxide in the presence of mercury also was reported.

(5) R. N. Haszeldine and J. Jander, *ibid.*, 4172 (1953).

(6) Both the Hunsdiecker reaction and the reaction of Haszeldine and Jander appear to involve generation of free radicals by decomposition of RCO·OX where X is halide or NO.

(7) J. F. Brown, *J. Am. Chem. Soc.*, **77**, 6341 (1955).

(8) R. N. Haszeldine, *J. Chem. Soc.*, 2075 (1953).

TABLE II

INFRARED ABSORPTION BANDS OF 1-NITROFLUORO ALKANES

Compound	NO_2 asym. stretch, μ	NO_2 sym. stretch, μ
CF_3NO_2	6.13, 6.18	7.78
$ClCFHCF_2NO_2$	6.24	7.33
$H(CF_2)_4NO_2$	6.18	7.40
$H(CF_2)_6NO_2$	6.16	7.40
$F_3C(CF_2)_7NO_2$	6.15	7.40

for its rationalization. It may progress through an acylnitrate intermediate, $H(CF_2)_5CF_2CO\cdot ONO_2$, akin to the nitrite intermediate proposed by Haszeldine and Jander[5] and analogous to the hypohalite intermediates, $RCO\cdot OX$, strongly implicated as precursors to the free radicals involved in the Hunsdiecker reaction.[2] Another possibility is that the fluorocarboxylic acid decarboxylates at the temperature of this reaction without participation of nitrogen dioxide.[9] Equation 2 represents reaction of the fluoroalkyl radical with the radical NO_2 to give a nitro compound.

Isolation of a waxy solid, m.p. 80°, having the structure $H(CF_2)_xH$ (x = unknown) from the reaction of 7*H*-dodecafluoroheptanoic acid and nitrogen dioxide supports the hypothesis that fluoroalkyl radicals participate in this reaction.

However, reflecting the over-all complexity of this reaction, a series of homologous 1-nitrofluoro alkanes is also found among the products.[10] Thus, fractional distillation of the liquid products from reaction of 7*H*-dodecafluoroheptanoic acid with nitrogen dioxide, after washing with base to remove possible nitrite esters, gave five fractions of colorless liquid boiling over the temperature range 79–111°. The highest boiling fraction was shown by gas chromatography to be 98% pure; by elemental analysis and n.m.r. and infrared analysis it clearly had the structure $H(CF_2)_6NO_2$. Spectral and gas chromatographic analysis of the lower fractions indicated that they were a mixture of homologous nitro compounds, $H(CF_2)_nNO_2$, one fraction of which appeared to be $H(CF_2)_4NO_2$, identical with the major product obtained from the reaction of 5*H*-octafluoropentanoic acid with nitrogen dioxide.

(9) Sodium salts of perfluorocarboxylic acids undergo thermal decomposition at 165–270° (to give perfluoro olefins). *Cf.* M. Hudlicky, "Chemistry of Organic Fluorine Compounds," Macmillan Co., New York, N. Y., 1961, p. 270 ff.

(10) A tempting explanation for the formation of homologous nitrofluoro alkanes would be as follows. Combination of the fluoroalkyl radical produced by reaction 1 with the "ambidentate" radical NO_2 could give an unstable fluoroalkyl nitrite (reaction 2a). Homolytic dissociation[11] of this nitrite would give a fluoroalkoxy radical (reaction 3).

$$H(CF_2)_5CF_2\cdot + NO_2 \longrightarrow H(CF_2)_5CF_2ONO \quad (2a)$$
$$H(CF_2)_5CF_2ONO \longrightarrow H(CF_2)_5CF_2O\cdot + NO \quad (3)$$
$$H(CF_2)_5CF_2O\cdot \longrightarrow H(CF_2)_4CF_2\cdot + CF_2O \quad (4)$$
$$H(CF_2)_4CF_2\cdot + NO_2 \longrightarrow H(CF_2)_4CF_2NO_2 \quad (5)$$
$$H(CF_2)_4CF_2\cdot + NO_2 \longrightarrow H(CF_2)_4CF_2ONO \quad (5a)$$

Haszeldine and Francis[12] have shown that such radicals, produced by photolysis of a fluoroalkyl iodide in the presence of oxygen, decompose by loss of carbonyl fluoride and formation of a fluorocarbon radical containing one less CF_2 group (reaction 4). This new radical could then undergo a similar cycle of reactions (5 and 5a) yielding a homologous 1-nitrofluoroalkane and, by way of the nitrite, more carbonyl fluoride, etc.

As reasonable as this reaction sequence may appear, it must at present be discounted on the basis of the fact that infrared and mass spectroscopic analysis of the gaseous products from the reaction of $H(CF_2)_6CO_2H$ and NO_2 at 160° for 6 hr. failed to detect the presence of even traces of COF_2. The major gaseous reaction product was instead carbon dioxide, accompanied by traces of several fluoro olefins. In another experiment it was shown that COF_2 is recovered unchanged after 8 hr. at 160° in the presence of a large excess of nitrogen dioxide. We are indebted to two referees who suggested that the validity of the reaction mechanism represented by equations 2a through 5a may be tested by analysis for carbonyl fluoride.

(11) For a summary of recent literature on pyrolysis of nitrites, *cf.* P. Gray, P. Rathbone, and A. Williams, *J. Chem. Soc.*, 3932 (1960), and A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 48 (1962).

(12) R. N. Haszeldine and W. C. Francis, *J. Chem. Soc.*, 2125 (1955).

Experimental[13]

1-Nitrofluoro Alkanes from Fluorocarboxylic Acids.[14] Reactions in an Autoclave.—Table I summarizes conditions employed for the reaction of nitrogen dioxide with fluorocarboxylic acids. The following experiments are typical.

A 400-ml. stainless-steel autoclave (Hastelloy-C) charged with 20 g. (0.06 mole) of 7*H*-dodecafluoroheptanoic acid and 20 g. (0.25 mole) of dinitrogen tetroxide was heated gradually to 160° over an 8-hr. period at a rate of about 20° per hr. and then maintained at 160° for 6 hr. The autoclave was cooled to room temperature and vented slowly; a liquid residue was obtained. After washing with aqueous sodium bicarbonate, the liquid product (5.5 g.) was distilled through a Nester[15] 8-in. spinning-band column to give the following fractions: (1) b.p. 78–79°, 0.3 ml.; (2) 89–111°, 0.5 ml.; (3) 111°, 0.6 ml.; (4) 111°, 0.5 ml.; (5) 111°, 0.5 ml. A nondistillable residue was obtained which after crystallization from benzene melted at 80° and weighed 1.0 g. Fractions 2 through 5 were shown by gas chromatography[16] to be mixtures of five components in common. Fractions 4 and 5 were 98% pure and contained about 1.5% of the major component of fraction 2. The proton magnetic resonance spectrum of fraction 4 consisted of a single triplet (J = 51 c.p.s.) at τ 3.25 split further into triplets (J = 5 c.p.s.) (HCF_2CF_2–). The infrared absorption spectra for fractions 4 and 5 showed, in addition to strong C–F absorption in the 9–10-μ region, strong bands at 6.16 and 7.40 μ ($\lambda_{CF_2NO_2}$).

Anal. Calcd. for $C_6HF_{12}NO_2$: F, 65.8; N, 4.08. Found for fraction 4: F, 65.9; N, 3.99.

Fraction 2 was shown by g.c. to be 92% pure and to contain about 6% of the major component of fraction 4. Significantly, the retention time of the major component of fraction 2 was within about 4% (10 sec.) of the retention time observed, in another experiment, for $H(CF_2)_4NO_2$ (b.p. 80°) prepared from 1*H*-octafluoropentanoic acid. The p.m.r. spectrum was similar to that of fraction 4, and the infrared absorption spectrum showed bands characteristic of fluoronitro alkane at 6.16–6.18 and 7.40 μ.

Infrared analysis of the whole solie, m.p. 80°, described before showed the absence of bands ascribable to carbonyl, carboxyl, or nitro groups. The p.m.r. spectrum was difficult to interpret because of low signal strength, but it appeared to consist of a weak triplet at about τ 3.2. In spite of a low fluorine analysis, an α,ω-dihydrofluorocarbon structure is proposed for this compound.

Anal. Calcd. for $C_nH_2F_2n$: F, 75.8; N, 0.0. Found: F, 74.0; N, nil.

In another experiment, 20 g. (0.05 mole) of perfluorooctanoic acid and 15 g. (0.33 mole) of nitrogen dioxide were heated in a 200-ml. Hastelloy-lined autoclave, the temperature being raised at the rate of 20° per hr. to 150° and held at 150° for 2 hr. The vessel was cooled to room temperature and slowly vented, leaving about 7 g. of liquid and a trace of green nickel salt. The liquid was washed with three 50-ml. portions of saturated aqueous sodium bicarbonate, then dried over magnesium sulfate, giving about 3 g. of a colorless, mobile liquid that was distilled through a 4-in. micro spinning-band[15] column. The following fractions were obtained: (1) b.p. 82°, 0.1 ml. (N, 3.78); (2) b.p. 82–100°, 0.2 ml. (*Anal.* Calcd. for $C_6F_{13}NO_2$: N, 3.84. Found: N, 3.65.); (3) b.p. 100–103°, 0.3 ml. (N, 3.50); (4) 103–113°, 0.5 ml. (N, 3.42); (5) b.p. 115–121°, 0.5 ml. (N, 3.31); (6) b.p. 121–122°, 0.6 ml. (N, 3.25); (7) 122°, 0.2 ml. (*Anal.* Calcd. for $C_7F_{15}NO_2$: N, 3.38. Found: N, 2.99.).

As shown by gas chromatographic analysis, each of the seven fractions was a mixture of 4–5 components. The major (90%) component of fraction 7 was also the major component of frac-

(13) Boiling points are uncorrected.

(14) R. M. Scribner, U. S. Patent 3,057,931 (1962).

(15) R. G. Nester, U. S. Patent 2,712,520.

(16) Gas chromatographic analyses were carried out on a column packed with Dow Corning DC-200 silicon oil (30 parts) on powdered firebrick (70 parts) and operated at 140°.

tions 5 (63%) and 4 (60%). Fraction 2 was composed of about 80% of another component. Infrared analysis of all the fractions showed strong bands characteristic of nitro groups (6.15–6.18 and 7.50 μ). That none of the 4–5 components was an olefin or nitrite ester was demonstrated by the fact that the gas chromatogram of fraction 5 was not changed either qualitatively or quantitatively by prolonged (24 hr.) shaking with aqueous potassium permanganate or concentrated sulfuric acid.

Reactions in a Hot Tube.—Passage of excess nitric oxide (2.5 ml./sec.) and 5*H*-octafluoropentanoic acid through a quartz-packed tube (described in ref. 1) at temperatures from 200–390° gave, at lower temperatures, mainly gaseous degradation products boiling below 0°. From 7*H*-dodecafluoroheptanoic acid and excess nitric oxide at 360°, a trace of $H(CF_2)_4CF{=}CF_2$ was isolated.

When 7*H*-dodecafluoroheptanoic acid and a nitric oxide–air mixture[1] were passed through a reaction tube packed with quartz chips and heated at 350°, there was obtained a 10% yield of 6*H*-1-nitrododecafluorohexane. The infrared absorption spectrum and g.c. retention time of this compound were essentially identical with those observed for the same nitrofluoro alkane obtained by synthesis in an autoclave.

Autoxidation of 2-Alkenyldioxolanes and 2-Alkenyl-1,3-dioxanes

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Eleven 2-alkenyldioxolanes and two 2-alkenyl-1,3-dioxanes were autoxidized under different conditions. Terminal products, such as peroxides, hydroperoxides, spirocyclic peroxides, α,β-unsaturated esters, and polymers, were isolated and identified. A mechanism which accounts for these products is presented.[2]

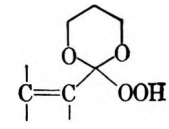
This paper describes the autoxidation of 2-alkenyldioxolanes and 2-alkenyl-1,3-dioxanes. While the literature on the autoxidation of hydrocarbons is voluminous[3–5] little has been reported on the autoxidation of acetals. Criegee[6] and Lederer oxidized 2-methyldioxolane with molecular oxygen and isolated di(2-methyldioxolan-2-yl) peroxide. Rieche, *et al.*,[7] autoxidized 2-phenyldioxolane and obtained 2-hydroperoxy-2-phenyldioxolane. No work on the autoxidation of 2-alkenyl-1,3-cyclic acetals has been reported in the literature.

We wish to report our findings on the autoxidation of a number of 2-alkenyl-1,3-cyclic acetals. The cyclic acetals (Table I) were autoxidized with (1) oxygen alone, (2) oxygen + a trace of Co(II), and (3) oxygen + a trace of *p*-toluenesulfonic acid. Five types of products were isolated and identified (a–e, col. 2).

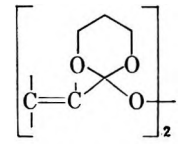
The principal product or products obtained from autoxidation of the cyclic acetals of Table I are summarized in Table II. Oxidations conducted in the absence of additives gave either hydroperoxides or spirocyclic peroxides. In the presence of Co(II) the products were generally α,β-unsaturated ester and polymer; in a few cases spirocyclic peroxide was the main product. Two oxidations conducted in the presence of *p*-toluenesulfonic acid also gave spirocyclic peroxides.

Thus, oxidation of 2-vinyl-4-methyldioxolane (I) in the absence of additives gave 2-hydroperoxy-2-vinyl-4-methyl dioxolane (XIV) and di(2-vinyl-4-methyldioxolan-2-yl) peroxide (XV). When the oxidation was conducted in the presence of a catalytic amount of cobaltous ion the products were 2-hydroxypropyl acrylate (XXV) and polymer XXVI.[8] Oxidation of I in the presence of toluenesulfonic acid gave the spirocyclic peroxide, 2-methyl-1,4,6,7-tetraoxaspiro[4.4]nonane (XXXV), as the major product.

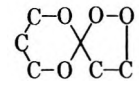
(a) Hydroperoxide



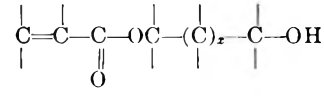
(b) Peroxide



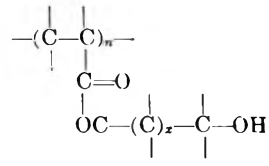
(c) Spirocyclic peroxide



(d) α,β-Unsaturated esters



(e) Complex polymers of α,β-unsaturated esters (where $x = 0$ or 1)



The reaction scheme (see eq. 1–5) accounts for the formation of the observed products in the case of 2-vinyl-4-methyldioxolane (I) (p. 287).

Reactions 2, 3, and 4 of this scheme comprise the free-radical sequence accounting for the formation of the hydroperoxide (XIV). Coupling reactions 5 and 6

(1) To whom any correspondence should be addressed.

(2) E. J. Burrell, Radiation Physics Laboratory, Engineering Department, E. I. du Pont de Nemours and Co., Wilmington, Del., has examined the kinetics and has measured the absolute reaction rate constants for every significant step for the cobalt-catalyzed autoxidation of 2-vinyl-4(4-hydroxybutyl)dioxolane using pulse radiolysis. His work is summarized in another paper which has been submitted to the *Journal of Chemical Physics*.

(3) K. U. Ingold, *Chem. Rev.*, **61**, 563 (1961).

(4) W. A. Waters, *Progr. Org. Chem.*, **5**, 1 (1961).

(5) F. R. Mayo, *Ind. Eng. Chem.*, **52**, 614 (1960).

(6) R. Criegee, "Methoden der Organische Chemie," Vol. III, 4th Ed., Georg Thieme Verlag, Stuttgart, 1952, p. 23.

(7) A. Rieche, E. Schmitz, and E. Beyer, *Ber.*, **91**, 1935 (1958).

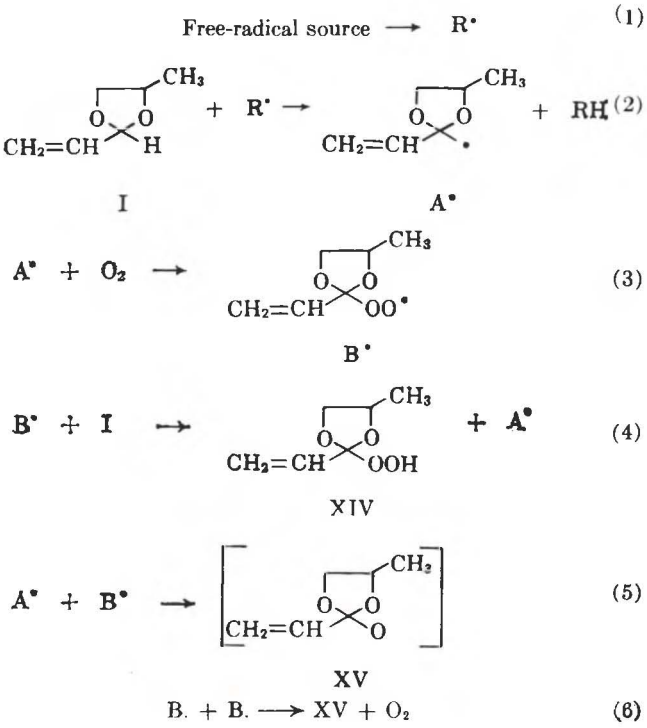
(8) Fractionation of polymer XXVI by gradient elution through acid-washed alumina with benzene, ether, and finally ethanol gave five fractions with molecular weights ranging from 530 to 1050. The structure of the polymer is much more complex than one would suspect from the infrared spectra of the fractions which were all substantially the same as poly(2-hydroxypropyl acrylate). Elemental analyses (C, H, and O) and functional group determinations (OH and ester equivalent), although close, do not correspond to the values for poly(2-hydroxypropyl acrylate). The presence of such groups as hydroperoxy, peroxy, and dioxolanyl in the various fractions were demonstrated by qualitative tests.

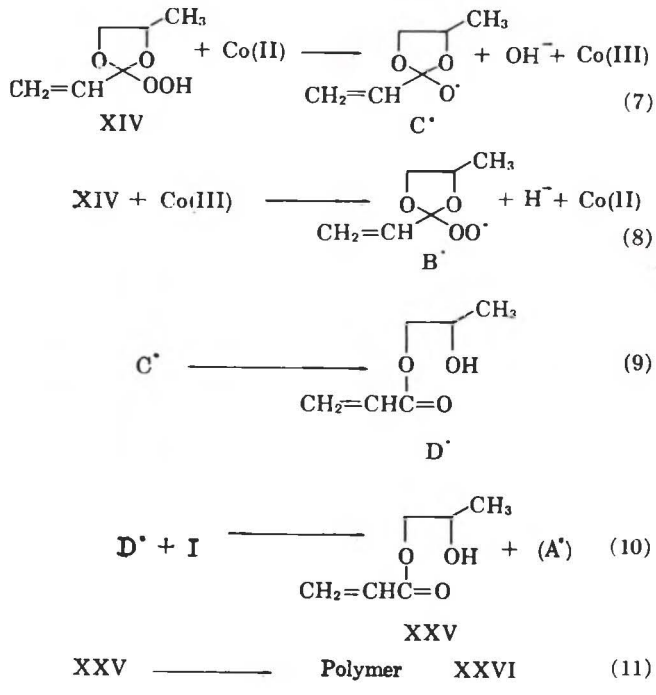
TABLE I

2-ALKENYLDIOXOLANES AND -1,3-DIOXANES OXIDIZED

	Dioxolane	Yield,[b] %	B.p.[c] (mm.), °C.	$n^{25}D$	Oxidation procedure[a] O_2 only	O_2 + Co(II)	O_2 + a
I	2-Vinyl-4-methyl	45	122 (760)	1.4211	A	B	A
II	2-Vinyl-4,5-dimethyl	68	94 (180)	1.4238	A	A	
III	2-Vinyl-4,4-dimethyl	42	126 (760)	1.4171	A	A	A
IV	2-Vinyl-4,4,5-trimethyl	70	76 (80)	1.4213	A	A	
V	2-Vinyl-4,4,5,5-tetramethyl	77	89 (80)	1.4289	A	B	
VI	2-Propenyl-4-methyl	47	76 (50)	1.4330	A	B	
VII	2-Propenyl-4,5-dimethyl	80	105 (100)	1.4345	A	A	
VIII	2-Propenyl-4,4,5,5-tetramethyl	91	102 (50)	1.4381	A	A	
IX	2-Isopropenyl-4-methyl	55	78 (90)	1.4279	A	B	
X	2-Isopropenyl-4,5-dimethyl	80	93 (100)	1.4300	A	A	
XI	2-Isopropenyl-4,4,5,5-tetramethyl	90	90 (51)	1.4352	A	A	
	1,3-Dioxane						
XII	2-Vinyl-4,4,6-trimethyl	91	65 (12)	1.4362	A	B	
XIII	2-Vinyl-4,4,6,6-tetramethyl	56	68 (16)	1.4384		A	

[a] See Experimental section. [b] Based on glycol. [c] Uncorrected. [d] *p*-Toluenesulfonic acid.





terminate the chain sequence and produce the dioxolanyl peroxide (XV).

When Co(II) is present another free-radical chain sequence involving the hydroperoxide (XIV) is possible. Hydroperoxide decomposition by Co(II) and Co(III) (reactions 7 and 8) has been the subject of many investigations.[9,10] These reactions explain the catalytic behavior of Co(II) in the oxidation. The driving force for the isomerization of radical C· to radical D· (eq. 9) is the formation of the conjugated acrylate double bond.

Because the acrylate is easily polymerized by free radicals (reaction 11) most of it was converted to the terminal product, polymer XXVI and gave a low (1:9) ester to polymer product ratio (See Table I). The more highly substituted 2-vinyl-4,5-dimethyldioxolane (II) and 2-vinyl-4,4,5-trimethyldioxolane (IV), which are oxidized to bulkier and, therefore, less reactive acrylates, gave substantially higher ester to polymer ratios, 1:3 and 1:1, respectively. The 2-isopropenyl-1,3-cyclic acetals also gave higher (1:2 or greater) ester to polymer ratios because they oxidize to methacrylates which polymerize less readily than acrylates.[11] Finally, 2-propenyl-4-methyldioxolane (VI) which oxidizes to a crotonate, a monomer class well-known for its sluggishness in addition polymerizations,[12] gave the highest (2:1) ester to polymer ratio.

An exothermic reaction occurred when a trace of Co(II) butyl phthalate was added to a toluene solution fo 2-hydroperoxy-2-vinyl-4-methyldioxolane (XIV). The infrared spectrum of the resultant polymer was substantially identical with polymer XXVI which formed during oxidation of acetal I and with poly(2-hydroxypropyl acrylate) obtained by polymerizing an authentic sample of ester XXV. These results support the reaction sequence 7–11.

(9) A. V. Tobolsky and R. B. Mesrobian, "Organic Peroxides," Interscience Publishers, Inc., New York, N. Y., 1954, p. 103.

(10) A. G. Davies, "Organic Peroxides," Butterworth and Co., London, 1961, p. 177.

(11) G. M. Burnett, "Mechanism of Polymerization Reactions," Interscience Publishers, Inc., New York, N. Y., 1954, p. 232.

(12) T. Alfrey, J. J. Bohrer, and H. Mark, "Copolymerization," Interscience Publishers, Inc., New York, N. Y., 1952, pp. 49–52.

TABLE II

CYCLIC PEROXIDE PRODUCTS FROM AUTOXIDATION OF 2-ALKENYLDIOXOLANES AND -1,3-DIOXANES

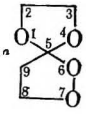
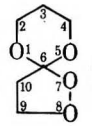
	Dioxolane oxidized	Principal product: O_2 only		O_2 + Co(II)[a]		O_2 + acid[b]	
I	2-Vinyl-4-methyl	XIV	Hydroperoxide	XXV	Ester	XXXV	Cyclic peroxide
		XV	Peroxide	XXVI	Polymer (1:9)		
II	2-Vinyl-4,5-dimethyl	XVI	Hydroperoxide	XXVII	Ester		
				XXVIII	Polymer (1:3)		
III	2-Vinyl-4,4-dimethyl	XVII	Hydroperoxide			XXXVI	Cyclic peroxide
IV	2-Vinyl-4,4,5-trimethyl	XVIII	Cyclic peroxide	XXIX	Ester (1:1)		
					Polymer		
V	2-Vinyl-4,4,5,5-tetramethyl	XIX	Cyclic peroxide	XIX	Cyclic peroxide		
VI	2-Propenyl-4-methyl	XX	Cyclic peroxide	XXX	Ester (2:1)		
					Polymer		
VII	2-Propenyl-4,5-dimethyl	XXI	Cyclic peroxide		Ester[c]		
VIII	2-Propenyl-4,4,5,5-tetramethyl	XXII	Cyclic peroxide	XXII	Cyclic peroxide		
IX	2-Isopropenyl-4-methyl		Hydroperoxide[c]	XXXI	Ester (1:2)		
					Polymer		
X	2-Isopropenyl-4,5-dimethyl		Hydroperoxide[c]		Ester[c]		
XI	2-Isopropenyl-4,4,5,5-tetramethyl	XXIII	Cyclic peroxide	XXXII	Ester		
					Polymer (1:1)		
XII	2-Vinyl-4,4,6-dimethyl	XXIV	Cyclic peroxide	XXXIII	Ester (1:1)		
					Polymer		
XIII	2-Vinyl-4,4,6,6-tetramethyl			XXXIV	Cyclic peroxide		

[a] Arabic numerals in parentheses indicate weight ratio of monomeric ester to polymer. [b] *p*-Toluenesulfonic acid. [c] By inference from infrared spectrum.

TABLE III

NEW SPIROCYCLIC PEROXIDES

1,4,6,7-Tetraoxaspiro-[4.4]nonanes[a]		Yield,[b] %	B.p.[c] (mm.), °C.	$n^{25}D$	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Mol. wt. Calcd.	Mol. wt. Found	Peroxide[d] Calcd.	Peroxide[d] Found
XVIII	2,2,3-Trimethyl-	47	55 (0.5)	1.4412	$C_8H_{14}O_4$							19.5	19.6
XIX	2,2,3,3-Tetramethyl-	72	58 (0.3)	1.4468	$C_9H_{16}O_4$	57.43	58.20	8.57	8.87	188	179	18.5	17.5
XX	2,8-Dimethyl-	61	51 (0.4)	1.4415	$C_7H_{12}O_4$	52.49	53.66	7.55	8.16	160	161	21.2	17.5
XXI	2,3,8-Trimethyl-	56	60 (1.1)	1.4408	$C_8H_{12}O_4$	55.16	56.78	8.10	8.71	174	171	19.5	16.4
XXII	2,2,3,3,8-Pentamethyl-	78	56 (0.2)	1.4432	$C_{10}H_{18}O_4$	59.39	60.34	8.97	9.20	202	196	16.8	12.5
XXIII	2,2,3,3,9-Pentamethyl-	72	66 (0.3)	1.4486	$C_{10}H_{18}O_4$	59.39	59.55	8.97	9.15	202	198	16.9	15.9
XXXV	2-Methyl-	22	50 (0.7)	1.4425	$C_6H_{10}O_4$	49.31	48.86	6.89	6.78	146	146	23.3	21.3
XXXVI	2,2-Dimethyl-	67	39 (0.4)	1.4365	$C_7H_{12}O_4$	52.49	52.55	7.55	7.38	160	158	21.2	17.5
1,5,7,8-Tetraoxaspiro-[4.5]decanes[e]													
XXIV	2,2,4-Trimethyl-	37	58 (0.6)[f]		$C_9H_{16}O_4$	57.43	57.90	8.57	8.81			18.1	18.5
XXXIV	2,2,4,4-Tetramethyl-	70	63 (0.6)	1.4501	$C_{10}H_{18}O_4$	59.39	60.12	8.97	9.21	202	181	16.9	17.0

[a]  [b] Based on O_2 consumed. [c] Uncorrected. [d] As % H_2O_2. [e]  [f] M.p. 34–38°.

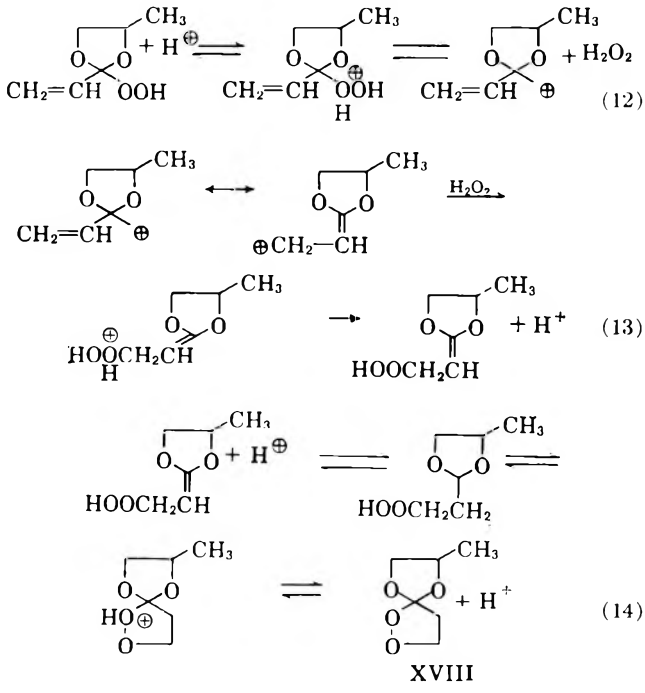
Although the spirocyclic peroxides of Table III, may form *via* a free-radical route,[13] an ionic route[14–17] is indicated, because in the oxidation of acetals I and III merely adding a trace of *p*-toluenesulfonic acid changed the major product from hydroperoxide to spirocyclic peroxide, Table II. Consistent with this observation is the mechanism shown in eq. 12–14, p. 289.

Addition of *p*-toluenesulfonic acid to crude 2-hydroperoxy-2-vinyl-4,4-dimethyldioxolane (XVII) produced a mild exotherm and a decrease in the 3.0-μ (hydroperoxy OH) band in the infrared. Further, all unoxidized cyclic acetals were neutral to moist pH paper while all oxidized acetals were acid with pH values of 2–4. The acids produced in seven of eleven of the oxidations (conducted in the absence of additives) were sufficient to cyclize the hydroperoxide. Like the acetals I and III, the acetals IX and X could undoubtedly be made to yield spirocyclic peroxides rather than hydroperoxides by acidifying with *p*-toluenesulfonic acid prior to oxidation.

The data (Table IV) abstracted from Table II makes it apparent that spirocyclic peroxide formation becomes progressively more difficult as the 2-alkenyl substituent is changed from propenyl to vinyl to isopropenyl.

A multiplicity of methyl groups on the ring carbon atoms favors cyclic peroxide formation. Thus, cyclic acetals V, VIII, and XV have four methyl substituents

(13) A. V. Tobolsky and R. V. Mesrobian, "Organic Peroxides," Interscience Publishers, Inc., New York, N. Y., 1954, p. 179.
(14) G. B. Payne, *J. Org. Chem.*, **23**, 310 (1958).
(15) R. Criegee and G. Paulig, *Ber.*, **88**, 712 (1955).
(16) A. Rieche, E. Schmitz, *et al.*, *ibid.*, **93**, 2443 (1960).
(17) A. Rieche, E. Schmitz, *et al.*, *Angew. Chem.*, **72**, 635 (1960).



(12)

(13)

(14)

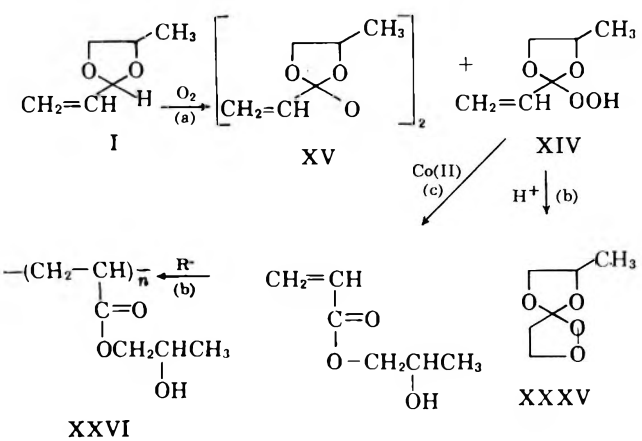
XVIII

TABLE IV

Acetal	2-Alkenyl group	No. of ring methyl substituents	Principal product
VI	Propenyl	1	Cyclic peroxide
VII	Propenyl	2	Cyclic peroxide
VIII	Propenyl	4 (Co^{+2})	Cyclic peroxide
I	Vinyl	1	Hydroperoxide
II	Vinyl	2	Hydroperoxide
IV	Vinyl	4 (Co^{+2})	Cyclic peroxide
IX	Isopropenyl	1	Hydroperoxide
X	Isopropenyl	2	Hydroperoxide
XI	Isopropenyl	4 (Co^{+2})	Ester

and each gave a cyclic peroxide, even when oxidations were conducted in the presence of Co(II). Perhaps the methyl groups shield the hydroperoxy group and make the hydroperoxides less reactive towards Co(II) (reaction 7). The opportunity for hydroperoxide cyclization (reactions 12 and 15) is increased and spirocyclic peroxides, rather than esters or polymers, become the principal product.

The following is a schematic representation of the product interrelationships for oxidation of 2-vinyl-4-methyldioxolane and is believed applicable to the 2-alkenyl-1,3-cyclic acetals generally.



Initial products are peroxide and hydroperoxide. Because the latter product can react further by two alternative reaction paths, one acid- and the other Co(II)-catalyzed, several different terminal products are possible. Spirocyclic peroxide is the principal product when Co(II) is absent and the reaction environment is sufficiently acid. α,β-Unsaturated ester and polymer are generally the terminal products when Co(II) is present. The ratio of ester to polymer obtained depends upon the susceptibility of the ester to addition polymerization.

Experimental

Preparation of 2-Alkenyldioxolanes and -1,3-dioxanes.—The acetals (Table I) used in this study were prepared by refluxing toluene solutions of α,β-unsaturated aldehydes (20 molar % excess) with appropriate diols in the presence of a catalytic amount of acid.[18] Oxalic acid was employed in the preparation of compounds III, VI, and IX; *p*-toluenesulfonic acid was used in the remaining preparations. Water of reaction was distilled azeotropically as formed and collected in a Dean–Stark trap. The reaction mixtures were washed with 5% sodium hydroxide solution, dried over anhydrous magnesium sulfate, and fractionated. The compounds prepared are listed in Table I.

Autoxidation of Cyclic Acetals. Procedure A. 2-Hydroperoxy-2-vinyl-4-methyldioxolane (XIV) and Di(2-vinyl-4-methyldioxolan-2-yl) Peroxide (XV) from I.—To a 500-ml. flask equipped with a stirrer, a thermometer, and a reflux condenser attached to a 1-l. gas buret was charged 2-vinyl-4-methyldioxolane (114 g., 1 mole). The stirrer was started and the apparatus evacuated to 10-mm. pressure and then filled with oxygen (atmospheric pressure). The reaction temperature was raised gradually until an oxygen absorption rate of about 2 l./hr. was achieved at about 85°. This temperature was maintained until 6.3 l. (0.28 mole) of oxygen was absorbed. After cooling, unchanged dioxolane (83.2 g., 0.62 mole) was recovered by distillation at 20° (1 mm.). The residue was fractionated to give 2-hydroperoxy-2-vinyl-4-methyldioxolane (XIV, 18.5 g.); b.p. 64–66° (0.15 mm.); maximum pot temperature, 105°; infrared spectrum, hydroperoxy OH, 3.0, and 2-vinyl-1,3-cyclic acetal bands at 10.2 and 10.6 μ.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90; O, 43.79; mol. wt., 146. Found: C, 49.27; H, 7.41; O, 43.70; mol. wt., 152.

The colorless liquid residue from the distillation was di-(2-vinyl-4-methyldioxolan-2-yl) peroxide.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.02; H_2 no. (for 2C=C and —O—O—), 0.0232; peroxide oxygen as % H_2O_2, 13.1. Found: C, 55.89; H, 7.10; H_2 no., 0.0232; peroxide oxygen as % H_2O_2, 12.9.

The hydroperoxide (XIV) reacted exothermically with a trace of Co(II) butyl phthalate to give a polymer whose infrared spectrum was substantially identical with that of poly(2-hydroxypropyl acrylate). Upon treatment with water, the hydroperoxide gave hydrogen peroxide and 2-hydroxypropyl acrylate (identified by infrared). The peroxide (XV) did not react with water or Co(II) and was considerably more stable towards heat than the hydroperoxide.

Autoxidation of Cyclic Acetals. Procedure B. 2-Hydroxypropyl Acrylate (XXV) and Polymer XXVI from I.—To a 190-mm. diameter crystallizing dish placed in a vacuum desiccator was added 2-vinyl-4-methyldioxolane (25 g., 0.22 mole) and 1.25 ml. of Co(II) butyl phthalate in toluene (10 mg. of Co(II)/ml.). The desiccator was evacuated to 30 mm. and filled with oxygen to atmospheric pressure. After standing under oxygen at room temperature for 6 hr. the contents of the dish were mixed with hydroquinone. Six runs were made in this manner, combined, and permitted to stand for 24 hr. The composite was filtered and fractionated through a short Vigreux column to yield polymer XXVI (47 g.) and a liquid (16 g.), b.p. 55–58° (0.5 mm.). Redistillation of the latter product gave additional polymer and 2-hydroxypropyl acrylate (6 g.), b.p. 49° (0.4 mm.). The infrared spectrum of the ester was identical with that of an authentic sample of 2-hydroxypropyl acrylate.

(18) R. F. Fischer and C. W. Smith, *J. Org. Chem.*, **25**, 319 (1960).

TABLE V

α,β-UNSATURATED ESTERS

	Ester	Yield,[a] %	B.p.[b] (mm.), °C.	$n^{25}D$	Sapon. equiv. Calcd.	C=C (g. of H_2/g.) Found	Calcd.	OH, % Found	Calcd.	Found
XXV	2-Hydroxypropyl acrylate	10	49 (0.4)		130	129		c		d
XXVII	1-Methyl-2-hydroxypropyl acrylate	30		1.4428		e		c		d
XXIX	1,2-Dimethyl-2-hydroxypropyl acrylate	45	50 (0.4)	1.4410	158	169		c		d
XXX	2-Hydroxypropyl crotonate	72	81 (1.2)	1.4537	144	144	0.0139	0.0142	11.8	11.9
XXXI	2-Hydroxypropyl methacrylate	30	57 (0.5)	1.4460	144	145		f	11.8	11.4
XXXII	1,1,2-Trimethyl-2-hydroxypropyl methacrylate	50	60 (0.3)	1.4482		e		f		d
XXXIII	1,1,3-Trimethyl-3-hydroxybutyl acrylate	40	42 (0.2)	1.4432	172	175	0.0117	0.0119	8.00	8.21
XXXVII	2-Methyl-2-hydroxypropyl acrylate		40 (0.3)	1.4420		e		c		d

[a] Based on O_2 consumed. [b] Uncorrected. [c] Acrylate C=C doublet at 6.1 and singlet at 12.2 μ (infrared). [d] Alcohol OH at 2.8 μ (infrared). [e] Ester C=O at 5.8 μ (infrared). [f] Methacrylate C=C singlet at 6.1 and 12.2 μ (infrared).

Anal. Calcd. for $C_6H_{10}O_3$: sapon. equiv., 130. Found: sapon. equiv., 129 and 130.

The infrared spectrum of the polymer (XXVI) produced upon work-up of the oxidation mixture was substantially identical with poly(2-hydroxypropyl acrylate) obtained by heating 2-hydroxypropyl acrylate with a catalytic amount of benzoyl peroxide.

2-Methyl-1,3,5,7-tetraoxaspiro[4.4]nonane (XXXV) from I.—2-Vinyl-4-methyldioxolane (57 g., 0.5 mole) containing *p*-toluenesulfonic acid (0.2 g.) reacted with oxygen (8 g., 0.25 mole) at 85° by procedure A. The oxidized mixture gave unconverted dioxolane (24 g.) and a moderately viscous oil (41 g.) on stripping at 25–30° (0.3 mm.). The oil was dissolved in benzene (70 ml.) and stirred vigorously with 10% caustic solution while cooling with an ice bath. The organic phase upon fractional distillation yielded polymer (11 g.) and the cyclic peroxide, 2-methyl-1,4,6,7-tetraoxaspiro[4.4]nonane (XXXV, 8 g.); b.p. 50° (0.7 mm.); $n^{25}D$ 1.4425.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.89; mol. wt., 146; peroxide oxygen as % H_2O_2, 23.3. Found: C, 48.86; H, 6.89; mol. wt., 146, 146; peroxide oxygen as % H_2O, 21.9, 20.7.

2-Hydroperoxy-2-vinyl-4,5-dimethyldioxolane (XVI) from II.—Oxygen (12 g., 0.37 mole) was added to 2-vinyl-4,5-dimethyldioxolane at 90° (procedure A). Unconverted dioxolane was removed by heating at 30–50° (1 mm.). The residue (64 g.) was a water white liquid whose infrared spectrum showed strong absorption at 3.0 μ. The crude product reacted exothermically with Co(II) butyl phthalate to give polymer and with water to give hydrogen peroxide and an acrylate ester.

Anal. Calcd. for $C_7H_{15}O_4$: peroxide oxygen as % H_2O_2, 21.2. Found: peroxide oxygen as % H_2O_2, 16.9.

Presumably the product is a mixture of hydroperoxide XVI and peroxide. No attempt was made at separation because of the possible explosion hazard.

1-Methyl-2-hydroxypropyl Acrylate (XXVII) from II.—By procedure A, 2-vinyl-4,5-dimethyldioxolane (92 g., 0.79 mole) containing Co(II) (40 mg.) as Co(II) butyl phthalate absorbed 11 g. (0.34 mole) of oxygen at 35°. The oxidized mixture, after standing 24 hr. over hydroquinone (10 g.), gave upon distillation starting acetal (38 g.), crude ester (23 g.), and polymer XXVIII (45 g.). The crude ester was taken up in benzene (25 ml.) and washed with 5% caustic solution. After drying and removal of volatiles by heating at 50° (0.5 mm.) for 30 min. a pale yellow oil (16 g.) was obtained, $n^{25}D$ 1.4428. The oil was identified as a hydroxyalkyl acrylate (XXVII) by inference from its infrared spectrum: strong band at 3.0 (OH), strong doublet at 6.1, and singlet at 12.2 μ which are characteristic of acrylates. Further, the oil gave a polymer when it was heated with a small amount of benzoyl peroxide. The infrared spectrum of this polymer was nearly identical with the spectrum of the polymer XXVIII isolated from the oxidation mixture.

2-Hydroperoxy-2-vinyl-4,4-dimethyldioxolane (XVII) from III.—2-Vinyl-4,4-dimethyldioxolane (102 g., 0.8 mole) reacted with oxygen (12 g., 0.36 mole) by procedure A. Elimination of unchanged dioxolane from the reaction mixture by heating at 30–40° (0.5 mm.) gave 55 g. of crude 2-hydroperoxy-2-vinyl-4,4-dimethyldioxolane (XVII). The product absorbed strongly at 3.0 μ (hydroperoxy OH) in the infrared. It ignited when heated on a hot plate and reacted exothermically when mixed with a small quantity of Co(II) butyl phthalate. Because of the possible explosion hazard, no attempt was made to purify the product.

2-Methyl-2-hydroxypropyl Acrylate (XXXVII) by Hydrolysis of Crude 2-Hydroperoxy-2-vinyl-4,4-dimethyldioxolane (XVII).—Crude XVII (56 g.) was stirred with water (58 ml.) while cooling in an ice bath. Sodium chloride (20 g.) was added and the mixture extracted with benzene (50 ml.). The organic layer was washed with saturated sodium chloride solution, dried over anhydrous magesium sulfate, and fractionally distilled to obtain 2-methyl-2-hydroxypropyl acrylate (20 g., XXXVII); b.p. 40° (0.3 mm.); $n^{25}D$ 1.4420; infrared, 2.9 (OH), 5.8 (ester C=O), 6.1 and 6.2 doublet and 12.2 μ singlet (acrylate C=C).

Anal. Calcd. for $C_7H_{12}O_3$: ester equiv., 144. Found: ester equiv., 142.

2,2-Dimethyl-1,4,6,7-tetraoxaspiro[4.4]nonane (XXXVI).—Fifty-six grams (0.44 mole) of 2-vinyl-4,4-dimethyldioxolane (III) was acidified with toluenesulfonic acid (0.1 g.) and allowed to absorb 7 g. (0.22 mole) of oxygen at 95° according to procedure A. The resulting mixture on fractionation gave unconverted dioxolane (25.5 g., 0.147 mole), nonvolatile peroxidic material (8 g.), and spirocyclic peroxide, 2,2-dimethyl-1,4,6,7-tetraoxaspiro[4.4]nonane (24 g., XXXVI), b.p. 39° (0.4 mm.), $n^{25}D$ 1.4365.

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55; mol. wt., 160; peroxide oxygen as % H_2O_2; 21.2. Found: C, 52.55; H, 7.38; mol. wt., 157, 158; peroxide oxygen as % H_2O_2, 18.6.

The remaining 2-alkenyl-1,3-cyclic acetals (IV–XIII) of Table I were oxidized either by procedure A or B. The oxidized mixtures were freed of unchanged acetal by heating at 30–40° (1 mm.) and the crude products examined by infrared. If the examination indicated that the principal product was ester or cyclic peroxide, the concentrates were worked up. Pertinent data on the products isolated and identified are summarized in Table III (cyclic peroxides) and Table V (esters). If hydroperoxide was indicated, confirmatory tests such as peroxide titer, behavior towards heat, and Co(II) butyl phthalate were run.

Analysis of Peroxide Content in Cyclic Peroxides.—The methods[19] normally used for determining peroxide were found to be highly unreliable in the case of cyclic peroxides. After a brief study the following method was adopted.

Approximately 0.2 g. of sample and 1.0 g. of sodium iodide were added to 10 ml. of acetic anhydride, blanketed with nitrogen heated on the steam bath for 15 min., and allowed to stand 6 hr. at room temperature. The mixture was diluted with 50 ml. of distilled water and titrated with standard sodium thiosulfate to a colorless end point. Peroxide as per cent hydrogen peroxide was calculated as follows.

$$\frac{\text{ml. of thiosulfate} \times \text{normality} \times 34 \times 100}{\text{wt. of sample} \times 2 \times 1000} = \text{peroxide as \% } H_2O_2$$

(19) A. V. Tobolsky and R. V. Mesrobian, "Organic Peroxides" Interscience Publishers, Inc., New York, N. Y., 1954, pp. 52–54.

Peroxides. Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazines]

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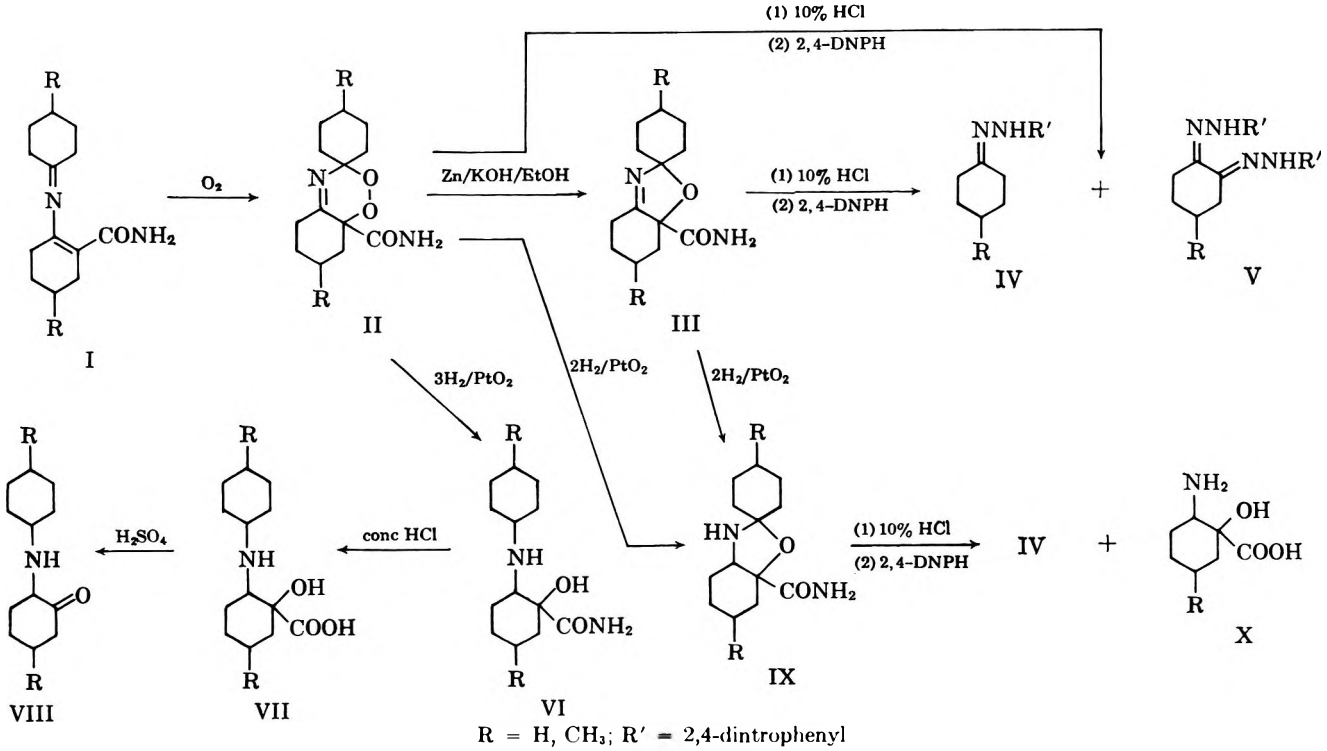
Cyclohexylidene-2-carbamylcyclohex-1-enylamine, 4-methylcyclohexylidene-2-carbamyl-4-methylcyclohex-1-enylamine, and 4-*t*-butylcyclohexylidene-2-carbamyl-4-*t*-butylcyclohex-1-enylamine readily absorb oxygen to form peroxides. The structures of these peroxides have been determined and some of their reactions are described.

Recently[1] the original structure assigned[2] to the condensation product from cyclohexanone and urea was confirmed and several compounds in this series were prepared[1] by condensing alicyclic ketones with urea. During the purification of these condensation products it was noted that they absorbed oxygen very readily. Cyclohexylidene-2-carbamylcyclohex-1-enylamine (I, R = H) in chloroform absorbed 1 mole equivalent of oxygen from an atmosphere of pure oxygen in approximately 50 min. In the presence of 0.1% of cobalt naphthenate, 1 mole equivalent of oxygen was absorbed in less than 5 min. The solid white peroxide (II, R = H) liberated iodine from iodide at room temperature. Titration of the free iodine can be used for the quantitative estimation of the peroxide.



R = H, CH_3; R′ = 2,4-dintrophenyl

The peroxide (II, R = H) on complete hydrogenation in the presence of platinum oxide catalyst gave a monohydroxy derivative VI (R = H). Its n.m.r. spectrum[3] showed no peak normally associated with the C*H*OH group (6–6.5 p.p.m.). A sharp peak at 5.7 p.p.m. was attributed to the O*H* group and the hydroxy was assumed to be attached to a quaternary carbon atom. This was confirmed by hydrolysis of the amide (VI, R = H) to the corresponding acid (VII, R = H) and decarbonylation of the α-hydroxy acid by warming with concentrated sulfuric acid to give the ketone (VII, R = H).[4,5] Thus one oxygen of the peroxide is attached to the carbon carrying the carboxamide group. The other oxygen must be attached as shown in structure II because complete hydrolysis yielded 1,2-cyclohexanedione and cyclohexanone. If the second oxygen had been bonded to another carbon atom in the ring, hydrolysis would have given an amino-substituted cyclohexanol instead of cyclohexanone. This shows that the peroxide is formed by 1,4-addition of oxygen to the conjugated diene system of cyclohexylidene-2-carbamylcyclohex-1-enylamine. Farmer[6] had observed earlier that all examined peroxides of nonaromatic conjugated dienes were known to be produced by addition of oxygen at the terminals of the diene system. He gave several examples of peroxides formed by the 1,4-addition of oxygen to con-

(1) A. F. McKay, C. Podesva, E. J. Tarlton, and J.-M. Billy, *Can. J. Chem.*, in press.

(2) A. F. McKay, E. J. Tarlton, and C. Podesva, *J. Org. Chem.*, **26**, 76 (1961).

(3) N.m.r. spectrum was measured with Varian Model HR-60 spectrometer at 60 Mc.

(4) H. von Pechmann, *Ber.*, **17**, 2542 (1884).

(5) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 368.

(6) H. Farmer, *Trans. Faraday Soc.*, **42**, 228 (1945).

TABLE I

INFRARED ABSORPTION BAND (CM.$^{-1}$) ASSIGNMENTS[a]

No.	R	Stretching modes: N—H[b]		C=N[b]	$CONH_2$[b]	Bending modes: N—H[b]
II	H	3210	3070	1695	1675	
II	CH_3	3220	3070	1690	1667	
II	$(CH_3)_3C$	3165	3045	1699	1673	
III	H	3200		1692	1662	
III	CH_3	3200	3060	1682	1665	
VI	H	3530 [OH]	3450 [OH]		1675	1566
VI	CH_3		3440 [OH]		1670	1566
VII·HCl	H	3327	3205	1733 [COOH]		1577
VIII·HCl	H	2505 [NH_3^+]	2400 [NH_3^+]	1730 [>C=O]		
X	H	3100				1615,[c] 1577,[c] 1525[c]
X	CH_3	3302	3135			1637,[c] 1584,[c] 1552[c]

[a] Infrared spectra were determined on Nujol mulls of the crystalline compounds. [b] Other group assignments noted in brackets. [c] Three bands characteristic of amino acid zwitterions and reflect NH_3^+ and COO^- vibrations.

jugated dienes. The position of the double bond in spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H) was corroborated by its infrared spectrum (*cf.* Table I).

When spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H) was reduced in an alkaline solution with zinc dust, one atom of oxygen was lost. The product was identified as spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = H). Compound III (R = H) on hydrolysis gave cyclohexanone and 1,2-cyclohexanedione which confirmed the positions of the oxygen linkages. The position of the double bond was noted from its infrared spectrum. This double bond was reduced in the presence of platinum oxide in acid solution. The product, spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (IX, R = H) on hydrolysis gave cyclohexanone and 2-amino-1-hydroxycyclohexanecarboxylic acid (X). The amino acid (X, R = H) was identified by analysis and infrared spectrum (*cf.* Table I).

The reactions described before for cyclohexylidene-2-carbamylcyclohex-1-enylamine (I, R = H) were repeated with 4-methylcyclohexylidene-2-carbamyl-4-methylcyclohex-1-enylamine (I, R = CH_3). Spiro-[4′-*t*-butylcyclohexane-1′,3-7-*t*-butyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = $(CH_3)_3C$–) also was prepared during these studies.

Experimental[7]

Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H).—A solution of cyclohexylidene-2-carbamylcyclohex-1-enylamine (22.7 g., 0.1 mole) in chloroform (750 ml.) in hydrogenation equipment was stirred under an atmosphere of pure oxygen at ambient temperature and pressure. One mole equivalent of oxygen was absorbed in 60 min. and the peroxide began to separate from solution within 15 min. The product (m.p. 194° dec.) was recovered by filtration; yield, 22.6 g. (87%). Recrystallization from ethanol (100 ml./g.) did not raise the melting point.

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.89; H, 7.99; N, 11.11. Found: C, 62.11; H, 7.86; N, 10.94.

Spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = CH_3).—This compound (m.p. 192° dec.) was prepared in 73% yield by the preceding method. One recrystallization from ethanol (100 ml./g.) raised the melting point to 199° dec.

Anal. Calcd. for $C_{15}H_{24}N_2O_3$: C, 64.30; H, 8.63; N, 9.98. Found: C, 64.37; H, 8.64; N, 10.01.

(7) All melting points are uncorrected. Microanalyses were performed by Dr. C. Daessle, Montreal, Quebec.

A sample (96.3 mg.) of this peroxide in glacial acetic acid (20 ml.) and water (10 ml.) containing sodium iodide (0.5 g.) was allowed to stand for 10 min. Titration of the liberated iodine with 0.0515 *N* sodium thiosulfate gave an equivalent weight for the peroxide of 282 (calcd. equiv. wt., 280.36).

Spiro[4′-*t*-butylcyclohexane-1′,3-7-*t*-butyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = $(CH_3)_3C$).—This peroxide (m.p. 215–220° dec.) was prepared in quantitative yield by the method described earlier for the preparation of spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine]. One crystallization from ethanol raised the melting point to 218–220° dec.

Anal. Calcd. for $C_{21}H_{36}N_2O_3$: C, 69.20; H, 9.95; N, 7.68. Found: C, 68.95; H, 9.76; N, 7.63.

Hydrolysis of Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = H).—A suspension of this dioxazine (1 g., 0.004 mole) in 10% aqueous hydrochloric acid was heated under reflux for 70 min. After the cooled solution was diluted with an equal volume of water, it was extracted with two 25-ml. portions of pentane. One-half the combined pentane extracts was taken to dryness and the residue was converted into a 2,4-dinitrophenylhydrazone (m.p. 157–158°); yield, 0.28 g. (50%). Crystallization from ethyl acetate raised the melting point to 159–160°. This melting point was not depressed on admixture with a known sample of cyclohexanone 2,4-dinitrophenylhydrazone (m.p. 159–160°).

One-half of the aqueous phase was heated under reflux for 15 min. with 2,4-dinitrophenylhydrazine (1.2 g. in 48 ml. of methanol containing 4% concentrated hydrochloric acid). On cooling adipoin 2,4-dinitrophenylosazone (m.p. 210° dec.) deposited as deep red crystals; yield, 0.26 g. (28%). One recrystallization from ethyl acetate raised the melting point to 232° dec. A mixture melting point determination with a known sample of adipoin 2,4-dinitrophenylosazone (m.p. 232–233° dec.) gave no depression.

Anal. Calcd. for $C_{18}H_{16}N_8O_8$: C, 45.80; H, 3.39; N, 23.70. Found: C, 45.88; H, 3.39; N, 23.60.

Hydrolysis of Spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (II, R = CH_3).—Two grams (0.007 mole) of this peroxide was hydrolyzed and the solution treated under the conditions described before for the hydrolysis of spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine]. The pentane extract gave the 2,4-dinitrophenylhydrazone (m.p. 127–130°) of 4-methylcyclohexanone in 44% yield. One recrystallization from ethyl acetate raised the melting point to 131–132°. A mixture melting point determination with a known sample of 4-methylcyclohexanone 2,4-dinitrophenylhydrazone (m.p. 131–132°) was not depressed.

The aqueous layer on treatment with 2,4-dinitrophenylhydrazine gave the di-2,4-dinitrophenylhydrazone (m.p. 187° dec.) of 4-methylcyclohexane-1,2-dione in 28% yield. Recrystallization from ethyl acetate raised the melting point to 199° dec.

Anal. Calcd. for $C_{19}H_{18}N_8O_8$: C, 46.91; H, 3.73; N, 23.03. Found: C, 47.19; H, 4.01; N, 23.31.

Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = H).—Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (5 g., 0.02 mole) was added to a suspension of zinc dust (25 g.) in ethano-

lic potassium hydroxide (25 g. of potassium hydroxide in 500 ml. of ethanol) and the mixture was heated under reflux for 30 min. After the hot reaction mixture was filtered, the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water and the aqueous solution was extracted with chloroform. Evaporation of the chloroform gave 4.9 g. of amber solid. Crystallization from ethyl acetate gave white needles (m.p. 136–137°); yield, 3.7 g. (79%). One recrystallization from ethyl acetate raised the melting point to 139–140°.

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.90; H, 8.53; N, 12.05.

Spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = CH_3).—Spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] was prepared from spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] by the method described before for the preparation of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole]. The residue from the chloroform extract crystallized from ether in large cubes (m.p. 170–178°); yield, 1.3, g. (67%). One recrystallization from ether raised the melting point to 180–181°.

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.14; H, 9.15; N, 10.60. Found: C, 68.12; H, 9.16; N, 10.48.

Hydrolysis of Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (III, R = H).—Hydrolysis of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] under the conditions described earlier for the hydrolysis of spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] gave a 49% yield of cyclohexanone 2,4-dinitrophenylhydrazone (159°) and a 72% yield of adipoin 2,4-dinitrophenylosazone (m.p. 232° dec.). The products were identified by mixture melting point determinations.

Cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine (VI, R = H).—Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (2 g., 0.008 mole) in absolute ethanol (250 ml.) containing concentrated hydrochloric acid (0.66 ml., 0.008 mole) and platinum oxide (200 mg.) was hydrogenated at ambient temperature and pressure. Three mole equivalents of hydrogen (597 ml.) were absorbed in 20 min. After the catalyst was removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from ethanol–ether solution, yield 1.6 g. (67%). The melting point of the hydrochloride salt was raised from 247° to 250–251° by a second crystallization from the same solvent.

Anal. Calcd. for $C_{13}H_{24}N_2O_2 \cdot HCl \cdot {}^1/_2C_2H_5OH$: C, 56.08; H, 9.41; Cl, 11.83; N, 9.34. Found: C, 55.95; H, 9.37; Cl, 12.07; N, 9.33.

The solvent of crystallization was not removed from this salt by prolonged heating at 100° *in vacuo*.

A sample of cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine hydrochloride (4 g.) was dissolved in water and the solution was made alkaline with 8% aqueous sodium hydroxide. The oil was removed by extraction with ether. Concentration of the ether extract gave crystals melting at 143–144°; yield, 2.8 g. (87%). One recrystallization from ether raised the melting point to 145°.

Anal. Calcd. for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.06; N, 11.66. Found: C, 65.21; H, 10.18; N, 11.67.

4-Methylcyclohexyl-2-hydroxy-2-carbamyl-4-methylcyclohexylamine (VI, R = CH_3).—Hydrogenation of spiro[4′-methylcyclohexane-1′,3-7-methyl-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] under the conditions described earlier for the preparation of cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine gave a 94% yield of 4-methylcyclohexyl-2-hydroxy-2-carbamyl-4-methylcyclohexylamine hydrochloride (m.p. 264–265° dec.). Several crystallizations from ethanol–ether solution raised the melting point to 279° dec.

Anal. Calcd. for $C_{15}H_{29}ClN_2O_2$: C, 59.09; H, 9.59; Cl, 11.63; N, 9.17. Found: C, 59.06; H, 9.62; Cl, 11.81; N, 9.12.

An aqueous solution of this hydrochloride (2.7 g., 0.009 mole) was made alkaline with aqueous sodium bicarbonate. An oil separated which was recovered by extraction with ether. Concentration of the ether solution gave crystals (m.p. 107–114°) of 4-methylcyclohexyl-2-hydroxy-2-carbamyl-4-methylcyclohexylamine; yield, 1.7 g. (71%). One recrystallization from ether raised the melting point to 114–115°.

Anal. Calcd. for $C_{15}H_{28}N_2O_2$: C, 67.11; H, 10.52; N, 10.44. Found: C, 67.11; H, 10.54; N, 10.46.

Cyclohexyl-2-hydroxy-2-carboxycyclohexylamine Hydrochloride (VII, R = H).—Cyclohexyl-2-hydroxy-2-carbamylcyclohexylamine hydrochloride (1 g., 0.003 mole) in concentrated hydrochloric acid (25 ml.) was heated on a steam bath for 2 hr. After evaporation of the solution to a small volume, crystals (m.p. 254–257° dec.) separated; yield, 0.8 g. (88%). One recrystallization from methanol–ether solution raised the melting point to 260–261° dec.

Anal. Calcd. for $C_{13}H_{24}ClNO_3$: C, 56.21; H, 8.71; Cl, 12.76; N, 5.04. Found: C, 56.27; H, 8.82; Cl, 12.95; N, 5.20.

Cyclohexyl-2-oxocyclohexylamine (VIII, R = H).—Cyclohexyl-2-hydroxy-2-carboxycyclohexylamine hydrochloride (1 g., 0.003 mole) was dissolved in concentrated sulfuric acid (7.5 g.). After the evolution of hydrogen chloride had subsided, the solution was heated at 80–90° for 30 min. or until carbon monoxide evolution ceased. The solution was cooled, diluted with water, and made alkaline with 10% aqueous sodium hydroxide. Colorless liquid cyclohexyl-2-oxocyclohexylamine separated from the alkaline solution; yield, 0.6 g. (85%). This liquid was unstable and it rapidly turned green.

A sample of freshly prepared cyclohexyl-2-oxocyclohexylamine (0.6 g., 0.003 mole) was treated with a solution of 2,4-dinitrophenylhydrazine (0.6 g., 0.003 mole) in methanol (30 ml.) containing 4% concentrated hydrochloric acid. The 2,4-dinitrophenylhydrazone of cyclohexyl-2-oxocyclohexylamine hydrochloride separated out in 59% yield. The melting point of 221–222° dec. was not changed by recrystallization.

Anal. Calcd. for $C_{18}H_{26}ClN_5O_4$: C, 52.49; H, 6.36; Cl, 8.61; N, 17.00. Found: C, 52.54; H, 6.50; Cl, 8.55; N, 16.84.

Dry hydrogen chloride was bubbled through an absolute ether solution (25 ml.) of cyclohexyl-2-oxocyclohexylamine (0.5 g., 0.002 mole). The hydrochloride salt precipitated immediately; yield, 0.56 g. (94%). Crystallization from ethanol–ether raised the melting point from 224–230° to 243–243.5° dec.

Anal. Calcd. for $C_{12}H_{22}ClNO$: C, 62.19; H, 9.57; Cl, 15.30; N, 6.04. Found: C, 62.43; H, 9.34; Cl, 15.57; N, 6.03.

Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (IX, R = H). Method A.—A solution of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] (1 g., 0.004 mole) in absolute ethanol (30 ml.) containing platinum oxide (40 mg.) was hydrogenated at ambient temperature and pressure. One mole equivalent of hydrogen was absorbed in 2.5 hr. After the catalyst was removed, the filtrate on concentration gave 0.76 g. (75%) of crude product (m.p. 157–172°). The melting point was raised to a constant value of 185–186° by crystallization from ethyl acetate.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.75. Found: C, 65.40; H, 9.54; N, 11.71.

Method B.—Spiro[cyclohexane-1′,3-9-carbamyl-3(*H*)-5,6,7,8-tetrahydrobenzo-1,2,4-dioxazine] (3 g., 0.012 mole) in absolute ethanol (300 ml.) containing platinum oxide (200 mg.) was hydrogenated at room temperature and pressure. Two mole equivalents of hydrogen were absorbed in 1 hr. after which the catalyst was removed by filtration. The residue from evaporation of the filtrate was crystallized from ethyl acetate; yield, 2.3 g. (82%). Three recrystallizations from ethyl acetate raised the melting point from 158–178° to 184–185°; yield, 1.2 g. This product did not depress the melting point of a sample of spiro[cyclohexane-1′,2-8-carbamyl-2[*H*]-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (m.p. 185–186°) prepared by method A.

Spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (IX, R = CH_3).—Hydrogenation of spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] under the conditions described above in method A for the hydrogenation of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-4,5,6,7-tetrahydrobenzo-1,3-oxazole] gave a 30% yield of spiro[4′-methylcyclohexane-1′,-2-6-methyl-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole] (m.p. 196–198°). One recrystallization from methanol–ether solution raised the melting point to 197–198°.

Anal. Calcd. for $C_{15}H_{26}N_2O_2$: C, 67.62; H, 9.84; N, 10.52. Found: C, 67.48; H, 9.81; N, 10.36.

Hydrolysis of Spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,-4,5,6,7-hexahydrobenzo-1,3-oxazole].—A solution of this oxazole (0.4 g., 0.0017 mole) in 10% aqueous hydrochloric acid (20 ml.) was heated on a steam bath for 90 min. After the solution was cooled to room temperature, it was extracted with two 20-ml. portions of pentane. The aqueous phase was taken to dryness and the residue (0.37 g.) in 50% aqueous ethanol was added to a column of Dowex 50-WX2 resin (20 ml.) in acid form. The

column was washed with aqueous ethanol until the eluate was free from chloride ion. After this the column was washed with 5% aqueous ammonium hydroxide solution and the ammoniacal eluate evaporated. The crude 2-amino-1-hydroxycyclohexanecarboxylic acid melted at 287–288° dec.; yield, 0.2 g. (78%). One crystallization from methanol raised the melting point to a constant value of 294–295° dec.; yield, 0.16 g.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.81. Found: C, 53.01; H, 8.03; N, 8.78.

The residue from the pentane extract on treatment with 2,4-dinitrophenylhydrazine in methanol–hydrochloric acid under the conditions previously described gave a 77% yield of cyclohexanone 2,4-dinitrophenylhydrazone (m.p. 159–160°). This product was identified by a mixture melting point determination.

Hydrolysis of Spiro[4′-methylcyclohexane-1′,2-6-methyl-8-carbamyl-2(*H*)-3,9,4,5.6,7-hexahydrobenzo-1,3-oxazole].—Spiro [4′-methylcyclohexane-1,2-6-methyl-8-carbamyl-4,5,6,7-tetrahydrobenzo-1,3-oxazole] was hydrolyzed under the conditions described earlier for the hydrolysis of spiro[cyclohexane-1′,2-8-carbamyl-2(*H*)-3,9,4,5,6,7-hexahydrobenzo-1,3-oxazole]. The pentane extract residue on treatment with 2,4-dinitrophenylhydrazine reagent gave a 57% yield of 4-methylcyclohexanone 2,4-dinitrophenylhydrazone (m.p. 132–133°). This product was identified by a mixture melting point determination.

The acidic aqueous solution from the pentane extract was evaporated to dryness and the residue in aqueous ethanol was added to a Dowex 50-WX2 resin. 2-Amino-1-hydroxy-5-methylcyclohexanecarboxylic acid (m.p. 279–280° dec.) was isolated in 56% yield in the same manner described before for the isolation of 2-amino-1-hydroxycyclohexanecarboxylic acid. One recrystallization from methanol–ether solution raised the melting point to 288–289° dec.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.48; H, 8.73; N, 8.09. Found: C, 55.66; H, 8.76; N, 8.14.

Solvent Effects. The Solvolysis Rates of Cyclopropylcarbinyl, 1-Methylcyclopropylcarbinyl, and 1-Phenylcyclopropylcarbinyl Arenesulfonate Derivatives

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The benzene-, *p*-methoxybenzene-, and *p*-toluenesulfonate derivatives of cyclopropylcarbinol (Ia–c), 1-methylcyclopropylcarbinol (IIa–c), and 1-phenylcyclopropylcarbinol (IIIa–c) have been solvolyzed in acetic acid at various temperatures. The relative first-order rates of acetolysis at 20° were found to be $k_{Ib} = 1$, $k_{IIb} = 4$, and $k_{IIIb} = 1.6$. The activation energy parameters for Ia–c differed greatly from those for IIa–c or IIIa–c and similarly Ib exhibited a different sensitivity to solvent ionizing strength. The β-substituent effects, differences in activation energy parameters, sensitivities to solvent ionizing strength, and solvolysis products of these arenesulfonates are discussed in terms of solvated transition state differences.

The observation that a phenyl substituent at the 1-ring position in cyclopropylcarbinyl benzenesulfonate produced no significant rate acceleration in an acetolysis reaction[1] led to a more detailed study of this phenomenon. It was of particular interest to determine the activation energy parameters for the acetolysis of cyclopropylcarbinyl arenesulfonate compounds. Such information would assist in a mechanistic diagnosis of the apparent lack of a substituent effect. In addition, the sensitivity of the solvolytic reactions of both cyclopropylcarbinyl and 1-phenylcyclopropylcarbinyl arenesulfonate derivatives to solvent ionizing strength and arenesulfonate leaving group were determined.

The kinetic data are summarized in Table I. Each of these esters was allowed to solvolyze in the indicated solvent and the course of reaction followed by titrating the liberated arenesulfonic acid. The acetolysis reactions of the cyclopropylcarbinyl arenesulfonates demonstrated the previously reported "internal return" rearrangement[2] which accounted for about one-third of the starting material. The solvolysis rates, consequently, of Ia–c were calculated from the initial slope of the rate curves.[3] All other reactions were strictly first order in arenesulfonate and furnished, within experimental error, 100% of the theoretical amount of acid present.

Table II compares the relative rates of acetolysis of three cyclopropylcarbinyl 1-methyl- and 1-phenylcyclopropylcarbinyl arenesulfonates at 20° with the relative rates of acetolysis of correspondingly substituted acyclic *p*-toluenesulfonates at 75°. It can be seen that, in the acetolysis of the cyclopropylcarbinyl esters, the rate-enhancing abilities of the methyl and phenyl groups are in distinct contrast to their effectiveness in the acetolysis of the acyclic analogs. This apparent lack of β-substituent effect is further emphasized by the fact that 1-methylcyclopropylcarbinyl chloride suffers solvolysis in 50 vol. % aqueous ethanol at 50°, some fifty times faster than cyclopropylcarbinyl chloride.[6]

Although the free energy of activation is similar for Ia–c, IIa–c, and IIIa–c, the partitioning of the thermodynamic functions of activation is markedly different for Ia–c in respect to IIa–c or IIIa–c. That the functions under discussion represent real differences and not random error is shown by the constancy of the data with the three different leaving groups.[7] While

(1) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, **27**, 3430 (1962).

(2) M. C. Caserio, W. H. Graham, and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960).

(3) S. Borcic, M. Nikoletic, and D. E. Sunko, *J. Am. Chem. Soc.*, **84**, 1615 (1962).

(4) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).

(5) S. Winstein, B. K. Morse, E. Grundwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 113 (1952).

(6) E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *ibid.*, **83**, 2719 (1961).

(7) The activation energy parameters for IIIa and IIIb previously were reported[1] on the basis of a three-point regression analysis over 12° and 15° temperature ranges, respectively. Fivefold replication of this work in the present study over 17° and 20° temperature ranges, respectively, revealed that the reported rate constant[1] for the acetolysis of IIIa at 18° was sufficiently displaced from the calculated regression line (20% low) to produce an erroneously high slope value. Also, the reported rate constant[1] for IIIb at 25° was sufficiently displaced from the calculated regression line (28% low) to produce an erroneously low slope value. Due to the few points over a limited temperature range, this error did not show up as significant in the regression analysis. Correlation coefficients of 0.999 were obtained in the present study for both IIIa and IIIb. The *t*-test gave $t = -134.3$, with 42 degrees of freedom, $P < .005$ for IIIa and $t = -239.0$ with 41 degrees of freedom, $P < .005$ for IIIb.

TABLE I

SUMMARY OF SOLVOLYSIS RATES

Arenesulfonate	Solvent	Temp., °C.	$k_1 \times 10^4$ sec.$^{-1}$
Cyclopropylcarbinyl arenesulfonates			
Benzenesulfonate (Ia)	AcOH	15.0	1.25 ± 0.09
		20.0	2.17 ± 0.08[a]
		25.0	3.45 ± 0.08
		30.0	5.43 ± 0.08
p-Toluenesulfonate (Ib)	AcOH	15.0	0.77 ± 0.10
		20.0	1.28 ± 0.08
		25.0	2.20 ± 0.09
		30.0	3.38 ± 0.07
	EtOH[b]	20.0	0.32 ± 0.01
		30.0	1.17 ± 0.03
		40.0	3.34 ± 0.02
	80% EtOH	20.0	11.33 ± 0.07
	MeOH	20.0	1.35 ± 0.02
p-Methoxybenzenesulfonate (Ic)	AcOH	20.0	0.92 ± 0.09
		25.0	1.38 ± 0.04
		30.0	2.40 ± 0.04
		35.0	3.83 ± 0.07
1-Methylcyclopropylcarbinyl arenesulfonates			
Benzenesulfonate (IIa)	AcOH	10.0	3.27 ± 0.10
		20.0	9.84 ± 0.05
		25.0	19.18 ± 0.20
p-Toluenesulfonate (IIb)	AcOH	15.0	2.88 ± 0.10
		18.0	4.12 ± 0.10
		20.0	5.06 ± 0.10
		25.0	10.38 ± 0.08
		30.0	16.67 ± 0.01
p-Methoxybenzenesulfonate (IIc)	AcOH	15.0	2.00 ± 0.07
		20.0	3.67 ± 0.10
		25.0	6.66 ± 0.10
		30.0	11.68 ± 0.15
1-Phenylcyclopropylcarbinyl arenesulfonates			
Benzenesulfonate (IIIa)	AcOH	13.0	1.10 ± 0.06[c]
		15.0	1.48 ± 0.02
		20.0	2.65 ± 0.03
		25.0	5.30 ± 0.09[d]
		30.0	9.17 ± 0.10
p-Toluenesulfonate (IIIb)	AcOH	15.0	1.03 ± 0.02
		18.0	1.53 ± 0.01[c]
		20.0	2.00 ± 0.03
		25.0	3.67 ± 0.05
		30.0	6.60 ± 0.03
	EtOH[e]	30.0	0.97 ± 0.04
		40.0	3.57 ± 0.10
		50.0	12.00 ± 0.15
	80% EtOH	20.0	6.17 ± 0.07
	MeOH	20.0	1.42 ± 0.03
p-Methoxybenzenesulfonate (IIIc)	AcOH	18.0	0.93 ± 0.01
		20.0	1.19 ± 0.01
		25.0	2.35 ± 0.02
		30.0	4.08 ± 0.08
p-Isopropylbenzenesulfonate (IIId)	AcOH[f]	20.0	1.78 ± 0.02
		25.0	3.30 ± 0.03
		30.0	5.67 ± 0.06
		35.0	10.00 ± 0.09
p-*t*-Butylbenzenesulfonate (IIIe)	AcOH[g]	20.0	1.75 ± 0.02
		30.0	5.60 ± 0.10
		35.0	10.00 ± 0.03

[a] Compares with a value of 2.19×10^{-4} sec.$^{-1}$ reported by Borcic, *et al.*[3]. [b] $\Delta H^* = 21.0$ kcal./mole, $\Delta S^* = -7.7$ e.u. [c] *Cf.* ref. 1. [d] Compares with previously reported[1] value of 6.18×10^{-4} sec.$^{-1}$. [e] $\Delta H^* = 23.9$ kcal./mole, $\Delta S^* = 1.8$. [f] $\Delta H^* = 20.6$ kcal./mole, $\Delta S^* = -5.5$ e.u. [g] $\Delta H^* = 20.5$ kcal./mole, $\Delta S^* = -6.6$ e.u.

TABLE II

RELATIVE RATES, ENTHALPIES, AND ENTROPIES OF ACTIVATION OF CYCLOPROPYLCARBINYL, 1-METHYLCYCLOPROPYLCARBINYL, AND 1-PHENYLCYCLOPROPYLCARBINYL ARENESULFONATES

(R, *p*-X-Benzenesulfonates)

R	X	Rel. rate, 20°	ΔH^*, kcal.[a]	ΔS^*, e.u.[b]
Cyclopropylcarbinyl	–H	1.0	16.3	–19.7
1-Methylcyclopropylcarbinyl	–H	4.5	19.0	–5.4
1-Phenylcyclopropylcarbinyl	–H	1.2	20.8	–4.0
Cyclopropylcarbinyl	$-CH_3$	1.0	16.7	–19.0
1-Methylcyclopropylcarbinyl	$-CH_3$	4.0	20.1	–5.2
1-Phenylcyclopropylcarbinyl	$-CH_3$	1.6	21.0	–4.2
Cyclopropylcarbinyl	$-OCH_3$	1.0	16.7	–20.0
1-Methylcyclopropylcarbinyl	$-OCH_3$	4.0	20.1	–5.6
1-Phenylcyclopropylcarbinyl	$-OCH_3$	1.3	20.9	–4.4
Isobutyl	$-CH_3$	1.0[c]	28.2	–8.0
Neopentyl	$-CH_3$	36[c]	31.5	1.0
Neophyl	$-CH_3$	93[d]	25.7	–6.4

[a] Standard deviation varied from ±0.2 to ±0.5 kcal. [b] Standard deviation varied from ±1.4 to ±3.0 e.u. [c] From data of Winstein[4] at 75°. [d] From data of Winstein[5] at 75°.

the activation energy parameters, by themselves, do not permit a rigorous assignment as to how the variation of ΔH^* or ΔS^* should be ascribed to changing solvation of either solvated ground state and solvated transition state,[8,9] the data presented in Table II along with the solvolysis products (*vide infra*) do suggest a significant difference[10] in the nature of the reactive intermediate derived from Ia–c in respect to that derived from IIa–c or IIIa–c.

Additional support is accorded this thesis by the finding that the rates of solvolysis of IIIb in four solvents at 20° are well-correlated (see Fig. 1, correlation coefficient = 0.997) by the log k_{ion} relationship,[13] whereas the rates of solvolysis of Ib are poorly correlated (see Fig. 1) by this relationship. According to Winstein, *et al.*,[13] relation 1 is equivalent to the linear relation 2 between log (f_{RX}/f_*) for the substrate RX

$$\log k_{reaction} = a \log k_{ion} + b \quad (1)$$

$$\Delta\log (f_{RX}/f_*)_{RX} = a\Delta\log (f_{RX}/f_*)_{p\text{-methoxyneophyl tosylate}} \quad (2)$$

and that of the reference substrate, *p*-methoxyneophyl *p*-toluenesulfonate. Consequently, the fact that IIIb is correlated by the given relationship in solvolytic reactions whereas Ib is not implies that

$$\Delta\log (f_{RX}/f_*)_{IIIb} \neq a' \Delta\log (f_{RX}/f_*)_{Ib}$$

(8) S. Winstein and A. Fainberg, *J. Am. Chem. Soc.*, **79**, 5937 (1957).

(9) R. E. Robertson, R. L. Hippolette, and J. M. W. Scott, *Can. J. Chem.*, **37**, 803 (1959).

(10) Admittedly, the absolute thermodynamic parameters for transition states, F^0_* where $F^0_* = F^0_g + \delta_s F + \Delta F^*$, should be compared as there is reason to believe that the gas phase ground state energy of the cyclopropylcarbinyl system (F^0_g) is lowered due to benzyl-type resonance[11] with 1-phenyl substitution and ground state solvation energy ($\delta_s F$) has been demonstrated to be of importance in benzyl chloride solvolysis.[12] Nonetheless, the activation parameters do exhibit a decided difference in the enthalpic and entropic contributions.

(11) L. S. Ingraham, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 518–522.

(12) S. F. Mason, *J. Chem. Soc.*, 808 (1958).

(13) S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Am. Chem. Soc.*, **83**, 618 (1961).

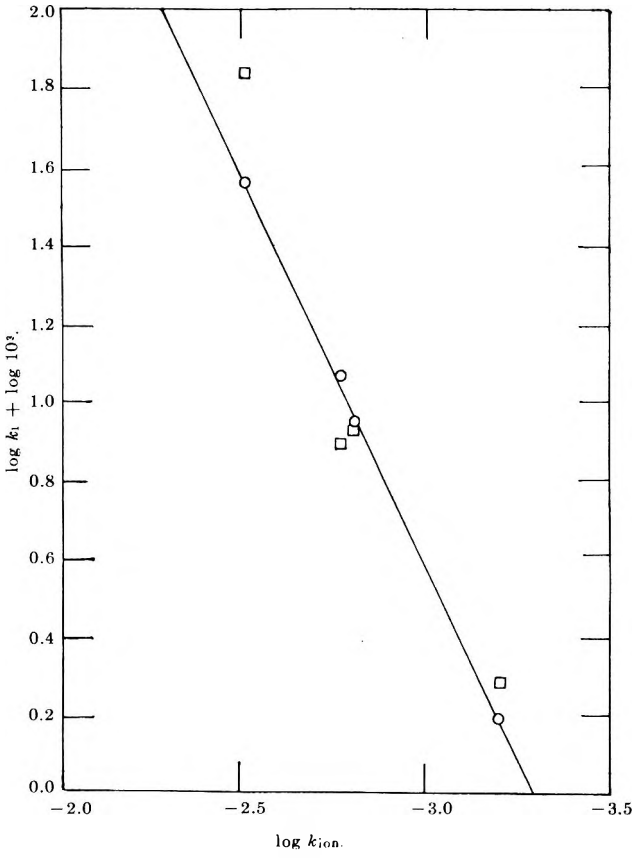
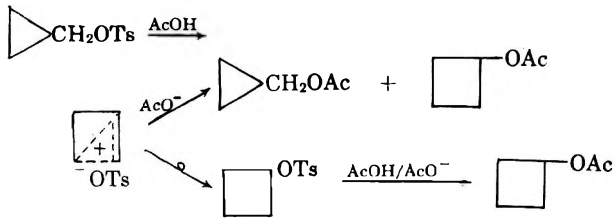


Fig. 1.—Plot of log k for 1-phenylcyclopropylcarbinyl p-toluenesulfonate (○) and cyclopropylcarbinyl p-toluenesulfonate (□) *vs.* log k for p-methoxymeophyl p-toluenesulfonate. Data taken from Table I.

This inequality buttressed with the product analysis suggests the importance of transition state coefficient differences in this study.

The evidence from kinetic data supports a difference in the nature of the solvated cationic intermediates involved in the solvolysis of I and III. The existence of a nonclassical "bicyclobutonium" ion has been well-established for the cyclopropylcarbinyl system in solvolytic reactions[2,6,14] and, therefore, one would expect a product distribution in accord with this intermediate.

The acetolysis of cyclopropylcarbinyl p-toluenesulfonate (liberation of 64–67% p-toluenesulfonic acid) gives a mixture of compounds of which approximately 96% were identified as cyclopropylcarbinyl acetate (71%) and cyclobutyl acetate (24%). Prolonged heating in the presence of the previously liberated p-toluenesulfonic acid (see Experimental for details) gave nearly 100% p-toluenesulfonic acid and approximately 95% of the product mixture was identified as cyclopropylcarbinyl acetate (55%) and cyclobutyl acetate (43%). The significant difference in reaction conditions precludes a comparison of the initial solvolysis products (liberation of 64–67% p-toluenesulfonic acid) with those obtained from complete solvolysis (liberation of nearly 100% p-toluenesulfonic acid).



The remainder of the product composition (3–7%) was accounted for by a single peak on the chromatogram, presumedly allylcarbinyl acetate, which was not identified.[15] The product identities and distributions were determined by v.p.c. The various peaks were identified by comparison with authentic samples.

Arguments previously have been advanced[1,6] to support the localization of positive charge at the methinyl carbon atom with substitution at the 1-ring position. In the case of the 1-phenylcyclopropylcarbinyl system, this would lead to a benzyl-like carbonium ion, which is supported by the finding[1] that 1-phenylcyclobutyl acetate is the exclusive product of acetolysis (in the presence of acetate ion). Based upon kinetic evidence and product analysis, the results reveal that the ion derived from the acetolysis of cyclopropylcarbinyl arenesulfonate derivatives behaves differently from ions from 1-methyl- and 1-phenylcyclopropylcarbinyl arenesulfonate derivatives. Furthermore, the results suggest that the lack of 1-ring position substituent effect can be attributed to transition state differences, due to increased localization of positive charge on the methinyl ring carbon atom with concomittant change in solvation forces.

Experimental

Cyclopropylcarbinol was prepared in 72% yield by lithium aluminum hydride reduction of cyclopropanecarboxylic acid, b.p. 124° (760 mm.), lit.[16] b.p. 126° (760 mm.).

1-Methylcyclopropylcarbinol was prepared in 70% yield by lithium aluminum hydride reduction of methyl 1-methylcyclopropanecarboxylate, b.p. 126–127° (760 mm.), lit.[6] b.p. 126° (760 mm.).

1-Phenylcyclopropylcarbinol was prepared in approximately 100% yield by lithium aluminum hydride reduction of 1-phenylcyclopropylcarbonyl chloride, m.p. 32–33°, lit.[1] m.p. 32.5–33°.

Cyclopropylcarbinyl arenesulfonates (Ia–c) were prepared according to published procedure.[16] The purities, calculated from "infinity" titers of the acetolyses at 60° and ethanolyses at 30°, ranged from 85–95%. V.p.c. revealed that most of the impurity was accounted for by unreacted cyclopropylcarbinol.

1-Methylcyclopropylcarbinyl arenesulfonates (IIa–c) were prepared according to the same procedure. Due to the thermal instability of the esters, it was necessary to use the product purified by extraction with methylene chloride followed by evaporation of the solvent at diminished pressure. The purities, calculated from infinity titers of the acetolyses at 30°, ranged from 82–96%.

1-Phenylcyclopropylcarbinyl arenesulfonates (IIIa–e) were prepared according to established procedure[1]: **1-phenylcyclopropylcarbinyl benzenesulfonate, IIIa**, m.p. 48° dec., lit.[1] m.p. 48° dec.; **1-phenylcyclopropylcarbinyl p-toluenesulfonate, IIIb**, m.p. 52° dec., lit.[1] m.p. 52° dec.; **1-phenylcyclopropylcarbinyl p-methoxybenzenesulfonate, IIIc**, m.p. 65° dec., too unstable for combustion analysis, purity calculated from infinity titers of the acetolyses at 30° was 100 ± 0.1%; **1-phenylcyclopropylcarbinyl p-isopropylbenzenesulfonate, IIId**, m.p. 58° dec., too unstable for combustion analysis, purity calculated from infinity titers of the acetolyses at 30° was 100 ± 0.1%; **1-phenylcyclopropylcarbinyl p-t-butylbenzenesulfonate, IIIe**, m.p. 66° dec., too unstable for combustion analysis, purity calculated from infinity titers of the acetolyses at 30° was 100 ± 0.1%.

(14) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 4390 (1959).

(15) Both ethanolysis and methanolysis of Ib appear to give one component accounting for more than 95% of the products. Positive assignments of structures of these compounds has yet to be made. However, based on other work,[16] it is believed that the product of ethanolysis is ethyl cyclopropylcarbinyl ether.

(16) C. G. Bergstrom and S. Siegel, *J. Am. Chem. Soc.*, **74**, 145 (1952).

Rate measurements were accomplished by the usual techniques.[5,17] The titrating solutions were for acetolyses, 0.050 *N* sodium acetate in acetic acid and, for ethanolyses and methanolyses, 0.04 1 *N* sodium methoxide in anhydrous methanol. The indicators used were bromophenol blue and bromothymol blue, respectively.

Solvents.—Absolute ethanol was prepared according to the method of Fieser.[18] Absolute methanol was prepared by distillation from magnesium turnings. Aqueous ethanol (80% by volume) was prepared volumetrically from absolute ethanol and distilled water. Acetic acid solvent was prepared from 985 ml. glacial acetic acid (Du Pont, 99.7% min.) and 15 ml. acetic anhydride.

Treatment of Kinetic Data.—The thermodynamic activation functions were obtained by IBM 1620 computer regression analysis. Solvent ionizing strength sensitivity, a, and the Hammett ρ-value also were obtained by IBM 1620 computer regression analysis.[19]

Product Studies. A. Acetolysis.—Cyclopropylcarbinyl *p*-toluenesulfonate (IIIb, 885 mg.) was solvolyzed in 25 ml. of acetic acid (*cf.* above for solvent composition) containing potassium acetate (500 mg.) at 30° for 20 half-lives in one run and at 60° for 10 days in a second run. The material was added to ice–water (200 ml.) and extracted with three 60-ml. portions of ether. The ether extract was washed with saturated sodium bicarbonate followed by water, dried over sodium sulfate, and most of the ether removed by distillation. Injection of a sample of this solution into a vapor fractometer (sucrose acetate isobutyrate, 125°) gave in addition to a solvent peak one small peak (A, 5.8-min. retention time) and two large, sharp peaks (B, 7.1-min. retention time, and C, 8.0-min. retention time). A sample of authentic cyclopropylcarbinyl acetate[20] in ether gave a chromatogram with a retention time identical with peak C and, similarly, a sample of authentic cyclobutyl acetate[20] in ether gave a chromatogram with a retention time identical with peak B.

B. Ethanolysis.—Cyclopropylcarbinyl *p*-toluenesulfonate (IIIb, 1.2 g.) was solvolyzed in 50 ml. of absolute ethanol at 30° for 20 half-lives. The material was added to ice–water (200 ml.) and extracted with three 40-ml. portions of ether, dried over sodium sulfate, and most of the solvent removed by distillation. Injection of a sample of this solution into a vapor fractometer (Apiezon grease, 100°) gave, almost immediately, a strong peak corresponding to volatile solvent. The only other peak was a strong, sharp peak with a retention time of 4.9 min.

(17) Aliquot samples were removed from a single container for titrations rather than individual ampoules. This modification reduced the "prerun" solvolysis and shortened the sampling time for each individual titration.

(18) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., Rev., D. C. Heath and Co., Boston, Mass., 1957, p. 285.

(19) These analyses were performed through the courtesy of the Louisiana Polytechnic Institute Computer Center, Ruston, La.

(20) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

The Conformations of Cyclic Compounds in Solution. I. Shikimic Acid

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The conformation of shikimic acid has been determined in solution and is shown to be essentially a half-chair conformation.

The importance of shikimic acid (I) as an intermediate in the conversion of carbohydrates to aromatic compounds in nature is well-known.[2] In view of this it is surprising that no attempt has been made previously to measure the precise conformation of this compound in solution. N.m.r. spectroscopy has been used to determine the precise conformations of several important cyclic biochemicals[3,4] in solution and this method has now been used to determine the conformation of shikimic acid.

Experimental

The compound used was a commercial sample from the Aldrich Chemical Co. and was used without further purification, m.p. 184.0–184.5°, $[\alpha]_D$ −175° (*c* 2, water). The spectrum (Fig. 1) was measured in deuterium oxide solution with a Varian 4302 B spectrometer and a Varian V 3521 integrator for base-line stabilization. Calibration was by the usual side-band technique and, in the absence of any generally accepted n.m.r. internal standard for aqueous solutions, acetonitrile[5] (7.98 τ) was used.

The assignment of the spectrum was straightforward. The signal at lowest field could be assigned with certainty to the olefinic proton (H-2) and the multiplets at highest field must have been due to the C-6 methylene protons. Allocation of the remaining multiplets then followed, and the first-order coupling constants and chemical shifts are shown in Table I. An explicit analysis of this spectrum would involve the solution of a six-spin system which would be tedious and in fact unnecessary. It seemed improbable that second-order effects would be significant and to check this a series of partial analyses were made. The spectrum was subdivided into five sections (H-5, H-6e, H-6a), (H-3, H-4, H-5), (H-2, H-3, H-4), (H-4, H-5, H-6a), (H-4, H-5, H-6e) and each of these was analyzed[6] separately. The values thus obtained are shown in Table I together with the first-order values, and it can be seen that both sets are in close agreement. In addition to the vicinal coupling constants, long-range couplings were observed between the C-6 protons and the C-2 and C-3 protons. In view of the opposite relative signs of these couplings,[7] the values shown in Table I are probably the averaged values.

TABLE I

SPECTRAL DATA FOR SHIKIMIC ACID

Chemical shifts (τ-values)[a]

	H-2	H-3	H-4	H-5	H-6e	H-6a
First order	3.12	5.59	6.31	6.00	7.23	7.86
From analysis	3.12	5.59	6.24	5.82	7.19	7.89

Coupling constants (c.p.s.)

	$J_{1,2}$	$J_{2,6}$	$J_{3,4}$	$J_{3,6}$	$J_{4,6a}$	$J_{5,6a}$	$J_{5,6e}$	$J_{6a,6e}$
First order	4.0	1.8	3.9	1.5	8.4	6.2	5.0	18.5
From analysis	4.0	1.8[b]	3.8	1.5[b]	8.4	5.9	4.8	18.5

[a] Since spectra were measured in deuterium oxide solution, no signals were observed from –OH or $-CO_2H$. [b] Uncorrected values.

(1) University of Ottawa Postdoctoral Fellow, 1962–1963; Department of Chemistry, University of British Columbia, Vancouver 8, B. C.

(2) "Biochemists Handbook," C. Long, Ed., E. and F. N. Spon Ltd., London, 1961, p. 594.

(3) C. D. Jardetsky, *J. Am. Chem. Soc.*, **83**, 2919 (1961), and previous references.

(4) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).

(5) R. A. Y. Jones, A. R. Katritzky, J. N. Murrel, and N. Sheppard, *J. Chem. Soc.*, 2576 (1962).

(6) The author is indebted to Miss O. Boshko of the Ottawa University Computing Centre for computing these analyses on an IBM 650 computer.

(7) D. D. Elleman and S. L. Manatt, *J. Chem. Phys.*, **36**, 2346 (1962).

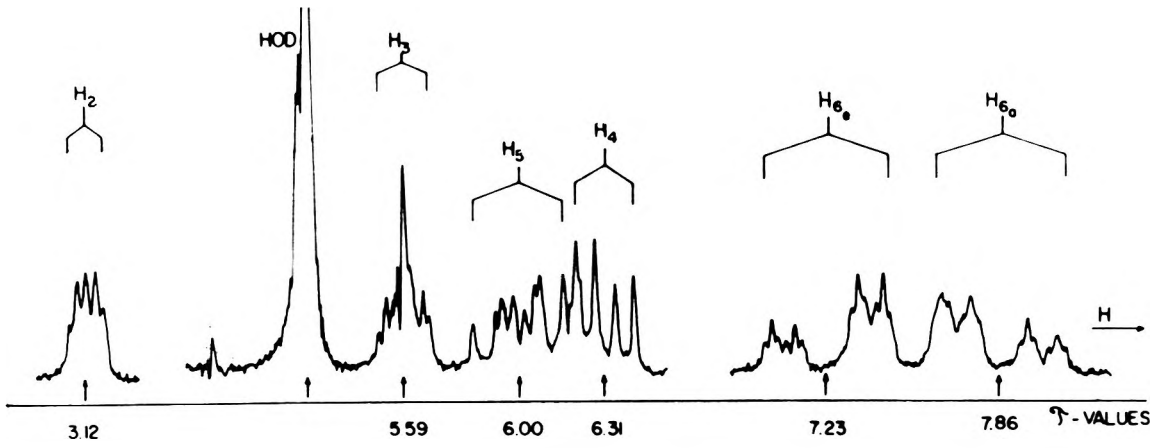

Fig. 1.—Nuclear magnetic resonance spectrum of shikimic acid in deuterium oxide, measured at 60 Mc./sec.

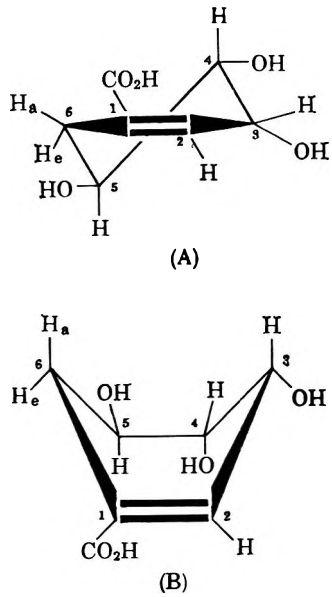

Fig. 2.—Conformations of shikimic acid: (A) the half-chair conformation; (B) the boat conformation.

Discussion and Results

The geometry of a cyclohexene ring is essentially defined by the double bond with its two sp^2-hybridized carbon atoms. These force the four adjacent carbon atoms of the double bond to be coplanar which prevents the ring from adopting the chair conformation commonly assumed by cyclohexanes. To accommodate this coplanarity the cyclohexene ring can adopt either a "boat" conformation or a "half-chair" conformation. Beckett, Freeman, and Pitzer[8] have calculated that for cyclohexene itself the half-chair conformation is energetically more favored than the boat form by 2.7 kcal./mole. However it was not known whether a similar energy difference would apply in the case of a substituted cyclohexene.

It is known that many cyclic systems, such as cyclohexane, undergo rapid conformational inversion at room temperature, and in such cases the observed conformation is "time-averaged" and represents a statistical average of all the conformational species participating in the inversion cycle. However, if the cyclohexane ring bears substituents which are arranged such that one conformational species is more favored energetically than any other, then the observed conformation of the ring will approximate to that of the favored species. Similar considerations can be applied to substituted cyclohexenes. In the case of shikimic acid, four "extreme" conformations are possible, two half-chair forms and two boat forms. The two most energetically favored of these are shown in Fig. 2. In the following discussion it is assumed that the shape of shikimic acid can be considered in terms of these two basic conformations and that conformational inversion can occur between the two. The most energetically favored species will contribute most to the observed time-averaged conformation. Contributions of the other less favored species to the observed conformation are likely to be small. The approximate dihedral angles for the theoretical half-chair and boat conformations were measured with Barton[9] models and the values obtained are shown in Table II. Although such measurements make no allowance for angular strain, the agreement between these values and those calculated by Corey and Sneen[10] is quite good, and they serve to indicate the relative magnitudes of the dihedral angles.

TABLE II

DIHEDRAL ANGLES FOR SHIKIMIC ACID[a]

(Deg.)

	H-2, H-3	H-3, H-4	H-4, H-5	H-5, H-6a	H-5, H-6e
Half-chair	43	50	180	170	50
Boat	115	60	120	180	60

[a] Using Barton Models.

The experimental dihedral angles were obtained from the coupling constants by the Karplus[11] equation. Since this relationship can only be applied to hydrogens attached to carbon atoms which are approximately sp^3-hybridized no estimate could be made of the angle between H-2 and H-3. Since there is at present some uncertainty[12] as to the precise values of the J_0-parameters, the values originally suggested by Karplus ($J_0 = 8.5$ for $0° \leq \phi \leq 90°$ and $J_0 = 9.5$ for $90° \leq \phi \leq 180°$)

(8) C. W. Beckett, N. K. Freeman, and K. S. Pitzer, *J. Am. Chem. Soc.*, **70**, 4227 (1948).

(9) D. H. R. Barton, *Chem. Ind.* (London), 1136 (1956).

(10) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).

(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959). The Karplus equation has the form $J = J_0 \cos^2 \phi - 0.28$ where J is the coupling constant between two hydrogens attached to adjacent carbon atoms and separated by a dihedral angle ϕ. J_0 is a parameter of the particular system.

(12) K. L. Williamson [*J. Am. Chem. Soc.*, **85**, 516 (1963)] has shown that there is a definite relationship between the J_0 parameters of a system and the electronegativity of its substituents.

and those subsequently adopted[13] for carbohydrates ($J_0 = 9.3$ for $0° \leq \phi \leq 90°$ and $J_0 = 10.4$ for $90° \leq \phi \leq 180°$) were used. The two sets of angles thus obtained are shown in Table III. It is clear that the modified parameters only make significant changes for larger dihedral angles.

TABLE III
EXPERIMENTAL DIHEDRAL ANGLES FOR SHIKIMIC ACID (DEG.)

Parameters	3, 4	4, 5	5, 6a	5, 6e
Unmodified[a]	46	163	144	39
Modified[b]	48	156	141	42

[a] See ref. 11. [b] See ref. 13.

Comparison of the experimental and theoretical dihedral angles shows immediately that shikimic acid adopts a conformation which approximates most closely to the half-chair form (A) shown in Fig. 2. In terms of a "time-averaged" conformation this means that the half-chair species makes the major contribution and is hence more favored energetically than the boat form. Alternatively the difference between the calculated and experimental angles can be rationalized on a "static" basis, if it is assumed that the angle between H-4 and H-5 is *genuinely* less than 180°, which is reasonable. Then rotation about the C-3, C-4 and C-4, C-5 bonds could decrease the H-4, H-5 angle. This also would decrease the H-3, H-4, and H-5, H-6a angles which is again in accord with the experimental finding. On this basis it seems that the conformation of shikimic acid is essentially the half-chair conformation (A) shown in Fig. 2, with some deformation towards the boat conformation (B).

This work represents the first complete p.m.r. analysis of a substituted cyclohexene.[14] It also indicates that fairly accurate conformational deductions can be made from first-order coupling constants *providing* that sufficient care is taken. Although the *experimental* errors in the dihedral angles are only *ca.* ±1° due to the errors in the coupling constants, a *systematic* error of much greater magnitude is introduced by the uncertainty of the Karplus parameters. Clearly the method is generally applicable to cyclic molecules as long as suitably modified J_0 values are used.

Acknowledgment.—The author is indebted to Dr. F. A. L. Anet for the facilities used and wishes to thank the National Research Council for financial support.

(13) R. J. Abraham, L. D. Hall, L. Hough and K. A. McLauchlan, *J. Chem. Soc.*, 3699 (1962).

(14) Since the completion of this work, E. W. Garbisch [*J. Org. Chem.*, **27**, 4249 (1962)] has published data which he considers indicative that 6-substituted 1-phenylcyclohexenes also adopt a half-chair conformation, but his investigation did not yield any complete analyses.

The Function of Base in the Catalytic Dehalogenation of Aliphatic Halides. Reduction of Dichloromethylmethylcyclohexanones in the Presence of Potassium Hydroxide and Triethylamine

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In order to elucidate the function of base in the catalytic dehalogenation of aliphatic halides, the effect of two bases of widely different character, potassium hydroxide and triethylamine, on the hydrogenolysis of 2-dichloromethyl-2-methylcyclohexanone and 4-dichloromethyl-4-methylcyclohexanone was investigated. With the 2-substituted dichloro ketone the only difference was in the time required for reduction. This difference was shown not to be due to poisoning of the catalyst and was ascribed to a basic dissimilarity in mechanism. In the case of the 4-substituted dichloro ketone, dehalogenation proceeded smoothly in the presence of hydroxide ion but led to substantial amounts of 4-dichloromethyl-4-methylcyclohexanol in the presence of triethylamine. This facile reduction of the carbonyl group of the dichloro ketone, as well as the inertness of the chlorine atoms of the dichloro alcohol to hydrogenolysis under the dehalogenation conditions, are explained in terms of intermolecular interactions, probably on the catalyst surface, involving the chlorine atoms, the oxygen function, and the amine. Possible functions of the amine in this interaction, and of bases in dehalogenations in general, are considered.

Catalytic hydrogenolysis is a useful method for the removal of halogen atoms from organic compounds under relatively mild conditions.[1] In acidic or neutral solutions aryl halides are reduced while alkyl halides are not, except certain ones activated by adjacent unsaturation.[2] In basic solutions, however, aliphatic halides are so readily and completely dehalogenated that the reaction has been used as an analytical method for the determination of halogen.[3] A similar activation of aryl halides occurs if the molecule contains a basic nitrogen atom.[2] This marked effect of base on catalytic dehalogenation often influences the selective reduction of other functional groups in the presence of halogen atoms[4-6] and is, therefore, of interest to the synthetic organic chemist.

Originally,[3] base was used in catalytic dehalogenations to prevent disintegration of the palladium-on-calcium carbonate catalyst by the halogen acid formed in the reaction. A similar reason for the necessity of base has been suggested for other catalysts,[7] including nickel[6,8] and palladium on charcoal,[9] but without supporting evidence.

(1) W. Theilheimer, "Synthetic Methods of Organic Chemistry," Vol. I–XV, Interscience Publishers, Inc., New York, N. Y., 1947–1962, lists over eighty applications of this reaction.

(2) R. Baltzly and A. Phillips, *J. Am. Chem. Soc.*, **68**, 261 (1946).

(3) M. Busch and H. Stove, *Ber.*, **49**, 1063 (1916).

(4) M. Freifelder, W. Martin, G. Stone, and E. Coffin, *J. Org. Chem.*, **26**, 383 (1961).

(5) R. Adams and R. Miller, *J. Am. Chem. Soc.*, **58**, 787 (1936).

(6) W. Whitmore and A. Revukas, *ibid.*, **62**, 1692 (1940).

(7) K. Rosenmund and F. Zetzsche, *Ber.*, **51**, 578 (1918).

(8) C. Kelber, *ibid.*, **50**, 305 (1917).

(9) M. Mladenovic, *Bull. soc. chim. roy. Yougoslav.*, **4**, 187 (1933).

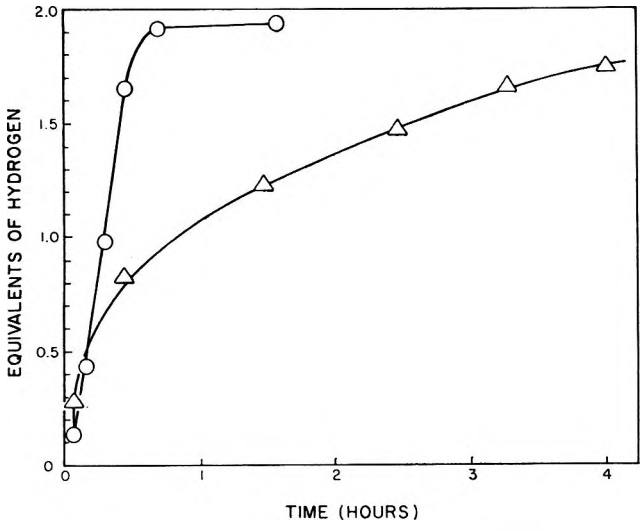


Fig. 1.—Hydrogenation of 2-dichloromethyl-2-methylcyclohexanone in the presence of triethylamine (-Δ-Δ-Δ-) and potassium hydroxide (-O-O-O-).

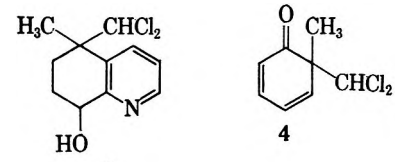
In the gas phase, inhibition of dehalogenation by halogen acids has been reported,[10] but this is not surprising since the catalysts were in the form of metallic films which are notably susceptible to poisoning.[11] In solution studies utilizing supported catalysts, only the dehalogenations of aromatic halides containing a basic nitrogen atom and certain aliphatic halides with adjacent unsaturation were impeded by acids and then merely to the extent of reducing the rates to those of compounds without such activating groups.[2]

Finally, the use of base in excess of that necessary for neutralization of the halogen acid has been found to accelerate the rate of reduction.[3,8]

These observations suggest that the sole function of base in catalytic dehalogenations is not, as has been assumed, the destruction of halogen acid, but rather that the base plays a direct role in aiding the reductive cleavage of the carbon–halogen bond.[12]

If the previous hypothesis is correct, then the ease of removal of aliphatic halogen atoms in basic solution may be related to any of a number of properties of the base such as its type (Lewis or Brønsted), nucleophilicity, ionization constant, ionization potential, etc. Considerable information on the role of base might, therefore, be obtained by comparing dehalogenations carried out in the presence of bases whose properties are quite different, as for example amines and hydroxides.

The present paper describes the results of such a study, the reduction of 2-dichloromethyl-2-methylcyclohexanone (**1**) and 4-dichloromethyl-4-methylcyclohexanone (**2**) in the presence of triethylamine and potassium hydroxide. These particular compounds were selected as substrates because, as might be expected for neopentyl-type halides, they have been reported to be quite inert to bases,[14] thus decreasing the probability of troublesome side reactions. Furthermore, Isogai recently has noted that the 4-substituted dichloro ketone (**2**) was resistant to catalytic dehalogenation in the presence of hydroxide ion, while the closely related dichloro alcohol (**3**) was readily dehalogenated under identical conditions.[15] To the extent that this difference in reactivity is due to the presence of a basic nitrogen atom in the latter compound, it was expected that dehalogenations of halides **1** and **2** in the presence of an amine or an hydroxide also would differ.[16]



3 **4** **5**

Results and Discussion

Catalytic hydrogenation of the dienones **4** and **5** in neutral solution led to the starting dichloro ketones **1** and **2**, respectively, in good yield without any evidence of carbonyl reduction or dehalogenation. This once again[2] demonstrates the inertness of aliphatic halides to hydrogenolysis in the absence of base and also shows that the presence of the carbonyl group does not in itself promote removal of the chlorine atoms from **1** and **2**.

All dehalogenations were carried out under conditions similar to those of Isogai[15] in that a methanol solution of the halide containing at least a tenfold excess of base and half as much 10% palladium-on-charcoal catalyst as substrate was hydrogenated at ambient pressure and temperature.

The dehalogenation of 2-dichloromethyl-2-methylcyclohexanone (**1**) in the presence of triethylamine proceeded smoothly to give chiefly 2,2-dimethylcyclohexanone and a small amount of what was probably a partially dechlorinated product.

When potassium hydroxide was used as a base, however, 2,2-dimethylcyclohexanone was obtained in much lower yield and the amount of hydrogen absorbed not only was inconsistent with the expected stoichiometry but also varied from run to run. This anomalous behavior was traced to a slow reduction of the carbonyl group of 2,2-dimethylcyclohexanone[19] and to reaction of the starting dichloro ketone **1** with hydroxide ion. One of the products of this latter reaction was identified as 6-methylheptanoic acid (**6**) by comparing its infrared spectrum and retention time by v.p.c. with those of an authentic sample. This acid probably is formed during the dehalogenation by reduction of 7-chloro-6-methyl-

(10) J. S. Cambell and C. Kemball, *Trans. Faraday Soc.*, **57**, 809 (1961).

(11) H. S. Taylor, *Discussions Faraday Soc.*, **8**, 9 (1950).

(12) A further indication that the base actively participates in the dehalogenation process is that side reactions such as Wurtz-type coupling occur only if base is present.[13] Baltzly and Phillips (ref. 2, footnote 3) also have commented on the existence of a different mechanism for dehalogenations in basic media.

(13) M. Busch and W. Schmidt, *Ber.*, **62B**, 2612 (1929), and succeeding papers; E. C. Ladd and H. Sargent, U. S. Patent 2,644,835 (1953); *Chem. Abstr.*, **48**, 5878c (1954).

(14) N. Kreutzkamp, H. Meerwein, and R. Stroh, "Methoden der Organischen Chemie" (Houben-Weyl), Vol. 5, part 4, Eugen Müller, Ed., Georg Theime Verlag, Stuttgart, 1960, p. 686.

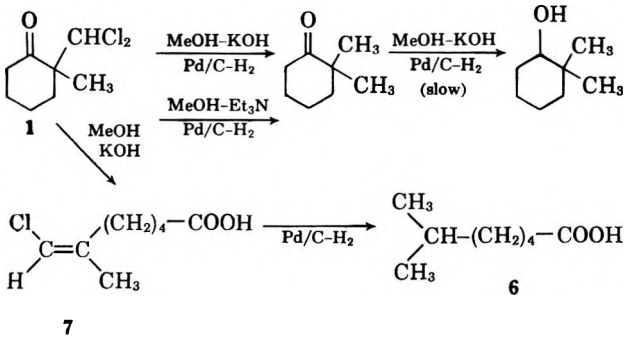
(15) K. Isogai, *Nippon Kagaku Zasshi*, **81**, 1594 (1960).

(16) Dehalogenation of the dienone precursors **4** and **5** of the dichloro ketones **1** and **2**, respectively, also have been reported to be quite sluggish when hydroxide ion was used as the base.[3] These compounds were not chosen for this study, however, because side reactions with the base were anticipated.[17,18]

(17) R. M. Dodson, J. R., Lewis, W. B. Webb, E. Wenkert, and R. D. Youssefyeh, *J. Am. Chem. Soc.*, **83**, 938 (1961).

(18) J. Leitch, *J. Org. Chem.*, **27**, 1081 (1962).

(19) The slow reduction of carbonyl groups under similar conditions has been noted previously: E. Breitner, E. Roginski, and P. N. Rylander, *ibid.*, **24**, 1855 (1959).



6-heptenoic acid (7) which has been shown to be a product of the reaction of methanolic potassium hydroxide with the dichloro ketone 1.[20]

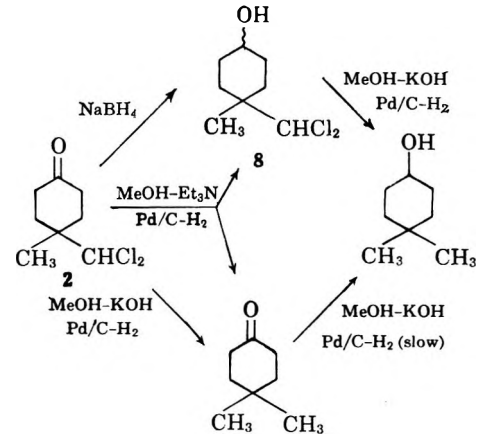
By adding the halide to the methanolic potassium hydroxide immediately before carrying out the hydrogenation under conditions which favored rapid reduction (rapid stirring, pressure, etc.), 2,2-dimethylcyclohexanone could be isolated in good yield if the reaction was stopped after two equivalents of hydrogen had been absorbed.

Except for the side reactions mentioned previously, the only difference between amine and hydroxide ion-promoted dehalogenations of the dichloro ketone 1 was that the former reaction took much longer to pick up the theoretical amount of hydrogen. As can be seen from Fig. 1, this is not due to differences in the initial rates of hydrogenation but rather to the fact that in the presence of potassium hydroxide the rate of hydrogen uptake was constant, whereas in the presence of triethylamine this rate steadily decreased as the reaction progressed. This suggests that poisoning of the catalyst by triethylamine[21] probably is not responsible for the difference in reaction time, but poisoning by one of the products could be. This possibility might seem to be eliminated by the fact that with the exception of triethylammonium ion, which would not be expected to be a catalyst poison,[21] the same products are formed in both dehalogenations. Poisoning of the catalyst by chloride ion[22] cannot be eliminated on this basis, however, since, although triethylammonium chloride is readily soluble in methanol, potassium chloride is not and might, therefore, be unable to inhibit the reduction. This hypothesis was tested and rejected, because when tetramethylammonium hydroxide was used as a base (tetramethylammonium chloride is quite soluble in methanol) the rate of hydrogenation was similar to that of the potassium hydroxide-promoted dehalogenation in that it did not decrease during the course of the reaction.

Since poisoning of the catalyst is not responsible for the differences in the rates of hydrogen uptake shown in Fig. 1, differences in the mechanism of the amine and hydroxide ion-promoted dehalogenations might be.[23] This view is substantiated by the results of the dehalogenation of 4-dichloromethyl-4-methylcyclohexanone (2) in the presence of the two bases.

In disagreement with the results of Isogai,[15] the 4-substituted dichloro ketone (2) was readily dehalogenated with potassium hydroxide as the base to give primarily 4,4-dimethylcyclohexanone. A small amount of partially dechlorinated product was once again obtained, but no side reactions with the exception of the slow reduction of the carbonyl group of the product[19] were observed. Isogai's[15] failure to observed dehalogenation under essentially identical conditions is puzzling although this may be due to the nature of the palladium-on-charcoal catalyst which was used.

Dehalogenation of the dichloro ketone 2 in the presence of triethylamine was anomalous in that in addition to 4,4-dimethylcyclohexanone and a little partially dechlorinated material, an approximately equal amount of a third product was isolated which, from the equivalents of hydrogen consumed (1.6) and chloride ion produced (1.0), as well as its broad melting point (45–60°), v.p.c. retention time, and infrared spectrum, appeared to be a mixture of the stereoisomeric 4-dichloromethyl-4-methylcyclohexanols (8). This structure assignment was shown to be correct by comparing the physical properties mentioned before with those of an authentic sample prepared from the dichloro ketone 2 by reduction with sodium borohydride.



The formation of the dichloro alcohol 8 during the hydrogenation of 2 is surprising since reduction of the carbonyl group would not be expected to occur under these conditions whereas hydrogenolysis of the chlorine atoms would. Thus, with the exception of 8, no other products of carbonyl reduction were detected from the dehalogenations of dichloro ketones 1 and 2 in the presence of triethylamine or from the attempted reduction of cyclohexanone under the same conditions. Similarly, although no systematic studies have been made, amines have been used successfully as bases in catalytic dehalogenations before,[1] and furthermore both the 2- and to some extent the 4-substituted dichloro ketone (1 and 2, respectively) were dehalogenated by this method.

The inertness of the chlorine atoms of the dichloro alcohol 8 is not due to poisoning of the catalyst by one of the other reaction products, since, on subjecting the isolated mixture of stereoisomers to the dehalogenation conditions, only a very slow uptake of hydrogen was observed. The fact that in the presence of potassium

(20) M. G. Reinecke, *J. Org. Chem.*, **28**, 3574 (1963).

(21) G. C. Bond, "Catalysis by Metals," Academic Press, New York, N. Y., 1962, p. 99.

(22) Halide ion has been reported to inhibit dehalogenations.[1]

(23) The rate of disappearance of the dichloro ketone in the presence of triethylamine, as measured by the rate of hydrogen uptake, appears to be approximately first order. Because of the complexity of heterogeneous reactions and the wide variety of experimental factors which could effect their rate, a mechanistic interpretation of this observation would seem to be unwarranted in the absence of additional, more carefully controlled, kinetic experiments.

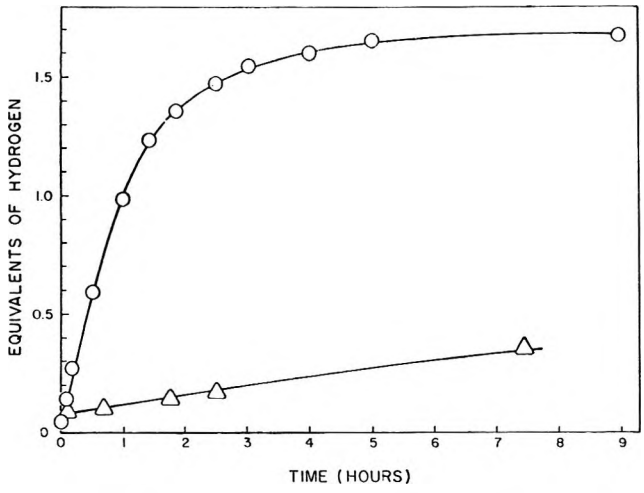


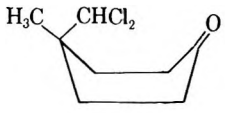
Fig. 2.—Hydrogenation of 4-dichloromethyl-4-methylcyclohexanol in the presence of triethylamine (-Δ-Δ-Δ-) and potassium hydroxide (-O-O-O-).

hydroxide the same mixture of dichloro alcohols is rapidly dehalogenated to 4,4-dimethylcyclohexanol (see Fig. 2) indicates that the inertness of these halogen atoms is dependent on the presence of triethylamine.

Triethylamine also appears to be necessary for the reduction of the carbonyl group of the dichloro ketone **2**, since, with the exception of the very slow follow up hydrogenation of 2,2- and 4,4-dimethylcyclohexanone noted previously, no such reaction was observed either in the presence of potassium hydroxide or in the absence of base altogether.

These results suggest that, during the hydrogenation of dichloro ketone **2** and the dichloro alcohol **8**, specific interactions between the chlorine atoms, the oxygen function, and triethylamine take place, probably on the catalyst surface, which are responsible for the inertness of the chlorine atoms and the lability of the carbonyl group to reduction. Although the details of these interactions are obscure, some of their general features can be discussed.

If the interactions of the chlorine and oxygen atoms are intramolecular then species such as **9** or **10** in which the cyclohexane ring is in the boat form must be involved.[24] This would predict that (1) the reduction



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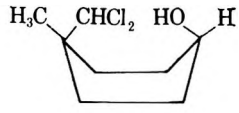

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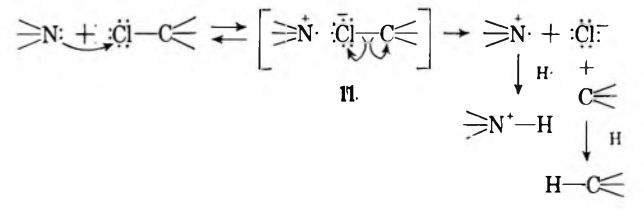
of the carbonyl group of the dichloro ketone **2** should be stereospecific, and (2) only one stereoisomer of the dichloro alcohol **8** should possess the uniquely inert chlorine atoms. Since the dichloro alcohol **8** was actually isolated as a mixture of stereoisomers, however, which after separation by fractional crystallization were shown to be equally inert to dehalogenation, it can be concluded that the chlorine–oxygen interactions are probably inter- rather than intramolecular. The possibility that the reduction of the dichloro ketone **2** was actually stereospecific but that the single stereoisomer of the dichloro alcohol **8** formed was subsequently isomerized, either in the reaction mixture or on work-up, was rejected, since, on subjecting each of the separated dichloro alcohols to the dehalogenation conditions (including the presence of 4,4-dimethylcyclohexanone which might catalyze the isomerization *via* an Oppenauer-type oxidation), the unchanged portions were recovered without any evidence of isomerization.

Additional features of the interaction responsible for the reduction of the carbonyl group of **2** are suggested by the observation that the relative amounts of dichloro alcohols **8** and 4,4-dimethylcyclohexanone formed in the dehalogenation were approximately equal whan an active catalyst was used.[25] This might simply mean that two independent reaction paths are available, one leading to normal dehalogenation and one leading to carbonyl reduction *via* the proposed intermolecular interaction. An attractive alternative is that both reaction products arise from the same intermolecular "complex" in which only the carbonyl group and chlorine atoms taking part in the interaction are reduced. If this were the case, the interaction must involve only two molecules of the dichloro ketone **2**, since a polymeric interaction in which both the carbonyl group and chlorine atoms of a molecule of **2** are involved is eliminated by the absence of the expected product of such an interaction, 4,4-dimethylcyclohexanol.

Of particular interest in terms of the original goal of this research, *i.e.*, to elucidate the function of base in catalytic dehalogenations, is the role of the triethylamine in this interaction. This role must involve primarily some other property of the amine besides its basicity, since otherwise hydroxide ion ought to produce a similar effect. One such property is the very strong tendency of amines,[26] but not hydroxides,[27] to form charge-transfer complexes. Such complexes recently have been suggested as intermediates in certain reactions of polyhalomethanes with amines which lead to homolytic cleavage of the carbon–halogen bond.[28] A similar complex (**11**), perhaps on the catalyst surface,



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might be responsible for the lability of carbon–halogen bonds to hydrogenolysis in the presence of amines. In the case of the dichloro ketone **2** and the dichloro alcohol **8** the oxygen function may be able to interact with this complex in some way so as to promote reduction of the carbonyl group and inhibit hydrogenolysis of the chlorine atoms, respectively.

If charge-transfer complex formation were the only way base could promote dehalogenation, then hydroxide ion ought to be much less effective than amines in this regard.[26,27] Since the opposite appears to be true,

(24) For a recent review on boat forms of six-membered rings as reaction intermediates, see M. Balasubramanion, *Chem. Rev.*, **62**, 591 (1962).

(25) When a less active catalyst was used, the reaction time was increased and some of the dichloro alcohol was partially dehalogenated. In this case the amount of 4,4-dimethylcyclohexanone was similar to the combined amount of dichloro and what is probably monochloro alcohol.

(26) D. Booth, *Sci. Progr.* (London), **48**, 435 (1960).

(27) E. M. Kosower, *J. Am. Chem. Soc.*, **78**, 3497 (1956).

(28) D. P. Stevenson and G. M. Coppinger, *ibid.*, **84**, 149 (1962).

however, either this type of interaction is not important or hydroxide ion promotes dehalogenation by a basically different process. This latter possibility is supported by the experiments discussed in this paper which indicate that the course of catalytic dehalogenation is not the same in the presence of triethylamine and potassium hydroxide.

Experimental[29]

2-Dichloromethyl-2-methylcyclohexanone (1).—A solution of 1.91 g. of 2-dichloromethyl-2-methyl-3,5-cyclohexadien-1-one (**4**)[30] in 50 ml. of 95% ethanol containing 200 mg. of 10% palladium-on-charcoal catalyst[31] was hydrogenated at room temperature and atmospheric pressure. After the uptake of hydrogen had stopped (1 hr., 2.1 equiv.), the catalyst was separated by filtration and the ethanol removed with a rotary evaporator. The colorless oil which remained (1.8 g., 93% yield) was dissolved in a minimum amount of petroleum ether (b.p. 30–60°) Upon being cooled in a Dry Ice bath, this solution deposited white crystals of **1**, m.p. 31.5–32.5°, lit.[32] m.p. 33°.

4-Dichloromethyl-4-methylcyclohexanone (2).—The reduction of a solution of 2.87 g. of 4-dichloromethyl-4-methyl-2,5-cyclohexadien-1-one (**5**)[30] in 50 ml. of 95% ethanol containing 300 mg. of 10% palladium-on-charcoal catalyst was complete (2.1 equiv. of hydrogen) in 45 min. After the catalyst and solvent were removed in the same manner as before, 2.8 g. (95%) of white crystals of **2** were obtained which after recrystallization from petroleum ether (b.p. 30–60°) melted at 46.5–47.5°, lit.[32] m.p. 47–48°.

Hydrogenation of 2-Dichloromethyl-2-methylcyclohexanone (1). A. In the Presence of Triethylamine.—A solution of 4.875 g. of 2-dichloromethyl-2-methylcyclohexanone (**1**) in 160 ml. of absolute methanol and 40 ml. of triethylamine containing 2.5 g. of 10% palladium-on-charcoal catalyst was hydrogenated at room temperature and atmospheric pressure. After the absorption of hydrogen had stopped (2.0 equiv., 20 hr.), the catalyst was removed by filtration and the filtrate distilled through a 40-cm. Vigreux column to remove the major portion of the methanol and triethylamine. The semisolid residue was partially dissolved in 20 ml. of water and extracted with three 20-ml. portions of ether. Neutralization of the aqueous layer with dilute nitric acid and titration with standard silver nitrate solution to a silver chromate end point indicated the presence of 1.8 equiv. of chloride ion.

The combined ether extracts were washed with two 25-ml. portions of 0.1 *M* phosphoric acid, successively dried over sodium sulfate and Drierite, and freed of ether by distillation through a micro Vigreux column to leave 2.7 g. of a colorless oil which according to a vapor phase chromatogram was a 10:1 mixture of a low- and a high-boiling substance, respectively.

The major component was obtained pure by fractional distillation and was identified as 2,2-dimethylcyclohexanone by its infrared spectrum (1702 cm.$^{-1}$), b.p. 168–169° (745 mm.), 78–79° (35 mm.), lit.[33] b.p. 168° (740 mm.); semicarbazone,[34] m.p. 199–200.5°, lit.[33] m.p. 199.6–199.8°; and oxime, m.p. 93–94°, lit.[33] m.p. 93–93.5°.

The minor, higher-boiling component had a v.p.c. retention time midway between those of the starting material (**1**) and 2,2-dimethylcyclohexanone. Although insufficient material was available for characterization, the infrared spectrum of this component was obtained and had peaks at 1702 cm.$^{-1}$ (C=O) and 743 cm.$^{-1}$ (C–Cl) thus suggesting that this substance was 2-chloromethyl-2-methylcyclohexanone.

B. In the Presence of Potassium Hydroxide.—A solution of 5 g. of 2-dichloromethyl-2-methylcyclohexanone (**1**) in 200 ml. of absolute methanol containing 2.5 g. of 10% palladium-on-charcoal catalyst and 20 g. of potassium hydroxide was hydrogenated at room temperature under atmospheric pressure. At the end of 2 hr., 1.2 equiv. of hydrogen had been absorbed, and the rate of hydrogen pickup suddenly decreased. The reduction was permitted to proceed for a total of 45 hr. (2.0 equiv. of hydrogen), the catalyst removed by filtration, the filtrate neutralized with hydrochloric acid, and most of the methanol removed by distillation through a micro Vigreux column to leave a residue which was taken up in 50 ml. of benzene. After extraction with three 30-ml. portions of 15% sodium carbonate solution, the benzene layer was dried over sodium sulfate and fractionally distilled to give 1.3 g. (40%) of a colorless oil, b.p. 89° (35 mm.), which was identified as 2,2-dimethylcyclohexanol by the melting point of its phenylurethane[35] (87.5–88.5°, lit.[36] 84–85°) and by a comparison of its infrared spectrum and v.p.c. retention time with those of an authentic sample synthesized from 2,2-dimethylcyclohexanone by reduction with sodium borohydride in methanol.[37]

The residue remaining after the above distillation contained at least three higher-boiling products (by v.p.c.) which were not identified.

The combined sodium carbonate extracts were acidified with hydrochloric acid and extracted with three 30-ml. portions of benzene which were combined and dried over sodium sulfate. The residue which remained after distillation of the benzene through a micro Vigreux column was identified as 6-methylheptanoic acid (**6**) by its neutralization equivalent (140 ± 3; calculated, 142), and by a comparison of its infrared spectrum and v.p.c. retention time with those of an authentic sample prepared from 1-bromo-4-methylpentane and diethyl malonate by conventional methods[38] or from 7-chloro-6-methyl-6-heptenoic acid (**7**) by catalytic reduction.[20]

In experiments similar to the previous in which reduction was stopped immediately after the rate of hydrogen pickup slowed down (1.6, 1.7, 1.9 equiv. of hydrogen absorbed), the chief neutral product consisted of 2,2-dimethylcyclohexanone, once again contaminated with several unidentified, higher-boiling (v.p.c.) impurities. When the reduction was run in a Parr apparatus at 60 p.s.i. immediately after mixing the reactants, 2 equiv. of hydrogen were absorbed in the first 4 min., and no further pressure drop was observed in the next 10 min. The 2,2-dimethylcyclohexanone formed in this reaction (70% yield) contained a small amount (5%) of only one higher-boiling substance.

C. In the Presence of Tetramethylammonium Hydroxide.—To 20 ml. of absolute methanol containing 0.032 mole of tetramethylammonium hydroxide (prepared from tetramethylammonium chloride and silver oxide in the absence of carbon dioxide and standardized by titration with standard acid) was added 487 mg. of **1** and 250 mg. of 10% palladium-on-charcoal catalyst, and the resulting mixture immediately hydrogenated at ambient pressure and temperature. After 45 min. (1.6 equiv. of hydrogen) the rate of hydrogenation suddenly decreased and after 80 min. (1.7 equiv. of hydrogen) the reaction was stopped, the catalyst removed by filtration, the filtrate saturated with solid potassium carbonate and extracted with three 20-ml. portions of ether. The combined ether extracts were successively dried over sodium sulfate and Drierite and the ether removed by distillation through a micro Vigreux column to leave 225 mg. (70%) of an oil which according to its v.p.c. retention time and infrared spectrum was essentially pure 2,2-dimethylcyclohexanone.

Hydrogenation of 4-Dichloromethyl-4-methylcyclohexanone (2). A. In the Presence of Potassium Hydroxide.—A freshly prepared solution of 2 g. of potassium hydroxide and 489 mg. of 4-dichloromethyl-4-methylcyclohexanone (**2**) in 20 ml. of absolute methanol was hydrogenated at room temperature and atmospheric pressure in the presence of 250 mg. of palladium-on-charcoal catalyst. The rate of hydrogen absorption decreased abruptly after the first hour (2.0 equiv. of hydrogen), and only 0.15 additional equivalents of hydrogen were taken up in the next half hour so the reaction was stopped and the catalyst removed by filtration and washed with methanol and water. An aliquot of this filtrate was neutralized with nitric acid and evaporated to dryness at reduced temperature and pressure. Titration of the

(29) Melting points and boiling points are uncorrected unless otherwise stated. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer, and analysis were carried out by Mr. C. F. Geiger, Ontario, Calif.

(30) K. Auwers and G. Keil, *Ber.*, **35**, 4207 (1902); *Chem. Zentr.*, **74**, I, 160 (1903).

(31) Matheson Coleman and Bell brand catalyst was used throughout this study.

(32) K. Auwers and E. Lange, *Ann.*, **401**, 303 (1913).

(33) W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1365 (1947).

(34) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 218.

(35) Ref. 34, p. 211.

(36) H. Meerwein, *Ann.*, **405**, 129 (1914); *Chem. Zentr.*, **85**, III, 230 (1914).

(37) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(38) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall Inc., New York, N. Y., 1950, p. 302.

aqueous solution of this residue with standard silver nitrate to a silver chromate end point indicated the presence of 1.92 equiv. of chloride ion in the original filtrate.

After the methanol was removed from the filtrate by evaporation at reduced pressure, the remaining aqueous residue was extracted with three 10-ml. portions of ether which were dried over sodium sulfate and evaporated at reduced pressure to leave 200 mg. of a colorless oil consisting of a 7:1 mixture of low- and high-boiling components, respectively, as determined by gas chromatography. The lower-boiling component of this mixture was identified as 4,4-dimethylcyclohexanone by the melting point of its semicarbazone[34] (205–207°, lit.[32] 202–204°), its infrared spectrum (1723 cm.$^{-1}$), and by conversion to 4,4-dimethylcyclohexanol on treatment with methanolic sodium borohydride.[37]

Insufficient of the higher-boiling component of the reaction mixture was available for characterization, but its v.p.c. retention time and infrared spectrum [1726 cm.$^{-1}$ (C=O) and 741 cm.$^{-1}$ (C—Cl)] suggested that this substance was probably 4-chloromethyl-4-methylcyclohexanone.

B. In the Presence of Triethylamine.—A solution of 489 mg. of 4-dichloromethyl-4-methylcyclohexanone (**2**) in 16 ml. of absolute methanol and 4.2 ml. of triethylamine containing 250 mg. of 10% palladium-on-charcoal catalyst was hydrogenated at ambient pressure and temperature. After the absorption of hydrogen had stopped (1.6 equiv., 9 hr.), the catalyst was removed by filtration and the major portion of the methanol and triethylamine evaporated at reduced pressure. The remaining semisolid residue was dissolved in 100 ml. of water and extracted with three 20-ml. portions of ether. Neutralization of the aqueous layer with nitric acid and titration with standard silver nitrate to a silver chromate end point indicated the presence of 1.0 equiv. of chloride ion.

The combined ether extracts were washed with three 20-ml. portions of 1 *M* nitric acid, dried successively over sodium sulfate and Drierite, and freed of ether by evaporation at reduced pressure. According to a vapor phase chromatogram, the 333 mg. of colorless oil which remained contained a trace of starting material and a mixture of three products in the ratio 4:1:4, in order of increasing retention time. From the retention times and infrared spectra of v.p.c.-collected samples, the low- and intermediate-boiling substances were identified as 4,4-dimethylcyclohexanone and the "4-chloromethyl-4-methylcyclohexanone" obtained from the hydrogenation of **2** in the presence of potassium hydroxide, respectively.

The high-boiling component had a longer retention time than the starting material **2**; a v.p.c.-collected sample was obtained as a white, crystalline solid (m.p. 45–60°) and had strong peaks in the infrared at 3200 (O–H), 1120 (C–O), and 746 cm.$^{-1}$ (C–Cl). This substance was identified as a mixture of the two stereoisomers of 4-dichloromethyl-4-methylcyclohexanol (**8**) by (1) a comparison of its v.p.c. retention time and infrared spectrum with those of an authentic sample synthesized from **2** and sodium borohydride (see following) and (2) conversion to 4,4-dimethylcyclohexanol by catalytic hydrogenolysis in the presence of potassium hydroxide (see following).

Under conditions identical with the previous hydrogenation, except for the use of a different batch of catalyst, 1.4 equiv. of hydrogen were picked up in 48 hr. and 1.2 equiv. of chloride ion produced. The ratio of products, according to the v.p.c. and in order of increasing retention time, was 5:2:3. The high- and low-boiling components were identified as **8** and 4,4-dimethylcyclohexanone, respectively, but the intermediate-boiling substance had an infrared spectrum which indicated it was probably a mixture of "4-chloromethyl-4-methylcyclohexanone" and its corresponding alcohol.

Preparation of 4-Dichloromethyl-4-methylcyclohexanol (8).—A solution of 2.00 g. of 4-dichloromethyl-4-methylcyclohexanone (**2**) and 1.75 g. of sodium borohydride in 210 ml. of absolute ethanol was stirred at room temperature for 45 min. After the ethanol had been removed on a rotary evaporator, 50 ml. of water was added to the remaining residue and the resulting mixture extracted with three 20-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and the chloroform removed on a rotary evaporator to leave 1.80 g. (89%) of **8** as a white crystalline solid, m.p. 48–74°,[39] whose v.p.c. retention time and infrared spectrum were identical (except for slight differences in the intensities of some infrared peaks) with those of the high-boiling component obtained from the hydrogenation of **2** in the presence of triethylamine.

Fractional crystallization of **8** from petroleum ether (b.p. 30–60°) gave a more soluble fraction (**8a**, prisms, m.p. 47–49°,[39] lit.[15] 49–50°) and a less soluble fraction (**8b**, needles, m.p. 82–82.5°[39]), whose v.p.c. retention times were identical but whose infrared spectra were readily distinguishable in the fingerprint region.

Anal. Calcd. for $C_8H_{14}OCl_2$ (**8b**): C, 48.75; H, 7.16. Found: C, 48.85; H, 7.23.

Hydrogenation of 4-Dichloromethyl-4-methylcyclohexanol (8).

A. In the Presence of Potassium Hydroxide.—A solution of 300 mg. of **8** and 1.2 g. of potassium hydroxide in 12 ml. of absolute methanol was hydrogenated at ambient pressure and temperature in the presence of 150 mg. of 10% palladium-on-charcoal catalyst. After 9 hr. the reaction was stopped (1.7 equiv. hydrogen absorbed) and the catalyst removed by filtration and washed with methanol and water. Titration of a neutralized aliquot of the filtrate with standard silver nitrate to a silver chromate end point indicated the presence of 1.8 equiv. of chloride ion.

The remaining filtrate was saturated with potassium carbonate, extracted with three 20-ml. portions of ether and the combined ether extracts dried successively over sodium sulfate and Drierite. The residue which remained after distillation of the ether through a micro Vigreux column gave only one peak in the v.p.c. which was identified as 4,4-dimethylcyclohexanol by a comparison of its v.p.c. retention time and infrared spectrum with those of an authentic sample prepared from 4,4-dimethylcyclohexanone by reduction with methanolic sodium borohydride.[37]

B. In the Presence of Triethylamine.—After 67 hr. at ambient pressure and temperature, a mixture of 300 mg. of **8**, 150 mg. of 10% palladium-on-charcoal catalyst, 9.6 ml. of absolute methanol, and 2.5 ml. of triethylamine had picked up only 0.6 equiv. of hydrogen. After the catalyst was removed by filtration, the filtrate was neutralized with hydrochloric acid and the major portion of the methanol and triethylamine removed by distillation through a micro Vigreux column. The two-phase distilland was extracted with three 20-ml. portions of benzene and the combined benzene extracts dried over sodium sulfate and freed of benzene by distillation through a micro Vigreux column. A vapor phase chromatogram of the remaining residue indicated the presence of three substances in the ratio 3:1:2.5, in order of decreasing retention time, which were identified by v.p.c. retention time and infrared spectra as **8**, "4-chloromethyl-4-methylcyclohexanol," and 4,4-dimethylcyclohexanone, respectively.

The separated isomers of **8** (**8a** and **8b**) were hydrogenated under conditions identical with the previous except that 400 mg. of 4,4-dimethylcyclohexanone was added to the reaction mixture. After 33 hr., each of these isomers had absorbed about 0.5 equiv. of hydrogen. Work-up of the reaction mixtures in the previous manner gave v.p.c.-collected samples of recovered starting materials whose infrared spectra and melting points were the same as those of the pure isomers (**8a** and **8b**).

Attempted Reduction of Cyclohexanone in the Presence of Triethylamine.—A mixture of 295 mg. of cyclohexanone, 2.5 ml. of triethylamine, 10 ml. of absolute methanol, and 150 mg. of 10% palladium-on-charcoal catalyst picked up 0.05 equiv. of hydrogen in the first 2 min. of reduction at ambient pressure and temperature, but failed to pick up any additional hydrogen in the next 6 hr. The catalyst was removed by filtration and the major portion of the methanol and triethylamine distilled through a micro Vigreux column. The remaining residue had only one peak in the v.p.c. besides solvent, and the infrared spectrum of a v.p.c.-collected sample was identical with cyclohexanone.

Acknowledgment.—This research was supported by a Frederick Gardner Cottrell grant from the Research Corporation and by funds from the Research Committee of the University of California.

(39) Taken on a Kofler hot stage and corrected.

Acylquinolinium Ions. Formation and Reactions of 2-Benzamidocinnamaldehyde[1]

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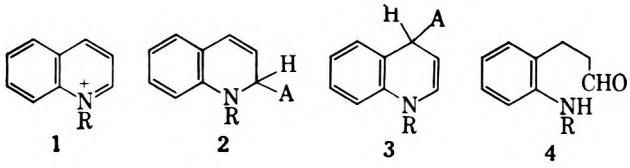
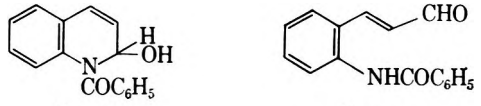
Spectroscopic evidence is presented in support of the open-chain form, 2-benzamidocinnamaldehyde, for the product of the reaction between quinoline, benzoyl chloride, and sodium hydroxide. Several substituted quinolines are converted to the corresponding cinnamaldehydes in low yield, but lepidine, 6-nitro-, 7-nitro-, and 3-acetamidoquinoline could not be cleaved successfully. Ultraviolet light promotes the decomposition of 2-benzamidocinnamaldehyde. The corresponding acid fails to undergo photodimerization, but a photodimer of carbostyril is reported.

Quinolinium salts (**1**) add a variety of anions to either the 2- or 4-position to give dihydro derivatives (**2** or **3**).[2,3] Among the compounds of type **2** are the Reissert compounds (**2**, R = acyl; A = CN) and the pseudobases (**2**, R = alkyl; A = OH).[4,5] The



1 **2** **3** **4**

pseudobases generally are assumed to exist in the isomeric open-chain form (**4**) in basic solution, but a recent spectroscopic study of the pseudobase from 1-cyanoquinolinium ion (**2**, R = CN; A = OH) showed no evidence for the aminoaldehyde.[6] By analogy with the pseudobases, the product of the reaction of quinoline with benzoyl chloride in aqueous sodium hydroxide has been represented by the isomeric pair **5** and **6**. We were interested in determining whether **5** or **6** best constituted the reaction product and offer spectroscopic evidence in support of structure **6**.



5 **6**

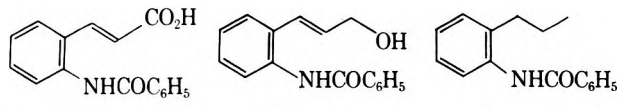
Reissert originally proposed that 1-benzoyl-1,2-dihydro-2-quinolinol (**5**) was formed from quinoline under Schotten–Baumann conditions, but he later revised the structure to 2-benzamidocinnamaldehyde (**6**) on the basis that the compound forms an oxime, and a phenylhydrazone, and is oxidized by silver oxide to the corresponding cinnamic acid (**7**).[4] However, the chemical behavior does not discriminate between **5** and **6** if a facile equilibrium exists between the two isomers.

In addition to the chemical evidence offered by Reissert, the ultraviolet and infrared spectra provide new information in support of the aldehyde **6**. 2-Benzamidocinnamaldehyde exhibits absorption maxima at 225, 256, and 285 mμ in the ultraviolet region, and the spectrum of this compound is similar in the positions of the maxima and the intensities of absorption with that for 2-benzamidocinnamic acid (**7**).[7] In the infrared spectrum the aldehyde **6** shows absorption bands at 3.05 (N–H), 3.67 (aldehyde C–H), 5.87 (conjugated aldehyde), and 6.05 μ (amide carbonyl group). These spectral features are in accord with **6** but not **5**.

The spectroscopic data suggest further that the aldehyde is isolated as the *trans* isomer although the ring cleavage might yield directly the *cis* form. The comparable intensities of the ultraviolet spectra of the aldehyde **6** and the known *trans* acid **7** may be interpreted as due to a similar stereochemistry.[8] The presence of a band at 10.19 μ in the infrared spectrum of **6** is ascribed to the out-of-plane hydrogen deformation vibration of a *trans* olefin; this band appears consistently in other unsaturated compounds of this series (*e.g.*, the acid **7** and the alcohol **8**). Moreover, there is no absorption in the region attributed to a *cis* double bond. The infrared spectrum of the crude aldehyde shows the same features as the recrystallized product, indicating that the *cis*-to-*trans* isomerization in an easy process and is probably facilitated both by conjugation and by the bulky *ortho* substituent. The predominant *trans* configuration for the aldehyde may in large part preclude a mobile equilibrium between **5** and **6**.

2-Benzamidocinnamaldehyde (**6**) is readily reduced to the cinnamyl alcohol (**8**) by sodium borohydride. The structure of the alcohol is confirmed by its elemental analysis and spectra. Although the aldehyde **6** was too insoluble in the available solvents to obtain the n.m.r. spectrum, the alcohol **8** was sufficiently soluble in deuteriochloroform. The *J*-value for the olefinic protons was found to be 17 c.p.s., consistent with a *trans* configuration.

Catalytic hydrogenation of either 2-benzamidocinnamaldehyde (**6**) or 2-benzamidocinnamyl alcohol (**8**) at moderate pressures gave a mixture of products that was difficult to separate. When **8** was reduced in the presence of acid, hydrogenolysis occurred to afford 2-(*n*-propyl)benzanilide (**9**).



7 **8** **9**

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

(2) W. Bradley and S. Jeffrey, *J. Chem. Soc.*, 2770 (1954).

(3) N. J. Leonard and R. L. Foster, *J. Am. Chem. Soc.*, **74**, 2110 (1952); A. Kaufmann and A. Albertini, *Ber.*, **42**, 3776 (1909).

(4) A. Reissert, *ibid.*, **38**, 1603, 3415 (1905).

(5)(a) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955); (b) N. Campbell, "Chemistry of the Carbon Compounds," Vol. IVA, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1957, p. 597.

(6) M. D. Johnson, *J. Chem. Soc.*, 283 (1962).

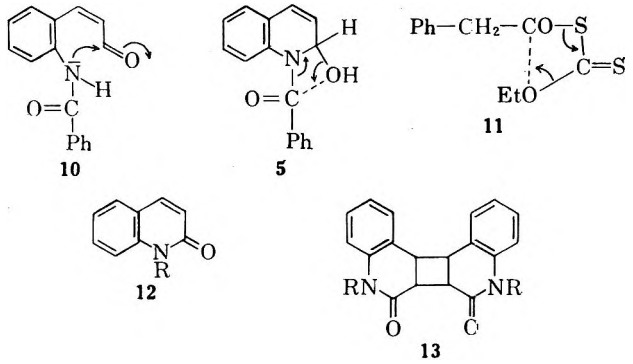
(7) The structure of the acid **7** is shown by acid hydrolysis to carbostyril[4] and by an independent synthesis from 2-aminocinnamic acid: see G. Heller, *Ber.*, **43**, 1918 (1910).

(8) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," E. Arnold, Ltd., London, 1954, p. 223.

Cleavage of the quinoline ring system by aroyl halides in alkaline solution has not been studied extensively although the reaction provides a convenient one-step route to polyfunctional compounds of possible synthetic utility. This ring opening is extended to several substituted quinolines to give the corresponding 2-benzamidocinnamaldehyde in low yield. The apparent disadvantage of the small yield is partially offset by the fact that the unchanged quinoline can be recovered. The compounds that were successfully converted to the aldehyde are 6-methyl-, 6-chloro-, 6-methoxy-, and 6-bromoquinoline. The same method applied to lepidine, 3-acetamido-, 6-nitro-, or 7-nitroquinoline failed to afford the cinnamaldehyde derivatives.

Photochemical Transformations.—Light-catalyzed dimerization of α,β-unsaturated carbonyl compounds is well-known although generally applied to acid derivatives and ketones.[9] Aldehydes have not been included in these studies. In the attempt to prepare a photodimer of 2-benzamidocinnamaldehyde (**6**), we observed that a benzene solution of **6** slowly turned yellow when exposed to ultraviolet radiation for several days. The solution contained no dimeric product, but quinoline was isolated from the reaction mixture. To test whether the degradation was truly light-catalyzed or occurred merely when a benzene solution of **6** was allowed to stand, parallel solutions of 2-benzamidocinnamaldehyde in dry benzene were allowed to reflux for 24 hr. One solution was exposed to ultraviolet light, and the second solution was kept in the dark. Only in the irradiated sample was quinoline formed and isolated as the picrate. The decomposition of 2-benzamidocinnamaldehyde was substantially complete as indicated by the failure of the light-exposed solution to afford the 2,4-dinitrophenylhydrazone of **6**. In the "dark" experiment the reverse was found. The aldehyde **6** was largely unchanged, and no quinoline could be detected.

One plausible hypothesis for the degradation of **6** to yield quinoline and benzoic acid would require a prior *trans*-to-*cis* isomerization to bring the aldehyde carbonyl into juxtaposition with the amide function. The *cis* isomer (**10**) could then form the tautomeric carbinol (**5**), and hydroxyl group transfer and formation of the heteroaromatic ring can be accounted for through a four-membered transition state in **5**. The proposed intermediate (**5**) is structurally analogous to one (**11**) suggested by Barton for thermal decomposition of S-acyl xanthates.[10]



10 **5** **11**

12 **13**

2-Benzamidocinnamic acid (**7**) could not be induced to dimerize when exposed to ultraviolet radiation, but, when 2-benzamidocinnamic acid is converted to carbostyril (**12**, R = H), the later formed a photodimer. In a parallel experiment, a solution of N-methyl-2-quinolone (**12**, R = CH_3) in benzene readily dimerized.[11] After the completion of this work Taylor and Paudler reported the preparation of a photodimer of N-methyl-2-quinolone and showed it to have structure **13**.[12] Our additional evidence for the saturated (cyclobutane) nature of the photodimers is obtained from the ultraviolet spectrum of the more soluble dimer (**13**, R = CH_3) that is very different from the starting N-methyl-2-quinolone.[13] The absorption band in the infrared spectra arising from the amide carbonyl vibration shows a consistent shift to shorter wave lengths on dimerization for the two carbostyrils (**13**) and coumarin (Table I).

TABLE I

INFRARED BAND FOR C=O STRETCHING VIBRATION

Compound	Monomer, μ	Dimer, μ
Coumarin	5.80	5.66
Carbostyril	6.00	5.81
N-Methylcarbostyril	6.03	5.95

Experimental

2-Benzamidocinnamaldehyde (**6**).—The reaction between quinoline (24 g.), benzoyl chloride (70 ml.), and 10% aqueous sodium hydroxide (200 ml.) by the method of Reissert gave the aldehyde (13% yield) that was recrystallized from acetonitrile as colorless feathery crystals, m.p. 185.5–186.0° (lit.[4] m.p. 186–187°); λ_{max}^{EtOH} 285 mμ (log ϵ 4.28), 256 (4.22), and 225 (4.29); λ_{min} 265 mμ (log ϵ 4.19), 243 (4.18); infrared spectrum (Nujol and perfluorocarbon mulls), 3.05, 3.67, 5.87, 6.05, and 10.19 μ.

The 2,4-dinitrophenylhydrazone of **6** was obtained as rust colored plates, m.p. 263–264°.

Anal. Calcd. for $C_{22}H_{17}N_5O_5$: C, 61.25; H, 3.98; N, 16.24. Found: C, 61.38; H, 3.67; N, 16.32.

A thiosemicarbazone of 2-benzamidocinnamaldehyde was prepared in acetic acid and isolated as yellow needles, m.p. 203–204°.

Anal. Calcd. for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.92; N, 17.27; S, 9.88. Found: C, 63.08; H, 5.28; N, 17.29; S, 10.06.

2-Benzamidocinnamic Acid.—Silver hydroxide oxidation of the aldehyde afforded the acid in high yield as reported. The acid was recrystallized from acetic acid as colorless needles, m.p. 263–265° (lit.[3] m.p. 261–262°); λ_{max}^{EtOH} 265 mμ (log ϵ 4.30), 227 (4.31); infrared spectrum (Nujol), 3.02, 5.87, 6.01, 6.10, 6.20 (sh), 8.13, 10.20, 10.45, 10.65 μ.

2-Benzamido-5-chlorocinnamaldehyde.—Adaptation of Reissert's method of ring cleavage to 6-chloroquinoline gave the corresponding aldehyde in 3% yield; the product was recrystallized from acetic acid as colorless needles, m.p. 190–191°.

Anal. Calcd. for $C_{16}H_{12}O_2NCl$: C, 67.25; H, 4.24; N, 4.90; Cl, 12.41. Found: C, 67.36; H, 4.10; N, 5.11; Cl, 12.46.

The 2,4-dinitrophenylhydrazone of 2-benzamido-5-chlorocinnamaldehyde was prepared in acetic acid and melted at 278–279° dec.

Anal. Calcd. for $C_{22}H_{16}O_5N_5Cl$: C, 56.75; H, 3.46; N, 15.03. Found: C, 56.77; H, 3.54; N, 15.23.

2-Benzamido-5-methylcinnamaldehyde.—From 23 g. of 6-methylquinoline, by the usual procedure, there was isolated 9.2 g. of aldehyde, m.p. 201–202°.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.06; H, 5.81; N, 5.09.

The 2,4-dinitrophenylhydrazone melted at 275–276°.

(9) A. Mustafa, *Chem. Rev.*, **51**, 1 (1952); P. DeMayo, "Advances in Organic Chemistry," Vol. 2, R. A. Raphael, E. C. Taylor and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N.Y., 1960, p. 367.

(10) D. H. R. Barton, M. V. George, and M. Tomoeda, *J. Chem. Soc.*, 1967 (1962).

(11) M. S. Barry, M. A. thesis, Fisk University, 1960.

(12) E. C. Taylor and W. W. Paudler, *Tetrahedron Letters*, **No. 25**, 1 (1960); Dr. Taylor has kindly compared a sample of our photodimer, prepared in homogeneous benzene solution, with his, from irradiation of an aqueous or cyclohexane suspension, and found them to be identical.

(13) H. Ley and H. Specker, *Ber.*, **72**, 192 (1939).

Anal. Calcd. for $C_{23}H_{19}N_5O_5$: C, 62.02; H, 4.30; N, 15.72. Found: C, 61.95; H, 4.34; N, 15.55.

5-Bromo-2-benzoylaminocinnamaldehyde.—From 5 g. of 6-bromoquinoline, by the usual method, a crude oily product was obtained that was recrystallized from acetonitrile as colorless crystals, 0.3 g., m.p. 191–193°.

Anal. Calcd. for $C_{16}H_{12}NO_2Br$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.46; H, 3.70; N, 4.11.

5-Methoxy-2-benzamidocinnamaldehyde.—The reaction between 6-methoxyquinoline (25 g.), benzoyl chloride (50 ml.), and cold 10% sodium hydroxide (220 ml.) gave a difficultly separable oil. After careful decantation of the aqueous layer the oil was washed twice with 10% hydrochloric acid, then with water, and redissolved in methanol containing a small quantity of acetonitrile. The aldehyde slowly separated as pale yellow needles, 3.5 g., m.p. 197–198° after several recrystallizations.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.56; H, 5.38; N, 4.98. Found: C, 71.90; H, 5.20; N, 5.32.

The 2,4-dinitrophenylhydrazone, m.p. 269–271°, was prepared in acetic acid.

Anal. Calcd. for $C_{23}H_{19}N_5O_6$: C, 59.86; H, 4.15; N, 15.18. Found: C, 60.12; H, 3.89; N, 15.16.

2-Benzamidocinnamyl Alcohol.—To 2.0 g. of 2-benzamidocinnamaldehyde suspended in 40 ml. of hot ethanol was added all at once 1.0 g. of sodium borohydride. A yellow color quickly developed and soon faded. After 10 min. water was added until the clear solution became turbid, the mixture was heated to boiling for 2 min. and allowed to cool. The mixture deposited glistening colorless crystals, 1.8 g., m.p. 141–143°. Recrystallization from aqueous ethanol raised the m.p. to 144–145°; λ_{max} 234 mμ (ϵ 22,800); infrared spectrum (Nujol), 3.07, 6.04, 10.35 μ.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 76.07; H, 6.30; N, 5.37.

Hydrogenolysis of 2-Benzamidocinnamyl Alcohol to 2-(*n*-Propyl)benzanilide.—A solution of 2.2 g. of 2-benzamidocinnamyl alcohol in 125 ml. of methanol was added to a suspension of prereduced platinum from 0.1 g. of Adam's catalyst in 50 ml. of methanol containing 1 ml. of concentrated hydrochloric acid. The initial pressure of hydrogen was 45 p.s.i. and after 0.75 hr. the uptake of hydrogen virtually ceased. The catalyst was removed by filtration, and the filtrate was concentrated to one-third of the original volume under reduced pressure. The solution was heated to boiling, and water was slowly added to the point of turbidity. The solution was covered and allowed to cool slowly, affording 1.1 g. of colorless needles, m.p. 114–115°; ultraviolet spectrum inflections at ϵ_{225} 12,200 and ϵ_{270} 4400; infrared spectrum (KBr), 3.27, 3.39 (asym. CH_3 str.), 3.49 (asym. CH_2 str., sym. CH_3 str.), 3.55 (sym. CH_2 str.), 6.15, 6.70, 7.30 μ.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.61, 80.35; H, 7.35, 7.29; N, 5.60.

Photochemical Degradation of 2-Benzamidocinnamaldehyde.—A solution of 0.6 g. of 2-benzamidocinnamaldehyde in 300 ml. of dry benzene was divided into two equal portions. The first solution (A) was refluxed for 24 hr. in a 500-ml. Pyrex conical flask and continuously exposed to ultraviolet radiation from a Hanovia utility model lamp. The second portion (B) was refluxed for the same period in the dark. At the end of this time solution A was colored faintly yellow; B was colorless. After cooling, a 50-ml. aliquot of A was treated with 10 ml. of a saturated solution of picric acid. Crystals began to form after 5 min. These were collected at the end of 2 hr. and identified by melting point and mixture melting point determinations as quinoline picrate (0.08 g., 57% yield, or 100% compared with a standard solution of quinoline in benzene).

A second 50-ml. portion of A was treated with 10 ml. of solution of 2,4-dinitrophenylhydrazine in hydrochloric acid–ethanol. No precipitate formed during a 2-hr. period.

The final 50 ml. of A was extracted with three 20-ml. portions of 5% potassium hydroxide and the aqueous layer acidified with concentrated hydrochloric acid and re-extracted with ether. Evaporation of the ether and recrystallization of the residue from water gave a few crystals identified as benzoic acid by infrared spectrum and melting point.

Solution B was similarly treated. A 50-ml. portion gave no precipitate with 10 ml. of saturated picric acid solution after 2 hr. The second 50-ml. portion of B when mixed with the 2,4-dinitrophenylhydrazine reagent rapidly formed a red precipitate, 0.09 g. [52%, or 90% based on comparison with a standard benzene solution (50 ml.) containing 0.10 g. of 2-benzanmidocinnamaldehyde], which was identified as 2-benzamidocinnamaldehyde-2,4-dinitrophenylhydrazone.

Irradiation of N-methyl-2-quinolone.[11]—A solution of 3.0 g. of N-methyl-2-quinolone in benzene was irradiated under an ultraviolet lamp for 15 days. During this period a solid precipitated from the solution. The precipitate, 1.7 g., was recrystallized from ethanol–benzene solution as colorless crystals, m.p. 213–214° (lit.[12] m.p. 211.5–212°); λ_{max}^{EtOH} 260 mμ (log 3.83), shoulder at 225 (4.15); λ_{min} 240 mμ (log ϵ 3.56); infrared spectrum (Nujol), 5.90, 7.70, 8.75, 11.80, 13.15 μ.

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.46; H, 5.69; N, 8.80; mol. wt., 322. Found: C, 75.76; H, 5.80; N, 9.09; mol. wt., 314.

Photodimerization of Carbostyril.—A solution of 5 g. of carbostyril in benzene was irradiated by an ultraviolet lamp for 2 months. A fine white precipitate slowly separated from the solution, and 2 g. of a very insoluble solid, m.p. 271–273°, was collected. Recrystallization of this product from a large volume of acetic acid gave first a tan amorphous product that did not melt below 320°. The main recrystallized fraction was a colorless microcrystalline solid, m.p. 274–275°.

Anal. Calcd. for C_9H_7NO: C, 74.56; H, 4.86. Found: C, 74.69; H, 5.06.

Attempted Photodimerizations A. 2-Benzamidocinnamic Acid.—Five grams of powdered 2-benzamidocinnamic acid was exposed for 3 weeks to ultraviolet radiation, and the sample was stirred daily to ensure complete exposure. At the end of this period the crude material and a recrystallized portion had the same melting point and mixture melting point as the starting acid.

A sample of 1.0 g. of acid was suspended in benzene and irradiated for 2 weeks. The recrystallized product proved to be unreacted starting material.

B. Isocarbostyril.—A solution of 1.0 g. of isocarbostyril in benzene was exposed to ultraviolet radiation for 2 months. The solution was concentrated and the solid obtained was unreacted isocarbostyril by melting point and mixture melting point determinations.

Attempted Cleavage of Some Quinoline Derivatives.—When the bases lepidine, 6-nitroquinoline, 7-nitroquinoline, or 3-acetamidoquinoline were allowed to react with benzoyl chloride in aqueous sodium hydroxide, no corresponding cinnamaldehyde could be isolated. In practically all cases benzoic anhydride was obtained in high yield. With lepidine, a high-melting amorphous solid was obtained that was not studied further.

Synthesis of Unsymmetrically Substituted Malonamidines

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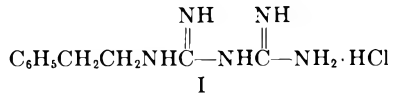
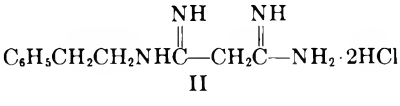
Unsymmetrically substituted malonamidines have been synthesized by a stepwise route which should be of general applicability. Ethyl cyanoacetimidate hydrochloride (VI) derived from malononitrile formed 2-cyano-N-phenethylacetamidine hydrochloride (VII) when treated with phenethylamine. Transformation of VII to ethyl N-phenethylamidinoacetimidate dihydrochloride (IX) was followed by reaction with ammonia to yield N-phenethylmalonamidine dihydrochloride (II). The parallel dependence of the ultraviolet spectra of biguanides and malonamidines on pH is discussed.

Phenethylbiguanide hydrochloride (I) is a clinically effective agent for the oral treatment of some types of diabetes.[1] A search for new, related systems has directed us to the synthesis of an isosteric compound, phenethylmalonamidine dihydrochloride (II). Al-



I



II

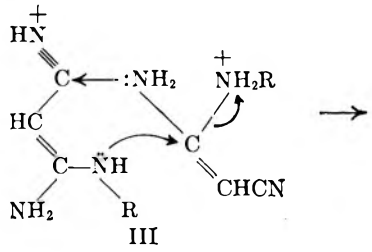
though II failed to display hypoglycemic activity, the stepwise path employed for its preparation should be of interest as a general synthetic route to unsymmetrically substituted malonamidines.

Malonamidines are a little studied class of compounds; only malonamidine[2] itself and several N,N'' symmetrically substituted derivatives[3] have been described in the literature.

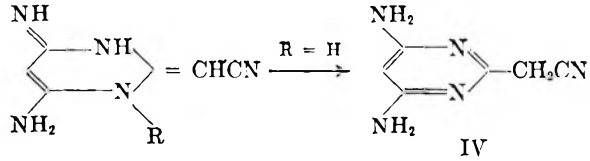
Our initial experiments directed toward the synthesis of unsymmetrical malonamidines were predicated upon the reaction of diethyl malonimidate dihydrochloride[2] with limited amounts of the requisite amines. Under these conditions, however, only symmetrically substituted products were isolated.

Attention was next directed toward a stepwise sequence by way of a substituted cyanoacetamidine hydrochloride. Although McElvain and Tate[4] had shown that cyanoacetamidine hydrochloride (III, R = H) spontaneously self-condenses to a pyrimidine (IV), the introduction of an N-alkyl substituent would prevent the final aromatization reaction and might, therefore, inhibit self-condensation[5] (col. 2).

Malononitrile (V) was converted to ethyl cyanoacetimidate hydrochloride (VI) as described by Cook, *et al.*[6] The preparation of cyano-N-phenethylacetamidine hydrochloride (VII) from VI proved to be extremely sensitive to experimental conditions. When phenethylamine was allowed to react with VI at room temperature in ethanol, ethyl cyano-N-phenethylacetimidate (VIII) was obtained. If heat was employed during solvent removal, variable amounts of the



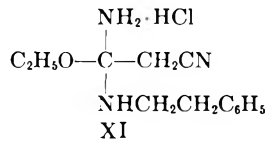
III



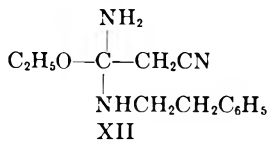
IV

desired amidine VII were isolated. When commerical sodium methoxide (one equivalent) was added to the reaction mixture, VII was sometimes isolated, but a reproducible procedure could not be developed (p. 309).

A more satisfactory method was developed from the assumption that under acidic conditions the initially formed amine–imidate adduct XI would lose ammonia



XI



XII

or phenethylamine more rapidly than ethanol to yield the starting imidate VI or the new imidate VIII. Under basic conditions, however, the uncharged adduct XII might be expected to eliminate ethoxide rather than the more basic amide anion, and lead to the formation of the amidine VII.[7] Based on these considerations, the imidate hydrochloride VI and phenethylamine were allowed to react in the presence of one equivalent of triethylamine in dioxane. The use of ethanol as the solvent was avoided to overcome a possible mass action effect. Under these conditions, the amidine VII was produced consistently.

The reaction of VII with anhydrous hydrogen chloride and one equivalent of ethanol in ether provided

(1) G. Ungar, L. Freedman, and S. L. Shapiro, *Proc. Soc. Exptl. Biol. Med.*, **95**, 190 (1957).

(2) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 574 (1943).

(3) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **80**, 2185 (1958); P. Oxley and W. F. Short, *J. Chem. Soc.*, 449 (1949); E. Richter and E. C. Taylor, *J. Am. Chem. Soc.*, **78**, 5848 (1956).

(4) S. M. McElvain and B. E. Tate, *ibid.*, **73**, 2761 (1961).

(5) We wish to thank Dr. E. Cohen for bringing this point to our attention.

(6) A. H. Cook, G. Harris, and A. L. Levy, *J. Chem. Soc.*, 3227 (1949).

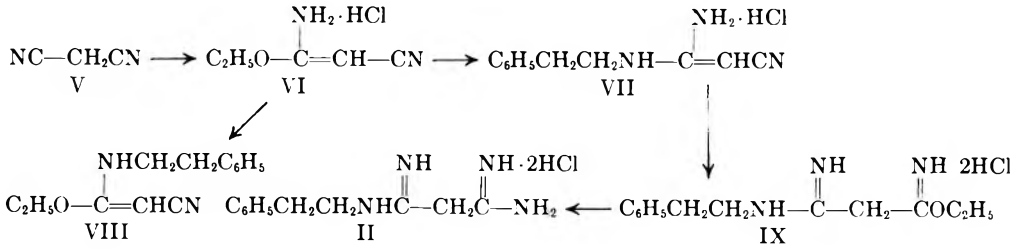
(7) A similar argument has been proposed[8] to explain the results of tracer experiments on the mechanism of amide hydrolysis.[9] Under basic conditions, the original O^{18} label of the amide was lost to the solvent. This was interpreted as evidence for the collapse of a "tetrahedral intermediate" to starting amide (hence, preference for loss of OH^- rather than NH_2^-). During acidic hydrolysis, exchange did not occur (hence, NH_3 elimination is faster than H_2O loss).

(8) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., 1962, p. 139.

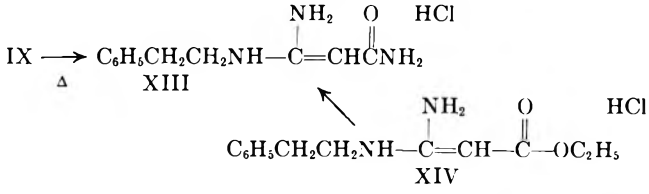
(9) M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955).

(10) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(11) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).



ethyl N-phenethylamidinoacetimidate dihydrochloride (IX). The structure of IX was confirmed by pyrolysis[10] to N-phenethylamidinoacetamide hydrochloride (XIII). The identity of XIII was established by independent synthesis. Thus, ethyl ethoxycarbonylacetimidate hydrochloride[11] and phenethylamine gave



ethyl N-phenethylamidinoacetate hydrochloride (XIV), which yielded XIII by the action of ammonia.

The conversion of IX to N-phenethylmalonamidine dihydrochloride (II) with ammonia proceeded smoothly. Similarly, methylamine gave N-methyl-N''-phenethylmalonamidine dihydrochloride.

The ultraviolet spectra of phenethylbiguanide hydrochloride (I) and phenethylmalonamidine dihydrochloride (II) exhibit a strikingly parallel pH dependence (Table I). In strongly acidic media, the spectra of both compounds display only end absorption in addition to weak aromatic bands. As the acidity decreases, maxima develop. In strongly basic media, these peaks disappear, and end absorption is again observed.[12]

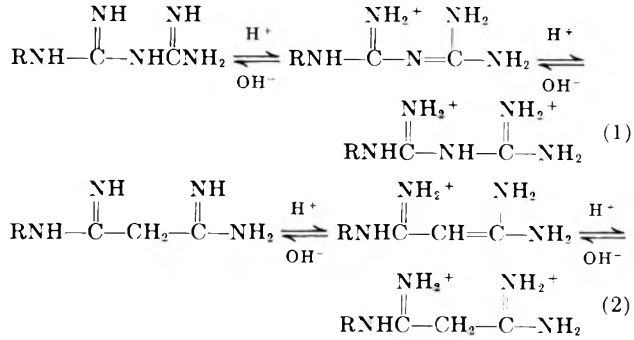
TABLE I

ULTRAVIOLET MAXIMA FOR PHENETHYLBIGUANIDE AND PHENETHYLMALONAMIDINE

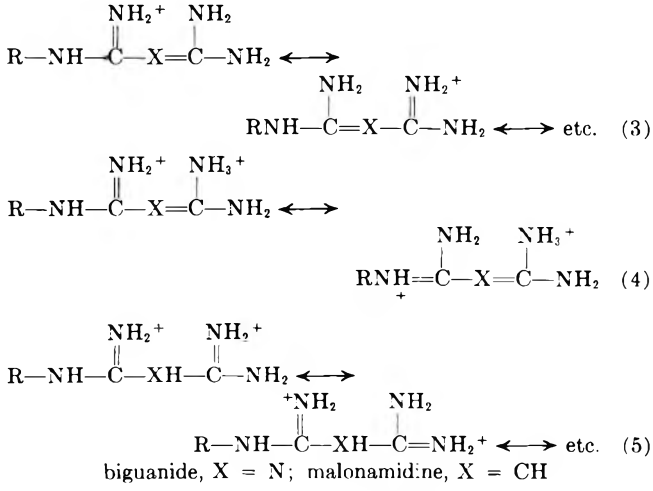
Solvent[a]	λ_{max}, mμ (ε)	
	I	II
0.01 *N* HCl	End absorption	End absorption
0.001 *N* HCl	237 (sh)	End absorption
Solvent (neat)	236 (18,100)	288 (2490)
0.0001 *N* NH_3	236 (18,100)	288 (25,500)
0.1 *N* NH_3	236 (17,500)	288 (17,900)
1 *N* NH_3	236 (15,600)	288 (9140)
0.01 *N* *i*-PrONa	End absorption, 235 (sh)	End absorption

[a] Spectra were determined on $10^{-4}M$ solutions of I and II. Solutions were prepared with standard anhydrous acid or base in isopropyl alcohol.

These observations are best interpreted by equilibria between dication, monocation, and free base having the structures given in eq. 1 and 2.[13] The conjugated chromophores of the monocations are destroyed by protonation on the central atoms (N in I, C in II) to yield the nonconjugated dications. Unexpectedly, the free bases appear to exist largely as the nonconjugated tautomers, although the appearance of a weak shoulder in the spectrum of phenethylbiguanide base suggests the presence of a small amount of conjugated tautomer at equilibrium.



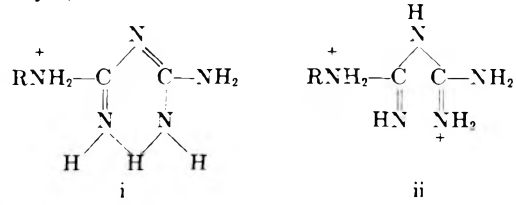
In classical terms, the preference for the conjugated systems of the monocations is clear; the positive charge can be distributed over the four terminal nitrogen atoms in both the biguanide and the malonamidine (eq. 3). On the other hand, in the conjugated forms of the dications, only one positive charge can be stabilized by delocalization (eq. 4), while the nonconjugated structures for the dications (eq. 5) permit distribution of both positive charges. Therefore, the nonconjugated tautomers should be favored. In the free bases, resonance stabilization must be provided by contributors



biguanide, X = N; malonamidine, X = CH

(12) The pH dependent spectral changes are all reversible; the possibility of destruction of the compounds under basic conditions is, therefore, precluded. When the 0.01 *N* *i*-PrONa solution of phenethylbiguanide hydrochloride was acidified, base line instability, probably caused by accumulation of sodium chloride, rendered the spectrum unreliable. However, reversibility was confirmed by spectra determined on the free base (see Experimental).

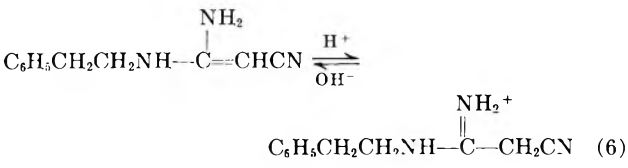
(13) The structures included in the equilibria are preferred over those advanced by Shapiro, *et al.*,[14] for the monocation (i) and the dication (ii) of phenethylbiguanide.



(14) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 2220 (1959).

in which charge separation develops and is, therefore, probably less important than in the protonated forms. This permits no ready prediction for the position of equilibrium of the biguanide free bases, and indeed the energy difference between the two forms is probably quite small. However, the malonamidine free bases have the same forces favoring the "nonenolized" forms as obtain in simple enol–ketone equilibria: namely, the electron promotion energy of enolization, which is apparently sufficiently high to counteract the additional delocalization in the "enol" form.[15]

The ultraviolet spectrum of the cyanoacetamidine hydrochloride IX is also pH dependent. In acidic medium only end absorption appears; in basic solution a maximum develops. These observations are accommodated by equilibrium 6, in which the conjugated system of the base is destroyed by carbon protonation.



(6)

Experimental[17]

2-Cyano-N-phenethylacetamidine Hydrochloride (VII). A.—To a solution of 0.57 g. (0.01 mole) of sodium methoxide in 20 ml. of anhydrous ethanol was added with stirring 1.5 g. (0.01 mole) of ethyl cyanoacetimidate hydrochloride.[6] The mixture was filtered, and 1.2 g. (0.01 mole) of phenethylamine was added to the filtrate. The solution was stirred at room temperature for 30 min. and was concentrated under reduced pressure to a yellow liquid. Acidification with a benzene–hydrogen chloride solution and concentration under reduced pressure gave a yellow gum, which formed a colorless solid upon trituration with ether. Recrystallization from ethanol–ether and then from isopropyl alcohol left 0.62 g. (28%) of colorless microcrystals, m.p. 155–156°. These results were not consistently reproducible. An analytical sample, m.p. 155–156°, was obtained after an additional recrystallization from isopropyl alcohol.

The ultraviolet spectrum exhibits λ_{max} 258 mμ (ε 10,900) in 0.1 *N* sodium hydroxide, end absorption in water.

Anal. Calcd. for $C_{11}H_{13}N_3 \cdot HCl$: C, 59.06; H, 6.27; N, 18.79; Cl, 15.88. Found: C, 59.15; H, 6.17; N, 19.02; Cl, 15.67.

B.—A solution of 6.0 g. (0.04 mole) of ethyl cyanoacetimidate hydrochloride and 4.8 g. (0.04 mole) of phenethylamine in 80 ml. of ethanol was stirred at room temperature for 30 min. and then concentrated under reduced pressure in a 60° bath to a tacky tan solid. Two recrystallizations from isopropyl alcohol afforded 2.2 g. (25%) of colorless crystals, m.p. 155–156°. The melting point was not depressed upon admixture with a sample of 2-cyano-N-phenethylacetamidine hydrochloride described before. These results were not consistently reproducible.

C.—To a solution of 12 g. (0.10 mole) of phenethylamine and 11 g. (0.11 mole) of triethylamine in 200 ml. of dioxane was added with stirring 15 g. (0.10 mole) of ethyl cyanoacetimidate hydrochloride. After 2 hr. at room temperature, the mixture was filtered. The filtrate was concentrated under reduced pressure to a viscous brown liquid, which was suspended in chloroform and acidified with a benzene–hydrogen chloride solution. The supernatant liquid was decanted. Two recrystallizations of the tacky solid residue afforded 4.9 g. (22%) of colorless crystals, m.p. 155–156.5°. The melting point was not depressed upon admixture with authentic 2-cyano-N-phenethylacetamidine hydrochloride. Under these conditions, yields of 20 to 25% were obtained consistently.

Ethyl N-Phenethylamidinoacetimidate Dihydrochloride (IX).—A mixture of 2.05 g. (9.2 mmoles) of 2-cyano-N-phenethylacetamidine hydrochloride, 0.44 g. (9.5 mmoles) of dry ethanol, and 200 ml. of dry ether was saturated with anhydrous hydrogen chloride at 0° with vigorous stirring. The mixture was stirred at room temperature for 20 hr., and the white solid was collected. The product, colorless crystals, m.p. 135° (dec., gas evolution followed by resolidification) amounted to 2.3 g. (81%).

The ultraviolet spectrum exhibits λ_{max} 281 mμ (ε 7700) in methanol solution.

Anal. Calcd. for $C_{13}H_{19}N_3O \cdot 2HCl$: C, 50.98; H, 6.86; N, 13.73; Cl, 23.20. Found: C, 50.68; H, 6.99; N, 14.11; Cl, 23.07.

N-Phenethylmalonamidine Dihydrochloride (II).—A mixture of 1.0 g. (3.3 mmoles) of ethyl N-phenethylamidinoacetimidate dihydrochloride and 100 ml. of isopropyl alcohol containing 3.3 mmoles of ammonia was stirred at room temperature for 2 hr., and the solvent was removed under reduced pressure. Recrystallization of the white solid residue from isopropyl alcohol afforded 0.40 g. (44%) of colorless crystals, m.p. 228–230° dec. Three additional recrystallizations gave colorless prisms, m.p. 231–231.5° dec.

Anal. Calcd. for $C_{11}H_{16}N_4 \cdot 2HCl$: C, 47.65; H, 6.50; N, 20.22; Cl, 25.63. Found: C, 47.48; H, 6.55; N, 19.94; Cl, 25.64.

N-Methyl-N''-phenethylmalonamidine Dihydrochloride.—A solution of 2.0 g. (6.5 mmoles) of ethyl N-phenethylamidinoacetimidate dihydrochloride in 200 ml. of isopropyl alcohol containing 6.5 mmoles of methylamine was stirred at room temperature for 2 hr. The precipitate which separated amounted to 1.3 g. (68%) of colorless plates, m.p. 284–286° dec. Recrystallization from methanol provided the analytical sample, m.p. 284–286° dec.

Anal. Calcd. for $C_{12}H_{18}N_4 \cdot 2HCl$: C, 49.48; H, 6.87; N, 19.24; Cl, 24.00. Found: C, 49.48; H, 7.05; N, 18.95; Cl, 24.53.

Ethyl 2-Cyano-N-phenethylacetimidate (VIII).—To a solution of 4.8 g. (0.04 mole) of phenethylamine in 80 ml. of anhydrous ethanol was added 6.0 g. (0.04 mole) of ethyl cyanoacetimidate hydrochloride.[6] The mixture was stirred at room temperature for 30 min. and then concentrated at room temperature under reduced pressure to a white solid. Recrystallization from isopropyl alcohol afforded 4.5 g. (51%) of colorless crystals, m.p. 70–71°. Two recrystallizations from ethanol provided the analytical sample, m.p. 70–72°.

The ultraviolet spectrum exhibits λ_{max} 256 mμ (ε 22,400) in methanol.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95; OC_2H_5, 20.80. Found: C, 72.18; H, 7.33; N, 13.16; OC_2H_5, 19.90.

Pyrolysis of Ethyl N-Phenethylamidinoacetimidate Dihydrochloride.—Ethyl N-phenethylamidinoacetimidate dihydrochloride, 313 mg. (1.0 mmole), was heated at 150–160° for 15 min. Crystallization of the resulting yellow glass from isopropyl alcohol yielded 89 mg. (37%) of colorless needles, m.p. 166–168°. The melting point was not depressed upon admixture with a sample of N-phenethylamidinoacetamide hydrochloride (XIII) prepared as described later.

Ethyl N-Phenethylamidinoacetate Hydrochloride (XIV).—A mixture of 19.6 g. (0.1 mole) of ethyl ethoxycarbonylacetimidate hydrochloride,[11] λ_{max} 260 mμ (ε 10,000) in 0.1 *N* methanolic sodium methoxide, in 75 ml. of anhydrous ethanol was treated with 5.4 g. (0.095 mole) of sodium methoxide in 25 ml. of ethanol, and the resulting mixture was filtered. To the filtrate was added 12.2 g. (0.1 mole) of phenethylamine. The solution was stirred at room temperature for 3 hr., acidified with ethanolic hydrogen chloride, and concentrated under reduced pressure to a tacky white solid. Two recrystallizations from ethanol afforded 5.2 g.

(15) A molecular orbital explanation for the sites of protonation of biguanides and malonamidines was considered. LCAO-MO calculations for each possible tautomer of the free bases, monocations, and dications were developed, by means of Streitweiser's suggested parameters[16] modified for the specific properties of the atoms in the molecules. The calculated energies were then adjusted to take into account the electron promotion energies involved in "enolization" of the malonamidine derivatives (estimated from the keto–enol equilibrium constant of acetone and LCAO-MO calculations on a simple enamine). While the calculated energies predict qualitatively the positions of the protons in malonamidine, biguanide, and the dications of malonamidine and biguanide, they are ambiguous for biguanide monocation and misleading with respect to malonamidine monocation. The failure to predict the protonation positions in the monocations probably results from the failure of the calculations to take adequate account of stabilization due to delocalization of the positive charge.

(16) A. Streitweiser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 135.

(17) Melting points were taken in capillary tubes in a Hershberg apparatus and are uncorrected. Ultraviolet spectra were determined with a Cary 11 spectrophotometer.

(19%) of colorless prisms, m.p. 129.5–132°. Two additional recrystallizations from isopropyl alcohol gave the analytical sample, m.p. 134.5–135.5°.

The ultraviolet spectrum exhibits λ_{max} 271 mμ (ε 41,000) in 0.1 *N* methanolic sodium methoxide.

Anal. Calcd. for $C_{13}H_{18}N_2O_2 \cdot HCl$: C, 57.67; H, 7.02; N, 10.35; Cl, 13.12. Found: C, 57.64; H, 7.18; N, 10.15; Cl, 13.30.

N-Phenethylamidinoacetamide Hydrochloride (XIII).—A solution of 1.4 g. (5.0 mmoles) of ethyl N-phenethylamidinoacetate hydrochloride in 75 ml. of saturated ammoniacal ethanol was stirred at room temperature for 4 days and then concentrated under reduced pressure to a viscous oil, which slowly crystallized. Recrystallization from isopropyl alcohol afforded 0.6 g. (50%) of colorless needles, m.p. 168.5–169.5°. An additional recrystallization gave the analytical sample, m.p. 169.5–170.5°.

The ultraviolet spectrum exhibits λ_{max} 276 mμ (ε 10,000) in 0.1 *N* methanolic sodium methoxide.

Anal. Calcd. for $C_{11}H_{15}N_3O \cdot HCl$: C, 54.66; H, 6.63; N, 17.39; Cl, 14.70. Found: C, 54.57; H, 6.73; N, 17.38; Cl, 14.57.

N,N''-Diphenethylmalonamidine Dihydrochloride.—To a solution of 0.25 g. (0.011 g.-atom) of sodium in 15 ml. of anhydrous ethanol was added 2.5 g. (0.011 mole) of diethylmalonimidate dihydrochloride[2] and 1.3 g. (0.011 mole) of phenethylamine. The mixture was heated under reflux for 2.5 hr. and filtered. The filtrate was acidified with concentrated hydrochloric acid and concentrated under reduced pressure to an oily yellow solid. Recrystallization from water afforded 1.0 g. (48%) of colorless plates, m.p. 311–313° dec.

Anal. Calcd. for $C_{19}H_{24}N_4 \cdot 2HCl$: C, 59.84; H, 6.82; N, 14.70; Cl, 18.64. Found: C, 59.70; H, 6.93; N, 14.43; Cl, 18.47.

N,N',N'',N'''-Tetraphenethylmalonamidine Dihydrochloride and Hydrochloride.—A solution of 4.6 g. (0.02 mole) of diethylmalonimidate dihydrochloride,[2] 12.0 g. (0.099 mole) of phenethylamine, and 0.099 mole of ammonia in 300 ml. of anhydrous ethanol was stirred at room temperature for 5 days. The solution was concentrated under reduced pressure to about 75 ml., and the white precipitate (5.3 g.) which separated was collected. This solid was partially dissolved in hot ethanol. The insoluble colorless crystals, m.p. 308–311° dec., amounted to 3.3 g. (43%). The melting point was not depressed upon admixture with authentic N,N''-diphenethylmalonamidine dihydrochloride. The ethanol-soluble fraction was recovered by concentration of the solution to dryness. Recrystallization of the solid residue from acetone, followed by recrystallization from isopropyl alcohol, afforded 0.05 g. (0.4%) of N,N',N'',N'''-tetraphenethylmalonamidine dihydrochloride as colorless needles, m.p. 193–194°.

Anal. Calcd. for $C_{35}H_{40}N_4 \cdot 2HCl$: C, 71.31; H, 7.13; N, 9.51; Cl, 12.05. Found: C, 71.16; H, 7.31; N, 9.38; Cl, 12.12.

Concentration of the remainder of the original reaction solution under reduced pressure left oily crystals. Two recrystallizations from isopropyl alcohol afforded 1.6 g. (14%) of N,N',N'',N'''-tetraphenethylmalonamidine hydrochloride as long colorless prisms, m.p. 155–156°. Two more recrystallizations gave the analytical sample, m.p. 157.5–158°.

Anal. Calcd. for $C_{35}H_{40}N_4 \cdot HCl$: C, 76.02; H, 7.42; N, 10.14; Cl, 6.43. Found: C, 75.71; H, 7.53; N, 10.15; Cl, 6.49.

The ultraviolet spectrum of N,N',N'',N'''-tetraphenethylmalonamidine hydrochloride exhibits λ_{max}^{MeOH} 308 mμ (ε 21,200).

The monohydrochloride was converted to the dihydrochloride with ethanolic hydrogen chloride.

Phenethylbiguanide.—A solution of 2.30 g. (0.10 g.-atom) of sodium in 500 ml. of anhydrous ethanol was prepared, and 24.15 g. (0.10 mole) of phenethylbiguanide hydrochloride was added at room temperature with stirring. After 1 hr., the mixture was filtered, and the filtrate was concentrated to a colorless oil which crystallized on standing. Two recrystallizations from ethanol and three from acetonitrile afforded colorless prisms, m.p. 94–95°.

Anal. Calcd. for $C_{10}H_{15}N_5$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.21; H, 7.22; N, 34.07.

The ultraviolet spectrum exhibits λ_{max} 236 mμ (ε 17,100) in 10^{-6} *N* methanolic hydrochloric acid, 233 (ε 1410) in water, 235 μ (sh) in 0.04 *N* methanolic sodium methoxide, 232 (sh) in acetonitrile or dioxane.

Acknowledgment.—We wish to thank Mr. L. M. Brancone and associates for the analytical data and Mr. W. Fulmor and associates for ultraviolet spectra

Synthesis of Azoxy Compounds from Nitrosohydroxylamine Tosylates[1]

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A convenient synthesis of azoxy compounds from organonitrosohydroxylamine tosylates, R—N(→O)=N—OTs, and Grignard reagents is outlined. Displacement on sulfur, with the expulsion of nitrosohydroxylamine anion and the formation of sulfones, predominated when the nitrosohydroxylamine tosylates were exposed to nucleophiles such as phenyllithium, alkoxides, and phenoxides. The azoxy ether structure, R—N(→O)=N—OR', is assigned to the stable alkylation products of organonitrosohydroxylamines.

Unsymmetrical azoxy compounds usually are obtained by oxidation of an unsymmetrical azo compound,[2,3] by condensation of a nitroso compound and an hydroxylamine[4,5] or by selective substitution on an aromatic azoxy compound.[5,6] The first two methods often give a mixture of isomers.

More selective methods, such as the oxidation of indazole oxides[7] or the reaction of Grignard reagents, and the stable alkylation products of organonitrosohydroxylamines[8] also are reported.

An attractive approach to a general synthesis of azoxy compounds would be one where the R—N(→O)=N— group possessed a substituent capable of easy displace-

(1) This research was supported by the Advanced Research Projects Agency under Army Ordnance Contract No. DA-01-021 ORD-11909.

(2) See C.-S. Hahn and H. H. Jaffé [*J. Am. Chem. Soc.*, **84**, 949 (1962)] for references and a table of properties of substituted azoxybenzenes.

(3) Oxidation of hydrazones has produced many azoxy compounds: B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **27**, 413 (1962).

(4) Y. Ogata, M. Tsuchida, and Y. Takagi, *J. Am. Chem. Soc.*, **79**, 3397 (1957).

(5) W. J. Hickinbottom, "Chemistry of Carbon Compounds," Vol. IIIA, E. H. Rodd, Elsevier Publishing Co., New York, N. Y., 1954, p. 314.

(6) J. J. Courtney, L. E. Geipel, and R. L. Shriner, *Proc. Iowa Acad. Sci.*, **62**, 264 (1955).

(7) L. C. Behr, *J. Am. Chem. Soc.*, **76**, 3672 (1954); L. C. Behr, E. G. Alley, and O. Levand, *J. Org. Chem.*, **27**, 65 (1962).

(8) M. V. George, R. W. Kierstead, and G. F. Wright, *Can. J. Chem.*, **37**, 679 (1959).

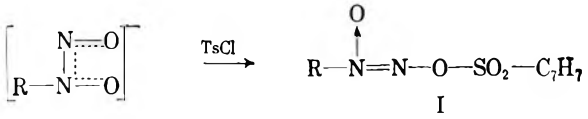
TABLE I

N-SUBSTITUTED N′-TOSYLOXYDIIMIDE N-OXIDES, R—N(→O)=N—OTs

		Analysis, %					
		Calcd			Found		
R	M.p., °C.	C	H	N	C	H	N
Phenyl	136[a]	53.41	4.14	9.59	53.66	4.43	9.44
p-Chlorophenyl	144[a]	47.78	3.39	8.57	47.25	3.24	8.67
p-Bromophenyl	150[a]	42.06	2.99	7.55	42.09	3.00	7.65
p-Tolyl	126[a]	54.89	4.61	9.15	54.95	4.62	8.98
Benzyl	92	54.89	4.61	9.15	54.70	4.74	8.94
Butyl	Oil	48.51	5.92	10.29	48.71	5.98	12.01
Methyl	86	41.73	4.38	12.17	41.76	4.35	11.92

[a] The melting of these samples usually took place with vigorous decomposition, and the temperature of this decomposition was dependent on the rate of heating.

ment. In order to test this preparation of azoxy compounds and to obtain more information on the alkylation products of nitrosohydroxylamines,[8] several *p*-toluenesulfonyl derivatives of organonitrosohydroxylamines were prepared. These tosylates, which are assigned the N-substituted N′-tosyloxydiimide N-oxide[9,10] structure (I) on the basis of the experiments to be outlined, are listed in Table I.



The aromatic nitrosohydroxylamine tosylates were prepared *via* tosyl chloride in aqueous bicarbonate solution, in acetone–aqueous sodium hydroxide mixtures, or in benzene solution with a preformed salt of the nitrosohydroxylamine; the same product was obtained in each case.

To prepare the tosylates of methyl and butyl nitrosohydroxylamine, the appropriate Grignard reagents were allowed to react with nitric oxide,[11] and the basic aqueous extract of this reaction mixture, containing the alkylnitrosohydroxylamine anion, was treated with tosyl chloride in the usual fashion. Details are given in the Experimental section.

However one views the multifunctional azoxy sulfonates (I), several potentially reactive sites are present. It was of some interest, then, to observe the center of nucleophilic attack, nitrogen or sulfur, in this ambient electrophile.[12]

Conversion of the aromatic nitrosohydroxylamine tosylates to azoxy compounds by means of Grignard reagents took place readily; there was no indication that sulfones, resulting from attack on sulfur and expulsion of the nitrosohydroxylamine anion, were formed. Tables II and III summarize the results of these reactions.

TABLE II

AROMATIC AZOXY COMPOUNDS, Ar—N(→O)=N—Ar′

		M.p., °C.		Yield,
Ar	Ar′	Observed	Reported	%
Phenyl	Phenyl	36	36[a]	71[b]
p-Chlorophenyl	Phenyl	82	62[c]	69
p-Bromophenyl	Phenyl	95	94[d]	69
Phenyl	*p*-Tolyl	50	50[a]	73
p-Chlorophenyl	*p*-Tolyl	109.5	*e*	83
p-Bromophenyl	*p*-Tolyl	125	122[d]	83
Phenyl	*p*-Chlorophenyl	68	68[c]	39
p-Tolyl	*p*-Chlorophenyl	107	*g*	57[h]
p-Bromophenyl	*p*-Chlorophenyl	160	*i*	46
Phenyl	*p*-Anisyl	72	68[f]	30
p-Chlorophenyl	*p*-Anisyl	145	*j*	51

[a] See ref. 8. [b] Azoxybenzene was obtained in 70% yield from the phenyl Grignard reagent–N-phenyl-N′-*p*-bromophenylsulfonoxydiimide N-oxide reaction. [c] See ref. 14. [d] See ref. 7. [e] *Anal.* Calcd. for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.65; H, 4.51; N, 11.28. [f] See ref. 2. [g] *Anal.* Calcd. for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.24; H, 4.60; N, 11.09. [h] Reaction conducted in methylene chloride solution. [i] *Anal.* Calcd. for $C_{12}H_8BrClN_2O$: N, 8.99. Found: N, 9.21. [j] *Anal.* Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.43; H, 4.22; N, 10.67. Found: C, 59.65; H, 4.44; N, 10.83.

The reactions using aryl Grignard reagents were conducted in tetrahydrofuran solution for 2 to 5 hr. at 50–60°, but those involving alkyl Grignards were much cleaner when conducted in methylene chloride solution[13] at ambient temperature with a reaction time of 16 to 20 hr.

The azoxybenzenes were isolated by chromatography on silica gel, and yield figures given were based on the weight of the azoxy benzene fraction obtained from the column. One recrystallization from hexane produced

(9) The designation diimide oxide for azoxy compounds, as suggested by G. F. Wright,[8] appears to be a straightforward method of nomenclature for the azoxy derivatives to be discussed here.

(10) In assigning structure I to the nitrosohydroxylamine tosylates, structure ii was ruled out, since attack of the Grignard reagent on the —N=O function, and displacement of the tosyloxy function would lead to azoxy

compounds isomeric with those actually obtained. A Grignard reagent and iii might be expected to produce a diimide dioxide (displacement of the sulfinate ion) or other products; in any event structure I explains the formation of azoxy compounds much more readily.

(11) M. H. Abraham, J. H. N. Garland, J. A. Hill, and L. F. Larkworthy, *Chem. Ind.* (London), 1615 (1962).

(12) Azoxysulfones, Ar—N(→O)=N—SO2Ar′, are well-known compounds: W. V. Farrar and J. Masson Gulland, *J. Chem. Soc.*, 368 (1944). Diaryl azoxy compounds could not be obtained from these sulfones and aryl Grignard reagents under our experimental conditions.

(13) H. G. Viehe and M. Reinstein, *Ber.*, **95**, 2557 (1962).

TABLE III

AROMATIC AZOXYALKANES, Ar—$\overset{\overset{O}{\uparrow}}{N}$=N—R

Ar	R	$n^{20}D$ (m.p., °C.)	Yield, %	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found[a] C	Found[a] H	Found[a] N
Phenyl	*n*-Butyl	1.5280	62	67.39	7.92	15.72	67.47	7.97	16.08[b]
p-Chlorophenyl	*n*-Butyl		56	56.77	6.21	13.17	56.46	6.16	13.68[b]
p-Chlorophenyl	Methyl	(40)	30	49.28	4.14	16.42	49.76	4.13	15.91[b]
Phenyl	Ethyl	1.5434	44	63.98	6.71	18.66	63.92	6.49	19.60[b]
Phenyl	Isopropyl	1.5296	30	65.82	7.37	17.06	65.46	7.47	17.45[c]
p-Chlorophenyl	Isopropyl	1.5438	30	54.41	5.58	14.10	54.08	5.65	14.35[d]

[a] Nitrogen analyses by the Dumas method often gave high results with these compounds, but the Kjeldahl method gave acceptable results. [b] Dumas value. [c] Kjeldahl value, Dumas result was 17.94%. [d] Kjeldahl value, Dumas result was 16.05%.

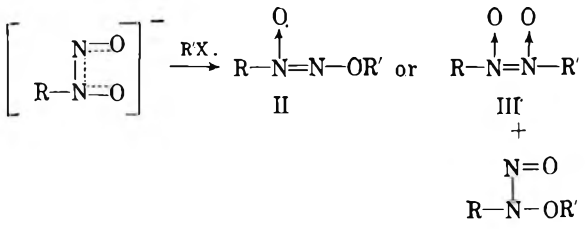
the melting point listed in the tables,[14] and the recovery of the azoxybenzene from the crude fraction usually was greater than 90%. The liquid azoxy compounds were purified by chromatography.

A small amount of the azobenzene corresponding to the azoxybenzene also was formed in these reactions. It undoubtedly arose from reduction of the azoxybenzene by the Grignard reagent.

Sulfone formation did occur when the preparation of the azoxy compounds was attempted from the aromatic tosylates and phenyllithium; only a small amount of diaryl azoxy compound was formed.

Unfortunately, alkazoxyalkanes could not be obtained from the alkylnitrosohydroxylamine tosylates. When these tosylates were treated with 2 equiv. of a Grignard reagent,[15] sulfone formation occurred and no sign of the azoxy compound could be found. No definite products could be obtained from reactions using aryllithium reagents.

In an earlier study of the alkylation of organonitrosohydroxylamines, structure III, rather than II, was preferred for the stable, α-alkylation products of nitrosohydroxylamines.[8] Another isomer, designated β, was

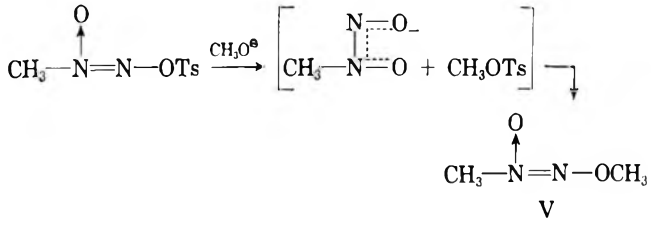


formed in these alkylations and was shown to have structure IV. As mentioned earlier, unsymmetrical azoxy compounds could be obtained from these α-alkylation products and Grignard reagents.[8] In view of the structure assigned to the nitrosohydroxylamine tosylates and of a recent n.m.r. study on azoxy compounds,[16] the α-alkylation products now are assigned the azoxy ether structure (II).[17]

Assignment of structure II to the α-alkylation products of nitrosohydroxylamines implied that the α-methylation products of organonitrosohydroxylamines should be available from the nitrosohydroxylamine tosylates (I) and methoxide ion presuming, of course, that displacement on nitrogen would occur.

Although both phenyl- and *p*-chlorophenylnitrosohydroxylamine tosylate and sodium methoxide in refluxing methanol indeed did produce the α-methylation products reported earlier,[8] all indications were that these methylated nitrosohydroxylamines arose from the interaction of the nitrosohydroxylamine anion and the methyl tosylate initially formed by displacement on sulfur. Not only was methyl tosylate isolated in high yield (79%) when the methoxide ion–phenylnitrosohydroxylamine tosylate reaction was quenched early, but also ethoxide, phenoxide, and *p*-nitrophenoxide anions were observed to attack the nitrosohydroxylamine tosylates exclusively on sulfur.

However, the dimethylnitrosohydroxylamine obtained from sodium methoxide and methylnitrosohydroxylamine tosylate appeared to be N-methyl-N′-methoxydiimide N-oxide (V); the properties of this



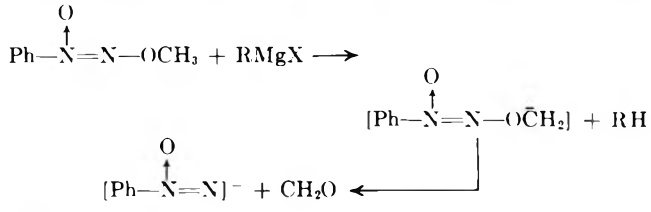
product were vastly different from those of dimeric nitrosomethane (III, R = R′ = CH_3).[18]

(14) A melting point of 62° is reported for 4-chloroazoxybenzene[6]; this material proved to be (infrared spectra, mixture melting points) a 1:1 mixture of 4- and 4′-chloroazoxybenzene. The author is indebted to Professor R. L. Shriner for supplying his samples of these azoxy compounds.

(15) The active hydrogen available to the organometallic reagents probably account for these results. However, the alkyl tosylates and 1 equiv. of the phenyl Grignard reagent gave tosyl bromide (displacement on sulfur by bromide ion) and phenyl tosylate (oxidation–reduction reaction). The details are outlined in the Experimental section.

(16) The n.m.r. evidence in favor of structure II was recently published: J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).

(17) Almost overwhelming evidence [see B. G. Bownlock and W. Lüttke, *Quart. Rev.* (London), **12**, 321 (1958)] requires that structure III be reserved for nitroso dimers. The main reason structure III was preferred over II for the α-methylation product of phenylnitrosohydroxylamine (R = phenyl, R′ = methyl) was that the methylated product liberated methane when treated with a methyl halide Grignard reagent.[8] One explanation of this in terms of structure II is shown below. Such a cleavage is not without



analogy; azoxy sulfones readily cleave in basic solution to give sulfonic acid and diazotate ion.[11]

(18) T. Emery and J. B. Neilands, *J. Am. Chem. Soc.*, **82**, 4903 (1960). The n.m.r. spectrum (Table IV) of this methyl azoxy methoxyl compound exhibits two peaks: *cis* and *trans* dimeric nitrosomethane each have only one n.m.r. peak at τ-values different from those of V.[16]

TABLE IV

N.M.R. SPECTRA OF AZOXY COMPOUNDS

Compound	Chemical shift (τ)[a]
Ph—N(→O)=N—$CH_2C_3H_7$-*n*	6.38[b]
p—ClC_6H_4—N(→O)=N—CH_3	6.60
Ph—N(→O)=N—CH_2CH_3	6.22[c]
CH_3—N(→O)=N—OTs	6.03
$PhCH_2$—N(→O)=N—OTs	4.82
n-$C_3H_7CH_2$—N(→O)=N—OTs	5.95[b]
n-$C_3H_7CH_2$—N(→O)=N—OCH_3	6.06[d]
CH_3—N(→O)=N—OCH_3	6.07, 6.20[e]

[a] The spectra were measured on 10% solutions in carbon tetrachloride containing tetramethylsilane on a Varian Associates A-60 spectrometer. [b] Triplet. [c] Quadruplet, measurement reported is of the center. [d] Triplet, but integrated intensities confirmed that the indicated methyl and methylene groups absorbed at the same place. [e] Two single peaks, assignment uncertain.

Table IV summarizes some of the n.m.r. spectral data on the compounds prepared in this work. A recent publication[16] discussed in detail the n.m.r. spectra and structure of aliphatic azoxy compounds.

Experimental[19]

Preparation of Phenylnitrosohydroxylamine Tosylate.—A solution of 16 g. (0.10 mole) of cupferron (ammonium salt of N-phenyl-N-nitrosohydroxylamine, from Eastman Kodak) in 200 ml. of 10% aqueous sodium bicarbonate was stirred at ambient temperature while 20 g. (0.1 mole) of tosyl chloride was added in one portion; there was no noticeable exotherm of the reaction mixture. After 2 hr. an additional 2 g. of tosyl chloride was added. The mixture was stirred overnight, and then extracted with methylene chloride. The dark residue obtained by evaporation of the methylene chloride was stirred with 30 ml. of methanol, filtered, and the solid thus obtained was recrystallized from chloroform–hexane. A total of 19 g. of N-phenyl-N′-tosyloxydiimide N-oxide was obtained, m.p. 136–137° dec.

Preparation of Methylnitrosohydroxylamine Tosylate.—A mixture of 450 ml. of ether and 50 ml. of an ether solution of the methyl Grignard reagent (Arapahoe, about 3 *M*) was stirred at 20° while nitric oxide, diluted with nitrogen, was passed through the solution for 40 min. The reaction mixture was flushed with nitrogen, cooled to 5°, and 100 ml. of 2 *N* aqueous hydrochloric acid was added. The aqueous layer was separated, and the ether was washed with 130 ml. of 8% sodium hydroxide solution in three portions. All aqueous washes were combined, 18 g. of *p*-toluenesulfonyl chloride was added, and the mixture was stirred overnight. It then was acidified and extracted with methylene chloride. The residue obtained on evaporation of the methylene chloride was recrystallized from chloroform–hexane. A total of 9.05 g. of N-methyl-N′-tosyloxydiimide N-oxide was obtained, m.p. 86–88°.

Preparation of N-*p*-Chlorophenyl-N′-tosyloxydiimide N-Oxide.—N-*p*-Chlorophenylhydroxylamine (25 g.) was prepared and nitrosated according to the procedure of Wright.[8] The crude N-nitrosohydroxylamine thus obtained was dissolved in 220 ml. of acetone, and 35 g. of tosyl chloride was added in one portion. The solution was stirred in an ice bath while 90 ml. of 2.24 *N* aqueous sodium hydroxide was added dropwise. Stirring was continued for 15 min., then the ice bath was removed, 50 ml. of water was added, and stirring was continued for 30 min. After the addition of 125 ml. of water, the solution was filtered, and the filter cake was washed with a little methanol. The solid was recrystallized twice from chloroform–hexane to give the desired tosylate (18.2 g.), m.p. 144–145° dec.

Preparation of N-*p*-Tolyl-N′-tosyloxydiimide N-Oxide.—A solution of 52 g. of *p*-tolylhydroxylamine in 300 ml. of ether was cooled to 0°, and gaseous ammonia was passed into the solution at a rapid rate for 15 min. The ammonia flow was adjusted to a slow rate, and 46 ml. of butyl nitrite was added dropwise over a 20-min. period. The temperature of the mixture was not allowed to exceed 5°. After an additional 15 min. of stirring, the solution was filtered, and the precipitate was washed well with ether. The 30.5 g. of the ammonium salt of N-*p*-tolyl-N-nitrosohydroxylamine thus obtained was dissolved in 450 ml. of 10% aqueous sodium bicarbonate. The solution was stirred at ambient temperature while 35 g. of tosyl chloride was added over 1 hr. After stirring overnight the solution was filtered. The precipitate was recrystallized from ethanol to give the tosyloxydiimide, 30.5 g., m.p. 126° dec.

Reaction of *p*-Tolylmagnesium Bromide and N-Phenyl-N′-tosyloxydiimide N-Oxide.—A solution of 2.20 g. (7.5 mmoles) of the tosyloxydiimide N-oxide in 40 ml. of tetrahydrofuran was stirred at ambient temperature while 9 ml. of 1.2 *M* *p*-tolyl Grignard reagent (in tetrahydrofuran, THF) was added dropwise. The mixture was stirred at 50–60° for 2 hr., then cooled, and poured into an ice–dilute hydrochloric acid mixture. The organic product was isolated by extraction with methylene chloride. After concentration of the organic layer at reduced pressure, the residue was chromatographed on silica gel. Elution of the column with pentane–methylene chloride (3:1) gave 4-methylazobenzene, 0.06 g., m.p. 69–70°. Continued elution of the column with pentane–methylene chloride (2:1 and 1:1), gave 4′-methylazoxybenzene (N-phenyl-N′-*p*-tolyldiimide N-oxide), 1.16 g., 73%. After one recrystallization from hexane 1.05 g. of the azoxybenzene, m.p. 50–51°, lit.[8] m.p. 50–51°, was obtained.

Reaction of Phenylmagnesium Bromide and N-*p*-Bromophenyl-N′-tosyloxydiimide N-Oxide.—A solution of 2.23 g. (6.0 mmoles) of the tosyloxy diimide in 50 ml. of tetrahydrofuran was stirred at ambient temperature while 3 ml. of a 2.5 *M* ether solution of the phenyl Grignard reagent was added dropwise. After the mixture had been stirred at 50–60° for 2 hr., the mixture was processed as described above. The 4-bromoazoxybenzene fraction from the column weighed 1.14 g. (69%). This fraction was recrystallized from hexane to give N-*p*-bromophenyl-N′-phenyldiimide N-oxide, 1.04 g., m.p. 95–96°.

Reactions of the Butyl Grignard Reagent and N-Phenyl-N′-tosyloxydiimide N-Oxide.—A solution of 2.20 g. (7.5 mmoles) of the tosyloxydiimide in 40 ml. of methylene chloride was cooled while 3 ml. of about 3 *M* *n*-butylmagnesium chloride (Arapahoe) was added dropwise. The cooling bath was removed and the mixture was stirred at ambient temperature for 18 hr. The reaction was processed as usual, and the organic residue was chromatographed on silica gel. Pentane–methylene chloride (1:1) eluted phenylazoxybutane (N-phenyl-N′-*n*-butyldiimide N-oxide), a yellow oil, 0.834 g., $n^{20}D$ 1.5280; ultraviolet (cyclohexane), λ_{max} 245 mμ (ε 10,800).

Reaction of Phenyllithium and N-Phenyl-N′-tosyloxydiimide N-Oxide.—A solution of 2.92 g. (10 mmoles) of the tosyloxydiimide N-oxide in 50 ml. of THF was stirred at ice-bath temperature while 10 mmoles of phenyllithium in 7.2 ml. of ether was added slowly. The ice bath was allowed to melt, and the mixture was stirred overnight at ambient temperature. The reaction was processed in the usual way, and the organic residue obtained was chromatographed on silica gel. Pentane–methylene chloride eluted about 0.1 g. of azoxybenzene, identified by infrared spectrum, from the column. The major fraction was eluted by methylene chloride–ethyl acetate. After recrystallization from hexane–chloroform, this fraction, phenyl *p*-tolyl sulfone, weighed 1.75 g. (75%) and melted at 124–126°, lit.[20] m.p. 124.5°.

Reaction of Phenyllithium and N-*p*-Chlorophenyl-N′-tosyloxydiimide N-oxide.—The reaction of 1.63 g. (5 mmoles) of the

(19) Melting points are uncorrected.

(20) A. Michael and A. Adair, *Ber.*, **11**, 116 (1878).

tosyloxydiimide N-oxide in 30 ml. of THF and 6 mmoles of phenyllithium in 6 ml. of ether was carried out as described earlier. Chromatography on silica gel gave a trace of 4-chloroazoxybenzene (infrared spectrum) and 0.82 g. (71%) of phenyl *p*-tolyl sulfone, m.p. 124–126°.

Reaction of the Phenyl Grignard Reagent and Methylnitrosohydroxylamine Tosylate.—A solution of 1.15 g. (5.0 mmoles) of the tosylate in 25 ml. of methylene chloride was stirred at ice-bath temperature while 2.0 ml. of Arapahoe 3 *M* phenyl Grignard reagent was added. The mixture was stirred overnight at ambient temperature, and then was processed as usual. The residue was chromatographed on silica gel. Elution of the column was carried out with pentane–methylene chloride, methylene chloride, and ethyl acetate in methylene chloride. The first fraction eluted (after the biphenyl cut), 0.17 g., was identified as tosyl bromide by infrared spectrum, ultimate analysis, and m.p. 95–96°, lit.[21] m.p. 95–96°. The next fraction eluted, 0.365 g., was phenyl tosylate, m.p. 93–94°, lit.[22] m.p. 94–95°, identified by infrared spectrum and ultimate analysis. The last fraction from the column, eluted by ethyl acetate in methylene chloride, was recovered starting material, 0.188 g.

Reaction of the Phenyl Grignard Reagent and N-*n*-butyl-N′-tosyloxydiimide N-oxide.—A solution of 1.30 g. (5.0 mmoles) of the butylnitrosohydroxylamine tosylate in 35 ml. of methylene chloride was stirred at 3° while 12.2 ml. of 0.83 *M* phenyl Grignard in ether was added dropwise. The reaction was processed as usual and the residue was chromatographed on silica gel. The only fraction of the eluate that could be identified was that eluted by 10% ethyl acetate in methylene chloride. This was phenyl *p*-tolyl sulfone, 0.86 g., 74%, m.p. 126–127°.[20]

Reaction of N-Phenyl-N′-tosyloxydiimide N-Oxide and Sodium Methoxide.—A mixture of 5.84 g., (20 mmoles) of the above diimide N-oxide, 20 mmoles of sodium methoxide, and 75 ml. of methanol was stirred until the tosylate dissolved. The solution was refluxed for 1 hr., and then was cooled, poured into water, and extracted with methylene chloride. The residue was chromatographed on silica gel. Pentane in methylene chloride, methylene chloride, and ethyl acetate in methylene chloride were used to elute the column. The first fraction from the column was azobenzene (by infrared and melting point), 0.09 g.; the second was azoxybenzene (by infrared), 0.18 g. The infrared spectrum of the third fraction, 0.60 g., identified it as methyl tosylate (15%). Continued elution of the column gave N-phenyl-N′-methoxydiimide N-oxide, 1.24 g., 41%, m.p. 38–40° (from hexane), lit.[8] m.p. 39.5–40.5°. The infrared spectrum of this diimide was identical with that of a sample prepared from cupferron and dimethyl sulfate.[8]

When 10 mmoles of sodium methoxide in methanol was added slowly to a suspension of the tosyloxy diimide N-oxide in 50 ml. of methanol at ambient temperature, the tosylate dissolved slowly. As soon as solution was complete (*ca.* 15 min.), the methanolic solution was poured into water and processed as described before. A total of 1.48 g. (79%) of methyl tosylate and only a trace of N-phenyl-N′-methoxydiimide N-oxide was eluted from the silica gel column.

Reaction of Sodium Methoxide and N-Methyl-N′-tosyloxydiimide N-Oxide.—A mixture of 2.30 g. (10 mmoles) of the tosylate of methylnitrosohydroxylamine and 25 ml. of 0.49 *M* sodium methoxide (12 mmoles) in methanol was refluxed for 4 hr. The solution was cooled, diluted with 150 ml. of salt water, and extracted seven times with methylene chloride. The extract was dried over magnesium sulfate. After removal of all but about 2 ml. of the methylene chloride by distillation, the residual solution was distilled *in vacuo* through −30° and −80° traps. The −30° trap retained the N-methyl-N′-methoxydiimide N-oxide, 0.46 g., 51%. The sample was purified by preparative v.p.c. at 100° using a silicone (GE-SF-96) on Chromosorb column. A sample thus purified had $n^{20}D$ 1.4488; ultraviolet (cyclohexane), λ_{max} 238 mμ (ε 9730).

Anal. Calcd for $C_2H_6N_2O_2$: C, 26.66; H, 6.72; N, 31.10. Found: C, 27.03; H, 6.76; N, 32.35.[23]

Sodium Methoxide and N-*n*-Butyl-N′-tosyloxydiimide N-Oxide.—A mixture of 1.30 g. (5 mmoles) of the tosylate of *n*-butylnitrosohydroxylamine in 20 ml. of methanol and 12.0 ml. of 0.42 *M* sodium methoxide in methanol was refluxed for 3 hr. After the usual processing, the organic residue was chromatographed on silica gel. Methylene chloride eluted methyl tosylate, 0.08 g., 9%, identified by infrared spectrum; and 10% ethyl acetate in methylene chloride eluted N-*n*-butyl-N′-methoxydiimide N-oxide, 0.29 g., 44%, as a colorless oil. The n.m.r. spectrum is summarized in Table IV.

Anal. Calcd. for $C_5H_{12}N_2O_2$: C, 45.43; H, 9.15; N, 21.1. Found: C, 45.65; H, 9.27; N, 22.3.[23]

Potassium Phenoxide and N-Phenyl-N′-tosyloxydiimide N-Oxide.—A mixture of 2.92 g. (10 mmoles) of the tosylate of phenylnitrosohydroxylamine, 1.0 g. (11 mmoles) of phenol, 50 ml. of *t*-butyl alcohol, and 1.12 g. (10 mmoles) of solid potassium *t*-butoxide was refluxed for 3 hr. The mixture was cooled, poured into water, and extracted with methylene chloride. The methylene chloride was evaporated and the residue recrystallized from hexane yielding phenyl tosylate, 2.13 g., 86%, m.p. 94–95°.[22]

(21) R. Otto and O. Gruber, *Ann.*, **142**, 92 (1867).

(22) R. Otto, *Ber.*, **19**, 1832 (1886).

(23) As mentioned in footnote *a*, Table III, high nitrogen values were often obtained on compounds of this type in the Dumas analysis.

Synthesis of Chonemorphine Stereoisomers

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The four diastereoisomers of 3-amino-20-dimethylamino-5α-pregnane have been prepared by known reactions. One of these, the 3β,20α isomer, has been proved to be identical with the steroidal alkaloid chonemorphine. Some new observations on the stereoselectivity of reductions of 3-keto steroid oximes are reported and also some work on the preparation of $\Delta^{8(9)}$- and $\Delta^{8(14)}$-5α-pregnen-3β-ol-20-one acetates.

Chonemorphine is a steroidal alkaloid which has been isolated from the reputedly medicinal Indian herb, *Chonemorpha macrophylla*,[2] and from the similar Malayan plant, *Chonemorpha penangensis*.[3] In 1960 Chatterjee and Das[4] proposed that chonemorphine is a 3-amino-20-dimethylaminopregnene with the double bond possibly located at the 8,9-position.

Our initial work to establish the structure of this alkaloid was aimed at the synthesis of $\Delta^{8(9)}$- and $\Delta^{8(14)}$-3-amino-20-dimethylaminopregnenes having different stereochemical relationships at C-3 and C-20. 5,7-Pregnadien-3β-ol-20-one acetate, prepared by the action of N-bromosuccinimide on pregnenolone acetate with subsequent dehydrobromination,[5] was isomerized by acid to the corresponding $\Delta^{8,14}$-diene.[6] Hydrogenation

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(2) K. G. Das and P. P. Pillay, *J. Sci. Ind. Res.* (India), **13B**, 602, 701 (1954).

(3) A. Chatterjee and B. Das, *Chem. Ind.* (London), 1445 (1959).

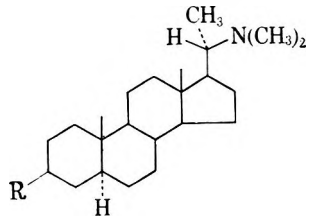
(4) A. Chatterjee and B. Das, *ibid.*, 290 (1960).

(5) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1126 (1951).

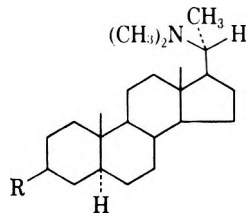
(6) L. F. Fieser and G. Ourisson, *J. Am. Chem. Soc.*, **75**, 4404 (1953).

of the diene over Raney nickel furnished Δ^{8}-5α-pregnen-3β-ol-20-one acetate,[7] which could be isomerized readily to the $\Delta^{8(14)}$ isomer.[8,9]

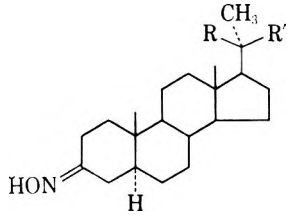
At this point Chatterjee and Das[10] reported new data showing that chonemorphine is actually a *saturated* compound and that its structure is 3β-amino-20α-dimethylamino-5α-pregnane (Ia). The evidence consisted of the observation that nitrous acid deamination of chonemorphine yields predominantly 20α-dimethylamino-5α-pregnan-3β-ol (Ib). Consequently, our efforts were shifted to prove unequivocally by synthesis the stereochemistry at C-3 of this proposed structure and also to prepare the three remaining C-3 and C-20 isomers in order to make them available for pharmacological testing of possible hypotensive or hypocholestereolemic activity.[11]



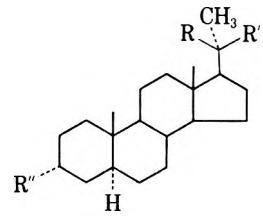
Ia, R = NH_2
b, R = OH
c, R = OAc
d, R = OTs



IIa, R = NH_2
b, R = OH
c, R = OAc
d, R = OTs



IIIa, R = H, R′ = $N(CH_3)_2$
b, R = $N(CH_3)_2$, R′ = H



IVa, R = H; R′ = $N(CH_3)_2$; R″ = NH_2
b, R = H; R′ = $N(CH_3)_2$; R″ = N_3
c, R = $N(CH_3)_2$; R′ = H; R″ = NH_2
d, R = $N(CH_3)_2$; R′ = H; R″ = N_3

The epimeric 20α- and 20β-dimethylamino-5α-pregnan-3β-ol acetates (Ic and IIc, respectively) used as starting materials in our work were prepared from 5α-pregnan-3β-ol-20-one acetate oxime by reduction and subsequent N-methylation.[12] To increase the yield of the 20α epimer (Ic) we utilized catalytic hydrogenation[13] of the oxime in acetic acid solution over Adams' catalyst in place of the sodium–alcohol reduction described by Sörm and co-workers.[12] The catalytic method gave the chromatographically separable 20α and 20β epimers (Ic and IIc) roughly in the ratio of 5:2, whereas reduction with sodium in alcohol furnished these epimers in a ratio of 1:2. Hydrolysis and oxidation of the resulting 3β-ols (Ib and IIb) to the corresponding ketones, with subsequent conversion into their respective oximes (IIIa and IIIb), was carried out as described by the Sörm group.[12] Reduction of the oximes to the corresponding equatorial 3β amines was effected with lithium aluminum hydride or by the action of sodium in amyl alcohol. It is of interest that catalytic hydrogenation of these oximes in acetic acid over Adams' catalyst gave predominantly the same 3β-amino products. This was somewhat surprising, since, according to Goutarel,[13b] catalytic hydrogenation of these oximes gives mainly the corresponding 3α-amino products.[14]

3β-Amino-20α-dimethylamino-5α-pregnane (Ia), prepared by the foregoing sequence, was found to have physical properties and derivatives identical with those of naturally occurring chonemorphine (*cf.* Table I). At about the time this phase of our work had been completed, an account of essentially the same synthesis appeared,[15] but no derivatives or direct comparisons with authentic samples were reported. Consequently, our work provides a more definitive verification of the structure of chonemorphine as 3β-amino-20α-dimethylamino-5α-pregnane (Ia).

Finally, in order to obtain the corresponding 3α-amino isomers IVa and IVc we prepared the 3β-*p*-toluenesulfonates (Id and IId) and submitted them to nucleophilic displacement reactions with sodium azide in dimethyl sulfoxide.[16] Reduction of the resulting azides with lithium aluminum hydride readily gave the axial 3α amines (IVa and IVc), which, along with their derivatives, were found to be distinctly different from the corresponding 3β epimers (*cf.* Table I). These results thus provide additional confirmation of the assignment of the equatorial 3β-amino structure (Ia) to chonemorphine.

Experimental[17]

5α-Pregna-8,14-dien-3β-ol-20-one Acetate.—A solution of 2.0 g. of 5,7-pregnadien-3β-ol-20-one acetate (prepared according to the method of Antonucci, *et al.*,[5] from pregnenolone acetate) in 10 ml. of benzene and 40 ml. of acetic acid was refluxed in the presence of 3 drops of concentrated hydrochloric acid. Isomerization of the 5,7-diene system was found to be nearly complete after 1 hr., as indicated by the appearance of a new absorption peak at 250 mμ and the disappearance of the 282-mμ absorption of the 5,7-diene. The solution was then partially neutralized with potassium carbonate and the product isolated by extraction with ether. The residue, after evaporation of the ether, crystallized from methanol to afford 0.75 g. of 5α-pregna-8,14-dien-3β-ol-20-one acetate, m.p. 128–131°. Recrystallization from

(7) F. Gautschi and K. Bloch, *J. Biol. Chem.*, **233**, 1343 (1958).

(8) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957).

(9) It is of interest that the n.m.r. spectrum of Δ^{8}-5α-pregnen-3β-ol-20-one acetate shows the C-18 and C-19 methyl proton signals at 32.5 and 58.3 c.p.s., respectively, from tetramethylsilane as an internal standard in carbon tetrachloride solution on a 60-Mc. instrument, while $\Delta^{8(14)}$-5α-pregnan-3β-ol-20-one acetate shows these signals at 42.5 and 48.7 c.p.s. These differences may offer a convenient method to distinguish $\Delta^{8(9)}$ and $\Delta^{8(14)}$ steroids in the absence of other interfering C-methyl absorptions.

(10) A. Chatterjee and B. Das, *Chem. Ind.* (London), 1247 (1960).

(11) *Cf.* R. E. Counsell, P. D. Klinstra, R. E. Ranney, and D. L. Cook, *J. Med. Pharm. Chem.*, **5**, 720, 1224 (1962).

(12) V. Černý, L. Labler, and F. Sörm, *Collection Czech. Chem. Commun.*, **22**, 76 (1957).

(13) (a) R. A. Lucas, D. F. Dickel, R. L. Dziemian, M. J. Ceglowski, B. L. Hensle, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **82**, 5688 (1960); (b) R. Goutarel, *Tetrahedron*, **14**, 126 (1961).

(14) In this connection it is perhaps pertinent to note that the stereochemistry of the reduction of a series of 3-keto steroid oximes with lithium aluminum hydride has been found to vary with the nature of the side chain as well as with the stereochemistry of the A/B ring junction [*cf.* C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956)].

(15) M. M. Janot, F. Laire, Q. Khuong-Huu, and R. Goutarel, *Bull. soc. chim. France*, 111 (1962).

(16) *Cf.* W. R. Hertler and E. J. Corey, *J. Org. Chem.*, **23**, 1221 (1958); H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 954 (1962); also, A. K. Bose, J. F. Kistner, and L. Farber, *J. Org. Chem.*, **27**, 2925 (1962).

(17) Melting points were taken in open capillaries and are uncorrected. Optical rotations were taken in chloroform solution. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

TABLE I

PROPERTIES AND ANALYSES OF SYNTHETIC CHONEMORPHINE AND STEREOISOMERS

Compound	M.p., °C.	[α]D, deg.	Formula	Analyses: %C Calcd.	%C Found	%H Calcd.	%H Found	%N Calcd.	%N Found
3β-Amino-20α-dimethylamino-5α-pregnane (Ia)	149–149.5[a]	+25[a]	$C_{23}H_{42}N_2$	79.70	79.51	12.22	12.06	8.08	7.85
N-Benzylidene deriv.[b]	182–183[c]	+36	$C_{30}H_{46}N_2$	82.89	82.92	10.67	10.80	6.44	6.64
N-Acetyl deriv.	262–265[d]	+17	$C_{25}H_{44}N_2O$	77.26	77.07	11.41	11.52	7.21	7.21
3α-Amino-20α-dimethylamino-5α-pregnane (IVa)	153–153.5	+29	$C_{23}H_{42}N_2$	79.70	79.76	12.22	12.43	8.08	7.94
N-Benzylidene deriv.[b]	202.5–203.5	+23	$C_{30}H_{46}N_2$	82.89	82.89	10.67	10.71	6.44	6.65
N-Acetyl deriv.[e]	206–208	+31	$C_{25}H_{44}N_2O \cdot H_2O$	73.84	74.25	11.40	11.22	6.89	7.02
3β-Amino-20β-dimethylamino-5α-pregnane (IIa)	149–151	+10	$C_{23}H_{42}N_2$	79.70	79.46	12.22	12.26	8.08	8.02
N-Benzylidene deriv.[b]	153–154	+27	$C_{30}H_{46}N_2$	82.89	82.60	10.67	10.92	6.44	6.60
N-Acetyl deriv.[e]	209–212	+ 5	$C_{25}H_{44}N_2O \cdot {}^1/_2H_2O$	75.51	75.31	11.41	11.21	7.05	7.20
3α-Amino-20β-dimethylamino-5α-pregnane (IVc)	163–164	+17	$C_{23}H_{42}N_2$	79.70	79.61	12.22	11.97	8.08	8.36
N-Benzylidene deriv.[b]	117–118	+27	$C_{30}H_{46}N_2$	82.89	82.66	10.67	10.97	6.44	6.52
N-Acetyl deriv.	208–211	+30	$C_{25}H_{44}N_2O$	77.26	77.33	11.41	11.44	7.21	7.14

[a] Janot, *et al.*,[15] report m.p. 149°, [α]D +25°. Our sample of natural chonemorphine melted at 147–149°, [α]D +25° (lit.[3] m.p. 144–146°, [α]D +25°). [b] This derivative showed λ_{max} 248, 277, and 287 mμ. [c] Chatterjee and Das[3] report m.p. 184° for this derivative of chonemorphine. [d] Chatterjee and Das[3] reported m.p. 270° for the chonemorphine derivative. [e] The indicated amount of water of crystallization was lost on prolonged drying at 130°.

ethanol afforded material with m.p. 133–134°, [α]D +64° (*c* 1.54), λ_{max} 250 mμ (ε 25,500).

Anal. Calcd. for $C_{23}H_{32}O_3$ (356.49): C, 77.49; H, 9.05. Found: C, 77.76; H, 8.98.

5α-Pregna-8-en-3β-ol-20-one Acetate and 5α-Pregna-8(14)-en-3β-ol-20-one Acetate.—Hydrogenation of 0.90 g. of the foregoing product was conducted in absolute ethanol over Raney nickel in a Parr hydrogenator. After 1 hr. the catalyst was removed by filtration and the solvent evaporated. The crude hydrogenation product, m.p. 142–147°, was recrystallized from ethanol five times to give pure 5α-pregna-8-en-3β-ol-20-one acetate, m.p. 160–162°, [α]D +89° (*c* 1.05). This gave a positive osmium tetroxide test[18] in about 20 min. No vinyl proton signal was observed in the n.m.r. spectrum.[19]

Anal. Calcd. for $C_{23}H_{34}O_3$ (358.50): C, 77.05; H, 9.56. Found: C, 77.30; H, 9.74.

The residue from the mother liquors was dissolved in acetic acid and shaken under hydrogen in the presence of palladium–charcoal for 20 hr. to effect the isomerization of double bond to the 8(14) position. The 5α-pregna-8(14)-en-3β-ol-20-one acetate thus obtained melted at 156–157°, [α]D +99° (*c* 1.48) (lit.[20] m.p. 156–157°, [α]D +90°). Its melting point was significantly depressed (below 130°) on admixture with the $\Delta^{8(9)}$ isomer. The n.m.r. spectrum[19] also indicated the absence of any vinyl proton.

20α- and 20β-Dimethylamino-5α-pregnan-3β-ol Acetate (Ic and IIc).—These two compounds were prepared according to the method described by Sörm, *et al.*,[12] or by a modification in which catalytic hydrogenation[13a] was used in the place of reduction by sodium in alcohol for the conversion of 5α-pregnan-3β-ol-20-one acetate oxime into the corresponding 20α and 20β amines. In a typical run by the hydrogenation method, with subsequent N-methylation and reacetylation of the hydroxyl group, 0.916 g. of Ic and 0.390 g. of IIc (ratio, 5:2) were obtained from 3.75 g. (0.01 mole) of 5α-pregnan-3β-ol-20-one acetate oxime. A total of more than 30 g. each of Ic and IIc was prepared.

20α- and 20β-Dimethylamino-5α-pregnan-3-one Oxime (IIIa and IIIb).—These oximes were prepared according to the method of Sörm, *et al.*,[12] from their respective ketones, which in turn were obtained by chromic acid oxidation of Ib and IIb in acetic acid. IIIa had m.p. 232–235° dec. (lit.[12] m.p. 241°, lit.[15] m.p. 233–235° dec.); IIIb had m.p. 240–243° dec. (lit.[12] m.p. 240–244° dec.).

3β-Amino-20α-dimethylamino-5α-pregnane (Ia) and 3β-Amino-20β-dimethylamino-5α-pregnane (IIa) from Oximes IIIa and IIIb. A. By Lithium Aluminum Hydride Reduction.—To a solution of 0.721 g. (2 mmoles) of IIIa in 200 ml. of anhydrous ether was added 2.3 g. of lithium aluminum hydride (0.06 mole). The resulting mixture was refluxed on a steam bath for 9 hr. It was then allowed to stand at room temperature overnight. Concentrated sodium hydroxide solution was added to the mixture after the excess of lithium aluminum hydride had been cautiously destroyed with water. The mixture was extracted with ether, and the combined extracts were washed thoroughly with water and dried over anhydrous potassium carbonate. The solid residue obtained by evaporation of the solvent was recrystallized from ethyl acetate. It afforded 0.185 g. (27%) of the desired amine (Ia), m.p. 145–147°, after three recrystallizations from the same solvent. The analytical sample (see Table I) melted at 149–149.5°, [α]D +25° (*c* 0.43) (lit.[15] m.p. 149°, [α]D +25°). A mixture melting point with chonemorphine (m.p. 147–149°) showed no depression. The infrared spectrum also was found to be superimposable with that of chonemorphine.[21]

Similarly, 0.721 g. (2 mmoles) of the oxime IIIb gave 0.197 g. (28%) of IIa, m.p. 148–150°. Purified IIa melted at 149–151°, [α]D +10° (*c* 1.01). Its melting point was significantly depressed by Ia (below 125°).

The N-benzylidene and N-acetyl derivatives of both Ia and IIa were prepared in the usual manner. Those of Ia were found to be identical with the corresponding derivatives of chonemorphine.

B. By Catalytic Hydrogenation.—The oxime IIIa (1.082 g., 3 mmoles) in 20 ml. of acetic acid was reduced in a microhydrogenator in the presence of 0.25 g. of Adams' catalyst which had been prereduced in 20 ml. of the same solvent. Reduction appeared to be essentially complete in 4 hr., and after filtration the solution was neutralized and made alkaline with ammonium hydroxide, and the precipitated solid was dissolved in ether. The resulting solution was washed with water and dried over anhydrous potassium carbonate. Evaporation of the ether gave 0.956 g. of crude product (m.p. below 133°), from which 0.298 g. (29%) of Ia, m.p. 145–147°, was obtained. An additional 0.100 g. of less pure Ia, m.p. 141–143°, was recovered from the mother liquors. After recrystallization from ethyl acetate the product melted at 147–149° (not depressed by the lithium aluminum hydride reduction product), [α]D +25° (*c* 1.15). Its N-benzylidene and N-acetyl derivatives also were found to be identical with those of the lithium aluminum hydride reduction product and the corresponding ones of chonemorphine.

In a similar manner, there was obtained 0.235 g. (34%) of IIa, m.p. 148–150°, from 0.721 g. (2 mmoles) of the oxime IIIb.

C. By Sodium and Amyl Alcohol Reduction.—Sodium metal (3.2 g., 0.14 g.-atom) was added in small pieces over 2 hr. to a boiling solution of 0.360 g. (1 mmole) of IIIa in 50 ml. of distilled amyl alcohol. The amyl alcohol was removed by steam distilla-

(18) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 214 (1949).

(19) We wish to thank Dr. H. Y. Chen, U. S. Industrial Chemicals Co., Cincinnati, Ohio, for this spectrum.

(20) O. Mancera, D. H. R. Barton, G. Rosenkranz, and C. Djerassi, *J. Chem. Soc.*, 1021 (1952).

(21) Chonemorphine was isolated by N. T. I. from *Chonemorpha macrophylla* and purified as the dihydrochloride.

tion and the yellow product recovered by extraction with ether. It afforded 0.082 g. (24%) of Ia, m.p. 145–147°, still slightly yellow after three recrystallizations from ethyl acetate.

In the same manner, 0.721 g. (2 mmoles) of IIIb yielded 0.315 g. (46%) of the fairly pure but yellow IIa, m.p. 147–150°.

20α-Dimethylamino-5α-pregnan-3β-ol Tosylate (Id) and 3α-Azido-20α-dimethylamino-5α-pregnane (IVb).—A solution of 3.5 g. of recrystallized *p*-toluenesulfonyl chloride in 10 ml. of anhydrous pyridine was added in portions with cooling to 1.74 g. (5 mmoles) of Ib in 30 ml. of the same solvent. The solution immediately turned yellow, then light red. Some solid also formed. After having been kept at 0° for 13 days, the reaction mixture was poured into cold dilute sodium bicarbonate solution containing crushed ice and was then extracted with a mixture of benzene and petroleum ether (b.p. 35–60°). The combined extracts, after having been dried over anhydrous sodium sulfate, were evaporated under reduced pressure at room temperature, giving 2.10 g. of slightly yellow residue. The pure tosylate was isolated and characterized in another run. It crystallized from acetone in needles, m.p. 151–151.5°, $[\alpha]_D$ +11° (*c* 1.00).

Anal. Calcd. for $C_{30}H_{47}NO_3S$ (501.76): C, 71.81; H, 9.44; N, 2.79; S, 6.39. Found: C, 72.04; H, 9.57; N, 2.67; S, 6.17.

A mixture of the crude tosylate (2.10 g.) and 4.45 g. of sodium azide in 70 ml. of dimethyl sulfoxide was heated in an oil bath at 95–100° with stirring for 6 hr. The mixture was then poured into ice water and extracted with petroleum ether. The extracts were evaporated *in vacuo* and the residue crystallized from acetone, giving 1.00 g. of the azide IVb as needles, m.p. 153—155°. An additional 0.15 g. was obtained from the mother liquor making the total yield 62%. The purified product melted at 156–158°, $[\alpha]_D$ +17° (*c* 0.83).

Anal. Calcd. for $C_{23}H_{40}N_4$ (372.58): C, 74.14; H, 10.82; N, 15.04. Found: C, 73.99; H, 11.04; N, 14.78.

20β-Dimethylamino-5α-pregnan-3β-ol Tosylate (IId) and 3α-Azido-20β-dimethylamino-5α-pregnane (IVd).—To a solution of 4.40 g. of recrystallized *p*-toluenesulfonyl chloride in 30 ml. of anhydrous pyridine was added 1.95 g. (5.6 mmoles) of IIb with cooling. The resulting solution was allowed to stand at 0° for 5 days. No solid was formed during this period, but the solution became red. The reaction product was isolated as described for Id to yield 2.50 g. (89%) of slightly yellow tosylate, m.p. 166°. The pure tosylate formed needles (from acetone), m.p. 166–167°, $[\alpha]_D$ 0° (*c* 1.01).

Anal. Calcd. for $C_{30}H_{47}NO_3S$ (501.76): C, 71.81; H, 9.44; N, 2.79; S, 6.39. Found: C, 71.78; H, 9.65; N, 2.78; S, 6.45.

The azide IVd was prepared in the same manner as IVd; yield, 77%. After recrystallization it formed plates (from acetone), m.p 139–141°, $[\alpha]_D$ +8° (*c* 1.02).

Anal. Calcd. for $C_{23}H_{40}N_4$ (372.58): C, 74.14; H, 10.82; N, 15.04. Found: C, 74.35; H, 10.98; N, 15.24.

3α-Amino-20α-dimethylamino-5α-pregnane (IVa) and 3α-Amino-20β-dimethylamino-5α-pregnane (IVc).—A solution of 0.65 g. of the azide IVb in 150 ml. of anhydrous ether was reduced with 0.9 g. of lithium aluminum hydride. Nitrogen gas evolved immediately on addition of the hydride. The reaction mixture was stirred at room temperature overnight. After the excess of hydride had been consumed by slow addition of water, the mixture was treated with concentrated sodium hydroxide solution and extracted with ether. The combined extracts were washed with water and dried over potassium carbonate and evaporated. The residue crystallized from ethyl acetate to yield 0.52 g. (86%) of the desired amine IVa, m.p. 148–150°. After further recrystallization from the same solvent it melted at 153–153.5°, $[\alpha]_D$ +29° (*c* 1.00). When mixed with the 3β epimer (Ia) this melted at 120–125°.

The azide IVd (1.12 g. 3 mmoles), on reduction with an excess of lithium aluminum hydride in a similar manner, afforded 0.719 g. (69%) of IVc, m.p. 161–163°. The analytical sample melted at 163–164°, $[\alpha]_D$ +17° (*c* 1.00). The mixture melting point with IIa was depressed to below 130°.

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A New Type of Naturally Occurring Polyunsaturated Fatty Acid

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The seed oil of *Crepis foetida* L., a member of the plant family Compositae, contains 60% of a fatty acid that has been shown to be *cis*-9-octadecen-12-ynoic acid. For convenience it is called crepenynic acid. This nonconjugated polyunsaturated acid is the first known member of a new class of naturally occurring acetylenic fatty acids, analogous to linoleic acid in containing methylene-interrupted unsaturation. The new compound may find considerable importance in mechanistic studies of fatty acid biosynthesis and of fatty acid metabolism. Crepenynic acid readily autoxidizes on standing. Two derivatives have been synthesized, *cis*-9,10-epoxyoctadec-12-ynoic and *threo*-9,10-dihydroxyoctadec-12-ynoic acids.

During analytical investigation of the seed oil of *Crepis foetida* L., family Compositae, by procedures conventionally applied to seed oils,[2] it became apparent that the oil must contain compound(s) of novel structure. The presence of 88% of linolenic acid in the oil was indicated by an analysis based on conjugation developed after isomerization in alkali and measured by ultraviolet absorption.[3] However, gas–liquid chromatographic (g.l.c.) analyses of fatty acid methyl esters derived from the oil revealed no linolenic acid, but showed 60% of a component that had retention characteristics unlike those of any of the common naturally occurring fatty acids. Many of the observed properties could be rationalized by assuming a nonconjugated enynic structure for this new acid component, but precedents for this type of compound are lacking.

In this paper we report the isolation, purification, and proof of structure of this new fatty acid from *Crepis* oil, for which we suggest the name crepenynic acid, since the postulated presence of both olefinic and acetylenic unsaturation has been confirmed.

Results

Neither infrared nor ultraviolet spectral analyses provided evidence relevant to the structure of crepenynic acid since the parent oil gave spectra much like

(1) A laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) R. W. Miller and F. R. Earle, presentation before the American Oil Chemists' Society, Atlanta, Ga., April 22–24, 1963.

(3) American Oil Chemists' Society, "Official and Tentative Methods," Ed. 2, Rev., 1959, cd 7–58.

those of soybean oil which contains predominantly linoleic and oleic acids, together with smaller quantities of linolenic, palmitic, and other saturated acids. Therefore, countercurrent distribution of the fatty acid methyl esters derived from *Crepis* oil was undertaken to obtain a purified sample of the new acid for structural studies.

A 730-transfer countercurrent distribution of the mixed methyl esters, using a hexane–acetonitrile system in a Craig–Post[4] apparatus, yielded nearly pure methyl crepenynate (Fig. 1, peak C). Figure 1 is the weight distribution plot obtained after removing solvent from selected fractions. G.l.c. analyses of the material in peak A showed that it contained methyl palmitate, stearate, oleate, and a trace of linoleate. Peak B contained predominantly methyl linoleate.

During the course of this work pure methyl crepenynate (I) was stored under nitrogen at −18°. In spite of these precautions the later experiments showed that autoxidation had taken place. The infrared spectrum of the autoxidized ester indicated hydroxyl absorption, 3420 cm.$^{-1}$, and conjugated *trans*-enynic absorption, 95 cm. The ultraviolet spectrum showed conjugated unsaturation, λ_{max} 234 mμ. G.l.c. analyses indicated no unusual long-chain contaminants, but a number of short-chain materials were present. These probably resulted from cleavage of hydroperoxides formed by autoxidation. Little is known about the autoxidation of acetylenic fatty acids. However, Khan, *et al.*,[5] have shown that stearolic acid (9-octadecynoic acid) has no induction period and that it autoxidizes more rapidly than oleic acid. The rapid autoxidation of this enynic acid is, therefore, not surprising.

Methyl crepenynate took up 1.08 moles of hydrogen using Lindlar catalyst.[6,7] The partially reduced free acid (III) on the basis of treatment with lipoxidase as described by MacGee[8] assayed 60.1% *cis,cis* methylene interrupted unsaturation. Using identical assay conditions, crepenynic acid (IV) was not a substrate for lipoxidase.

Methyl crepenynate was optically inactive and took up 3.06 moles of hydrogen using platinum oxide catalyst. G.l.c. analyses of the recovered product (II) showed only methyl stearate. The recovered material was further identified as methyl stearate by melting point and mixture melting point. These data establish that crepenynic acid has a straight-chain C_{18} skeleton.

Methyl crepenynate was converted to the corresponding acid (IV) by cold saponification. The infrared and ultraviolet spectra[7] of the free acid were similar to the spectra of the usual *cis* C_{18}-unsaturated acids. The neutralization equivalent of IV was 279.1 and the iodine value (Wijs, 1 hr.) was 175.6. This iodine value is consistent with formulation IV since under the conditions used acetylenic bonds are known to absorb only 1 mole of iodine.[9] The calculated iodine value on the basis of this assumption is 182.3. The acid IV

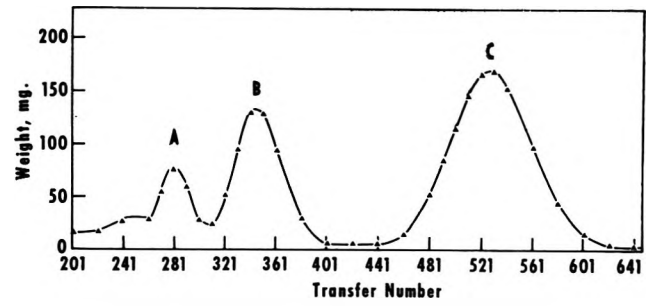


Fig. 1.—Countercurrent distribution of *Crepis foetida* L. methyl esters in acetonitrile–hexane.

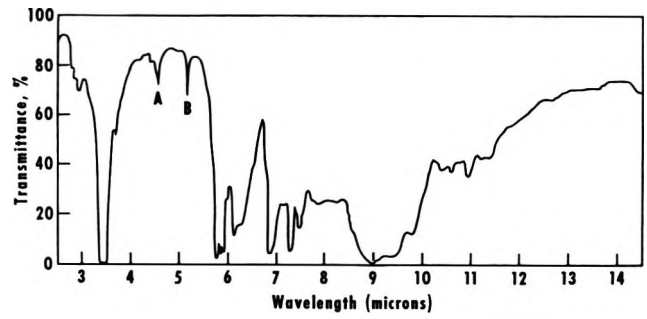


Fig. 2.—Infrared spectrum of steam-volatile aldehydes (2.5% in carbon tetrachloride) obtained by acid periodate oxidation of *threo*-9,10-dihydroxyoctadec-12-ynoic acid (IX).

was oxidized with periodate–permanganate,[10] and g.l.c. analyses of methyl esters prepared from the crude oxidation mixture showed predominantly nonanedioic acid (VIII, 52.5%) and *n*-hexanoic acid (VI, 30.6%). The monobasic acid (VI) obtained by steam distillation, was identified as *n*-hexanoic acid by melting point and the mixture melting point of its anilide. These data place the unsaturation at C-9 and C-12.

The double bond in IV was epoxidized with peracetic acid.[11] The purity of the epoxide was determined by titration with hydrobromic acid in glacial acetic acid according to Durbetaki.[12] This acid (V) has not been reported in the literature.

The epoxidized acetylenic acid (V) was converted to the *threo*-acetylenic diol[13] (IX) by acetylation and saponification. After purification, this acid absorbed 2.04 moles of hydrogen. The product was identified as *threo*-9,10-dihydroxystearic acid by mixture melting point and by oxidative cleavage.

The dihydroxy acetylenic acid (IX) also was cleaved by acid periodate as described by King.[14] The steam volatile aldehydes (X) were not identified; however, the infrared spectrum (Fig. 2) shows a band at 2205 cm.$^{-1}$ (A) and a weaker band at 2275 cm.$^{-1}$. One band is probably due to an α,β-acetylenic aldehyde and the other to a β,γ-acetylenic aldehyde.[15] The band at 1940 cm.$^{-1}$ (B) is probably due to an allene.[16] Precedents for bond migration during acid periodate

(4) Mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

(5) N. A. Khan, J. B. Brown, and F. E. Deatherage, *J. Am. Oil Chemists' Soc.*, **28**, 105 (1951).

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

(7) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths Scientific Publications, Ltd., London, England, 1955, pp. 200, 209.

(8) J. MacGee, *Anal. Chem.*, **31**, 298 (1959).

(9) E. M. Meade, "Progress in the Chemistry of Fats and Other Lipids," Vol. 4, R. T. Holman, W. O. Lundberg, and T. Malkin, Ed., Pergamon Press, London, England, 1957, p. 58.

(10) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955); E. von Rudloff, *J. Am. Oil Chemists' Soc.*, **33**, 126 (1956).

(11) J. G. Sharefkin and E. M. Boghosian, *Anal. Chem.*, **33**, 640 (1961).

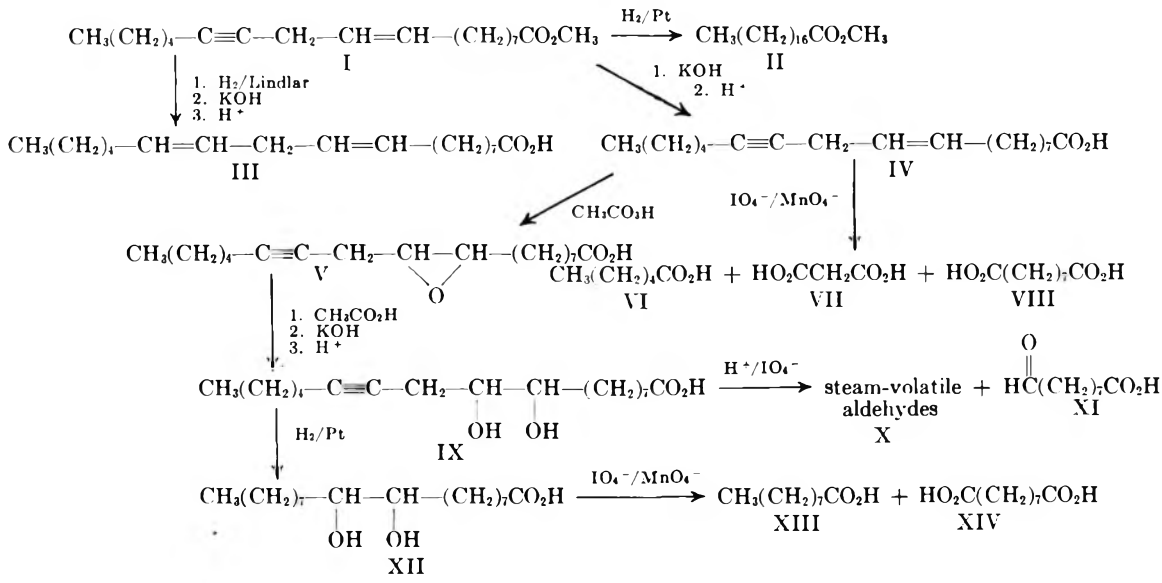
(12) A. J. Durbetaki, *ibid.*, **28**, 2000 (1956).

(13) R. A. Raphael, *J. Chem. Soc.*, S44 (1949).

(14) G. King, *ibid.*, 1826 (1938).

(15) L. M. Piaux, M. Durand, and L. Henry, *Compt. rend.*, **242**, 2650 (1956).

(16) J. H. Wotiz and W. D. Celmer, *J. Am. Chem. Soc.*, **74**, 1860 (1952).



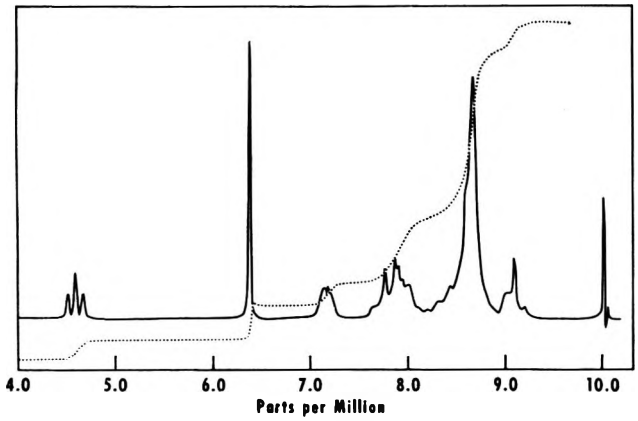


Fig. 3.—Nuclear magnetic resonance spectrum of methyl crepenynate.

oxidation of β,γ olefins are known[17,18]; however, the only acid periodate oxidation of an acetylenic diol involved α,β unsaturation.[19] Thin layer chromatography of the 2,4-dinitrophenylhydrazones of the steam volatile aldehydes also demonstrated that a mixture was obtained.

The aldehyde acid (XI) was obtained by extraction of the steam nonvolatile residue and identified as azelaaldehydic acid by melting point and mixture melting point of its 2,4-dinitrophenylhydrazone. These results establish that the *cis* double bond is in the 9,10-position, and that the triple bond is in the 12,13-position. Therefore, the structure of crepenynic acid is the previously unknown *cis*-9-octadecen-12-ynoic acid.

The n.m.r. spectrum of methyl crepenynate (see Fig. 3) is in accord with the structure assigned on chemical grounds. The observed peaks for methyl crepenynate were assigned based on structure I, and the number of protons was determined by the relative areas. Table I summarizes the data.

TABLE I

SHIFTS, ASSIGNMENTS, AND NUMBER OF PROTONS OBSERVED IN THE NUCLEAR MAGNETIC RESONANCE SPECTRUM OF I[a]

Assignment	τ-values	Number of protons
CH_3 terminal	9.08	3
CH_2 in chain	8.64	16
CH_2 α to unsaturated carbons	7.9	4
CH_2 α to carboxyl	7.77	2
CH_2 of 1,4-unsaturation	7.16	2
OCH_3	6.37	3
Olefinic H	4.58	2

[a] The chemical shifts are given in terms of τ-values as defined by G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

The appearance of a poorly defined doublet for the methylene of the 1,4-enyne system (τ 7.16) contrasts to the usual triplet obtained from the methylene of the 1,4-diene of methyl linoleate.[20]

Discussion

Crepenynic acid has not been reported in the literature, although in recent years numerous syntheses of long-chain acids containing triple bonds have been accomplished using acetylenic intermediates. Osbond[21] and de Gaudemaris and Arnaud[22] synthesized *cis*-12-octadecen-9-ynoic acid, and the latter authors also reported preparation of the *trans* isomer of crepenynic acid.

Meade[23] has published a comprehensive review of the known naturally occurring acetylenic fatty acids. Since appearance of that review, ximenynic (*trans*-11-octadecen-9-ynoic) acid has been found in numerous seed oils of the Santalaceae.[24–27] In general, previously known naturally occurring acetylenic fatty acids fall in one of two classes: The acetylenic group either comprises the only center of unsaturation in the

(17) F. D. Gunstone, *J. Chem. Soc.*, 1611 (1954).

(18) C. R. Smith, Jr., M. O. Bagby, R. L. Lohmar, C. A. Glass, and I. A. Wolff, *J. Org. Chem.*, **25**, 218 (1960).

(19)(a) F. D. Gunstone and W. C. Russell, *J. Chem. Soc.*, 3782 (1955); (b) NOTE ADDED IN PROOF.—Since this paper was submitted, Winter has reported a periodate oxidation of a β,γ-acetylenic diol that resulted in formation of a β,γ-acetylenic aldehyde, a conjugated allenic aldehyde, and the enol form of the acetylenic aldehyde [M. Winter, *Helv. Chim. Acta*, **46**, 1749 (1963)].

(20) W. H. Storey, Jr., *J. Am. Oil Chemists' Soc.*, **37**, 676 (1960).

(21) J. M. Osbond, *J. Chem. Soc.*, 5270 (1961).

(22) M. de Gaudemaris and P. Arnaud, *Bull. soc. chim. France*, 315 (1962).

(23) Ref. 9, pp. 45–62.

(24) H. H. Hatt and R. Schoenfeld, *J. Sci. Food Agr.*, **7**, 130 (1956).

(25) H. H. Hatt, A. C. K. Triffett, and P. C. Wailes, *Australian J. Chem.*, **12**, 190 (1959).

(26) H. H. Hatt, A. C. K. Triffett, and P. C. Wailes, *ibid.*, **13**, 488 (1960).

(27) K. L. Mikolajczak, F. R. Earle, and I. A. Wolff, *J. Am. Oil Chemists' Soc.*, **40**, 342 (1963).

molecule or is conjugated with another double or triple bond. The discovery of crepenynic acid provides a new class of natural acetylenic acids having close relationship to the nutritionally important and widely occurring[30] polyolefinic fatty acids, such as linoleic and linolenic acid, which contain methylene interrupted unsaturation. The positions of unsaturation in crepenynic acid follow the biogenetic patterns proposed by Lovern[28] and by Klenk and Debuch,[29] whereas the previously known naturally occurring polyunsaturated[30] acetylenic fatty acids do not. Crepenynic acid may be biosynthetically related to such other acids as linoleic or vernolic (*cis*-12,13-epoxyoleic) acids, since both of these also occur frequently in substantial quantities in seed oils of Compositae. It is conceivable that the dihydroxyoleic acid speculated to be an intermediate in vernolic acid biosynthesis[31] may in this plant be dehydrated enzymatically to crepenynic acid. However, no experimental evidence has yet been obtained on its mode of biosynthesis.

Limited screening for antimicrobial activity showed that crepenynic acid methyl ester has good inhibition toward *Trichophyton rubrum* and *Microsporum nanum*.[32]

Further research is in progress in the authors' laboratory on the mechanism of the rearrangement of crepenynic acid which occurs under the influence of alkali. The existence of this acid in substantial quantities in *Crepis* seed oil suggests that cultivation of the plant be tried to provide a convenient source of the acid for nutritional experiments, synthesis of labeled olefinic acids, studies of biosynthesis of unsaturated fatty acids, and for study of its possible utility as an industrial raw material.

Experimental[33]

Preparation and Isomerization of *Crepis foetida* L. Seed Oil.—Ground seeds of *Crepis foetida* were extracted overnight with petroleum ether (b.p. 30–60°) in a Soxhlet apparatus. Most of the solvent was removed on a steam bath in a stream of nitrogen, and the remainder was removed *in vacuo* with a rotary evaporator. The ground seeds yielded 22.0% oil.

Alkali isomerization[3] of *Crepis* oil gave ultraviolet absorption equivalent to 88% of conjugated linolenic acid after the 25-min. reaction time. An aliquot removed after only 3 min. gave absorption equivalent to 142% of conjugated linolenic acid, λ_{max}^{EtOH} 268 mμ ($E_{1\ cm}^{1\%}$ 721).

Isolation of Methyl *cis*-9-Octadecen-12-ynoate (I) from *Crepis foetida* L. Seed Oil.—Methyl esters were prepared by refluxing 14.1 g. of oil with 110 ml. of *ca.* 4% hydrochloric acid in methanol, and 80 ml. of benzene under nitrogen for 3 hr. The reaction mixture was concentrated, diluted with four volumes of water and extracted with ethyl ether. The extract was dried over anhydrous sodium sulfate. G.l.c. analyses of the methyl esters (13.7 g.) gave the following composition[34]: $C_{14:0}$, 0.1%, $C_{16:0}$, 4.8%; $C_{16:1}$, trace; $C_{18:0}$, 2.9%; $C_{18:1}$, 4.3%; $C_{18:2}$, 27.8%; $C_{20:1}$, 0.3%; and methyl crepenynate, 59.8%. The equivalent chain lengths[35] of methyl crepenynate are 18.10 from an Apiezon L column and 20.65 from an LAC-2-R446 column (both 20% liquid phase on 60–80-mesh Celite). Infrared examination of the esters as a film on sodium chloride plates showed no unusual bands, and ultraviolet analysis of an ethanolic solution of the esters showed 1.6% conjugated diene and 0.7% conjugated triene.

The mixed methyl esters (13.5 g.) were divided evenly among the first six tubes of a 200-tube countercurrent distribution apparatus with 40 ml. of lower phase (acetonitrile) and 12.5 ml. of upper phase (*n*-hexane). The remaining tubes each contained 40 ml. of acetonitrile. The instrument was set to deliver 12.5 ml. of upper phase into the first tube after each transfer. Fraction collection began with transfer 201, allowing two transfers (25 ml.) to collect in each tube. A total of 530 transfers was collected, and the solvent was removed from selected fractions to obtain the weight distribution plot (Fig. 1). Based on g.l.c. analyses of significant fractions, transfers 481–500 were combined to give 0.82 g. of material containing 99.1% of methyl crepenynate and 0.9% of apparent methyl linoleate. Likewise, transfers 501–582 were combined to give 5.20 g. of methyl esters containing 99.8% of the acetylenic material. Ultraviolet analysis indicated only a trace of absorption in the diene region. Total recovery of the acetylenic ester from countercurrent distribution was 6.75 g. of essentially pure material. Recovery of all material was 12.2 g. or 90.5%.

Hydrogenation of Methyl *cis*-9-Octadecen-12-ynoate (I). A. With Platinum Oxide Catalyst.—A 0.024-g. portion of I, dissolved in ethanol, absorbed 3.06 moles of hydrogen using platinum oxide catalyst. G.l.c. analyses of the reduced material (II, 0.018 g.) showed only methyl stearate. This was confirmed by melting point (35.5–36.0°) and mixture melting point (35.0–35.5°) with an authentic specimen melting at 34–35°.

B. With Lindlar Catalyst.—A 0.049-g. portion of I in ethanol was hydrogenated at room temperature and atmospheric pressure using 20 mg. of freshly prepared Lindlar catalyst and 0.1 mg. of quinoline. The reaction ceased after 1.08 moles of hydrogen per mole of I had been taken up. G.l.c. analyses of the reduced product indicated 71.4% of apparent linoleate, 11.1% of I, 3.1% of conjugated triene, and 14.4% of short-chain material. Crude III, obtained by saponifying the reduction mixture with ethanolic potassium hydroxide, had 60.1% of *cis,cis* methylene interrupted unsaturation as determined by lipoxidase isomerization.[8] Crepenynic acid (IV) showed no reaction with lipoxidase. The differences in apparent per cent linoleate can probably be accounted for by the formation of *trans* unsaturation during the reduction[36] and by autoxidation of methyl crepenynate (I).

Saponification of I.—A 1.0-g. sample of I was saponified by stirring with 25 ml. of 0.5 *N* ethanolic potassium hydroxide for 2.5 hr. under nitrogen at room temperature. The saponification mixture was acidified, extracted with ethyl ether, and dried over sodium sulfate. The recovered acid (IV) had a neutralization equivalent of 279.1, (theoretical, 278.4) and an iodine value (Wijs, 1 hr.) of 175.6 (theoretical, 182.3). Infrared and ultraviolet spectra showed no unusual absorption.

Periodate–Permanganate Oxidation of *cis*-9-Octadecen-12-ynoic Acid (IV).—A 0.204-g. portion of IV was stirred at room temperature for 19 hr. with 300 ml. of an aqueous solution containing 0.023 g. of potassium permanganate, 2.570 g. of sodium periodate, and 0.404 g. of potassium carbonate. The resulting solution was treated with sodium metabisulfite and acidified. The acidified solution was saturated with sodium chloride and extracted exhaustively with ethyl ether; a yield of 0.190 g. of products was obtained. Methyl esters were prepared from a portion of this mixture by refluxing with *ca.* 4% hydrochloric acid in methanol, recovered, and subjected to g.l.c. analysis. The following composition was obtained: methyl hexanoate, 30.6%; methyl nonanedioate, 52.5%; other dibasic acid esters, 12.6%; and unidentified components, 4.2%.

(28) J. A. Lovern, *J. Sci. Food Agr.*, **9**, 773 (1958).

(29) E. Klenk and H. Debuch, "Annual Reviews of Biochemistry," Vol. 28, J. M. Luck, *et al.*, Ed., Annual Reviews, Inc., Palo Alto, Calif., p. 39.

(30) For convenience, polyunsaturated acids refer to all acids with two or more unsaturated centers.

(31) T. K. Miwa, F. R. Earle, G. C. Miwa, and I. A. Wolff, *J. Am. Oil Chemists' Soc.*, **40**, 225 (1963).

(32) Private communication, A. K. Novak, Department of Food, Science, and Technology, Louisiana State University, Baton Rouge, La.

(33) Infrared spectra were obtained with a Perkin-Elmer Model 137-0061 spectrophotometer. Ultraviolet spectra were obtained with either a Beckman DU or a Cary recording spectrophotometer. The n.m.r. spectrum was determined with a Varian A-60 spectrometer on a carbon tetrachloride solution containing 1.2% of tetramethylsilane. G.l.c. analyses were obtained using a Burrell Kromo-Tog K-5 equipped with both Apiezon L and LAC-2-R 446 columns. All g.l.c. identifications are based on retention characteristics of the materials in both polar and nonpolar columns as compared to the retention characteristics of similar known compounds (see ref. 35). Per cents of components obtained by g.l.c. analyses are area per cents. Melting points were determined on a Fisher-Johns block and are uncorrected.

(34) Subscripts indicate the number of carbon atoms and the number of double bonds in the fatty acids.

(35) T. K. Miwa, K. L. Mikolajczak, F. R. Earle, and I. A. Wolff, *Anal. Chem.*, **32**, 1739 (1960).

(36) R. R. Allen, *J. Am. Oil Chemists' Soc.*, **33**, 301 (1956).

The remaining oxidation mixture was steam distilled. The distillate was saturated with sodium chloride and extracted with ethyl ether to yield 0.025 g. of VI, which was reacted with 0.050 g. of aniline according to McElvain.[37] The anilide that separated as an oil was extracted from ethanol with 1:1 benzene–petroleum ether solution. After recrystallization from this solvent system, the anilide of VI melted at 92–94°. After two additional recrystallizations, 0.008 g. of product was obtained, m.p. 94.0–94.5°. The melting point of this material mixed with authentic caproanilide (m p. 95.5°) was 94.5–95.0°.

The steam nonvolatile residue was extracted with ethyl ether to yield 0.065 g. of crude VIII, m.p. 80–86°. No further work was done with this mixture of dibasic acids. The malonic acid fragment was not recovered.

Epoxidation of IV.—A sample of IV (0.900 g.) was stirred at 23–25° for 4 hr. with 7.0 ml. of a 9.0% solution of peracetic acid in glacial acetic acid. The mixture was diluted with an equal volume of ice water, and the oil that separated was extracted with ethyl ether. The extract was concentrated to 15 ml., washed thoroughly with water, and dried over sodium sulfate. A light yellow oil (0.917 g.) remained after removal of solvent. The Durbetaki titration with hydrobromic acid[12] showed 4.6% of oxirane oxygen (equivalent to 85.5% epoxyacetylenic acid) in the crude product (V). Recrystallization from petroleum ether (b.p. 30–60°) at 0° yielded 0.632 g. of a white solid, m.p. 35–37° A second recrystallization from petroleum ether at 8° gave nearly pure V, m.p. 37.5–38°, hydrobromic acid titration equivalent to 99.8% of epoxyacetylenic acid.

Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.42; H, 10.27. Found: C, 73.5; H, 10.4.

Preparation of *threo*-9,10-Dihydroxyoctadec-12-ynoic Acid (IX).—A sample of V (0.346 g.) was refluxed with 10 ml. of glacial acetic acid; the product was recovered and saponified essentially as described by Smith, *et al.*[18] The crude IX obtained (0.296 g.) melted at 69–71.5°. The crude dihydroxyacetylenic acid was recrystallized first from ethyl acetate–petroleum ether at −18° and then from ethyl acetate at −18° to yield 0.217 g. of product, m.p. 72–72.5°.

Anal. Calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.5; H, 10.3.

Preparation of *threo*-9,10-Dihydroxystearic Acid (XII).—A 0.049-g. portion of IX was hydrogenated at room temperature and atmospheric pressure using platinum oxide catalyst. Compound IX took up 2.04 moles of hydrogen per mole of acid. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to give 0.044 g. of crude XII, m.p. 93°. Compound XII mixed with *threo*-9,10-dihydroxystearic acid (m.p. 92–93°) melted at 92–93°. An admixture of XII with *threo*-12,13-dihydroxystearic acid (m.p. 94–96°) melted at 82–90°.

Periodate–Permanganate Oxidation of XII.—The remaining portion (0.041 g.) of XII was oxidized and recovered as described for IV, except that the reaction time was 16 hr. Methyl esters of the crude oxidation mixture (0.012 g.) were prepared by refluxing with hydrochloric acid–methanol. G.l.c. analyses of the methyl esters showed 36.8% of methyl nonanoate (XIII, pelargonate), 59.2% of methyl nonanedioate (XIV, azelate), and 4.0% of minor components. Compound XIII was identified only by its g.l.c. retention characteristics.[35] The remaining oxidation mixture was triturated with petroleum ether (b.p. 30–60°) to give crude XIV, m.p. 92–99°. After recrystallization from a large volume of ethyl acetate–petroleum ether at 5°, compound XIV melted at 106.5–107°. An admixture with authentic nonanedioic acid (m.p. 104.5–106°) melted at 105–106°.

Periodate Oxidation of IX.—A portion (0.026 g.) of IX was dissolved in 3 ml. of ethanol, 0.022 g. of sodium metaperiodate in 2.5 ml. of 1 *N* sulfuric acid was added and the solution stirred at 40 ± 2° for 15 min. The mixture was diluted with ice water and extracted with ethyl ether. Solvent was removed *in vacuo* at room temperature, and the product was steam distilled. The steam nonvolatile residue was extracted with ethyl ether and 0.013 g. of crude XI was obtained. The steam volatile portion (X) was shown by infrared spectroscopy to be a complex mixture (Fig. 2). Attempts to prepare the 2,4-dinitrophenylhydrazone resulted in an oil which was shown to be a mixture by thin layer chromatography.

The entire 0.013 g. of crude XI was redissolved in ethyl ether (5 ml.), and 2.5 ml. of this solution was placed in a test tube. The ether was removed with a stream of nitrogen and the 2,4-dinitrophenylhydrazone was prepared.[38] The mixture was allowed to stand at room temperature, and a yellow precipitate formed in 3 min. The crystals were filtered off by suction, washed well with water, and dried to yield 0.010 g. of a yellow crystalline product, m.p. 106–112°. Two recrystallizations from benzene–petroleum ether (b.p. 30–60°) yielded 0.006 g. of product, m.p. 120–121°, lit.[39] m.p. 122–122.5°. The mixture melting point of this product with authentic azelaaldehyde 2,4-dinitrophenylhydrazone (m.p. 120–121°) was also 120–121°.

Purification of Autoxidized I.—Carbon and hydrogen analyses of I were not obtained until after autoxidation had begun; hence a portion was purified for these analyses. Pure methyl crepenynate was separated from the oxidation products by countercurrent distribution between acetonitrile and *n*-hexane in a 30-tube apparatus. The course of the separation was followed by thin layer chromatography on silica gel G plates developed in 3% ethyl ether–petroleum ether. The chromatograms were charred with 50% sulfuric acid. Pure methyl crepenynate was obtained in transfers 40–65, and the oxidized material remained in the first 12 tubes. The combined fractions, 40–65, were placed in a nitrogen atmosphere, and the solvent was removed *in vacuo* under subdued light. Carbon and hydrogen analyses as well as the n.m.r. spectrum (Fig. 3) were obtained on this purified material.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.8; H, 11.0.

Acknowledgment.—The authors are grateful to C. A. Glass for the n.m.r. analysis, to Mrs. Bonita Heaton for microanalyses, to J. W. Hagemann and Mrs. Donna Thomas for gas chromatographic analyses, and to Quentin Jones, Crops Research Division, Agricultural Research Service, Beltsville, Maryland, for supplying seeds and the necessary botanical information.

(37) S. M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1953, p. 189.

(38) 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. 219.

(39) G. King, *J. Chem. Soc.*, 1791 (1936).

Multinuclear Ferrocenes. II. Syntheses of Substituted Biferrocenyls[1-3]

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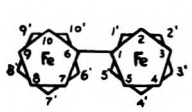
It has been found possible to effect coupling of substituted haloferrocenes by means of treatment with activated copper bronze to yield substituted biferrocenyls. In addition to coupling products, significant amounts of ferrocene derivatives are obtained which appear to result from formal replacement of halogen by hydrogen in the starting material.

Study of systems composed of directly bonded ferrocene nuclei has thus far encompassed only methods of preparation of the simplest member of this group, biferrocenyl (**1**).[4] It is apparent that progress in this field would be enhanced with the availability of reliable methods for obtaining biferrocenyl derivatives with known disposition of substituents. Since a large number of isomers are possible *via* direct substitution of biferrocenyl, the uncertainties surrounding preparation of a desired biferrocenyl derivative by means of a direct substitution process are obvious. In an effort to circumvent these difficulties, we have explored the feasibility of obtaining substituted biferrocenyls by means of direct coupling of substituted haloferrocenes. This strategy proved to be successful, and we wish to report representative examples of such syntheses.

Before doing so, however, it is necessary, because of the complexity of isomeric possibilities, to establish a nomenclature convention which will allow unambiguous designation of individual isomeric biferrocenyl derivatives. This purpose is accomplished in a simple way by merely defining a numbering system for the biferrocenyl nucleus in which unprimed numbers are assigned to the two directly bonded cyclopentadienyl rings with the lowest numbers (1 and 6) reserved for the ring-assembly atoms. Carbon atoms of each of the two nondirectly bonded rings are assigned primed numbers which correspond to the unprimed numbers assigned directly "above" when the molecule is oriented in the conformation shown in **1**. In this way, position isomers are readily and unequivocally designed. Thus, 2,6′-dimethylbiferrocenyl represents **2** and not **3** (1′,2-dimethylbiferrocenyl).



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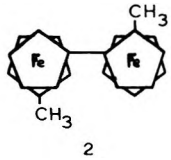

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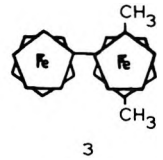

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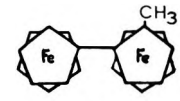
This numbering system also may be used eventually to designate absolute configuration of enantiomers by specifying the sequence (clockwise or counterclockwise) in which the numbers are assigned. If, for example, a clockwise sequence is used then absolute configurations of the two enantiomers, **4** and **5**, are incorporated into



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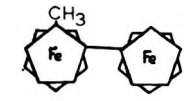

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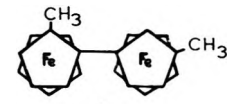
the systematic names, 2-methylbiferrocenyl and 10-methylbiferrocenyl, respectively.

Use of the specified numbering sequence possesses another advantage, perhaps even more important. The convention eliminates the difficulty of distinguishing between isomers in which the location of one substituent relative to another would be otherwise ambiguous. Thus, **6** and **7** may be unequivocally designated as 3,10-dimethylbiferrocenyl and 4,10-dimethylbiferrocenyl, respectively.



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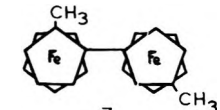

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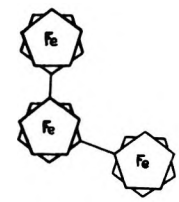
Finally, while systems composed of more than two directly bonded ferrocene nuclei have not been reported as yet, appearance of such molecules may be expected and the presently proposed nomenclature convention may be used as a basis for naming these molecules and their derivatives. For example, the three isomeric terferrocenyls, **8**, **9**, and **10**, may be conveniently named as substituted biferrocenyls, 1′-ferrocenylbiferrocenyl, 2-ferrocenylbiferrocenyl, and 3-ferrocenylbiferrocenyl, respectively.



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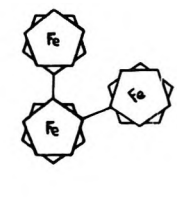

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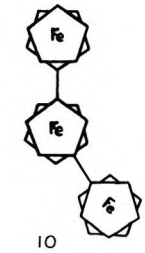

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The key compound used in the present investigation for the representative syntheses described later was 1-bromo-1′-acetylferrocene (**11**) which was obtained *via* acetylation of bromoferrocene (**12**). Compound **11** was prepared originally by Nesmeyanov, Sazonova, and Drozd[5] who, as did Hall and Richards[6] after them, assigned the heteroannular structure because of the absence of absorption near 9 and 10 μ in the infrared spectrum determined from this acetylation product. While the 9–10 rule has proved to be a reliable empirical

(1) Previous paper in this series: S. I. Goldberg, D. W. Mayo, and J. A. Alford, *J. Org. Chem.*, **28**, 1708 (1963).

(2) We are pleased to acknowledge generous support of this work by the National Science Foundation, Grant G24083. We also wish to express our sincere gratitude to that agency for an institutional grant which made possible the purchase of the n.m.r. spectrometer used in this work.

(3) Taken in part from the M.S. thesis of R. L. Matteson, University of South Carolina, 1963.

(4) See ref. 1 and work cited therein.

(5) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **137**, 102 (1961).

(6) D. W. Hall and J. H. Richards, *J. Org. Chem.*, **28**, 1549 (1963).

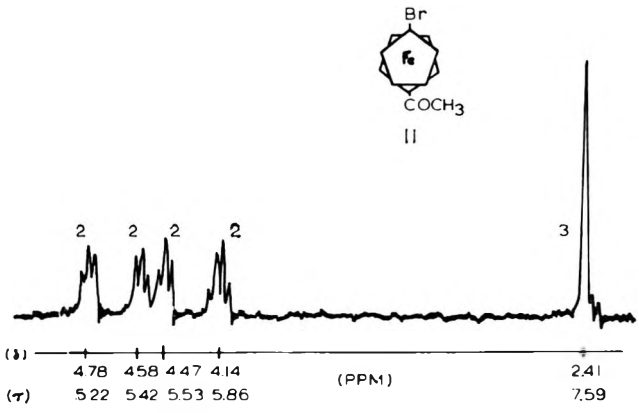

Figure 1.

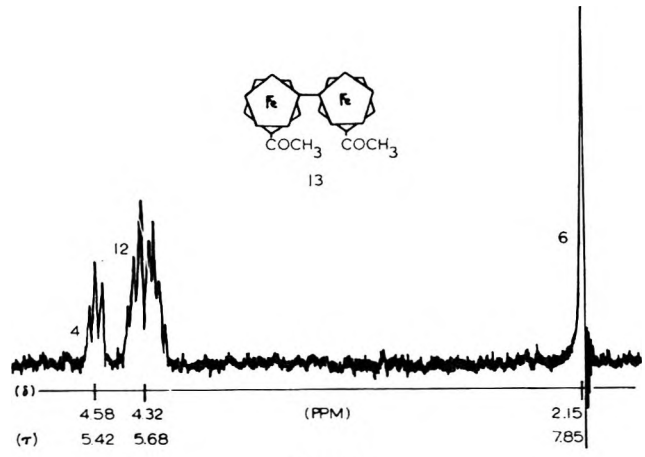

Figure 2.

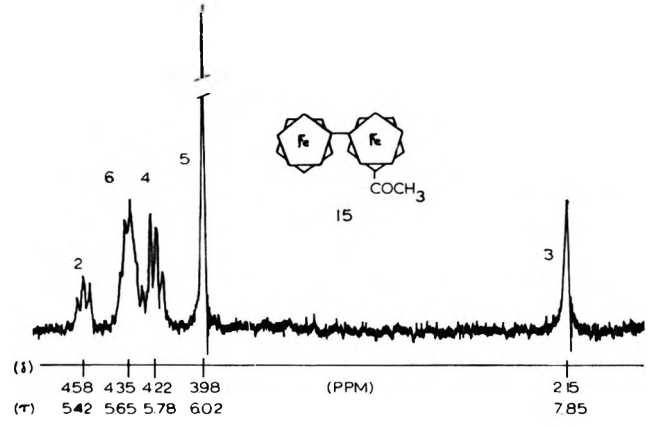

Figure 3.

generalization,[7] it was highly desirable for our purpose to obtain independent evidence for the heteroannular disposition of bromo and acetyl groups. Confirmation was readily obtained by examination of the n.m.r. spectrum (Fig. 1) determined from the acetylation product (**11**) of bromoferrocene. The absence of a signal near τ 6 provided the desired confirmation since this is the region in which a signal due to the equivalent protons of an unsubstituted cyclopentadienyl ring in a ferrocene compound appears. The signals present in the spectrum (Fig. 1) may be assigned by means of comparison with the individual n.m.r. spectra obtained from acetylferrocene and bromoferrocene. Thus, the two-proton triplet (J = 2 c.p.s.) at 5.22 τ is due to the two equivalent protons (2′ and 5′) which flank the acetyl group in **11** [two-proton triplet (J = 2 c.p.s.) at 5.25 τ from acetylferrocene]. The pair of two-proton triplets (J = 2 c.p.s.) at 5.42 and 5.53 τ are assigned to each pair of equivalent protons at 3′ and 4′, and 2 and 5, respectively, since the β-protons in acetylferrocene appear at lower field (5.53 τ) than do the α-protons of bromoferrocene (5.78 τ). The remaining two-proton triplet (J = 2 c.p.s.) at 5.86 τ arises from the equivalent protons at 3 and 4 (5.83 τ for β-protons in bromoferrocene). Finally, the three-proton singlet at 7.59 τ of the acetyl methyl group in **11** is found at 7.63 τ in acetylferrocene.

Treatment of **11** with activated copper bronze[8] gave rise to one product (31% yield) which was shown to be 1′,6′-diacetylbiferrocenyl (**13**) by means of its n.m.r. spectrum (Fig. 2). The four-proton triplet (J = 2 c.p.s.) at 5.42 τ is assigned to the four equivalent protons which flank the two equivalent acetyl groups [seen as the six-proton singlet at 7.85 τ]. The remaining metallocene protons give rise to the complex twelve-proton signal centered at 5.68 τ.

The reaction also produced acetylferrocene (**14**) in 39% yield. This result is not surprising in light of the fact that similar treatment of iodoferrocene leads to ferrocene as well as biferrocenyl.[4]

Formal replacement of halogen by hydrogen as well as coupling of haloferrocenes appears to be a consistent feature of this Ullmann-like process. Thus, treatment of a mixture of bromoferrocene (**12**) and 1-bromo-1′-acetylferrocene (**11**) gives rise to the three coupling products, 1′,6′-diacetylbiferrocenyl (**13**), 1′-acetylbiferrocenyl (**15**), and biferrocenyl (**1**), as well as the debromo compounds, ferrocene and acetylferrocene. Assignment of structure to **15** was readily made on the basis of the n.m.r. spectrum (Fig. 3) determined from the purified material. The two equivalent protons adjacent the acetyl group (seen as a three-proton singlet at 7.85 τ) give rise to the two-proton triplet (J = 2 c.p.s.) at 5.42 τ, and the four equivalent protons flanking the ring assembly atoms appear as a four-proton triplet (J = 2 c.p.s.) at 5.78 τ. The presence of one unsubstituted cyclopentadienyl ring is seen by the five-proton singlet at 6.02 τ, while the remaining protons appear as a broad complex signal centered at 5.65 τ.

Production of the coupling products and formation of the debromo compounds is suggestive of a free-radical process. While this explanation is attractive and does account for the observed results, no direct evidence has been obtained which supports generation and participation of ferrocenyl free radicals. Indeed, formation of the coupling products may occur by a different process and the debromo compounds may be accounted for in terms of electrophilic (proton) replacement of bromine. This latter mechanism represents a real possibility since the copper catalysts used are activated with acid[8] and it is likely that some acid is retained in spite of numerous acetone washings (see Fig. 4).

(7) K. L. Pirelart, Jr., K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957); M. Rosenblum and R. B. Woodward, *ibid.*, **80**, 5443 (1958); A. N. Nesmeyanov, L. A. Kazitsyna, B. V. Lokshin, and V. D. Vilchesskaya, *Dokl. Akad. Nauk SSSR*, **128**, 1037 (1959).

(8) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans Green and Co., Inc., New York, N. Y., 1948, p. 188.

Our studies have not as yet proceeded to the point where we are able to distinguish among the mechanistic possibilities.

Experimental

Temperature measurements are uncorrected. Ultraviolet spectra were determined with a Carey, Model 14, recording spectrophotometer, infrared spectra with a Perkin-Elmer, Model 21, recording spectrophotometer, and n.m.r. spectra with a Varian, A-60, spectrometer at 60 Mc., employing a room temperature probe with chloroform solvent containing approximately 5% (v./v.) tetramethylsilane as interval standard. Combustion analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

All column chromatograms were performed on Merck, acid-washed alumina, using purified elution solvents. Columns were wrapped with aluminum foil to protect the developed chromatograms from light.

Ferroceneboronic Acid and 1,1′-Ferrocenediboronic Acid.[9]—Ferrocene (30.0 g., 0.160 mole), dissolved in a mixture of 330 ml. of pure dry tetrahydrofuran and 50 ml. of pure dry ether, was cooled to −40° with an external Dry Ice–acetone bath and kept under an atmosphere of purified nitrogen while *n*-butyllithium (286 ml. of 1.5 *N*) in hexane solution[10] was added at such a rate so as not to allow the temperature of the reaction mixture to rise above −30°. After all of the *n*-butyllithium had been added, the reaction mixture was stirred during 3 hr. at −30° and then allowed to warm to room temperature and remain, with stirring, overnight. The entire solution was then transferred carefully to an addition funnel through which it was added to a cold (−50°) solution of tri-*n*-butyl borate (72.5 g., 0.310 mole in 50 ml. of pure dry ether) at a rate which did not allow a rise in temperature. The reaction mixture was stirred during 3 hr. at −50° after the addition was completed, then allowed to warm to room temperature, and stirred continuously at room temperature overnight. Addition of 150 ml. of 10% aqueous sodium hydroxide solution was followed by another 3-hr. period during which the mixture was stirred at room temperature. The basic aqueous phase was separated, and the organic phase extracted with portions of 10% aqueous sodium hydroxide until the extracts appeared colorless. The combined basic extracts were then carefully acidified with 10% sulfuric acid at 0°, resulting in precipitation of the crude boronic acids which were collected, thoroughly washed with water, and air-dried. Separation of ferroceneboronic acid from the mixture was achieved by submitting the crude product to continuous extraction with ether in a Soxhlet apparatus and obtaining the monoacid by evaporation of the ether extract, 2.0 g. (11% yield). This material possessed an ill-defined melting point (135–150°) which is in agreement with previous observations.[9] The extraction residue was presumed to be crude ferrocenediboronic acid, 2.5 g. (11% yield), m.p. 177° dec., lit.[9] m.p. 180° dec.

Bromoferrocene (12).[9]—Ferroceneboronic acid (2.0 g., 0.009 mole) was heated in the presence of an aqueous solution of copper(II) bromide (1.00 g., 0.009 mole in 400 ml. of water) until the presence of a yellow oil could no longer be detected in the steam distillate. The distillate was phase separated, and the aqueous phase exhaustively extracted with ether. The combined organic material was dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 1.79 g. (74% yield) of bromoferrocene as an orange oil which crystallized upon cooling, m.p. 27–28°, lit.[9] m.p. 31–32°.

Acetylation of Bromoferrocene. 1-Bromo-1′-Acetylferrocene (11).[5]—Bromoferrocene (0.400 g., 0.0016 mole) was mixed with 2 ml. of polyphosphoric acid [2:1 (w./w.), 85% phosphoric acid–phosphorus(V) oxide] and 10 ml. of acetic anhydride and heated with agitation during 10 min. on a steam bath. After the reaction mixture was allowed to cool to room temperature, it was carefully poured into a cold aqueous saturated solution of sodium carbonate and allowed to stand until the odor of acetic acid could no longer be detected. Exhaustive ether extraction of the aqueous mixture was followed by combination drying and evaporation of the ether extracts, giving rise to a semisolid residue which was chromatographed on alumina. Elution with hexane provided some unchanged bromoferrocene, while elution with benzene gave rise to monoacetylated bromoferrocene, 0.280 g. (56% yield), m.p. 57–58° (lit.[5] m.p. 62–63°), which was shown to possess a heteroannular disposition of substituents by an n.m.r. spectrum (13% w./w.) determined from the material.

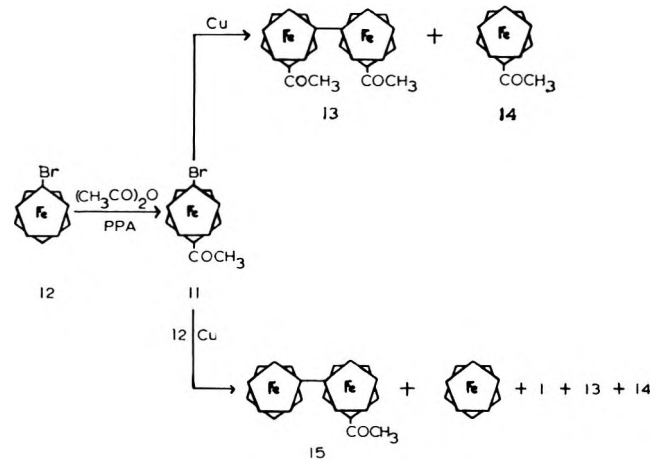

Figure 4.

Anal. Calcd. for $C_{12}H_{11}BrFeO$: C, 46.95; H, 3.61; Br, 26.03. Found: C, 47.16; H, 3.66; Br, 26.06.

Treatment of 1-Bromo-1′-Acetylferrocene (11) with Activated Copper Bronze. Preparation of 1′,6′-Diacetylbiferrocenyl (13).—1-Bromo-1′-acetylferrocene (255 mg., 0.831 mmole) was intimately mixed with 14 g. of activated copper bronze[8] and heated in an atmosphere of purified nitrogen at 75–85° during 18 hr. After the reaction mixture was allowed to cool to room temperature, it was repeatedly extracted with portions of chloroform until the chloroform extracts appeared colorless. The combined chloroform extracts were filtered and evaporated to a solid residue which was chromatographed on alumina. Elution with benzene yielded acetylferrocene (73 mg., 39% yield) which was identified by means of direct comparison with authentic material. Continued elution with 10:1 (v./v.) ether–methanol yielded 1′,6′-diacetylbiferrocenyl (57 mg., 31% yield), m.p. 187–188°; ultraviolet (ethanol), λ_{max} 227 mμ (log ε 4.4), 284 (4.2). For discussion of n.m.r. spectrum (Fig. 2, 5% w./w.), see text.

Anal. Calcd. for $C_{24}H_{22}Fe_2O_2$: C, 63.47; H, 4.88. Found: C, 63.16; H, 4.78.

Treatment of a Mixture of 1-Bromo-1′-Acetylferrocene (11) and Bromoferrocene (12) with Acetylated Copper Bronze.—1-Bromo-1′-acetylferrocene (11, 2.027 g., 0.00662 mole) and bromoferrocene (12, 3.083 g., 0.0122 mole) were intimately mixed with 14 g. of activated copper bronze[8] and heated in an atmosphere of purified nitrogen at 90–92° during 28 hr. The reaction was exhaustively extracted with chloroform at room temperature, and the combined and filtered chloroform extracts yielded a solid residue upon evaporation. Chromatography of the residue on alumina yielded the following compounds in order of their elution.

Elution with hexane provided ferrocene (0.965 g., 42.4% yield)[11] which was identified by means of direct comparison with authentic material.

Continued elution with 4:1 (v./v.) hexane–benzene gave rise to biferrocenyl (1, 0.361 g., 29.6% yield)[12] whose identity was also established by direct comparison with authentic material.

Further elution with 3:2 (v./v.) hexane–benzene caused development of two reddish orange bands. Collection and evaporation of the faster moving band yielded acetylferrocene (14, 0.930 g., 61.6% yield[12]) which was again identified by comparison with authentic acetylferrocene.

Collection of the slower moving, reddish orange band yielded 1′-acetylbiferrocenyl (15, 0.444 g., 16.3% yield), b.p. 137–137.8°;

(9) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **126**, 1004 (1959).

(10) Foote Mineral Co., New Johnsonville, Tenn.

(11) Calculation based upon assumption that bromoferrocene served as the exclusive source of this product.

(12) Calculation based upon assumption that 1-bromo-1′-acetylferrocene served as the exclusive source of this product.

ultraviolet (ethanol), λ_{max} 217 mμ (log ε 4.66), λ_{sh} 260 mμ (log ε 4.10), 292 (4.00). For discussion of n.m.r. spectrum (Fig. 3, 3% w./w.), see text.

Anal. Calcd. for $C_{22}H_{20}Fe_2O$: C, 64.12; H, 4.89. Found: C, 64.23; H, 4.90.

Final elution with 4:1 (v./v.) benzene–ether provided an eluent which, upon evaporation, yielded 1′,6′-diacetylbiferrocenyl (**13**, 0.172 g., 11.4% yield) which was found to be identical with the 1′,6′-diacetylferrocenyl obtained *via* coupling of 1-bromo-1′-acetylferrocene described previously.

Synthesis of 1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline and Perhydro-1*H*-pyrazino[1,2-*a*]quinoline

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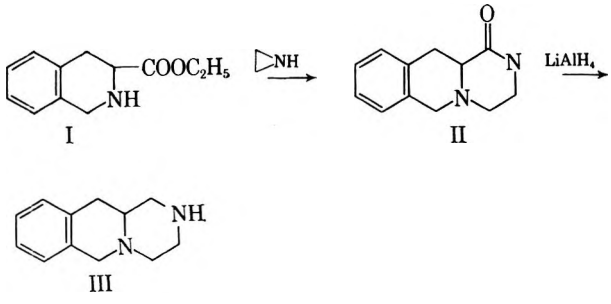
The reactions of ethyleneimine with ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate and ethyl decahydroquinoline-2-carboxylate are reported. Two diastereoisomeric forms of perhydro-1*H*-pyrazino[1,2-*a*]quinoline have been obtained.

In 1960 Freed and Day reported the reaction of ethyleneimine with ethyl 2-piperidinecarboxylate and with ethyl 2-pyrrolidinecarboxylate to form lactams which were reduced with lithium aluminum hydride to the corresponding fused ring piperazines containing a bridgehead nitrogen.[1] Thus a two-step route is available for the synthesis of 1,4-diazabicyclo[4.4.0]decanes and 1,4-diazabicyclo[4.3.0]nonanes. In the present paper we report the reactions of ethyleneimine with ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate and ethyl decahydroquinoline-2-carboxylate.

Ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (I) reacted readily with ethyleneimine to form 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (II). The latter was then reduced with lithium aluminum hydride to give 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline (III).

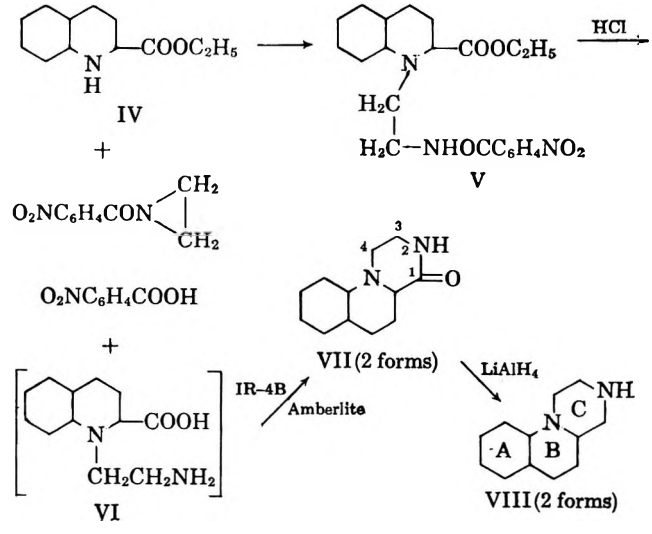


I II III

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline, when heated in benzene solution with one equivalent of ethyl iodide or benzyl chloride, respectively, gave quantitative yields of 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline hydroiodide or the corresponding hydrochloride. These products appear to result from elimination reactions involving tertiary amines or quaternary ammonium compounds, but they were not studied further.

Ethyl decahydroquinoline-2-carboxylate (IV) failed to form a lactam when treated with ethyleneimine and most of the starting ester was recovered. *N*-*p*-Nitrobenzoylethyleneimine has been used for the aminoalkylation of primary and secondary amines[2] and it was found in the present work that it condensed readily with ethyl decahydroquinoline-2-carboxylate. The resulting *p*-nitrobenzamidoethyl derivative (V) was difficult to purify, due, in part, to contamination with 2-*p*-nitrophenyloxazoline which results from a rearrangement of *N*-*p*-nitrobenzoylethyleneimine.[2] Hydrolysis of the *p*-nitrobenzamidoethyl derivative with hydrochloric acid gave a quantitative yield of *p*-nitrobenzoic acid, but efforts to isolate ethyl 1-(2-*p*-nitrobenzamidoethyl) decahydroquinoline-2-carboxylate (VI) by adjusting the pH of the filtrate from the *p*-nitrobenzoic acid were unsuccessful.

An attempt was made to neutralize the filtrate from the *p*-nitrobenzoic acid by passing it through a column of an ion-exchange resin (Amberlite IR-4B). It had been anticipated that compound VI could be isolated from the eluent from the column. Actually this intermediate cyclized spontaneously and separated as lustrous white plates on the resin and in the eluent. The yield of lactam VII was found to be a function of the pH of the eluent, the best yield being obtained at pH 6.0–6.2. The cyclization apparently was resin catalyzed, since a similar adjustment of the pH with sodium bicarbonate was ineffective in causing ring closure. Two compounds were obtained from the crude lactam, by fractional crystallization, melting at 150° and 200°, respectively. Each of the two compounds analyzed correctly for the desired lactam. Their infrared spectra were practically identical.

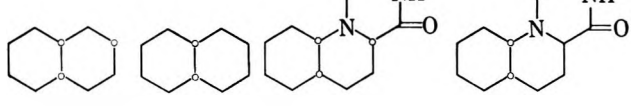


(1) M. E. Freed and A. R. Day, *J. Org. Chem.*, **25**, 2105, 2108 (1960).

(2) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959).

Reduction of the higher melting isomer with lithium aluminum hydride in ether solution proceeded smoothly to give a compound melting at 70–72°. The lower melting lactam failed to reduce in either but was reduced in tetrahydrofuran to form a compound which melted at 50–60°. Both compounds proved to be perhydro-2*H*-pyrazino[1,2-*a*]quinolines (VIII).

In order to arrive at some conclusions concerning the nature of the two forms of VII and the two forms of VIII, an effort was first made to determine the nature of the ring junction in decahydroquinoline-2-carboxylic acid. Since 2-quinolinecarboxylic acid was hydrogenated in glacial acetic acid, it was at first assumed that the ring junction was *trans*. This conclusion was based on the observation of Skita and Meyer[3] that reduction of quinoline to decahydroquinoline in glacial acetic acid gave predominantly the *trans* isomer. However, when decahydroquinoline-2-carboxylic acid was decarboxylated, by heating its acetate at its melting point, to decahydroquinoline, only the *cis* form could be found. The *cis* and *trans* decahydroquinolines have been identified by Clemo, *et al.*[4] They may be separated by fractional crystallization of their hydrochlorides. The latter have widely different melting points, the *cis* form melting at 218° and the *trans* at 283°. The *cis* form was isolated in almost quantitative yield from the decarboxylation process. Thus it would appear that both compounds VII and VIII have a *cis* ring junction in the decahydroquinoline nucleus. The fact that two forms of the lactam were isolated as well as two forms of the final product, perhydro-1*H*-pyrazino[1,2-*a*]quinoline, indicates that the two forms, in each case, must be due to the formation of ring C. The two diasteroisomeric forms of the lactam (VII), and of the perhydro derivative (VIII) are related in the same way as are the two diasteroisomeric forms of *cis*-*β*-decalol. Both diastereoisomers under discussion are *racemic* forms.



Diastereoisomeric forms of *cis*-*β*-decalol

Diastereoisomeric forms of lactam VII

It follows that the starting material, ethyl decahydroquinoline-2-carboxylate, is either a mixture of epimers or is isomerized during its conversion to the lactam so that a mixture of epimers is formed. That the latter is what actually happened is indicated by the fact that the ethyl decahydroquinoline-2-carboxylate hydrochloride appeared to a pure compound; *i.e.*, it had a sharp melting point, could not be fractionally crystallized into two forms, and paper chromatography indicated only one form present.

Experimental

Ethyl 1,2,3,4-Tetrahydroisoquinoline-3-carboxylate Hydrochloride.—1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (100 g., 0.47 mole)[5] was suspended in 4 l. of absolute ethanol. The mixture was saturated with dry hydrogen chloride and then refluxed for 36 hr. The hot mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was extracted with ether and then recrystallized from chloroform–ether, 66% yield, m.p. 178–180°.

Anal. Calcd. for $C_{12}H_{16}NO_2Cl$: C, 59.63; H, 6.66; N, 5.79; Cl, 14.66. Found: C, 59.74; H, 6.68; N, 5.71; Cl, 14.53.

Ethyl 1,2,3,4-Tetrahydroisoquinoline-3-carboxylate (I).—Ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (70 g., 0.29 mole) was suspended in 600 ml. of ether, 100 ml. of triethylamine added, and the mixture stirred for 3 hr. The triethylamine hydrochloride was removed by filtration and the ether and excess triethylamine removed *in vacuo*. Vacuum distillation of the residual oil gave 44 g. (89%) of the free base, b.p. 134° at 0.8 mm.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.36; N, 6.82. Found: C, 70.25; H, 7.34; N, 6.77.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one (II).—Ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (48.8 g., 0.24 mole) and 0.58 g. (0.0024 mole) of its hydrochloride were dissolved in 200 ml. of absolute ethanol. Ethyleneimine (4.7 g., 0.12 mole) in 100 ml. of ethanol was added dropwise, over a period of 3 hr., to the refluxing solution. After 24 hr., an additional 4.7 g. of ethyleneimine was similarly added and refluxing continued for 48 hr. The ethanol was removed *in vacuo*. The residual solid was washed with dry ether and recrystallized from chloroform–ether, 52% yield, m.p. 185–187°; infrared absorption bands, $cm.^{-1}$, phase chloroform: 3400 (m), 2995 (s), 2940 (s), 2750 (m), 1655 (s), 1490 (s), 1320 (s), 1082 (m).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.97; N, 13.84. Found: C, 71.17; H, 7.03; N, 13.61.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline (III).—Lithium aluminum hydride (7.2 g., 0.19 mole) was suspended in 500 ml. of dry ether. To this was slowly added 35 g. (0.17 mole) of 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one. After refluxing for 36 hr., the remaining hydride was decomposed by the careful addition of 50 ml. of water. The mixture was filtered and the residue washed with 100 ml. of 2-propanol. The ether and 2-propanol were removed under reduced pressure. The solid was extracted with ether and the residue removed by filtration. The residue proved to be pure starting material (3 g.), 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-1-one. The ether solution was evaporated leaving an oil, b.p. 170–176° at 5 mm. The oil solidified on standing, 89% yield. The free base was dissolved in dry ether and dried over anhydrous magnesium sulfate. The ether was then evaporated and the residue recrystallized from methanol–hexane, m.p. 85–90°. The analytical data agreed fairly for a monohydrate.

Anal. Calcd. for $C_{12}H_{16}N_2 \cdot H_2O$: C, 69.87; H, 8.79; N, 13.57. Found: C, 70.40; H, 9.19; N, 13.70.

Various conditions were used to dry the product, but it has not been possible up to now to obtain either a pure sample of the free base or a pure sample of a monohydrate. Karl Fischer titrations confirmed the presence of water but the amount varied from sample to sample; infrared absorption bands, $cm.^{-1}$, phase chloroform: 3405 (m), 2930 (s), 2805 (m), 2760 (w), 1655 (s), 1485 (m), 1448 (s), 1340 (m), 1295 (m), 1185 (m), 1085 (m).

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline Methiodide.—The free base was treated with 1 equiv. of methyl iodide. After 30 min. the solid which separated was recrystallized from ethanol–ether, 90% yield, m.p. 250–251°.

Anal. Calcd. for $C_{13}H_{19}N_2I$: C, 47.28; H, 5.80; N, 8.48; I, 38.43. Found: C, 47.45; H, 5.97; N, 8.33; I, 38.23.

N-Phenylthiocarbamyl-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline.—The free base was heated in hexane with a slight excess of phenyl isothiocyanate. On cooling a solid separated which was recrystallized from hexane, m.p. 168–170°, almost quantitative yield.

Anal. Calcd. for $C_{19}H_{21}N_3S$: C, 70.55; H, 6.54; N, 12.98; S, 9.91. Found: C, 70.63; H, 6.30; N, 12.98; S, 9.76.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline Hydrochloride and Hydroiodide.—The free base in benzene solution was refluxed with an equivalent of ethyl iodide. A quantitative yield of 1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline hydroiodide was formed, m.p. 285° dec.

Anal. Calcd. for $C_{12}H_{16}N_2 \cdot HI$: C, 45.58; H, 5.41; N, 8.85; I, 40.14. Found: C, 45.49; H, 5.56; N, 8.75; I, 39.85.

In another experiment the ethyl iodide was replaced with benzyl chloride and a quantitative yield of the hydrochloride was obtained, m.p. 290° dec.

(3) A. Skita and W. A. Meyer, *Ber.*, **46**, 3593 (1913).

(4) G. R. Clemo, J. G. Cook, and R. Raper, *J. Chem. Soc.*, 1183 (1938).

(5) P. L. Julian, W. J. Karpel, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.*, **70**, 182 (1948).

Anal. Calcd. for $C_{12}H_{16}N_2 \cdot HCl$: C, 64.14; H, 7.62; N, 12.46; Cl, 15.77. Found: C, 64.05; H, 7.66; N, 12.32; Cl, 15.68.

2-Benzyl-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline.—1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino[1,2-*b*]isoquinoline (1.9 g., 0.01 mole), 0.01 mole of benzyl chloride, and 0.01 mole of sodium bicarbonate were dissolved in 25 ml. of 1:1 aqueous ethanol and the solution was refluxed for 12 hr. The solvents were removed under reduced pressure. The solid residue was extracted with hot benzene, the mixture filtered, and the filtrate evaporated to dryness. The solid so obtained was recrystallized from hexane, 79% yield, m.p. 106°.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.96; N, 10.05. Found: C, 81.80; H, 7.91; N, 10.10.

2-(β-Hydroxyethyl)-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino 1,2-*b*]isoquinoline.—1,3,4,6,11,11a-Hexahydro-2*H*-pyrazino-[1,2-*b*]isoquinoline (18.8 g., 0.1 mole) and 5 g. (0.11 mole) of ethylene oxide were dissolved in 50 ml. of methanol and the solution allowed to stand for 12 hr. in a pressure bottle. The solvent was then removed and the residual solid was recrystallized from ethanol–hexane, 79% yield, m.p. 145–147°.

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 72.38; H, 8.67; N, 12.05. Found: C, 72.65; H, 8.72; N, 11.85.

Ethyl Decahydroquinoline-2-carboxylate (IV).—Quinoline-2-carboxylic acid (20 g., 0.12 mole) was added, along with 300 mg. of platinum oxide, to 120 ml. of glacial acetic acid and hydrogenated for 2 hr. at 50°. After removing the catalyst, 20 ml. of concentrated hydrochloric acid was added and the solution was evaporated. The solid residue was washed with ether and dried. The crude decahydroquinoline-2-carboxylic acid hydrochloride, 99% yield, m.p. 268–278°, was used directly for the preparation of the ethyl ester.

Decahydroquinoline-2-carboxylic acid hydrochloride (25 g., 0.11 mole) was refluxed for 16 hr. in 400 ml. of dry ethanol that had been first saturated with dry hydrogen chloride. The solution was concentrated *in vacuo* to about 50 ml. and then 200 ml. of ether was added. After cooling, the hydrochloride of the ester was removed and washed with ether. The ester hydrochloride was recrystallized from ethanol–ether, 85% yield, m.p. 256.5–257.5°.

Anal. Calcd. for $C_{12}H_{22}NO_2Cl$: C, 58.17; H, 8.94; N, 5.65; Cl, 14.31. Found: C, 58.06; H, 8.94; N, 5.64; Cl, 14.21.

To a rapidly stirred suspension of ethyl decahydroquinoline-2-carboxylate hydrochloride (20 g., 0.08 mole) in 300 ml. of dry ether was added 50 ml. of triethylamine. After 3 hr. the triethylamine hydrochloride was removed by filtration and the filtrate distilled *in vacuo* to yield an oil. The latter was redistilled *in vacuo*, b.p. 126–128° at 0.8 mm., 60% yield of a pale yellow oil, $n^{20}D$ 1.4848.

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.62. Found: C, 68.19; H, 10.11; N, 6.56.

Ethyl 1-(2-*p*-Nitrobenzamidoethyl)decahydroquinoline-2-carboxylate (V).—A mixture of *p*-nitrobenzoylethyleneimine[2] (19.2 g., 0.1 mole) and 21.1 g. (0.1 mole) of ethyl decahydroquinoline-2-carboxylate were heated on a steam bath for 4 days. The resulting dark colored oil was extracted with successive portions of hot hexane until it was evident that no more of the oil was going into solution. A sticky semisolid separated from the hexane solution when it was cooled overnight at 10°. The supernatant liquid was decanted and the semisolid material was triturated with fresh hexane until it solidified. The supernatant liquid on further condensation and cooling gave more of the product. The combined products were recrystallied from hexane, 56% yield, m.p. 100–101°.

Anal. Calcd. for $C_{21}H_{29}N_3O_5$: C, 62.51; H, 7.24; N, 10.41. Found: C, 62.65; H, 7.45; N, 10.34.

Perhydro-2*H*-pyrazino[1,2-*a*]quinolin-1-ones (VII).—Ethyl 1-(2-*p*-nitrobenzamidoethyl)decahydroquinoline-2-carboxylate (20.2 g., 0.05 mole) was refluxed in 150 ml. of 6 *N* hydrochloric acid. After 16 hr., the mixture was cooled and the *p*-nitrobenzoic acid removed. The filtrate was evaporated and the oily solid dissolved in water and treated with decolorizing carbon. The solution was then passed through a column (25 cm. × 3 cm.) containing 70 ml. of ion-exchange resin (Amberlite IR-4B) which had been washed previously with dilute ammonium hydroxide and thoroughly rinsed with distilled water. Since the eluent gave a positive test for chloride ion, it was passed through the column a second time. During the second passage, a white solid began to form on the column and in the eluent. The eluent at this point had a pH of 6.0–6.2. The aqueous phase was evaporated and the solid obtained was added to the solid obtained by eluting the column with chloroform and evaporating to dryness. The combined solids were fractionally crystallized from chloroform–hexane (1:10). The first fraction was recrystallized from chloroform–hexane, 21% yield, m.p. 148–150°. The second fraction also was recrystallized from chloroform, 23% yield, m.p. 198–200°; infrared absorption bands, cm.$^{-1}$, phase potassium bromide, isomer, m.p. 198–200°: 2938 (s), 2852 (m), 2790 (m), 2753 (w), 1667 (s), 1496 (m), 1464 (m), 1332 (m), 1299 (m), 1190 (m), 1052 (m); isomer, m.p. 148–150°: 2922 (s), 2852 (s), 2770 (w), 2750 (m), 1662 (s), 1494 (m), 1425 (m), 1348 (s), 1299 (m), 1189 (m), 1055 (m).

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.67; N, 13.44. Found (148–150°): C, 69.39; H, 9.62; N, 13.46. Found (198–200°): C, 69.48; H, 9.84; N, 13.24.

Perhydro-2*H*-pyrazino[1,2-*a*]quinolines (VIII).—Perhydro-2*H*-pyrazino[1,2-*a*]quinolin-1-one (m.p. 198–200°, 2.1 g., 0.01 mole) was refluxed with 1 g. of lithium aluminum hydride in 100 ml. of anhydrous ether for 36 hr. The excess lithium aluminum hydride was destroyed by the careful addition of 25 ml. of water and the mixture filtered. The precipitate was extracted with ether and the combined ether solutions was dried over anhydrous magnesium sulfate. Partial evaporation of the ether gave 0.11 g. of starting material. Complete evaporation of the ether gave an oil which distilled at 98–104° (0.7–0.8 mm.). The oil solidified on short standing and was recrystallized from hexane, 68% yield, m.p. 71–72°; infrared absorption bands, cm.$^{-1}$, phase chloroform, isomer, m.p. 71–72°: 2930 (s), 2855 (m), 2797 (m), 2755 (w), 1460 (m), 1440 (s), 1322 (s).

Anal. Calcd. for $C_{12}H_{22}N_2$: C, 74.18; H, 11.41; N, 14.41. Found: C, 74.06; H, 11.41; N, 14.26.

Treatment of the free base with phenyl isothiocyanate in hexane solution gave a 78% yield of perhydro-3-(N-phenylthiocarbamyl)pyrazino[1,2-*a*]quinoline, after recrystallization from hexane, m.p. 158–160°.

Anal. Calcd. for $C_{19}H_{27}N_3S$: C, 69.26; H, 8.26; N, 12.74; S, 9.73. Found: C, 69.12; H, 8.38; N, 12.98; S, 9.92.

Perhydro-2*H*-pyrazino[1,2-*a*]quinolin-1-one (m.p. 148–150°, 1 g., 0.005 mole) was refluxed with 1 g. of lithium aluminum hydride in 75 ml. of tetrahydrofuran for 36 hr. Ten milliliters of water was carefully added to the stirred mixture and the solid removed by filtration. The precipitate was washed with 2-propanol and the washings added to the tetrahydrofuran filtrate. After removing the solvents by distillation, the residual oil was distilled under reduced pressure, b.p. 98° at 0.8 mm. The oil solidified on standing, 54% yield, m.p. 50–60°; infrared absorption bands, cm.$^{-1}$, phase chloroform, isomer, m.p. 50–60°: 2930 (s), 2858 (m), 2759 (w), 1457 (s), 1327 (m).

It has not been possible to obtain a pure sample to date, although both recrystallization and chromatographic methods have been used. The impure product, however, when treated with phenyl isothiocyanate in hexane solution, gave an almost quantitative yield of a perhydro-3-(N-phenylthiocarbamyl)pyrazino-[1,2-*a*]quinoline, m.p. 129–131°. This thiourea derivative melts much lower than the thiourea derivative obtained from the isomeric perhydro-2*H*-pyrazino[1,2-*a*]quinoline.

Anal. Calcd. for $C_{19}H_{27}N_3S$: C, 69.26; H, 8.26; N, 12.74; S, 9.73. Found: C, 69.05; H, 8.05; N, 13.00; S, 9.86.

Decarboxylation of Decahydroquinoline-2-carboxylic Acid.—Quinoline-2-carboxylic acid was catalytically hydrogenated in glacial acetic acid as previously described. After the catalyst was removed, ether was added to precipitate decahydroquinoline-2-carboxylic acid acetate. The latter decomposed sharply at 278°. The acetate was heated at 275–280° in a small distillation flask until no distillate condensed in the receiver which was cooled in an acetone–Dry Ice bath. The condensate was neutralized with potassium hydroxide solution and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, the ether removed, and the residual oil was distilled *in vacuo*, 72% yield. The decahydroquinoline was converted to its hydrochloride by treatment with hydrogen chloride in ethanol–ether solution. The hydrochloride was recrystallized from ethanol–ether. The yield was almost quantitative, m.p. 215–218°. The melting point observed agrees with the reported melting point of *cis*-decahydroquinoline hydrochloride.[4]

Anal. Calcd. for $C_9H_{18}NCl$: C, 61.52; H, 10.32; N, 7.96; Cl, 20.18. Found: C, 61.57; H, 10.45; N, 7.94; Cl, 19.97.

The Swamping Catalyst Effect. VI. The Halogenation of Isoquinoline and Quinoline[1]

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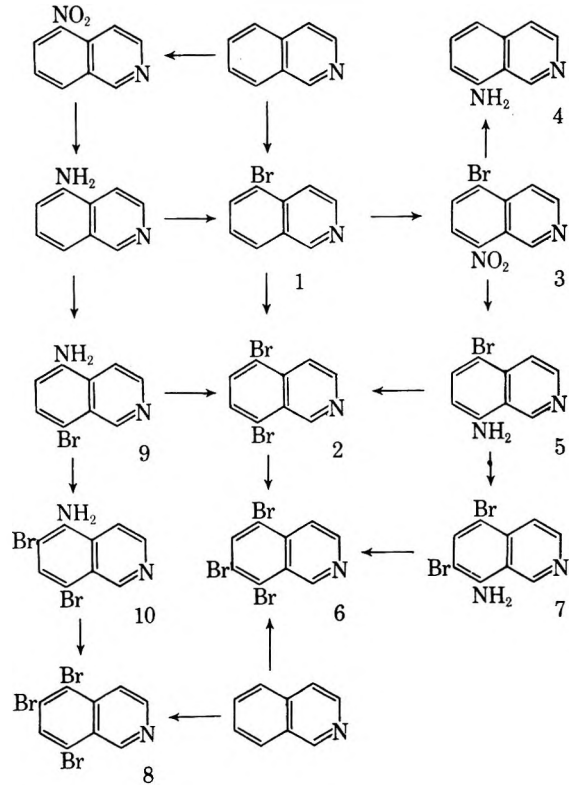
Halogenation of the aluminum chloride complexes of isoquinoline or quinoline gave in good yield halogen derivatives substituted in the benzenoid ring. Bromination of the aluminum chloride–isoquinoline complex gave the following sequence in substitution: 5-bromo-, 5,8-dibromo-, 5,7,8-tribromo-. To obtain good yields of 5,7,8-tribromoisoquinoline, it was necessary to brominate 5,8-dibromoisoquinoline, not isoquinoline itself. Bromination of the aluminum chloride complex of quinoline gave similar results except that 5,6,8-tribromoquinoline was obtained by bromination of 5,8-dibromoquinoline. Chlorination of the aluminum chloride complexes of both quinoline and isoquinoline gave results very similar to bromination. 5,6,7,8-Tetrabromo- and 5,6,7,8-tetrachloroquinoline were isolated also. Identification of many of these compounds was carried out by synthesis from known compounds as shown in the Scheme I.

In a previous communication[3] the complex of pyridine and aluminum chloride was shown to brominate in the 3-position. Only a 50% yield or less was obtained because the hydrogen bromide eliminated formed a new complex, probably $C_5H_5N\dot{H}\cdot\bar{A}lCl_3Br$, which was inert toward substitution. The question then arose whether isoquinoline and quinoline would behave in the same manner. Precedent was established for answering the question concerning the bromination of quinoline. De Le Mare and co-workers[4] had shown that the protonated form of quinoline (as obtained in concentrated sulfuric acid) is brominated by a mixture of silver sulfate and bromine to give 28% 5-bromo-, 29% 8-bromo-, and 43% 5,8-dibromoquinoline (Derbyshire–Waters procedure). A greater proportion of bromine gave higher yields of 5,8-dibromoquinoline and subsequently 5,6,8-tribromoquinoline. Quinoline as the free base, on the other hand, forms a complex with bromine which on heating is transformed to 3-bromoquinoline.[4,5] Eisch has attempted to explain this rather strange orientation.[6]

The aluminum chloride complexes of quinoline and isoquinoline were found to be brominated in a manner very similar to quinoline hydrogen sulfate[4] except that less 8-bromoquinoline was formed, perhaps indicating that the aluminum chloride complexes at the nitrogen atom serves as a hindering agent to 8-substitution. The yields were practically quantitative except for the distribution among mono-, di-, and trihalogenated products. Indeed the problem of selective halogenation became acute enough to warrant the development of a new method of introducing bromine in a diffused state. Dropwise addition led to momentary high concentrations of bromine which gave a spread of mono-, di-, and tribrominated products. The use of gaseous bromine, however, minimized the distribution of products and permitted an acceptable synthesis of a mono-, di-, or tribromoisoquinoline (or quinoline) depending on the amount of gaseous bromine added.

Since De La Mare concentrated on the halogenation of quinoline using the Derbyshire–Waters method, we concentrated on the halogenation of isoquinoline using the swamping catalyst method, leading us to many new compounds which remained to be identified. The sequence of substitution is interesting as shown in the middle column of Scheme I. The first bromine atom

SCHEME I



enters the 5-position, the second the 8-position, and the third predominantly the 7-. The latter compound is 5,7,8-tribromoisoquinoline (6). The results of bromination of quinoline are very similar except that bromination of 5,8-dibromoquinoline gave 5,6,8-tribromoquinoline in place of 5,7,8- as was found with isoquinoline. The orientation sequence could be explained as follows: the complex of aluminum chloride with the nitrogen atom deactivates the heterocyclic ring to such an extent that substitution occurs *only in*

(1) Paper V, D. E. Pearson, W. E. Stamper, and B. R. Suthers, *J. Org. Chem.*, **28**, 3147 (1963).

(2) Abstracted mainly from the Ph.D. thesis of M. G.

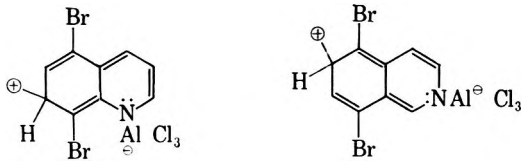
(3) D. E. Pearson, W. W. Hargrove, J. K. T. Chow, and B. R. Suthers, *J. Org. Chem.*, **26**, 789 (1961).

(4) P. B. D. De La Mare, M. Kiamud-din, and J. H. Ridd, *J. Chem. Soc.*, 561 (1960); *Chem. Ind.* (London), 361 (1958).

(5) A. Edinger, *J. prakt. Chem.*, [2] **54**, 357 (1896); E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IVA, Elsevier Publishing Co., New York, N. Y., 1957, p. 654; H. E. Jansen and J. P. Wibaut, *Rec. trav. chim.*, **56**, 699 (1937). The latter authors state that, at 500°, 2-bromoquinoline is formed.

(6) J. J. Eisch, *J. Org. Chem.*, **27**, 1318, 4682 (1962).

the benzenoid ring. The 6- and 8-positions of the quinoline complex are the most deactivated viewing the benzenoid ring as benzene with a deactivated group attached.[7] The 5- should be more active than the 7-position, because it has some of the characteristics of the α-position in naphthalene. Thus, the first bromine atom should enter the 5-position. The second bromine atom should enter the 8-position because the 5-bromo atom controls the point of attack through resonance contributions. The orientation in bromination of the 5,8-dibromo- leading to 5,6,8-tribromoquinoline and of 5,8-dibromo-leading to 5,7,8-tribromoisoquinoline is remarkable insofar as it is predictable from the molecular orbital calculations of Dewar[8] for the protonated forms of quinoline and isoquinoline. These calculations show the 6- more active than the 7-position in quinoline and the reverse for isoquinoline. In terms other than molecular orbital calculations we can say that the orientation suggests that the following canonical forms are important enough contributors to the hybrid to favor 6-substitution for 5,8-dibromoquinoline and 7-substitution for 5,8-dibromoisoquinoline.[9]



The chlorination of the quinoline– and isoquinoline–aluminum chloride complexes followed much the same pattern as bromination except for the less selective action of the chlorinating agent. Indeed, it was reactive enough to form 5,6,7,8-tetrachloroquinoline, a new compound, in good yield on exhaustive chlorination.

Identification of the haloisoquinolines was carried out according to Scheme I, confirmation being obtained by cross references to known compounds as described in the Experimental. Essentially, the proofs of structure depended on the isolation of 5-bromo-8-nitro- and 8-bromo-5-nitroisoquinolines, their conversion to the identical compound, 5,8-dibromoisoquinoline, as a cross reference, and their further conversion to isomeric trihaloisoquinolines. The identification was simplified greatly by the elimination of all structures with halogen in the heterocyclic ring. The three hydrogen atoms in the heterocyclic ring of isoquinoline had very characteristic n.m.r. peaks [H_1 τ 1.05, H_3 (doublet) 1.7, H_4 (doublet) 2.35; $J_{34} = J_{43} = 5$ c.p.s.; the τ-values became uniformly smaller when halogen atoms were attached to the benzenoid ring]. When H_4 in the heterocyclic ring was substituted by bromine (*i.e.*, in 4-bromoisoquinoline), the H_3 doublet was reduced to a singlet (H_1 τ 0.65, H_3 1.3). All haloisoquinolines obtained by the swamping catalyst method retained the characteristic peaks for the unsubstituted heterocyclic ring. The spectra of the haloquinolines showed 12 peaks of a typical ABX grouping for the hydrogen atoms at the 2-, 3-, and 4-position.[10]

Experimental[11]

Purity of the Bromoquinolines.—In the bromination of isoquinoline in the presence of aluminum chloride the possibility exists that chlorine may substitute or replace one of the bromine atoms. The possibility is remote because bromine is always the positive end of the dipole moment in any combination with chlorine and because the temperatures are low enough to avoid any exchange. However, to make certain, the haloquinolines obtained by the swamping catalyst method were analyzed by gas chromatography (2-ft. silicon column at 200° with He flow rate of 40 ml./min. using thermal conductivity detector). The retention times were quinoline, 40 sec., 5,6-dichloro, 105 sec., 5-bromo-6-chloro, 165 sec., 5,6-dibromo, 222 sec. As can be noted, the replacement of a bromine atom by a chlorine atom lowers the retention time by at least 60 sec. Less than 1% of 5-bromo-6-chloroquinoline could be detected in a mixture with 5,6-dibromoquinoline. All bromoquinolines examined had single peaks in gas chromatography, and we conclude that chlorine in aluminum chloride does not substitute or exchange for bromine in the bromoquinolines or isoquinolines.

5-Bromoisoquinoline (1).—The apparatus and general procedure previously described[12] was used except that the addition funnel was changed to permit the introduction of gaseous bromine. The bromine was allowed to drip slowly from a separatory funnel into an attached glass tube (10 × 150 mm.), the bottom of which was closed by sintered-glass tip (porosity E, Ace Glass Co.). The sintered-glass tip was positioned just above the surface of the stirred, molten complex. The bromine dripped slowly into the glass tube, diffused as a vapor through the sintered glass, and was absorbed by the complex. The rate of addition was controlled by the rate of bromine dripping from the separatory funnel. The brown complex from 0.42 mole of isoquinoline and 0.85 mole of anhydrous aluminum chloride was brominated over a 4-hr. period at 75° by 0.28 mole of bromine and heated an additional hour after completion of the addition. The almost black, fluid complex was poured carefully on to vigorously hand-stirred cracked ice. The cold mixture was treated with enough concentrated aqueous sodium hydroxide to dissolve all the aluminum salts as sodium aluminate and the oily layer extracted with ether. After being dried with sodium sulfate and concentrated, the ether extract was distilled at 0.3 mm., all fractions boiling below 120° being discarded. The solid distillate (40.6 g.) was recrystallized from pentane to give 1 as white needles, 38 g., 78%, m.p. 79.5–80.5°, lit.[13] m.p. 82–84°.

Anal. Calcd. for C_9H_6NBr: Br, 38.42. Found: Br, 38.16.

The same compound prepared from 5-aminoisoquinoline by the method of Osburn[13] melted at 80–82°. Mixture melting point, infrared spectra, and n.m.r. patterns were identical.

5,8-Dibromoisoquinoline (2).—The bromination was carried out as before except that the second equivalent of bromine was added to the complex maintained at 110° rather than at 75°. The precipitate which resulted from decomposing the complex with water and ice was filtered, washed thoroughly with water, air-dried, and sublimed at 0.1 mm. giving a colorless sublimate, 44 g., 55%, m.p. 110–114°. Considerable 1 remained dissolved in the acidic filtrate. Further purification of 2 was accomplished by countercurrent extraction. Twenty-gram portions of the impure dibromide were dissolved in 200 ml. of benzene and extracted six times with 100-ml. portions of 2.5% by weight of hydrochloric acid, yielding 1.3 g. of impure 5-bromoisoquinoline in the acid fractions. The 6th acid extract contained very

(7) The 8-position may be as active as the 5- judging from the results of nitration of quinoline using nitric–sulfuric acids.[8] In this case, the 8-position may be sterically hindered when the nitrogen atom is complexed with aluminum chloride.

(8) M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2521 (1957).

(9) If substitution occurs through the free base, dissociated from the complex of aluminum chloride and the weakly basic 5,8-dibromoquinoline (or isoquinoline), canonical forms with negative charges at the 6- and 7-positions, respectively, must be invoked.

(10) We are indebted to Dr. D. L. Tuleen for obtaining and interpreting these spectra. The spectra were recorded with a Varian Associates, A-60, spectrometer at 60 Mc. per second. Spectra were obtained in methylene chloride solution. Chemical shifts are expressed as shielding values, τ.

(11) All melting points are uncorrected. Analyses were by Galbraith Laboratories. All the di- or trihaloquinolines were isolated simply by filtration of the acidic mixture from aqueous decomposition of the aluminum chloride complexes. The monohaloquinolines were isolated by making the acidic mixtures strongly alkaline. The aluminum chloride used was an anhydrous resublimed grade.

(12) D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Syn.*, **40**, 7 (1960).

(13) A. R. Osburn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 4191 (1956).

little quinoline. The benzene layer was extracted sixteen times with 5% hydrochloric acid and six times with 10% hydrochloric acid. Compound **2**, 12.2 g., 61%, m.p. 114–115°, was isolated by neutralizing and filtering the 5% hydrochloric acid portions 5 through 12 and the 10% acid portions 3 and 4. Also, the isoquinoline remaining in the benzene layer after all these extractions was pure **2**.

Anal. Calcd. for C_9H_5NBr: Br, 55.7. Found: Br, 55.76.

Identification of 5,8-Dibromoisoquinoline (2).—Ring closures using typical isoquinoline procedures failed. Nitration of **1** by the procedure of Osburn, *et al.*,[13] gave a 96% yield of 5-bromo-8-nitroisoquinoline (**3**) as yellow needles, m.p. 138–140°. The orientation of the groups in **3** was ascertained by simultaneous catalytic hydrogenation and hydrogenolysis to give 8-aminoisoquinoline (**4**). **3** (5 g.) was dissolved in 150 ml. of acetic acid containing ammonium acetate (10 g.) and suspended catalyst (4 g., 5% palladium on calcium carbonate). The mixture was hydrogenated for several hours in the Parr apparatus, filtered to remove catalyst, and made alkaline. The dark precipitate was filtered, air-dried, and sublimed at 140° (0.1 mm.), yielding 1.9 g., 67%, of **4** as yellow crystals, m.p. 170–172°, lit.[14] m.p. 174°.

Compound **3** was reduced to 5-bromo-8-aminoisoquinoline (**5**) without hydrogenolysis by means of 5% palladium on Norit. **3** (4 g.) was dissolved in 100 ml. of glacial acetic acid containing 1 g. of the catalyst. Isolation similar to the previous hydrogenation yielded **5** as yellow crystals, 2.7 g., 77%, m.p. 185–187°.

Anal. Calcd. for $C_9H_7N_2Br$: Br, 35.82; N, 12.56. Found: Br, 35.88; N, 12.41.

Compound **5** (1.0 g.) was converted to crude **2**, m.p. 110–114°, after sublimation, by the Sandmeyer reaction. Recrystallization from acetone gave pure **2** (0.45 g., m.p. 114–115°).

Anal. Calcd. for $C_9H_5NBr_2$: Br, 55.70. Found: Br, 55.57.

The infrared spectrum, melting point, and mixture melting point were identical with 5,8-dibromoisoquinoline obtained by dibromination of isoquinoline.

5,7,8-Tribromoisoquinoline (6).—Tribromination of isoquinoline led to a mixture of **6** and 5,6,8-tribromoisoquinoline (**8**), but monobromination of **2** gave pure **6**. It is recommended that to obtain tribromoquinolines in good yields the monobromination of the dibromoquinolines should be carried out. A complex of **2** (16.5 g., 0.05 mole) and aluminum chloride (23 g., 0.17 mole), prepared by stirring together at 150°, was brominated with bromine vapors (9.2 g., 0.058 mole) over a period of 2 hr. at this temperature. The usual isolation procedure including sublimation yielded crude **6**, m.p. 195–200°. The crude **6** was purified by the countercurrent extraction procedure described previously using a saturated solution of **6** in benzene and omitting the 2.5% hydrochloric acid extraction. Pure **6**, m.p. 200–201°, was obtained in 75% over-all yield.

Anal. Calcd. for $C_9H_4NBr_3$: Br, 65.53. Found: Br, 65.65.

The structure of **6** was ascertained by its synthesis from 5-bromo-8-aminoisoquinoline (**5**). Aluminum chloride (4.6 g., 27 mmoles) and **5** (2 g., 9 mmoles) were complexed at 120° and brominated at 150° with gaseous bromine (0.8 g., 4.5 mmole). The bromine was made the limiting agent to avoid the formation of the $AlCl_3$–**6**–HBr complex which might not brominate *ortho* to the amino group.[15] The usual isolation procedure including the countercurrent extraction technique yielded 1 g. of **5** and 1.5 g. of a light orange solid, m.p. 285° dec., presumed for the present to be 5,7-dibromo-8-aminoisoquinoline (**7**).

Anal. Calcd. for $C_9H_6N_2Br_2$: Br, 52.92; N, 9.27. Found: Br, 53.05; N, 9.14.

Compound **7** was diazotized in concentrated hydrobromic acid and the diazonium salt treated with freshly prepared cuprous bromide. After standing overnight, the mixture was made basic and the precipitate filtered, air-dried, and sublimed at 1-mm. pressure. The 5,7,8-tribromoquinoline isolated proved to be identical with **6** by mixture melting point and infrared spectrum comparison. The only assumption in this synthesis is that bromination takes place *ortho* to the amino group.

5,6,8-Tribromoisoquinoline (8).—The tribromination of isoquinoline led to a mixture of products which by sublimatography[16] appeared to have roughly the following composition: 16% of **1**, m.p. 78–80°; 34% of **2**, m.p. 112–114°; 6% of **6**: and 6% of an unknown isomer, m.p. 184–186°, suspected to be **8**. This compound was synthesized, therefore, by a known route. 5-Aminoisoquinoline (10 g., 0.074 mole) was mixed with aluminum chloride (29.3 g., 0.22 mole) and heated to 80°. Bromine vapor (5.9 g., 0.037 mole) was added to the stirred mixture. The usual isolation procedure yielded a mixture of 5-aminoisoquinoline and 5-amino-8-bromoisoquinoline (**9**). They were separated by sublimatography[16]; the yield was 5.5 g. of pure **9**, as pale yellow crystals, m.p. 158–160°.

Anal. Calcd. for $C_9H_7N_2Br$: Br, 35.82; N, 12.56. Found: Br, 35.76; N, 12.50.

To confirm the structure of **9**, a small portion was converted by the Sandmeyer reaction to **2**; melting point and mixture melting point with authentic **2**, 114–115°. Pure **9** (5 g., 0.022 mole) and aluminum chloride (9 g., 0.067 mole) were brominated at 125° with bromine vapor (2.0 g., 0.011 mole). The usual isolation together with sublimatography gave 2.6 g. of yellow crystals, m.p. 203–205°, after recrystallization from ethyl acetate. These crystals were 6,8-dibromo-5-aminoisoquinoline (**10**), assuming that the bromine atom was substituted *ortho* to the amino group. Pure **10** (1 g.) was diazotized in 5 ml. of concentrated hydrobromic acid with 0.5 g. of sodium nitrite. The cold diazonium solution was added to approximately 1 g. of freshly prepared cuprous bromide in 10 ml. of hydrobromic acid held at 75°. The cooled mixture was made alkaline and the precipitate filtered and air-dried. Sublimation at 0.1 mm. gave 1.5 g. of white crystals, m.p. 183–185°.

Anal. Calcd. for $C_9H_4NBr_3$: Br, 65.53. Found: Br, 65.32.

The mixture melting point with **8**, obtained from tribromination of isoquinoline, was undepressed and the infrared spectra were identical. Another indication of the structures of **6** and **8** is that all starting materials were known compounds (or related to known compounds) with substituents in the 5- and 8-positions. Therefore, assuming no substitution in the heterocyclic part of the ring which is not likely judging from its deactivation, the third bromine atom could substitute only in the 6- or 7-position. Classical procedures then gave 6-substitution by one route as expected and 7-substitution by the second route as expected. The cross references in synthesis shown in Scheme I strengthen the arguments for the structures of 5,7,8- (**6**) and 5,6,8-tribromoisoquinoline (**8**).

5-Chloroisoquinoline.—The procedure for chlorination has been described.[12] The aluminum chloride–isoquinoline complex was chlorinated at 75° over a period of 14 hr. Fractionation of the crude product gave 15 g., 41%, of recovered isoquinoline, b.p. 57° (0.2 mm.), and 14.2 g. (31%) of 5-chloroisoquinoline as white needles from pentane, m.p. 72–74°, lit.[17] m.p. 73–74°.

Anal. Calcd. for C_9H_6NCl: Cl, 21.67. Found: Cl, 21.65.

Some 5,8-dichloroisoquinoline was found in the residue.

5,8-Dichloroisoquinoline.—Isoquinoline (0.14 mole) was chlorinated with 2 equiv. of chlorine at 90–130° over a period of 12 hr. The precipitate from the complex decomposed with ice and water was filtered, air-dried, and sublimed, yielding 78% crude 5,8-dichloroisoquinoline, m.p. 110–115°. Further purification using the countercurrent extraction technique described and recrystallization from acetone gave colorless crystals, 57% over-all yield, m.p. 115–116°, lit.[18] m.p. 117°.

Anal. Calcd. for $C_9H_5NCl_2$: Cl, 35.80. Found: Cl, 35.36.

Infrared and n.m.r. patterns of this compound and the following chloroisoquinolines were very similar to those of the corresponding bromo compounds.

5,7,8-Trichloroisoquinoline.—The complex of 5,8-dichloroisoquinoline (0.1 mole) and aluminum chloride (0.3 mole) was chlorinated at 145° over a period of 2 hr. The usual isolation followed by recrystallization from isopropyl acetate gave 20 g. (87%), of white needles, m.p. 177–178°.

Anal. Calcd. for $C_9H_4NCl_3$: Cl, 45.75. Found: Cl, 46.02.

Bromination of Quinoline.—The bromination of quinoline was undertaken before the method of introducing bromine vapors had been perfected. Therefore, the products showed a greater distribution of bromine as indicated in Table I.[19] The yields and distribution of products are similar to those of De La Mare and co-workers[10] using sulfuric acid, silver sulfate, and bromine.

(14) R. A. Robinson, *J. Am. Chem. Soc.*, **69**, 1944 (1947).

(15) B. R. Suthers, P. H. Riggins, and D. E. Pearson, *J. Org. Chem.*, **27**, 447 (1962).

(16) H. Sugisawa and K. Aso, *Chem. Ind.* (London), 781 (1961).

(17) R. H. F. Manske and M. Kulka, *Can. J. Research*, **27B**, 161 (1949).

(18) H. Andersag, "Medicine in Its Chemical Aspects," Vol. II, I. G. Farbenindustrie, A. G. Leverkusen, 1934, p. 359. This author gives no experimental details.

(19) We are indebted to Mr. G. W. Senter and Mr. R. Woodberry, Tennessee Agricultural and Industrial State College, Nashville, Tenn., for obtaining the results in Table I. The work was done under the auspices of a National Science Summer Research Grant, 1960.

TABLE I

PER CENT YIELD IN BROMINATION OF QUINOLINE–ALUMINUM CHLORIDE COMPLEX

Bromination process	5-Bromo-[a]	5,6-Dibromo-	5,8-Dibromo-	5,6,8-Tribromo-
Mono-	46	3	8	
Di-		9	62	
Tri-		10	41	9

[a] Appreciable amounts of 8-bromoquinoline were noted.

To demonstrate that the introduction of gaseous bromine gave better selectivity the following two compounds were synthesized.

5,8-Dibromoquinoline.—The complex of quinoline (0.56 mole) and aluminum chloride (1.7 moles) was brominated at 80° with bromine vapor (0.6 mole) for 6 hr. and at 110° with more bromine vapor (0.6 mole). The usual isolation gave 144 g. (86%) of 5,8-dibromoquinoline, m.p. 120–125°. Purification by the countercurrent extraction procedure gave the pure compound, m.p. 126–128°, in approximately 70% yield.

5,6,8-Tribromo- and 5,6,7,8-Tetrabromoquinoline.—The complex of 5,8-dibromoquinoline (0.07 mole) and aluminum chloride (0.21 mole) was brominated at 145° with gaseous bromine (0.08 mole) over a period of 2 hr. The usual isolation procedure gave the crude tribromo compound in 78% yield, m.p. 145–150°. The crude compound was sublimed. Since the compound did not dissolve in benzene, the finely ground crystals were leached with a series of 5% hydrochloric acid solutions, followed by a series of 10% hydrochloric acid solutions. The extracted samples of m.p. 157–159° obtained by neutralization of the acid and filtration were combined. The reported melting point of 5,6,8-tribromo[20] is 159° and of 5,7,8-tribromoquinoline[21] is 141°. The remaining crude product from the extraction was leached with 20% hydrochloric acid and yielded a new compound which was probably 5,6,7,8-tetrabromoquinoline, recrystallized from amyl acetate, m.p. 241–243°.

Anal. Calcd. for $C_9H_3NBr_4$: Br, 71.85. Found: Br, 71.37.

5,6,7,8-Tetrachloroquinoline.—The complex of 5,8-dichloroquinoline (m.p. 97–98°, 0.09 mole, made by the swamping catalyst method) and aluminum chloride (0.27 mole) was chlorinated at 150° with chlorine (0.18 mole) over a period of 4 hr. The usual isolation followed by sublimation gave 22 g. (91%) of white crystals, m.p. 185–187°. The usual absorption band for the three adjacent hydrogen atoms at 12.7 μ was found in the infrared.

Anal. Calcd. for $C_9H_3NCl_4$: Cl, 53.10. Found: Cl, 52.93.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this work.

(20) A. Claus, *J. prakt. Chem.*, [2] **53**, 30 (1896).

(21) A. Claus and A. Ammelburg, *ibid.*, [2] **50**, 35 (1894).

Quinazolines and 1,4-Benzodiazepines. XVIII.[1] The Acetylation of Chlordiazepoxide[2] and Its Transformation into 6-Chloro-4-phenyl-2-quinazolinecarboxaldehyde[3]

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Acetylation of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide gave three products, the normal N-acetyl derivative (II), a 3-acetoxy compound (III) produced by rearrangement of the N-oxide, and the diacetyl compound (IV). In acidic medium, 1,4-benzodiazepines bearing an oxygen in position 3 rearranged to the corresponding 2-quinazolinecarboxaldehyde. The structures of these compounds were proved and the general applicability of the reactions is discussed.

A study of the acetylation of chlordiazepoxide[2] (I) led to the discovery that under varying reaction conditions three different products could be obtained, the normal N-acetylated reaction product,[4] described earlier, an isomeric monoacetyl derivative, and a diacetyl derivative, respectively.

Acetylation of I with acetic anhydride in pyridine at room temperature yielded the N-acetylated product (II), while reaction with acetyl chloride in DMF[5] gave an isomeric monoacetyl derivative which has been found to be 3-acetoxy-7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III), formed by rearrangement of the N-oxide to a compound bearing an oxygen on the adjacent carbon atom. Under more energetic reaction conditions (heating with acetic anhydride, with or without pyridine), the diacetyl compound (IV) was obtained. (See p. 333, col. 1.)

The rearrangement of I to III is analogous to the Polonovski rearrangement of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide to the corresponding 3-acetoxy compound VI.[6]

Assignment of structures II, III, and IV was readily made on the basis of the characteristic infrared spectra of the three compounds.[7] The absence of any bands in the NH region and the presence of an amide carbonyl band at 1683 cm.$^{-1}$ confirmed the chemical structural proof[4,8] of II, while a strong NH stretching band[9] at 3480 cm.$^{-1}$ and a typical ester carbonyl band at 1758 cm.$^{-1}$ were consistent with the structure postulated for III. The diacetyl derivative (IV) showed both an amide carbonyl band at 1680 cm.$^{-1}$ and an ester carbonyl band at 1758 cm.$^{-1}$.

The structure of the rearrangement products was confirmed by hydrolysis of the diacetyl derivative IV with one equivalent of acid to VI.[6] Hydrolysis of compound IV with 2 moles of alkali at room temperature led to the hydroxy derivative V [ν (cm.$^{-1}$) 3550 (OH), 3440 (NH)]. This compound could be reacetylated to yield compound III.

(1) Paper XVII, R. I. Eryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, in press.

(2) Generic name for 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (Librium(R)).

(3) (a) While this paper was being prepared, an abstract of a paper by S. C. Bell, C. Gochman, and S. J. Childress appeared in Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963, p. 37-O, indicating that its contents probably overlap, in part, the material described in this paper. (b) NOTE ADDED IN PROOF.—See S. C. Bell, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **28**, 3010 (1963).

(4) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

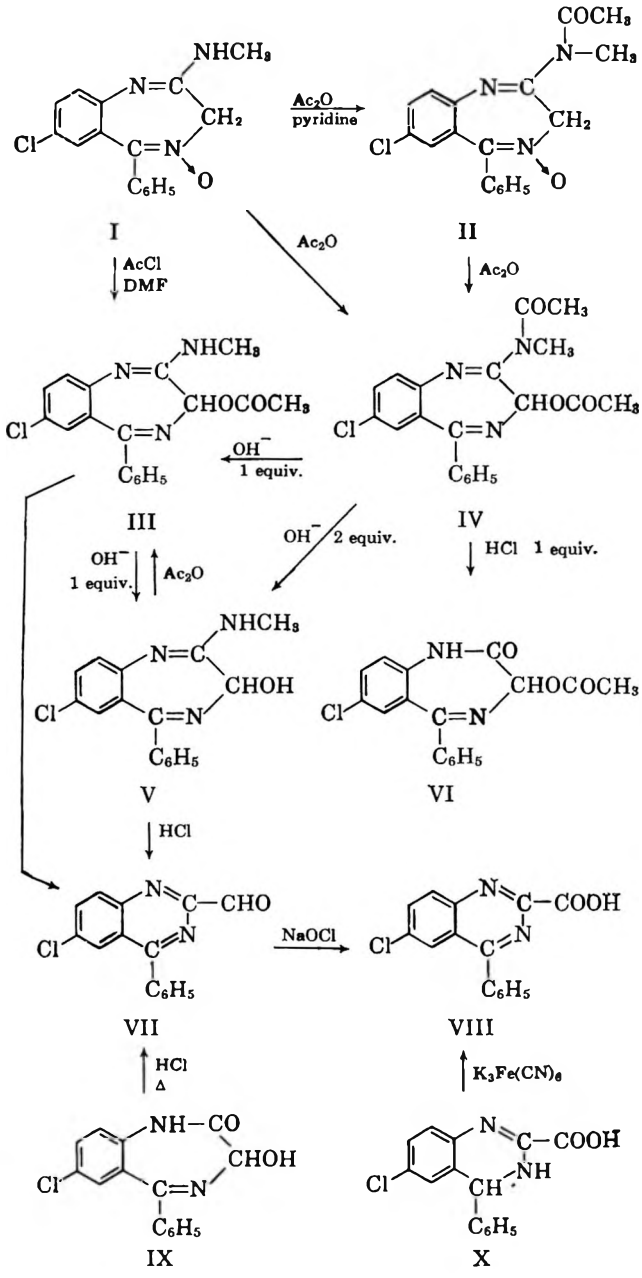
(5) DMF is N,N-dimethylformamide.

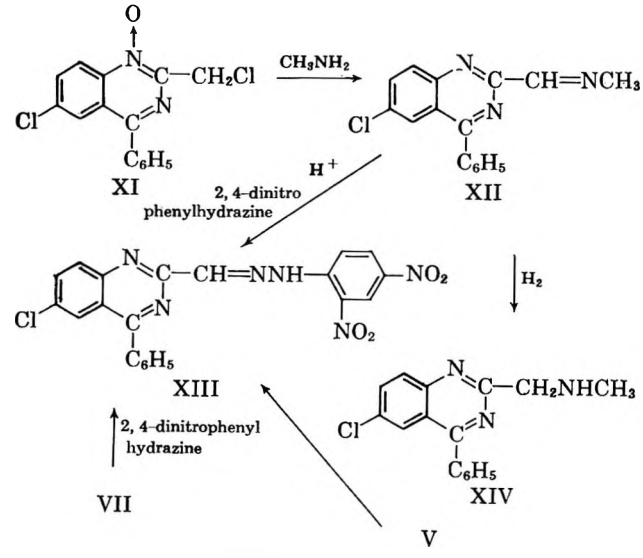
(6) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(7) All infrared spectra were determined in 3% solution in chloroform unless otherwise noted.

(8) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(9) Chlordiazepoxide (I) itself shows a weak band in this region (3474 cm.$^{-1}$). The intensity of this absorption band increases with dilution (3% → 0.3%) indicating intermolecular bonding.

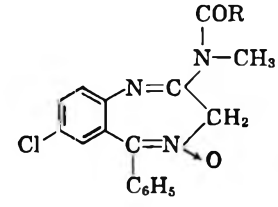




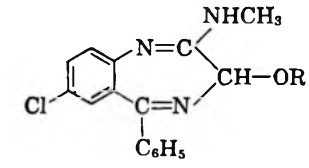
An interesting rearrangement, confirming the potential aldehyde character of C-3 in III, V, and IX,[6] occurred on treatment of these compounds with mineral acid. The methylamino group was lost in III and V and a ring contraction occurred, resulting in the formation of quinazoline aldehyde VII (strong carbonyl stretching band at 1728 cm^{-1}). Under the same conditions compound IX yielded the same aldehyde (VII). When the hydrolysis was carried out in alcohol, VII was isolated as the hemiacetal. The structure of the aldehyde (VII) was proved by its oxidation to the quinazoline carboxylic acid (VIII) ,which was shown to be identical with the one obtained by oxidation of the 3,4-dihydro derivative (X).[6]

A second proof of structure of the quinazoline aldehyde (VII) was based on the rearrangement of XI[10] with methylamine to the methylimine (XII), a compound which also could be obtained from VII by treatment with methylamine. The rearrangement of XI to XII is reminiscent of the reaction of α-picoline N-oxide with acetic anhydride.[11] However, the fact that it occurs under basic conditions suggests that a different mechanism may be involved. On catalytic reduction of XII, the known compound XIV[12] was isolated thus proving the structure of XII. Treatment of XII with 2,4-dinitrophenylhydrazine in an acidic medium gave the hydrazone (XIII). This compound was identical with the hydrazone prepared from VII and V.

Further study of the acylation of chlordiazepoxide (I) showed that on acylation with various acylating agents, depending on the reaction conditions, the N-acyl or O-acyl derivatives were obtained.[13] The propionyl and butyryl compounds (XVa,b and XVIa,b) were prepared in the same way as the corresponding acetyl derivatives. However, benzoyl chloride in pyridine or DMF gave only the ester XVIc.



XVa,b



XVIa,b,c
a, R = propionyl
b, R = butyryl
c, R = benzoyl

Walker,[14] on acetylation of 7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 4-oxide, obtained a product to which he ascribed the N-acetyl structure (XVII). Since no experimental data were given and, since his infrared data [λ^{Nujol} 3.05, 5.74, 6.14, 6.23 μ = ν^{Nujol} ($cm.^{-1}$) 3279, 1742, 1629, 1605] suggested this compound to be the 3-acetoxy derivative, we studied this acetylation and found that as in the earlier discussed cases two acetylation products could be obtained. Using acetic anhydride in pyridine as acetylating agent we obtained the normal N-acetyl

(10) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

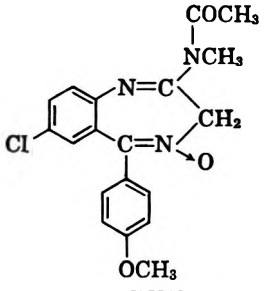
(11) V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1286 (1954).

(12) Described as the hydrochloride by S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).

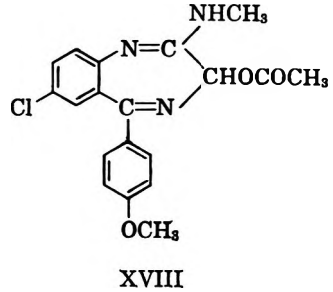
(13) The structure assignment was based on the presence of the characteristic ester carbonyl band at 1760–1740 $cm.^{-1}$, the amide carbonyl band at 1690–1680 $cm.^{-1}$, and the NH band at 3480–3410 $cm.^{-1}$ in the infrared spectrum.

(14) G. N. Walker *J. Org. Chem.*, **27**, 1930 (1962).

derivative (XVII) [ν^{CHCl_3} (cm.$^{-1}$) 1680, 1620, 1605]. Or acetylation with acetyl chloride in DMF we obtained the 3-acetoxy derivative (XVIII), which showed the same infrared absorption bands as reported by Walker for his acetyl derivative[14,15] [ν^{CHCl_3} (cm.$^{-1}$) 3410, 1745, 1620, 1598 and ν^{Nujol} (cm.$^{-1}$) 3270, 1745, 1623, 1605]. This indicates that the compound reported by Walker is in fact the 3-acetoxy derivative (XVIII).



XVII



XVIII

The study of the acetylation of other 2-methylamino-5-phenylbenzodiazepine 4-oxides has led to the finding that the course of this reaction is quite general; acetic anhydride in pyridine at room temperature yields the normal N-acetyl derivatives, whereas acetyl chloride in DMF leads to the rearranged 3-acetoxy compounds.

Experimental

All melting points are corrected and were determined in a Thomas–Hoover melting point apparatus. The infrared spectra were determined in 3% chloroform solution unless otherwise indicated. Identity of compounds was established by mixture melting point and comparison of infrared spectra.

3-Acetoxy-7-chloro-2-(N-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine (IV). **A.**—A solution of 31 g. (0.103 mole) of I[4] in a mixture of 360 ml. of pyridine and 180 ml. of acetic anhydride was heated to 50° for 20 min. then left at room temperature for 4 days. After concentration *in vacuo* to a small volume, the residue was treated with ether and petroleum ether,[16] which caused the precipitation of crystals. The first fraction isolated (19.1 g., 54%) consisted of almost pure 7-chloro-2-(N-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (II).[4] After the addition of more petroleum ether a second fraction (11.8 g.) was obtained which melted below 140°. Repeated recrystallization from ether or a mixture of methylene chloride, ether, and petroleum ether, gave 8.7 g. (34%) of pure 3-acetoxy-7-chloro-2-(N-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine (IV). The product was dimorphic and formed colorless prisms melting at 145–146° or at 159–160° [ν (cm.$^{-1}$) 1758, 1680].

B.—A solution of 10 g. (29.3 mmoles) of II[4] in 25 ml. of acetic anhydride was heated for 10 min. to 80°. The solution was concentrated *in vacuo* and the residue recrystallized from a mixture of acetone and petroleum ether. The first fraction consisted of 3.6 g. of unchanged starting material. After the addition of more petroleum ether, 4.7 g. (42%) of crude crystalline IV was obtained. The product was purified as described previously.

Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; O, 12.51; acetyl, 22.43. Found: C, 62.56; H, 4.47; O, 12.91; acetyl, 22.81.

3-Acetoxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (III) Hydrochloride.—To a solution of 64 g. (0.214 mole) of I in 600 ml. of dimethyl formamide, 25.2 ml. (0.354 mole) of acetyl chloride was added with cooling. Crystallization began after a short time and after about 1 hr. 44 g. (54%) of III hydrochloride was separated by filtration. After recrystallization from a mixture of ethanol and petroleum ether the product formed colorless needles melting at 212–213°.

Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O_2$: C, 57.15; H, 4.53. Found: C, 56.99; H, 4.80.

Free Base (III). **A.**—The free base prepared from III crystallized from a mixture of methylene chloride and ether to yield colorless prisms melting at 202–203° [ν (cm.$^{-1}$) 3480, 1758].

B.—A solution of 3.8 g. (0.01 mole) of IV in 50 ml. of dioxane was treated with 10 ml. of 1 *N* sodium hydroxide. After 1.5 hr. at room temperature, the mixture was concentrated *in vacuo* to a small volume and diluted with water and ether. The ether layer was separated, dried, concentrated to a small volume, and the precipitated crystals filtered off. Thus, 1.3 g. (34%) of colorless prisms were obtained, which after recrystallization from acetone proved to be identical with the material prepared by method A.

Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.30; acetyl, 12.6. Found: C, 63.12; H, 4.77; N, 12.46; acetyl, 12.94.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepin-3-ol (V). **A.**—A solution of 3.4 g. (0.01 mole) of III in a mixture of 50 ml. of dioxane and 10 ml. of 1 *N* sodium hydroxide was stirred at room temperature for 4 hr. and then concentrated *in vacuo* to a small volume. Water was added and the reaction product was extracted with methylene chloride. The organic layer was dried, concentrated *in vacuo*, and the residual oil was crystallized from ether. After recrystallization from a mixture of methylene chloride and petroleum ether, 2.6 g. (87%) of colorless needles melting at 184–186° were obtained. The product is dimorphic and when recrystallized from dilute dimethylformamide forms colorless prisms melting at 191–192° dec. [ν (cm.$^{-1}$) 3550, 3440]. The product (V) could be reconverted into the O-acetyl derivative (III) by treatment at room temperature with an excess of acetic anhydride in pyridine.

B.—Compound V also was obtained by the same procedure from the diacetyl derivative (IV) using 2 moles of alkali for the hydrolysis.

Anal. Calcd. for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.11; H, 4.98; N, 13.58.

3-Acetoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (VI).—A solution of 1.9 g. (0.005 mole) of IV in a mixture of 50 ml. of dioxane and 5 ml. of 1 *N* hydrochloric acid was heated within 5 min. to 50°. The reaction mixture was cooled to room temperature, concentrated *in vacuo* to a small volume, neutralized with 5 ml. of 1 *N* sodium hydroxide, and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo*. Crystallization of the residue from ether yielded 0.3 g. (17%) of crude VI. On recrystallization from acetone, the pure product was obtained and proved to be identical with a sample prepared as described in the literature[6] [ν^{KBr} (cm.$^{-1}$), 3230, 1750, 1723].

7-Chloro-2-(N-methylpropionamido)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (XVa).—Treatment of I with propionic anhydride in pyridine, as described for the acetyl derivative[4], gave the N-propionyl derivative (XVa) as colorless prisms, recrystallized from a mixture of methylene chloride and acetone, melting at 213–214° [ν (cm.$^{-1}$) 1685].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$: C, 64.13; H, 5.10; Cl, 9.97. Found: C, 64.76; H, 5.12; Cl, 9.98.

7-Chloro-2-methylamino-5-phenyl-3-propionoxy-3*H*-1,4-benzodiazepine (XVIa).—To a solution of 12 g. (0.04 mole) of I in 100 ml. of dimethylformamide, 5.5 g. (0.06 mole) of propionyl chloride was added. The solution was cooled, left at room temperature for 1 hr., then diluted with ice–water and dilute sodium hydroxide. The mixture was extracted with methylene chloride, the organic layer washed with water, dried, and concentrated *in vacuo*. Crystallization from ether or from a mixture of ether and petroleum ether gave 3.5 g. (25%) of XVIa as colorless prisms melting at 197–198° [ν (cm.$^{-1}$) 3480, 1760].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$: C, 64.12; H, 5.10; N, 11.81. Found: C, 64.15; H, 5.38; N, 11.70, 11.71.

7-Chloro-2-(N-methylbutyramido)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (XVb).—Six grams (0.02 mole) I was treated with 3 ml. (0.029 mole) of butyryl chloride in 75 ml. of pyridine. The reaction mixture was worked up as described for XVa and yielded colorless prisms of XVb melting at 169–170°, when crystallized from ether or acetone [ν (cm.$^{-1}$) 1685]. The compound gave a melting point depression with isomeric XVIb.

Anal. Calcd. for $C_{20}H_{20}ClN_3O_2$: C, 64.95; H, 5.45. Found: C, 65.07; H, 5.48.

3-Butyryloxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XVIb).—Compound XVIb was prepared, using butyryl chloride as acylating agent, in the same manner as described

(15) The melting point of our product is 202–203° and not as reported by Walker 218.5–219.5°. This could possibly be due to dimorphism.

(16) In all cases petroleum ether indicates a fraction boiling at 30–60°.

for XVIa. It formed colorless crystals melting at 171–172°. The compound gave a melting point depression with the isomeric XVb [ν (cm.$^{-1}$) 3470, 1750].

Anal. Calcd. for $C_{20}H_{20}ClN_3O_2$: C, 64.95; H, 5.45. Found: C, 64.87; H, 5.34.

3-Benzoyloxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XVIc).—This compound was prepared in the same manner described earlier for XVIa, using benzoyl chloride as acylating agent. The use of pyridine as solvent gave the same reaction product. After recrystallization from acetone, the product formed prisms melting at 215–216° [ν (cm.$^{-1}$) 3480, 1740].

Anal. Calcd. for $C_{23}H_{18}ClN_3O_2$: C, 68.40; H, 4.49. Found: C, 68.47; H, 4.11.

7-Chloro-5-(4-methoxyphenyl)-2-(N-methylacetamido)-3*H*-1,4-benzodiazepine 4-Oxide (XVII).—Acetylation of 7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 4-oxide,[14] as described in the literature[4] for the 5-phenyl derivative, gave the N-acetyl derivative, crystallizing as colorless plates from a mixture of methylene chloride and hexane and melting at 188–190° [ν (cm.$^{-1}$) 1680].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 61.37; H, 4.88; acetyl, 11.58. Found: C, 61.57; H, 4.93; acetyl, 11.40.

3-Acetoxy-7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine (XVIII).—The product XVIII was prepared from 7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 4-oxide[14] and acetyl chloride in the same manner as compound XVIa. Crystallization from acetonitrile followed by recrystallization from a mixture of tetrahydrofuran and hexane gave colorless crystals melting at 202–203° [ν (cm.$^{-1}$) 3410, 1745].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 61.37; H, 4.88; acetyl, 11.58. Found: C, 61.29; H, 4.93; acetyl, 12.09.

6-Chloro-4-phenyl-2-quinazoline Carboxaldehyde (VII). A. From III.—A suspension of 3.4 g. (0.01 mole) of III in 140 ml. of water and 10 ml. of 1 *N* hydrochloric acid was stirred and heated to 85° for 10 min. The precipitate was then separated by filtration and dissolved in ether. The ether solution was dried, concentrated to a smaller volume, and 1.3 g. (49%) of almost pure crystalline VII was separated by filtration. Recrystallization from ether gave slightly yellow prisms melting at 177–178° [ν (cm.$^{-1}$) 3000, 1728].

Anal. Calcd. for $C_{15}H_9ClN_2O$: C, 67.04; H, 3.37; N, 10.42; Cl, 13.19. Found: C, 67.14; H, 3.07; N, 10.48; Cl, 13.22.

B. From V.—A solution of 2.9 g. (0.01 mole) of V in a mixture of 640 ml. of water and 20 ml. of 1 *N* hydrochloric acid was left at room temperature for 72 hr. The crystalline reaction product (1.2 g., 45%, m.p. 177–178°) was separated by filtration.

C. From IX.—A suspension of 5.6 g. (0.02 mole) of IX[6] in a mixture of 200 ml. of dioxane, 200 ml. of water, and 40 ml. of 1 *N* hydrochloric acid was heated on the steam bath for 15 min., cooled to room temperature, and concentrated *in vacuo* to a smaller volume. Methylene chloride and 40 ml. of 1 *N* sodium hydroxide were added and some undissolved starting material was removed by filtration. The organic layer was separated, dried, and concentrated *in vacuo*. Crystallization of the residue from ether yielded 3.2 g. of crude VII. After recrystallization from ether, 1.2 g. (22%) of the pure product was obtained.

6-Chloro-4-phenyl-2-quinazoline Carboxaldehyde Ethyl Hemiacetal. A.—A solution of 3 g. (0.01 mole) of V in 50 ml. of ethanol and 10 ml. of 1 *N* hydrochloric acid was heated on the steam bath for 10 min. The solution was concentrated *in vacuo* to a smaller volume and the crude crystalline product (2.7 g., 86%) was separated by filtration. After recrystallization from ethanol the pure product crystallized, as colorless needles which melted at 101–103° then resolidified and melted at the melting point of VII [ν (cm.$^{-1}$) 3480, 1725 (w), 1078].

The very weak aldehyde carbonyl band (1725 cm.$^{-1}$) indicating the presence of about 6% of aldehyde may be due to decomposition in solution.

The instability of this compound was shown by the following experiment. A solution of 0.7 g. of the hemiacetal in 25 ml. of benzene was refluxed for 7 min. with azeotropic distillation of the solvent. The solution was concentrated *in vacuo* to dryness and the residue crystallized from ether to give 0.3 g. of the aldehyde (VII).

B.—A suspension of 2.7 g. (0.01 mole) of VII in 100 ml. of ethanol containing 0.1 ml. of concentrated hydrochloric acid was stirred at room temperature for 20 min. The solution thus obtained was concentrated *in vacuo* to a small volume and yielded 2.5 g. (76%) of crystalline hemiacetal.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; EtO, 14.32. Found: C, 65.08; H, 4.99; EtO, 14.00.

6-Chloro-4-phenyl-2-quinazolinecarboxylic Acid (VIII). A. From VII.—A suspension of 1.0 g. (36 mmoles) of VII in 50 ml. of 10% sodium hydroxide and 20 ml. of sodium hypochlorite (16.7% active chlorine) was stirred and heated on a steam bath for 2.5 hr. During this time there was a change in the crystal form. After cooling, the solid was separated by filtration and partitioned between chloroform and dilute hydrochloric acid. The chloroform layer was separated, washed with water, and concentrated to dryness after drying over sodium sulfate. The residue of 900 mg. was crystallized from a mixture of acetone and hexane to give 350 mg. (32%) of VIII melting at 207–209° dec. Further crystallization from benzene raised the melting point to 212.5–213.5° dec. [ν (cm.$^{-1}$) 3300 (OH), 1775 (carboxyl C=O)]. In a chloroform solution containing piperidine, amine salt bands appeared in the 2500-cm.$^{-1}$ region and a strong COO^- band at 1615 cm.$^{-1}$.

B. From X.—To a suspension of 1.0 g. of X[6] in 50 ml. of 2.5 *N* sodium hydroxide, a solution of 2.1 g. of potassium ferricyanide in 50 ml. of water was added. After stirring at room temperature for 1 hr., the reaction mixture was acidified with acetic acid and the crystalline precipitate separated by filtration. The crude material was partitioned between chloroform and dilute hydrochloric acid and the organic layer then washed with water and dried over sodium sulfate. After filtration and evaporation of solvent, a residue of 900 mg. was obtained. Crystallization from a mixture of chloroform and hexane gave 600 mg. (60%) of colorless needles of VIII.

Anal. Calcd. for $C_{15}H_9ClN_2O_2$: C, 63.27; H, 3.19; N, 9.84. Found: C, 63.15; H, 3.24; N, 9.65.

6-Chloro-2-(N-methylformimidoyl)-4-phenylquinazoline (XII). A. From XI.—A suspension of 6.4 g. (0.021 mole) of 2-chloromethyl-4-phenyl-6-chloroquinazoline 1-oxide[10] in 100 ml. of methanolic methylamine (37%) was stirred at room temperature. After 2.5 hr. the solid had dissolved and the resulting solution was allowed to stand for 20 hr. The solvent was evaporated *in vacuo* and the solid residue was partitioned between 200 ml. of methylene chloride and 75 ml. of water. The organic layer, after washing with water, drying over sodium sulfate, and evaporation *in vacuo*, yielded 5.4 g. of crude product. Recrystallization from ethyl acetate gave 3.3 g. (56%) of XII melting at 155–156°.

B. From VII.—A solution of 0.5 g. (1.8 mmoles) of VII in 25 ml. of a 14.5% solution of methylamine in methanol was kept at room temperature for 3.5 hr. After removal of solvent *in vacuo* and crystallization from ether, 0.2 g. (40%) of XII, identical with the previous material, was obtained.

Anal. Calcd. for $C_{16}H_{12}ClN_3$: C, 68.20; H, 4.29; N, 14.91; Cl, 12.58. Found: C, 68.54; H, 4.29; N, 14.95; Cl, 12.33.

6-Chloro-2-methylaminomethyl-4-phenylquinazoline (XIV).—A solution of 1.0 g. (0.0036 mole) of XII in 50 ml. of methanol was hydrogenated under atmospheric pressure in the presence of 1.0 g. of Lindlar's catalyst. Hydrogen uptake was rapid and 0.0036 mole of hydrogen was absorbed. After filtration of catalyst and evaporation of the solvent *in vacuo*, crude XIV was obtained. Recrystallization from a mixture of ether and petroleum ether gave material melting at 93–95°, which was identical with a sample liberated from the hydrochloride prepared according to Bell, *et al.*[12]

Anal. Calcd. for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97. Found: C, 67.82; H, 4.82.

XIV Hydrochloride.—This salt was identical with the product prepared as described in the literature.[12]

2,4-Dinitrophenylhydrazone of 6-Chloro-4-phenyl-2-quinazolinecarboxaldehyde (XIII) A. From XII.—A sample of 0.4 g. (1.4 mmoles) of XII was converted to the 2,4-dinitrophenylhydrazone as described by Shriner, *et al.*[17] The crude product (0.6 g.) was recrystallized from dimethylformamide and formed yellow needles melting at 275–276°.

B. From VII.—Treatment of VII with dinitrophenylhydrazine as described before gave a product identical with material prepared from XII.

(17) R. L. Shriner, R. C. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 219.

C. From V.—To a solution of 5 g. (0.025 mole) of 2,4-dinitrophenylhydrazine in 25 ml. of concentrated sulfuric acid, 36 ml. of water, and 125 ml. of ethanol, 3 g. (0.01 mole) of V was added. The reaction mixture was stirred at room temperature for 16 hr. The crystalline reaction product, formed in almost quantitative yield, was separated by filtration. After recrystallization from dimethylformamide, yellow needles of XIII were obtained.

Anal. Calcd. for $C_{21}H_{13}ClN_6O_4$: C, 56.20; H, 2.92; N, 18.72; Cl, 7.90. Found: C, 55.84; H, 3.12; N, 18.34; Cl, 7.77.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and to Mr. S. Traiman and his co-workers for the infrared spectra.

Heterocyclic Studies. X. A Steroidal 1,2-Diazepin-4-one[1]

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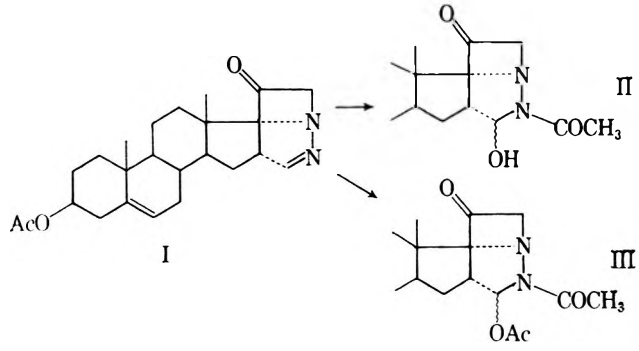
Acylation of the diazabicyclic ketone system (I) results in addition of acid or anhydride to the C=N bond. I is isomerized to the diazepinone (IV) by heating in acetic acid with sodium acetate. The steroidal diazepinone differs greatly in reactivity from the methylphenyldiazepinone (VI) and fails to undergo the characteristic ring contractions and transannular reaction of the latter.

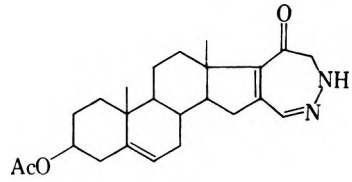
In a previous article we recorded the preparation of a series of nitrogenous steroid derivatives in which the 1,2-diazabicyclo[3.2.0]heptene ring system is fused to the pregnane D-ring.[2] The compounds in this series are of interest, *per se*, as an addition to the growing catalog of nitrogen-containing steroids, some of which have proven to be of pharmacological importance.[3] From a chemical standpoint, however, the steroid nucleus represents a convenient framework to which the heterocyclic rings can be attached in a sterically restricted way, providing an opportunity to expand our knowledge of the 1,2-diazabicyclo[3.2.0]heptane and 1,2-diazepine systems.

A number of nuclear transformations of the bicyclic ketone (I) have been described in which the heterocyclic system remained intact, and it was observed that the compound displays the high carbonyl reactivity characteristic of four-membered cyclic ketones.[2] We now report the results of further study on the heterocyclic chemistry of I.

The diazabicycloheptenone system in I is resistant to mild hydrolysis or oxidation, but reaction occurs with acetyl chloride or, under forcing conditions, with acetic anhydride. With both reagents two products can be isolated which involve the addition of the elements of acetic acid in one case and of acetic anhydride in the other. The infrared spectra of these derivatives contain three and four carbonyl bands, respectively; in both cases the characteristic low wave-length band at 5.56–5.57 μ indicates retention of the four-membered cyclic ketone group. A band at 6.01–6.06 μ in both spectra must be due to an amide carbonyl, and the structures of these products can be assigned as II and III, resulting from addition to the azomethine bond in the pyrazoline ring of I. Similar additions have been observed in the indolenine series[4]; benzoyl chloride in aqueous alkali leads to the 1-benzoyl-2-indolinol, and acetic anhydride to the N-acetylcarbinolamine acetate. The formation of III with acetyl chloride is rather surprising, however, and this reaction, as well as the transformations of the adducts, is being studied further.



One of the primary aims of this work has been the conversion of I to the diazepinone (IV) and a comparative study of the reactions of this compound with those of the counterpart (VI) in which methyl and phenyl substituents replace the ring D residues. The chemistry of the latter compound has been explored extensively,[5] and a number of ring-contraction and transannular reactions have been encountered. Some of these transformations that are of importance in connection with the present work are recapitulated in Scheme I. The reactions of the steroid series have revealed a much diminished tendency for rearrangement and interconversion of the bicyclic and seven-membered ring systems.



IV

In the previous paper[2] it was noted that the conditions sufficient for the conversion V → VI (Scheme I), namely treatment with very mild acid or base, were without effect on the steroidal bicyclic ketone (I). A number of attempts to bring about a parallel isomerization by employing more vigorous acid or basic condi-

(1) Supported by Grant A-3629 from the National Institute of Arthritis and Metabolic Diseases.

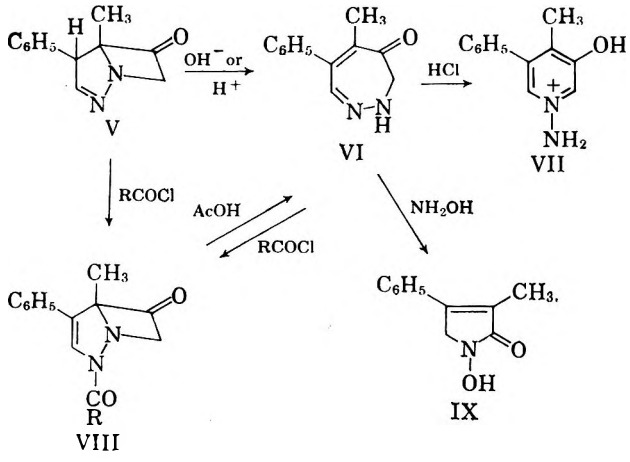
(2) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.*, **84**, 390 (1962).

(3) M. Alauddin and M. Martin-Smith, *J. Pharm. Pharmacol.*, **14**, 325, 469 (1962).

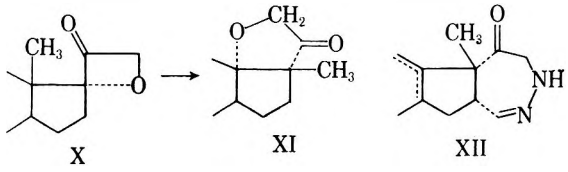
(4) H. Leuchs, A. Heller, and A. Hoffmann, *Ber.*, **62**, 871 (1929), and earlier references cited there.

(5) (a) J. A. Moore and R. W. Medeiros, *J. Am. Chem. Soc.*, **81**, 6026 (1959); (b) J. A. Moore and J. Binkert, *ibid.*, **81**, 6029 (1959); (c) J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *ibid.*, **84**, 3022 (1962).

SCHEME I



tions were fruitless. Refluxing in dilute ethanolic sulfuric acid caused only hydrolysis of the 3-acetate group. These conditions bring about cleavage of the related 17,21-oxido 20-ketone (X) with attendant methyl migration to give the 17β-methyl 13α,21-oxide (XI),[6] and there is a possibility that acid-catalyzed rearrangement of I might lead to a corresponding 17β-methyldiazepine (XII) rather than IV. More drastic acid

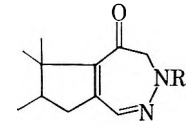


treatment of I gave dark amorphous resins in which the 5.6-μ infrared band characteristic of I was absent, but no crystalline products were obtained. Similarly, vigorous alkaline conditions caused destruction of the four-membered ring, but products could not be isolated.

Successful conditions were found when I was heated on the steam bath in acetic acid solution containing a large amount of sodium acetate. Dilution with water gave an olive precipitate which on chromatography furnished brilliant deep yellow needles of an isomeric compound in 16% yield based on the bicyclic ketone consumed. The ultraviolet spectrum was remarkably similar to that of the diazepinone (VI), with a long wavelength maximum at 405 mμ; a similar bathochromic shift occurred in alkaline solution. The infrared spectrum contained a sharp band at 2.89 and a carbonyl band at 6.04 μ. In the n.m.r. spectrum,[7] besides the typical skeletal proton resonances, peaks were present at 7.08 (—C*H*=N), 6.76 (broad, N*H*), and 3.58 p.p.m. (slightly split, COCH_2NH).

The structural assignment IV for this product rests on these physical properties and analogy to the isomerization V → VI (Scheme I). The alternative diazepine structure XII can be dismissed on the basis of the infrared and particularly the ultraviolet spectra. The reactions that have been observed are consistent, with structure IV, but a number of the important transformations of VI so far have failed when applied to the steroidal diazepinone.

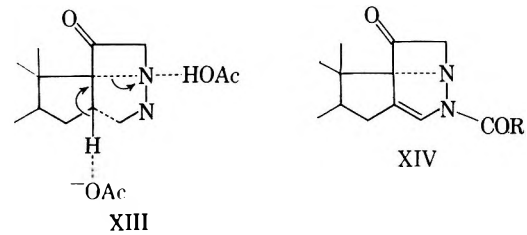
Treatment of IV with methyl sulfate in alkali followed by reacetylation gave a single yellow monomethyl derivative which must be IVb. The infrared spectrum contained the same carbonyl bands as that of IV but no NH band. The n.m.r. spectrum contained a sharp peak at 3.39 p.p.m. (NCH_3) superimposed on a symmetrical pair of doublets with midpoint 3.48 p.p.m. ($\delta_B - \delta_A$ = 13.9 c.p.s., J_{AB} = 13 c.p.s.) due to the COCH_2N group. This splitting of the methylene protons, which is not seen in the n.m.r. spectrum of the corresponding 2-methyl derivative of the nonsteroidal diazepinone (VI), indicates nonequivalence of these protons due to a fairly rigid nonplanar heterocyclic ring in IVb. Acetylation of IV with acetic anhydride or acetyl chloride gave a yellow monoacetyl derivative, assigned structure IVc. These simple substitutions have been observed with the methylphenyldiazepinone (VI),[5b] but in the latter case a major product also results from attack at the N-1 position (—N=), *e.g.*, the formation of VIII in the reaction with acid chlorides.[5c]



IVb, R = CH_3
c, R = $COCH_3$

Although a conjugated carbonyl group in IV is clearly indicated by the infrared spectrum, no reaction was observed with either semicarbazide or hydroxylamine, both of which react readily with VI, the latter in a transannular manner to give IX.[5b] Attempts to bring about a ring contraction of IV to an aminopyridine with acid, parallel to the transformation VI → VII so far have been unsuccessful; partially deacetylated IV was recovered at room temperature, and on heating only resinous material was produced.

The pronounced differences in reactivity of both the diazabicycloheptenone and diazepinone systems in the two series must arise from a combination of steric and electronic factors. The ease with which V is converted to VI, especially in base, is presumably due to the lability conferred on the C-4 proton in V by the phenyl substituent. The resistance of I to isomerization in acid or base alone can be attributed to the absence of a similar mobilization of the 16β proton, since there must be some relief of strain in passing from I to IV. The role of acetate ion in the isomerization of I is quite clear-cut, and it appears that we are dealing here with simultaneous catalysis by acid and base in the debridging reaction as indicated in XIII.



(6) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.* **77**, 4784 (1955); J. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *ibid.*, **78**, 4813 (1956); R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker, and J. M. Chemerda, *ibid.*, **78**, 4814 (1956).

(7) N.m.r. spectra were measured at 60 Mc. in deuteriochloroform solution; peak positions are expressed in parts per million relative to internal tetramethylsilane.

The failure of I to furnish product XIV, analogous to VIII, on acylation has been rationalized previously on steric grounds[2]; the establishment of a double bond exocyclic to ring D in the bicyclic system would introduce severe additional strain. This consideration also would apply to the nonformation of XIV from the diazepinone (IV), but very probably an additional factor in this case is the greater rigidity of IV compared to the monocyclic diazepinone (VI), which is revealed by the n.m.r. spectrum of IVb and would preclude a 1,4-transannular interaction. This situation also may be responsible for the failure of IV to undergo ring contraction to a pyridine; the reaction VI → VII is considered to involve transannular formation of a diazabicyclo[4.1.0] system rather than a ring opening and reclosure sequence,[5b] requiring conformational mobility which is absent in IV.

Experimental[8]

Starting Material.—The ketone (I) was prepared as previously described.[2] The required 3β-hydroxy-5,16-etiadienic acid was prepared by the alkaline hydrolysis of 21-pyridinium-5,16-pregnadien-3β-ol-20-one iodide by an improved procedure in which the sparingly soluble sodium salt of the acid was crystallized and then acidified to give the crystalline acid directly, avoiding a rather troublesome extraction. The hypobromite degradation described[9] for the preparation of 3β-hydroxy-5-etienic acid gave only traces of the etiadienic acid when applied to dehydropregnenolone.

3β,3'-Diacetoxy-2'-acetyl-16α,17α,21-(3',1',1'-pyrazolidino)-5-pregnen-20-one (III).[10] A.—To a solution of 100 mg. of the bicyclic ketone (I) in 3 ml. of pyridine was added, with stirring at 5°, 0.55 ml. of acetyl chloride. A white precipitate of pyridinium chloride separated immediately, and, after adding an additional 2 ml. of pyridine, the reaction mixture was allowed to warm to 25°. The solid dissolved and the color of the solution became yellow and finally dark amber. After 6 hr. the solution was washed, dried, and evaporated, and the brown residue was chromatographed on 4 g. of neutral alumina. The first fraction, eluted with benzene, was crystallized from acetone–hexane to give 24 mg. of white needles of the diacetyl compound (III); m.p. 183–185°; λ^{KBr} 5.56, 5.70, 5.83, 6.01 μ; O.R.D. (*c* 0.116, dioxane), $[\alpha]_{589}$ −86°, $[\alpha]_{370}$ −207°, $[\alpha]_{325}$ +638, $[\alpha]_{300}$ −1230, $[\alpha]_{270}$ −1720, $[\alpha]_{242}$ −518.[11]

Anal. Calcd. for $C_{28}H_{38}N_2O_6$ (498.6): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.27; H, 7.69; N, 5.72.

After elution of some oily material, later fractions eluted with chloroform–2% methanol crystallized from acetone–hexane as colorless leaflets, 15 mg., m.p. 191–194°, of the monoacetyl derivative (II), identical with material described in the following experiment.

B. **3β-Acetoxy-2'-acetyl-3'-hydroxy-16α,17α,21-(3',1',1'-pyrazolidino)-5-pregnen-20-one (II).**—A solution of 500 mg. of I in 20 ml. of pyridine containing 0.36 ml. of acetyl chloride was stirred at 0° for 2 hr. and the pale yellow solution then was poured into ice–water and extracted with ether. The residue after evaporation, 524 mg. of white solid, was crystallized from ether to give 200 mg. of colorless prism, m.p. 193–195°, and 75 mg., m.p. 189–192°. Chromatography of the mother liquor on alumina gave an additional 80 mg. of the same product, m.p. 193–194° (total yield, 62%); none of the diacetyl derivatives was isolated. Recrystallization from ether–hexane gave colorless cubes; m.p. 194°; λ^{KBr} 5.57, 5.79, 6.06 μ; O.R.D. (c 0.094, dioxane), $[\alpha]_{589}$ −106°, $[\alpha]_{380}$ −234°, $[\alpha]_{323}$ +447°, $[\alpha]_{280}$ −1920, $[\alpha]_{250}$ −530.

Anal. Calcd. for $C_{26}H_{36}N_2O_5$ (456.6): C, 68.39; H, 7.95. Found: C, 67.87; H, 7.83.

For further acetylation of this compound to the diacetyl derivative, a solution of 50 mg. in 2 ml. of pyridine and 0.1 ml. of acetic anhydride was heated for 6 hr. on the steam bath. After pouring into water and extracting with ether, 57 mg. of brown solid was obtained and was chromatographed on 2 g. of alumina. The main fraction, 37 mg. after treatment with charcoal, was crystallized from ether–hexane to give 19 mg. of colorless crystals, m.p. 179–181°, infrared spectrum identical with that of III.

C. **Using Acetic Anhydride.**—A solution of 200 mg. of I in 0.5 ml. of acetic anhydride and 2.0 ml. of pyridine was heated on the steam bath for 17 hr. The solution then was poured into water, and the dark brown solid was collected and chromatographed on alumina. The fractions, eluted with benzene–chloroform, were crystallized from ether–hexane to give 30 mg. of colorless rosettes, m.p. 163–183°. Recrystallization gave rods, m.p. 166–176°, with infrared spectrum nearly identical with that of III prepared by procedure A. Later fractions gave 44 mg. of prisms, m.p. 180–185°, with infrared spectrum corresponding to the monoacetyl derivative (II).

3β-Acetoxy-1',7'-dihydro-5,16-androstadieno[16,17:4,5']-6'*H*-1',2'-diazepin-6'-one (IV).—A solution of 3.0 g. of I and 15 g. of freshly fused sodium acetate in 300 ml. of glacial acetic acid was heated on the steam bath for 12 hr. The dark brown solution then was cooled and poured into 1.2 l. of water and the olive-brown solid was filtered, washed with water, and dried, giving 2.30 g. The filtrate was extracted with methylene chloride and the combined solids, 3.1 g., were chromatographed from benzene solution on 75 g. of neutral Grade I alumina. The first fractions, eluted with benzene and chloroform, contained 1.15 g. of brown solid which on several crystallizations from acetone–hexane gave 0.89 g. of unchanged I in several crops with melting points of 170–190°. The next fractions (0.83 g.) were partly oily and partly solid; after combining selected fractions with the mother liquor from I and rechromatographing, a total of 327 mg. of IV was obtained, m.p. 238–241. Recrystallization from benzene–hexane furnished glistening golden needles; m.p. 241–242°; λ_{max}^{EtOH} 220 ($\epsilon \times 10^{-3}$, 10.5), 253 (3.6), 321 (4.0), 405 mμ (2.8); $\lambda_{max}^{EtOH+NaOH}$ 283 (3.4), 323 (2.1), 410 mμ (4.8); λ^{KBr} 2.89, 5.78, 6.04 μ; O.R.D. (*c* 0.104, dioxane), $[\alpha]_{589}$ −120°, $[\alpha]_{455}$ +600°, $[\alpha]_{330}$ −3000°, $[\alpha]_{250}$ +5400°.

Anal. Calcd. for $C_{24}H_{32}N_2O_3$ (396.5): C, 72.69; H, 8.13; N, 7.07. Found: C, 72.48; H, 8.09; N, 6.84.

From later fractions in the chromatogram, eluted with chloroform–methanol, a very sparingly soluble colorless substance was isolated. Recrystallization from chloroform–hexane gave 60 mg. of white fluffy needles, m.p. 288–293°, λ_{max}^{EtOH} 250 mμ (ε 1600). Analysis suggested a dihydro composition; this compound has not been characterized further.

Anal. Calcd. for $C_{24}H_{34}N_2O_3$ (398.5): C, 72.33; H, 8.60; N, 7.03. Found: C, 72.23, 72.05; H, 8.63, 8.80; N, 6.80.

Acetylation of IV.—A solution of 50 mg. of IV in 5 ml. of pyridine was treated with 0.25 ml. of acetic anhydride and was allowed to stand overnight. After dilution with water and extraction with methylene chloride, the crude yellow product was crystallized from ether–hexane as needles, 34 mg., m.p. 204–209°. Further crystallizations from ether–hexane gave golden needles of IVc, m.p. 211–212°; λ^{KBr} 5.74, 5.94, 6.01, 6.33 μ.

Anal. Calcd. for $C_{26}H_{34}N_2O_4$ (438.5): C, 71.20; H, 7.82. Found: C, 71.31; H, 7.89.

Acetylation of 25 mg. of IV with acetyl chloride in pyridine gave mainly brown insoluble amorphous material; from the ether extracts was obtained 6 mg. of yellow crystals of IV with an infrared spectrum the same as that of the product from acetic anhydride.

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(8) Infrared spectra were obtained in potassium bromide disks with a Perkin-Elmer Infracord. Melting points were determined on Fisher-Johns block with calibrated thermometer.

(9) C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, **83**, 741 (1961).

(10) The nomenclature of the compounds in this series has presented some difficulties since existing rules for steroid nomenclature do not provide for the naming or numbering of compounds with a heterocyclic ring fused to the steroid nucleus. In constructing a fusion name, it seems desirable to place the steroid name first and to use a genetic numbering system in which the usual steroid numbering is retained and the atoms of the heterocyclic rings are primed, as in the name which has been used for IV.

The nomenclature of compounds with the ring system of I–III presents an additional problem since a fusion name is not possible. In the name originally used[2] for the parent system of I, 16α,17α,21-[3,1,1-(2-pyrazolino)]-pregnane, the attachment of the heterocyclic rings is indicated by the bonds between atoms of the steroid and heterocyclic rings (16α-3, 17α-1, and 21-1). Until some systematic alternative is developed this name will be retained with the modification of primed numbers for the three atoms comprising the pyrazoline or pyrazolidine ring.

We wish to thank Dr. Harriet Geer, Parke, Davis and Co., and Dr. Leonard Capell and Donald Walker of Chemical Abstracts Service for their contributions and helpful discussions on these questions.

(11) We wish to express our thanks to Professor Carl Djerassi, Stanford University, for obtaining the optical rotatory dispersion data.

Alkaline Hydrolysis of IV.—A solution of 50 mg. of IV in 6 ml. of ethanol (containing some undissolved solid) was treated with 0.5 ml. of 5% aqueous sodium hydroxide solution. After stirring for 30 min., a heavy yellow precipitate began to separate. The mixture was stirred for an additional 18 hr. and then was diluted with water and filtered. The bright yellow powder, 43 mg., m.p. 250–252°, was recrystallized from acetone–hexane to give tiny golden flakes of the 3-hydroxydiazepine, m.p. 252–254°.

Anal. Calcd. for $C_{22}H_{30}N_2O_2$ (354.5): C, 74.54; H, 8.53. Found: C, 74.13; H, 8.68.

Methylation of IV.—To a solution of 100 mg. of IV in 15 ml. of ethanol at 0° was added 0.6 ml. of 10% potassium hydroxide solution and 0.07 ml. of methyl sulfate. Solid began to separate after 10 min., and the mixture then was kept at room temperature for 2 hr., diluted with water, acidified, and extracted with chloroform. The yellow solid obtained from the chloroform solution was reacetylated with acetic anhydride and the crude acetate was chromatographed on alumina. Crystallization of the first three fractions (79 mg.) from ether–hexane gave 55 mg. of glistening yellow flakes of IVb, m.p. 219°.

Anal. Calcd. for $C_{25}H_{34}N_2O_3$ (410.5): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.16; H, 8.07; N, 6.55.

Steroids with Functional Sulfur Groups. IV.[1] The Isomerization of Some 2′-Methoxythiazolino[4′,5′:11α,9α]-11β-hydroxy Steroids

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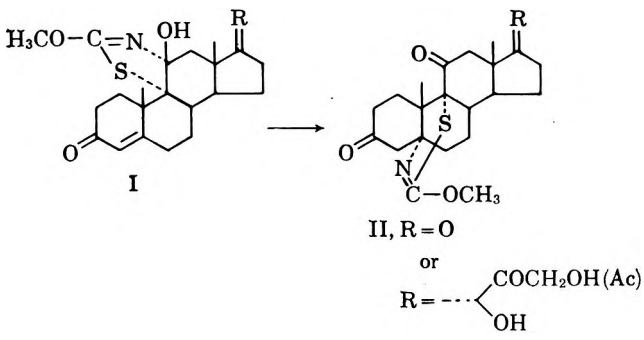
The effect of some modifications in ring A on the course of the rearrangement of 2′-methoxythiazolino[4′,5′:-11α,9α]-11β-hydroxy steroids to 2′-methoxydihydrothiazino steroids was studied. It was found that the α,β-unsaturated oxo system is the minimum requirement for such an isomerization. The $\Delta^{1,4}$-dien-3-one system led to the formation of a 2′-methoxydihydrothiazino[4′,5′,6′:1α,10,9α] steroid (X) and a 2′-methoxydihydrothiazino[4′,5′,6′:5α,10,9α] steroid (IX) in the ratio of 7:1.

In a preceding paper,[1c] we reported a novel isomerization reaction involving the rupture of the C–N bond at C-11 of the thiazoline ring and reattachment of the nitrogen bearing function to C-5 with the resultant formation of a dihydrothiazine ring as shown (I → II).



It had appeared to us that this isomerization required the presence of an α,β-unsaturated oxo system in certain proximity to the thiazolino moiety. This study is a partial attempt to define more precisely the scope and limitations of this rearrangement, particularly with respect to ring A of the steroid molecule.

As expected, attempts to rearrange the 3-oxo saturated derivative, 2′-methoxythiazolino[4′,5′:11α,9α]-5α-androstan-11β-ol-3,17-dione (VIIa), to the dihydrothiazino compound did not materialize, thus attesting to the necessity for the presence of unsaturation. The starting material VIIa was prepared from 9β,11β-epoxy-5α-androstane-3,17-dione (IVa) by a similar reaction sequence described previously[1c] for the preparation of I (R = O). Compound IVa was obtained by catalytic hydrogenation of 9β,11β-epoxy-Δ⁴-androstene-3,17-dione (III) over palladium–charcoal in ethyl acetate. The hydrogenation furnished a mixture of isomers whose separation was achieved by chromatography on alumina. As expected from the presence of an 11β-substituent,[3] the 5α isomer was shown to be the predominant product. VIIa, thus prepared, when refluxed in methanol for a period of 24 hr., remained unchanged; however, prolonged refluxing (6 days) yielded a negligible amount of unidentified substance as revealed by thin layer chromatography. When compound VIIa was refluxed in aqueous ethanolic potassium carbonate, 9α-methylthio-5α-androstane-3,11,17-trione (VIII) was formed in accordance with our earlier observation.[1c] A singlet peak at τ 8.05 in the n.m.r. spectrum corroborated[1c] this structural assignment. Further elaboration of the methylthio function to obtain the sulfoxide or sulfone derivative by oxidation with monoperphthalic acid[4] or with the pyridine chromic acid complex[5] failed. An attempt to obtain the 9α-thiocyano compound (VIa) with cyanogen bromide[6] was also unsuccessful.

That the double bond alone is also insufficient for isomerization was shown by the refractoriness of 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androstene-3ξ,11β,17β-triol (VIIc) toward prolonged refluxing (6 days) with methanol. VIIc was prepared by the methanolysis of VIc.[1c] The requirement of an α,β-unsaturated oxo system for isomerization to the dihydrothiazine derivative thus becomes apparent.

It became of some interest to study the effect of a 1,4-dienone system upon the isomerization of the thiazoline moiety. Accordingly, 9β,11β-epoxy-$\Delta^{1,4}$-andro-

(1) (a) In remembrance of the late Dr. Erich Mosettig of this Institute; (b) part II, Y. Ueda and E. Mosettig, *Steroids*, **1**, 361 (1963); (c) part III, I. Kitagawa, Y. Ueda, T. Kawasaki, and E. Mosettig, *J. Org. Chem.*, **28**, 2228 (1963).

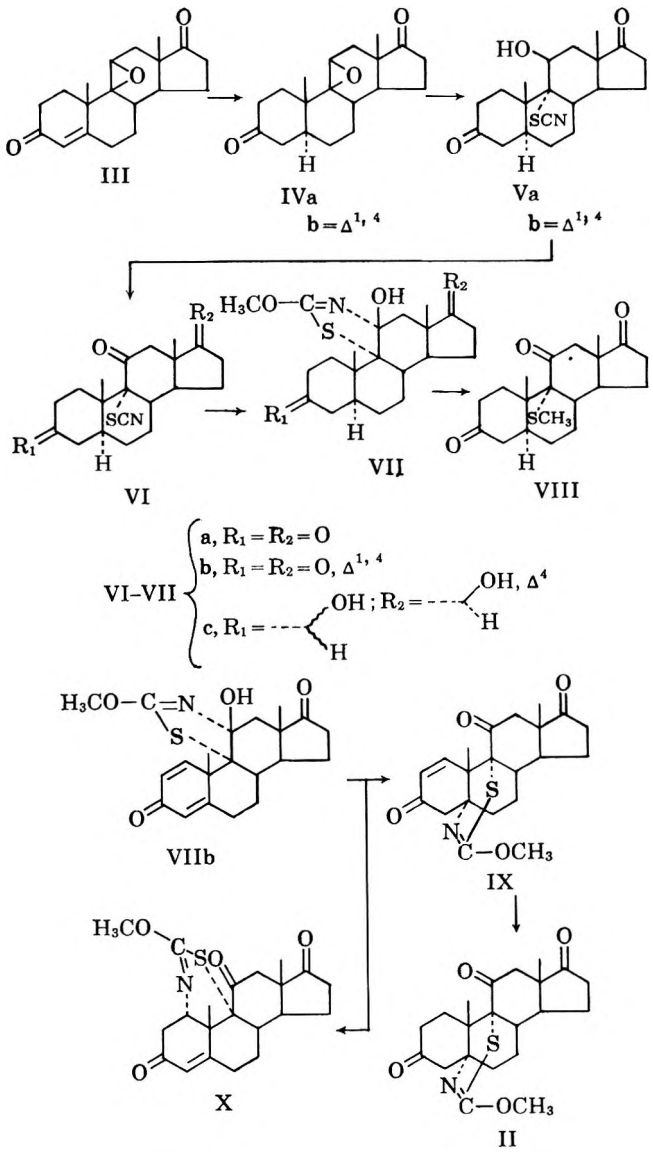
(2) Visiting Scientist (1961–1963), National Institutes of Health, under the sponsorship of the Cancer Chemotherapy National Service Center, National Cancer Institute; Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan.

(3) J. Pataki, G. Rosenkranz and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

(4) R. E. Shaub and M. J. Weiss, *J. Org. Chem.*, **27**, 2221 (1962).

(5) D. Edwards and J. B. Stenlake, *J. Chem. Soc.*, 3272 (1954).

(6) J. von Braun and R. Murjahn, *Ber.*, **59**, 1202 (1926); J. von Braun and P. Engelbertz, *ibid.*, **56**, 1573 (1923).



stadiene-3,17-dione (IVb)[7] was treated with thiocyanic acid[1,8] to afford 9α-thiocyano-Δ1,4-androstadien-11β-ol-3,17-dione (Vb) in a 68% yield. The reaction proceeded rather slowly[9] as compared with the formation of Va or 9α-thiocyano-Δ4-androsten-11β-ol-3,17-dione.[1c] Chromic acid oxidation of Vb, followed by methanolysis of VIb in base, yielded 2′-methoxythiazolino[4′,5′:11α,9α]-Δ1,4-androstadien-11β-ol-3,17-dione (VIIb).[10] The expected isomerization of VIIb in methanol required a longer period of refluxing than that for the conversion of I to II. Even after refluxing for 7 days, 10% of the starting compound was recovered. The mixture from the isomerization was separated by chromatography on alumina into three components, a major (seven parts) and a minor (one part) product and the starting material (one part). The minor product, exhibiting an ultraviolet absorption maximum at 222.5 mμ[11] (ε 10,700) and infrared bands at 5.72 (C-17 carbonyl), 5.83 (C-11 carbonyl), 6.0 μ (broad,[12] Δ1-C-3 carbonyl and C=N), is shown to be 2′-methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,9α]-Δ1-androstene-3,11,17-trione (IX) by its conversion into the known thiazino compound II (R = O)[1c] by catalytic hydrogenation over palladium–charcoal in ethyl acetate. The major product possessed an ultraviolet absorption maximum at 237.5 mμ[13] (ε 12,890) and infrared absorption bands at 5.73 (C-17 carbonyl), 5.86 (C-11 carbonyl), 5.97 μ (broad,[12] Δ4-C-3 carbonyl, and C=N). To it is ascribed the alternate structure X. N.m.r. data of the two isomers also support these structural assignments. Compound IX exhibited a singlet at τ 6.33 (CH_3O),[1c] a pair of doublets at 4.20 (proton at C-2) and 2.50 (proton at C-1) with J = 10 c.p.s.,[14] in addition to two peaks at 9.12 and 8.30, corresponding to the C-18, C-19 methyls, respectively. On the other hand, isomer X possessed a singlet at τ 4.19 (proton at C-4)[15] in addition to a singlet at 6.34 (CH_3O).[1c]

This apparent difference in the reactivity[16] of positions 1 and 5 in the isomerization of the dienone VIIb was also noted by Dodson and Tweit[17] in their study on the addition of alkanethiolic acids to Δ1,4-3-oxo steroids. They found that the Δ1 bond is selectively attacked by the nucleophilic alkanethiolic acid ion.

Experimental[18]

9β,11β-Epoxy-5α-androstane-3,17-dione (IVa).—A mixture of 9β,11β-epoxy-Δ4-androstene-3,17-dione[19] (III, 2.1 g.) and 10% palladium–charcoal (1.05 g.) in ethyl acetate (500 ml.) was hydrogenated at room temperature under atmospheric pressure. The product was purified by chromatography on alumina (Woelm, neutral, grade III, 100 g.) using 1:2 benzene–petroleum ether (b.p. 60–71°) mixture and benzene successively as eluents. Crystallization from acetone–hexane of the later fractions gave colorless crystals of IVa (1.58 g., 73.8%), melting at 166–172°. Repeated crystallization from benzene–hexane yielded an analytical sample melting at 175–176°, $[\alpha]_D$ +98.4° (c 0.42); λ_{max} 5.75, 5.83 μ (CO).

(7) Prepared from Δ1,4,9(11)-androstratriene-3,17-dione through the 9,11-bromohydrin according to the procedure developed by K. Tsuda, S. Nozoe, and Y. Okada (forthcoming publication). We wish to express our appreciation for a copy of the manuscript before publication. Physical constants of IVb [m.p. 167–169°, $[\alpha]_D$ +83° (c 0.68); found: C, 76.23; H, 7.65] agreed with their data [m.p. 164–169°, $[\alpha]_D$ +88° (c 0.71)].

(8) A more effective concentration of thiocyanic acid is needed. See the Experimental section.

(9) The epoxy-ring opening of 9β,11β-epoxy-Δ1,4-pregnadiene-17α,21-diol-3,20-dione by hydrogen fluoride proceeds more slowly than the corresponding 9β,11β-epoxy-Δ4-pregnene derivative [R. F. Hirschmann, R. Miller, J. Wood, R. E. Jones, *J. Am. Chem. Soc.*, **78**, 4956 (1956)].

(10) Further transformation of VIIb to a 9α-methylthio derivative failed.

(11) The calculated value for the ultraviolet absorption maximum of Δ1-3-keto steroid is 227 mμ [L. Dorfman, *Chem. Rev.*, **53**, 47 (1953)]. 9α-Fluoro-Δ1-pregnene-11β,17α,21-triol-3,20-dione acetate was shown to have an ultraviolet absorption maximum at 222 mμ (log ε 4.03) [R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett, M. Tishler, *J. Am. Chem. Soc.*, **77**, 3166 (1955)].

(12) Sufficient resolution could not be obtained even with use of a grating infrared spectrophotometer, Perkin-Elmer Model 421.

(13) Both compounds IX and X exhibit a hypsochromic shift of about 4 ~ 6 mμ from their calculated values.

(14) The spin–spin coupling constant for *cis* olefinic protons is shown to vary from 6–14 c.p.s. [L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 85].

(15) The chemical shift of a proton at C-4 in testosterone is shown to be at τ 4.18 [J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958)].

(16) Dreiding-stereomodel studies indicate an almost equal accessibility of C-1 or C-5 for the attack by a 9α function.

(17) (a) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959); (b) the isothiocyanate ion also adds predominantly at position 1 to produce 1α-isothiocyano-cortisone-21-acetate [K. Takeda, T. Kubota, J. Kawanami, *Chem. Pharm. Bull.* (Tokyo), **8**, 615 (1960)].

(18) All melting points were determined on a Kofler block and recorded as read. Optical rotations were measured in chloroform at 20° unless mentioned otherwise. The ultraviolet absorption spectra were measured in ethanol solution with a Cary self-recording spectrophotometer Model 15, infrared spectra in Nujol with a Perkin-Elmer double-beam spectrophotometer Model 21 unless specified otherwise. The n.m.r. spectra were taken in deuteriochloroform with a Varian A-60 spectrometer. Silica gel G was used for thin layer chromatography.

(19) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.62; H, 8.86.

9α-Thiocyano-5α-androstan-11β-ol-3,17-dione (Va).—A solution of IVa (1.0 g.) in glacial acetic acid (20 ml.) and thiocyanic acid solution[20] (20 ml.) was allowed to stand at room temperature for 24 hr. The yellow solution was then treated with ice–water and extracted with chloroform. The extracts yielded an amorphous residue, which was crystallized from acetone–hexane to yield needles melting at 147–150° dec., 0.412 g. (35.2%). The analytical sample was obtained by further recrystallization from the same solvent mixture, m.p. 149–150° dec., $[\alpha]_D$ +94.7° (*c* 0.40, dioxane); λ_{max} 2.88 (OH), 4.65 (SCN), 5.73, 5.85 μ (CO).

Anal. Calcd. for $C_{20}H_{27}O_3NS$: C, 66.45; H, 7.53; N, 3.88; S, 8.87. Found: C, 66.59; H, 7.77; N, 3.66; S, 9.2.

9α-Thiocyano-5α-androstane-3,11,17-trione (VIa).—A stirred solution of Va (0.2 g.) in glacial acetic acid (20 ml.) was treated with chromic acid solution (0.28 g. in 5.0 ml. water) and stirred further for 1 hr. at room temperature. The reaction mixture was then poured into ice-cooled water and allowed to stand in a refrigerator for 2 hr. The colorless crystalline mass was recrystallized from methanol to yield 0.093 g. of leaflets melting at 212–214.5°. Extraction of the aqueous filtrate with chloroform afforded a second crop of leaflets (0.027 g.) melting at 210–212°; total yield, 0.12 g. (60%). The analytical sample was recrystallized from methanol, m.p. 214–215°, $[\alpha]_D$ +273.5° (*c* 0.34, dioxane); λ_{max} 4.66 (SCN), 5.72, 5.86 μ (CO).

Anal. Calcd. for $C_{20}H_{25}O_3NS$: C, 66.82; H, 7.01; N, 3.90; S, 8.99. Found: C, 66.52; H, 7.07; N, 4.09; S, 9.05.

2′-Methoxythiazolino[4′,5′:11α,9α]-5α-androstan-11β-ol-3,17-dione (VIIa).—A colorless suspension of VIa (0.336 g.) in methanol (8.5 ml.) with 10% aqueous potassium carbonate solution (1.56 ml., previously saturated with nitrogen) was stirred under nitrogen atmosphere at room temperature for 2 hr. The mixture was then treated with glacial acetic acid (0.26 ml.), poured into water (100 ml.), and the precipitate crystallized from acetone–hexane to yield colorless prisms (0.266 g., 72.0%) melting at 219–228°. Repeated crystallization from the same solvent mixture afforded an analytical sample, m.p. 226–228°, $[\alpha]_D$ +213.9° (*c*, 0.18); λ_{max} 3.12 (OH), 5.76, 5.86 (CO), 6.16 μ (C=N); n.m.r., τ 6.17 (CH_3O), 8.48 (CH_3 at C-19), 8.94 (CH_3 at C-18).

Anal. Calcd. for $C_{21}H_{29}O_4NS$: C, 64.42; H, 7.47; N, 3.58; S, 8.19; CH_3O, 7.93. Found: C, 64.56; H, 7.77; N, 3.99; S, 8.09; CH_3O, 7.86.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androstene-3ξ,11β,-17β-triol (VIIc).—A solution of 9α-thiocyano-Δ⁴-androstene-3ξ,17β-diol-11-one[10] (0.55 g.) in methanol (20 ml.) was treated with 10% aqueous potassium carbonate solution (1.5 ml.) for 1.5 hr., as in VIIa. After the addition of glacial acetic acid (0.25 ml.) and water (200 ml.), the reaction mixture was extracted with ethyl acetate. The residue from the extraction which refused to crystallize[21] was repeatedly precipitated from ethyl acetate to free it of adhering impurities and the recovered substance (m.p. 151–156°, 0.03 g.) subjected to refluxing for 6 days in methanol (10 ml.). Even under this treatment a check by thin layer chromatography [ethyl acetate–water (15 ml.:9 drops), R_f 0.21], indicated that the starting material was substantially unchanged. Compound VIIc had λ_{max} 3.06 (OH), 5.74, 5.78 (weak, ester),[21] 6.15 μ (C=N).

9α-Methylthio-5α-androstane-3,11,17-trione (VIII).—To a suspension of VIIa (0.1 g.) in ethanol (12 ml.) was added a 10% aqueous potassium carbonate solution (4.5 ml., previously saturated with nitrogen), and the colorless mixture heated at 93–94° for 20 min. under nitrogen aeration. The cooled reaction mixture was treated with glacial acetic acid (1.0 ml.), poured into water (100 ml.), and extracted with chloroform. The product was crystallized from acetone–hexane to give VIII (yield, 0.071 g., 79.8%), melting at 170–173°. An analytical sample was prepared by repeated crystallization from the same solvent mixture, m.p. 179–182°, $[\alpha]_D$ +312.3° (*c* 0.53, dioxane); λ_{max} 5.76, 5.87 (shoulder), 5.92 μ (CO); n.m.r., τ 8.05 (SCH_3), 8.72, 9.11 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{20}H_{28}O_3S$: C, 68.93; H, 8.10; S, 9.20. Found: C, 69.01; H, 8.25; S, 9.25.

9α-Thiocyano-Δ¹,⁴-androstadien-11β-ol-3,17-dione (Vb).—A mixture of 9β,11β-epoxy-Δ¹,⁴-androstadiene-3,17-dione[7] (IVb, 2.13 g.), glacial acetic acid (70 ml.), and thiocyanic acid solution[22] (210 ml.) was stirred continuously at room temperature for 6 days. The resulting yellow suspension yielded 1.82 g. (71.2%) of slight yellow prisms (methanol) melting at 191–195° dec. The analytical sample was obtained by repeated crystallization from methanol and from acetone–hexane, m.p. 202–204° dec., $[\alpha]_D$ +314.3° (*c* 0.68, dioxane); λ_{max} 242 mμ (ε 12,760); 3.14 (OH), 4.66 (SCN), 5.74, 6.03 (CO), 6.20, 6.25 μ (C=C).

Anal. Calcd. for $C_{20}H_{23}O_3NS$: C, 67.20; H, 6.49; N, 3.92; S, 8.97. Found: C, 67.32; H, 6.65; N, 3.95; S, 8.90.

9α-Thiocyano-Δ¹,⁴-androstadiene-3,11,17-trione (VIb).—A solution of Vb (0.482 g.) in glacial acetic acid (40 ml.) was treated with aqueous chromic acid solution (0.56 g. in 10 ml. water) as in VIa. It yielded colorless leaflets (0.362 g., 77.7%, from methanol) melting at 204–207° dec. An analytical sample melted at 203–205° dec., $[\alpha]_D$ +533.9° (*c* 0.43); λ_{max} 238 mμ (ε 13,570); 4.67 (SCN), 5.78, 5.83, 5.97 (CO), 6.15, 6.22 μ (C=C).

Anal. Calcd. for $C_{20}H_{21}O_3NS$: C, 67.58; H, 5.96; N, 3.94; S, 9.02. Found: C, 67.87; H, 6.12; N, 3.87; S, 8.80.

2′-Methoxythiazolino[4′,5′:11α,9α]-Δ¹,⁴-androstadien-11β-ol-3,17-dione (VIIb).—Treatment of VIb (0.979 g.) in methanol (25 ml.) with 10% aqueous potassium carbonate solution (2.3 ml.) as in VIIa, followed by addition of glacial acetic acid (0.78 ml.), water (500 ml.), and extraction with ethyl acetate, gave a solid residue, which was crystallized from acetone–hexane to yield prisms (0.760 g., 71.2%). An analytical sample melted at 222–223° dec., $[\alpha]_D$ +412.1° (*c* 0.44); λ_{max} 244 mμ (ε 13,600); 3.00 (OH), 5.81, 6.01 (CO), 6.14 (C=N and C=C), 6.22 μ (C=C); n.m.r., τ 2.56 (d),[23] 3.78 (d, *J* = 10 c.p.s., proton at C-1 and C-2), 3.85 (proton at C-4), 6.23 (CH_3O), 8.26, 8.77 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50; N, 3.62; S, 8.27; CH_3O, 8.01. Found: C, 65.16; H, 6.38; N, 3.78; S, 8.22; CH_3O, 8.24.

The Isomerization of VIIb into IX and X.—A solution of VIIb (0.40 g.) in methanol (100 ml.) was refluxed continuously for 7 days. During this period, the solution was checked by thin layer chromatography (ethyl acetate–cyclohexane–water, 70:30:0.2). Evaporation of the solvent yielded a resinous residue, which was chromatographed on alumina (Woelm, neutral, grade III, 10 g.) and eluted with the following solvent systems: benzene–hexane (4:1), benzene, and benzene–acetone (1:1). The latter fractions of the benzene–hexane eluates along with the succeeding benzene eluates afforded compound X (0.191 g.) of m.p. 228–235° (acetone–hexane). Unchanged starting material (0.043 g.) was obtained from the benzene–acetone eluates. It was unambiguously identified as VIIb by its melting point, infrared spectrum, specific rotation, and chromatographic behavior (t.l.c.). The earlier fractions of the above chromatography together with the mother liquor from the crystallization of X were combined and rechromatographed on alumina (Woelm, neutral, grade II, 10 g.), using the following eluents: benzene–hexane (4:1), benzene, and benzene–ether (9:1). The earlier fractions of the benzene–hexane eluate afforded IX (0.034 g.) of m.p. 268–272° (acetone–hexane), and the latter eluents (mostly from benzene–ether) yielded an additional amount of compound X (0.045 g.). The analytical sample of IX possessed the following physical characteristics: m.p. 269–271°; λ_{max} 222.5 mμ (ε 10,700); 5.72, 5.83 (CO), 6.00 μ (broad, CO and C=N); n.m.r., τ 2.50 (d),[23] 4.20 (d, *J* = 10 c.p.s., proton at C-1 and C-2), 6.33 (CH_3O), 8.30, 9.12 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50. Found: C, 65.33; H, 6.71.

Compound X melted at 240–243° and exhibited the following physical properties: $[\alpha]_D$ +207.1° (*c* 0.39); λ_{max} 237.5 mμ (ε 12,890); 5.73, 5.86 (CO), 5.97 μ (broad, CO and C=N); n.m.r., τ 4.19 (proton at C-4), 6.34 (CH_3O), 8.40, 9.05 (CH_3 at C-19 and C-18).

Anal. Calcd. for $C_{21}H_{25}O_4NS$: C, 65.09; H, 6.50; N, 3.62;

(20) T. Kawasaki and E. Mosettig, *J. Org. Chem.*, **27**, 1374 (1962).

(21) Although thin layer chromatography of the product indicated homogeneity, a contaminant is probably responsible for the phenomenon. Correct analytical values for this compound could not be obtained (*Anal.* Calcd. for $C_{21}H_{31}O_4NS$: C, 64.09; H, 7.95. Found: C, 62.65, 62.36; H, 8.14, 8.18.). We believe that this is due to difficulties involved in removing the solvent from the compound since the infrared spectrum shows an absorption at 5.78 μ due probably to the ethyl acetate used in the precipitation.

(22) Prepared by adding in order: potassium thiocyanate (58.4 g.), water (30 ml.), glacial acetic acid (240 ml.), and 4 *N*-sulfuric acid (150 ml.) with ice cooling. The supernatant was used for the reaction (approximately equal to 1.43 *N* thiocyanic acid in 57% acetic acid).

(23) d, a doublet peak.

S, 8.27; CH_3O, 8.01. Found: C, 65.23; H, 6.77; N, 3.92; S, 8.5; CH_3O, 8.30.

The Catalytic Hydrogenation of IX into II (R = O).—A mixture of IX (0.010 g.) and 10% palladium–charcoal (0.005 g.) in ethyl acetate (5.0 ml.) was hydrogenated at room temperature under atmospheric pressure for 5 hr. The compound crystallized from methanol to afford prisms, melting at 226–228°. Its identity with II (R = O) was established by mixture melting point determination and comparison of their infrared spectra.

Acknowledgment.—The authors wish to express their great indebtedness to Dr. Edwin D. Becker of this institute for the interpretation of the n.m.r. spectra and to Mr. Robert B. Bradley for running the spectra. We wish also to thank the Cancer Chemotherapy National Service Center for the supply of valuable starting materials.

Investigations on Steroids. XXXV. Pseudostrophanthidin and Related Compounds[1,2]

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An improved method for the conversion of strophanthidin (I) into pseudostrophanthidin (II) is reported. Old and new evidence in support of the structure of II is discussed. In particular, II has been correlated with a number of steroids previously investigated in this laboratory. The earlier literature in this area has been reviewed and is presented in a revised form, *viz.*, in the light of present concepts. The structure of II appears now firmly established.

As a continuation of our studies on 19:8-lactone analogs of progesterone and cortexone[4] it appeared desirable also to prepare compounds of the 19:8-hemiacetal series. In an early investigation, Jacobs and Collins[5] had demonstrated that, by treatment with concentrated hydrochloric acid, strophanthidin (I) is converted into a crystalline isomer which was named pseudostrophanthidin. Its correct structure (II) was recognized by Fieser and Fieser,[6] and this interpretation is in agreement with our own investigations in this area.

Because of its structural features, pseudostrophanthidin (II) was considered as starting material for the synthesis of a variety of steroids with a 19:8-hemiacetal bridge. As the first task, it appeared necessary to repeat and consolidate some of the early experimental work. Furthermore, since it is cumbersome and sometimes confusing to excerpt and interpret data in the early literature, it was deemed advisable to arrange the pertinent findings in a revised form, *viz.*, in the light of present concepts.

Pseudostrophanthidin (II) was prepared in improved yield by a modified procedure. The deviations from the early literature[5] concerning the melting point and optical rotation are recorded in the Experimental section. Pseudostrophanthidin (II) was characterized by the preparation of several derivatives. Refluxing of II with methanol in the presence of a catalytic amount of hydrochloric acid gave pseudostrophanthidin methylal (III),[7] which could be reconverted into II by treatment with 70% acetic acid. The methylal (III) in turn was characterized as the dinitrobenzoate and acetate, *viz.*, pseudostrophanthidin methylal 3,5-dinitrobenzoate (IV) and pseudostrophanthidin methylal 3-acetate (V), respectively. On demethylating V, pseudostrophanthidin 3-monoacetate (VI) resulted which could be further acetylated at an elevated temperature, yielding pseudostrophanthidin 3,19-diacetate (VII). Acetylation of II at room temperature gave a mixture of the 3-monoacetate (VI) and the 3,19-diacetate (VII).

Pseudostrophanthidin (II) could be correlated with a number of compounds structurally connected with strophanthidinic acid lactone (X) which is prepared from strophanthidinic acid (IX).[8] X recently has served as a starting material for synthetic work in this laboratory.[4] In agreement with earlier observations,[8] oxidation with chromic acid of either II or X gave strophanthidonic acid lactone (XI). In addition, acetylation of X gave strophanthidinic acid 19:8-lactone 3-acetate (XII) which also was obtained by oxidation of VI with chromic acid. Another product belonging to this series is 3-dehydropseudostrophanthidin methylal (VIII) which resulted from the oxidation of III with chromic acid.

Experimental

Melting Points.—The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The

(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7 and CY757-C8) from the National Cancer Institute of the National Institutes of Health.

(2) The findings reported in this paper were presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein, "Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press. For abstract see, "Excerpta Medica," International Congress Series, No. 51, International Congress on Hormonal Steroids, Round Table Discussions, p. 57). In addition, this paper was presented by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Universität Hamburg, Universitätskrankenhaus Eppendorf (July 23, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

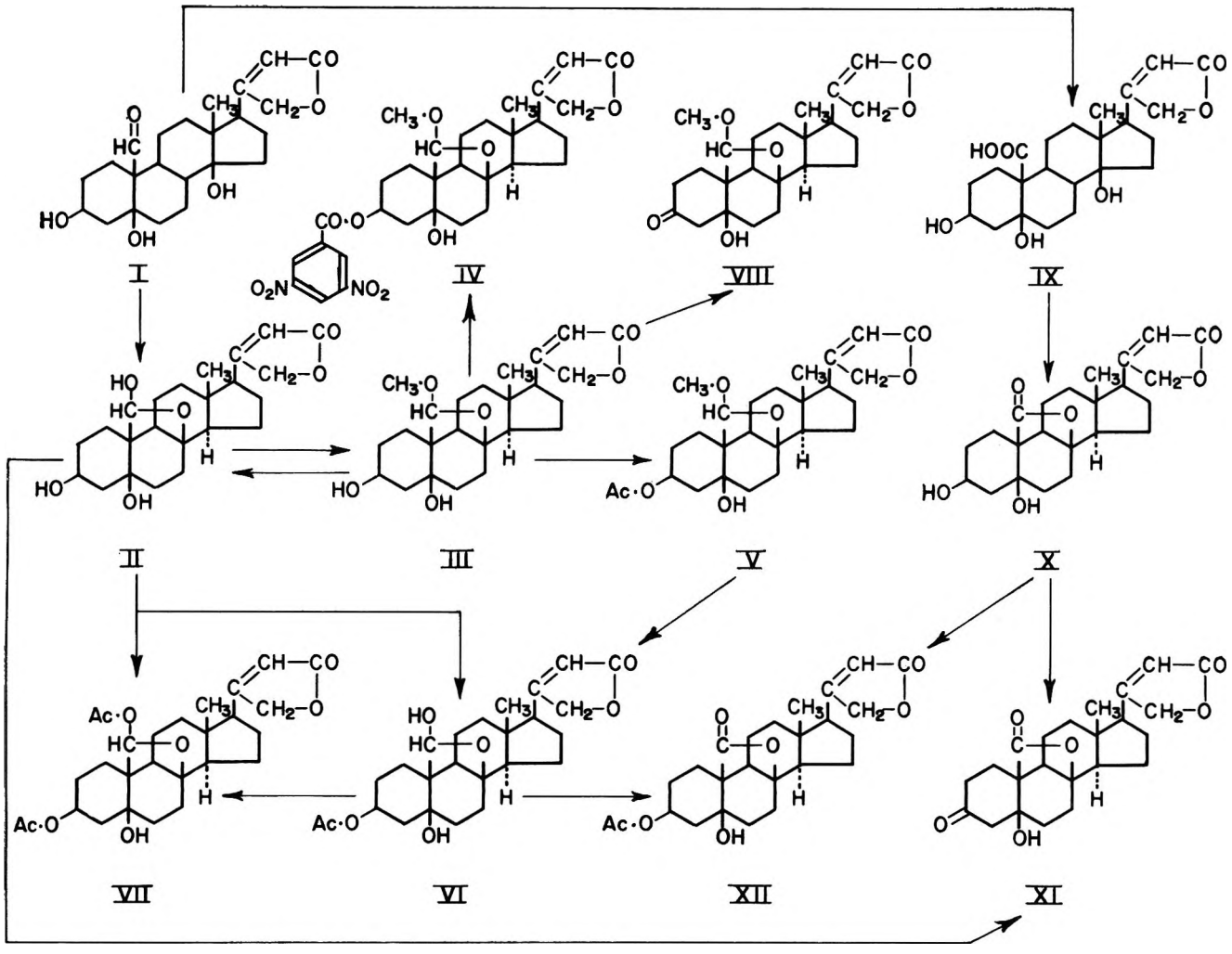
(4) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **26**, 1230 (1961).

(5) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **63**, 123 (1925).

(6) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corporation, New York, N. Y., 1949, pp. 523–524; *cf.* also L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp. 742–744.

(7) From a theoretical point of view, one may consider the existence of two epimeric forms in the series of the C-19 methyals. Only one form was isolated in the present instance.

(8) W. A. Jacobs and A. M. Collins, *J. Biol. Chem.*, **65**, 491 (1925).



true melting points are approximately 3° lower than those reported.

Absorption Spectra.—Ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer.

Analyses.—Unless stated otherwise, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus pentoxide, 80°). The per cent loss of weight on drying is recorded.

Optical Rotation.—No correction for crystal solvent has been made. Unless stated otherwise, the sample was dissolved in chloroform to make 2 ml. of solution and the rotation was determined in a 2-dm. semimicrotube.

Pseudostrophanthidin (II) from Strophanthidin (I).—A solution of 15 g. of I (recrystallized from methanol–water, m.p. 147–160°) in 30 ml. of methanol was evaporated *in vacuo* to give a brittle foam to which 150 ml. of cold concentrated hydrochloric acid was added while cooling in an ice bath. The resulting solution was kept in the ice bath for 4 hr. and was then poured into 1200 ml. of ice–water yielding a white amorphous precipitate (a) which was filtered and washed with water giving the combined aqueous phase (b). The dried precipitate (a), wt., 7.423 g., was taken up in acetone[9] and the solution was evaporated to give a foam which was dissolved in 80 ml. of cold concentrated hydrochloric acid. The mixture was kept in an ice bath for 1 hr. and was then poured into 640 ml. of ice–water, yielding a precipitate (a1), dry wt., 3.883 g., which was filtered from the aqueous phase (a2). Immediately after its isolation, the aqueous phase (b) was extracted with one 500-ml. and six 250-ml. portions of ethyl acetate, and the combined extracts were washed successively with water, 0.5 *N* sodium carbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, evaporation to dryness gave 6.322 g. of a foam (bα). The aqueous phase (a2) was worked up in analogous fashion, yielding 3.006 g. of a foam (a2α). Fractions bα and a2α were combined and crystallized from 60% aqueous acetone yielding 5 654 g. of prisms, m.p. 154–158°. Further recrystallization from aqueous acetone gave 5.142 g. of prisms, m.p. 158–161°. The analytical sample, derived from a repeat experiment, had the m.p. 157–159°, $[\alpha]^{23}D$ +61.5°, $M^{23}D$ +248° (20.8 mg. in 2 ml. of chloroform containing 5 drops of methanol, α +1.28°) [lit.[5] m.p. softening between 123° and 127°, followed by frothing on further heating; $[\alpha]D$ +51° (alcohol)].

Anal. Calcd. for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.98. Found: C, 68.63; H, 8.05; wt. loss, 6.0.

Pseudostrophanthidin Methylal (III) from Pseudostrophanthidin (II).—To a solution of 1.000 g. of II, m.p. 156–158°, in 20 ml. of methanol was added 0.2 ml. of concentrated hydrochloric acid. The mixture was refluxed for 30 min. and, after the addition of 30 ml. of water and cooling, the resulting precipitate was collected and dried. Crystallization from methanol gave 0.947 g. of prisms, m.p. 220–226°. Subsequent recrystallization from ethyl acetate yielded plates, m.p. 225–228°. The analytical sample was recrystallized from acetone to yield needles, m.p. 233–235°, Legal test positive, $[\alpha]^{23}D$ +34.0°, $M^{23}D$ +142° (20.1 mg., α +0.68°), λ_{max}^{alc} 217 mμ (ϵ 17,300).

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 68.84; H, 8.28.

Reconversion of Pseudostrophanthidin Methylal (III) into Pseudostrophanthidin (II).—A solution of 20 mg. of III, m.p. 233–235°, in 2 ml. of 70% acetic acid was heated on a water bath (50–80°) for 50 min. and was then concentrated *in vacuo* to leave an oily residue which was dissolved in a small amount of acetone. On adding water, small needles were obtained, 13.9 mg., m.p. 150–152°. This product showed no depression of the melting point on admixture with an authentic sample of II, m.p. 157–159°. Furthermore, the two specimens yielded identical paper chromatograms (system: formamide–chloroform; reagent: *m*-dinitrobenzene, sodium hydroxide).

3,5-Dinitrobenzoate of Pseudostrophanthidin Methylal (IV).—To a solution of 100 mg. of III, m.p. 232–234°, in 1 ml. of pyridine

(9) At this point the use of methanol must be avoided because there is a tendency to form the methylal (III), due to the presence of traces of hydrochloric acid.

was added 200 mg. of 3,5-dinitrobenzoyl chloride and the mixture was allowed to stand at room temperature for 20 hr. After decomposing the excess reagent by the addition of ice, 10 ml. of 2 *N* hydrochloric acid was added and the reaction product was extracted with three 10-ml. portions of ethyl acetate. The combined extracts were washed successively with 10-ml. portions of *N* hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 123.9 mg. of a brittle foam was obtained which crystallized upon the addition of methanol, 76.5 mg. of plates, double m.p. 145–151° and 212–214° dec. After further recrystallization from methanol and drying in a vacuum desiccator, 62.5 mg. of plates resulted, m.p. 211–214° dec., $[\alpha]^{24}D$ +50.9°, $M^{24}D$ +312° (19.8 mg., α +1.01°).

Anal. Calcd. for $C_{31}H_{36}N_2O_{11}$ (612.61): C, 60.77; H, 5.92; N, 4.57. Found: C, 60.87; H, 6.08; N, 4.43.

Pseudostrophanthidin Methylal 3-Acetate (V) from Pseudostrophanthidin Methylal (III).—To 200 mg. of III, m.p. 232–234°, in 2 ml. of pyridine was added 2 ml. of acetic anhydride and the solution was kept at room temperature overnight. After adding ice, the mixture was extracted with ethyl acetate, and the extract was washed twice with 15 ml. of 2 *N* hydrochloric acid, twice with 15 ml. of 5% sodium bicarbonate, and then with 15-ml. portions of water and saturated aqueous sodium chloride. After drying over sodium sulfate and removing the solvent *in vacuo*, the crystalline residue (215.3 mg.) was recrystallized from methanol yielding 178.1 mg. of long prisms, m.p. 204–205°, Legal test positive, $[\alpha]^{23}D$ +50.0°, $M^{23}D$ +230°(20.1 mg., α +1.0.°).

Anal. Calcd. for $C_{26}H_{36}O_7$ (460.55): C, 67.80; H, 7.88. Found: C, 68.01; H, 7.94.

Pseudostrophanthidin 3-Monoacetate (VI) from Pseudostrophanthidin Methylal 3-Acetate (V).—A solution of 130 mg. of V, m.p. 204–205°, in 13 ml. of 70% acetic acid was heated at 90° for 45 min. and was then evaporated to dryness *in vacuo*. The residue was completely freed from acetic acid by taking it up in benzene and evaporating the solvent. The resulting brittle foam was crystallized from acetone–hexane yielding 85.8 mg. of prisms, constant m.p. 226–228°, $[\alpha]^{26}D$ +74.5°, $M^{26}D$ +333° (19.20 mg., α +1.43°).

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68. Found: C, 67.38; H, 7.77; wt. loss, 0.14.

Pseudostrophanthidin 3,19-Diacetate (VII) from Pseudostrophanthidin Monoacetate (VI).—A solution of 50 mg. of VI, m.p. 224–228°, in 1 ml. of pyridine and 1 ml. of acetic anhydride was heated at 83–85° for 1 hr. After cooling, the mixture was treated with ice and was then extracted with two 15-ml. and three 10-ml. portions of ethyl acetate. The extract was washed successively with water, 5% hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, the solvent was removed *in vacuo*, and the oily residue, 53.6 mg., was crystallized from ethyl acetate, yielding 22.5 mg. of needles, m.p. 190–191°. Repeated recrystallization from acetone-hexane gave 18.7 mg. of needles, m.p. 193–194°, $[\alpha]^{24}D$ +81.4°, $M^{24}D$ +398° (11.8 mg., α +0.96°).[10]

Anal. Calcd. for $C_{27}H_{36}O_8$ (488.56): C, 66.38; H, 7.43. Found: C, 65.94; H, 7.52; wt. loss, 0.23.

Acetylation of Pseudostrophanthidin (II). Pseudostrophanthidin 3-Monoacetate (VI) and Pseudostrophanthidin 3,19-Diacetate (VII).—A solution of 300 mg. of II, m.p. 157–159°, in 3 ml. of pyridine and 3 ml. of acetic anhydride was kept at room temperature overnight. After the addition of ice and 15 ml. of 3 *N* hydrochloric acid, the mixture was extracted with five 20-ml. portions of ethyl acetate, and the extract was washed successively with 2 *N* hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 358 mg. of an oily residue resulted which resisted attempts at crystallization. Separation was achieved by chromatography on alumina. Benzene–chloroform, 9:1, eluted 126.3 mg. of material which on crystallization from ethyl acetate gave 60.0 mg. of needles, m.p. 179–180°. Repeated recrystallization from ethyl acetate and from acetone–hexane gave needles, constant m.p. 191–192°. There was no depression of the melting point on admixture with an authentic sample of pseudostrophanthidin 3,19-diacetate (VII). Benzene–chloroform, 4:1 and 1:1, eluted a total of 66.7 mg. of material which on repeated recrystallization did not furnish a uniform product. Elution with chloroform gave 126.9 mg. of material. Crystallization from acetone–hexane yielded 78.5 mg. of crystals, m.p. 216–218°. By repeated recrystallization the melting point was raised to 224–227°. The mixture melting point with an authentic sample of pseudostrophanthidin 3-monoacetate (VI) was not depressed.

3-Dehydropseudostrophanthidin Methylal (VIII) from Pseudostrophanthidin Methylal (III).—To 100 mg. of III, m.p. 233–235°, in 2 ml. of glacial acetic acid was gradually added 0.25 ml. of a solution of 33.3 mg. of chromium trioxide (approximately 100% excess) in 4 *N* sulfuric acid while cooling in an ice bath. After keeping the mixture in the ice bath for 15 min., it was diluted with 30 ml. of water and extracted with two 25-ml. portions of ethyl acetate. The extract was washed successively with water, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, evaporation of the solvent gave 103 mg. of a brittle foam which was crystallized from methanol to yield 63.1 mg. of prisms, m.p. 231–233°. Recrystallization from acetone did not alter the melting point, Legal test positive. The mixture melting point with the starting material (III, m.p. 233–235°) was 220–224°, $[\alpha]^{24}D$ +24.0°, $M^{24}D$ +100° (20.9 mg., α +0.50°).

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.50): C, 69.20; H, 7.74. Found: C, 68.93; H, 7.72; wt. loss, 0.97.

Strophanthidonic Acid 19:8-Lactone (XI). A. From Pseudostrophanthidin (II).—To 100 mg. of II, m.p. 155–159°, in 2 ml. of glacial acetic acid cooled in an ice bath was added 0.25 ml. of a solution of 33.3 mg. of chromium trioxide in 4 *N* sulfuric acid, and the mixture was kept in the ice bath for 20 min. This was followed by the addition of 30 ml. of water which caused the precipitation of lustrous leaflets. The reaction product was extracted with six 25-ml. portions of ethyl acetate and the extract was washed to neutrality as described in the preceding experiment. After drying over sodium sulfate and evaporating the solvent, 89 mg. of crystalline material resulted which was recrystallized from acetone yielding 42.5 mg. of prisms, m.p. 255–263° dec. Further recrystallization from methanol gave 38.3 mg. of prisms, decomposing gradually between 263° and 271° [lit.[8] m.p. 285° with effervescence, after preliminary softening], Legal test positive.

B. From Strophanthidinic Acid 19:8-Lactone (X).—To 100 mg. of X, m.p. 220–224° (effervescence,)[11] in 2 ml. of glacial acetic acid cooled in an ice bath was added 0.25 ml. of a solution of 33.3 mg. of chromium trioxide in 4 *N* sulfuric acid. The mixture was kept in the cold for 20 min. and was then worked up as described under A, furnishing a total of 81 mg. of crystalline material. The product was recrystallized from acetone and from ethanol, yielding 40.8 mg. of prisms, m.p. 269–273° dec., Legal test positive. When compared by paper chromatography in the system formamide–chloroform (reagent: *m*-dinitrobenzene), the products obtained by method A and B gave single spots in the same location.

Strophanthidinic Acid 19:8-Lactone 3-Acetate (XII). A. From Strophanthidinic Acid 19:8-Lactone (X).—A solution of 100 mg. of X, m.p. 220–224° (effervescence), in 1 ml. of pyridine and 1 ml. of acetic anhydride was kept at room temperature overnight. After the addition of ice, the mixture was extracted with four 15-ml. portions of ethyl acetate and the extract was washed successively with *N* hydrochloric acid, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 102.0 mg. of a crystalline residue, m.p. 245–247° dec., resulted. Recrystallization from methanol gave 76.6 mg. of needles, constant m.p. 265–267°, $[\alpha]^{24}n$ +111.0°, $M^{24}D$ +493° (20.1 mg., α +2.23°).

Anal. Calcd. for $C_{25}H_{32}O_7$ (444.51): C, 67.55; H, 7.26. Found: C, 67.81, 67.94[12]; H, 7.24, 7.19.[12]

B. From Pseudostrophanthidin 3-Monoacetate (VI).—To 20.1 mg. of VI, m.p. 221–223°, in 1 ml. of 90% acetic acid cooled in an ice bath was added 0.05 ml. of a solution of 6.66 mg. of chromium trioxide in 4 *N* sulfuric acid. The mixture was kept in the cold for 20 min. and was then diluted with 15 ml. of water

(10) Determination by Dr. Hiroyuki Ageta.

(11) $[\alpha]^{26}D$ +89.8°, $M^{26}D$ +361° (21.7 mg., α +1.95°). For preparation, *cf.* ref. 4, p. 1239.

(12) Analysis by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

and extracted with four 10-ml. portions of ethyl acetate. The extract was washed successively with water, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 19.7 mg. of crystalline material resulted. Recrystallization from methanol gave 14.9 mg. of needles, m.p. 266–268° dec. There was no depression of the melting point when mixed with the analytical sample, m.p. 265–267° dec., obtained by acetylation of X.

Investigations on Steroids. XXXVI. Conversion of Pseudostrophanthidin into 19-Hydroxy-8,19-epoxycortexone and 8-Hydroxy-19-norcortexone[1,2]

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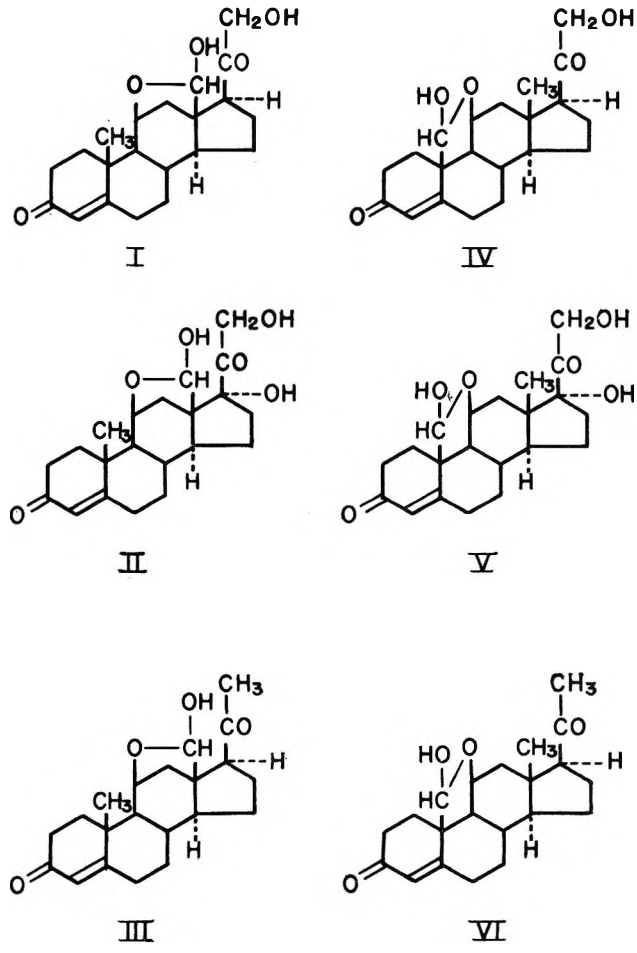
Received June 14, 1963

The conversion of pseudostrophanthidin (VII) into a structural isomer of aldosterone, *viz.*, 19-hydroxy-8,19-epoxycortexone (XV), is reported. In this procedure VII was first subjected to ozonization, yielding the amorphous 3β,5,19,21-tetrahydroxy-8,19-epoxy-5β-pregnan-20-one (VIII); this was converted into the crystalline methylal (IX) which was characterized as the 3,21-diacetate (X). Selective oxidation of IX with N-bromoacetamide gave 5,21-dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (XI) which by demethylation was converted into 5,19,21-trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (XII). Dehydration of XI yielded 19-methoxy-8,19-epoxycortexone (XIII) which was transformed into XV by demethylation. Acetylation of XIII gave 19-methoxy-8,19-epoxycortexone 21-acetate (XIV) which was demethylated to yield 19-hydroxy-8,19-epoxycortexone 21-monoacetate (XVI). Oxidation of XVI with chromic acid gave 19:8-lactocortexone acetate (XVII) which had been described previously. This conversion lends support, especially, to the structures proposed for XIII, XIV, XV, and XVI. The conversion of XI into XIII was associated with an abnormal levorotatory shift, and the products derived from XIII, *i.e.*, XIV, XV, and XVI, show this unexpected feature of optical rotation. On treating either XII or XV with mild alkali, conversion occurred into 8-hydroxy-19-norcortexone (XVIII) which was characterized as the 21-acetate (XIX). Compound XVIII appears to be the first 8-hydroxy analog of a steroid hormone ever prepared.[15c] 19-Hydroxy-8,19-epoxycortexone (XV) produced no mineralocorticoid effects and was found to be inactive as a cortexone inhibitor. 8-Hydroxy-19-norcortexone (XVIII) caused sodium retention of a low order.

Recent investigations in a number of laboratories have opened pathways for the introduction of a functional group at the angular carbon atom 18. Outstanding in this respect is the photolytic approach of Barton and co-workers which resulted in a partial synthesis of aldosterone and of a number of structurally related 3-oxo-Δ^4 steroids. In these synthetic products, we find the C-18:C-11β oxygen bridge present as a lactone, hemiacetal, or ether grouping. By variation of the side chain at carbon atom 17, steroids with the ketol, dihydroxyacetone, and methyl ketone groupings have been prepared. Among the compounds of especial interest may be listed aldosterone (I),[4,5] 17α-hydroxyaldosterone (II),[5] and 21-desoxyaldosterone (III).[6,7]

The photolytic procedure of Barton, as it is applied to an 11β nitrite, not only permits the functionalization of the angular carbon atom 18, but it also results in a functionalization of carbon atom 19. Hence a number of steroids have become available which have a C-19:C-11β, rather than a C-18:C-11β oxygen



(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7 and CY757-C8) from the National Cancer Institute of the National Institutes of Health.

(2) The essential findings of this paper were presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein, "Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press. For abstract see, "Excerpta Medica," International Congress Series, No. 51, International Congress on Hormonal Steroids, Round Table Discussions, p. 57). In addition, this paper was reported by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Universität Hamburg, Universitätskrankenhaus Eppendorf (July 23, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

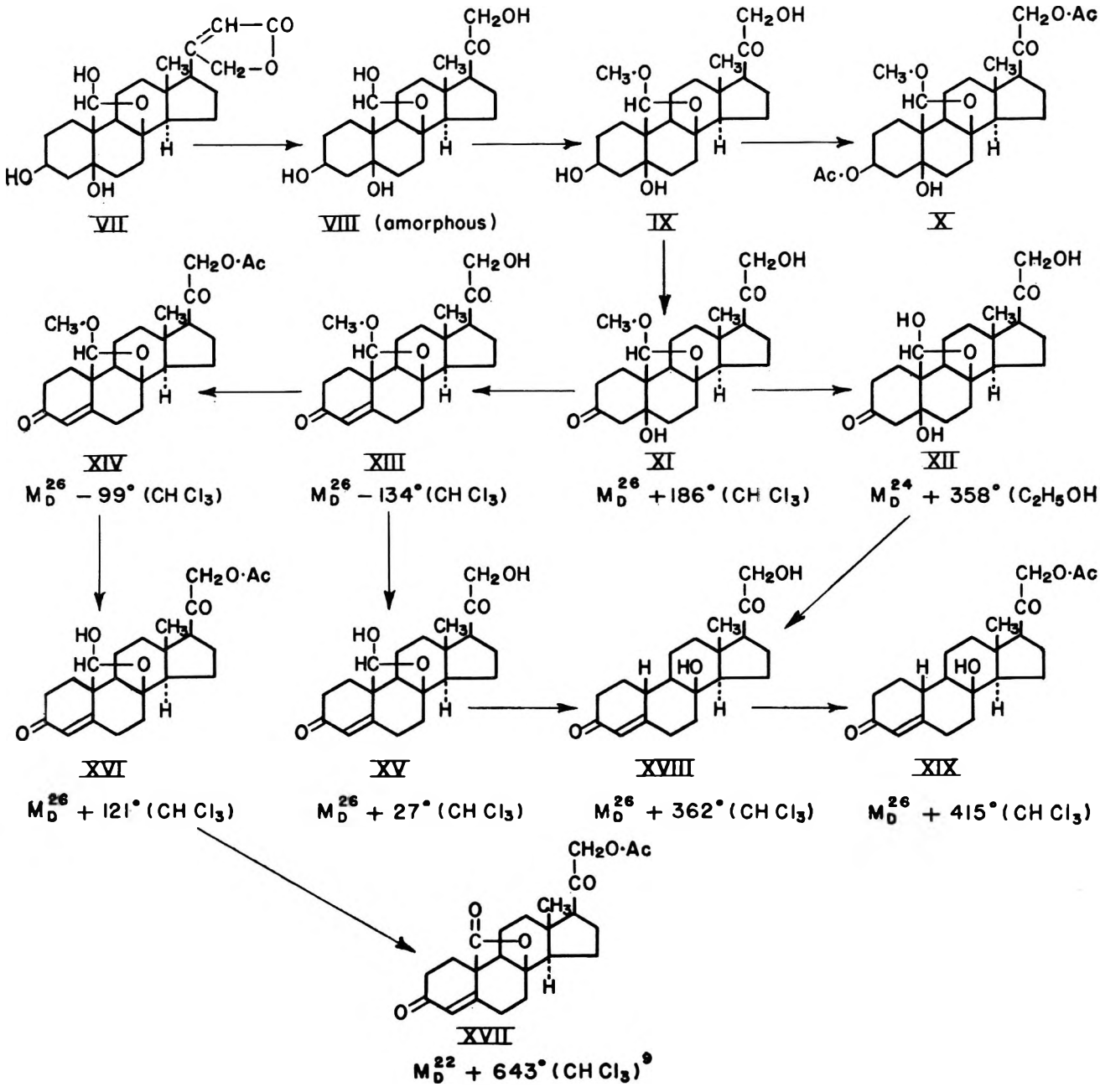
(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

(4) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **83**, 4083 (1961).

(5) D. H. R. Barton and J. M. Beaton, *ibid.*, **84**, 199 (1962).

(6) R. H. Hesse, H. Kohler, and M. M. Pechet, Abstracts, Division of Biological Chemistry, 141st National Meeting of the American Chemical Society, Washington, D. C., 1962, pp. 22C–23C.

(7) *Cf.* also, K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **45**, 347 (1962).



bridge. Among others, the compounds analogous in structure to I, II, and III, have been reported, *viz.*, 19-oxocorticosterone 19:11-hemiacetal (IV),[5] 19-oxocortisol 19:11-hemiacetal (V),[5] and 19-oxo-11β-hydroxyprogesterone 19:11-hemiacetal (VI),[6] respectively.

It is to be noted that compound IV is a structural isomer of aldosterone (I). It contains the same functional groups and differs from I only regarding the location of the hemiacetal bridge which extends from C-19 to C-11β. Among the aims of our laboratory has been the preparation of a related structural isomer of aldosterone, namely the one in which the hemiacetal bridge extends from C-19 to C-8, *viz.*, 19-hydroxy-8,19-epoxycortexone (19-oxo-8-hydroxycortexone 19:8-hemiacetal) (XV).[8] We previously have reported other compounds belonging to this series. These products contain a C-19:C-8 lactone[9] or a C-19:C-8 ether bridge.[10]

For the preparation of XV, pseudostrophanthidin (VII)[11] served as starting material. VII was subjected to ozonolysis and, after reductive cleavage of the ozonide and hydrolysis of the 21-glycolate, 3β,5,19,21-tetrahydroxy-8,19-epoxy-5β-pregnan-20-one (VIII) was obtained in an amorphous state. Subsequent treatment of VIII with methanol in the presence of a trace of hydrochloric acid gave the crystalline methylal, namely 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (IX).[12] IX was characterized as the 3,21-diacetate, *i.e.*, 5-hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (X). On treating the methylal (IX) with N-bromoacetamide, selective oxidation occurred in the 3-position yielding 5,21-dihydroxy-

(8) In agreement with the proposals of Fieser, the trivial name cortexone is preferred to 11-desoxycorticosterone (*cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp. 602 and 706).

(9) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **26**, 1230 (1961).

(10) K. Otto and M. Ehrenstein, *ibid.*, **26**, 2871 (1961).

(11) T. Kubota and M. Ehrenstein, *ibid.*, **29**, 342 (1964).

(12) From a theoretical point of view, one may consider the existence of two epimeric forms in the series of the C-19 methylals. Only one form was isolated in the present instance.

TABLE I

THE SODIUM-RETAINING EFFECT OF 8-HYDROXY-19-NORCORTEXONE (XVIII) IN THE SALINE-TREATED ADRENALECTOMIZED RAT

Experiment designation	Compound	Total dose, μg.	No. of rats	Sodium excretion, mg./2 hr. ± S.E.	Potassium excretion, mg./2 hr. ± S.E.
I	0	0	5	3.17 ± 0.57	2.42 ± 0.21
	Cortexone	3	5	1.23 ± 0.16	3.46 ± 0.27
		9	5	0.19 ± 0.07	3.40 ± 0.06
	8-Hydroxy-19-norcortexone (XVIII)	1	5	2.49 ± 0.31	3.23 ± 0.16
		5	5	2.57 ± 0.35	2.77 ± 0.28
		25	5	2.27 ± 0.39	2.65 ± 0.24
II	0	0	7	2.42 ± 0.24	2.03 ± 0.18
	8-Hydroxy-19-norcortexone (XVIII)	200	7	1.57 ± 0.13	1.83 ± 0.07

19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (XI). Demethylation of XI, by heating with 70% acetic acid, gave 5,19,21-trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (XII). Dehydration of XI furnished 19-methoxy-8,19-epoxycortexone (XIII). In order to forestall simultaneous demethylation, this reaction was carried out by refluxing in a solution of methanol in the presence of a small amount of concentrated hydrochloric acid. XIII was characterized as the acetate, namely, 19-methoxy-8,19-epoxycortexone 21-acetate (XIV). The demethylation of XIII and XIV was achieved by heating with 70% acetic acid leading to 19-hydroxy-8,19-epoxycortexone (XV) and 19-hydroxy-8,19-epoxycortexone 21-monoacetate (XVI), respectively. Oxidation of XVI with chromic acid gave a product which was identical with 19:8-lactocortexone acetate (21-acetoxy-8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone) (XVII) reported previously from this laboratory.[9] This proves in particular that the dehydration of XI to XIII was not connected with inversion of the configuration at C-17.[13]

An interesting phenomenon in the series of 19:8-hemiacetal compounds is the abnormal levorotatory shift which occurs on converting the 5β-hydroxy 3-ketone (XI) into the Δ^4-3-ketone (XIII). The infrared spectra of the Δ^4-3-ketones of this group appear to be normal (*cf.* Experimental section, compounds XIV, XV, XVI). The abnormal levoratatory shift has been previously observed in the series of the 8,19-ethers[10] where the infrared spectra of the Δ^4-3-ketones are likewise normal. Conversely, in the series of the 19:8-lactones, no levorotatory shift was observed on dehydrating the 5β-hydroxy 3-ketones to the Δ^4-3-ketones, and yet the infrared spectra of the latter show abnormalities.[9] The optical rotatory dispersion curves of some 19:8-hemiacetal compounds will be recorded in a subsequent paper.[14]

To the best of our knowledge, no 8-hydroxy analogs of steroid hormones have been described definitely. In a sense, the 8β-position is analogous to that of the 11β-position, because it is "axial" and, in the same relative location between the angular carbon atoms 18 and 19. Therefore, it was of interest to prepare 8β-hydroxy steroids and to study their physiological activities. For the synthesis of such compounds, the microbiological approach has to be ruled out because so far no enzyme has been found capable of hydroxylating in the 8-position.[15] Some of the compounds of the 19:8-hemiacetal series appear eminently suitable for the preparation of the desired products. Cleavage of the 19:8-hemiacetal bridge under appropriate conditions should lead to 8β-hydroxy analogs of steroid hormones including those of the 19-nor series. Various possibilities will be investigated in this laboratory. As a first step in this direction, the facile preparation of 8β-hydroxy-19-nor compounds has been achieved.[13]

Barton recently[5] reported the smooth conversion of 19-oxocorticosterone 19:11-hemiacetal (IV) into 19-norcorticosterone by treatment with mild base at room temperature. In similar fashion, refluxing of XV[16] with 0.1 *N* methanolic sodium hydroxide gave a satisfactory yield of 8-hydroxy-19-norcortexone (XVIII). By the same procedure, XVIII also can be obtained from XII. Acetylation of XVIII yielded 8-hydroxy-19-norcortexone 21-acetate (XIX).

Biological Activity.—The bioassays were conducted at the Endocrine Laboratories (Director, Dr. Elva G. Shipley) in Madison, Wis.[17] 19-Hydroxy-8,19-epoxycortexone (XV), in doses of 1.0 and 25.0 μg., produced no sodium retention or potassium excretion in salt (sodium chloride) loaded adrenalectomized male rats. This means that, if XV has sodium-retaining activity, it is less than 1/250th as active as aldosterone. When tested in similar fashion as a cortexone inhibitor (6 μg. of cortexone plus 1000 μg. of XV), it was found to be inactive.

8-Hydroxy-19-norcortexone (XVIII) exhibited sodium retention of a low order and the dose–response curve was more shallow than that of cortexone. The 25-μg. dose caused a 28% decrease in sodium excretion (experiment I), but increasing the dose eight times (experiment II) did not significantly increase the response (*cf.* Table I).

For comparison, it should be stated that the mineralocorticoid activity of 19-norcortexone is approximately twice that of cortexone.[18] Apparently no data have

(13) *Cf.* the pertinent discussion in the subsequent paper: T. Kubota and M. Ehrenstein, *J. Org. Chem.*, **29**, 351 (1964).

(14) T. Kubota and M. Ehrenstein, *ibid.*, **29**, 357 (1964).

(15) (a) Ch. Tamm, *Angew. Chem.*, **74**, 225 (1962), p. 227. (b) S. H. Eppstein, P. D. Meister, H. C. Murray, and D. H. Peterson [*Vitamins Hormones*, **14**, 389 (1956)] have discussed the possible 8-hydroxylation of cortexone and progesterone. Although no definite conclusions were reached, the authors discussed the possibility that a compound prepared microbiologically by Fried may well be 8β-hydroxyprogesterone. (c) NOTE ADDED IN PROOF, DECEMBER 30, 1963.—The 8β-hydroxylation of Reichstein's compound S by a microorganism recently has been reported. *Cf.* K. Tori and E. Kondo, *Tetrahedron Letters*, No. **10**, 645 (1963).

(16) Treatment at room temperature yielded a fair amount of unchanged starting material (XV).

(17) The authors are indebted to Dr. Ralph I. Dorfman, Worcester Foundation for Experimental Biology, for the interpretation of these bioassays.

(18) A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 148 (1955).

been recorded on the mineralocorticoid and glucocorticoid activities of 19-norcorticosterone (11β-hydroxy-19-norcortexone).[19] The glucocorticoid activity is assumed to be negligible because, in this respect, 19-norhydrocortisone and 19-norcortisone are considerably less active than hydrocortisone.[19]

Experimental

Melting Points.—The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The true melting points are approximately 3° lower than those reported.

Absorption Spectra.—Unless otherwise stated, the ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer. The infrared studies including the tentative assignment of bands were carried out in the Division of Pure Chemistry of the National Research Council of Canada in Ottawa, Ontario, through the courtesy of Dr. R. Norman Jones. The spectra were measured in chloroform solution on the Perkin-Elmer 421 grating instrument (PE-421) or on the Perkin-Elmer 21 instrument with a sodium chloride prism (PE-21). The values of the reported frequencies are corrected.

Analyses.—Unless otherwise stated, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus pentoxide, 80°). The per cent loss of weight on drying is recorded.

Optical Rotation.—No correction for crystal solvent has been made. Unless otherwise stated, the sample was dissolved in chloroform to make 2 ml. of solution and the rotation was determined in a 2-dm. semimicrotube.

Nomenclature.—In the headings alternative names are given, the one in brackets expressing the true character of the functional groups.

3β,5,19,21-Tetrahydroxy-8,19-epoxy-5β-pregnan-20-one [3β,-5,8,21-Tetrahydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal] (VIII) and 3β,5,21-Trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IX) from Pseudostrophanthidin (VII).—A solution of 5.178 g. (12 mmoles of $C_{23}H_{32}O_6 \cdot 1^1/_2H_2O$) of VII, m.p. 155–158°, in 420 ml. of ethyl acetate was divided equally between two reaction bottles. Each part was cooled in Dry Ice–acetone, and oxygen containing approximately 3% ozone was passed in for 15 min. The lilac colored solution was allowed to remain in the cold bath for 15 min. After this time the color had faded and the ozonization was resumed for 15 more min. The mixture was then kept in the cold for 1 hr. (retention of color) and, after removing the excess ozone by passing oxygen through, the solvent was evaporated *in vacuo* at room temperature. The combined residues were dissolved in 60 ml. of glacial acetic acid and 3 g. of zinc dust was added gradually. The mixture was kept at room temperature for 30 min. and, after subsequently heating it at 70–90° for 45 min., the potassium iodide–starch reaction was negative. The precipitate was filtered and washed with acetic acid. The filtrate was evaporated *in vacuo*, leaving an oily residue which was taken up in 50 ml. of methanol and 550 ml. of chloroform. The solution was successively washed with 100 ml. of water, 100 ml. of *N* sodium carbonate, and two 100-ml. portions of water. After drying over sodium sulfate, evaporation of the solvent yielded 4.240 g. of neutral material (foam), representing the crude 21-glycolate of VIII. From the carbonate phase there was isolated, in the usual fashion, 0.516 g. of acidic material as a foam.

To the neutral fraction, dissolved in 100 ml. of methanol, a solution of 3.0 g. of potassium carbonate in 50 ml. of water was added under an atmosphere of nitrogen. The mixture was allowed to stand at room temperature for 2 hr. and, after the addition of 300 ml. of saturated aqueous sodium chloride, it was repeatedly extracted with a total of 600 ml. of chloroform. The extract was washed with two 100-ml. portions of saturated aqueous sodium chloride and, after drying over sodium sulfate, the solvent was evaporated, yielding 2.878 g. of a foam representing crude VIII.[20] From the aqueous phase there was isolated, after acidification, 0.360 g. of acidic material as a foam.

A solution of the crude VIII (2.878 g.) in 60 ml. of methanol containing 0.6 ml. of concentrated hydrochloric acid was refluxed for 20 min. and, after diluting with 250 ml. of water, it was repeatedly extracted with a total of 550 ml. of chloroform. The extract was washed with 100 ml. of 0.2 *N* sodium carbonate and two 100-ml. portions of water, and was then dried over sodium sulfate and evaporated to dryness, leaving 2.853 g. of a foam, representing crude IX. This was chromatographed over 90 g. of Florisil (30 × 270 mm.). Chloroform and chloroform–acetone, 19:1, eluted a total of 0.381 g. of material which did not crystallize. Chloroform–acetone, range 19:1 to 4:1, eluted a total of 1.7134 g. of fractions which could be crystallized from acetone–hexane. This material was combined and recrystallized from acetone–hexane yielding 1.3177 g. of prisms, m.p. 175–178°. Repeated recrystallization gave 1.0830 g. of pure IX, m.p. 190–193°. The mixture melting point with the analytical sample[20] was not depressed. The terminal eluates of the chromatogram gave a total of 0.387 g. of material which could not be crystallized.

5-Hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [5,8-Dihydroxy-3β,21-diacetoxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (X) from 3β,5,21-Trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IX).—A solution of 500 mg. of IX, m.p. 187–189°, in 5 ml. of pyridine and 5 ml. of acetic anhydride was kept at room temperature for 16 hr. After the addition of ice, the mixture was extracted with ether and the extract was washed successively with 5% hydrochloric acid, water, 1 *N* sodium carbonate, and water. After drying over sodium sulfate and evaporating the solvent, 591.0 mg. of a foamy residue resulted. Crystallization from aqueous methanol gave 550.5 mg. of prisms, m.p. 93–97°. By further recrystallization from aqueous methanol the melting point was not altered, $[\alpha]^{26}D$ +77.4°, $M^{26}D$ +370° (18.7 mg., α +1.45°).

The infrared spectrum showed (PE-421, 60 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3566 (lightly bonded –OH), 3004 (probably solvent artifact), 2950 and 2925 (doublet only partially resolved, C–H stretch), 2875 (C–H stretch), 1740[21] (acetate, C=O stretch), ~1727[21] (shoulder, 20-keto-21-acetoxy, C=O stretch), 1453 (shoulder), 1441, 1408 (C-21 methylene, C-H scissor), 1374 (CH_3 groups), 1303, 1148, 1087, 1043, ~1016, 975, 955, 918, 843, 835 $cm.^{-1}$.

Anal. Calcd. for $C_{26}H_{38}O_8$ (478.59): C, 65.25; H, 8.00. Found: C, 65.00, 65.21[22]; H, 7.51, 8.13.[22]

5,21-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (XI) from 3β,5,21-Trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5-β-pregnane 19:8-Hemiacetal 19-Methylal] (IX).—To a solution of 700 mg. of IX, m.p. 190–193°, in 24.5 ml. of *t*-butyl alcohol and 10.5 ml. of water, was added 500 mg. of N-bromoacetamide[23] in an atmosphere of nitrogen. After keeping the mixture in the dark at room temperature for 22 hr., 60 ml. of water was added

(19) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6110 (1958).

(20) In a similar preliminary experiment the crude reaction product VIII (442.6 mg.) was chromatographed over 13 g. of Florisil. The early and late eluates gave a weak blue tetrazolium reaction and were discarded. The other fractions gave a very strong blue tetrazolium reaction, but none could be crystallized. They were combined (404.4 mg.) and converted into the 19-methylal (IX) by refluxing for 30 min. with 10 ml. of methanol containing 0.1 ml. of concentrated hydrochloric acid. After adding 40 ml. of water, the mixture was repeatedly extracted with a total of 100 ml. of chloroform. The extract was washed with 20 cc. of 0.5 *N* sodium carbonate and 20 ml. of water, and after drying over sodium sulfate, the solvent was removed *in vacuo*, yielding 402.4 mg. of crude IX as a foam. Crystallization from acetone–hexane, followed by standing in a refrigerator overnight, yielded 202.1 mg. of clusters of needles, m.p. 168–173°. Recrystallization from acetone–hexane and ethyl acetate raised the melting point to 188–191° (after drying the product over calcium chloride *in vacuo*). $[\alpha]^{26}D$ +55.4°, $M^{26}D$ +219° (19.4 mg., α +1.07°). *Anal.* Calcd. for $C_{28}H_{44}O_8$ (396.49): C, 66.98; H, 8.69. Found: C, 67.26; H, 8.61.

(21) There is a slight anomaly in the shape of the C=O band envelope. Normally in the spectra of 3,21-diacetoxy-20 ketones the peak at the lower wave number is the more intense. *Cf.* Charts No. 183, 184, 186, 191, 504, 510, and 511 in the Atlas of "Infrared Absorption Spectra of Steroids," Vol. I and II, Interscience Publishers, Inc., New York, N. Y., 1953 and 1958.

(22) Analysis by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

(23) Freshly precipitated from a chloroform solution by the addition of hexane, 97.3% purity by titration [*cf.* R. S. Schreiber, *Org. Syn.*, **31**, 17 (1951)].

and an amount of solid sodium thiosulfate sufficient to remove the free bromine. The mixture was then repeatedly extracted with a total of 150 ml. of chloroform. After washing the extract with water and drying over sodium sulfate, evaporation of the solvent yielded 735 mg. of a foam. Crystallization from acetone–hexane gave 538.3 mg. of needles, m.p. 211–213°. Further recrystallization from acetone–hexane furnished plates, m.p. 211.5–213.5°, $[\alpha]^{26}D$ +47.5°, $M^{26}D$ +186° (22.80 mg., α +1.08°).

Anal. Calcd. for $C_{22}H_{32}O_6$ (392.48): C, 67.32; H, 8.22; CH_3O, 7.91. Found: C, 66.97; H, 8.03; CH_3O, 5.10.

5,19,21-Trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal] (XII) from 5,21-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (XI).—A solution of 100 mg. of XI, m.p. 208–211°, in 10 ml. of 70% acetic acid was heated at 85–95° for 40 min. and was then evaporated to dryness *in vacuo*. By adding a little benzene to the residue and again evaporating the solvent, crystalline material resulted which by recrystallization from acetone gave 65.6 mg. of small prisms, constant m.p. 231–235° dec., $[\alpha]^{24}D$ +94.6°, $M^{24}D$ +358° (13.0 mg. in 2 ml. of 95% ethanol).[24]

Anal. Calcd. for $C_{21}H_{30}O_6$ (378.47): C, 66.65; H, 7.99. Found[25]: C, 66.94; H, 7.95 (dried over P_2O_5 for 48 hr.).

19-Methoxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal] (XIII) from 5,21-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,29-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (XI).—A solution of 200 mg. of XI, m.p. 212–214°, in 10 ml. of methanol and 0.1 ml. of concentrated hydrochloric acid was refluxed for 30 min. After the addition of 50 ml. of water the mixture was extracted with one 40-ml. and three 20-ml. portions of chloroform. The extract was washed with water, and after drying over sodium sulfate, it was evaporated to dryness leaving 191.4 mg. of a foam. Crystallization from acetone–hexane gave 119.3 mg. of prisms, m.p. 185–193°. By repeated recrystallization the melting point was raised to 190–193°, $[\alpha]^{26}D$ −35.8°, $M^{26}D$ −134° (17.50 mg., α −0.63°), λ_{max}^{alc} 241.5 mμ (ϵ 17,000).

Anal. Calcd. for $C_{22}H_{30}O_5$ (374.48): C, 70.56; H, 8.08. Found: C, 70.36; H, 8.08.

19-Methoxy-8,19-epoxycortexone 21-Acetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal 21-Acetate] (XIV) from 19-Methoxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal] (XIII).—A solution of 160 mg. of XIII, m.p. 189–192°, in 2 ml. of pyridine and 2 ml. of acetic anhydride was kept at room temperature for 16 hr. The addition of ice and water produced a white crystalline precipitate. After extracting with three 20-ml. portions of ether, the extract was washed successively with 5% hydrochloric acid, 1 *N* sodium carbonate, and water. After drying over sodium sulfate, evaporation of the solvent yielded 177.2 mg. of a crystalline residue, m.p. 160–172°. Repeated recrystallization from acetone–hexane gave 130.4 mg. of prisms, constant m.p. 183.5–185°, $[\alpha]^{26}D$ −23.8°, $M^{26}D$ −99° (14.05 mg., α −0.33°), λ_{max}^{alc} 241 mμ (ϵ 15,600).

The infrared spectrum showed (PE-421, 50 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 2978 (probably solvent artifact), 2949 (C–H stretch), 2915 (C–H stretch), 1748 (20-keto-21-acetoxy), 1725 (20-keto-21-acetoxy), 1665 (Δ^4-3-ketone), 1621 (Δ^4-3-ketone), 1448, 1410 (C-21 methylene), 1372 ($-CH_3$ groups), 1340, 1323 (19-methoxy-8,19-epoxy Δ^4-3-ketone ring system), 1267, 1161, 1111 (as 1323), 1096 (as 1323), 1078 (as 1323), 1050, 1012, 997 (as 1323), 974 (as 1323), 948 (as 1323), 904 (as 1323), 869 (as 1323), 839 (as 1323) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.52): C, 69.21; H, 7.74. Found: C, 69.64; H, 7.79.

19-Hydroxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal] (XV) from 19-Methoxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal] (XIII).—A solution of 191.5 mg. of XIII, m.p. 189–192°, in 20 ml. of 70% acetic acid was heated at 100° for 1.5 hr. in a stream of nitrogen[26] and was then evaporated to dryness *in vacuo*. A small amount of acetic acid was removed by adding benzene to the residue and evaporating once more. The crude reaction product was chromatographed over 6 g. of Florisil. Elution with chloroform (40 ml.) and with chloroform–acetone, 49:1 (60 ml.) and 19:1 (60 ml.), gave a total of 72.0 mg. of material which could not be crystallized. Chloroform–acetone, 19:1 (40 ml.), 9:1 (60 ml.), and 4:1 (100 ml.), eluted a total of 111.0 mg. of fractions which crystallized from acetone–hexane. Recrystallization of the combined fractions gave 98.2 mg. of needles, m.p. 185–188°, $[\alpha]^{26}D$ +7.6°, $M^{26}D$ +27° (18.80 mg., α +0.14°), λ_{max}^{alc} 243 mμ (ϵ 15,100).

The infrared spectrum showed (PE-421, 45 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3603 (free –OH), ~3440 (very broad, bonded –OH), 3000 (probably solvent artifact), 2950 (C–H stretch), 2917 (C–H stretch), 2872 (C–H stretch), 1709 (20-ketone, C=O stretch), 1665 (Δ^4-3-ketone, C=O stretch), 1622 (Δ^4-3-ketone, C=C stretch), 1450, 1383 (angular methyl C–H bend), 1360, 1325 (19-hydroxy-8,19-epoxy Δ^4-3-ketone ring system), 1269 (not too well-resolved), 1163 (as 1325), 1115, 1079, 1050, 1011 (as 1325), 977 (as 1325), 922, 901 (as 1325), 875 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_5$ (360.46): C, 69.98; H, 7.83. Found: C, 69.97; H, 7.72; wt. loss, 0.24.

19-Hydroxy-8,19-epoxycortexone 21-Monoacetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 21-Acetate] (XVI) from 19-Methoxy-8,19-epoxycortexone 21-Acetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal 21-Acetate] (XIV).—To 100 mg. of XIV, m.p. 183.5–185°, was added 10 ml. of 70% acetic acid and the solution was heated at 100° for 1.5 hr. whereby it turned dark red.[27] The solvent was evaporated *in vacuo* and, for the removal of small amounts of acetic acid, the evaporation was repeated after the addition of some benzene. The product was chromatographed over 3 g. of Florisil and each fraction was examined by paper chromatography (system: formamide–benzene; reagent: blue tetrazolium). The first 12 eluates, obtained with benzene and benzene–chloroform (range 9:1 to 1:1), were practically empty. Fractions 13 to 18, eluted with a total of 60 ml. of chloroform (total wt., 15.3 mg.), consisted essentially of starting material XIV. Fractions 19 to 33, obtained by elution with chloroform–acetone, ratios 49:1 (60 ml.), 19:1 (50 ml.), and 9:1 (40 ml.) (combined wt., 73.0 mg.), all gave the same single spot in the paper chromatogram, indicating the reaction product XVI. Fractions 34 to 39 eluted with chloroform–acetone (range 4:1 to 1:1) and with acetone yielded a total of 16.6 mg. of yellow oil. The reaction product XVI (73.0 mg.) was crystallized from acetone–hexane yielding 44.3 mg. of prisms, m.p. 180–182°. Further recrystallization from acetone–hexane gave plates, m.p. 181–182°, $[\alpha]^{26}D$ +30.0°, $M^{26}D$ +121° (10.00 mg., α +0.30°), λ_{max}^{alc} 243 mμ (ϵ 14,100).

The infrared spectrum showed (PE-421, 50 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3600 (free–OH), 3405 (very broad, bonded –OH), 3000 (probably solvent artifact), 2965 (C–H stretch), 2915 (C–H stretch), 2865 (C–H stretch,) 1747 (20-keto-21-acetoxy), 1727 (20-keto-21-acetoxy), 1659 (Δ^4-3-ketone), 1623 (Δ^4-3-ketone), 1450 ($-CH_2-C=C-$), 1413 (C-21 methylene), 1374 (CH_3 groups), 1341, 1326 (19-hydroxy-8,19-epoxy Δ^4-3-ketone ring system), 1163 (as 1326), 1100, 1065, 1051, 1013 (as 1326), 977 (as 1326), 924 (as 1326), 903 (as 1326) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.49): C, 68.64; H, 7.51. Found: C, 68.66; H, 7.38.

19:8-Lactocortexone Acetate [21-Acetoxy-8-hydroxy-3,20-dioxo-Δ^4-pregnene-19-oic Acid 19:8-Lactone] (XVII) from 19-Hydroxy-8,19-epoxycortexone 21-Monoacetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 21-Acetate] (XVI).—To 8.0 mg. of XVI, m.p. 181–182°, in 5 ml. of acetone was added 0.015 ml. of a solution of 4.00 mg. of chromium trioxide (approximately 200% excess) in 2 *N* sulfuric acid. The mixture was kept at room temperature (28°) for 15 min. and, after the addition of 15 ml. of water, it was repeatedly extracted with chloroform. The extract was washed with water and, after drying over sodium sulfate, the solvent was evaporated, leaving 8.3 mg. of an oil which did not crystallize. Tested in a paper chromatogram (system: formamide–benzene; 2.5 hr.; reagent: blue tetrazolium), the product showed a spot corresponding to that of 19:8-lactocortex-

(24) Determination by Dr. Hiroyuki Ageta.

(25) Analysis by Mikrolaboratorium (Director, W. Manser), Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zürich, Switzerland. We wish to thank Professor V. Prelog for this courtesy.

(26) In preliminary experiments it was shown that heating at 80° for 1 hr. and chromatography of the reaction product resulted in the isolation of a substantial amount of starting material (XIII). Under more vigorous conditions a red discoloration occurs (*cf.* preparation of XVI), unless one operates in an atmosphere of nitrogen. It has generally been found that the cleavage of the C-19 methoxy group in the Δ^4-3 ketones of this series is more difficult to achieve than in the saturated compounds.

(27) For explanation, see ref. 26.

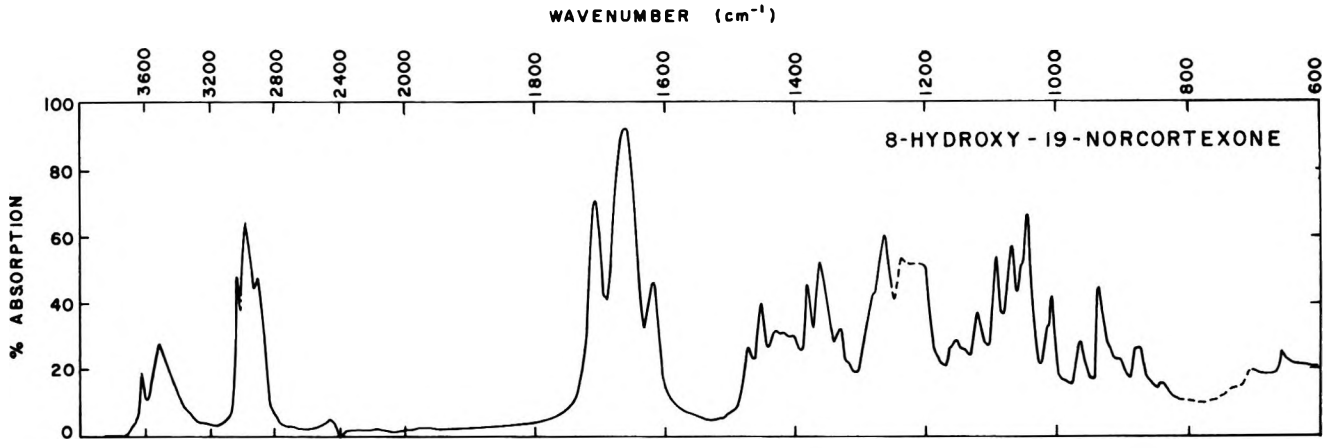


Fig. 1.—Infrared spectrum of 8-hydroxy-19-norcortexone (XVIII). The dotted lines in Fig. 1 and 2 indicate that chloroform distorts the region 3020–3000 cm.$^{-1}$ and obliterates the regions 1250–1200 cm.$^{-1}$ and 800–700 cm.$^{-1}$.

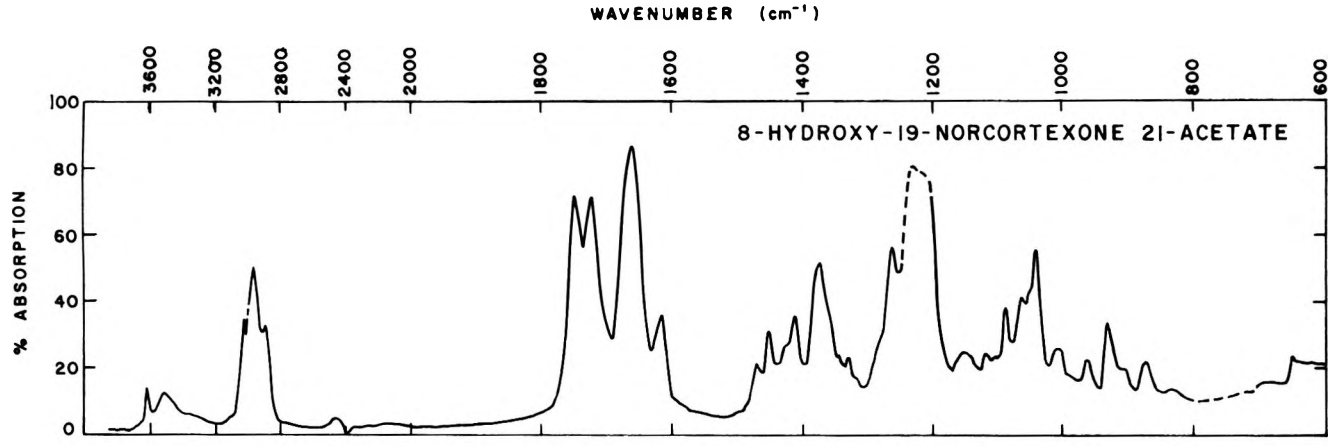


Fig. 2.—Infrared spectrum of 8-hydroxy-19-norcortexone 21-acetate (XIX).

one acetate (XVII)[9] and differing from that of the somewhat faster moving 19:8-lacto-17α-cortexone.[9] Therefore, the crude product was chromatographed over 400 mg. of Florisil. Elution with chloroform (10 ml.), and chloroform–acetone, 9:1 (10 ml.) and 4:1 (10 ml.) gave residues weighing 3.0 mg., 3.2 mg., and 1.8 mg., respectively. In a paper chromatogram, the first fraction (3.0 mg.) gave a single spot indicating identity with XVII. Crystallization from acetone–hexane gave needles, m.p. 177–180°. The second (3.2 mg.) and third (1.8 mg.) fractions, when tested by paper chromatography, gave two spots, indicating the presence of XVII and of the starting material XVI. They were combined (5.0 mg.) and subjected to further oxidation by treatment in 2 ml. of acetone for 10 min. at room temperature (26°) with 0.02 ml. of a solution of 2.67 mg. of chromium trioxide in 4 *N* sulfuric acid. The reaction mixture was worked up as described above, and the crude product (4.5 mg.) was chromatographed over 150 mg. of Florisil. Elution with 20 ml. of chloroform and 10 ml. of chloroform-acetone (9:1) gave a total of 2.9 mg. of crystalline material, melting points between 177 and 182°. This was combined with the crystalline reaction product mentioned before (m.p. 177–180°). Recrystallization yielded 3.7 mg. of needles, m.p. 177–180°. There was no depression of the melting point upon admixture with an authentic sample of 19:8-lactocortexone acetate (XVII).[9]

8-Hydroxy-19-norcortexone (XVIII). A. From 19-Hydroxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal] (XV).—A solution of 140 mg. of XV, m.p. 185–188°, in 14 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed for 30 min. under a stream of nitrogen. The reaction mixture was neutralized with dilute acetic acid and, after the addition of 70 ml. of water, extracted with one 50-ml. and three 25-ml. portions of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, leaving 135.0 mg. of an oily residue which on paper chromatography (system: formamide–(benzene–chloroform) (7:5); reagent: blue tetrazolium) gave a spot indicating faster mobility than that of the starting material. The crude product was chromatographed over 4.5 g. of Florisil. Elution with chloroform–acetone, 49:1 (30 ml.), 19:1 (75 ml.), 9:1 (45 ml.), and 4:1 (60 ml.) yielded a total of 111.1 mg. of material which was crystallized from acetone–hexane to give 62.1 mg. of prisms, m.p. 178–189°. Repeated recrystallization from acetone–hexane raised the melting point to 196–199°, $[\alpha]^{26}D$ +109.0°, $M^{26}D$ + 362° (20.35 mg., α +2.22°), λ_{max}^{alc} 243 mμ (ϵ 18,400).

The infrared spectrum showed (PE-21, 57.5 mg./ml., 0.1-mm. cell, Fig. 1) $\nu_{max}^{CHCl_3}$ 3620 (free –OH), 3500 (bonded –OH), 3035 (possibly solvent artifact), 2965 (CH stretch in alicyclic rings), 2890 (CH stretch in alicyclic rings), 1709 (C-20 ketone), 1661 (not sharp, Δ^4-3-ketone, C=O), 1617 (Δ^4-3-ketone, C=C), 1471, 1452, 1420 (C-2 methylene), 1382 (angular methyl group), 1365, 1264 (19-nor-Δ^4-3-keto-8-ol?), 1121, 1091.5 (as 1264?), 1055, 1045, 1008, 962, 936 (as 1264?), 878 (as 1264?), 844, 660 (as 1264?) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{28}O_4$ (332.44): C, 72.26; H, 8.49. Found[25]: C, 71.98; 8.36 (dried over P_2O_5 for 48 hr.).

B. From 5,19,21-Trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal] (XII).—A solution of 64.3 mg. of XII, m.p. 228–233° dec., in 7 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed for 30 min. in an atmosphere of nitrogen. The reaction mixture was neutralized with dilute acetic acid and, after the addition of 35 ml. of water, extracted with one 30-ml. and three 15-ml. portions of chloroform. After washing the extract with water and drying over sodium sulfate, evaporation of the solvent left 53.4 mg. of an oily residue. Paper chromatography of this material indicated identity with the product obtained by method A (*vide supra*). The crude material was chromatographed over 2.0 g. of Florisil. Elution with chloroform–acetone, 49:1 (14 ml.), 19:1 (21 ml.), 9:1 (21 ml.), and 4:1 (14 ml.), yielded a total of 38.9 mg. of a product which on crystallization from acetone–hexane gave 21.1 mg. of prisms, m.p. 178–186°. There was no depression of the melting point upon admixture with an authentic sample of XVIII

(*cf.* method A). Identity with XVIII was established also by comparison of the paper chromatogram.

8-Hydroxy-19-norcortexone 21-Acetate (XIX) from 8-Hydroxy-19-norcortexone (XVIII).—A solution of 24.3 mg. of XVIII, m.p. 192–197°, in 1.0 ml. of pyridine and 0.5 ml. of acetic anhydride was kept at room temperature for 17 hr. The excess acetic anhydride was decomposed with ice and, after the addition of water, the mixture was repeatedly extracted with ether. The extract was washed successively with 5% hydrochloric acid, water, 5% sodium carbonate, and water. After drying over sodium sulfate, evaporation of the ether yielded 23.8 mg. of a residue which crystallized on short standing, m.p. 164–172°. Recrystallization from acetone–hexane gave 18.6 mg. of prisms, m.p. 179–181°, $[\alpha]^{26}D$ +111.0°, $M^{26}D$ +415° (11.2 mg., α +1.24°), λ_{max}^{nic} 242 mμ (ϵ 17,000).[28]

The infrared spectrum showed (PE-21, 62 mg./ml., 0.1-mm. cell, Fig. 2) $\nu_{max}^{CHCl_3}$ 3620 (free –OH), 3500 (bonded –OH), 3030 (possibly solvent artifact), 2960 (CH stretch in alicyclic rings), 2890 (CH stretch in alicyclic rings), 1749 (21-acetoxy-20 ketone), 1724 (21-acetoxy-20 ketone), 1660 (Δ^4 3 ketone, C=O), 1616 (Δ^4-3 ketone, C=C), 1469.5, 1450, 1420 (C-2 methylene), 1413 (–CO–CH_2–OC, methylene in α position to carbonyl), 1380 (shoulder, angular methyl group), 1374 (acetate methyl group), 1263 (19-nor-Δ^4-3-keto-8-ol?), 1091 (as 1263?), 1066, 1044, 969, 938 (as 1263?), 879 (as 1263?), 660 (as 1263?) $cm.^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_5$(374.48): C, 70.56; H, 8.08. Found[25]: C, 70.38; H, 8.00 (dried over P_2O_5 for 48 hr).

(28) Determination in 95% ethanol on a Cary Model 14 recording spectrophotometer by courtesy of Mr. Richard J. Warren, Smith Kline and French Laboratories, Philadelphia, Pa.

Investigations on Steroids. XXXVII. Conversion of Pseudostrophanthidin into 19-Hydroxy-8,19-epoxy-17α-progesterone and the C-17 Epimers of 8-Hydroxy-19-norprogesterone[1,2]

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5-Hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (I) which has been synthesized from pseudostrophanthidin was converted into 19-hydroxy-8,19-epoxy-17α-progesterone (VI). In this procedure, I first reacted with methylmagnesium bromide yielding the amorphous 3β,5,20,21-tetrahydroxy-19-methoxy-8,19-epoxy-bisnor-5β-cholane (II) which possibly represented a mixture of C-20 epimers. Oxidation of II with sodium periodate gave the crystalline 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (III) which was converted by several oxidation methods into 5-hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (IV). Unexpectedly, dehydration of IV by treatment with methanol in the presence of a small amount of hydrochloric acid was associated with inversion of the configuration at C-17, thus leading to 19-methoxy-8,19-epoxy-17α-progesterone (V) which was converted into 19-hydroxy-8,19-epoxy-17α-progesterone (VI) by demethylation. The α configuration of the side chain in V and VI follows from the fact that the oxidation of VI with chromic acid resulted in the formation of 19:8-lacto-17α-progesterone (VII) which had been described previously. Demethylation of IV gave the amorphous 5,19-dihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (IX) which was converted into 8-hydroxy-19-norprogesterone (X) by treatment with mild alkali. When VI was treated with mild alkali, a product (VIII) resulted which represents 8-hydroxy-19-nor-17α-progesterone. VI produced no significant progestational effects and was found to be inactive as a progesterone inhibitor. Both X and VIII produced no significant progestational effects. X, when tested as a progesterone inhibitor, was found to be inactive.

In the preceding publication from this laboratory,[4] the conversion of pseudostrophanthidin into 19-hydroxy-8,19-epoxycortexone and 8-hydroxy-19-norcortexone was described. As a continuation of this work, the preparation of analogous compounds of progesterone type appeared to be indicated.

The reaction of a ketol ester with methylmagnesium bromide, followed by oxidation of the resulting product with sodium bismuthate has been reported as a useful method for the conversion of a ketol side chain to the corresponding methyl ketone.[5] Hence, 5-hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (I)[4] was considered a suitable starting material for the synthetic work in mind. Treatment of I with tenfold the required amount of methylmagnesium bromide yielded the amorphous 3β,5,20,21-tetrahydroxy-19-methoxy-8,19-epoxy-bisnor-5β-cholane (II) which possibly represented a mixture of C-20 epimers. For the oxidation of II to the methyl ketone we preferred the use of sodium periodate[6] to that of sodium bismuthate. Hence, treatment of the amorphous II with sodium periodate gave the crystalline 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (III) which by oxidation was converted into 5-hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (IV). This oxidation was achieved in three different ways: (1) with N-bromoacetamide, (2) with chromic acid in an acetone solution, and (3) by means of the chromic acid–pyridine complex. The first two procedures resulted in incomplete reaction, and a small amount of the remaining starting material III could not be removed by recrystallization. The last procedure appears to be the most convenient one. When IV was treated with methanol in the presence of a small amount of hydrochloric acid, dehydration oc-

(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7, CY757-C8, and CA00757-10) from the National Cancer Institute of the National Institutes of Health.

(2) The essential findings of this paper were presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein, "Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press). In addition, this paper was presented by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Universität Hamburg, Universitätskrankenhaus Eppendorf (July 23, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

(4) T. Kubota and M. Ehrenstein, *J. Org. Chem.*, **29**, 345 (1964).

(5) M. Uskokovic, R. I. Dorfman, and M. Gut, *ibid.*, **23**, 1947 (1958).

(6) *Cf.*, *e.g.*, P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).

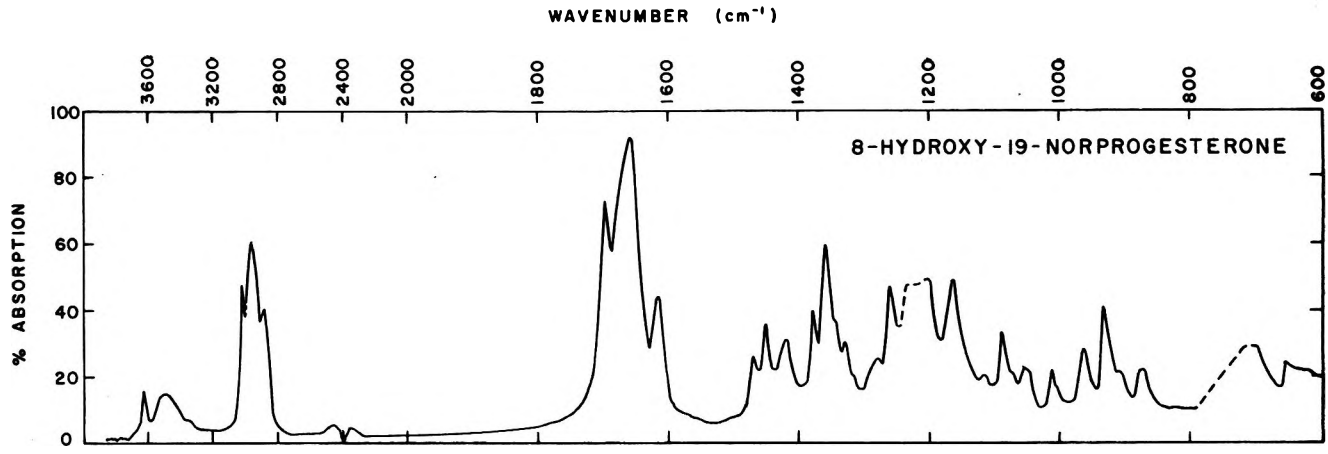


Fig. 1.—Infrared spectrum of 8-hydroxy-19-norprogesterone (X). The dotted lines in Fig. 1 and 2 indicate that chloroform distorts the region 3020–3000 cm.$^{-1}$ and obliterates the regions 1250–1200 cm.$^{-1}$ and 800–700 cm.$^{-1}$.

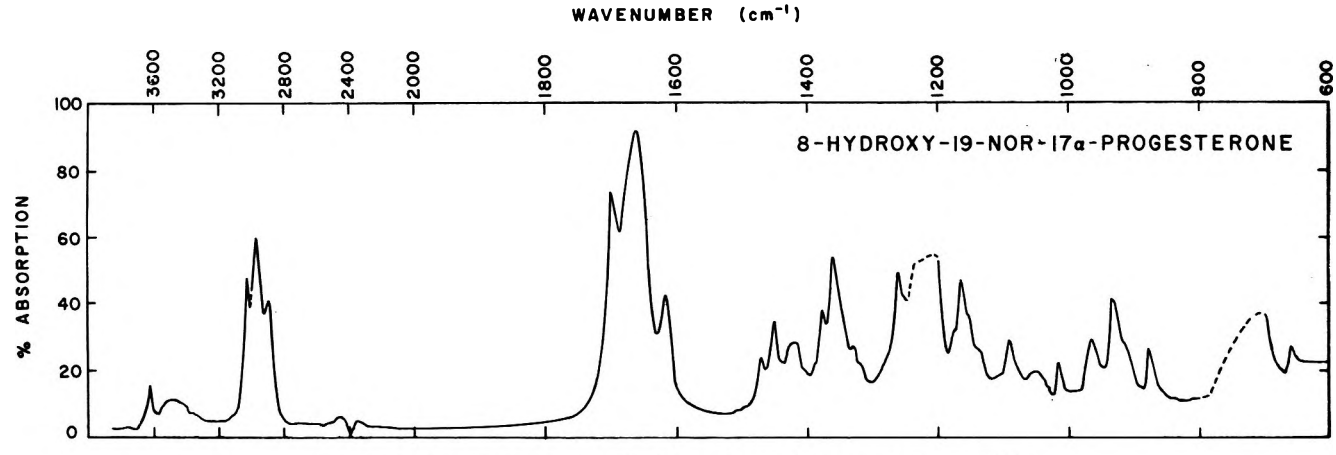


Fig. 2.—Infrared spectrum of 8-hydroxy-19-nor-17α-progesterone (VIII).

curred. The levorotatory change in the molecular rotation associated with the conversion of the 5β-hydroxy 3-ketone (IV) to the Δ^4-3-ketone (V) (ΔM_D −499°) was found to be considerably greater than that observed in the analogous case of the C-17 ketol[4] (ΔM_D −320°). It was surmised, therefore, that in the present instance (C-17 methyl ketone) the reaction was connected with inversion of the configuration at C-17[7,8] resulting in the formation of 19-methoxy-8,19-epoxy-17α-progesterone (V). This interpretation was substantiated by the subsequent reactions, namely the demethylation of V to 19-hydroxy-8,19-epoxy-17α-progesterone (VI) which on oxidation with chromic acid was converted into a 19:8-lactone that is not identical with an authentic sample of 19:8-lacto-progesterone [8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone] prepared in our laboratory previously,[9] but identical with 19:8-lacto-17α-progesterone [8-hydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone] (VII).[9] It may be noted that the infrared spectra of the Δ^4-3-ketones of this group appear to be normal (*cf.* Experimental section, compounds V and VI).

As in the cortexone series,[4] refluxing of VI with 0.1 *N* methanolic sodium hydroxide gave the corresponding 19-nor compound, 8-hydroxy-19-nor-17α-progesterone (VIII), m.p. 155–156°, $[\alpha]_D$ +38.9°, and a by-product which probably represents the 17β epimer (X).

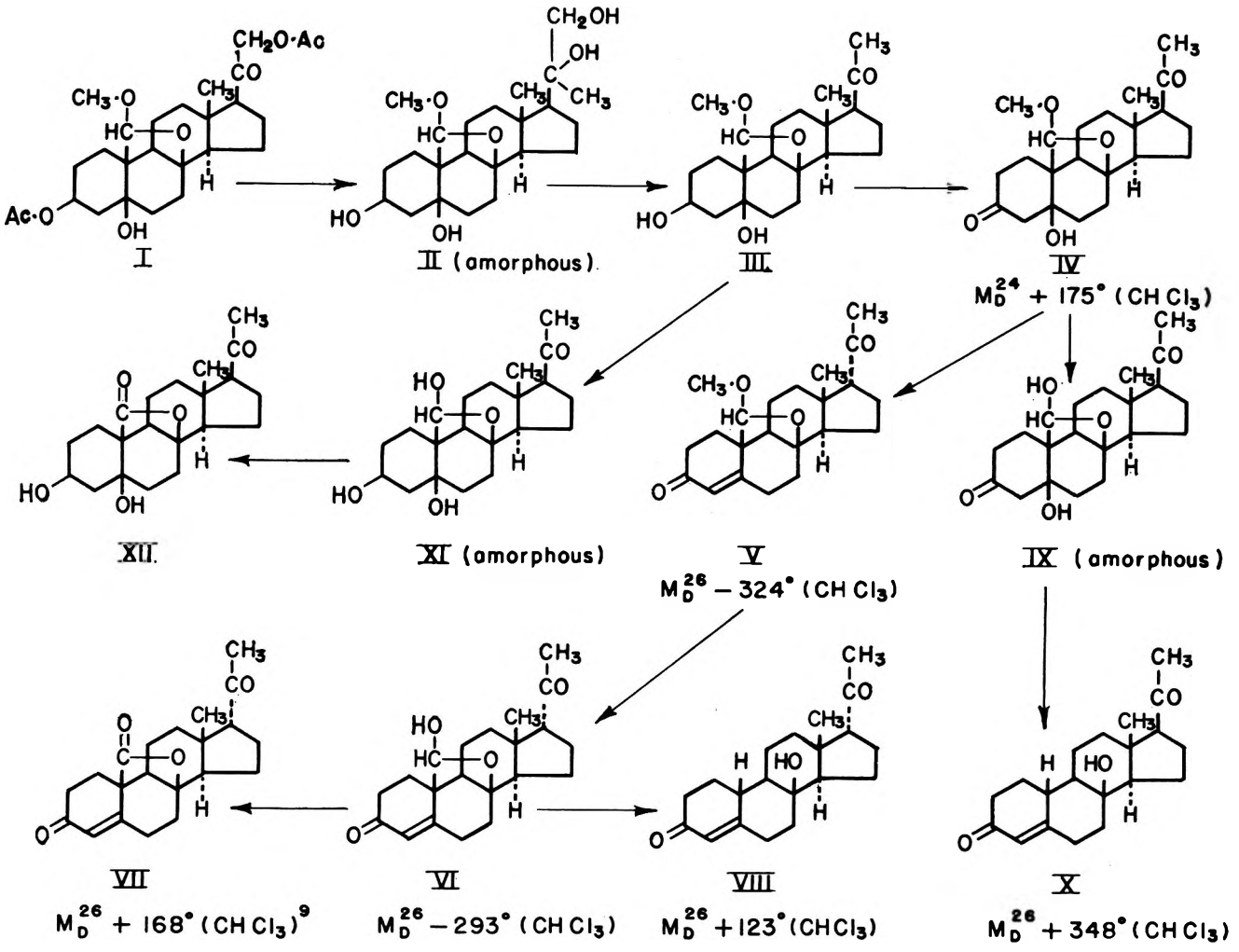
In another approach to obtaining 19-nor compounds, we followed an alternative procedure which had been applied in the cortexone series.[4] IV was first demethylated by treatment with 70% acetic acid. This yielded amorphous material considered to be 5,19-dihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (IX). Subsequent refluxing with 0.1 *N* methanolic sodium hydroxide gave as main product a compound, m.p. 178–180°, $[\alpha]_D$ +110°, that is clearly different from VIII. On the other hand, the analytical values and the ultraviolet and infrared findings satisfy the structure of an 8-hydroxy-19-norprogesterone. One must conclude, therefore, that this compound is a stereoisomer of VIII. Because of its more pronounced dextrorotation[7] it may be assigned the structure of the 17β isomer, *i.e.*, 8-hydroxy-19-norprogesterone (X). In this reaction a small amount of a by-product was isolated which probably represents the 17α isomer (VIII). It is noteworthy that the infrared absorption spectra of X (Fig. 1) and VIII (Fig. 2) are remarkably similar. The only significant qualitative difference is the extra band near 1118 cm.$^{-1}$ in X (Fig. 1).

From the foregoing findings it must be concluded that IV still contains the original 17β-CO·CH$_3$ grouping. On subjecting IV to dehydration by refluxing with methanol containing hydrochloric acid, simul-

(7) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 566.

(8) *Cf.* also W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961).

(9) G. W. Barber and M. Ehrenstein, *ibid.*, **26**, 1230 (1961).



taneously epimerization of the 17β-CO·CH$_3$ side chain occurred. This probably proceeded by way of the 17,20-enol, and resulted in the formation of the 17α-CO·CH$_3$ grouping (V). Although normally in steroids having the C/D *trans* fusion, the 17β-CO·CH$_3$ side chain is relatively stable,[7] there are known exceptions, for instance, in the 18:11β-lactones the 17α-CO·CH$_3$ side chain represents the most stable configuration.[10a] Nevertheless, it was surprising that treatment of IV with methanol containing a small amount of concentrated hydrochloric acid gave predominantly the epimeric 17α compound (V). It may be assumed that this epimerization is the result of a long-range effect caused by the deformation of the steroid ring system owing to the 19:8-bridged structure. In future work, attempts will be made to prepare the C-17 epimer of V, *i.e.*, 19-methoxy-8,19-epoxyprogesterone, and to demonstrate its epimerization to V by the action of hydrochloric acid.

As stated earlier, IX was treated with 0.1 *N* methanolic sodium hydroxide which is a well-known reagent for the epimerization of unstable substituents in the α-position to ketone groups. The reaction proceeded predominantly with retention of the original 17β side chain, yielding as main product 8-hydroxy-19-norprogesterone (X). In this reaction, the 8-hydroxy-19-oxo grouping was possibly present in the unbridged form which shows less strain than the hemiacetal structure.

It is interesting to note that in our work in the 19-hydroxy-8,19-epoxycortexone series,[4] the 21-hydroxy analog of compound IV did not undergo epimerization of the 17β-ketol side chain on refluxing with methanol containing hydrochloric acid. One might reason that, in the cortexone series, the 20-ketone grouping is stabilized by hydrogen bonding with the vicinal 21-hydroxyl group, thus preventing the formation of the 17,20-enol.

Although compound VIII has been assigned the structure of 8-hydroxy-19-nor-17α-progesterone, it should be mentioned that the available data on molecular rotations (Table I, examples 1–4) support the alternate structure of 8-hydroxy-19-nor-14β,17α-progesterone. However, epimerization at C-14 on alkaline treatment of VI appears unlikely. Inversion at carbon atoms 10 and 8 also would not be anticipated in view of analogous experiments with 19:11β-bridged compounds.[10b]

With the intention of exploring an alternative route for the preparation of IX, III was first demethylated to the amorphous 3β,5,19-trihydroxy-8,19-epoxy-5β-pregnan-20-one (XI). By subsequent selective oxidation with N-bromoacetamide, we then expected to arrive at IX which had been obtained in amorphous form by the earlier approach. The product resulting from the oxidation of XI with N-bromoacetamide was crystalline and, furthermore, on heating in a solution

(10) (a) J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **40**, 2291 (1957); *cf.* also P. Wieland, K. Heusler, H. Ueberwasser, and A. Wettstein, *ibid.*, **41**, 416 (1958), p. 420; P. Wieland, K. Heusler, and A. Wettstein, *ibid.*, **44**, 2121 (1961), p. 2122. (b) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **84**, 199 (1962).

TABLE I

COMPARISON OF MOLECULAR ROTATIONS

	Compound	Ref.	MD, deg.	ΔMD (b − a)
1.	(a) Compound X	*a*	+348	−225
	(b) Compound VII	*a*	+123	
2.	(a) Progesterone	*b*	+641	−204
	(b) 14β,17α-Progesterone	*c*	+437	
3.	(a) 19-Hydroxyprogesterone	*d*	+611	−243
	(b) 19-Hydroxy-14β,17α-progesterone	*e*	+368	
4.	(a) 19-Norprogesterone	*f*	+441	−270
	(b) 19-Nor-14α,17α-progesterone	*g*	+171	
5.*	(a) Progesterone	*h*	+459 (dioxane)	−585
	(b) 17α-Progesterone	*h*	−126 (dioxane)	

[a] This paper. [b] F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953). [c] Pl. A. Plattner, H. Heusser, and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948). [d] G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **19**, 1758 (1954). [e] M. Ehrenstein and M. Dünnenberger, *ibid.*, **21**, 783 (1956). [f] C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4440 (1953). [g] G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957). [h] W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961).

* NOTE ADDED IN PROOF, DECEMBER 30, 1963.—For detailed discussion of the differences of the molecular rotations of 17β-20-ketopregnanes and 17α-20-ketopregnanes, including additional pairs of examples, *cf.* "17α-20-Ketopregnanes. A Review," by Mordecai B. Rubin, *Steroids*, **2**, 561 (1963).

of dioxane in the presence of a trace of hydrochloric acid, did not yield an α,β-unsaturated ketone. This permits the conclusion that the oxidation product is 3β,5,8-trihydroxy-20-oxo-5β-pregnan-19-oic acid 19:8-lactone (XII), although the infrared spectrum shows a slight abnormality (*cf.* Experimental section). In other words, the hemiacetal grouping underwent selective oxidation and the resulting lactone (XII) is resistant to further oxidation. It was reported earlier that a compound of the structural type of XII may be resistant to oxidation by N-bromoacetamide.[11]

Biological Activity.—Bioassays for progestational and antiprogestational activity were carried out by Dr. Roy Hertz, Chief of the Endocrinology Branch of the National Cancer Institute. 19-Hydroxy-8,19-epoxy-17α-progesterone (VI) was tested in each of three Clauberg rabbits at a total dose per rabbit of 5.0 mg. No evidence of progestational or estrogenic activity was apparent at this dose, whereas control animals simultaneously injected with 0.5 mg. of progesterone showed the expected response. In bioassays for possible antagonism of progestational activity, a mixture of 0.1 mg. of progesterone and 1.0 mg. of VI was given daily for 5 days to each of three Clauberg rabbits. This failed to have any effect upon the expected response to the administered progesterone.

8-Hydroxy-19-norprogesterone (X) and 8-hydroxy-19-nor-17α-progesterone (VIII) were both subjected to the Clauberg test in each of three rabbits at a total dose of 1.0 mg. The results were negative, whereas in this test 0.25 mg. of progesterone gives a moderate effect. Hence X and VIII are less than one-fourth as active as progesterone, if at all. X also was tested for antiprogestational activity and was found to be inactive at a total dose of 5.0 mg. when assayed against a total dose of 0.5 mg. of progesterone in each of three Clauberg rabbits.

For comparison, it should be noted that both 19-norprogesterone[12] and 19-nor-14β,17α-progesterone[13] were found to be four to eight times as active as progesterone with regard to progestational potency.

(11) *Cf.* ref. 9, p. 1232.

Experimental

Melting Points.—The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The true melting points are approximately 3° lower than those reported.

Absorption Spectra.—Ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer. The infrared studies including the tentative assignment of bands were carried out in the Division of Pure Chemistry of the National Research Council of Canada in Ottawa, Ontario, through the courtesy of Dr. R. Norman Jones. The spectra were measured in chloroform solution on the Perkin-Elmer 421 grating instrument (PE-421) or on the Perkin-Elmer 21 instrument with a sodium chloride prism (PE-21). The values of the reported frequencies are corrected.

Analyses.—Unless stated otherwise, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus pentoxide, 80°). The per cent loss of weight on drying is recorded.

Optical Rotation.—No correction for crystal solvent has been made. Unless stated otherwise, the sample was dissolved in chloroform to make 2 ml. of solution and the rotation was determined in a 2-dm. semimicrotube.

Nomenclature.—In the headings alternative names are given, the one in brackets expressing the true character of the functional groups.

3β,5,20,21-Tetrahydroxy-19-methoxy-8,19-epoxybisnor-5β-cholane [3β,5,8,20,21-Pentahydroxy-19-oxobisnor-5β-cholane 19:8-Hemiacetal 19-Methylal] (II) from 5-Hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [5,8-Dihydroxy-3β,21-diacetoxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (I).—Through a mixture of 2.440 g. of magnesium[14] and 40 ml. of ether, methyl bromide was passed until the metal was completely dissolved. The mixture was refluxed with stirring for 15 min. to remove the excess methyl bromide. A solution of 800 mg. of I, m.p. 92–96°, in 120 ml. of tetrahydrofuran[15] was added dropwise to the Grignard reagent at 15–20° over a period of 20 min. This produced a small amount of a precipitate which went into solution on heating.[16] The heating was continued until the boiling point of the mixture had been raised to 55° (after approximately 30 min., water of condenser turned off). The reaction mixture was then refluxed at this temperature for 5 hr.[17] and, after cooling, it was poured into a mixture of 24 g. of ammonium chloride and crushed ice. The product was then extracted with one 200-ml. and two 150-ml. portions of ethyl ether. The extract was washed with saturated aqueous sodium chloride and, after drying over sodium sulfate, evaporation of the solvent yielded 727 mg. (calcd., 686 mg.) of crude II as a foam. The product gave a slightly positive reaction with blue tetrazolium. By paper chromatography, only a small amount of the deacetylated starting material, *i.e.*, 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one, could be detected as contaminant.

(12) (a) C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 4440 (1953); (b) W. W. Tullner and R. Hertz, *Endocrinology*, **52**, 359 (1953).

(13) (a) M. Ehrenstein *J. Org. Chem.*, **9**, 435 (1944); (b) W. M. Allen and M. Ehrenstein, *Science*, **100**, 251 (1944); (c) G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957); (d) M. Ehrenstein, G. W. Barber, and R. Hertz, *Endocrinology*, **60**, 681 (1957); (e) C. Djerassi, M. Ehrenstein, and G. W. Barber, *Ann.*, **612**, 93 (1958).

(14) Fisher magnesium metal, turnings for Grignard reaction.

(15) Fisher certified reagent, treated with solid potassium hydroxide, followed by distillation over lithium aluminum hydride.

(16) In preliminary experiments carried out under essentially the same conditions, benzene was used as a solvent instead of tetrahydrofuran. A copious precipitate separated from the reaction mixture during the period of heating. It probably consisted of an incompletely reacted Grignard complex which prevented the reaction from going to completion.

(17) In a repeat experiment refluxing at 58° for 2.5 hr. proved sufficient.

3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (III) **from 3β,5,20,21-Tetrahydroxy-19-methoxy-8,19-epoxy-bisnor-5β-cholane [3β,5,8,20,21-Pentahydroxy-19-oxo-bisnor-5β-cholane 19:8-Hemiacetal 19-Methylal]** (II).—To 1.469 g. of crude II (containing a trace of solvent, resulting from 1.600 g. of I, m.p. 92–96°) in 80 ml. of methanol was added a solution of 2.160 g. of sodium periodate in 60 ml. of water. The mixture was allowed to stand at room temperature for 18 hr. and, after the addition of 250 ml. of water, it was extracted with one 250-ml. and three 100-ml. portions of ethyl acetate. The extract was washed successively with water, two 100-ml. portions of 1 *N* sodium carbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, the solvent was evaporated yielding 1.088 g. of a foam. Crystallization from acetone–hexane gave 762 mg. of plates, m.p. 220–223°. By concentrating the mother liquor, an additional yield of 149 mg. of crystalline material, m.p. 213–218°, was obtained (total yield, 911 mg.; 72% from I). Recrystallization gave the analytical sample, m.p. 220–223°, $[\alpha]^{26}D$ +49.9°, $M^{26}D$ +189° (18.2 mg., α +0.91°).

The infrared spectrum showed (PE-421, 53 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3600 (free –OH), 3458 (broad, bonded –OH), 2997 (probably solvent artifact), 2942 (C–H stretch), 2922 (C–H stretch), 1700 (C-20 ketone), 1453, 1444, ~1413 (broad), 1381, 1358, 1188 (weak), 1173 (weak), 1151, 1128 (weak), 1090, 999, 978, 965, 947, 915, 899, 855, 821 $cm.^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_5$ (378.51): C, 69.81; H, 9.05. Found: C, 70.02; H, 9.07; wt. loss, 0.49.

The carbonate phase was acidified by the addition of 10% hydrochloric acid and was then extracted with ethyl acetate. The extract was washed with water and saturated aqueous sodium chloride and, after drying over sodium sulfate, the solvent was evaporated, leaving 100.5 mg. of a foam. Crystallization from acetone–hexane gave 32.2 mg. of needles, m.p. 209–212°. In a repeat experiment the melting point was 220–223°. There was no depression of the melting point upon admixture with an authentic sample of 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-etianic acid (m.p. 223–226°).[18] This product has obviously originated from 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (*cf.* the preparation of II).

5-Hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IV) **from 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19-8 Hemiacetal 19-Methylal]** (III). **A. By Oxidation with N-Bromoacetamide.**—To 100 mg. of III, m.p. 210–213°, in 4.9 ml. of *t*-butyl alcohol and 2.1 ml. of water was added 73 mg. of N-bromoacetamide.[19] The mixture was kept at room temperature for 21 hr., diluted with 20 ml. of water, and decolorized by the addition of a sufficient amount of solid sodium thiosulfate. After extracting with four 15-ml. portions of chloroform, the extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 97.9 mg. of a foam which was crystallized from acetone–hexane, yielding 66.9 mg. of prisms, m.p. 185–188°. Repeated recrystallization from acetone–hexane gave 28.6 mg. of prisms, m.p. 192–195°. The mixture melting point with the starting material was depressed (182–192°). In a paper chromatogram (system: formamide–benzene; reagent: 70% phosphoric acid) the product, unexpectedly, gave a spot less mobile than that of the starting material, $[\alpha]^{26}D$ +47.1°, $M^{26}D$ +177° (12.7 mg., α +0.60°).

The infrared spectrum showed (PE-421, 52 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3593 (free –OH), ~3455 (very broad, bonded –OH), 2997 (probably solvent artifact), 2945 and 2921 (doublet, not too well resolved, C–H stretch), 2870, 2816 (very weak), 1703 (C-3 ketone and C-20 ketone), 1453, 1418 (C-2 and C-4 methylenes), 1381 (angular methyl group), 1357 (C-21 methyl), 1315 (very weak), 1160, 1088, 1044 (very weak), 1004, 964, 920, 901 (weak), 854 (very weak) $cm.^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_5$ (376.50): C, 70.18; H, 8.57. Found: C, 70.37; H, 8.61; wt. loss, 0.73.

B. By Oxidation with Chromic Acid in a Solution of Acetone.—To 95 mg. of III, m.p. 220–223°, in 25 ml. of acetone kept at 2° was added by drops 0.07 ml. of an aqueous solution containing 18.69 mg. of chromium trioxide and 0.016 ml. of sulfuric acid. The mixture was kept at 2–6° for 25 min. and, after the addition of 75 ml. of water, was extracted with three 25-ml. portions of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, leaving 93.1 mg. of a foam which was crystallized from acetone–hexane, yielding 61.0 mg. of prisms, m.p. 191–194°. Concentration of the mother liquor gave an additional 11.8 mg. of crystals, m.p. 191–193°; total yield, 72.8 mg. The mixture melting point with the product obtained by method A was not depressed. As became evident in a subsequent reaction (dehydration to V), the isolated product still contained a substantial amount of the starting material III.

C. By Oxidation with the Chromic Acid–Pyridine Complex.—To a complex prepared from 12 ml. of pyridine and 1.2 g. of chromium trioxide was added a solution of 1.208 g. of III, m.p. 222–224°, in 18 ml. of pyridine. After keeping the mixture at room temperature for 18 hr., it was diluted with 400 ml. of water and extracted with one 300-ml. and three 100-ml. portions of chloroform–ether, 1:4. The extract was washed successively with 10% hydrochloric acid, 5% hydrochloric acid, water, 0.5 *N* sodium carbonate, and water. After drying over sodium sulfate, evaporation of the solvent gave 1.125 g. of a foam, which was crystallized from acetone–hexane, yielding 869.7 mg. of crystals m.p. 188–192°. Recrystallization from acetone–hexane gave 735.9 mg. of crystals, m.p. 195–196°, $[\alpha]^{24}D$ +46.6°, $M^{24}D$ +175° (19.3 mg., α +0.90°).[20]

Anal. Calcd. for $C_{22}H_{32}O_5$ (376.50): C, 70.18; H, 8.59. Found[21]: C, 70.31; H, 9.02.

19-Methoxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal 19-Methylal] (V) **from 5-Hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal]** (IV).—To 200.0 mg. of IV, m.p. 195–196° (obtained by oxidation method C), in 20 ml. of methanol was added 0.2 ml. of concentrated hydrochloric acid. The mixture was refluxed for 20 min. and was then diluted with 100 ml. of water and extracted with one 60-ml. and three 30-ml. portions of chloroform. The extract was washed with 2% sodium bicarbonate and with water. After drying over sodium sulfate and evaporating the solvent, 194.8 mg. of a residue resulted which was chromatographed over 6 g. of Florisil. Elution with benzene–chloroform, ratios 4:1 (20 ml.) and 1:1 (120 ml.), and with chloroform (80 ml.) gave a total of 143.9 mg. of fractions which could be crystallized. The combined material was crystallized from acetone–hexane yielding 132.0 mg. of prisms, m.p. 134–140°. By repeated recrystallization from acetone–hexane the melting point was raised to 142–145°, $[\alpha]^{26}D$ −90.3°, $M^{26}D$ −324° (18.65 mg., α −1.68°), λ_{max}^{alc} 241.5 mμ (ε 14,200).

The infrared spectrum showed (PE-421, 51 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3005 (probably solvent artifact), 2955, 2925, 2875, 1700 (C-20 ketone), 1665 (Δ⁴-3-ketone), 1623 (Δ⁴-3-ketone), 1448, 1419, 1382 (angular methyl group), 1357 (C-21 methyl), 1325 (19-methoxy-8,19-epoxy Δ⁴-3-ketone ring system), 1272, 1171, 1160, 1112 (as 1325), 1097 (as 1325), 1081 (as 1325), 1011 (shoulder, as 1325), 995 (as 1325), ~975 (as 1325), 949 (as 1325), 905 (as 1325), 870 (as 1325), 840 (as 1325) $cm.^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_4$ (358.48): C, 73.71; H, 8.44. Found: C, 73.49; H, 8.15; residue, 0.5.

The yield of V depends on the purity of the starting material IV which sometimes contains appreciable amounts of the unoxidized compound III, especially when it is prepared by oxidation methods A or B. If this is the case, III is eluted in the chromatogram as a second, more polar compound.

19-Hydroxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal] (VI) **from 19-Methoxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal 19-Methylal]** (V).—A solution of 140 mg. of V, m.p. 142–145°, in 30 ml. of 70% acetic acid was heated at 100° for 80 min. and was then evaporated *in vacuo* yielding a reddish brown oil[22] which was chromatographed over 4.5 g. of Florisil (13 × 80 mm.). Elution with chloroform (90 ml.) and chloroform–acetone, 9:1 (45 ml.) yielded fractions which crystallized from acetone–hexane. Hence these fractions were combined (96.5 mg.) and the material was crystallized from acetone–hexane yielding 57.3 mg. of needles, m.p. 158–179°. Recrystallization

(18) T. Kubota and M. Ehrenstein, *J. Org. Chem.*, **29**, 357 (1964).

(19) Freshly precipitated from a chloroform solution by the addition of hexane; 97.3% purity by titration [*cf.* R. S. Schreiber, *Org. Syn.*, **31**, 17 (1951)].

(20) Determination by Dr. Hiroyuki Ageta.

(21) Analysis by Mikrolaboratorium (Director, W. Manser), Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zürich, Switzerland. We wish to thank Professor V. Prelog for this courtesy.

(22) *Cf.* ref. 4, footnote 26.

gave 32.9 mg. of needles of constant m.p. 196.5–199.5°, $[\alpha]^{26}D$ −85.0°, $M^{26}D$ −293° (13.60 mg., α −1.16°), λ_{max}^{alc} 243 mμ (ε 12,900).

The infrared spectrum showed (PE-421, 45 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3603 (free -OH), ~3398 (broad, bonded -OH), 3002 (probably solvent artifact), 2957 (C-H stretch), 2919 (C-H stretch), 2875 (C-H stretch), 1699 (C-20 ketone), 1665 (Δ⁴-3-ketone), 1622 (Δ⁴-3-ketone), 1470, 1448, 1416, 1381, 1358 (C-21 methyl), 1325 (19-hydroxy-8,19-epoxy Δ⁴-3-ketone ring system), ~1165 (broad, as 1325), 1101, 1062, 1025, 1011 (as 1325), 975 (as 1325), 920 (as 1325), 898 (as 1325), 872, 825 cm.⁻¹.

Anal. Calcd. for $C_{21}H_{28}O_3$(344.45): C, 73.23; H, 8.19. Found: C, 73.01; H, 8.15; residue, 0.3.

19:8-Lacto-17α-progesterone [8-Hydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic Acid 19:8-Lactone] (VII) from 19-Hydroxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal] (VI).—To 5.0 mg. of VI, m.p. 196–199°, in 7 ml. of acetone was added 0.01 ml. of a solution of 1.33 mg. of chromium trioxide (approximately 33% excess) in 4 *N* sulfuric acid. The mixture was kept at 11–13° under nitrogen for 6 min. and, after the addition of 20 ml. of water, was extracted with two 25-ml. portions of chloroform–ether (4:1). The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, yielding 5.2 mg. of an oil. Crystallization from acetone–hexane gave 4.8 mg. of needles, m.p. 187–193°. Examination by paper chromatography (system: propylene glycol–toluene; reagent: phosphoric acid) showed, in addition to a faster moving spot, a strong spot corresponding to the starting material VI. Therefore, the crystals and mother liquors were combined and subjected to further oxidation. A solution of the product in 5 ml. of acetone was treated with 0.01 ml. of a solution of 1.33 mg. of chromium trioxide in 4 *N* sulfuric acid at 15° under nitrogen for 20 min. The mixture was worked up as described above, yielding 5.2 mg. of an oil which on crystallization from acetone–hexane gave 4.6 mg. of plates, m.p. 202–205°. There was no depression of the melting point on admixture with an authentic sample of 19:8-lacto-17α-progesterone (VII,[9] m.p. 203–206°). On admixture with 19:8-lactoprogesterone[9] (m.p. 161–163°) the melting point was depressed to 142–154°. Upon admixture with the starting material VI (m.p. 196–199°), the melting point was depressed to 177–181°. The reaction product was recrystallized once more from acetone–hexane giving 4.2 mg. of plates, m.p. 203–206°. Again there was no depression of the melting point upon admixture with VII.

8-Hydroxy-19-nor-17α-progesterone (VIII) from 19-Hydroxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8 Hemiacetal] (VI).—A solution of 40.6 mg. of VI, m.p. 186–190°, in 5 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed for 30 min. under an atmosphere of nitrogen. The reaction mixture was neutralized with dilute acetic acid and, after the addition of 25 ml. of water, it was extracted with one 30-ml. and three 15-ml. portions of ether–chloroform (4:1). The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, leaving 36.4 mg. of an oil which was chromatographed over 1.5 g. of Florisil. Elution with benzene–chloroform, 1:1 (5 ml.), chloroform (15 ml.), and chloroform–acetone, ratios 49:1 (15 ml.) and 19:1 (15 ml.), gave a total of 31.9 mg. of material which was crystallized from acetone–hexane yielding 23.1 mg. of VIII as prisms, m.p. 148–151°. This was contaminated by a small amount of felt-like needles, m.p. 100–140°, probably representing, although in an impure state, 8-hydroxy-19-norprogesterone (X). Repeated recrystallization of the major product (VIII) from acetone–hexane gave an analytical sample as plates, m.p. 155–156°, $[\alpha]^{26}D$ +38.9°, $M^{26}D$ +123° (11.80 mg., α +0.46°), λ_{max}^{alc} 242.5 mμ (ε 15,700).

The infrared spectrum showed (PE-21, 55 mg./ml., 0.1-mm. cell, Fig. 2) $\nu_{max}^{CHCl_3}$ 3622 (free -OH), 3475 (very broad, bonded -OH), 3030 (possibly solvent artifact), 2970 (CH stretch in alicyclic rings), 2890 (CH stretch in alicyclic rings), 1701 (C-20 ketone), 1663 (Δ⁴-3-ketone, C=O), 1617 (Δ⁴-3-ketone, C=C), 1472, 1452, 1420 (C-2 methylene), 1381 (angular methyl group), 1361 (methyl group in CH_3–CO–), 1263 (19-nor-Δ⁴-3-keto-8-ol?), 1165 (CH_3–CO–?), 1093 (as 1263?), 1017, 967, 937 (as 1263?), 882 (as 1263?), 661 (as 1263?) cm.⁻¹.

Anal. Calcd. for $C_{20}H_{28}O_3$ (316.44): C, 75.91; H, 8.92. Found[21]: C, 76.20; H, 8.90 (dried over P_2O_5 for 48 hr.).

5,19-Dihydroxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal] (IX) and 8-Hydroxy-19-norprogesterone (X) from 5-Hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IV).—A solution of 200 mg. of IV, m.p. 195–196°, in 20 ml. of 70% acetic acid was heated at 90° for 40 min. in a stream of nitrogen. Evaporation to dryness *in vacuo*, treatment of the residue with benzene, and renewed evaporation yielded the crude product IX which resisted attempts at crystallization. A solution of this material in 20 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed in a stream of nitrogen for 30 min. The reaction mixture was neutralized with dilute acetic acid, and, after the addition of 80 ml. of water, it was extracted with one 75-ml. and three 30-ml. portions of chloroform–ether (1:4). After washing the extract with water and drying over sodium sulfate, evaporation of the solvent gave 168.9 mg. of a foam which was chromatographed over 6.0 g. of Florisil. Elution with benzene–chloroform, 1:1 (40 ml.), chloroform (60 ml.), and chloroform–acetone, ratios 49:1 (60 ml.) and 19:1 (40 ml.), gave ten individual fractions, of which eight could be made to crystallize. No one fraction depressed the melting point of any other. Therefore, this material, including the two amorphous residues, was combined (157.3 mg.) and crystallized from acetone–hexane, giving 114.1 mg. of needles, m.p. 167–175°. Repeated recrystallization from acetone–hexane yielded 84.7 mg. of needles, constant m.p. 178–180°. The mixture melting points with VIII and VI showed pronounced depressions, $[\alpha]^{26}D$ +110°, $M^{26}D$ +348° (19.7 mg., α + 2.17°), λ_{max}^{alc} 242.5 mμ (ε 17,300).

The infrared spectrum showed (PE-21, 55 mg./ml., 0.1-mm. cell, Fig. 1) $\nu_{max}^{CHCl_3}$ 3622 (free -OH), 3490 (broad, bonded -OH), 3030 (possibly solvent artifact), 2965 (CH stretch in alicyclic rings), 2885 (CH stretch in alicyclic rings), 1699 (C-20 ketone), 1661 (Δ⁴-3-ketone, C=O), 1617 (Δ⁴-3-ketone, C=C), 1471, 1451, 1420 (C-2 methylene), 1380 (angular methyl group), 1361 (methyl group in CH_3–CO–), 1333, 1263 (19-nor-Δ⁴-3-keto-8-ol?), 1167 (CH_3–CO–?), 1118, 1089.5 (as 1263?), 1058, 1015.5, 970, 937 (as 1263?), 880 (as 1263?), 659 (as 1263?) cm.⁻¹.

Anal. Calcd. for $C_{20}H_{28}O_3$ (316.44): C, 75.91; H, 8.92. Found[21]: C, 76.00; H, 8.91 (dried over P_2O_5 for 48 hr).

From the mother liquors of the recrystallizations 9.9 mg. of prisms, m.p. 138–145°, was isolated. The mixture melting point with VIII was not depressed.

3β,5,19-Trihydroxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal] (XI) and 3β,5,8-Trihydroxy-20-oxo-5β-pregnan-19-oic Acid 19:8-Lactone (XII) from 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (III).—A solution of 50 mg. of III, m.p. 210–213°, in 5 ml. of 70% acetic acid was heated at 75–85° for 1 hr. and was then evaporated to dryness *in vacuo*. The residue was treated with benzene and the solvent was removed again, leaving 47.9 mg. of a foam representing crude XI. Attempts at crystallization failed.

To the crude XI (47.9 mg.) in 3.5 ml. of *t*-butyl alcohol and 1.5 ml. of water was added 36 mg. of N-bromoacetamide.[19] The mixture was kept at room temperature overnight, then diluted with 20 ml. of water, decolorized by the addition of sodium thiosulfate, and extracted with chloroform. Evaporation of the solvent gave 43.9 mg. of a foam. Crystallization and recrystallization from acetone–hexane gave 18.0 mg. of XII as prisms, m.p. 228–232° dec. In the original belief that this was a 3-oxo compound as represented by structure IX, the product was subjected to the conditions of dehydration[23] with the result that no α,β-unsaturated ketone was obtained. The recovered material (XII) was repeatedly recrystallized, yielding plates of m.p. 242–246°.

The infrared spectrum showed (PE-21, ~10 mg./ml., 1-mm. cell) $\nu_{max}^{CHCl_3}$ 3710, 3610 (shoulder, free -OH), 3510 (broad), 2970, 2890 (shoulder), 1759[24] (19:8 lactone[24]), 1704 (C-20 ketone), 1387 (angular methyl), 1359 (C-21 methyl), 1158, 1129, 1102, 1083, ~1016 (broad), 987, ~942 and ~923 (unresolved doublet) cm.⁻¹.

Anal. Calcd. for $C_{21}H_{30}O_5$(362.47): C, 69.59; H, 8.34. Found[21]: C, 69.23; H, 7.76.

(23) The product was dissolved in 5 ml. of dioxane and, after the addition of 0.05 ml. of concentrated hydrochloric acid, the solution was kept at 70–75° for 20 min.

(24) This band is exceptionally low and is significantly displaced from other 19:8-lactenes which have been examined.[9] The band is still within the low acceptable range for a γ-lactone.

Investigations on Steroids. XXXVIII. Etio Acids of the 19:8-Hemiacetal Series[1,2]

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By oxidation with periodic acid, 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (I) was converted into 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-etianic acid (II) from which the following compounds were prepared by conventional methods: 5-hydroxy-3β-acetoxy-19-methoxy-8,19-epoxy-5β-etianic acid (III), methyl 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-etianate (IV), and methyl 5-hydroxy-3β-acetoxy-19-methoxy-8,19-epoxy-5β-etianate (V). Oxidation of IV with the pyridine–chromic acid complex gave methyl 5-hydroxy-3-oxo-19-methoxy-8,19-epoxy-5β-etianate (VI) which was converted into methyl 3-oxo-19-methoxy-8,19-epoxy-Δ⁴-etienate (VII) by dehydration. The dehydration was associated with a pronounced levorotatory shift, and hence VI and VII were subjected to rotatory dispersion studies. The α,β-unsaturated ketone (VII) shows an unusual Cotton effect which can be rationalized in terms of a conformational distortion.

In an earlier publication[4] we have reported instances in which the dehydration of a 3-oxo-5β-hydroxy steroid to the 3-oxo-Δ⁴ compound was connected with a striking levorotatory shift. This abnormal behavior was observed with steroids having an ether bridge between carbon atoms 8 and 19. Thus, 8,19-epoxyprogesterone and 8,19-epoxycortexone show pronounced levorotation. In order to exclude interference by the powerful 20-keto chromophore, the rotatory dispersion was studied on the more suitable etio acids of the 8,19-epoxy series. The 3-oxo-5β-hydroxyetio acid gave a normal curve, whereas with the 3-oxo-Δ⁴-etio acid a positive multiple Cotton effect curve was obtained which was enantiomorphic in type with those of ordinary 3-oxo-Δ⁴ steroids, including the 19-hydroxy and 19:8-lactone series.[5] The view was expressed[4] that the abnormality in the 8,19-epoxy series is due to "some obscure conformational effect."

In more recent investigations we also have observed this levorotatory shift with C-17 ketols[6a] and C-17 methyl ketones[7,8] having the grouping of a 19:8-hemiacetal or that of a 19:8-hemiacetal methylal. For the study of the rotatory dispersion it also became necessary to prepare some of the etio acids of this series.

The facile conversion of pseudostrophanthidin into 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (I) has been described in a preceding publication.[6a] Oxidation of I with periodic acid gave 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-etianic acid (II). By acetylation, II was converted into 5-hydroxy-3β-acetoxy-19-methoxy-8,19-epoxy-5β-etianic acid (III). Treatment of II with diazomethane gave methyl 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-etianate (IV). Acetylation of IV yielded methyl 5-hydroxy-3β-acetoxy-19-methoxy-8,19-epoxy-5β-etianate (V). The same compound also was obtained by treating III with diazomethane. (See p. 358, col. 2.)

For the purpose of studying the rotatory dispersion, a 3-oxo-5β-hydroxy compound and the corresponding 3-oxo-Δ⁴ steroid were required. Products containing both the methyl ester and the methylal groupings appeared to be most suitable for this task. The presence of the methylal grouping was considered desirable, in particular to ensure a stable arrangement at C-19, thus excluding any possibility of tautomerization. Hence, IV was oxidized with the pyridine–chromic acid complex[10] yielding methyl 5-hydroxy-3-oxo-19-methoxy-8,19-epoxy-5β-etianate (VI) which in turn was converted into methyl 3-oxo-19-methoxy-8,19-epoxy-Δ⁴-etienate (VII) by refluxing with methanol in the presence of a small amount of concentrated hydrochloric acid. In the dehydration, the levorotatory shift from $M^{26}D$ +72° for VI to $M^{26}D$ −198° for VII (ΔMD −270°) was in agreement with that observed in the analogous reaction in the 19-hydroxy-8,19-epoxycortexone series (ΔMD −320°).[6a]

(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7 and CY757-C8) from the National Cancer Institute of the National Institutes of Health.

(2) Part of the findings of this paper was presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein, "Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics: Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press. For abstract see, "Excerpta Medica," International Congress Series, No. 51, International Congress on Hormonal Steroids, Round Table Discussions, p. 57). In addition, this paper was reported by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

(4) K. Otto and M. Ehrenstein, *J. Org. Chem.*, **26**, 2871 (1961).

(5) G. W. Barber and M. Ehrenstein, *ibid.*, **26**, 1230 (1961).

(6) (a) T. Kubota and M. Ehrenstein, *ibid.*, **29**, 345 (1964); (b) this paper.

(7) T. Kubota and M. Ehrenstein, *J. Org. Chem.*, **29**, 351 (1964).

(8) In the case of the C-17 methyl ketones of this series, the dehydration is associated with inversion of the configuration at C-17 which produces a levorotatory shift *per se*.[9] No judgment can be made at this time as to whether or not the observed levorotatory shift can be explained exclusively on the basis of this configurational change.

NOTE ADDED IN PROOF, DECEMBER 30, 1963.—The difference between the molecular rotation of 19-hydroxy-8,19-epoxycortexone 21-monoacetate (MD +121°)[6a] and that of 19:8-lactocortexone acetate (MD +643°)[5,6a] is −522. In analogous fashion, the difference between the molecular rotation of 19-hydroxy-8,19-epoxy-17α-progesterone (MD −293°)[7] and that of 19:8-lacto-17α-progesterone (MD +168°)[5,7] is −461. In both pairs of compounds, the same molecular change is involved (conversion of the hemiacetal grouping at C-19 into a lactone grouping)[6a,7] and the ΔMD values are in reasonable agreement. There is no evidence of conformational distortion in either 19:8-lactocortexone acetate[5] or 19:8-lacto-17α-progesterone.[5] Hence, if 19-hydroxy-8,19-epoxycortexone 21-monoacetate[6a] is conformationally distorted, this is probably also the case with 19-hydroxy-8,19-epoxy-17α-progesterone.[7] In other words, the ΔMD values are largely an expression of the disappearance of conformational distortion. Based on this consideration, the levorotatory shift associated with this dehydration reaction (*vide supra*) is not due merely to the inversion of the configuration at C-17, but reflects in addition the resulting conformational distortion.

(9) *Cf., e.g.*, (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corporation, New York, N. Y., 1959, p. 566; (b) W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961).

(10) In an attempt to oxidize IV with N-bromoacetamide, the major part of IV was recovered unchanged by direct crystallization. In the mother liquor some of the 3-oxo compound VI was present, as evidenced by the formation of an α,β-unsaturated ketone upon refluxing with methanol in the presence of a small amount of concentrated hydrochloric acid. Additional instances of resistance to oxidation with N-bromoacetamide are discussed in the preceding publication (ref. 7).

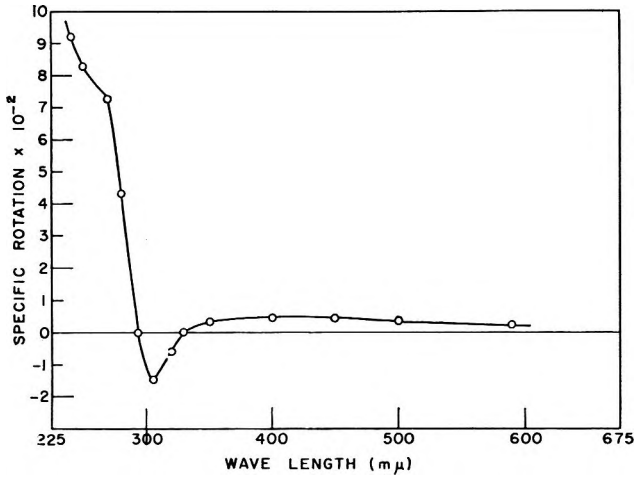


Fig. 1.—Rotatory dispersion curve of methyl 5-hydroxy-3-oxo-19-methoxy-8,19-epoxy-5β-etianate (VI, m.p. 173–175°) in methanol (c 0.117, 589–250 mμ, l = 0.5).

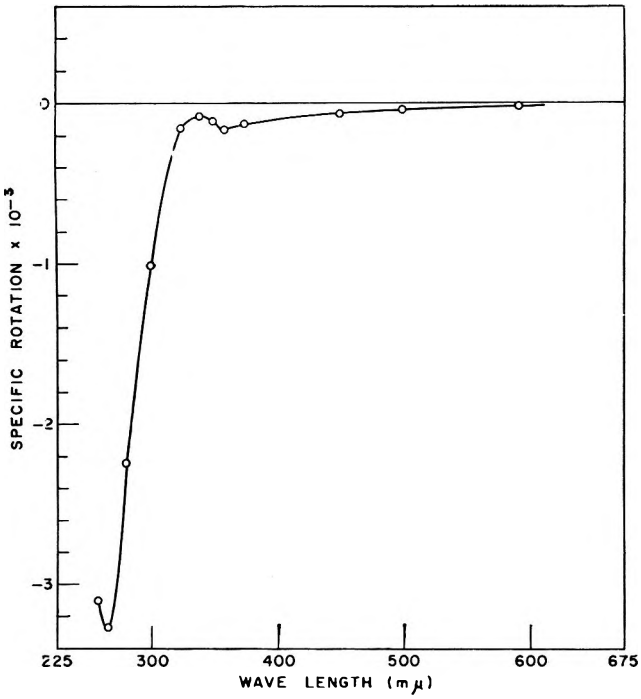
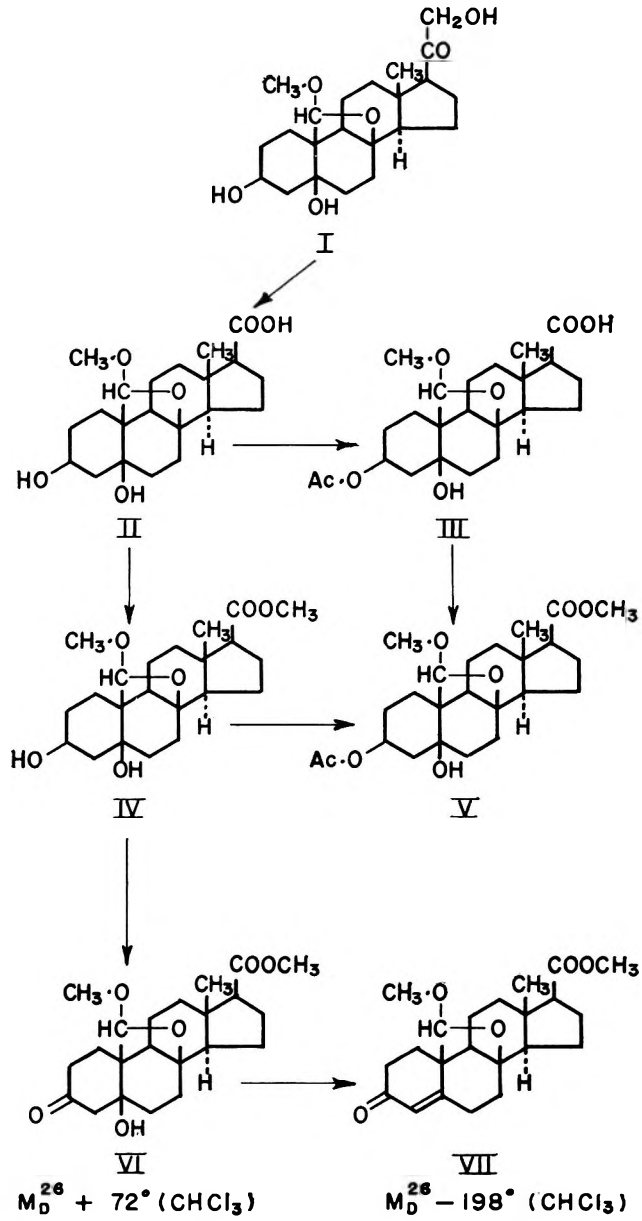


Fig. 2.—Rotatory dispersion curve of methyl 3-oxo-19-methoxy-8,19-epoxy-Δ^4-etienate (VII, m.p. 145–146.5°) in methanol (c 0.119, 589–339 mμ, l = 0.5; 339–267 mμ, l = 0.1).

The rotatory dispersion curves of VI and VII were determined through the courtesy of Professor Carl Djerassi at Stanford University. The 3-oxo-5β-hydroxy compound VI (Fig. 1) shows the expected rotatory dispersion curve of the coprostanone type.[11] As in the series of the 8,19 epoxides,[4] the α,β-unsaturated ketone VII (Fig. 2) shows an unusual Cotton effect which can be rationalized in terms of a conformational distortion as indicated in a recent publication by Djerassi, *et al.*[12] It should be noted that the rotatory dispersion curves of VI and VII were determined in methanol rather than in dioxane. Thus, the region of the K bands was included and, as can be seen from the curve of compound VII (Fig. 2), the trough of the negative Cotton effect was reached at 270 mμ.

(11) *Cf.* C. Djerassi and W. Closson, *J. Am. Chem. Soc.*, **78**, 3761 (1956).
(12) C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowitz, *ibid.*, **84**, 870 (1962).



There are certain discrepancies in the optical rotatory dispersion and infrared data observed in the 19:8-lactone series[5] as compared with those observed in the 8,19-ether[4] and 19:8-hemiacetal series.[6a,b] These discrepancies can be reconciled by modifications of the conformations of rings A and B. This will be discussed in detail in a forthcoming paper by R. N. Jones and J. B. DiGiorgio.

Investigations are under way to prepare the C-17 epimers of compounds VI and VII for the study of the rotatory dispersion. The reasons for this are implied in our observations on the rotation of 19-hydroxy-8,19-epoxy-17α-progesterone.[7,8]

Experimental

Melting Points.—The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The true melting points are approximately 3° lower than those reported.

Absorption Spectra.—The ultraviolet spectrum was determined in 95% ethanol with a Cary Model 14 recording spectrophotometer.

Analyses.—Unless otherwise stated, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus

pentoxide, 80°). The per cent loss of weight on drying is recorded.

Optical Rotation.—No correction for crystal solvent has been made. Unless otherwise stated, the sample was dissolved in chloroform to make 2 ml. of solution and the rotation was determined in a 2-dm. semimicrotube.

Nomenclature.—In the headings alternative names are given, the one in brackets expressing the true character of the functional groups.

3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-etianic Acid [3β,5,-8-Trihydroxy-19-oxo-5β-etianic Acid 19:8-Hemiacetal 19-Methylal] (II) from 3β,5,21-Trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (I).—To 200 mg. of I, m.p. 184–188°, in 5 ml. of methanol was added a solution of 220 mg. of sodium periodate in 5 ml. of water. The mixture was kept at room temperature for 16 hr. and, after the addition of 20 ml. of water, it was extracted with one 40-ml. and two 20-ml. portions of ethyl acetate. After washing the organic phase with 20 ml. of water and extracting it with two 20-ml. portions of *N* sodium carbonate, evaporation of the solvent gave 3.9 mg. of crystalline neutral material. The carbonate phase was acidified by adding 10% hydrochloric acid and was then extracted with one 40-ml. and two 20-ml. portions of ethyl acetate. The extract was washed with water and with saturated aqueous sodium chloride; after drying over sodium sulfate, the solvent was evaporated, leaving 179.8 mg. of acidic material as a foam. Crystallization and recrystallization from acetone–hexane gave 136 mg. of needles, m.p. 233.5–236°. The analytical sample, m.p. 229–232°, was obtained in a preliminary experiment, $[\alpha]^{26}D$ +10.2°, $M^{26}D$ +38° [19.1 mg. in 2 ml. of chloroform–methanol (19:1), α +0.19°].

Anal. Calcd. for $C_{21}H_{32}O_6$ (380.47): C, 66.29; H, 8.48. Found: C, 66.62; H, 8.44; wt. loss, 0.43.

5-Hydroxy-3β-acetoxy-19-methoxy-8,19-epoxy-5β-etianic Acid [5,8-Dihydroxy-3β-acetoxy-19-oxo-5β-etianic Acid 19:8-Hemiacetal 19-Methylal] (III) from 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-etianic Acid [3β,5,8-Trihydroxy-19-oxo-5β-etianic Acid 19:8-Hemiacetal 19-Methylal] (II).—To 100 mg. of II, m.p. 228–231°, in 1 ml. of pyridine was added 1 ml. of acetic anhydride. After keeping the solution at room temperature for 22 hr., ice was added to decompose the excess reagent. After the addition of 20 ml. of water, the mixture was extracted with three 20-ml. portions of ether. The extract was washed successively with water, 5% hydrochloric acid, and water. The extract was then dried over sodium sulfate and the ether was evaporated, yielding 110.9 mg. of a foam. Crystallization from aqueous acetone gave 86.0 mg. of scales, m.p. 180–186°. Repeated recrystallization from aqueous acetone yielded plates of constant m.p. 187–190°, $[\alpha]^{26}D$ +38.7°, $M^{26}D$ +163° (15.80 mg., α +0.61°).

Anal. Calcd. for $C_{23}H_{34}O_7$ (422.53): C, 65.38; H, 8.11. Found: C, 65.37; H, 8.08; wt. loss, 0.25.

Methyl 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-etianate [Methyl 3β,5,8-Trihydroxy-19-oxo-5β-etianate 19:8-Hemiacetal 19-Methylal] (IV) from 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-etianic Acid [3β,5,8-Trihydroxy-19-oxo-5β-etianic Acid 19:8-Hemiacetal 19-Methylal] (II).—To 100 mg. of II, m.p. 229–232°, was added an excess of ethereal diazomethane (prepared from N-methyl-N-nitroso-N′-nitroguanidine). Although in the beginning the acid dissolved with effervescence, new crystalline material separated which made it difficult for the reaction to proceed. Acetone was added to dissolve the crystals and the solution was then evaporated to dryness yielding a crystalline residue, m.p. 228–234°. Recrystallization from acetone gave 83.7 mg. of prisms, m.p. 233–236°. The mixture melting point with the starting material was depressed to 215–225°, $[\alpha]^{26}D$ +26.8°, $M^{26}D$ +106° (20.60 mg., α +0.55°).

Anal. Calcd. for $C_{22}H_{34}O_6$ (394.51): C, 66.98; H, 8.69. Found: C, 67.26; H, 8.58; wt. loss, 0.25.

Methyl 5-Hydroxy-3β-acetoxy-19-methoxy-8,19-epoxy-5β-etianate [Methyl 5,8-Dihydroxy-3β-acetoxy-19-oxo-5β-etianate 19:8-Hemiacetal 19-Methylal] (V). A. From Methyl 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-etianate [Methyl 3β,5,8-Trihydroxy-19-oxo-5β-etianate 19:8-Hemiacetal 19-Methylal] (IV).—To 50 mg. of IV, m.p. 233–236°, in 0.5 ml. of pyridine was added 0.5 ml. of acetic anhydride. The solution was kept at room temperature for 17 hr. and, after decomposing the excess reagent with ice, the mixture was diluted with 10 ml. of water and extracted with one 20-ml. and two 10-ml. portions of ether. The extract was washed successively with 5% hydrochloric acid, *N* sodium carbonate, and water. After drying over sodium sulfate, evaporation of the ether yielded 59.9 mg. of an oil. Crystallization was achieved from aqueous methanol after standing for several days, 44.8 mg. of plates, m.p. 167–168°. There was no change of the melting point by further recrystallization from aqueous methanol, $[\alpha]^{26}D$ +37.9°, $M^{26}D$ +165° (18.7 mg., α +0.71°).

Anal. Calcd. for $C_{24}H_{36}O_7$ (436.55): C, 66.03; H, 8.31. Found: C, 66.22; H, 8.31; wt. loss, 1.47.

B. From 5-Hydroxy-3β-acetoxy-19-methoxy-8,19-epoxy-5β-etianic Acid [5,8-Dihydroxy-3β-acetoxy-19-oxo-5β-etianic Acid 19:8-Hemiacetal 19-Methylal] (III).—To 3.3 mg. of III, m.p. 187–190°, was added an excess of ethereal diazomethane. The solution was then evaporated to dryness leaving an oily residue which crystallized from aqueous methanol upon seeding with an authentic sample of V (method A), plates, m.p. 167–168°. The mixture melting point with V was not depressed.

Methyl 5-Hydroxy-3-oxo-19-methoxy-8,19-epoxy-5β-etianate [Methyl 5,8-Dihydroxy-3,19-dioxo-5β-etianate 19:8-Hemiacetal 19-Methylal] (VI) from Methyl 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-etianate [Methyl 3β,5,8-Trihydroxy-19-oxo-5β-etianate 19:8-Hemiacetal 19-Methylal] (IV).—To a complex prepared from 1.5 ml. of pyridine and 150 mg. of chromium trioxide was added in an ice bath a solution of 150 mg. of IV, m.p. 231–236°, in 2.5 ml. of pyridine. The reaction mixture was then kept at room temperature for 16 hr. and, after adding 50 ml. of water, it was extracted with one 50-ml. and three 30-ml. portions of ethyl acetate. The extract was washed successively with 5% hydrochloric acid, 2.5% aqueous sodium bicarbonate, and saturated aqueous sodium chloride. After drying over sodium sulfate, removal of the solvent yielded 147.1 mg. of a foam. Crystallization from acetone–hexane gave 120.1 mg. of plates, m.p. 166–167.5°. Repeated recrystallization from the same combination of solvents gave the analytical sample, m.p. 173–175°, as prisms, $[\alpha]^{26}D$ +18.4°, $M^{26}D$ +72° (18.1 mg., α +0.33°).

Anal. Calcd. for $C_{22}H_{32}O_6$ (392.50): C, 67.32; H, 8.22. Found[13]: C, 67.45; H, 8.44 (dried over P_2O_5 for 48 hr.).

Methyl 3-Oxo-19-methoxy-8,19-epoxy-Δ⁴-etienate [Methyl 8-Hydroxy-3,19-dioxo-Δ⁴-etienate 19:8-Hemiacetal 19-Methylal] (VII) from Methyl 5-Hydroxy-3-oxo-19-methoxy-8,19-epoxy-5β-etianate [Methyl 5,8-Dihydroxy-3,19-dioxo-5β-etianate 19:8-Hemiacetal 19-Methylal] (VI).—To a solution of 120 mg. of VI (93.3 mg., m.p. 165–168°, 26.7 mg., m.p. 173–175°) in 15 ml. of methanol was added 0.15 ml. of concentrated hydrochloric acid. The mixture was refluxed for 30 min., then diluted with 75 ml. of water, and extracted with one 50-ml. and two 30-ml. portions of ethyl acetate. The extract was washed successively with 2% aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, evaporation of the solvent gave 108.9 mg. of an oil. Crystallization from acetone–hexane gave prisms: first crop, 59.8 mg., m.p. 146–150°; second crop, 33.3 mg., m.p. 149–152.5°. The total reaction product (crystals and mother liquor material combined) was chromatographed over Florisil. Elution with benzene–chloroform (1:1) and chloroform gave ten fractions which crystallized from acetone–hexane. The individual melting points fluctuated between 146.5–147.5° and 150–151.5°. When any crystalline fraction was mixed with any other, there was no depression of the melting point. From the chromatogram it must be concluded that the crystalline product, as isolated before chromatography (92.1 mg., *vide supra*), represented uniform material. The optical rotation was measured with a sample melting at 151–153°. The analytical sample, which also was used for the determination of the rotatory dispersion, had m.p. 145–146.5°, $[\alpha]^{26}D$ −52.9°, $M^{26}D$ −198° (13.3 mg., α −0.70°), λ_{max}^{alc} 242 mμ (ϵ 16,300).[14]

Anal. Calcd. for $C_{22}H_{30}O_5$ (374.48): C, 70.56; H, 8.08. Found: C, 70.48,[13] 70.44; H, 7.99,[13] 8.07.

(13) Analysis by Mikrolaboratorium (Director, W. Manser), Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zürich, Switzerland. We wish to thank Professor V. Prelog for this courtesy.

(14) Determination by courtesy of Mr. Richard J. Warren, Smith Kline and French Laboratories, Philadelphia, Pa.

The Preparation of *meso*- and DL-α,α'-Stilbenedithiol, *meso*- and DL-2,3-Butanedithiol, and DL-1,2,3,4-Butanetetrathiol

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Received September 19, 1963

The preparation of the *meso* and DL isomers of 2,3-butanedithiol and α,α'-stilbenedithiol are described. The synthetic route employed was the conversion of *cis*- and *trans*-2,3-epoxybutane and *cis*- and *trans*-stilbene oxide to the *trans* and *cis* cyclic trithiocarbonates, respectively, followed by reduction with lithium aluminum hydride to the dithiols. Verification of isomer assignments was obtained by infrared and n.m.r. spectroscopy. The preparation of DL-1,2,3,4-butanetetrathiol by a similar route also is described.

In earlier publications[2] we have described the preparation of a variety of mono- and polyfunctional mercaptans with the aim of studying the effect of structure on the rate of oxidation. As a continuation of this work, we thought it would be of interest to determine if the observed steric effects on the oxidation rates of dithiols[2a,b,d] would appear also in stereoisomeric symmetrical vicinal dithiols. This paper describes the synthesis of the *meso* and DL isomers of α,α'-stilbenedithiol and 2,3-butanedithiol, and DL-1,2,3,4-butanetetrathiol.

Results and Discussion

Iqbal and Owen[3a] prepared DL-2,3-butanedithiol by the following route: *cis*-2,3-epoxybutane reacted with potassium methyl xanthate to give *trans*-4,5-dimethyl-1,3-dithiolane-2-thione (IIIb), which was then reduced with lithium aluminum hydride to the DL dithiol. The isomer assignments were based on the assumption that three Walden inversions occur in going from the *cis* epoxide to the *trans* trithiocarbonate and that the reduction step takes place without racemization. Price and Kirk,[3b] and van Tamelen[4] have shown that the reaction of 1,2-disubstituted epoxides with thiocyanate occurs with two inversions, one at each asymmetric carbon atom. The proposed mechanism considers a *trans* opening of the epoxide ring and a *trans* closing of the episulfide ring. The reaction of 1,2-disubstituted epoxides with other sulfur nucleophiles, such as thiourea,[5] also has been shown to form episulfides *via* the same mechanism.[6] By analogy with these observations, it is reasonable to postulate that the reaction of 1,2-disubstituted epoxides with xanthate proceeds through two inversions, *e.g.*, *racemic* epoxide leads to *racemic* episulfide. The intermediate episulfide is then attacked by a second molecule of xanthate with inversion. Since the closing of the trithiocarbonate ring does not involve the breaking of bonds at the asymmetric centers, the trithiocarbonate of inverted configuration should be obtained; *e.g.*, *cis* epoxide is converted to *trans* trithiocarbonate (Scheme I).

This reaction sequence was used to prepare *meso*-2,3-butanedithiol from *trans*-2,3-epoxybutane, and *meso*- and DL-α,α'-stilbenedithiol from *trans*- and *cis*-stilbene oxide, respectively. Stereoisomer assignments were verified by n.m.r. and infrared spectroscopy.

***cis*- and *trans*-4,5-Dimethyl-1,3-dithiolane-2-thione.**—Trithiocarbonates IIIa and IIIb were prepared in 54% and 72% yields from epoxides Ia and Ib, respectively. The infrared spectra showed typical strong absorption bands in the 1100–1000-cm.$^{-1}$ region, which are due to C=S stretching.[3a] The *cis* isomer showed three high-intensity peaks at 1093, 1069 and 1031 cm.$^{-1}$, whereas the *trans* isomer showed two strong bands at 1088 and 1053 cm.$^{-1}$ and a medium intensity maximum at 1010 cm.$^{-1}$. These values were obtained from the pure liquids. Iqbal and Owen[3a] reported high-intensity maxima at 1093 and 1058 cm.$^{-1}$ for the *trans* isomer in carbon tetrachloride. Since there is sufficient variation in the location of these bands to permit differentiation between isomers, it can be concluded that the xanthate reaction proceeds with little or no racemization; *i.e.*, the *cis* oxide gives the *trans* trithiocarbonate, and vice versa.

Evidence for the indicated isomer assignments was obtained by n.m.r. spectroscopy. Anet[7] reported the spectra of the *cis*- and *trans*-4,5-dimethyl cyclic carbonates, which are the oxygen analogs of trithiocarbonates IIIa and IIIb. The τ-values for the four compounds are shown in Table I. The resonance of the methyl

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF *cis*- AND *trans*-4,5-DIMETHYL-1,3-DITHIOLANE-2-THIONE AND 4,5-DIMETHYL-1,3-DIOXOLAN-2-ONE

Compound	τ-Values: Methyl hydrogens *cis*	*trans*	$c - t$	Ethylenic hydrogen *cis*	*trans*	$c - t$
4,5-Dimethyl-1,3-dithiolane-2-thione[a]	8.48	8.38	0.10	5.62	5.89	−0.27
4,5-Dimethyl-1,3-dioxolan-2-one[b]	8.63	8.59	0.04	4.16	4.34	−0.18

[a] 10% solution in carbon tetrachloride measured at 60 Mc. in p.p.m. from tetramethylsilane as an internal standard. [b] Ref. 7; 39% solution in carbon tetrachloride measured at 60 Mc. in p.p.m. from tetramethylsilane as an internal standard.

hydrogens is shifted to higher field strengths when the methyl groups are *cis* to each other, as in both the *cis* trithiocarbonate and the *cis* carbonate. This can be

(1) This paper comprises a portion of a dissertation to be submitted by A. Drucker in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(2) (a) C. G. Overberger and J. J. Ferraro, *J. Org. Chem.*, **27**, 3539 (1962); (b) C. G. Overberger, J. J. Ferraro, and F. W. Orttung, *ibid.*, **26**, 3458 (1961); (c) C. G. Overberger and H. Aschkenasy, *ibid.*, **25**, 1648 (1960); *J. Am. Chem. Soc.*, **82**, 4357 (1960); (d) C. G. Overberger and P. V. Bonsignore, *ibid.*, **80**, 5427, 5431 (1958); (e) C. G. Overberger and A. Lebovits, *ibid.*, **78**, 4792 (1956).

(3) (a) S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1030 (1960); (b) C. C. Price and P. F. Kirk, *J. Am. Chem. Soc.*, **75**, 2396 (1953).

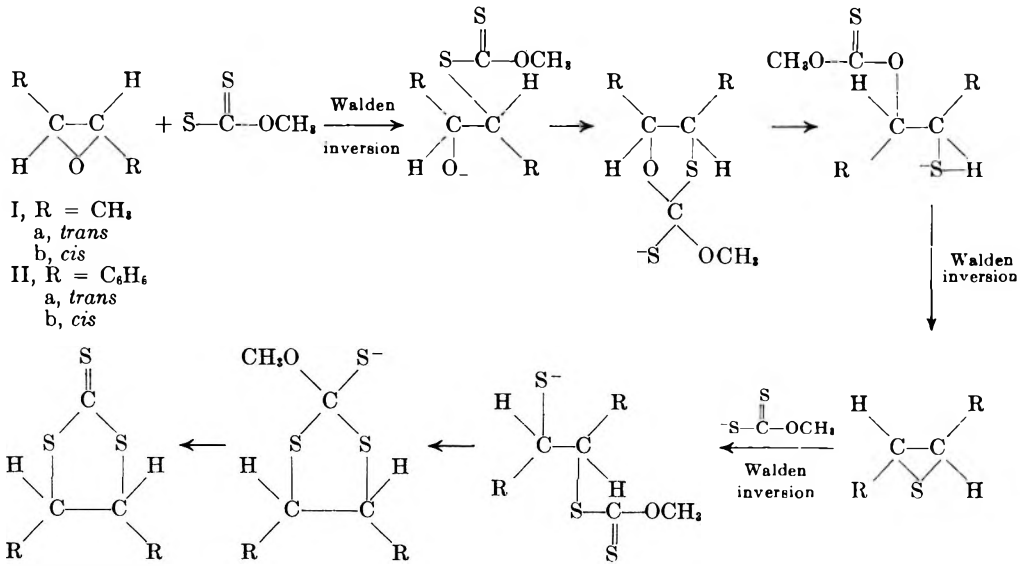
(4) E. E. van Tamelen, *ibid.*, **73**, 3444 (1951).

(5) C. C. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, 4480 (1952).

(6) R. Ketcham and V. P. Shah, *J. Org. Chem.* **28**, 229 (1963).

(7) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 747 (1962).

SCHEME I



I, R = CH_3
a, *trans*
b, *cis*
II, R = C_6H_5
a, *trans*
b, *cis*

III, R = CH_3
a, *cis*
b, *trans*
IV, R = C_6H_5
a, *cis*
b, *trans*

attributed to the increased shielding of the methyl groups by each other as compared to less shielding of the methyl groups in the *trans* isomers. The chemical shifts for the ethylenic hydrogens occur in the reverse sense. The resonance appears at higher field strengths for both *trans* isomers where the ethylenic hydrogens are shielded by adjacent methyl groups to a greater extent than in the *cis* isomers. Only two peaks appear in the spectra of the trithiocarbonates, a multiplet for the ethylenic hydrogens and a doublet for the methyl hydrogens. The shapes of the respective peaks were essentially identical. The area of the peaks were determined by cutting them from the spectra and weighing them on an analytical balance. The area ratio was found to be 3:1 CH_3:C–H. These observations are consistent with the indicated trithiocarbonate structures.

Further evidence for the isomer assignments was obtained by converting the *cis* and *trans* trithiocarbonates to the corresponding dithiocarbonates (*cis*- and *trans*-4,5-dimethyl-1,3-dithiolan-2-one) and comparing their infrared spectra with the spectrum of L-(−)-4,5-dimethyl-1,3-dithiolan-2-one recently reported by Corey and Mitra.[8] The optically active isomer, m.p. 51–51.5°, is necessarily *trans* and the infrared spectrum should be the same as the *trans* DL isomer, m.p. 41–42.5°, prepared from IIIb. The oxidations to the 2-one derivatives were performed with mercuric acetate in glacial acetic acid according to the general procedure of Challenger, *et al.*[9] The *cis* isomer could not be crystallized. The spectrum discussed later is that from liquid material which was washed and dried free of solvent after isolation from the reaction mixture. Insufficient material was available for further purification. However, its carbon and hydrogen analysis was in close agreement with the theoretical values. The optically active isomer was reported to show strong bands at 6.02, 11.4, and 11.6 μ and a medium-intensity doublet at 5.7 and 5.8 μ (presumably overtones of the 11.4 and 11.6-μ bands).[8] The *trans* DL isomer showed strong bands at 6.10 and 11.40 μ, a shoulder at 11.60 μ, and a medium-intensity doublet at 5.68 and 5.85 μ, whereas the *cis* isomer showed two strong bands at 6.07 and 11.6 μ and only one medium-intensity band at 5.78 μ. The closer correlation of the *trans* DL dithiocarbonate spectrum with the L-(−) isomer is apparent.

Indirect proof of the proposed mechanism was obtained by converting the *cis* oxide (Ib) to *cis*-2-butene episulfide by reaction with thiocyanate,[10a] followed by reaction of the episulfide with xanthate. The resulting trithiocarbonate had the identical infrared spectrum as the *trans* trithiocarbonate (IIIb) prepared directly from the *cis* oxide by reaction with xanthate.

***meso*- and DL-2,3-Butanedithiol.**—The *cis* trithiocarbonate (IIIa) and the *trans* trithiocarbonate (IIIb) were readily converted to *meso*- and DL-2,3-butanedithiol, respectively, by reduction with lithium aluminum hydride in ether solution at room temperature. Three derivatives of each dithiol were prepared and their melting points are listed in Table II. The *racemic* isomers melt higher than the *meso* isomers in all instances. This trend is the reverse of that found[10b] for a series of derivatives of *meso*- and DL-2,3-butanediol, where the *meso* isomers are higher melting. Two of these derivatives are listed in Table II.

The infrared absorption peaks of *meso*- and DL-2,3-butanedithiol, together with the spectrum of an optically active sample[11] prepared by a different route, are listed in Table III. The spectrum of the *racemic* dithiol is essentially identical with the optically active sample, whereas the *meso* isomer shows some significant

(8) E. J. Corey and R. B. Mitra, *J. Am. Chem., Soc.*, **84**, 2938 (1962).
(9) F. Challenger, E. A. Mason, E. C. Holdsworth, and R. Emmott, *J. Chem. Soc.*, 292 (1953).
(10)(a) N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **81**, 578 1959); (b) F. M. Robertson and A. C. Neish, *Can. J. Res.*, **26B**, 737 (1948).
(11) The authors are indebted to Professor E. J. Corey, Harvard University, for providing the infrared spectrum of the optically active isomer; see ref. 8 for the general method of preparation.

TABLE II

DERIVATIVES OF *meso*- AND DL-2,3-BUTANEDITHIOL AND 2,3-BUTANEDIOL

2,3-Butanedithiol derivatives	Melting point, °C. *meso*	DL
Bis-*p*-nitrobenzoate	154–156	185–186.5
Bisphenylurethane	208–210	229–231[a]
Bis-α-naphthylurethane	230–232	236–238
2,3-Butanediol derivatives		
Bis-*p*-nitrobenzoate	193–193.5	128–128.5
Bis-3,5-dinitrobenzoate	247–247.5	185–186

[a] Iqbal and Owen[3a] reported m.p. 208–209° for this derivative of DL-2,3-butanedithiol. The apparent discrepancy is due to a typographical error; the actual value they obtained was 228–229° (private correspondence).

TABLE III

INFRARED ABSORPTION PEAKS OF OPTICALLY ACTIVE, DL- AND *meso*-2,3-BUTANEDITHIOL IN THE 6.5- TO 11.5-μ REGION

Optically active[a]	DL	*meso*
6.90 (s)	6.89 (s)	6.91 (s)
7.25 (s)	7.26 (s)	7.27 (s)
7.62 (sh), 7.70 (m)	7.65 (sh), 7.71 (m)	7.59 (m), 7.73 (m)
		8.00 (sh)
8.05 (m), 8.23 (m)	8.00 (w), 8.23 (m)	8.09 (m), 8.23 (m), 8.33 (sh)
8.50 (w)		
8.72 (sh)		8.74 (w)
8.82 (w–m), 9.05 (m)	8.85 (w–m), 9.00 (w–m)	
9.24 (sh), 9.40 (m)	9.28 (sh), 9.40 (m)	9.20 (sh), 9.35 (m–s), 9.51 (sh)
9.80 (w–m), 10.00 (w–m), 10.13 (sh)	9.82 (w–m), 10.02 (m), 10.19 (w)	9.95 (w–m), 10.15 (m), 10.37 (m)
10.43 (w)	10.46 (w)	
11.47 (m)	11.49 (m)	11.50 (m)

[a] See ref. 11.

differences. Thus, the reduction of the trithiocarbonates occurred without racemization.

***cis*- and *trans*-4,5-Diphenyl-1,3-dithiolane-2-thione.**—*trans*- and *cis*-Stilbene oxide were converted to the *cis* trithiocorbonate (IVa) and the *trans* trithiocarbonate (IVb), respectively, by reaction with potassium methyl xanthate in methanol solution at room temperature for five days. The reaction proceeded without difficulty in the case of the *cis* oxide; a 67% yield was obtained with m.p. 156.5–157.5°. However, xanthate reaction with the *trans* oxide gave only an 18% yield of *cis* trithiocarbonate and chromatographic separation on alumina followed by recrystallization from large volumes of *n*-hexane were required to isolate pure product, m.p. 123.5–124.5°. Although the yield of *cis* isomer was low, no *trans* isomer was formed since all of the yellow material in the crude solids isolated from the reaction mixture was accounted for in the chromatography (all trithiocarbonates are bright yellow compounds). The low yield of the *cis* trithiocarbonate may be due to the instability of the intermediate *trans* stilbene episulfide. Culvenor and co-workers[12] were unsuccessful in their attempt to prepare stilbene sulfide by the reaction of stilbene oxide, presumably the *trans* isomer, with thiourea. The only products obtained were stilbene, sulfur, and urea. Ketcham and Shah[6] were able to prepare *trans*-stilbene sulfide, but it slowly decomposed when stored at room temperature unprotected from light. The xanthate reaction with *trans*-stilbene oxide was carried out at room temperature in daylight. If the ring opening of the intermediate *trans*-stilbene sulfide by xanthate is slow, the possibility of decomposition must be considered. Another possible explanation is based on the steric factor. It was found that the reaction of *trans*-2,3-epoxybutane with xanthate was considerably slower than with the *cis* isomer and the yield of trithiocarbonate was lower (see Experimental section). Backside attack of xanthate in the reactions in which the epoxide and episulfide rings are opened may be more difficult in the case of the *trans* isomer because of greater steric hindrance provided by the ring substituents. This effect would be more pronounced when the bulkier phenyl groups are involved.

The *cis*–*trans* assignments were verified by a comparison of the n.m.r. spectra of the trithiocarbonates with the spectra of related 1,2-diphenyl five-membered ring compounds. It was felt that the most interesting model compounds for this study would be the oxygen analogs, *i.e.*, *cis*- and *trans*-4,5-diphenyl-1,3-dioxolan-2-one. The *cis*- and *trans* cyclic carbonates were prepared by the condensation of *meso*- and DL-hydrobenzoin, respectively, with diethyl carbonate, according to the procedure of Sarel.[13] The *cis* isomer melted at 126.5–128° and the *trans* isomer melted a 110–111.5°. Sarel, *et al.*,[14] reported the preparation of a 4,5-diphenyl-

TABLE IV

NUCLEAR MAGNETIC RESONANCE SPECTRA OF *cis*- AND *trans*-1,2-DIPHENYL ISOMERS

Compound	τ-Values *cis*	*trans*	*c* − *t*	*cis*	*trans*	*c* − *t*
4,5-Diphenyl-1,3-dithiolane-2-thione[a]	2.97	2.76	0.21	4.33	4.35	−0.02
4,5-Diphenyl-1,3-dioxolan-2-one[a]	3.15	2.73	0.42	4.23	4.69	−0.46
1,2-Diphenylcyclopentane[b]	3.22	3.01	0.21	6.68	7.00	−0.32
3,4-Diphenylcyclopentanone[c]	3.10	2.83	0.27	6.17	6.52	−0.35
1,2-Diphenylcyclopropane[d]	3.04	2.87	0.17	7.55	7.87	−0.32
1,2-Bis(*p*-chlorophenyl)cyclopropane[e]	3.08	2.73	0.35	7.63	7.90	0.27
Stilbene oxide[f]	2.81	2.61	0.20	5.63	6.12	−0.49
Stilbene sulfide[f]	2.85	2.64	0.21	5.60	6.02	−0.42

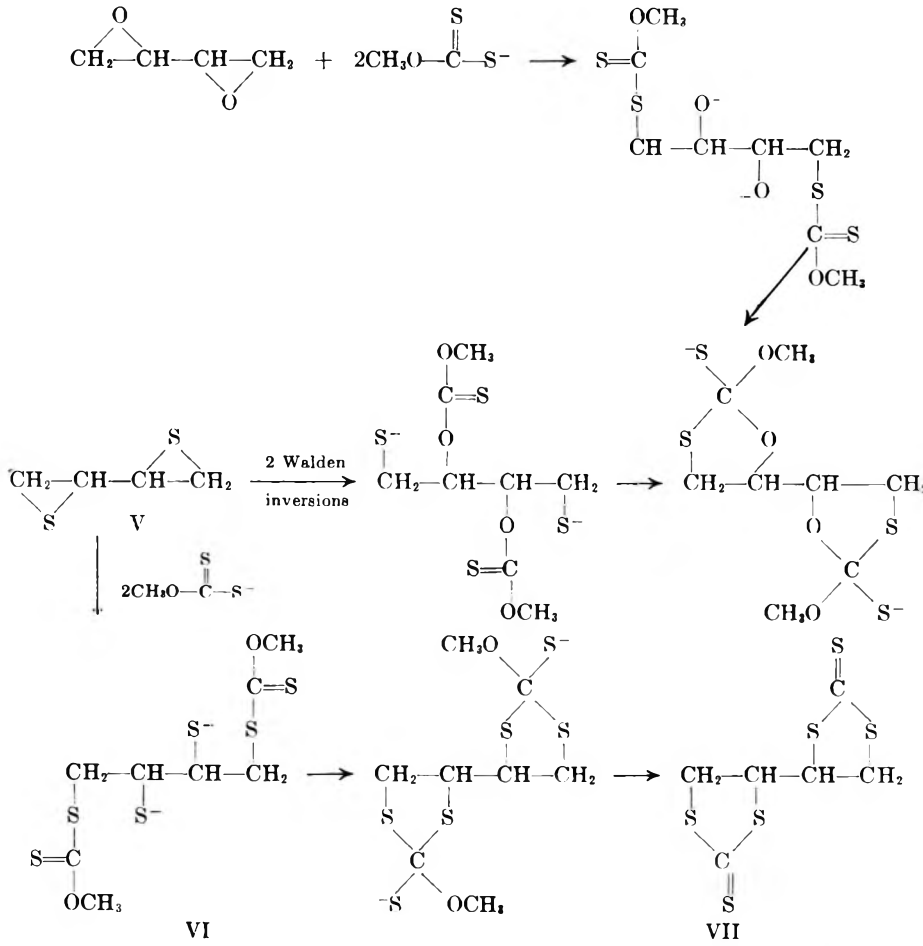
[a] *Ca.* 8% solution in deuteriochloroform measured at 60 Mc. in p.p.m. from tetramethylsilane (TMS) as an internal standard. [b] Ref. 15; in carbon tetrachloride solution measured from TMS as an internal standard at 60 Mc. [c] Ref. 15; value of 5% solution in deuteriochloroform with TMS. [d] Ref. 15; calculated from value obtained from extrapolation of infinite dilution in carbon tetrachloride at 40 Mc. in p.p.m. relative to water. [e] C. G. Overberger and J. P. Anselme, unpublished results; in carbon tetrachloride solution measured in p.p.m. from TMS. [f] Ref. 6, measured in deuteriochloroform at 60 Mc. with TMS.

(12) C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 278 (1949).

(13) S. Sarel and L. A. Pohoryles, *J. Am. Chem. Soc.*, **80**, 4596 (1958).

(14) S. Sarel, L. A. Pohoryles, and R. Ben-Shoshan, *J. Org. Chem.*, **24**, 1873 (1959).

SCHEME II



1,3-dioxolan-2-one, m.p. 127°, from hydrobenzoin. This evidently was the *cis* isomer.

The chemical shifts observed in the n.m.r. spectra of the isomeric pairs of trithiocarbonates and carbonates are shown in Table IV. A significant aspect of the spectra is the appearance of the aromatic hydrogen resonance as sharp singlets in both *trans* isomers and as unsymmetrical complex multiplets in both *cis* isomers. Similar results were obtained by Curtin, *et al.*[15] for the *cis* and *trans* isomers of 1,2-diphenylcyclopentane and 3,4-diphenylcyclopentanone.

The resonance of the phenyl groups of all the *cis* isomers mentioned before are shifted to higher field strengths relative to the *trans* compounds (Table IV). This is due to the closer proximity of the phenyl groups to each other in the *cis* compounds, where phenyl–phenyl shielding occurs to a greater extent than in the *trans* isomers.

The α-hydrogen spectra of the *cis* and *trans* trithiocarbonates and carbonates were sharp singlets. Curtin[16] reported that the α-hydrogen resonances for both *cis* and *trans* diphenylcyclopentane appeared as multiplets. These differences can be attributed to the splitting of the α-hydrogens by the ring methylene hydrogens in the cyclopentane cases, since these protons are not present in the trithiocarbonates and carbonates.

The α-hydrogen resonance of all the *trans* isomers are shifted to higher field strengths. Again, this can be attributed to increased phenyl–α-proton shielding in the *trans* isomers relative to the *cis* isomers. The low value of τ-*cis*–τ-*trans* for the trithiocarbonates is difficult to explain.

Data for four *cis*–*trans* isomeric pairs of 1,2-diphenyl three-membered ring compounds are included in Table IV. The trends in chemical shifts discussed earlier, *i.e.*, a positive value for τ-*cis*–τ-*trans* for the phenyl proton resonance and a negative value for the α-proton resonance, appear to be general in nature.

***meso*- and DL-α,α'-Stilbenedithiol.**—Reduction of trithiocarbonates IVa and IVb with lithium aluminum hydride in tetrahydrofuran at reflux gave the *meso*- and DL-α,α'-stilbenedithiols in 49% and 40% yields, respectively. When the reductions were carried out at room temperature in ether solution, the *meso* dithiol was formed in low yield and the *trans* trithiocarbonate gave a mixture of products from which any DL dithiol which may have formed could not be isolated.

The *meso* dithiol, identified as the diacetate and bisphenylurethane derivatives, melted at 220.5–222.5° and the DL dithiol, identified as the diacetate, melted at 70–71°. The melting points of the isomers did not change on standing in air at room temperature for several weeks, indicating that oxidation to disulfide products did not occur.

DL-1,2,3,4-Butanetetrathiol.—The reaction of DL-butadiene dioxide with potassium methyl xanthate afforded DL-butadiene-1,2:3,4-bis(trithiocarbonate) (VII) in 54% yield. The product was soluble in concentrated sulfuric acid, and it was recovered unchanged

(15) D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *J. Am. Chem. Soc.*, **83**, 4838 (1961); **84**, 863 (1962).

(16) D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind.* (London), 1205 (1958).

from the solution as shown by the constancy of the infrared spectrum. However, it was insoluble in a variety of refluxing organic solvents. It did not melt, but rather passed through a series of color changes with increasing temperature, going from the original yellow to orange to red and finally decomposing to a black tar at 225–235°. Elemental analysis, which was performed on the precipitate from the reaction mixture (since the product could not be purified by recrystallization or distillation), was in agreement with the calculated values.

The reaction of xanthate with monosubstituted epoxides has been shown to give the trithiocarbonate of inverted configuration.[17] Initial attack by xanthate occurs at the unsubstituted carbon atom and the only inversion which takes place is in the closing of the episulfide ring. It is reasonable to predict a similar mechanism for the reaction of DL-butadiene dioxide with xanthate. The two epoxide rings are opened *via* xanthate attack at positions 1 and 4, followed by closing of the episulfide rings with inversions at the asymmetric centers 2 and 3. These steps do not necessarily occur simultaneously and the mechanism (Scheme II) is written in this manner for convenience. The over-all effect of the two inversions is the formation of *racemic* episulfide (V). Since further attack by xanthate occurs at the nonasymmetric positions 1 and 4 and the closing of the trithiocarbonate rings does not involve the asymmetric centers, the resulting bistrithiocarbonate is the *racemic* form.

The infusibility and poor solubility of the reaction product (VI) raises the question of polymer formation. Intermolecular reactions which could lead to polymer would have to occur beyond the episulfide (V) stage. Reactions of this nature in earlier steps would give products containing oxygen atoms, which is in conflict with the element analysis for $C_6H_6S_6$. A sulfur anion of intermediate VI could conceivably attack the carbon atom of a thione group in another molecule followed by elimination of methoxide to form noncyclic trithiocarbonate (although intramolecular cyclization would be strongly favored). The infrared spectrum of the product showed only one strong absorption peak in the C=S stretching region at 1052 cm.$^{-1}$. The spectrum in this region is sensitive to the structural environment, and the presence of cyclic and linear trithiocarbonate functions would be expected to show more than one band. In any event, assuming the slight possibility of polymerization, the product obtained on reduction of the trithiocarbonate would be the *racemic* tetrathiol since the bonds of the asymmetric carbon atoms 2 and 3 would not be affected. The contention that only one isomer of the tetrathiol formed is supported by the formation of a sharp melting tetraacetate derivative in high yield.

The reduction of the *dl*-bistrithiocarbonate (VII) to *dl*-1,2,3,4-butanetetrathiol was carried out by adding it as the solid to lithium aluminum hydride in ether at room temperature. By analogy with the conversion of trithiocarbonates IIIa and IIIb to *meso*- and *dl*-2,3-butanedithiol, the reduction in this instance also proceeds without racemization, and the tetrathiol is the *racemic* isomer. The -SH infrared absorption band at 2550 cm.$^{-1}$ is usually of weak to medium intensity, as was found for the four dithiols previously discussed. The *dl* tetrathiol, however, had a very strong absorption band at 2550 cm.$^{-1}$.

(17) A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1024 (1960).

Experimental

trans-**4,5-Dimethyl-1,3-dithiolane-2-thione.**—A slightly modified procedure of Iqbal and Owen[3a] was used. A solution of potassium methyl xanthate was prepared by dissolving 35.1 g. (0.625 mole) of potassium hydroxide and 57.0 g. (0.75 mole) of carbon disulfide in 150 ml. of methanol. To this solution was added 18.0 g. (0.25 mole) of *cis*-2,3-epoxybutane,[18] n^{20}D 1.3834 (lit.[19] n^{20}D 1.3828), in small portions with shaking at room temperature. The solution was allowed to stand at room temperature for 4 days. The solid precipitate, most of which formed over the first 12 hr., was filtered and washed with several portions of water until the filtrate was colorless. After drying *in vacuo* at room temperature, 13.8 g. of a yellow solid was obtained, m.p. 41.5–42.5°. More product was isolated by evaporating the solvent from the reaction filtrate, stirring the residual solids with water for several hours, filtering the undissolved solids, washing with water as before, and drying. The recovery was 15.7 g., m.p. 41–42°. The total yield was 72%. An analytical sample was obtained by recrystallization from petroleum ether (75 ml./1 g.) as long yellow needles, m.p. 42.5–43.2° (lit.[3a] m.p. 40–41°). Infrared analysis revealed C=S absorption at 1088 (s), 1053 (s), and 1010 (m) cm.$^{-1}$ (pure liquid); lit.[3a] 1093 (s) and 1058 (s) cm.$^{-1}$ (in carbon tetrachloride).

Anal. Calcd. for $C_5H_8S_3$: C, 36.55; H, 4.91; S, 58.54. Found: C, 36.66; H, 5.17; S, 58.72.

cis-**4,5-Dimethyl-1,3-dithiolane-2-thione.**—To a solution of potassium methyl xanthate prepared by dissolving 41.9 g. (0.75 mole) of potassium hydroxide and 68.1 g. (0.9 mole) of carbon disulfide in 190 ml. of methanol was added 21.5 g. (0.3 mole) of *trans*-2,3-epoxybutane,[18] n^{30}D 1.3677 (lit.[19] n^{25}D 1.3705), in small portions with shaking at room temperature. The reaction mixture was allowed to stand at room temperature for 13 days. The formation of a precipitate was slower than in the reaction of *cis*-2,3-epoxybutane. About 3 to 4 days were required for the formation of a precipitate comparable in quantity to that formed after 12 hr. in the xanthate reaction of the *cis* isomer. Since the *cis* trithiocarbonate existed as an oil prior to purification, isolation of the product required a modification of the prior procedure. Solvent was removed *in vacuo* at 30° and to the residual solids were added 250 ml. of ether and 150 ml. of water. The ether layer was separated, washed with water, dried over anhydrous sodium sulfate, and filtered. The ether was removed *in vacuo* at room temperature. The residual cloudy oil, 37.0 g., was distilled at 101° (0.18 mm.) to give 26.2 g. (53%) of a bright yellow oil which crystallized immediately when touched to Dry Ice. The crystals had m.p. 37–39.5°. The C=S absorption occurred at 1093 (s), 1053 (s), and 1031 (s) cm.$^{-1}$ (pure liquid).

Anal. Found: C, 36.89; H, 5.24; S, 58.72.

meso- **and** *dl*-**2,3-Butanedithiol.**—*cis*- and *trans*-4,5-Dimethyl-1,3-dithiolane-2-thione were reduced to the *meso* and *dl* dithiols, respectively, with lithium aluminum hydride in ether solution according to the procedure of Iqbal and Owen.[3a] The *meso* isomer, obtained in 42% yield, had b.p. 62–64° (35 mm.), n^{25}D 1.5171; lit.[20] b.p. 67° (29 mm.), n^{25}D 1.5173.

Anal. Calcd. for $C_4H_{10}S_2$: C, 39.30; H, 8.25; S, 52.46. Found: C, 39.12; H, 8.09; S, 52.24.

The *dl* isomer, obtained in 34% yield, had b.p. 63–65° (35 mm.), n^{25}D 1.5179; lit.[3a] b.p. 50–51° (22 mm.), n^{21}D 1.5315.

Anal. Found: C, 39.45; H, 8.15; S, 52.28.

The bis-*p*-nitrobenzoates of the isomeric dithiols were prepared by heating a mixture of the dithiol with excess *p*-nitrobenzoyl chloride in dry pyridine in a boiling water bath for 1 hr. The *dl* derivative had m.p. 185–186.5° (pale yellow plates from nitro benzene–methanol). The *meso* derivative had m.p. 154–156° (tan needles from acetone).

Anal. Calcd. for $C_{18}H_{16}N_2O_6S_2$: C, 51.42; H, 3.84; N, 6.66; S, 15.25. Found for *dl* isomer: C, 51.48; H, 4.00; N, 6.73; S, 14.96. Found for *meso* isomer: C, 51.63; H, 3.87; N, 6.51.

(18) The samples of *cis*- and *trans*-2,3-epoxybutane were obtained through the courtesy of Dr. E. J. Vandenberg, Hercules Powder Co., Wilmington, Del.

(19) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939).

(20) Reference 2a; the values given are for 2,3-butanedithiol of unspecified isomer composition.

The bisphenylurethane and bis-α-naphthylurethanes were prepared by adding a drop of dry pyridine to a solution of the dithiol in excess phenyl isocyanate and α-naphthyl isocyanate, respectively, and heating in a boiling water bath for 10 min. The α-naphthylurethanes were insoluble in large volumes of several refluxing solvents and, therefore, the analyses were performed on unrecrystallized samples. The phenylurethanes were recrystallized from methanol, in which the *meso* compound was much more soluble.

The bisphenylurethan *dl* isomer had m.p. 229–231°, lit. m.p. 228–229° (see Table II, footnote *a*).

Anal. Calcd. for $C_{18}H_{20}N_2O_2S_2$: C, 59.97; H, 5.59; N, 7.77; S, 17.79. Found: C, 59.46; H, 5.49; N, 7.52.

The bisphenylurethane *meso* isomer had m.p. 208–210°.

Anal. Found: C, 59.77; H, 5.71; N, 7.75; S, 17.52.

The bis-α-naphthylurethane *dl* isomer had m.p. 236–238°.

Anal. Calcd. for $C_{26}H_{24}N_2O_2S_2$: C, 67.79; H, 5.25; N, 6.08. Found: C, 67.28; H, 5.41; N, 6.07.

The bis-α-naphthylurethane *meso* isomer had m.p. 230–232°.

Anal. Found: C, 67.44; H, 5.27; N, 6.07.

***trans*-4,5-Dimethyl-1,3-dithiolane-2-thione from *cis*-2-Butene Episulfide.**—The *cis* episulfide was prepared from *cis*-2,3-epoxybutane by reaction with thiocyanate according to the procedure of Neureiter and Bordwell,[10a] b.p. 41.5–43° (131 mm.), $n^{23.5}$D 1.4761, infrared bands at 1147 (s) and 1028 (s) cm.$^{-1}$; lit.[10a] b.p. 51–51.5 (130 mm.), n^{20}D 1.4765, infrared at 1146 (s) and 1029 (s) cm.$^{-1}$. To a solution of potassium methyl xanthate prepared by adding 1.79 g. (0.032 mole) of potassium hydroxide and 2.81 g. (0.037 mole) of carbon disulfide in 12 ml. of methanol was added 0.70 g. (0.008 mole) of *cis*-2-butene episulfide. After standing at room temperature for 3 days, half the solvent was evaporated and 20 ml. of water was added with stirring. The yellow solids were filtered and washed with several portions of water. The dry product weighed 1.28 g. (69%), m.p. 40.5–42°. The infrared spectrum was identical with that of the *trans* trithiocarbonate prepared by the reaction of *cis*-2,3-epoxybutane with xanthate.

***cis*- and *trans*-4,5-Dimethyl-1,3-dithiolan-2-one.**—The *cis* and *trans* trithiocarbonates (IIIa and IIIb) were oxidized to the 2-one derivative according to a general procedure of Challenger, *et al.*,[9] for this type of compound. To a solution of 5.0 g. of mercuric acetate in 50 ml. of glacial acetic acid was added dropwise with stirring a solution of 0.50 g. of trithiocarbonate in 6 ml. of chloroform. After standing for 15 hr., the white precipitate was filtered and washed with chloroform. The combined filtrate and chloroform wash was diluted with 70 ml. of water. The acid layer was extracted with several small portions of chloroform. The combined chloroform layers were washed with two 10-ml. portions of water and dried over anhydrous sodium sulfate. After filtration the chloroform was distilled *in vacuo* at room temperature. The residue was an oil in both cases. The *trans* isomer, 0.29 g. (64%), crystallized readily in the cold and had m.p. 41–41.5°, which remained unchanged after two recrystallizations from petroleum ether.

Anal. Calcd. for $C_5H_8OS_2$: C, 40.51; H, 5.44; S, 43.26. Found: C, 40.88; H, 5.49; S, 43.19.

The *cis* isomer could not be crystallized.

Anal. Found: C, 40.51; H, 5.28.

***trans*-4,5-Diphenol-1,3-dithiolane-2-thione.**—*cis*-Stilbene oxide was prepared by the reaction of *cis*-stilbene with perbenzoic acid[21] according to the procedure of Lynch and Pausacker.[22] A solution of potassium methyl xanthate was prepared by dissolving 7.50 g. (0.13 mole) of potassium hydroxide and 12.17 g. (0.16 mole) of carbon disulfide in 35 ml. of methanol. To this solution was added 10.46 g. (0.053 mole) of *cis*-stilbene oxide. The reaction mixture, which never became homogeneous, was stirred at room temperature for 5 days. The yellow solids were filtered, washed with several portions of water until the filtrate was colorless, and dried *in vacuo* at room temperature. The recovery was 11.50 g., m.p. 148–155°. Recrystallization from hexane–benzene yielded 9.07 g. of small lustrous plates, m.p. 156.5–157.5°. A second crop of 1.30 g., m.p. 155–157°, also was obtained. The total yield was 67%. Further recrystallization gave an analytical sample, m.p. 157–158°. The infrared spectrum showed only one strong absorption band in the C=S stretching region at 1068 cm.$^{-1}$ (potassium bromide disk).

Anal. Calcd. for $C_{15}H_{12}S_3$: C, 62.45; H, 4.20; S, 33.35. Found: C, 62.75; H, 4.01; S, 33.60.

***cis*-4,5-Diphenyl-1,3-dithiolane-2-thione.**—To a solution of potassium methyl xanthate prepared by dissolving 11.28 g. (0.20 mole) of potassium hydroxide and 18.24 g. (0.24 mole) of carbon disulfide in 65 ml. of methanol was added 15.68 g. (0.08 mole) of *trans*-stilbene oxide (prepared as before). The mixture was stirred at room temperature for 5 days. The solids were filtered, pulverized, washed with several portions of water, and dried *in vacuo* at room temperature. The recovery was 16.60 g., m.p. 95–121°. Two grams of this solid was purified by chromatography on an alumina column (Fisher Scientific Co., neutral grade, Brockman activity I). Elutions were made with increasing ratios of benzene (solvent)–hexane (nonsolvent). The bright yellow eluents yielded a total of 1 g. of solid, average m.p. 115–120°. Recrystallization from hexane gave 0.50 g. of yellow needles, m.p. 123.5–124.5°. The total yield was 18%. A strong absorption band appeared in the infrared spectrum in the C=S stretching region at 1060 cm.$^{-1}$ and a shoulder at 1075 cm.$^{-1}$ (potassium bromide disk).

Anal. Found: C, 62.54; H, 4.48; S, 33.33.

***meso*- and *dl*-α,α'-Stilbenedithiol.**—The *cis* and *trans* trithiocarbonates (IVa and IVb) were reduced to *meso*- and *dl*-α,α'-stilbenedithiol, respectively, with lithium aluminum hydride. To 0.30 g. (0.0079 mole) of lithium aluminum hydride in 8 ml. of tetrahydrofuran was added a solution of 1.00 g. (0.0035 mole) of the trithiocarbonate in 12 ml. of tetrahydrofuran dropwise over 25 min. with stirring at room temperature. The reaction mixture was heated to reflux for 7 hr. and then it was allowed to stand at room temperature for 11 hr. After cooling to 0°, 3 ml. of water was added dropwise (caution) to decompose the excess hydride and the mixture was then acidified with cold 6 *N* hydrochloric acid. The solution was then extracted with 50 ml. of ether. The acid layer was extracted with 10 ml. of ether and the combined ether layers were washed with saturated aqueous sodium chloride. The *meso* isomer was not completely soluble in ether and 100 ml. of benzene was required to dissolve the residual white solids suspended in the acid layer. The organic layers were dried over anhydrous sodium sulfate. After filtration and removal of solvent *in vacuo* at room temperature, 0.80 g. of crude product was obtained in each case.

Final purification was effected as follows. The crude *dl* isomer, m.p. 53–62°, was recrystallized twice from hexane to give 0.34 g. (40%) of product, m.p. 70–71°.

Anal. Calcd. for $C_{14}H_{14}S_2$: C, 68.24; H, 5.73; S, 26.03. Found: C, 68.31; H, 5.90; S, 26.27.

The diacetate, m.p. 119–121° (methanol), was prepared by adding excess acetic anhydride to the *dl* dithiol in dry pyridine solution.

Anal. Calcd. for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49; S, 19.41. Found: C, 65.18; H, 5.65; S, 19.65.

The crude *meso* isomer, m.p. 205–215°, was recrystallized twice from benzene to give 0.42 g. (49%) of product, m.p. 220.5–222.5°.

Anal. Found: C, 68.57; H, 5.97; S, 26.00.

The diacetate, m.p. 188–190° (methanol), was prepared as before.

Anal. Found: C, 65.17; H, 5.52; S, 19.21.

The bisphenylurethane, m.p. 258–260° dec., from ethyl acetate, was prepared by refluxing a solution of the *meso* dithiol and excess phenyl isocyanate in decalin for 1 hr.

Anal. Calcd. for $C_{28}H_{24}N_2O_2S_2$: C, 69.39; H, 4.99; N, 5.78. Found: C, 68.68; H, 5.10; N, 5.67.

***cis*-4,5-Diphenyl-1,3-dioxolan-2-one.**—The procedure of Sarel, *et al.*,[12] was used in this preparation. A mixture of 4.29 g. (0.02 mole) of *meso*-hydrobenzoin, which was prepared by the reduction of benzyl with sodium borohydride,[23] 2.98 g. (0.025 mole) of diethyl carbonate and 0.041 g. (0.00075 mole) of sodium methoxide was heated to 130° in an oil bath kept at 150–160°. As ethanol formed, the temperature fell to 107°. The ethanol was removed by distillation and the temperature went to 130° where it was maintained for 1 hr. Excess diethyl carbonate was distilled at reduced pressure. After cooling to room temperature, the residual white solid was dissolved in 75 ml. of benzene, washed with water, dried over anhydrous sodium sulfate, and filtered. The benzene was distilled *in vacuo*. The residue, 4.49 g., m.p. 115–122°, was recrystallized twice from 95% ethanol to give 3.00 g.

(21) "Organic Syntheses," Coll. Vol. I, H. Gilman and A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

(22) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).

(23) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed.; Rev., D. C. Heath and Co., Boston, Mass., 1957, p. 175.

(63%) of product, m.p. 126.5–128°. Sarel[14] reports m.p. 126° for the cyclic carbonate prepared from hydrobenzoin.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.98; H, 5.04. Found: C, 75.19; H, 4.88.

trans-**4,5-Diphenyl-1,3-dioxolan-2-one.**—*dl*-Hydrobenzoin, prepared by the sequence *trans*-stilbene → *meso*-stilbene dibromide (Br_2)[24] → *dl*-hydrobenzoin monoacetate (silver acetate–wet glacial acetic acid) → *dl*-hydrobenzoin (sodium hydroxide–ethanol[25]), was converted in 74% yield by the prior procedure to the *trans* cyclic carbonate, m.p. 110–111.5°.

Anal. Found: C, 75.11; H, 5.11.

dl-**Butadiene-1,2:3,4-bis(trithiocarbonate) (VII).**—A solution of 21.51 g. (0.25 mole) of *dl*-butadiene dioxide (obtained from the Koppers Co., Pittsburgh, Pa.) in 25 ml. of methanol was added over 10 min. to a stirred solution of 70.13 g. (1.25 moles) of potassium hydroxide and 114.21 g. (1.4 moles) of carbon disulfide in 325 ml. of methanol cooled to 0–5°. After about one-half of the dioxide was added, gentle reflux occurred and a precipitate formed. The mixture was kept at room temperature for 64 hr. The precipitate was filtered, washed with several portions of water, and dried *in vacuo* at room temperature. The product, 36.48 g. (54%), did not melt, but changed from yellow to orange to red to a black tar at 225–235°. It was insoluble in refluxing dimethylformamide, benzene, acetone, ether, and tetrahydrofuran, but dissolved readily in concentrated sulfuric acid at room temperature. The sulfuric acid solution was poured into ice–water and the precipitated product, after washing and drying, had an infrared spectrum which was identical with the original compound. The infrared spectrum showed only one absorption band in the C=S stretching region at 1052 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_6H_6S_6$: C, 26.64; H, 2.24; S, 71.12. Found: C, 26.94; H, 2.48; S, 70.82.

dl-**1,2,3,4-Butanetetrathiol.**—To 3.80 g. (0.1 mole) of lithium aluminum hydride in 175 ml. of anhydrous ether was added 5.41 g. (0.02 mole) of the bistrithiocarbonate (VII) in small portions over 10 min. with stirring. Immediately thereafter the reaction mixture began to reflux vigorously. After 19 hr. at room temperature all of the yellow solid had reacted. The mixture was cooled to 0° and water was added (caution) to decompose the excess hydride. After acidifying with cold 6 *N* hydrochloric acid, the ether layer was separated and washed with two 100-ml. portions of 10% aqueous sodium bicarbonate, two 50-ml. portions of water, dried over anhydrous sodium sulfate, and filtered. The ether was distilled *in vacuo* at room temperature. Fractional distillation of the residual oil, 4.03 g., yielded 1.57 g. (42%) of a water white liquid, b.p. 131–132° (0.6 mm.).

Infrared analysis revealed a high-intensity mercaptan absorption band at 2550 cm.$^{-1}$ (pure liquid).

Anal. Calcd. for $C_4H_{10}S_4$: C, 25.78; H, 5.40; S, 68.82. Found: C, 25.70; H, 5.80; S, 68.41.

The tetraacetate, prepared as before, had m.p. 87–88.5°.

Anal. Calcd. for $C_{12}H_{18}O_4S_4$: C, 40.65; H, 5.12; S, 36.18. Found: C, 40.83; H, 5.31; S, 35.90.

Acknowledgment.—We wish to acknowledge gratefully support of this work by the National Institutes of Health under Grant No. AI-01425-09.

(24) L. I. Smith and M. M. Falkof, "Organic Synthesis," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 350.

(25) Reference 23, p. 189.

Seven-Membered Heterocycles. II. The Reactions of Benzo[*b*]thiepin 1,1-Dioxide[1-3]

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The light-catalyzed addition of 1 or 2 moles of bromine to benzo[*b*]thiepin 1,1-dioxide proceeded on the heterocyclic ring, while attempted additions of piperidine and hydrogen bromide failed. Electrophilic nitration of I gave two mononitro derivatives with substitution taking place on the benzene ring. The nitration of 2,3-dihydrobenzo[*b*]thiepin 1,1-dioxide formed an adduct which decomposed to 4-nitrobenzo[*b*]thiepin 1,1-dioxide.

In a previous paper[1] the literature of thiepin chemistry was reviewed and the synthesis of benzo[*b*]-thiepin 1,1-dioxide described. This report deals with the chemical properties of that compound, in particular, thermal stability, the addition of bromine, and the effects of electrophilic and nucleophilic reagents.

When benzo[*d*]thiepin-2,4-dicarboxylic acid was placed in refluxing ethanol, sulfur and naphthalene-2,3-dicarboxylic acid resulted,[5,6] while benzo[*d*]thiepin 3,3-dioxide required elevated temperatures for conversion to naphthalene.[7] Unlike these materials benzo[*b*]thiepin 1,1-dioxide, a colorless crystalline solid, was stable in refluxing ethanol and distilled with slight decomposition when inserted into a Wood's metal bath at 250°; however, when it was refluxed in diethylcarbitol for several hours, resinification took place. In no experiment was naphthalene detected.

Thianaphthene sulfone undergoes facile nucleophilic additions with a variety of reagents such as piperidine, diethylamine, and hydrogen bromide to cite a few examples.[8] The product formed in each reaction is the 3-substituted (3-piperidino, 3-diethylamino, 3-bromo) 2,3-dihydrothianaphthene sulfone. When benzo[*b*]thiepin 1,1-dioxide was allowed to react with piperidine or with concentrated hydrobromic acid under conditions which resulted in addition to thianaphthene sulfone,[8] no reaction was observed and good recoveries of starting benzo[*b*]thiepin 1,1-dioxide were made. These observations indicate that the heterocyclic ring of benzo[*b*]thiepin 1,1-dioxide does not behave as an ordinary α,β-unsaturated sulfone.

While 2,3-dihydrobenzo[*b*]thiepin 1,1-dioxide added bromine readily in both warm chloroform or glacial acetic acid, the reaction of benzo[*b*]thiepin 1,1-dioxide (I) with bromine occurred only in the presence of sunlight or ultraviolet light. Addition of 1 mole of bromine produced a dibromide (II) in 71% yield which could add a 2nd mole of bromine to form a tetrabromide (III) (60% yield). Alternately, the tetrabromide was formed by the addition of 2 moles of bromine to I (84% yield).

(1) For paper I in this series, see V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).

(2) Presented in part at the 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(3) Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for partial support of this research.

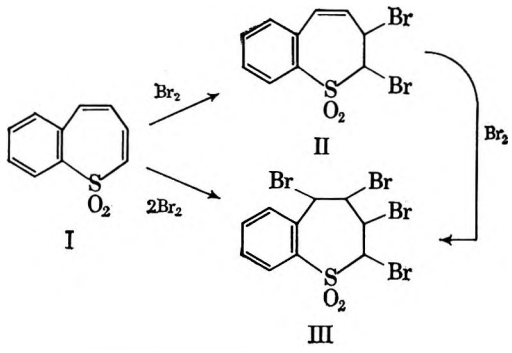
(4) Socony Mobil Fellow 1956–1957; Eastman Kodak Fellow 1957–1958; abstracted from part of the Ph.D. dissertation of R. F. Love, June, 1960.

(5) G. P. Scott, *J. Am. Chem. Soc.*, **75**, 6332 (1953).

(6) K. Dimroth and G. Lenke, *Ber.*, **89**, 2608 (1956).

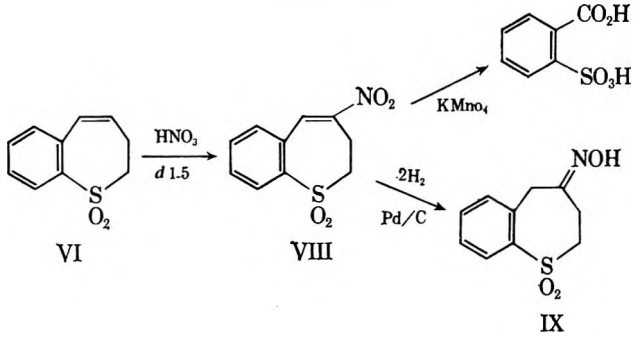
(7) W. E. Truce and F. J. Lotspeich, *J. Am. Chem. Soc.*, **78**, 848 (1956).

(8) F. G. Bordwell and W. H. McKellin, *ibid.*, **72**, 1985 (1950).



The structural assignment of the tetrabromide as 2,3,4,5-tetrabromo-2,3,4,5-tetrahydrobenzo[*b*]-thiepin 1,1-dioxide (III) was based primarily on a comparison of the ultraviolet spectrum with model compounds. Table I contains a listing of these data which clearly show a similarity between III and other 2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxides. In the case of the dibromide one must consider that the addition of 1 mole of bromine to I may proceed by 1,2-addition to produce II or 4,5-dibromo-4,5-dihydrobenzo-[*b*]thiepin 1,1-dioxide or by 1,4-addition forming 2,5-dibromo-2,5-dihydrobenzo[*b*]thiepin 1,1-dioxide. Examination of the ultraviolet spectra in Table I clearly points to a styrene-like chromophore which requires structure II for the dibromide.

The study of nitration as an example of electrophilic substitution was initiated with 2,3-dihydrobenzo[*b*]-thiepin 1,1-dioxide (VI) which formed a mononitro derivative in yields ranging from 50 to 64%. Upon



oxidation this nitro compound gave *o*-sulfobenzoic acid isolated and identified as the S-benzylthiouronium salt, m.p. 204–205° (lit.[9] m.p. 205–206°). A mixture melting point with an authentic sample was not depressed. A quantitative semimicro hydrogenation of the nitro derivative stopped after the absorption of 2 moles of hydrogen with the formation of the oxime (IX). This oxime, m.p. 186–187°, differed from the oxime of 5-oxo-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide, m.p. 199–200°, and had an n.m.r. spectrum (see Experimental section) which was consistent with the assigned structure IX. These data provided evidence that the nitro group entered the heterocyclic ring and was attached to C-4 as shown in structure VIII. Supporting evidence of this assignment was found in the ultraviolet spectrum of VIII (see Table I) showing the presence of a β-nitrostyrene chromophore.

Although attachment of the nitro group to an olefinic position was unexpected, the literature[10] contains examples of nitration of olefins to produce nitroolefins.

(9) S. Veibel and H. Lillelund, *Bull. soc. chim. France*, [5] **5**, 1153 (1938).

TABLE I.—ULTRAVIOLET SPECTRA

Compound	λ_{max}, mμ	log ε	Solvent
IV	270	3.15	Dioxane
	277	3.15	
V	(267)[a]	3.30	Dioxane
	274	3.35	
	(281)[a]	3.29	
III	277	3.34	Dioxane
	(284)[a]	3.30	
VI	<224		
	250	3.99	95% ethanol
	291	3.74	
VII	224		
	261	3.86	95% ethanol
	294	3.78	
	(302)[a]	3.73	
II	230	3.48	95% ethanol
	259	3.23	
	296	3.13	
IV	262	3.51	95% ethanol
	269	3.56	
	277	3.54	
III	278	3.54	95% ethanol
	284	3.51	
$C_6H_5SO_2CH{=}CH_2$[c]	225	4.1	95% ethanol
	267	3.02	
VIII	225	3.00	95% ethanol
	311	3.10	
$C_6H_5CH{=}CHNO_2$[d]	227	3.98	95% ethanol
	309	4.22	
$C_6H_5CH{=}C(NO_2)CH_3$[d]	226	4.00	95% ethanol
	305	4.09	

[a] Shoulder. [b] See ref. 1. [c] C. C. Price and H. Morita, *J. Am. Chem. Soc.*, **75**, 4747 (1953). [d] E. A. Braude, E. R. H. Jones, and G. G. Rose, *J. Chem. Soc.*, 1104 (1947).

In the reaction of VI with red fuming nitric acid an intermediate adduct was isolated. This material melted over a range 60–80°, appeared unstable, and decomposed at temperatures over 110° with the evolution of a gas. The infrared spectrum contained bands which could be attributed to sulfone,[11] nitro,[12] and nitrite[13] functions. Nitrate esters did not appear likely due to the absents of strong absorption between 6.0 and 6.2 μ and in the region of 13.3 μ.[12] These data suggest that the intermediate adduct is a 4-nitro-5-nitrite derivative, although one cannot exclude the presence of some of the 4,5-dinitro derivative. The nature of this addition reaction is not clear at this time.

When 2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide (X) was treated with red fuming nitric acid, a mononitro derivative was isolated in 64% yield. This substance was assigned the structure 8-nitro-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide (XI) on the

(10) R. Anschutz and A. Hilbert, *Ber.*, **54**, 1854 (1921); H. Wieland and F. Rahn, *ibid.*, 1770 (1921); J. Mauthner and W. Suida, *Monatsh.*, **24**, 648 (1903).

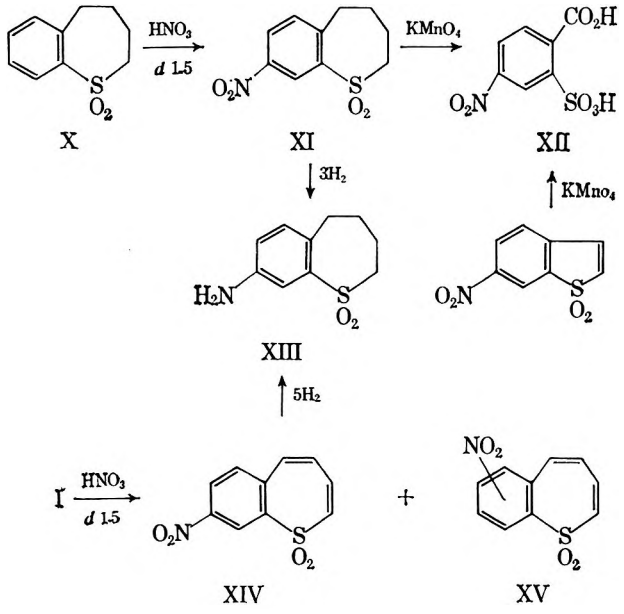
(11) K. C. Schriber, *Anal. Chem.*, **21**, 1168 (1949).

(12) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **77**, 6341 (1955).

(13) P. Tarte, *J. Chem. Phys.*, **20**, 1570 (1952).

basis of its oxidation to 4-nitro-2-sulfobenzoic acid (XII) isolated as the S-benzylthiouronium salt. An authentic sample of this derivative was prepared by the oxidation of 6-nitrothianaphthene.[14]

The nitration of benzo[*b*]thiepin (I) under similar conditions produced two isomeric mononitro derivatives, separated by column chromatography. The isomer melting at 180–181° (45% yield) absorbed 5 moles of hydrogen and gave an amine whose infrared spectrum was identical with that of amine XIII obtained by reduction of XI. Therefore, the structure assigned to this isomer is 8-nitrobenzo[*b*]thiepin 1,1-dioxide



(XIV). No structural assignment has been established for the other isomer (XV), m.p. 185–186 (31% yield); however, in view of the directive effects of the sulfone group, a vinyl group, and the position of substitution in compound XIV, isomer XV is probably 6-nitrobenzo[*b*]thiepin 1,1-dioxide.

In review of our studies of benzo[*b*]thiepin 1,1-dioxide, one can summarize the chemical properties as (1) the failure of thermal extrusion to produce naphthalene, (2) the failure of nucleophilic additions to the heterocyclic ring, (3) light-catalyzed addition of 1 or 2 moles of bromine to the heterocyclic ring, (4) the attack of the heterocyclic ring by potassium permanganate, and (5) the electrophilic substitution of nitration proceeds in the benzene ring *meta* with respect to the sulfone group. These results suggest appreciable olefinic character of the bonds in the heterocyclic ring.

Experimental[15]

Benzo[*b*]thiepin 1,1-Dioxide.—This compound, m.p. 139–140°, was available from the synthesis described previously.[1]

Thermal Stability of Benzo[*b*]thiepin 1,1-Dioxide.—Benzo[*b*]thiepin 1,1-dioxide was recovered unchanged after 20 hr. of reflux in 95% ethanol; however, when refluxed in diethylcarbitol (b.p. 183°) under nitrogen for 12 hr., only a dark resinous material separated upon dilution with water.

A flask fitted with a cold-finger, nitrogen inlet tube and an outlet attached to a solution of sodium hydroxide was charged with benzo[*b*]thiepin 1,1-dioxide (102 mg., 0.53 mmole). When the flask was immersed in a Wood's metal bath at 250° which was slowly raised to 280°, 80 mg. (79%) of benzo[*b*]thiepin 1,1-dioxide, m.p. 137–139° (infrared spectrum identical with authentic sample), collected on the cold finger. Above 280° the small residue resinified rapidly.

The sodium hydroxide solution was treated with 5 ml. of 30% hydrogen peroxide and acidified with nitric acid; the addition of barium nitrate solution gave 10 mg. (8%) of barium sulfate.

2,3-Dibromo-2,3-dihydrobenzo[*b*]thiepin 1,1-Dioxide.—A solution of bromine (200 mg., 1.25 mmoles) and benzo[*b*]thiepin 1,1-dioxide (234 mg., 1.22 mmoles) in 10 ml. of glacial acetic acid was decolorized after exposure to ultraviolet light for 30–45 min. or more quickly when exposed to sunlight. After the slightly yellow solution was poured into water containing a small amount of sodium bisulfite, the precipitate was collected, and crystallization from acetone gave 305 mg. (71%) of dibromide, m.p. 147–148°.

Anal. Calcd. for $C_{10}H_8Br_2O_2S$: C, 34.12; H, 2.29. Found: C, 34.30; H, 2.67.

2,3,4,5-Tetrabromo-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-Dioxide.—A solution of benzo[*b*]thiepin 1,1-dioxide (103 mg., 0.53 mmole) and bromine (180 mg., 1.13 mmoles) in 10 ml. of glacial acetic acid was exposed to ultraviolet light for 1 hr. and processed as described before. Crystallization from dioxane gave 227 mg. (84%) of the tetrabromide, m.p. 222° dec.

Anal. Calcd. for $C_{10}H_6Br_4O_2S$: C, 23.46; H, 1.57. Found: C, 23.80; H, 1.81.

The dibromide (109 mg., 0.31 mmole) from the previous experiment was treated with 70 mg. (0.44 mmole) of bromine and the reaction processed as described before. The yield of the tetrabromide, m.p. 220° dec., was 96 mg. (60%). A mixture melting point with this tetrabromide was not depressed and both infrared spectra were identical.

Attempted Reaction of Benzo[*b*]thiepin 1,1-Dioxide with Piperidine.—A blend of 111 mg. (0.57 mmole) of benzo[*b*]thiepin 1,1-dioxide, 98 mg. (1.15 mmoles) of piperidine, and 5.0 ml. of absolute ethanol was refluxed 30 min. and evaporation under a stream of nitrogen afforded a quantitative recovery of the starting material, m.p. 138–140°.

Attempted Reaction of Benzo[*b*]thiepin 1,1-Dioxide with Hydrobromic Acid.—Benzo[*b*]thiepin 1,1-dioxide (105 mg., 0.54 mmole) in 4 ml. of 48% hydrobromic acid was refluxed for 30 min. and upon cooling deposited 91 mg. (87%) of unchanged starting material, m.p. 139–140°.

Nitration of 2,3-Dihydrobenzo[*b*]thiepin 1,1-Dioxide.—A solution of 500 mg. (2.58 mmoles) of 2,3-dihydrobenzo[*b*]thiepin 1,1-dioxide in 25 ml. of nitric acid (*d* 1.5) was kept at 5–10° for 20–30 min., poured into water, and the solid filtered. Slow crystallization of this solid from acetone gave 390 mg. (64%) of 4-nitro-2,3-dihydrobenzo[*b* thiepin 1,1-dioxide, m.p. 197–198°.

Alternately, this diluted acid solution was heated at 80–85° for 0.5 to 1 hr. Upon cooling the same nitroolefin crystallized as pale yellow needles.

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79. Found: C, 50.11; H, 4.04.

In another experiment the precipitate from dilution of the reaction mixture was collected and air-dried. It appeared unstable on standing, melted at 60–80°, and decomposed at temperatures over 110° with the evolution of a gas. A sample was suspended in dilute sulfuric acid and after short warming gave nitrous acid. The infrared spectrum (potassium bromide disk) showed strong absorption at (all values listed as μ) 2.4,[16] doublet 2.7, 2.76,[16] 3.3, 4.2, 5.96, 6.37, 6.56, 6.75, 7.0, 7.51, 7.65, 7.80, 8.14, 8.35, 8.57, 8.71, 8.91, 9.4, 9.6, 10.8, 11.75, 12–12.5 broad, 1.4–14.7 broad, and 15.2.

Oxidation of 4-Nitro-2,3-dihydrobenzo[*b*]thiepin 1,1-Dioxide.—A mixture of 4-nitro-2,3-dihydrobenzo[*b*]thiepin 1,1-dioxide (500 mg., 2.1 mmoles), potassium hydroxide (600 mg., 10.0 mmoles), potassium permanganate (3.0 g., 19 mmoles) in 35 ml. of water was heated on a steam plate for 6 hr. After cooling the excess potassium permanganate was destroyed with 30% hydrogen peroxide and the solution acidified with hydrochloric acid, fil-

(14) F. Challenger and P. H. Clapham, *J. Chem. Soc.* 1615 (1948).

(15) All melting points are uncorrected. The microanalyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were determined with a Perkin-Elmer Model 21 or a Baird Associates infrared spectrophotometer by R.F.L. and Anthony Saraceno. The n.m.r. spectra were measured with a Varian Associates 60-Mc. high resolution n.m.r. spectrometer, Model V-4300-B.

(16) Reference 13 contains a reproduction of the infrared spectrum of methyl nitrite and shows bands at 2.2, 3.0 and 3.1, 3.4, 4.0, 4.4 μ, and others.

tered, made nearly neutral, and concentrated to 30 ml. The addition of 500 mg. (2.5 mmoles) of S-benzylthiouronium chloride in 5 ml. of water gave a precipitate which was filtered and recrystallized from aqueous ethanol. The yield of the S-benzylthiouronium salt of *o*-sulfobenzoic acid, m.p. 204–206° (lit.[9] m.p. 205–206°) was 0.50 g. (41%). A mixture melting point with authentic material was not depressed.

Hydrogenation of 4-Nitro-2,3-dihydrobenzo[*b*]thiepin 1,1-Dioxide.—A stirred mixture of 4-nitro-2,3-dihydrobenzo[*b*]thiepin (110.7 mg., 0.465 mmole) dissolved in 10 ml. of freshly distilled dioxane and 17 mg. of 10% palladium–charcoal was exposed to hydrogen at atmospheric pressure in a semimicro hydrogenation apparatus.[17]

When 0.95 mmole of hydrogen was absorbed, the reaction appeared to stop. After the catalyst was filtered and the solvent evaporated, the residue was crystallized from ethanol with a charcoal treatment and gave 71.4 mg. (68%) of 4-oxo-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide oxime, m.p. 183–184°. Repeated crystallizations from an ethyl acetate and petroleum ether (b.p. 30–60°) mixture gave an analytical sample, m.p. 186–187°.

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.32, H, 4.92. Found: C, 53.38, 53.53; H, 5.26, 5.18.

The n.m.r. spectrum[18] had the following peaks: singlet, τ 5.06 (hydroxyl proton); singlet, 5.57 (benzylic proton); multiplet, center 6.48; multiplet, center 6.97 (these peaks are attributed to the protons α to the sulfone and oxime functions).

In a second experiment 1.04 g. (4.37 mmoles) of the nitro compound in 40 ml. of dioxane was reduced to 0.79 g. (81%) of the oxime, m.p. 182–183°, in the same apparatus using 36 mg. of platinum oxide catalyst and hydrogen at atmospheric pressure.

The reaction was also carried out in 76% yield using a Paar hydrogenation apparatus and 10% palladium–charcoal catalyst.

5-Oxo-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-Dioxide Oxime.—The reaction of 5-oxo-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide (1.0 g., 4.75 mmoles) and hydroxylamine hydrochloride (1.0 g., 14.4 mmoles) in 6 ml. of pyridine and 6 ml. of absolute ethanol for 3 hr. on a steam bath produced 0.95 g. (89%) of the oxime, m.p. 195–197°. An analytical sample, m.p. 199–200°, was obtained by repeated recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92. Found: C, 53.72, 53.60; H, 5.06, 5.01.

The n.m.r. spectrum[18] had the following peaks: singlet, 4.94 (hydroxyl proton); triplet, center 6.32; triplet, center 6.63 (these peaks are attributed to the protons α to the sulfone and oxime functions); multiplet, center 7.73 τ (C-3 methylene protons).

Nitration of 2,3,4,5-Tetrahydrobenzo[*b*]thiepin 1,1-Dioxide.—A solution of 2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide (0.94 g., 0.47 mmole) in 20 ml. of nitric acid (*d* 1.5) was kept at 5–10° for 1 hr. and upon dilution with water gave 923 mg. (80%) of crude nitro compound, m.p. 184–190°. Crystallization from benzene gave 735 mg. (64%) of 8-nitro-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide, m.p. 197–198°, as fine white needles. An analytical sample, m.p. 198°, was obtained by recrystallization from benzene and from absolute ethanol.

Anal. Calcd. for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.59. Found: C, 49.74, 49.87; H, 4.64, 4.81.

Hydrogenation of 8-Nitro-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-Dioxide.—After a mixture of 8-nitro-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide (1.2 g., 5.0 mmoles) in 50 ml. of dioxane and 10% paladium–charcoal (100 mg.) was exposed to 40 lb. of hydrogen pressure for 1 hr. in a Paar hydrogenation apparatus, the mixture was filtered, the solvent evaporated from the filtrate, and the residue taken up in 20% hydrochloric acid. The acidic solution was treated with decolorizing charcoal, filtered, and divided into two parts. To one part was added 3 g. of sodium acetate and 2 ml. of acetic anhydride and upon rapid stirring a crystalline precipitate formed. After filtration, crystallization from ethanol gave 0.32 g. (25% based on the starting nitro compound) of 8-acetamido-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide, m.p. 224–225°.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.97. Found: C, 57.06; H, 5.93.

The other part of the acidic solution was made alkaline and gave 0.34 g. (32%) of 8-amino-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide, m.p. 169–170°. An analytical sample was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.84; H, 6.20. Found: C, 56.62; H, 6.26.

Oxidation of 8-Nitro-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-Dioxide.—A suspension of 300 mg. (1.25 mmoles) of 8-nitro-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide in a solution of 400 mg. (7.1 mmoles) of potassium hydroxide in 25 ml. of water was heated to gentle reflux and 1.5 g. (9.5 mmoles) of potassium permanganate was added in small portions over 5 hr. After cooling, the mixture was acidified with concentrated hydrochloric acid, treated with 4 ml. of 30% hydrogen peroxide, and filtered. After the filtrate was adjusted to pH 5, the solution was concentrated until precipitation began. The solid was dissolved by addition of water and the solution treated with 300 mg. (1.5 mmoles) of S-benzylthiouronium chloride in 3 ml. of water. A crystalline product was formed and crystallization of this substance from 50% aqueous ethanol gave 107 mg. (16%) of the S-benzylthiouronium salt of 4-nitro-2-sulfobenzoic acid, m.p. 240.5–242°. A mixture melting point with the salt obtained from the oxidation of 6-nitrothianaphthene showed no depressions and the infrared spectra of the two samples were identical.

6-Nitrothianaphthene Sulfone.—Using the procedure of Bordwell, Lampbert, and McKellin,[19] thianaphthene was oxidized to thianaphthene sulfone, m.p. 140–142° (lit.[14] m.p. 142–143°), in 70% yield and nitration of the sulfone by the method of Challenger and Clapham[14] produced 6-nitrothianaphthene sulfone, m.p. 187–188° (lit.[14] m.p. 188°).

Oxidation of 6-Nitrothianaphthene Sulfone.—The previous procedure for oxidation of 8-nitro-2,3,4,5-tetrahydrobenzo[*b*]-thiepin 1,1-dioxide was employed with 500 mg. (2.4 mmoles) of 6-nitrothianaphthene sulfone, 400 mg. (7.1 mmoles) of potassium hydroxide in 35 ml. of water and 1.2 g. (7.6 mmoles) of potassium permanganate. After 2 days at 40°, 103 mg. of unchanged sulfone was recovered along with 382 mg. (44%) of the S-benzylthiouronium salt of 4-nitro-2-sulfobenzoic acid, m.p. 242–243°.

Anal. Calcd. for $C_{23}H_{26}N_8S_3O_7$: C, 47.64; H, 4.35. Found: C, 47.81; H, 4.45.

Nitration of Benzo[*b*]thiepin 1,1-Dioxide.—Benzo[*b*]thiepin 1,1-dioxide (207 mg., 108 mmoles) was added in small portions with stirring to 8 ml. of nitric acid (*d* 1.5) at 5–10°. After this solution was kept at 5–15° for 45 min. and poured into ice–water and the precipitate was filtered and quickly crystallized from acetone. The yield of the yellow crystalline nitro derivative (mixture of two isomers), m.p. 146–160°, was 167 mg. (65%).

Anal. Calcd. for $C_{10}H_7NO_4S$: C, 50.62; H, 2.97. Found: C, 50.59; H, 3.16.

In a second experiment the reaction of 309 mg. (1.61 mmoles) of benzo[*b*]thiepin 1,1-dioxide and 13 ml. of nitric acid (*d* 1.5) was processed as before and the crude precipitate dried, dissolved in 20 ml. of benzene, and placed on 75 g. of Alcoa activated alumina F-20. With 90% benzene–10% ether as eluent, 119 mg. (31%) of (?)-nitrobenzo[*b*]thiepin 1,1-dioxide was collected. Solutions of this material turned purple upon prolonged exposure to light. An analytical sample, m.p. 185–186°, was prepared by repeated recrystallization from absolute ethanol.

Anal. Calcd. for $C_{10}H_7NO_4S$: C, 50.62; H, 2.97. Found: C, 50.23; H, 3.16.

A second fraction which was eluted with 70% benzene–30% ether was 177 mg. (46%) of 8-nitrobenzo[*b*]thiepin 1,1-dioxide, m.p. 180–181°. Several recrystallizations from absolute ethanol failed to raise the melting point.

Anal. Calcd. for $C_{10}H_7NO_4S$: C, 50.62; H, 2.97. Found: C, 50.29; H, 3.18.

Hydrogenation of 8-Nitrobenzo[*b*]thiepin 1,1-Dioxide.—A stirred mixture of 8-nitrobenzo[*b*]thiepin 1,1-dioxide (41 mg., 0.17 mmole) dissolved in 5 ml. of freshly distilled dioxane and 10 mg. of 10% palladium–charcoal was exposed to hydrogen at atmospheric pressure in a semimicro hydrogenation apparatus.[17] After 0.84 mmole of hydrogen was absorbed, the catalyst was filtered, washed, and the solvent evaporated. The residue, m.p. 162–165°, was 21 mg., 66%, and had an infrared spectrum identical with that of 8-amino-2,3,4,5-tetrahydrobenzo[*b*]thiepin 1,1-dioxide.

(17) For a diagram of the apparatus, see A. A. Baldoni, Ph.D. dissertation, University of Notre Dame, 1951, p. 54.

(18) The n.m.r. spectra were recorded in pyridine using tetramethylsilane as an internal standard. Only the aliphatic and hydroxylic protons were considered.

(19) F. G. Bordwell, B. B. Lampbert, and W. H. McKellin, *J. Am. Chem. Soc.*, **71**, 1702 (1949).

2-Amino-2-oxazolin-4-ones. III. Spectral Studies

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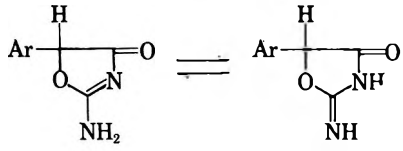
2-Dimethylamino-5-phenyl-2-oxazolin-4-one (II) exhibits n.m.r. signals for two different N-methyl groups which collapse at 70–80° to a single resonance. These signals are attributed to delocalization of the nonbonded electrons throughout the π-system which results in restricted rotation. Solutions of 2-methylamino-5-phenyl-2-oxazolin-4-one (VI) exhibit two unequal n.m.r. signals for each type of proton present. Concentration dependence of n.m.r. and infrared spectra indicate that a dimerization equilibrium (k_2 = 0.3) occurs. 2-Amino-5-(2,3-dimethoxyphenyl)-2-oxazolin-4-one (VIIIa) was shown to exist as the conjugated tautomer similar to other members of the series and unlike previous formulations as the 2-imino tautomer (Ib).

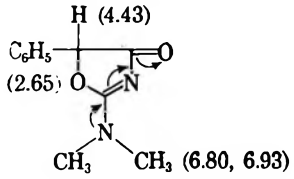
Recently we presented evidence[1] that 2-amino-2-oxazolin-4-ones (Ia) exist, at least in polar solvents, in this form rather than as the tautomers Ib previously formulated.[2,3] These conclusions were based largely



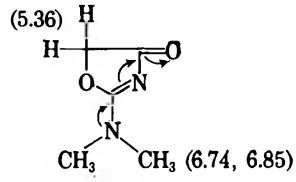
Ia Ib

upon the ultraviolet spectra of I and the methylated derivatives II–VI, and upon their chemical transformations.[1,4] Ionization constants are difficult to obtain in this series because of the limited solubility of these substances and because the pH-dependent changes in the ultraviolet spectra are apparently small and occur at 200–230 mμ. Difficulties in the interpretation of the infrared spectra have already been described.[1,3]

To obtain another type of evidence regarding tautomerism in this series,[5] the n.m.r. spectra of typical N-methyl derivatives (II–VI) were determined in deuteriochloroform. The positions of the n.m.r. peaks in τ units are appended to appropriate groups in the structures given.



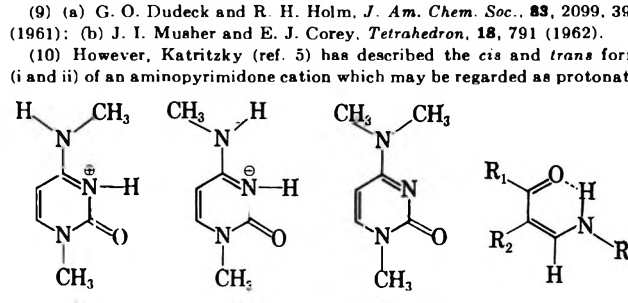
II



III

The presence of two separate N-methyl resonances (each due to 3 protons) in the spectrum of 2-dimethylamino-5-phenyl-2-oxazolin-4-one (II) had not been anticipated. This behavior could not result from coupling since the structure of II apparently does not permit this[6] and, particularly, since the signals at τ 2.65 and 4.43 are singlets. The integrated intensities (5:1:3:3) eliminate the possibility that enolization at C-5 could be involved, and, moreover, there is no hydroxyl signal. The unsymmetrical substitution at C-5 is not responsible for the two N-methyl signals of II, since the symmetrical derivative III behaves similarly. The two N-methyl resonances of II broaden and merge as the temperature is raised from 28° to 67° and collapse to a single broad peak at 84°. This becomes a single sharp signal at higher temperature. Compound III behaves similarly with the temperature of coalescence (T_c) at about 70–75°. This behavior is entirely analogous to that of dimethylformamide[7a,b] (T_c = 148.5° at 60 Mc.),[7c] dimethylacetamide (T_c = 87.2°), other dimethylamides[7c] and alkyl nitrites, nitrosamines, etc.[7d,e] Our spectra are similar to these published examples. The energy of activation (E_a) for this rotation about the partial C–N double bond of dimethylformamide has been variously determined as 7 ± 3,[7a] 9.6 ± 1.5,[7b] or 18.3 ± 0.7 kcal./mole.[7c] Determination of this activation energy for II requires more precise control of temperature and usually larger chemical shifts (8 and 3 c.p.s. for the peak separation and half-band width, respectively, at 25° and 56.4 Mc.) than were available to us. Relatively few N,N-disubstituted vinylogous amides have been investigated by n.m.r. techniques,[8] and hindered rotation apparently has not been reported in such systems.[8-10]

The twin peaks for the N-methyl resonances in II and III result from delocalization of the free pair of electrons of the dimethylamino moiety throughout the vinylogous amides. Since our work was completed two N-methyl signals have been observed (ref. 5b) for iii which may be attributed to restricted rotation. Many vinylogous amides exist as chelated ketamines (iv) (ref. 9) wherein one configuration is stabilized by strong hydrogen bonding.



i ii iii iv

(1) C. F. Howell, N. Q. Quinones, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 1679, 1686 (1962).

(2) W. Traube and R. Ascher, *Ber.*, **46**, 2077 (1913).

(3) (a) H. Najer, R. Giudicelli, E. Joannic-Voisinet, and M. Joannic, *Bull. soc. chim. France*, 1226 (1961); (b) H. Najer and R. Giudicelli, *ibid.*, 1231 (1961).

(4) (a) H. Najer, R. Giudicelli, J. Menin, and J. Loiseau, *Compt. rend.*, **254**, 2173, 2591 (1962); (b) *Bull. soc. chim., France*, 1186 (1962); (c) 328 (1963).

(5) (a) See A. R. Katritzky, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 223 (1962), for a review of some applications of n.m.r. to problems in heterocyclic chemistry; (b) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 3046 (1963).

(6) However, M. A. Weinberger and R. Greenhalgh [*Can. J. Chem.*, **41**, 1038 (1963)] have described the coupling of the methyl group of 2-methyl-2-oxazoline with the 4-methylene moiety (J = 1.3 c.p.s.).

(7) (a) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); (b) G. Fraenkel and C. Franconi, *J. Am. Chem. Soc.*, **82**, 4478 (1960); (c) M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962); (d) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958); (e) W. D. Phillips, "Determination of Organic Structures by Physical Methods," Vol. II, F. C. Nachod and W. D. Phillips, Ed., Academic Press, New York, N. Y., 1962, p. 437 ff.

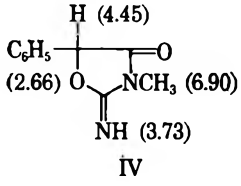
(8) G. N. Walker, *J. Org. Chem.*, **27**, 4227 (1962).

(9) (a) G. O. Dudeck and R. H. Holm, *J. Am. Chem. Soc.*, **83**, 2099, 3914 (1961); (b) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

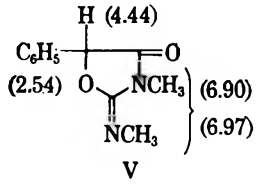
(10) However, Katritzky (ref. 5) has described the *cis* and *trans* forms (i and ii) of an aminopyrimidone cation which may be regarded as protonated

π-system. This restricts rotation about the bond from C-2 to the dimethylamino substituent and places the two methyl groups in different magnetic environments (near O and near N) as shown, while the amino nitrogen atom acquires a degree of planar (sp^2) character.

The proton resonances in IV and V are similar to those in II and III. The similarity of the N-methyl



IV

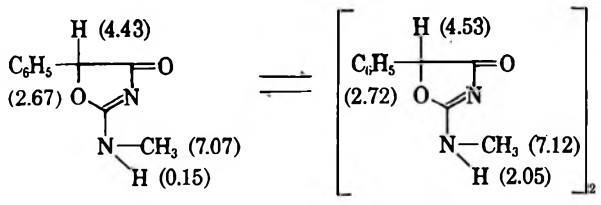


V

resonances suggests that the magnetic environments near N-3 and the 2-amino and 2-imino groups are similar. Compound V appears to exist in only one of the two possible *cis* and *trans* forms or the chemical shifts of the *cis*- and *trans*-N-methyl groups are indistinguishable.

The n.m.r. spectrum of a 13 mole % solution of VI in deuteriochloroform at room temperature was also unexpectedly complex (see Fig. 1, curve A). All the expected resonances appeared as pairs of peaks in a ratio of about 9:7.5 for each signal except for the N-methyl resonance at *ca.* τ 7.1 which is too broad for useful interpretation. Several alternative explanations of this behavior were discarded before the concentration dependence of these ratios was established. It seemed possible that a mixture of tautomeric forms like Ia and Ib might be involved. This interpretation was discarded when it was found that acetonitrile solutions of VI, which also exhibited doubled n.m.r. resonances, had essentially the same extinction coefficient in the ultraviolet spectrum [λ_{max} 223 mμ (ϵ 29,000)] as in methanol [λ_{max} 221 mμ (ϵ 27,800)].[1] In II, with a similar extinction coefficient, this type of tautomerism is impossible. Compound VI has been found to exist in two crystalline forms (one recrystallized from water, the other from ethyl acetate) which have different infrared spectra as solids (potassium bromide).[1] However, solutions of these forms had identical infrared, ultraviolet, and n.m.r. spectra.

The observed behavior is concentration dependent and is explained by the equilibrium formation of a dimer[11] in chloroform (or acetonitrile) solutions in



VIa (monomer) VIb (dimer)

which the lifetime of the dimer is sufficiently long (about 1.5×10^{-3} sec.)[12] and the chemical shifts are slightly different for monomer and dimer.

Magnetic shielding by the π-electrons[13a] in VI is

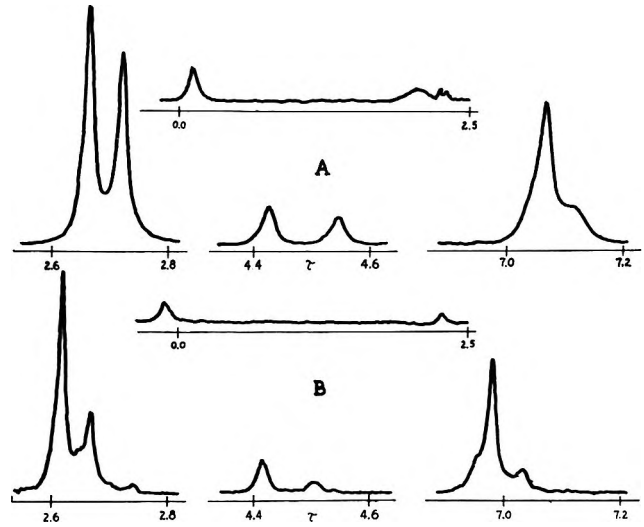


Fig. 1.—N.m.r. spectra of 2-methylamino-5-phenyl-2-oxazolin-4-one (VI) in deuteriochloroform: curve A, 13 mole %; curve B, 2.5 mole %.

responsible both for the relative positions of signals from VIa and VIb and for the general downfield shifts upon dilution. The π-systems effectively contribute more shielding in the dimer than in the monomer so that the dimer resonances appear at higher fields. In more dilute solutions all the signals appear at lower fields because there is less shielding by the reduced concentration of π-systems in the solution. The signals at τ 2.25 in Fig. 1 (curves A and B) appear to be spinning satellites of the aromatic signal and result from field inhomogeneity.[13a] Broad N–H resonances are centered at τ 0.15 and 2.05. Assignment of the τ 2.05 signal to the hydrogen-bonded NH of the dimer is necessitated by its virtual disappearance upon dilution even though hydrogen-bonded protons are usually shifted to lower fields,[9] *e.g.*, in aliphatic amines.[14] The N–H signals of associated pyrrole[15a] and porphyrins,[15b] however, shift to higher fields in more concentrated solutions.

The ratios of the integrated intensities of the two signals from the proton at C-5 (better separated than the other sharp pairs) in the monomer and the dimer are presented in Table I. From these values an association constant (k_2) of 0.3 l./mole was estimated.

TABLE I

DIMERIZATION OF 2-METHYLAMINO-5-PHENYL-2-OXAZOLIN-4-ONE (VI)

Mole % of VI	Ratio of dimer/monomer signals	k_2,[a] l./mole
2.6	0.22	0.37
4.8	0.37	0.29
7.7	0.43	0.26
12.7	0.83	0.34

[a] Association constant estimated on the assumption that dissolving VI in deuteriochloroform does not affect the volume.

(11) The "monomer" may also be hydrogen bonded to the solvent deuteriochloroform. Evidence (infrared) has been presented by C. M. Huggins and G. C. Pimentel [*J. Chem. Phys.*, **23**, 896 (1955)] for such association between N-ethylacetamide and deuteriochloroform.

(12) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 5126 (1956); **80**, 5203 (1958).

(13) (a) 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; (b) several hydrogen-bonded systems are reviewed (ref. 13a) where exchange is slow enough to produce nonaveraged n.m.r. signals, *e.g.*, ethanol and water in the absence of acid (p. 418), acetyl acetone and acetic acid (p. 439), and alkylammonium ions and aqueous acid (p. 454).

(14) J. Feeney and L. H. Sutcliffe, *J. Chem. Soc.*, 1123 (1962).

(15) (a) J. A. Happe, *J. Phys. Chem.*, **66**, 72 (1961); (b) R. J. Abraham, P. A. Burbidge, A. H. Jackson, and G. W. Kenner, *Proc. Chem. Soc.*, 134 (1963).

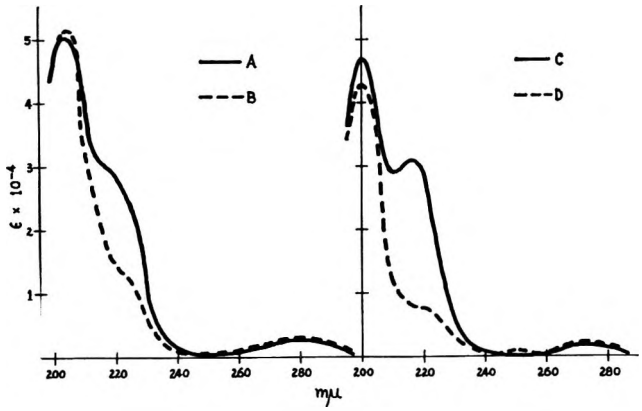
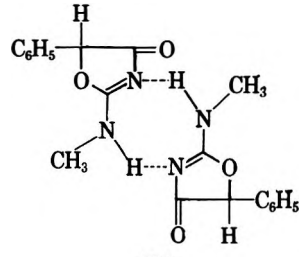


Fig. 2.—Ultraviolet spectra (in methanol) of A, 2-amino-5-(2,3-dimethoxyphenyl)-2-oxazolin-4-one (VIIIa); B, 5-(2,3-dimethoxyphenyl)-2-imino-3-methyl-4-oxazolidinone (IX); C, equimolar mixture of 2,3-dimethoxybenzyl alcohol and 2-amino-2-oxazolin-4-one; and D, 2,3-dimethoxybenzyl alcohol.

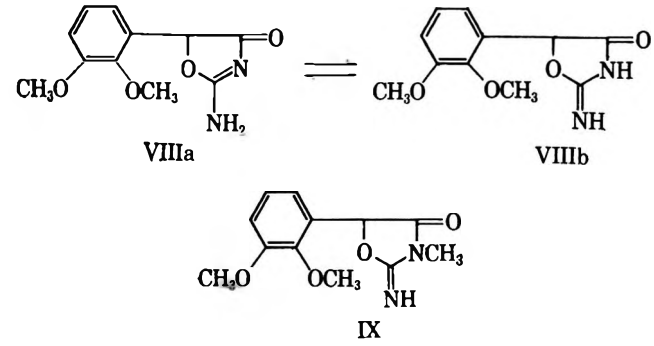
The signals from the dimer increased on cooling from +30° to −43° and disappeared when the temperature was raised from 53° to 77°. Only the relative intensity of the pairs of signals was affected rather than their shapes and positions as in II and III and is consistent with an exothermic dimerization.

The infrared spectra of chloroform solutions of VI are also concentration dependent and entirely parallel the n.m.r. spectra. Absorption at 2.9 (nonbonded N–H)[16] and 7.25 μ is more intense in dilute solutions and is associated with monomeric[12] VIa while bands at 3.4 (bonded N–H)[16] and 7.1 μ are associated with the dimer VIb. The intensities of bands due to bonded and nonbonded N–H stretching in aminopyridines have been studied[17] and used to calculate an association constant for 2-aminopyridine of *ca.* 0.1 l./mole in chloroform. By analogy to this association dimer of 2-aminopyridine,[17] the dimer of VI, an amphoteric compound, may be depicted as VII.



VII

The ultraviolet spectrum of VIIIa was recently reported[4a,b] and absorption at 206 mμ (ε 44,600) was interpreted to indicate a preponderance of VIIIb since derivatives of 2-imino-4-oxazolidinone absorb near this wave length.[1,4] The spectra in Fig. 2 indicate that most of the absorption at *ca.* 206 mμ results from a chromophore similar to 2,3-dimethoxybenzyl alcohol.[18] Although this chromophore is obviously not identical with the aromatic chromophore in VIII, the spectrum of an equimolar mixture of the alcohol and 2-amino-2-oxazolin-4-one[2] closely resembles that of VIII, particularly near 218 mμ where other 2-amino-2-oxazolin-4-ones absorb.[1] In contrast, the spectrum of the 2-imino compound IX (prepared from VIII and methyl iodide in dimethylformamide and characterized by hydrolysis to 5-(2,3-dimethoxyphenyl)-3-methyl-2,4-oxazolidinedione) is significantly different in this region. While these results cannot exclude the presence of small amounts of VIIIb, VIIIa appears to be the predominant tautomer.[1,4] The published spectrum[4] of 5-(3,4-dimethoxyphenyl)-2-amino-2-oxazolin-4-one suggests that it also exists predominantly as the 2-amino tautomer in ethanol.



VIIIa VIIIb

IX

Experimental

General.—N.m.r. spectra were determined with a Varian A-60 instrument operating at 60 Mc. except for the temperature dependence studies where a Varian HR-60 instrument operating at 56.4 Mc. was employed. Chemical shift values are relative to a tetramethylsilane internal standard.[19] Ultraviolet spectra were determined using a Cary Model 14 spectrophotometer, except that of IX where a Cary Model 11 was used. Melting points are uncorrected. The preparations of II, IV, V, VI,[1] and VIII[3a] have been described previously.

2-Dimethylamino-2-oxazolin-4-one (III).—A solution of 25 ml. (0.25 mole) of ethyl glycolate (Eastman, technical) in 300 ml. of benzene was distilled until 50 ml. of distillate was collected. The residual solution was cooled and treated with 1.8 g. of 50% sodium hydride–mineral oil dispersion followed by 20 ml. (0.25 mole) of dimethylcyanamide and refluxed for 3 hr.[1] The mixture was stored at room temperature for 60 hr., clarified by filtration, and concentrated to about 30 ml. Cooling gave 12.1 g. (38%) of colorless 2-dimethylamino-2-oxazolin-4-one, m.p. 107–109°. A sample for analysis was sublimed *in vacuo* and had m.p. 108.5–110.5°, λ_{max}^{MeOH} 227 mμ (ε 27,000).

Anal. Calcd. for $C_5H_8N_2O_2$: C, 46.85; H, 6.30; N, 21.87. Found: C, 47.15; H, 6.18; N, 21.59.

5-(2,3-Dimethoxyphenyl)-2-imino-3-methyl-4-oxazolidinone (IX).—A solution of 4.1 g. (0.017 mole) of 2-amino-5-(2,3-dimethoxyphenyl)-2-oxazolin-4-one[3a] in 17 ml. of freshly opened dimethylformamide was treated with 7.2 ml. of methyl iodide and stored in the dark at room temperature for 7 days.[1] The dark solution was then treated with 1.5 g. of sodium bicarbonate and concentrated under reduced pressure. The residue was suspended in 80 ml. of methylene chloride and then was filtered. The residue was washed with two more 25-ml. portions of methylene chloride. The combined solutions were extracted with 25 ml. of 0.1 *N* sodium thiosulfate, cooled, washed with 17 ml. of ice-cold 1 *N* sodium hydroxide, and dried over sodium sulfate. Concentration yielded an oil that resisted crystallization. This material was dissolved in 17 ml. of cold benzene and extracted with two 17-ml. portions of ice-cold 10% hydrochloric acid which were added at once to excess solid potassium carbonate. The product was extracted into methylene chloride and dried over sodium sulfate. Concentration yielded 1.2 g. (28%) of 5-(2,3-dimethoxyphenyl)-2-imino-3-methyl-4-oxazolidinone, m.p. 88–92°. A sample sublimed with the aid of a mercury diffusion pump had m.p. 94–96° and infrared absorption at 2.9 (sharp, =NH), 5.65, 5.75 and 5.9 μ.

(16) L. J. Bellamy ["The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958, p. 205] gives 2.9 and 3.0–3.25 μ for nonbonded and bonded N–H stretching of secondary amines.

(17) K. V. Ramiah and P. G. Puranik, *J. Mol. Spectry.*, **7**, 89 (1961).

(18) J. H. Burckhalter and S. H. Johnson, Jr., *J. Am. Chem. Soc.*, **73**, 4832 (1951).

(19) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.38; H, 5.82; N, 10.83.

5-(2,3-Dimethoxyphenyl)-3-methyl-2,4-oxazolidinedione. A.—The benzene solution from the preceding reaction, which had been washed with hydrochloric acid, was concentrated and the solid residue was recrystallized from benzene–cyclohexane to give 1.5 g. (34%) of 5-(2,3-dimethoxyphenyl)-3-methyl-2,4-oxazolidinedione, m.p. 92–95°. A sample for analysis was recrystallized and dried *in vacuo* over phosphorus pentoxide and had m.p. 95–96° and infrared absorption at 5.5 and 5.75 μ.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 57.35; H, 5.22; N, 5.58. Found: C, 57.10; H, 5.16; N, 5.35.

B.—Hydrolysis of 62 mg. of IX in 0.6 ml. of 10% hydrochloric acid at 90–100° for 10 min. gave 57 mg. (91%) of 5-(2,3-dimethoxyphenyl)-3-methyl-2,4-oxazolidinedione, m.p. 95.5–97°, with the characteristic infrared spectrum.

Acknowledgment.—We wish to thank G. Morton, L. Brancone, and Dr. J. E. Lancaster for generous assistance with spectral studies, microanalyses, and n.m.r. spectra at elevated temperatures, respectively. Our thanks also are extended to Dr. M. G. Howell for many helpful discussions and for assistance with the technical literature. Appreciation is extended to Dr. H. Najer (Labs Dausse, Paris) for reference samples of IX and 5-(3,4-dimethoxyphenyl)-2-amino-2-oxazolin-4-one.

2-Vinyloxazolidines and 2-Methylenemorpholines from N-Propargylethanolamines and N-(2-Haloallyl)ethanolamines[1]

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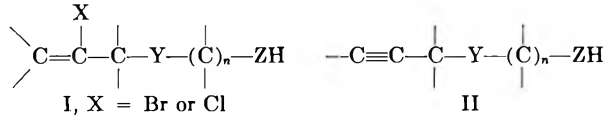
Received August 9, 1963

An N-alkyl-N-propargylethanolamine (III), as the alkoxide in ether, or on treatment with sodium hydroxide in dimethyl sulfoxide, or on treatment with potassium hydroxide in toluene or xylene, is converted to the corresponding 3-alkyl-2-vinyloxazolidine (VII). On treatment with aqueous sodium hydroxide, III is converted to the corresponding 4-alkyl-2-methylenemorpholine (VIII). Formation of VII is best understood as occurring *via* an intramolecular nucleophilic addition at C-1 of the allene moiety of the allenic amino alcohol (VI) formed by base-induced prototropic rearrangement of III. That an allenic amino alcohol is not an intermediate in the reaction leading to a 2-methylenemorpholine has been shown by tracer experiments. Treatment of an N-alkyl-N-(2-chloroallyl)ethanolamine (V) with an equivalent amount of sodium amide in ether gave the corresponding VII, but similar treatment of a 2-bromoallyl analog of V gave only the corresponding N-alkyl-N-propargylethanolamine (III).

Formation of an N-alkylallenimine (1-alkyl-2-methyleneaziridine) by the reaction of an N-(2-bromoallyl)-alkylamine with sodium amide in liquid ammonia occurs predominantly, if not exclusively, *via* an intramolecular nucleophilic addition to the central carbon of an intermediate allenic amine.[2] Another reaction that can be best interpreted as occurring by an intramolecular nucleophilic addition to an allenic amine intermediate is that of an N-propargylethanolamine with potassium hydroxide in boiling toluene or xylene.[3] The product is the 2-vinyloxazolidine, and nucleophilic addition occurs at C-1 of the allene moiety of the allenic amino alcohol, which can arise from the N-propargylethanolamine by base-induced prototropic rearrangement.[4] Substituted N-propargylethanolamines, which contain no propargylic hydrogens, were found recently to undergo cyclization to 2-methylenemorpholines when treated with potassium hydroxide in boiling toluene or xylene.[5]

The work described here was undertaken to determine the range of conditions under which N-(2-haloallyl)-ethanolamines and N-propargylethanolamines could be converted conveniently to cyclic products by treatment with base and, where practical, to learn the detailed mechanisms by which the products are formed. A large number of base-induced ring-closure reactions of suitably constituted 2-haloallyl and propargyl compounds, which are represented generally by I and II, are conceivable,[6] and the results reported here have already proved of value in further studies in these laboratories directed toward determining the scope and limitations of ring-closure reactions of compounds represented by I and II.



I, X = Br or Cl II

The reaction in liquid ammonia of N-(2-bromoallyl)-2-hydroxy-3-butenylamine with 2.1 equiv. of sodium amide gives a yield of the corresponding allenimine[7] that is comparable with yields obtained

(1) (a) Part VI. Amines Derived from Dihalopropenes; (b) previous paper in the series, A. T. Bottini, B. J. King, and R. E. Olsen, *J. Org. Chem.*, **28**, 3241 (1963); (c) presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963. This work was supported by Grant CA-05528 from the National Cancer Institute and Grant GM-10606 from the Division of General Medicine of the Public Health Service.

(2) A. T. Bottini and R. E. Olsen, *J. Am. Chem. Soc.*, **84**, 195 (1962).

(3) (a) W. J. Croxall and J. H. Mellema, U. S. Patent 2,960,508 (November 15, 1960); *Chem. Abstr.*, **55**, 14482 (1961); (b) see also W. J. Croxall, N. D. Dawson, P. D. Arseneau, J. H. Mellema, and J. Mirza, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960, p. 77P.

(4) A significant paper concerning prototropic rearrangements of acetylenes is by T. L. Jacobs, R. Akawie, and R. G. Cooper, *J. Am. Chem. Soc.*, **73**, 1273 (1951).

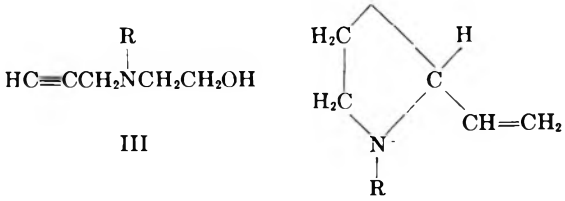
(5) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **28**, 448 (1963).

(6) Some recent examples of base-induced ring-closure reactions of 2-chloroallyl and propargyl compounds other than those already mentioned are given by W. J. Croxall and N. D. Dawson, U. S. Patent 3,021,341 (February 13, 1962); *Chem. Abstr.*, **57**, 11,205 (1962); K. Sisido, K. Hukuoka, M. Tuda, and K. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962); N. R. Easton, D. R. Cassady, and R. D. Dillard, *ibid.*, **27**, 2927 (1962); E. Kaiser, E. Domba, and M. Skibbe, *ibid.*, **27**, 2931 (1962); N. Shachat and J. J. Bagnell, Jr., *ibid.*, **28**, 991 (1963); and W. J. Croxall and N. D. Dawson, U. S. Patent 3,048,598 (August 7, 1962); *Chem. Abstr.*, **59**, 2828 (1963). See also I. Iwai, *Takamine Kenkyusho Nempo*, **14**, 1 (1962), and references cited therein to recent Japanese work.

(7) A. T. Bottini and V. Dev, *J. Org. Chem.*, **27**, 968 (1962).

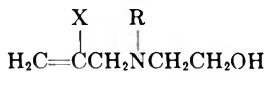
from simple N-(2-bromoallyl)alkylamines under optimum conditions for allenimine formation.[1b,8] Although the allenic amino alcohol, $CH_2{=}C{=}CHNHCH_2CHOHCH{=}CH_2$, an intermediate in the reaction leading to the allenimine, could conceivably undergo a ring-closure reaction in which a new carbon–oxygen bond is formed, no compound with an oxygen-containing ring was detected as a product.

As allenimine formation could be prevented by the simple expedient of replacing the amino hydrogen with an alkyl group, we treated N-ethyl-N-(2-bromoallyl)-ethanolamine (IVb) with an excess of sodium amide in liquid ammonia in order to determine if detectable quantities of an oxygen-containing ring compound could be formed from an N-(2-bromoallyl)ethanolamine under conditions similar to those used for preparation of an allenimine. When ether was added to the reaction mixture together with a small amount of water that was insufficient to convert all the excess base to sodium hydroxide, distillation of the ethereal solution gave in 10% yield an acrid liquid that was identified as 3-ethyl-2-vinyloxazolidine (VIIb). When excess water or ammonium chloride was added to the reaction mixture together with the ether, the only product isolated was N-ethyl-N-propargylethanolamine (IIIb), and yields were 78% and 88%, respectively. We concluded that little if any VIIb was formed in liquid ammonia from IVb[9] and that the ring-closure reaction occurred in ether. The latter conclusion was verified by the observation that N-ethyl-N-propargylethanolamine (IIIb) as the alkoxide in ether was converted in 40 hr. at room temperature to 3-ethyl-2-vinyloxazolidine (VIIb) in 21% yield.

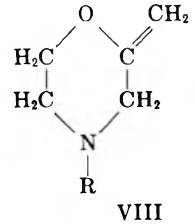


III

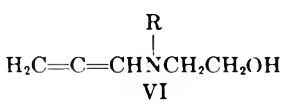
VII



IV, X = Br; V, X = Cl



VIII



VI

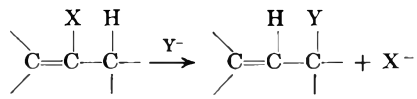
a, R = CH_3
b, R = C_2H_5
c, R = t-C_4H_9

Other 3-alkyl-2-vinyloxazolidines were prepared by treatment of the corresponding N-alkyl-N-propargylethanolamines with an equivalent of sodium amide in ether, and we have used this method to prepare a number of 3,5-dialkyl-2-vinyloxazolidines.[10] Yields, however, ranged from 13–35%, and the general utility of the method appears to be inferior to that used by Croxall and Mellema.[3]

We examined the reactions of the alkoxides of the N-t-butyl-N-(2-haloallyl)ethanolamines in ether in order to determine if cyclic products could be obtained directly from these compounds and, if so, if the mode of cyclization would be the same as observed for the corresponding propargyl compounds. N-t-Butyl-N-(2-chloroallyl)ethanolamine (Vc), on treatment with an equivalent amount of sodium amide in ether, gave after 40 hr. 3-t-butyl-2-vinyloxazolidine (VIIc) in 52% yield. Similar treatment of N-t-butyl-N-(2-bromoallyl)ethanolamine (IVc) gave only the corresponding propargylamino alcohol in 65% yield. These results are consistent with the interpretation that dehydrobromination of IVc occurs much more rapidly than dehydrochlorination of Vc and that oxazolidine formation occurs at about the same rate as the dehydrochlorination reaction. No detectable amount of VIIc is formed from Vc because the base necessary for prototropic rearrangement of N-t-butyl-N-propargylethanolamine (IIIc) has been destroyed during the rapid dehydrobromination reaction. Although the foregoing results show that dehydrobromination of IVc occurs exclusively across the double bond, they do not necessarily show that N-t-butyl-N-(2-chloroallyl)ethanolamine (Vc) dehydrohalogenates in the same way. Conceivably Vc can undergo dehydrochlorination directly to the intermediate allenic amino alcohol by either a concerted or stepwise process.

3-Methyl- and 3-ethyl-2-vinyloxazolidine (VIIa and VIIb) also were prepared from the corresponding N-(2-chloroallyl)ethanolamines, but the yields were less than 15%. In contrast, N-t-butyl-N-(2-chloroallyl)-1-amino-2-methyl-2-propanol, on treatment with a 28% excess of sodium amide in ether, gave a 51% yield of 3-t-butyl-5,5-dimethyl-2-vinyloxazolidine (IX).

We wish to note that formation of a 2-vinyloxazolidine from an N-(2-chloroallyl)ethanolamine appears to be the first example of a nucleophilic displacement reaction of the following type.



In the reaction, the nucleophile becomes bonded to the allylic carbon of the starting material which was adjacent to the vinylic carbon bonded to the leaving group.

We examined the ring-closure reactions of N-alkyl-N-propargylethanolamines (III) induced by sodium hydroxide in dimethyl sulfoxide at 70–90° and in water at 100°. The only products obtained from reactions of III carried out in dimethyl sulfoxide were the corresponding 3-alkyl-2-vinyloxazolidines (VII). Although the yields, which ranged from 36–58%, were higher than those obtained from reactions carried out in ether, they were less than those obtained by Croxall and Mellema.[3] In water, the sodium hydroxide-in-

(8) C. B. Pollard and R. F. Parcell, *J. Am. Chem. Soc.*, **73**, 2925 (1951).

(9) Failure to obtain a significant amount of VIIb from IVb in liquid ammonia does not allow one to conclude that little or no allenic amino alcohol (VIb) is formed during the reaction. Conceivably, under the particular reaction conditions, ring-closure reactions of the alkoxide of VIb are quite slow and do not compete successfully with rearrangement to the alkoxide of IIIb. J. J. Van Dealen, A. Kraak, and J. F. Arens, *Rec. trav. chim.*, **80**, 810 (1961), have observed that 1-t-butoxypropyne is isomerized to 3-t-butoxypropyne by sodamide in liquid ammonia, presumably *via* an allenic ether intermediate.

(10) We currently are examining the nature and degree of stereospecificity in the formation of 3,5-dialkyl-2-vinyloxazolidines from N-propargylalkanolamines. The diastereomers of 3-t-butyl-5-methyl-2-vinyloxazolidine appear to be formed in the ratio 3:2 as indicated by gas–liquid partition chromatography

TABLE I

YIELDS, PHYSICAL PROPERTIES, AND ANALYTICAL DATA OF UNSATURATED AMINO ALCOHOLS, 2-VINYLOXAZOLIDINES, AND 2-METHYLENEMORPHOLINES

Compound	R	Yield, %	B.p. (mm.), °C.	n_D	Temp., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
III	CH_3	42[h]	62–65 (10)	1.4673	24	63.68	9.80	12.38	63.64	9.98	12.16
III	C_2H_5	60[i]	59–61 (3)	1.4660	25	66.11	10.30	11.02	65.99	10.12	10.94
III	t-C_4H_9	51[h]	93–95 (10)	1.4677	24	69.63	11.03	9.02	69.52	11.08	9.21
IV	CH_3	52[i]	80–84 (15)	1.4951	25	37.13	6.23	7.22	37.31	6.25	7.31
IV	C_2H_5	40[i]	82–86 (4)	1.4886	25	40.40	6.78	6.73	40.66	6.78	6.32
IV	t-C_4H_9	74[h]	113 (10)	1.4908	22	45.97	7.71	5.96	45.63	7.41	5.87
V	CH_3	69[h]	85–90 (16)	1.4746	21	48.16	8.08	9.36	48.28	7.89	9.10
V	C_2H_5	58[i]	67–68 (2)	1.4700	25	51.37	8.62	8.56	51.39	8.30	8.39
V	t-C_4H_9	51[h]	84–85 (2)	1.4726	22	56.39	9.46	7.31	56.60	9.32	7.31
VII	CH_3	32[j]	36–38 (41)	1.4450	22	63.68	9.80	12.38	63.32	9.60	12.43
VII	C_2H_5	21[j]	52–53 (18)	1.4450	26	66.11	10.30	11.02	66.53	10.53	10.69
VII	t-C_4H_9	52[k]	70–73 (15)	1.4520	23	69.63	11.03	9.02	69.45	10.95	9.21
VIII	CH_3	39	46–48 (22)	1.4592	25	63.68	9.80	12.38	63.60	9.68	12.46
VIII	C_2H_5	48	44–46 (9)	1.4596	25	66.11	10.30	11.02	65.86	10.12	11.04
VIII	t-C_4H_9	65	75–77 (14)	1.4612	25	69.63	11.03	9.02	69.79	11.40	8.89
IX	t-C_4H_9	48[k]	73–75 (18)	1.4471	23	72.08	11.54		71.70	11.34	
XIV[a]	CH_3	86[h]	58 (10)	1.4534	24	66.11	10.30	11.02	65.92	10.39	10.90
XIV[a]	C_2H_5	71[l]	63–64 (6)	1.4510	26	68.05	10.70	9.92	68.11	10.57	10.06
XIV[a]	i-C_3H_7	72[k]	74–76 (6)	1.4550	20	69.63	11.03	9.02	69.81	10.81	8.91
XIV[a]	t-C_4H_9	61[i]	102–105 (19)	1.4579	22	70.96	11.31	8.28	71.09	11.26	8.30
XV[b]	CH_3	69[i]	91 (10)	1.4807	26	40.40	6.78	6.73	40.72	6.70	6.56
XV[b]	C_2H_5	74[i]	91 (10)	1.4800	25	43.25	7.26	6.30	43.27	7.22	6.17
XV[b]	i-C_3H_7	72[i]	60 (1)	1.4787	25	45.97	7.71		45.70	7.46	
XV[b]	t-C_4H_9	62[h]	115 (11)	1.4850	25			5.60			6.09
XVI[c]	CH_3	72[i]	65–67 (4)	1.4593	27	51.37	8.62	8.56	51.59	8.57	8.52
XVI[c]	t-C_4H_9	61[h]	95–97 (7)	1.4658	28	58.38	9.80	6.81	58.51	9.82	6.77
XVII[d]	t-C_4H_9	77[h]	85–87 (9)	1.4597	19	72.08	11.54	7.64	71.98	11.25	7.78
XVIII[e]	t-C_4H_9	37[h]	100–108 (10)	1.4673	22	60.12	10.09	6.38	59.85	9.88	6.46
XIX[f]	CH_3	13[j]	45–48 (10)	1.4351	26	66.11	10.30	11.02	65.95	10.39	10.85
XIX[f]	C_2H_5	14[j]	67 (30)	1.4379	28	68.05	10.70	9.92	67.86	10.51	9.61
XIX[f]	i-C_3H_7	6[j]	30 (3)	1.4418	28			9.02			8.64
XIX[f]	t-C_4H_9	54[m]	68–70 (13)	1.4464	23	70.96	11.31	8.28	71.10	11.09	8.41
XX[g]	CH_3	47	58 (42)	1.4518	26	66.11	10.30	11.02	65.92	10.53	11.12

[a] XIV is N-alkyl-N-propargyl-1-amino-2-propanol. [b] XV is N-alkyl-N-(2-bromoallyl)-1-amino-2-propanol. [c] XVI is N-alkyl-N-(2-chloroallyl)-1-amino-2-propanol. [d] XVII is N-t-butyl-N-propargyl-1-amino-2-methyl-2-propanol. [e] XVIII is N-t-butyl-N-(2-chloroallyl)-1-amino-2-methyl-2-propanol. [f] XIX is 3-alkyl-5-methyl-2-vinyloxazolidine. [g] XX is 4,6-dimethyl-2-methylenemorpholine. [h] From unsaturated halide and amino alcohol. [i] From unsaturated amine and oxirane. [j] From propargylamino alcohol in ether. [k] From 2-chloroallylamino alcohol in ether. [l] From dehydrobromination of XII, R = C_2H_5. [m] From XI, R = t-C_4H_9, in dimethyl sulfoxide.

duced reaction of N-alkyl-N-propargylethanolamines (III) took a different course, and the reactions gave the corresponding 4-alkyl-2-methylenemorpholines (VIII). Several 4-alkyl-2-methylenemorpholines were prepared in yields ranging from 45–67%, and conversions ranged from 39–56%.

Tentative assignment of the 4-alkyl-2-methylenemorpholine (VIII) structure to the products obtained from aqueous media was made on the basis of their infrared and n.m.r. spectra. The infrared spectrum of each VIII possessed an intense band at 1660 cm.$^{-1}$, which indicated the presence of a polar carbon–carbon double bond[11] and an intense band at 835–845 cm.$^{-1}$, which we could assign to the exocyclic methylene group. The n.m.r. spectrum of neat 4-methyl-2-methylenemorpholine (VIIIa), which has the bands common to other 4-alkyl-2-methylenemorpholines, consists of singlets at τ 5.57 and 5.79,[12] which are assigned to the exocyclic methylene protons, apparent triplets with J = 4.8 c.p.s. at τ 6.01 and 7.44, which are assigned to the C-6 and C-5 protons, respectively, and singlets at τ 6.99 and 7.63 which are assigned to the C-3 and N-methyl protons, respectively. The resonance frequencies and relative intensities of the bands are consistent with the 4-methyl-2-methylenemorpholine structure and are inconsistent with those expected for the isomeric 2,4-dimethyl-5,6-dihydro-1,4-oxazine. The skeletal structure of the 2-methylenemorpholines was established by hydrogenation of 4-ethyl-2-methylenemorpholine (VIIIb) to 4-ethyl-2-methylmorpholine (X), which was indistinguishable from X prepared from N-ethyl-N-(2-hydroxypropyl)ethanolamine by Médard's procedure.[13]

We interpret the difference in products obtained from N-alkyl-N-propargylethanolamines (III) on treatment with sodium hydroxide in dimethyl sulfoxide and in water as due to the difference in rates of prototropic rearrangement in the two solvents.[14] Prototropic rearrangement of III to the corresponding allenic amino alcohol (VI), which then rapidly cyclizes to the 2-vinyloxazolidine (VII), apparently occurs rapidly

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, Chapter 3.

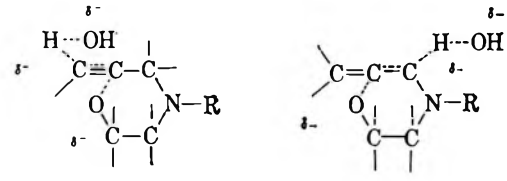
(12) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(13) L. Médard, *Bull. soc. chim. France*, [5] **3**, 1338 (1936).

(14) Examples of the dependence of rates of prototropic rearrangements on solvent are given by C. C. Price and W. H. Snyder, *J. Am. Chem. Soc.*, **83**, 1773 (1961); see also C. C. Price and W. H. Snyder, *J. Org. Chem.*, **27**, 4639 (1962).

enough in dimethyl sulfoxide to overshadow completely the competing ring-closure reaction of III to the 2-methylenemorpholine (VIII). Direct cyclization of III to VIII in dimethyl sulfoxide appeared conceivable because the alkoxide of III can be expected to exhibit enhanced basicity and nucleophilicity in dimethyl sulfoxide.[15] In water, rearrangement of III to VI apparently occurs sufficiently slowly so that the formation of VIII by nucleophilic addition of the alkoxide oxygen to acetylenic carbon can occur *via* a transition state represented by XI.[16]

We considered it necessary to obtain proof that the 4-alkyl-2-methylenemorpholines (VIII) were indeed formed by cyclization of the alkoxide of the corresponding III. Conceivably, formation of VIII could occur by cyclization through a transition state represented by XII of the allenic amino alcohol (VI) formed from III. Examples of reactions involving nucleophilic attack at the digonal carbon of a substituted allene are known,[2,17] and sodium hydroxide in dimethyl sulfoxide and in toluene (following) induces rearrangement of III to VI. Also, in this regard, a 3-alkyl-2-vinyloxazolidine (VIII) is destroyed within minutes when treated with aqueous sodium hydroxide under conditions used by us for the preparation of a 4-alkyl-2-methylenemorpholine (VIII). As material balances of only 70% or less were obtained in preparations of VIII, 30% or more of the N-alkyl-N-propargylethanolamine (III) used could have been converted to the corresponding VII *via* the allenic amino alcohol VI.



XI XII

In order to determine the mechanism of 2-methylenemorpholine formation, we prepared 4-methyl-2-methylenemorpholine (VIIIa) by treatment of N-methyl-N-propargylethanolamine (IIIa) with 3 *N* sodium deuterioxide in deuterium oxide and examined its n.m.r. spectrum. If the methylenemorpholine were formed by cyclization of the conjugate base of IIIa *via* a transition state represented by XI, no deuterium would be incorporated at C-3 of VIIIa. If the methylenemorpholine were formed by cyclization of the conjugate base of the allenic amino alcohol *via* a transition state represented by XII, one deuterium would be incorporated at C-3 of VIIIa. The n.m.r. spectra of deuterated and undeuterated VIIIa were indistinguishable except for the absence of bands due to the vinyl protons in the spectrum of deuterated VIIIa. Compound VIIIa and other 4-alkyl-2-methylenemorpholines also could be prepared from the corresponding N-alkyl-N-(2-bromoallyl)ethanolamines (IV). The VIIIa obtained by treatment of N-methyl-N-(2-bromoallyl)ethanolamine (IVa) with sodium deuterioxide in deuterium oxide had an n.m.r. spectrum identical with that of VIIIa obtained from similar treatment of IIIa. These results establish that an allenic amino alcohol is not involved significantly in the formation of a methylenemorpholine induced by aqueous sodium hydroxide at 100° and that the transition state leading to a methylenemorpholine is approximated by XI.

Reactions of several N-alkyl-N-propargyl-1-amino-2-propanols and N-alkyl-N-(2-bromoallyl)ethanolamines under conditions identical with those used for preparation of a 4-alkyl-2-methylenemorpholine (VII) gave conversions of only ~3–22% to the corresponding 2-methylenemorpholines. A propargylamino-2-propanol, a secondary alcohol, is a weaker acid than an N-propargylethanolamine, a primary alcohol. Therefore, on treatment with aqueous sodium hydroxide under identical conditions, the concentration of the conjugate base of a propargylamino-2-propanol is less than the concentration of the conjugate base of an N-propargylethanolamine. The presumed greater nucleophilicity of a secondary alkoxide as compared with that of a primary alkoxide is apparently insufficient to compensate for its lower concentration.

We found that treatment of N-*t*-butyl-N-propargylethanolamine (IIIc) with sodium hydroxide in refluxing toluene gave a 78% yield of a mixture consisting of 77% VIIc and 23% VIIIc. From a similar reaction using potassium hydroxide[3] instead of sodium hydroxide, the vinyloxazolidine (VIIc) was obtained free of 4-*t*-butyl-2-methylenemorpholine in over 80% yield. We examined the products obtained by treatment of several N-alkyl-N-propargylamino-2-propanols with sodium hydroxide in refluxing toluene, and these products were the corresponding 2-vinyloxazolidines containing less the 2% of the corresponding 2-methylenemorpholine.

We observed that 4-*t*-butyl-2-methylenemorpholine (VIIIc) is converted by treatment with potassium *t*-butoxide in ether to an unidentified, ether-insoluble material. Approximately 1 mole of potassium *t*-butoxide is required per mole of VIIIc, and the reaction occurs as fast or faster than the formation in ether of a 3-alkyl-2-vinyloxayolidine from either an N-alkyl-N-propargylethanolamine (III) or an N-alkyl-N-(2-chloroallyl)ethanolamine (V). This indicates that, if any VIII has been formed together with a 3-alkyl-2-vinyloxazolidine in ether in the presence of excess alkoxide, VIII would have been destroyed and not detected in the product.

We also treated VIIIc with sodium hydroxide in dimethyl sulfoxide and with potassium hydroxide in toluene under other conditions used by us for the preparation of 3-*t*-butyl-2-vinyloxazolidine (VIIc) from N-*t*-butyl-N-propargylethanolamine (IIIc). 4-*t*-Butyl-2-methylenemorpholine (VIIIc) was more stable under these conditions than in ether in the presence of potassium *t*-butoxide. The results of our control experiments indicated that, if more than 10% of the IIIc had been converted to VIIIc in toluene or dimethyl sulfoxide, the VIIIc would have been detected in the product. No VIIIc was detected in either of the products.

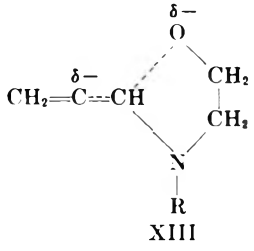
Interestingly, isolation of a 2-vinyloxazolidine in over 50% yield from reactions in dimethyl sulfoxide and toluene shows that the transition state leading to VII, which is represented by XIII, is of lower energy

(15) In this regard, see D. J. Cram, B. Rickborn, and G. R. Knox, *J. Am. Chem. Soc.*, **82**, 6412 (1960); and D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *ibid.*, **83**, 3678 (1961).

(16) A significant paper concerning the addition of an alkoxide to an acetylene is by S. I. Miller and G. Shkapenko, *ibid.*, **77**, 5038 (1955).

(17) A. N. Pudovik and I. M. Alajeva, *Zh. Obshch. Khim.* **33**, 708 (1963).

than the corresponding XII or analogous transition state that would lead to the 2-methyl-4-alkyl-5,6-dihydro-1,4-oxazine. Any electronic factors that might tend to make the transition states leading to six-membered ring products more stable than XIII are apparently more than counteracted by the lesser amount of angle strain in XIII.



XIII

Experimental

Boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-4 or a Beckman IR-5 spectrophotometer. N.m.r. spectra were obtained at 56.4 Mc. or 60 Mc. with a Varian Associates HR-60 system with samples contained in 5-mm. o.d. tubes. Resonance frequencies in n.m.r. spectra were determined relative to tetramethylsilane (TMS) using the side-band technique with a Packard OD-200 audiooscillator. Gas–liquid partition (g.l.p.) chromatograms were obtained using a 5-m. column that contained a packing of Carbowax 20M alkaline on firebrick in an Aerograph Model A-700 (Wilkens Instrument and Research, Inc., Walnut Creek, Calif.). Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif.

Unsaturated Amino Alcohols.—The N-alkyl-N-propargylalkanolamines and N-alkyl-N-(2-haloallyl)alkanolamines were prepared either by treatment of a propargyl halide or 2,3-dihalopropene with the corresponding N-alkylalkanolamine or by treatment of an N-alkylpropargylamine or N-(2-haloallyl)-alkylamine[1b,8] with the necessary oxirane. Procedures used for reactions of the unsaturated halides with N-alkylethanolamines were patterned after the procedure described for the preparation of (−)-N-(2-bromoallyl)-2-hydroxy-3-butenylamine.[7] Procedures used for reactions of unsaturated secondary amines with oxirane were patterned after a procedure described for the preparation of N-isopropylethanolamine.[18] A typical procedure for the preparation and isolation of an unsaturated amino alcohol from a substituted oxirane follows. To a cold stirred solution of 88 g. (0.69 mole) of N-*t*-butylpropargylamine and 50 ml. of 80% aqueous ethanol by volume contained in a 500-ml. round-bottomed flask equipped with a Dry Ice condenser charged with an ice–salt mixture was added dropwise 92 g. (1.6 moles) of propylene oxide. When the addition was complete, the reaction mixture was allowed to warm to room temperature, and it was heated at 50° for 16 hr. (Reaction times of >50 hr. were used for reactions of isobutylene oxide.) Distillation of the reaction mixture gave 78 g. (61%) of N-*t*-butyl-N-propargyl-1-amino-2-propanol, b.p. 102–105° (19 mm.), n^{23}D 1.4579. The yields, physical constants, and analytical data for all unsaturated amino alcohols, as well as 3-alkyl-2-vinyloxazolidines and 4-alkyl-2-methylenemorpholines, are given in Table I.

Attempted Ring-Closure Reaction of N-Ethyl-N-(2-bromoallyl)-ethanolamine (IVb) with Sodium Amide in Liquid Ammonia.—Compound IVb (52 g., 0.25 mole) was added dropwise to a stirred slurry of 35.1 g. (0.90 mole) of sodium amide and 2 l. of liquid ammonia. The mixture was stirred 4 hr., and 300 ml. of ether and 10 ml. (0.55 mole) of water were added cautiously with continued stirring. The ammonia was allowed to evaporate overnight. The ethereal solution was decanted from the reaction flask, and the residual material in the flask was washed three times with 100-ml. portions of ether. The ethereal solutions were combined, and most of the ether was removed by distillation through a 35 × 0.8 mm. column packed with glass helices. A yellow-orange precipitate with the consistency of ferric hydroxide separated from the ether solution during this distillation. The residue was distilled under vacuum in a nitrogen atmosphere through a semimicro Vigreux column, and two fractions were taken. The first fraction (3.3 g.) was an acrid colorless liquid, which had b.p. 52–53° (18 mm.), n^{21}D 1.4469, an elemental analysis, an infrared spectrum, and an n.m.r. spectrum that were compatible with the 3-ethyl-2-vinyloxazolidine (VIIb) structure, and were identical with VIIb obtained by the method of Croxall and Mellema.[3] The second fraction (3.4 g.) was a colorless, slightly viscous liquid, which had b.p. 52–53° (1 mm.), n^{25}D 1.4656, and was shown to be N-ethyl-N-propargylethanolamine (IIIb) by comparison with material prepared from N-propargylethylamine and ethylene oxide.

Compound IVb (52 g., 0.25 mole) was treated with 19.7 g. (0.51 mole) of sodium amide and 1 l. of liquid ammonia. After 3 hr., 250 ml. of ether and 22.1 g. (0.41 mole) of ammonium chloride were added to the mixture with continued stirring. The reaction mixture was worked up as described for the first run, and 28 g. (88%) of IIIb, n^{25}D 1.4650, was collected at 72–74° (6 mm.).

Compound IVb (52 g., 0.25 mole) was treated with 22 g. (0.56 mole) of sodium amide and 1 l. of liquid ammonia. After 5 hr., 100 ml. of ether and 18 ml. (1.0 mole) of water were added to the mixture with continued stirring. The reaction mixture was worked up as usual, and 24.6 g. (78%) of IIIb, n^{25}D 1.4667, was collected at 72–75° (6 mm.).

3-Alkyl-2-vinyloxazolidones. A. From N-Alkyl-N-propargylethanolamines and Sodium Amide in Ether.—A typical procedure follows. To a magnetically stirred slurry of 3.45 g. (0.088 mole) of sodium amide in 80 ml. of dry ether was added dropwise 10.0 g. (0.088 mole) of N-methyl-N-propargylethanolamine (IIIa) in 15 min. After the evolution of ammonia had slowed appreciably, the flask was stoppered with a cork containing an inverted capillary, and stirring was continued for 48 hr. The ether solution was decanted from a grey precipitate in the flask, and most of the ether was removed by distillation at atmospheric pressure. The residue was distilled under a pressure of 10 mm. of nitrogen, and 3.4 g. (34%) of 3-methyl-2-vinyloxazolidine (VIIa), n^{22}D 1.4455, was collected. Duplication of the prior procedure resulted in the isolation of 3.2 g. of VIIa, n^{22}D 1.4450. When 4.7 g. (0.088 mole) of ammonium chloride was added to the stirred reaction mixture after the 48-hr. reaction time, removal of the excess ammonium chloride and other solids by filtration and distillation of the ether solution gave 2.3 g. of VIIa, n^{21}D 1.4462. A duplication of this run gave 1.8 g. of VIIa, n^{22}D 1.4460. The infrared spectra of all samples of VIIa indicated that they were free of IIIa and 4-methyl-2-methylenemorpholine (VIIIa).

B. From N-Alkyl-N-(2-chloroallyl)ethanolamines and Sodium Amide in Ether.—The following procedure is typical. The mixture obtained by the addition of 10.0 g. (0.052 mole) of N-*t*-butyl-N-(2-chloroallyl)ethanolamine (Vc) to a stirred slurry of 2.04 g. (0.052 mole) of sodium amide and 80 ml. of dry ether was stirred at room temperature for 40 hr. The mixture was filtered, and most of the ether was removed from the filtrate by distillation. The residue was distilled under nitrogen, and 4.2 g. (52%) of 3-*t*-butyl-2-vinyloxazolidine (VIIc), n^{23}D 1.4250, was collected at 75–80° (15 mm.). The VIIc had an infrared spectrum and an n.m.r. spectrum that were identical with those of VIIc obtained in 83% yield by the method of Croxall and Mellema.[3]

Treatment of 10.0 g. (0.0424 mole) of N-*t*-butyl-N-(2-bromoallyl)ethanolamine (IVc) with 1.65 g. (0.0424 mole) of sodium amide in 80 ml. of dry ether gave 4.3 g. (65%) of light yellow N-*t*-butyl-N-propargylethanolamine (IIIc), $n^{22.5}$D 1.4693.

N-*t*-Butyl-N-(2-chloroallyl)-1-amino-2-methyl-2-propanol (8.4 g., 0.038 mole) was treated with 1.79 g. (0.046 mole) of sodium amide in 80 ml. of dry ether as described for IVc. The product was collected in two fractions: the first fraction (1.9 g.) had b.p. 73–75° (18 mm.), n^{23}D 1.4471, and the second fraction (1.7 g.) had b.p. 75–85° (18 mm.), n^{23}D 1.4508. Present in the infrared spectrum of each fraction was a band at 1740 cm.$^{-1}$, and the band was more intense in the spectrum of the second fraction. G.l.p. chromatograms of the two fractions indicated that the first fraction consisted of about 98% 3-*t*-butyl-5,5-dimethyl-2-vinyloxazolidine and that the second fraction consisted of about 90% of the oxazolidine. The impurity, which appeared to be the same in both fractions, had a slightly greater retention time than the oxazolidine. Interestingly, the products from reactions of N-*t*-butyl-N-(2-chloroallyl)-1-amino-2-propanol and N-*t*-butyl-N-(2-chloroallyl)-1-amino-2-methyl-2-propanol with 1 equiv. of sodium amide possessed bands at 1670 cm.$^{-1}$. As the 2-methylenemorpholines possess bands at 1660 cm.$^{-1}$, these minor

(18) J. H. Biel, *J. Am. Chem. Soc.*, **71**, 1306 (1949).

impurities may be the isomeric 2-methyl-5,6-dihydro-1,4-oxazines.

C. **From N-Alkyl-N-propargylethanolamines and Sodium Hydroxide in Dimethyl Sulfoxide.**—A mixture prepared from 50 ml. of dry dimethyl sulfoxide, 5.8 g. (0.142 mole) of coarsely powdered sodium hydroxide, and 8.0 g. (0.047 mole) of N-*t*-butyl-N-propargyl-1-amino-2-propanol was heated with stirring at 75–85° for 2 hr. The mixture was cooled, and 150 ml. of ether and 150 ml. of water were added in that order. The phases were separated, and the organic layer was washed successively with 150 ml. of water and 50 ml. of 6 *N* sodium chloride. Most of the ether was removed by distillation at atmospheric pressure, and the residue was distilled under nitrogen. 3-*t*-Butyl-5-methyl-2-vinyloxazolidine (4.3 g., 54%), n^{23}D 1.4464, was collected at 68–70° (13 mm.).

4-Alkyl-2-methylenemorpholines.—The following is a typical procedure. A heterogeneous mixture of 66 g. (0.428 mole) of N-*t*-butyl-N-propargylethanolamine (IIIc) and 425 ml. of 3 *N* aqueous sodium hydroxide was stirred under reflux for 20 hr. The reaction mixture was cooled in an ice bath and extracted with 250 ml. of ether. The aqueous phase was extracted twice with 50-ml. portions of ether, and the ether extracts were combined and dried with sodium hydroxide. Most of the ether was removed by distillation at atmospheric pressure, and the residue was distilled under nitrogen through a 60 × 0.8 mm. Podbielniak column equipped with a total reflux head. 4-*t*-Butyl-2-methylenemorpholine (VIIIc), n^{25}D 1.4612, was collected at 75–77° (14 mm.), and 17 g. of IIIc was collected at 96–100° (14 mm.). The VIIIc weighed 32 g. (48% conversion, 65% yield).

N-*t*-Butyl-N-propargyl-1-amino-2-propanol (10 g., 0.059 mole) was treated with 60 ml. of 3 *N* aqueous sodium hydroxide at reflux for 16 hr., and the reaction mixture was worked up in a manner similar to that described before. A 2.3-g. fraction, b.p. 82–88° (11 mm.), n^{21}D 1.4570, and a 5.7-g. fraction, b.p. 86–92° (11 mm.), n^{21}D 1.4588, were obtained by distillation of the ether solution. In the g.l.p. chromatogram of the first fraction, the area of the band due to 4-*t*-butyl-6-methyl-2-methylenemorpholine was approximately 20% of the area of the band due to the amino alcohol; in the g.l.p. chromatogram of the second fraction, the area of the band due to the 2-methylenemorpholine was 2% that of the band due to the amino alcohol. The infrared spectrum of the first fraction had a band of moderate intensity at 1660 cm.$^{-1}$.

4-Ethyl-2-methylmorpholine.—A mixture of 4.3 g. of 4-ethyl-2-methylenemorpholine (VIIIb), 100 ml. of absolute ethanol, and 0.2 g. of platinic oxide was shaken under 2.5 atm. of hydrogen for 4 hr. The catalyst was removed by filtration, and the filtrate was distilled. 4-Ethyl-2-methylmorpholine (3.0 g., 70%) was collected at 76–78° (67 mm.). It had n^{25}D 1.4344 and an infrared spectrum that was superimposable on that of 4-ethyl-2-methylmorpholine, b.p. 80–82° (86 mm.), n^{25}D 1.4350, which was prepared in 42% yield from 118 g. of N-ethyl-N-(2-hydroxyethyl)-1-amino-2-propanol and 262 g. of 96% sulfuric acid following the procedure of Médard.[13]

Spectral Characteristics of 3-Alkyl-2-vinyloxazolidines and 4-Alkyl-2-methylenemorpholines.—In contrast to the 2-methylenemorpholines, which have intense bands at 1660 cm.$^{-1}$, the 2-vinyloxazolidines have bands of weak intensity at 1630 cm.$^{-1}$.

Common to the n.m.r. spectra of the 2-vinyloxazolidines is a complex series of bands from approximately −355 to −285 c.p.s. relative to TMS at 56.4 Mc., which are assigned to the vinyl and allyl protons. The bonds common to the n.m.r. spectra of VIIIa–c have been noted in the discussion.

The n.m.r. spectra of 3-*t*-butyl-2-vinyloxazolidine (VIIIc) and 3-*t*-butyl-5,5-dimethyl-2-vinyloxazolidine (IX) at 56.4 Mc. are surprisingly simple, but the spectra of the other 2-vinyloxazolidines are complex as might be expected for compounds that contain an ABCD system (the C-4 and C-5 protons) or for mixtures of diastereomers. The spectrum of neat VIIIc consists of the vinyl and allyl bands from −355 to −287 c.p.s. relative to TMS, two apparent triplets (J_{app} = 6.4 c.p.s.) at τ 6.05 and 6.85, which are assigned to the C-5 and C-4 protons, respectively, and an intense singlet at τ 8.65, which is assigned to the *t*-butyl protons. The spectrum of neat IX at 56.4 Mc. consists of the vinyl and allyl bands from −364 to −280 c.p.s. relative to TMS, an AB quartet due to the C-4 protons centered at τ 6.92 (J = 8.3 c.p.s., δ_H = 9.8 c.p.s.), the bands due to the C-5 methyl protons centered at τ 8.42 (δ_H = 3.0 c.p.s.), and the singlet due to the *t*-butyl protons at τ 8.59.

For purposes of comparison, 3-*t*-butyl-2-phenyloxazolidine, b.p. 102–104° (2 mm.), n^{23}D 1.5130, was prepared in 38% yield from 21 g. of benzaldehyde and 21 g. of N-*t*-butylethanolamine.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.51; H, 9.07; N, 6.65.

The n.m.r. spectrum at 56.4 Mc. of 3-*t*-butyl-2-phenyloxazolidine as a 16 mole % solution in benzene possesses bands from −428 to −403 c.p.s. relative to TMS, which are due to the aromatic protons, a singlet at τ 4.5, which is assigned to the C-2 proton, 2 apparent triplets (J_{app} = 6.4 c.p.s.) at τ 6.5 and 7.3, which are assigned to the C-5 and C-4 protons, respectively, and an intense singlet at τ 9.0, which is assigned to the *t*-butyl protons. In the n.m.r. spectrum at 56.4 Mc. of VIIc as a 12 mole % solution in benzene, the bands due to the C-5, C-4, and *t*-butyl protons appear at τ 6.5, 7.35, and 9.1, respectively.

4-Methyl-2-deuteriomethylenemorpholine. A. From N-methyl-N-propargylethanolamine (IIIa).—Sodium (6.9 g.) was divided into approximately 30 pieces, and each piece was treated under a stream of nitrogen with 1.5–2.0 ml. of 99.83 % deuterium oxide (Bio-Rad Laboratories, Richmond, Calif.). The sodium deuterioxide solutions were combined and made up to a volume of 100 ml. with deuterium oxide. Compound IIIa (11.6 g., 0.10 mole) was added, and the heterogeneous mixture was stirred and heated under reflux overnight. The product was isolated as described for the isolation of VIIIa, and the 4.2-g. fraction with b.p. 30–32° (11 mm.), n^{24}D 1.4588, was examined. The n.m.r. spectrum of VIIIa was taken, and the n.m.r. spectrum of deuterated VIIIa was taken immediately after using identical instrument settings. The portions of the two spectra from τ 7.0–7.7, which contain the bands due to the C-3 protons and N-methyl protons as well as the triplet due to the C-5 protons, were superimposable. The bands due to the C-6 protons were also superimposable, but the spectrum of deuterated VIIIa did not have the bands at τ 5.6 and 5.8, which are due to the vinyl protons of VIIIa. The infrared spectra of VIIIa and deuterated VIIIa were markedly similar from 1060–4000 cm.$^{-1}$. A weak band at 2240 cm.$^{-1}$ was noted in the spectrum of deuterated Va, and the band at 1660 cm.$^{-1}$ in the spectrum of VIIIa was observed at 1630 cm.$^{-1}$ in the spectrum of deuterated VIIIa. The spectra of VIIIa and deuterated VIIIa from 650–1060 cm.$^{-1}$ were significantly different. The only band common to the two spectra in this region was at 840 cm.$^{-1}$, and the intensity of the band in the spectrum of deuterated VIIIa was considerably less than the intensity of the band in the spectrum of VIIIa.

B. From N-Methyl-N-(2-bromoallyl)ethanolamine (IVa).—Compound IVa (10.0 g., 0.05 mole) and 50 ml. of 3 *N* sodium deuterioxide were heated with stirring at 100° for 18 hr. The 1.2-g. fraction of VIIIa, which had b.p. 44–48° (22 mm.) and n^{23}D 1.44588, was examined and was found to be identical with the 4-methyl-2-deuteriomethylenemorpholine prepared from IIIa.

N-*t*-Butyl-N-propargylaminoethanol (IIIc) and Sodium Hydroxide in Toluene.—To a vigorously stirred slurry of 0.4 g. (0.01 mole) of coarsely powdered sodium hydroxide and 25 ml. of refluxing toluene was added dropwise 15.5 g. (0.1 mole) of IIIc in 20 min. The mixture was stirred for 2 hr. at reflux and cooled. The toluene solution was decanted from the solids and distilled at reduced pressure under nitrogen. The colorless product (12.1 g., 78%) was collected at 77–80° (19 mm.). It had n^{26}D 1.4537 and an infrared spectrum that indicated it was a mixture of 3-*t*-butyl-2-vinyloxazolidine (VIIc) and 4-*t*-butyl-2-methylenemorpholine (VIIIc). Analysis by g.l.p.c. of the product and mixtures prepared from known amounts of the product and VIIIc showed that the product was 77% VIIc and 23% VIIIc.

Treatment of 4-*t*-Butyl-2-methylenemorpholine (VIIIc) with Various Bases.—To a stirred mixture of 3.62 g. (0.032 mole) of potassium *t*-butoxide and 180 ml. of dry ether was added dropwise 10.0 g. (0.064 mole) of VIIIc. During the addition a flocculent white precipitate formed in the mixture. The mixture was stirred for 45 hr. at room temperature, and the solids were removed by suction filtration. The filtrate was distilled, and 4.5 g. of Vc was collected at 74–76° (16 mm.). A small amount of *t*-butyl alcohol, b.p. 27–30° (25 mm.), also was collected.

A stirred slurry of 1.8 g. of coarsely powdered potassium hydroxide, 20 ml. of toluene, and 5.0 g. of VIIIc was heated under reflux for 2 hr. and cooled. The solids were removed by suction filtration, and the filtrate was distilled. Compound VIIIc (3.4 g.) was collected at 68–71° (11 mm.), and the residue (0.7 g.) was mainly VIIIc.

A mixture of 3.6 g. of sodium hydroxide, 5.0 g. of VIIIc, and 30 ml. of dry dimethyl sulfoxide was stirred for 19 hr. at 80–85°. The mixture was cooled, and 100 ml. of ether and 100 ml. of water were added in that order. The phases were separated, and the organic layer was washed successively with 100 ml. of water and 30 ml. of 6 *N* sodium chloride. The ether solution was distilled, and 3.3 g. of VIIIc was collected. The residue, which was mainly VIIIc, weighed 0.8 g.

Glycidyl Ether Reactions with Urethanes and Ureas. A New Synthetic Method for 2-Oxazolidones

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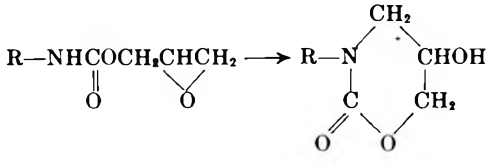
Tertiary amines and quarternary ammonium salts have been found to be efficient catalysts for the intermolecular addition reaction between urethane linkages and epoxy rings. Addition products of urethanes and epoxides undergo an intramolecular exchange of alcohols to give the oxazolidone derivatives in good yields.

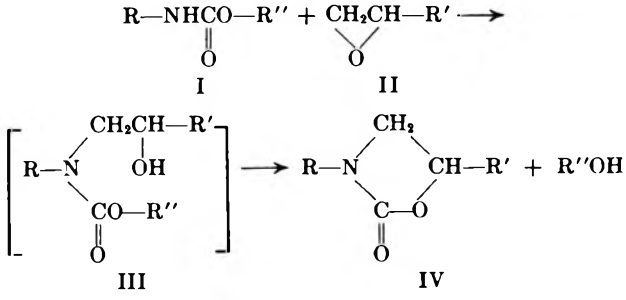
Epoxy compounds are known to produce ring-opened addition products with nucleophilic reagents,[1-4] but up to this time there has been no report about the reaction between epoxy compounds and the imide group of urethane linkages. Imide groups of urethane linkages are not reactive enough nucleophiles to react with epoxy rings without catalysts.

As we reported previously,[5] glycidyl urethanes are isomerized by heating to give N-substituted 5-hydroxytetrahydro-1,3-oxazin-2-ones. We attempted to extend these intramolecular reactions to intermolecular



addition reaction between urethanes and epoxides using catalysts.

Tertiary amines and quarternary ammonium salts are useful catalysts to accelerate the intermolecular nucleophilic addition reactions between imide groups of urethane linkages and epoxy compounds, and, since

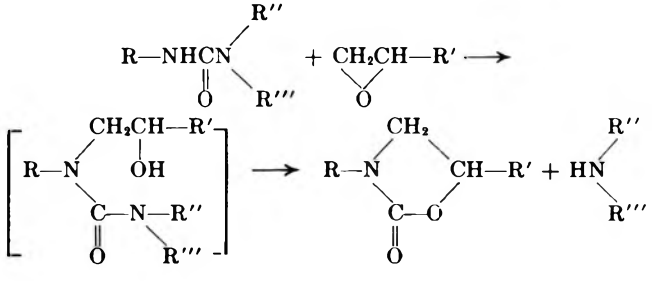


I II III IV

the reaction products (III) obtained by this addition split off alcohols rather rapidly to give the oxazolidone derivatives (IV), we can only isolate the oxazolidone derivatives as the final products in the intermolecular addition reactions between urethanes and epoxides.

As explained in detail in a later section, there is sufficient evidence that these reactions giving oxazolidone derivatives do not proceed *via* dissociation of urethanes to isocyanates and alcohols. According to Homeyer,[6] alkali-catalyzed reaction of α-amino alcohols and diethyl carbonate gives oxazolidones. From our experiments, it was found that condensation reactions of α-amino alcohols and ethyl chlorocarbonate also gave oxazolidones even at room temperature. These two results give support to reaction mechanisms involving nucleophilic addition and intramolecular exchange of alcohols as indicated by the previous formula.

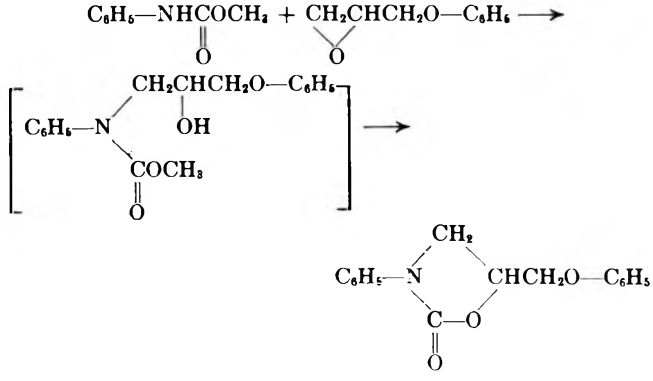
From the analogy of the mechanism of this reaction, we expect that ureas also would give the oxazolidones. In fact the intermolecular addition reaction between di- and trisubstituted ureas and epoxy



compounds gave the oxazolidone derivatives. In this case, the primary or secondary amines which are produced react with other epoxy compounds quickly; thus it is necessary that two or three molar equivalents of epoxy compounds be added.

Results and Discussion

Reaction between Urethanes and Epoxides.—To investigate the ability of intermolecular addition reaction of urethane linkages and epoxy rings, the reaction of N-phenylmethylurethane with phenyl glycidyl ether was examined expecting the following reaction. On

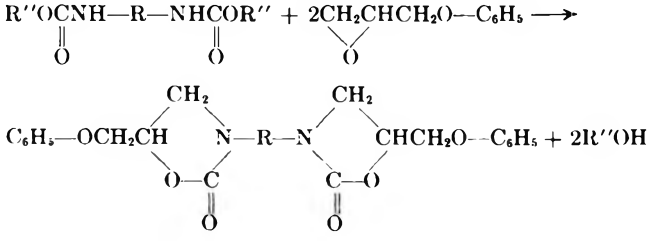


(1) L. Shechter, J. Wynstra and R. P. Kurkjy, *Ind. Eng. Chem.*, **48**, 86 (1956).
(2) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).
(3) R. M. Laird and R. E. Parker, *J. Am. Chem. Soc.*, **83**, 4277 (1961).
(4) R. E. Parker, *et al.*, *J. Chem. Soc.*, 1708 (1961).
(5) Y. Iwakura and Y. Taneda, *J. Org. Chem.*, **24**, 1992 (1959).
(6) A. H. Homeyer, U. S. Patent 2,399,118 (April 23, 1946).

heating without catalyst these two compounds did not show any changes at all in the temperature range from room temperature to 200°, and at high temperature there was observed only self-polymerization of epoxides. It was observed that tertiary amines and quarternary ammonium salts were effective catalysts for the intermolecular addition reaction between urethane linkages and epoxy rings and that these were also effective catalysts for isomerization of glycidyl carbamates. For example, at 25° using triethylamine, phenylmethylurethane and phenyl glycidyl ether gave 3-phenyl-5-phenoxymethyl-2-oxazolidone quantitatively in only two hours. The reaction using these catalysts was accompanied by no side reactions at all up to 140°, and the higher the reaction temperature used, the faster the reaction rate observed. At 140° in two or three minutes the reaction was almost completely finished. Attempted other catalysts, such as NaOH, $NaOCH_3$, BF_3OEt_2, and Lewis acids, were not effective in this reaction.

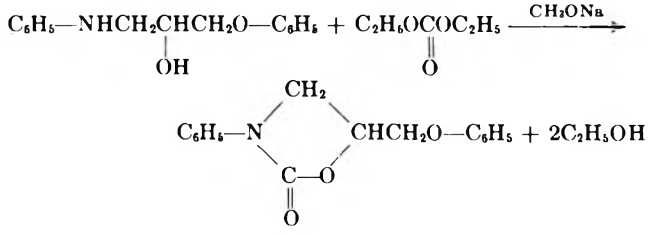
The reaction also proceeds in solvent with obviously decreased rate. The product obtained later was only an oxazolidone derivative. Solvents used were ethanol. benzene, toluene, chloroform, and dimethylformamide.

Reactivities of the urethanes having substituents (R) on nitrogen and substituents (R″) on oxygen to phenyl glycidyl ether were observed in order to investigate the effects of these substituents. The results are listed in Table I. The reactions were carried out without solvent, using triethylamine as catalyst, at 90° for one hour; an oxazolidone derivative was obtained quantitatively in the reaction between phenylmethylurethane and phenyl glycidyl ether. In the case of N-arylurethanes it was observed that the reaction products with phenyl glycidyl ether were quantitatively oxazolidone derivatives. In the case of N,N′-bifunctional arylurethanes which were synthesized from diisocyanates and alcohols, bisoxazolidone derivatives also were obtained quantitatively. N-Alkylurethanes, however, did not react with phenyl glycidyl ether under these conditions and the infrared spectra of reaction mixture showed little change before and after treatment.



The effects of substituents on the oxygen atom of urethane linkages were studied using N-phenylurethanes obtained from phenyl isocyanate and various hydroxy compounds. It was shown that the product of each reaction between these urethanes and phenyl glycidyl ether was 3-phenyl-5-phenoxymethyl-2-oxazolidone. The kind of substituent on the oxygen atom has no influence on the reaction mechanism, though we can not say anything quantitatively about the reaction rate.

As mentioned previously, the reactions between urethanes and phenyl glycidyl ether were generated by tertiary amines and quarternary ammonium salts in the case of N-arylurethane derivatives to give oxazolidone derivatives. 3-Phenyl-5-phenoxymethyl-2-oxazolidone obtained through this reaction route was identical with an authentic sample synthesized from N-phenyl-3-phenoxy-2-hydroxypropylamine and diethyl carbonate by Homeyer's method.[6]



The reaction of N-phenyl-3-phenoxy-2-hydroxypropylamine and ethyl chlorocarbonate at room temperature also gave 3-phenyl-5-phenoxymethyl-2-oxazoli-

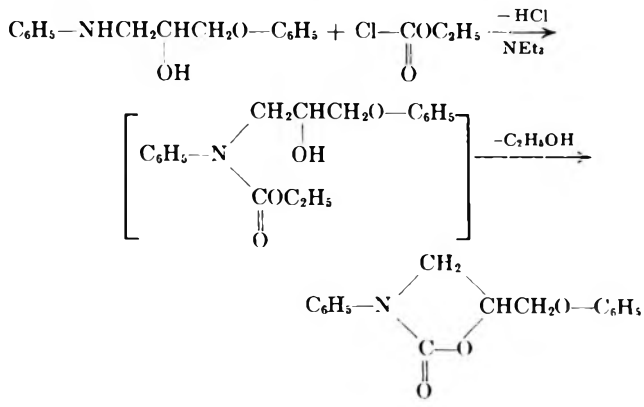


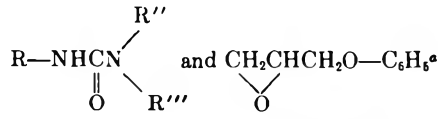
TABLE I

$R—NHCO—R''$ and $CH_2CHCH_2O—C_6H_5$ (O)

No.	R	R″	Results
1	C_6H_5-	$-CH_3$	Oxazolidone[b]
2	p-NO_2-C_6H_4-	$-C_2H_5$	Oxazolidone[c]
3	p-Cl-C_6H_4-	$-C_2H_5$	Oxazolidone[d]
4	p-C_2H_5O-C_6H_4	$-C_2H_5$	Oxazolidone[e]
5	p-CH_3-C_6H_4-	$-C_2H_5$	Oxazolidone[f]
6	2-C_5H_4N-	$-C_2H_5$	Oxazolidone[g]
11	C_2H_5-	$-C_3H_7$	No reaction[h]
12	C_2H_5-	$-C_6H_5$	No reaction[h]
13	C_4H_9-	$-C_2H_5$	No reaction[h]
14	$C_5H_{11}-$	$-C_3H_7$	No reaction[h]
21	C_6H_5-	$-C_2H_5$	Oxazolidone[b]
22	C_6H_5-	$-C_3H_7$	Oxazolidone[b]
23	C_6H_5-	$-C_6H_5$	Oxazolidone[b]

[a] Reaction conditions: without solvent, NEt_3 catalyst, 90°, 1 hr. [b] 3-Phenyl-5-phenoxymethyl-2-oxazolidone was obtained quantitatively. [c] 3-p-Nitrophenyl-5-phenoxymethyl-2-oxazolidone was recrystallized from acetone, m.p. 162–163°. *Anal.* Calcd. for $C_{16}H_{14}O_5N_2$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.03; H, 4.56; N, 8.83. [d] 3-p-Chlorophenyl-5-phenoxymethyl-2-oxazolidone was recrystallized from acetone, m.p. 158–160°. *Anal.* Calcd. for $C_{17}H_{16}O_3NCl$: C, 63.25; H, 4.64; N, 4.61. Found: C, 63.12; H, 4.76; N, 4.63. [e] 3-p-Ethoxyphenyl-5-phenoxymethyl-2-oxazolidone was recrystallized from acetone, m.p. 131–133°. *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.11; H, 6.07; N, 4.71. [f] 3-p-Tolyl-5-phenoxymethyl-2-oxazolidone was recrystallized from acetone, m.p. 149–151°. *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.71; H, 6.14; N, 5.03. [g] 3-(2-Pyridyl)-5-phenoxymethyl-2-oxazolidone was recrystallized from ethanol, m.p. 115–116°. *Anal.* Calcd. for $C_{15}H_{14}O_3N_2$: C, 66.67; H, 5.19; N, 10.37. Found: C, 66.81; H, 5.25; N, 10.29. [h] Infrared spectra of reaction mixture showed little change before and after treatment.

TABLE II

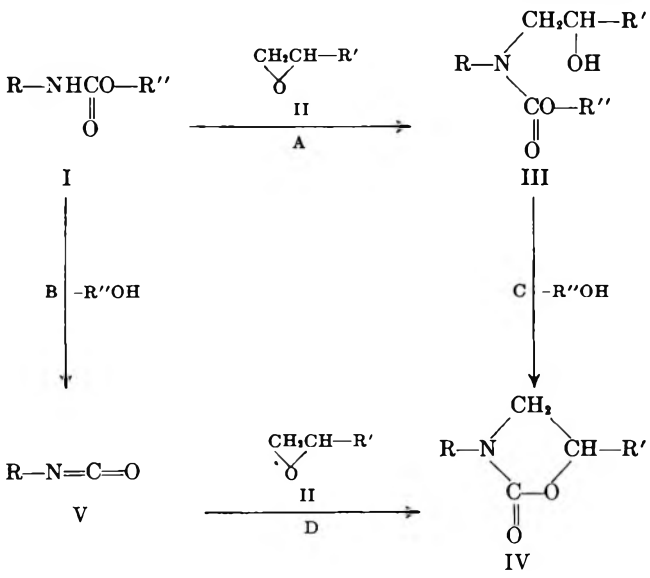


No.	R	R''	R'''	Epoxide (mole) / urea (mole)	Time, hr.	Results
1	C_6H_5-	C_2H_5-	C_2H_5-	1	1	Oxazolidone[b]
2	C_6H_5-	C_2H_5-	C_2H_5-	2	1	Oxazolidone[c]
3	C_6H_5-	C_4H_9-	C_4H_9-	2	1	Oxazolidone[c]
4	C_6H_5-	CH_3-	C_6H_5-	1	1	Oxazolidone[b]
5	C_6H_5-	CH_3-	C_6H_5-	2	1	Oxazolidone[c]
11	C_2H_5-	CH_3-	C_6H_5-	2	2	No reaction[d]
12	$C_6H_{11}-$	CH_3-	C_6H_5-	2	5	No reaction[d]
21	C_6H_5-	H-	C_6H_5-	2	1	Oxazolidone[b]
22	C_6H_5-	H-	C_6H_5-	3	1	Oxazolidone[c]
23	C_6H_5-	H-	C_4H_9-	3	1	Oxazolidone[c]

[a] Reaction conditions: without solvent, NEt_3 catalyst, 90°. [b] The infrared spectra of the reaction mixture indicated the presence of an unchanged urea derivative. [c] 3-Phenyl-5-phenoxymethyl-2-oxazolidone was isolated and the major part of the residue was an adduct of amine and epoxide. [d] The infrared spectrum of reaction mixture showed little change before and after treatment.

done; thus it was considered that it might be impossible to obtain the addition intermediate (III) in our case.

The reaction mechanism of oxazolidone formation from urethanes and epoxides is shown by process A and C in the reaction scheme. Thermal dissociation



of urethanes to isocyanates and alcohols has been reported in many cases.[7,8] In this reaction, however, processes B and D including dissociation of urethanes were completely eliminated by the observation that urethanes did not dissociate into isocyanates and alcohols under the conditions used as was demonstrated in an infrared heating cell. It is known that isocyanates (V) and epoxides (II) on heating with tertiary amines give an isocyanate trimer, and we observed that under these conditions oxazolidone derivatives were not isolated. Therefore, process D did not occur. Further, by the addition of alcohols to an isocyanates–epoxide–tertiary amine system, oxazolidone derivatives were obtained. This fact indicates that isocyanates and alcohols gave urethanes (I) by the reverse reaction of process B and that urethanes and epoxides gave oxazolidones (IV) by the processes A and C.

(7) Y. Iwakura and K. Nagakubo, *Bull. Tokyo Inst. Technol.*, **18**, 25 (1948).

(8) T. Mukaiyama and T. Akiba, *Bull. Chem. Soc. Japan*, **33**, 1707 (1960).

Reaction between Ureas and Epoxides.—From the consideration of the fact that the epoxy ring of phenyl glycidyl ether can react with urethanes catalyzed by tertiary amines and quarternary ammonium salts and that ureas and urethanes have the same imide group, the reactivity of the epoxy ring with urea linkages was studied. The reaction conditions used were the most suitable for the case of urethanes: 90° without solvent with triethylamine as catalyst.

The reactions between ureas and phenyl glycidyl ether were slightly complex compared with the urethanes. The intermolecular addition reaction between N-aryl-N′,N′-disubstituted ureas and phenyl glycidyl ether was accomplished easily under these conditions, and intramolecular substitution of newly produced secondary alcohols and urea linkages happened rather rapidly to give oxazolidone derivatives. It was impossible to obtain the addition intermediate in this case. Using these intramolecular reactions, amines were produced simultaneously and they reacted with the epoxy ring faster than the ureas did. Using 2 moles of phenyl glycidyl ether to 1 of urea the reaction occurred quantitatively to give 3-phenyl-5-phenoxymethyl-2-oxazolidone and N,N-disubstituted 3-phenoxy-2-hydroxypropylamine. In these reactions a difference in the effect of substituents on the nitrogen atom containing active hydrogen was obviously observed; *i.e.*, the reactivity of ureas with aryl groups was different from those with alkyl groups. N-Alkyl-N′,N′-disubstituted urea derivatives were almost ineffective to the ring-opening reaction of phenyl glycidyl ether. In the case of N,N′-disubstituted urea derivatives where R′′ was a hydrogen atom, by variation of R and R′′′ groups, various reaction products were produced. It was observed generally that the imide groups substituted by an aryl group reacted with the epoxy ring of phenyl glycidyl ether, and in this case 3 moles of epoxide were needed for 1 mole of urea. For example, N-phenyl-N′-*n*-butylurea reacted with 3 moles of phenyl glycidyl ether to give 80% or more of crystalline 3-phenyl-5-phenoxymethyl-2-oxazolidone and N,N-bis(3-phenoxy-2-hydroxypropyl)-*n*-butylamine as a viscous liquid which was confirmed by its infrared spectrum. These results are listed in Table II.

Experimental[9]

Phenyl Glycidyl Ether.—To a mixture of 84 g. (1.0 mole) of phenol and 370 g. (4 moles) of epichlorohydrin was added dropwise with stirring during 1 hr. at room temperature 54 g. (1.0 mole) of sodium methylate in 400 ml. of methanol, and the mixture was stirred for an additional 1 hr. After removal of epichlorohydrin, the residue was distilled under reduced pressure to obtain 115 g. (77%) of phenyl glycidyl ether, b.p. 102° (5 mm.).

Urethanes.—Urethanes were prepared by two methods: (A) an addition reaction of the corresponding isocyanates and alcohols, and (B) a condensation reaction of the corresponding amines and ethyl chlorocarbonate. Examples follow.

N-Phenylmethylurethane (Methyl Phenylcarbamate).—To a solution of 32.0 g. (1.0 mole) of methanol and 0.1 g. of triethylamine in 100 ml. of benzene was added dropwise with stirring during 1 hr. at 50° 59.5 g. (0.5 mole) of phenyl isocyanate in 300 ml. of benzene; the mixture was heated for an additional hour. After removal of benzene, the residue was recrystallized from ether–petroleum ether (b.p. 30–60°) to give 68.5 g. (90%) of phenylmethylurethane, m.p. 48–49°.

N-*p*-Chlorophenylethylurethane.—To a solution of 21.7 g. (0.2 mole) of ethyl chlorocarbonate in 150 ml. of benzene was added with stirring at 10° 25.5 g. (0.2 mole) of *p*-chloroamiline and 20.2 g. (0.2 mole) of triethylamine in 200 ml. of benzene, and the mixture was allowed to stand for 3 hr. After filtering the triethylamine hydrochloride and removal of the benzene, the crystalline solid was recrystallized from cyclohexane to give 30.5 g. (76%) of *p*-chlorophenylethylurethane, m.p. 67–69°.

(9) Melting points and boiling points are uncorrected. Microanalyses were performed in the Laboratory of Organic Chemistry, Tokyo Institute of Technology.

Ureas.—Ureas were prepared by addition reactions of corresponding isocyanates and primary or secondary amines.

N-Phenyl-N′,N′-diethylurea.—To a boiling solution of 23.9 g. (0.2 mole) of phenyl isocyanate in 100 ml. of benzene was added dropwise with stirring 14.6 g. (0.2 mole) of diethylamine in 100 ml. of benzene; this was heated under reflux for an additional hour. After removal of benzene, the residue was recrystallized from ether to give 30.2 g. (79%) of N-phenyl-N′,N′-diethyl urea, m.p. 86–88°.

3-Phenyl-5-phenoxymethyl-2-oxazolidone. A. From Phenylmethylurethane and Phenyl Glycidyl Ether.—A mixture of 15.1 g. (0.1 mole) of phenylmethylurethane, 15.0 g. (0.1 mole) of phenyl glycidyl ether, and 0.1 g. of triethylamine was heated at 90° for 15 min. After cooling, the adduct was recrystallized from acetone to give 24.5 g. (91%) of 3-phenyl-5-phenoxymethyl-2-oxazolidone, m.p. 139–140°. A mixture melting point with an authentic sample showed no depression. In the infrared spectrum there was found an absorption band at 1740 cm.$^{-1}$ for C=O and no absorption band arising from N—H, O—H, and an epoxy group was recognized.

Anal. Calcd. for $C_{16}H_{15}O_3N$: C, 71.38; H, 5.58; N, 5.20; mol. wt., 269. Found: C, 71.34; H, 5.54; N, 5.47; mol. wt., 258.

B. From N-phenyl-N′,N′-diethylurea and Phenyl Glycidyl Ether.—A mixture of 9.6 g. (0.05 mole) of N-phenyl-N′,N′-diethylurea, 15.0 g. (0.1 mole) of phenyl glycidyl ether, and 0.1 g. of triethylamine was heated at 90° for 1 hr. The resulting oily viscous substance was recrystallized from acetone to give 11.0 g. (81%) of 3-phenyl-5-phenoxymethyl-2-oxazolidone. After removal of acetone from the filtrate, the viscous oily residue was a mixture of 3-phenyl-5-phenoxymethyl-2-oxazolidone and N,N-diethyl-2-hydroxy-3-phenoxypropylamine, the infrared spectra of which was identical with that of an authentic sample.

Reactions of 2-Bromo-2-(α-halogenobenzyl)-1-indanones

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Reactions of 2-bromo-2-(α-bromobenzyl)-1-indanone (I) and 2-bromo-2-(α-chlorobenzyl)-1-indanone (IV) have been investigated. With nucleophilic reagents, three types of reaction have now been established. The *cis* and *trans* isomers of 2-(α-chlorobenzal)-1-indanone (III) have been prepared and separated. Structural assignments have been strengthened by an examination of the proton magnetic resonance spectra of deuterated derivatives.

It has long been known that 2-bromo-2-(α-bromobenzyl)-1-indanone (I) is readily debrominated to give 2-benzal-1-indanone (II).[2a] Suitable reagents are, for example, ethanolic solutions of sodium hydroxide, sodium acetate, or potassium iodide. More recently conditions have been found which lead, in addition to II, to substantial yields of 2-benzal-1-indanones substituted in the 3-position; these products are formed by endocyclic dehydrobromination followed by an allylic substitution.[2b,3]

Further reactions of I have been investigated. In most instances II has been found as the favored product. In one instance a third type of product, involving replacement of the bromine β to the carbonyl group accompanied by exocyclic dehydrobromination, is formed in good yield.

Reaction of I with piperidine in benzene is known[2b,3] to lead to a good yield of 3-piperidino-2-benzal-1-indanone. Reaction with piperidine in acetonitrile leads to a product no part of which can be extracted by acid and which on recrystallization gives a 50% yield of II. Reaction of I with N-methylpiperidine in benzene proceeds with precipitation of N-methylpiperidine hydrobromide and on work-up a good yield of 2-benzal-1-indanone is obtained.

Reaction of I with tetraethylammonium bromide in acetonitrile at 75° leads to a 95% yield of the debromination product, II. Reaction of I with excess tetraethylammonium chloride in acetonitrile at 90° differs markedly from the bromide ion-promoted reaction in that it leads to an 80% yield of a mixture of *cis*- and *trans*-2-(α-chlorobenzal)-1-indanone (81% IIIa and 19% IIIb). Reaction for a longer period of time and with a reduced chloride ion concentration leads to some tar formation and to some accompanying 2-benzal-1-indanone (II).

The addition of bromine chloride to α,β-unsaturated carbonyl compounds is established[4] as proceeding *via* 1,4-addition with chlorine entering the 4-position. In this way 2-bromo-2-(α-chlorobenzyl)-1-indanone (IV)

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(2) (a) F. S. Kipping, *J. Chem. Soc.*, **65**, 499 (1894); (b) 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).

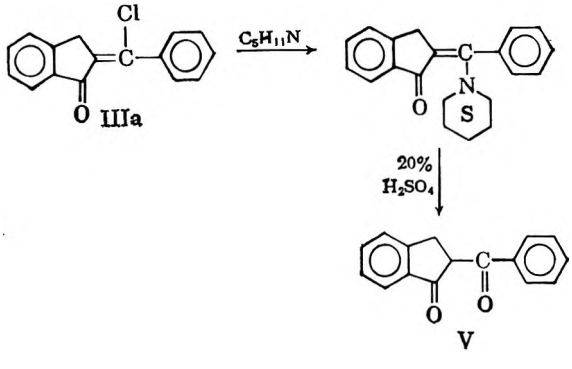
(4) E. P. White and P. W. Robertson, *J. Chem. Soc.*, 1509 (1939).

was prepared from 2-benzal-1-indanone (II). Compound IV reacted with tetraethylammonium chloride in acetonitrile to give, after recrystallization, a 78% yield of IIIa. When the reaction was repeated using tetraethylammonium radiochloride (NEt_4Cl^{36}), the product III isolated showed a quantitative uptake of Cl^{36}.

The *cis* and *trans* isomers of 2-(α-chlorobenzal)-1-indanone (III), as formed from I, were separated by column chromatography. The proton magnetic resonance spectra of IIIa and IIIb differ, among other aspects, in the position of the signal for the methylene protons, τ 6.03 for IIIa and 6.23 for IIIb. Ultraviolet irradiation of a deuteriochloroform solution of IIIa followed by analysis of the proton magnetic resonance spectrum showed an equilibrium mixture of 75% IIIa and 25% IIIb. Similarly, equilibration by hydrogen chloride in deuteriochloroform leads to 83% IIIa and 17% IIIb. The acid-catalyzed equilibration concentrations are almost identical with the product ratios obtained under the acid conditions in which III is formed from I. It appears that the product ratio of IIIa to IIIb, as formed from I, is governed by thermodynamic and not kinetic control.

The ultraviolet spectrum of IIIa includes λ_{max} 301 mμ (ε 17,900), corresponding to a λ_{max} 314 mμ (ε 34,900) for IIIb. On this basis IIIb is tentatively assigned the *trans* arrangement of phenyl and carbonyl groups and IIIa the corresponding *cis* arrangement. The higher melting point of IIIb (105–106.5°) relative to IIIa (70–71.5°) is consistent with this assignment.[5]

Treatment of 2-(α-chlorobenzal)-1-indanone (IIIa) with piperidine in benzene leads to an oil, probably a mixture of *cis*- and *trans*-2-(α-piperidinobenzal)-1-indanone. The oil, unstable to heat, was hydrolyzed instantaneously by 20% sulphuric acid to give 2-benzoyl-1-indanone (V).

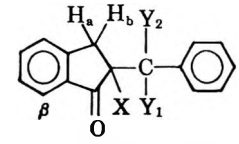


Features of the proton magnetic resonance spectra of several derivatives of 2-benzyl-1-indanone are reported in Table I. Of particular interest is the fact that the product resulting from bromine addition to 2-(α-deuteriobenzal)-1-indanone gives two doublets, corresponding to two methylene protons, with J_{ab} = 18 c.p.s. Such a proton magnetic resonance spectrum is consistent only with formulation as Ia and not with the alternative Ib.[3] Both Ia and Ib are feasible structures for explanation of the proton magnetic resonance spectrum of the nondeuterated dibromo-compound since a methylene group of type C_6H_5-$CH_2CR_1R_2R_3$, where $R_1 \neq R_2 \neq R_3$, can show a splitting pattern similar to the methylene group of Ia.

(5) For an excellent discussion of *cis–trans* isomerism in α,β-unsaturated carbonyl compounds, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chap. 12.

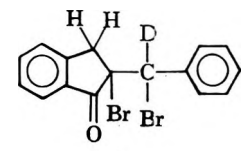
TABLE I

FEATURES OF THE PROTON MAGNETIC RESONANCE SPECTRA OF SEVERAL DERIVATIVES OF 2-BENZYL-1-INDANONE[a]

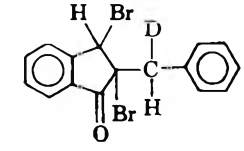


Substituents	τ-Values relative to tetramethylsilane: H_β	H_a or H_b	Y_1, Y_2
X = Y_1 = Y_2 = D[b]	2.37	6.98, 7.24	
X = Br, Y_1 = Y_2 = H[b]	2.25	6.40, 6.59	Y_1 = Y_2 = 6.51
X = Br, Y_1 = Y_2 = D[c]	2.17	6.33, 6.45	
X = Y_1 = Br, Y_2 = H[c]	2.03	5.40, 6.37	Y_2 = 4.20
X = Y_1 = Br, Y_2 = D[c]	2.03	5.40, 6.33	
X = Br, Y_1 = Cl, Y_2 = H[c]	2.08	5.55, 6.55	Y_2 = 4.30

[a] J_{ab} = 18 c.p.s. (except X = B, Y_1 = Y_2 = H when J_{ab} = 14 c.p.s.), $J_{\beta\gamma}$ = 7 c.p.s. (b) Determined in carbon tetrachloride. (c) Determined in deuteriochloroform.



Ia



Ib

Experimental[6]

Reaction of I with Piperidine in Acetonitrile.—A solution of 0.50 g. of I and 5.0 g. of piperidine in acetonitrile was maintained, in a sealed tube, at 90° for 24 hr. Evaporation and extraction with benzene–isopropyl ether was followed by water washing. The solution was extracted with 1 *N* hydrochloric acid. Neutralization of the hydrochloric acid solution by sodium carbonate did not lead to any precipitation. Evaporation of the benzene–isopropyl ether solution gave a product which on recrystallization from methanol gave 0.15 g. (50% yield) of II. It was identified by mixture melting point with an authentic sample.[7]

Reaction of I with N-Methylpiperidine in Benzene.—A solution of 2.5 g. of I and 4.1 g. of N-methylpiperidine in 25 ml. of benzene was allowed to stand at room temperature. After the solution had stood for 2 days, 0.2 g. of hygroscopic precipitate was filtered off and dried *in vacuo*, yielding a product with m.p. (determined in sealed tube) 179–181°, m.m.p. (with N-methylpiperidine hydrobromide) 179–180°. After 6 weeks, further precipitate was filtered off and the benzene solution extracted with 1 *N* hydrochloric acid. Neutralization of the hydrochloric acid solution with sodium carbonate did not lead to any precipitation. The benzene solution was evaporated to dryness to give a dark brown product whose proton magnetic resonance spectrum indicated it to be largely 2-benzal-1-indanone, accompanied by unidentified impurities. Recrystallization from methanol–water gave pure 2-benzal-1-indanone, identified by infrared and ultraviolet spectra and mixture melting point.

The proton magnetic resonance spectrum of 2-benzal-1-indanone shows the aromatic proton β to the carbonyl at τ 2.08 (J = 7 c.p.s.), eight aromatic and the vinylic proton represented by peaks in the range τ 2.2–2.8, and the methylene protons

(6) Melting points were read with a calibrated thermometer. Ultraviolet spectra were determined with a Cary Model 11-MS recording spectrophotometer using reagent grade methanol solutions. Infrared spectra were determined with a Perkin-Elmer Model 21 double beam recording instrument employing sodium chloride optics and matched sodium chloride cells with carbon tetrachloride 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.

(7) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

as a characteristic doublet at τ 5.96 (J = 2 c.p.s.). The splitting is due to a long-range coupling with the vinylic proton. Consistent with this explanation, the methylene protons of 2-(α-deuteriobenzal)-1-indanone are represented by a sharp singlet corresponding in intensity to two protons at τ 5.97. This presents additional evidence that 2-benzal-1-indanone does not possess the alternative 2-benzyl-1-indone structure.[3] In the presence of a deuterium substituent in the *exo*-benzylic methylene group, the proton magnetic resonance spectrum of 2-benzyl-1-indone would show two nonequivalent protons, one vinylic and one methylenic.

Reaction of I with Tetraethylammonium Bromide in Acetonitrile.—A solution of 2.5 g. of I and 4.0 g. of tetraethylammonium bromide was maintained, in a sealed tube, at 75° for 2 hr. Evaporation to dryness, extraction with benzene, and evaporation of benzene leaves a product whose proton magnetic resonance spectrum indicates it to be almost pure 2-benzal-1-indanone (II). After recrystallization from methanol the identity was confirmed by mixture melting point.

Reaction of I with Tetraethylammonium Chloride in Acetonitrile.—A solution of 6.1 g. of I and 4.0 g. of tetraethylammonium chloride in 30 ml. of acetonitrile was maintained, in a sealed tube, at 90° for 60 hr. Evaporation to dryness, ether extraction, and evaporation of the ether layer left a brown oil which was chromatographed on alumina using benzene–petroleum ether (b.p. 60–70°) as eluent. Obtained was a 50% yield of IIIa, followed by about 5% of IIIb, followed in turn by about 18% of II (identified by mixture melting point).

The *cis*(?)-2-(α-chlorobenzal)-1-indanone (IIIa) was recrystallized from methanol–water; m.p. 70–71.5°; λ_{max} 301 mμ (ϵ 17,900), 278 (sh, 14,900), 226 (8800); λ_{min} 243 mμ (ϵ 6000); $\gamma_{C=O}$ 1711 (vs); $\gamma_{C=C}$ 1620 (s) cm.$^{-1}$. The proton magnetic resonance spectrum shows the aromatic proton β to the carbonyl at τ 2.28, eight protons in the range τ 2.3–2.8, and two methylene protons at τ 6.03.

Anal. Calcd. for $C_{16}H_{11}OCl$: C, 75.49; H, 4.36; Cl, 13.93. Found: C, 75.56; H, 4.36; Cl, 14.02.

The *trans*(?)-2-(α-chlorobenzal)-1-indanone, m.p. 105–106.5°, has λ_{max} 314 mμ (ϵ 34,900), 227 (14,500); λ_{min} 247 mμ (ϵ 8200); $\gamma_{C=O}$, 1707 (vs); $\gamma_{C=C}$, 1637 (s), 1617 (s) cm.$^{-1}$. The proton magnetic resonance spectrum shows the aromatic proton β to the carbonyl group at τ 2.13, eight aromatic protons in the range τ 2.3–2.8, and two methylene protons at τ 6.23.

When, in a sealed tube, 1.0 g. of I was heated for 2 hr. at 90° with 10 g. of tetraethylammonium chloride and the solution evaporated to dryness, extracted with benzene, and the benzene solution evaporated to dryness, a crude product constituting an 80% yield of a mixture of *cis* and *trans* III was obtained (81% IIIa and 19% IIIb).

Equilibration of *cis*- and *trans*-2-(α-Chlorobenzal)-1-indanone (IIIa and IIIb).—Irradiation of a solution of IIIa in deuteriochloroform, contained in a Pyrex flask, by a B100-A "Blakray" ultraviolet source (Ultra-Violet Products, Inc.) over a period of 20 hr. leads to an equilibrium mixture of 75% of IIIa and 25% of IIIb as determined by a consideration of the relative intensities of the peaks in the proton magnetic resonance spectrum at τ 6.03 and 6.23.

Similarly, when IIIa is allowed (for 7 hr.) to equilibrate in deuteriochloroform containing a trace of hydrochloric acid, the proton magnetic resonance spectrum indicates a mixture of 83% of IIIa and 17% of IIIb.

Conversion of 2-(α-Chlorobenzal)-1-indanone (IIIa) to 2-Benzoyl-1-indanone (V).—A solution of 1.0 g. of piperidine and 0.50 g. of IIIa in 10 ml. of benzene was allowed to stand for 38 hr. and then refluxed for 4 hr. Addition of isopropyl ether precipitated 0.23 g. (96% yield) of piperidine hydrochloride. Evaporation to dryness gave an oil, unstable to heat, which was instantaneously hydrolyzed by 20% sulfuric acid to give 2-benzoylindanone,[2b] identified by mixture melting point with an authentic sample and by ultraviolet spectrum. The oil, presumed to be 2-(α-piperidinobenzal)-1-indanone, has an ultraviolet spectrum in methanol with major peaks at 263 and 392 mμ and with minor peaks at 292 and 301 mμ. The positions of the major peaks are very similar to those for the known 2-(α-piperidinobenzal)-3,3-dimethyl-1-indanone.[3]

2-Bromo-2-(α-chlorobenzyl)-1-indanone (IV).—To a solution of 1.1 g. of 2-benzal-1-indanone (II) in 10 ml. of acetic acid, maintained at 50°, was added dropwise and with stirring about 5 ml. of a solution containing 26 g. of BrCl in 200 ml. of acetic acid. When a slight red color remained, addition was curtailed. Evaporation to dryness gave a yellow oil which on recrystallization from methanol gave 0.60 g. of crude product. A further recrystallization (from benzene–petroleum ether, b.p. 60–70°) gave pure IV, m.p. 127–128°. Characteristics of the proton magnetic resonance spectrum of IV are included in Table I.

Anal. Calcd. for $C_{16}H_{12}OBrCl$: C, 57.25; H, 3.61; Br + Cl, 34.37. Found: C, 56.90; H, 3.86; Br + Cl, 34.61.

Reaction of IV with Tetraethylammonium Chloride in Acetonitrile.—A solution of 0.50 g. of IV and 3.3 g. of tetraethylammonium chloride in 25 ml. of acetonitrile was maintained, in a sealed tube, at 90° for 3 hr. Evaporation, extraction with benzene, and evaporation of the benzene gave a yellow oil. Recrystallization from methanol–water gave 0.30 g. (78% yield) of IIIa, identified by mixture melting point and proton magnetic resonance spectrum.

A solution of 0.30 g. of IV and 0.80 g of NEt_4Cl^{36} in 15 ml. of acetonitrile was maintained, in a sealed tube, at 90° for 3 hr. Evaporation to dryness, benzene extraction, several washings of the benzene layer with water, drying of the benzene layer over anhydrous magnesium sulfate, and evaporation to dryness gave a yellow oil. A 1.00-ml. portion of a 0.0286 M solution of the NEt_4Cl^{36} in acetonitrile gave 3075 counts per minute, corresponding to 2150 counts per minute for a 0.0200 M solution. A solution of 5.1 mg. of product in 1.00 ml. of acetonitrile (0.0200 M) gave 1567 counts per minute. For statistical distribution of Cl^{36} the predicted count is 1810 counts per minute and, since the product was counted in a crude condition, the agreement is fairly good. The counting technique has previously been described.[8]

Preparation of Derivatives Containing Deuterium.—Condensation of 1-indanone and deuteriobenzaldehyde (C_6H_5CDO) in the usual manner[7] gave 2-(α-deuteriobenzal)-1-indanone. A portion of this product was deuterated at atmospheric pressure using 10% palladium on charcoal as catalyst in carbon tetrachloride as solvent. A portion of this product was then brominated in the position α to the carbonyl by the method of Leuchs.[9]

A further portion of 2-(α-deuteriobenzal)-1-indanone was treated with an equimolar amount of bromine in carbon tetrachloride and the bromine addition product was obtained.

Acknowledgment.—This work was supported in part by Grants G-14469 and G-20149 from the National Science Foundation.

(8) D. N. Kevill, G. A. Coppens, and N. H. Cromwell, *J. Org. Chem.*, **28**, 567 (1963).

(9) H. Leuchs, J. Wutke, and E. Giesler, *Ber.*, **46**, 2200 (1913).

trans-β-Chlorovinyl Ketones and *trans*-(β-Acylvinyl)trimethylammonium Chlorides[1,2]

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Department of Chemistry, Colorado State University, Fort Collins, Colorado

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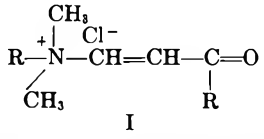
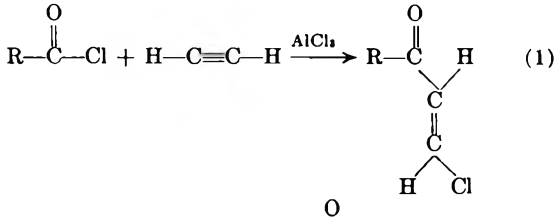
When acid chlorides were added to acetylene in the presence of aluminum chloride, *trans*-β-chlorovinyl ketones were formed as shown by n.m.r. spectra. When these ketones were treated with trimethylamine in an inert solvent, a series of β-acylvinyltrimethylammonium chlorides were formed which gave complete retention of the *trans* configuration. The ultraviolet and infrared spectra of these systems were examined and indicated the C=C-C=O system to be most likely in the transoid conformation.

In connection with the synthesis of compounds to be used as drugs,[5] it seemed of interest to investigate the synthesis of type I compounds.

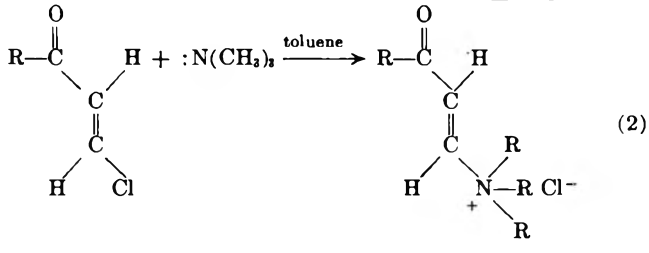


I

A possible preparative reaction scheme is outlined in eq. 1 and 2.



(1)



(2)

The acylation of unsaturated compounds is well-known, but no data have been reported on the geometry of the acyl and the chloro groups about the double bond where acetylene was used. Kroeger, Sowa, and Nieuwland[6] reported a number of condensations of acid chlorides with alkylacetylenes which led to two (probably *cis* and *trans*) isomers in most cases. Kochetkov and co-workers[7,8] have prepared many β-chlorovinyl ketones by adding acid chlorides to acetylene. To determine the *cis–trans* structure, Kochetkov reported[9] recently that methyl β-chlorovinyl ketone (I) was oxidized with sodium hypochlorite to the known *trans*-β-chloroacrylic acid. The 50% yield certainly gave an indication that one compound in the series was probably *trans*, but the method may have destroyed the *cis* isomer (if it was present) through isomerization, elimination, preferential oxidation, etc.

The addition of acid chlorides to vinyl chloride proceeds first by addition followed by elimination with the intermediate formation of β,β-dichloroethyl ketones.[10,11]

It was found that the β-chlorovinyl ketones prepared from vinyl chloride were very unstable, decomposing in short periods to hydrogen chloride and black tar. It has been shown that the instability could be avoided through the use of calcium carbonate or sodium bicarbonate.[10] However, when acetylene was used the products were much more stable and could be stored for several months at various temperatures with only a slight darkening in color. A list of the β-chlorovinyl ketones prepared is given in Table I.

In general it was found that the addition of acid chlorides to acetylene led to fairly good yields (60–70%) of stable β-chlorovinyl ketones. Benzoyl chloride, however, led to only 30.8% of VII while acetyl chloride gave a 92.7% yield of methyl β-chlorovinyl ketone (I). Pivaloyl chloride led to a mixture of at least six different products as indicated by gas–liquid chromatography (g.l.c.). Therefore, compound VI was prepared in a manner previously described by Kochetkov[12] and co-workers.

All of these colorless, vessicant, lachrymatory ketones exhibited the characteristic AB pattern in their n.m.r. spectra resulting from spin–spin interactions between the *trans* nonequivalent protons of the double bond. In the case of compound VII, the aromatic protons interfered with the protons on the double bond so that an interpretation of its spectrum was not possible. The J_{AB} values are given in Tables I and III. For absolute certainty, the constants of the *cis* compounds should be compared.[13]

Thus the addition of acid chlorides to acetylene in the presence of aluminum chloride after distillation resulted in pure *trans*-β-chlorovinyl ketones. When vinyl chloride was condensed with isobutyryl chloride, a product was formed with correct analysis, but its n.m.r. spectrum exhibited a pattern which could be considered a mixture of both the *cis* and the *trans* protons. This possibly could indicate that the second step, elimination, has led to both isomers. In all other

(1) Taken in part from the dissertation of A. E. Pohland which was submitted in partial fulfillment of the requirements of the doctorate degree, 1963.

(2) Supported in part by the Research Corporation, the Colorado State University Research Foundation, and the Institute for Neurological Diseases and Blindness (Project NB 04088-01).

(3) To whom correspondence should be addressed at Food and Drug Administration, Division of Food, Pesticides Branch, Department of Health, Education, and Welfare, Washington 25, D. C.

(4) Boettcher Foundation Fellow, 1962–1963.

(5) D. Nachmansohn and I. Wilson, "Molecular Biology," Academic Press, New York, N. Y. 1960, p. 168.

(6) J. W. Kroeger, F. J. Sowa, and J. A. Nieuwland, *J. Org. Chem.*, **1**, 163 (1936), and references therein.

(7) A. N. Nesmeyanov, N. K. Kochetkov, and M. I. Rubinskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 350 (1950); *Chem. Abstr.*, **45**, 1585 (1951).

(8) N. K. Kochetkov, *Dokl. Akad. Nauk SSSR*, **84**, 289 (1952); *Chem. Abstr.*, **47**, 3309 (1953).

(9) N. K. Kochetkov, B. P. Gottikh, and M. Ya Karpeiskii, *Khim. Nauka i Promy.*, **3**, 834 (1958); *Chem. Abstr.*, **53**, 10021 (1959).

(10) J. R. Catch, *et al.*, *J. Chem. Soc.*, 278 (1948).

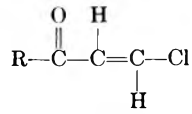
(11) V. J. Klimko, V. A. Mikhalev and A. P. Sholdinov, *J. Gen. Chem. USSR*, **27** 415 (1957).

(12) N. K. Kochetkov, *et al.*, *ibid.*, **28**, 3053 (1958).

(13) W. E. Truce and B. Groten, *J. Org. Chem.*, **27**, 128 (1962).

TABLE I

β-CHLOROVINYL KETONES



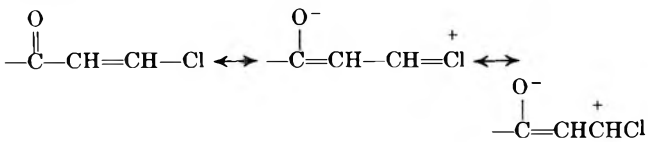
R	Compound	B.p. (mm.), °C.	Yield, %	Found n^t_D (temp., °C.)	Reported at 20°	J_{AB}, c.p.s.
CH_3	I	76 (98)	92.7	1.4678 (20)	1.4675[a]	13.0
C_2H_5	II	56 (22)	69.0	1.4628 (26.5)	1.4596[a]	14.0
n-C_3H_7	III	61–64 (18)	83.2	1.4641 (20)	1.4640[a]	14.0
i-C_3H_7	IV	69–69.5 (34)	67.6	1.4610 (20)	1.4585[a]	13.1
i-C_4H_9	V	84–80 (25)	78.4	1.4579 (28)	1.4590[a]	14.0
t-C_4H_9[d]	VI	72 (25)	71.1	1.4573 (24)	1.4593[b]	13.0
C_6H_5	VII	97–102 (7)	30.8	1.5836 (25)	1.5860[c]	

[a] See ref. 8. [b] See ref. 12. [c] See ref. 28. [d] Prepared by different method.

cases where acetylene was used, the *cis* isomer was not detectable to the limit of the n.m.r. instrument (less than 5%) and was not separable by g.l.c.

The conformation of the β-chlorovinyl ketone system was examined through the ultraviolet and infrared spectra of these compounds and spectra of similar systems.

Julia[14] found that methyl vinyl ketone itself absorbed at 210 mμ (ε 7000), whereas methyl β-chlorovinyl ketone absorbed at 228 mμ (ε 10,000). Thus substitution of a chlorine atom had resulted in a bathochromic shift of 18 mμ and a slight hyperchromic effect. Sanchez[15] found through the substitution of a second chlorine atom in the β-position that a further bathochromic shift of 13 mμ resulted. In the present study, it was found that the β-chlorovinyl ketones absorbed consistently at longer wave lengths (*ca.* 16 mμ) than their nonhalogenated analogs. A marked hyperchromic effect also was noted. These effects were undoubtedly due to an extension of the conjugated system by the chlorine atom through such dipolar structures as the following.



Although no data were found regarding the difference in energy of the cisoid and transoid forms, it might be suggested that the energy difference would be about the same as the difference in energy between cisoid and transoid butadiene, *ca.* 2.5 kcal./mole or somewhat higher for the unsubstituted α,β-unsaturated ketone. However, in the β-chlorovinyl ketones this energy difference may be much larger due to resonance structures. In such systems the transoid conformation generally has been considered to be the most stable.[16]

An examination of Dreiding models revealed that in all cases, except the *t*-butyl and phenyl β-chlorovinyl ketone, the transoid conformation was planar and free of steric strain. However, in the *t*-butyl and phenyl analogs there appeared to be some steric interference. The latter two compounds, therefore, conceivably could lie in the cisoid or some nonplanar conformation.

Turner and Voitle[17] assumed and Mecke and Noack[1] postulated that α,β-unsaturated carbonyl systems must lie either in the transoid or cisoid conformation since only in these instances is there maximum conjugation or resonance energy. However, Braude and Timmons[18] have pointed out that this need not be the case and that, indeed, when the transoid conformation is sterically unfavored, nonplanar conformations may result rather than a complete inversion to the cisoid conformation. These authors developed the equation $\epsilon/\epsilon_0 = \cos^2(\theta_1 - \theta_2)$ to obtain the value of the interplanar angle from spectral data in sterically hindered compounds, and this equation was revised recently by Forbes and Mueller[19] to account more rigorously for the spectra of unsymmetrical molecules. In these equations ϵ_0 is the molar absorption coefficient of the planar model, while ϵ is that of the nonplanar molecule. θ_1 represents the interplanar angle in the ground state between the plane of the carbonyl group and that of the double bond, whereas θ_2 represents the interplanar angle in the excited state (usually considered to be zero).

On examination of the ultraviolet data of the alkyl β-chlorovinyl ketones (see Table II), it was apparent that all of the these open-chained ketones absorbed maximally in the same wave-length range (229–232.5 mμ) and with approximately the same intensity (ε 14,600–11,200). This could indicate that all are of the same conformation.[14] Since, in methyl β-chlorovinyl ketone, both the cisoid and transoid forms are assumed to be unstrained and planar, one would predict that in this compound the transoid conformation predominates to the virtual exclusion of the cisoid form. If this is so, then the remainder of this series are probably transoid. However, as was noted before, in *t*-butyl β-chlorovinyl ketone the planar transoid conformation is sterically unfavored. Thus, one would expect this compound to be slightly nonplanar or cisoid. This may be the reason that a decrease in the intensity of the K-band of this compound, when compared with the intensity of the K-band of I, gave no accompanying hypsochromic effect. This phenomenon previously had been ascribed to electronic transitions between nonplanar ground states and near-planar excited states. However, even with the *t*-butyl derivative the effect was quite small and, if one uses Braude's equation for

(14) M. Julia, *Ann. chim.* (Paris), [12] **5**, 595 (1950).

(15) R. Sanchez, Ph.D. dissertation, Kansas State University, 1962, and references therein.

(16) R. Mecke and K. Noack, *Ber.*, **93**, 210 (1960); see also ref. 22.

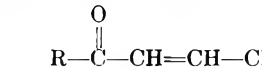
(17) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

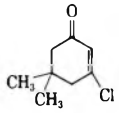
(18) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3766 (1955).

(19) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **33**, 1340 (1956).

TABLE II

SPECTRAL DATA ON β-CHLOROVINYL KETONES



R	Compound	Infrared spectra bands, cm.$^{-1}$ $\nu_{C=O}$	$\nu_{C=C}$	ν_{C-H}	ν_{C-Cl}	$\Delta_{C=O-C=C}$	Ultraviolet spectral data λ_{max}, mμ ($\epsilon \times 10^4$)	Lit. λ_{max}, mμ ($\epsilon \times 10^4$)
CH_3–	I	1678	1587	946.1	841.9	91	229 (1.46)	228 (1.00)
C_2H_5–	II	1686	1587	941.6	845.3	99	229 (1.32)	229 (1.26)
n-C_3H_7–	III	1678	1582	941.6	827	96	230 (1.24)	230
i-C_3H_7–	IV	1698	1592	940.7	846	106	232 (1.12)	
i-C_4H_9–	V	1689	1582	940.7	854.7	107	231.5 (1.16)	
t-C_4H_9–	VI	1686	1582	939.8	831.9	104	232.5 (1.22)	
C_6H_5–	VII	1664	1582	935.5		82	203 (1.04) 260 (1.65)	
	VIII (fixed transoid)	1681	1616		843.2	65	238 (1.35)	

calculation of the interplanar angle between the plane of the carbonyl group and the plane of the double bond, one arrives at an angle of 23° 55′. In view of the high intensity of the absorption maximum, one would not expect these compounds to be very highly nonplanar. We are still working on the *cis* compounds.

The infrared spectral data for the β-chlorovinyl ketones were collected in Table II and were in complete agreement with the proposed structures.

Examination of the infrared data indicated also a high degree of planarity, the carbonyl and double bond absorptions being significantly displaced to longer wave lengths. A split carbonyl peak has been found in the infrared spectrum of methyl vinyl ketone itself at 1701 and 1683 cm.$^{-1}$ corresponding possibly to the cisoid and transoid conformations, respectively.[20] All the β-chlorovinyl ketones exhibited only one carbonyl absorption band. In all cases, both the carbonyl and the double bond absorption were of about the same intensity, the double bond absorption band being slightly more intense than the carbonyl band. In addition, the carbonyl and double bond absorption bands were separated by *ca.* 99 cm.$^{-1}$. These data according to some hypotheses[22] would indicate that the compounds were in the cisoid form, since in the cisoid form the intensities of $\nu_{C=O}$ and $\nu_{C=C}$ are normally comparable and the difference between $\nu_{C=O}$ and $\nu_{C=C}$ is usually[21] greater than 75 cm.$^{-1}$. Erskine and Waight[22] concluded that the ratio of the integrated band intensities of the carbonyl and double bond stretching vibrations lies between 0.6 and 3.5 for cisoid and is greater than 6 for transoid ketones, but these authors also indicated that strongly electronegative substituents on the double bond may alter these values considerably.

This appeared to be the case in the β-chlorovinyl ketones. The above rules did not seem to apply because of the β-chlorine substituent whose effect appeared to be one of increasing the intensity of the double bond absorption band and displacement of this band to longer wave lengths without greatly affecting the carbonyl absorption band (normally[21] found at 1675 cm.$^{-1}$). The double bond absorption band of α,β-unsaturated ketones usually has been found in the 1650–1600-cm.$^{-1}$ region. In all the β-chlorovinyl ketones, this band was shifted to considerably longer wave lengths. Thus infrared data support transoid conformations.

Quaternary Salts.—Several reviews have been written on the replacement reaction of β-chlorovinyl ketones[23-25] and there are also reviews on their use as intermediates in the synthesis of a large variety of heterocyclic compounds.[26,27] However, no work has been reported on the stereochemistry of this replacement reaction.

β-Chlorovinyl ketones have been treated with tertiary amines,[28,29] but, with the exception of (β-acetyl- and β-benzoylvinyl)trimethylammonium chloride,[28] no β-acylvinyltrimethylammonium salts have been found in the literature.

When the β-chlorovinyl ketones were treated with trimethylamine in toluene, an immediate, exothermic reaction followed in all cases giving nearly a quantitative yield of the quaternary salt (eq. 2). These salts were white, water-soluble solids with variable melting point ranges, dependent presumably on the rate of heating; the solids appeared to decompose before the melting point was reached. On standing, unless carefully purified, they slowly turned light brown. The quaternary salts had correct analyses (see Table III).

The picrate of each salt was prepared because of the wide melting point ranges displayed by these quaternary salts. These light yellow picrates, after recrystallization from 95% ethanol, exhibited very sharp melting points (Table III).

Bromine was added to these quaternary salts in chloroform. In every case the bromine color rapidly disappeared, and the quaternary salt, originally only slightly soluble in chloroform, completely dissolved. In the case of the isopropyl derivative, a white solid

(20) K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

(21) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962.

(22) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(23) N. K. Kochetkov, *Prakt. Chem.*, **12**, 336 (1961).

(24) N. K. Kochetkov, L. I. Kudryaskov, and B. P. Gottikh, *Tetrahedron*, **12**, 63 (1961).

(25) N. Sugiyama and G. Inoui, *Yuki Gosei Kagaku Kyokai Shi*, **19**, 373 (1961); *Chem. Abstr.*, **55**, 17,484 (1961).

(26) A. N. Nesmeyanov and N. K. Kochetkov, *Uch. Zap. Mosk. Gos. Univ.*, **No. 175**, 85-95 (1956); *Chem. Abstr.* **51**, 10,470 (1957).

(27) M. Julia, *Compt. rend.* **228**, 1807 (1949).

(28) V. T. Klimko, *et al.*, *J. Gen. Chem. USSR*, **27**, 69 (1957).

(29) R. P. Hills and F. J. McQuillin, *J. Chem. Soc.*, 4060 (1953).

TABLE III

DATA FOR R—C(=O)—C(H)=C(H)—X

R	X	Compound	Found m.p. or b.p. (mm.), °C.	Reported m.p. or b.p. (mm.), °C.	Yield, %	Recrystallizing medium	Analyses or an (temp., °C.) Lit. or calcd.	Found	M.p., °C. (picrate $\nu_{C=O}$ infrared band, cm.$^{-1}$)	Splitting constants c.p.s. J_{AB}
CH_3	$N(CH_3)_3Cl^-$	X	154–158 dec.	150 dec. 135–136 dec.	90.5	1-Butanol acetonitrile			124.5–125.0 (1709)	14.2
C_2H_5	$N(CH_3)_3Cl^-$	XI	171–172 dec.		88.4	1-Butanol acetonitrile	$C_8H_{16}ClNO$ C, 54.10 H, 9.10 N, 7.80	 C, 54.00 H, 9.00 N, 7.96	114.0 (1715)	14.2
n-C_3H_7	$N(CH_3)_3Cl^-$	XII	142–150 dec.		89.0	Acetonitrile	$C_9H_{18}ClNO$ C, 56.39 H, 9.46 N, 7.31	 C, 56.18 H, 9.63 N, 7.09	104.0–104.5 (1712)	14.0
i-C_3H_7	$N(CH_3)_3Cl^-$	XIII	153–155 dec.		82.6	1-Butanol acetonitrile	$C_9H_{18}ClNO$ C, 56.39 H, 9.46 N, 7.31	 C, 56.39 H, 9.74 N, 7.28	141.5 (1712)	14.1
i-C_4H_9	$N(CH_3)_3Cl^-$	XIV	108–110 dec. (impure)		85.8	Acetonitrile (difficult)	$C_{10}H_{20}ClNO$ C, 58.38 H, 9.80 N, 6.81	 C, 56.78 H, 9.75 N, 6.58	...	14.0
t-C_4H_9	$N(CH_3)_3Cl^-$	XV	152–154 dec.		91.5	1-Butanol	$C_{10}H_{20}ClNO$ C, 58.38 H, 9.80 N, 6.81	 C, 58.31 H, 9.95 N, 6.87	148.0–148.5 (1706)	0
C_6H_5	$N(CH_3)_3Cl^-$	XVI	160–161 dec.	159 dec.	86.4	95% ethanol			185.5–186.5	
CH_3	-I	XVII	56.0–56.5	55–56	96.4	Petroleum ether (30–60)				15.0
CH_2	-SCN	XVIII	39–40	39–40	96.0	Petroleum ether				8.5
CH_3	$-N(CH_3)_2$	XIX	132–133 (20)	131–133 (20)	72.0	G.l.c. pure	1.5560 (20)	1.5562 (20)		13.0
CH_3	-CN	XX	71 (11)	73 (11)	54.9	G.l.c. pure	1.4622 (20)	1.4590 (27)		16.0
t-C_4H_9	-OH	XXI	53–56 (25)	53–56 (25)	47.9	G.l.c. pure	1.4503 (25)	1.4523 (20.5)		4.5

then precipitated quantitatively and it had the correct analysis for the desired dibromide. In all cases where a solid was recovered the strong double bond absorption band of the salts disappeared in the infrared spectrum leaving a low intensity band in its place. The carbonyl band remained unchanged. These results may be taken as evidence for unsaturation.

The substitution of vinylic halides is normally not a facile process.[30] However, if the vinylic halide is activated by an electron-withdrawing group or a group which may stabilize a negative charge in the α-position (to the stabilizing group), then replacement of the halide is known to occur quite easily.[15,31–33]

No work had been reported,[23] however, on the mechanism by which the β-chlorine atom of β-chlorovinyl ketones is replaced by the various nucleophiles.

As was discussed previously, the β-chlorovinyl ketones were found to be at least 95% *trans* through n.m.r. spectroscopy. The n.m.r. spectra of the β-acylvinyltrimethylammonium chlorides were then obtained. Inspection of these spectra revealed that the two hydrogens of the double bond were *trans* to one another, the splitting constants being *ca.* 14 c.p.s. as shown in Table III. It is safe to say from examination of these spectra that *at least* 95% of the *trans* product was obtained in these reactions.[34] The spectrum of the *t*-butyl derivative, however, was anomalous in that, instead of the characteristic quartet of lines of the AB pattern, a single broad band appeared. In some manner the electronic effect of the trimethylammonium moiety and the pivaloyl moiety has caused the protons of the double bond to experience identical magnetic fields. The protons thus have become equivalent under the resolution used. A satisfactory explanation of this must await further experimentation on similar structures.

Thus retention of configuration was observed in the reaction of β-chlorovinyl ketones with trimethylamine leading to *trans* products. The fact that these reactions were kinetically very fast and exothermic would appear to rule out the formation of acetylenic intermediates, as these could only be formed through *cis* elimination of hydrogen chloride which is usually a slower, more difficult process. However, it should be noted that there is a second route to these compounds which involves the addition of trimethylamine to acetylenic ketones in the presence of trimethylamine hydrochloride, but the stereochemistry and generality of this reaction has not been established.[35]

The addition–elimination reaction was unlikely in the present instance, because there were no hydrogen

(30) E. L. Eliel, "Stereochemistry of Organic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 368-70 and references therein.

(31) W. Autenreith, *Ann.*, **254**, 222 (1889); **259**, 332 (1890); F. Montanari, *Gazz. chim. ital.*, **86**, 747 (1956); G. Modena and P. E. Todesco, *ibid.*, **89**, 854 (1959).

(32) S. I. Miller and P. K. Yonan, *J. Am. Chem. Soc.*, **79**, 5931 (1957).

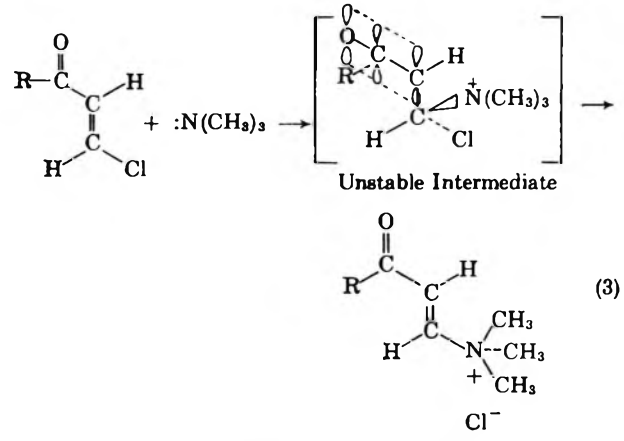
(33) D. E. Jones, *et al.*, *J. Chem. Soc.*, 2349 (1960).

(34) M. Hanna, private communication, University of Colorado.

(35) C. J. Cavallito, *J. Am. Chem. Soc.*, **77**, 4159 (1955).

atoms readily available for formation of the intermediate proposed for this path.

Thus the most likely path for the reaction of β-chlorovinyl ketones with trimethylamine probably involved conjugate addition elimination (eq. 3).



(3)

Essentially the same mechanism was proposed by Miller and Yonan,[32] Jones and co-workers,[33] and Sanchez[15] for other systems.

The stereochemistry might be explained well by using bimolecular nucleophilic displacements on aromatic rings as a model. We have not been able as yet to prepare the pure acyclic *cis* β-chlorovinyl carbonyl compounds to see if this reaction is stereospecific. β-Chlorovinyl aldehydes which are *cis* due to a fixed ring system even at higher temperatures gave no reaction with trimethylamine.[36] *trans* compounds may be preferred, however, as indicated in the conversion of *cis* XXI to *trans* V.

The infrared and ultraviolet spectral data seen in Table IV indicate that there is less interaction of the C=O with the C=C in these β-acylvinyltrimethylammonium chlorides than normally found.

TABLE IV

SPECTRAL DATA FOR (β-ACYLVINYL)TRIMETHYLAMMONIUM CHLORIDES

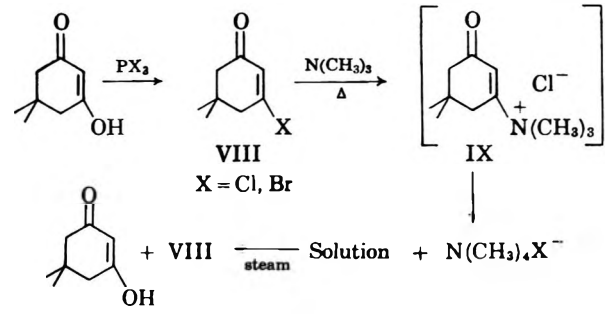
$RCOCH{=}CH{-}\overset{+}{N}Me_3\ Cl^-$

R	Compound	Infrared data, cm.⁻¹ νC=O	νC=C	νHC=CH	Ultraviolet data λmax mμ, (ε × 10⁴)
-CH3	X	1686	1645	937.2	206.5 (7.30)
-C2H5	XI	1686	1645	938.1	207.5 (6.95)
n-C3H7	XII	1684	1661	934.6	208 (7.20)
-i-C3H7	XIII	1712	1637	944.3	208 (7.41)
-i-C4H9	XIV	1712	1645	945.2	208 (7.80)
-t-C4H9	XV	1704	1642	944.3	207.5 (8.44)
-C6H5	XVI	1681	1639	943.4	206.5 (8.98) 216 sh (7.19) 267 (7.82)
$CH_2C(=O)CH{=}CH_2$					212.5 (7.00)

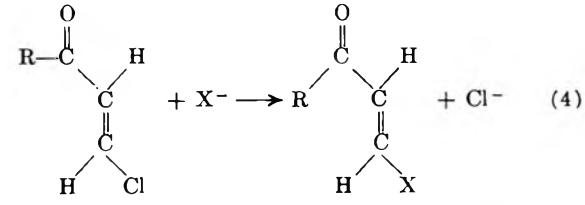
When compared with the β-chlorovinyl ketones, it was observed that the double bond absorption bands lay at shorter wave lengths in the quaternary salts. It also was observed that in the quaternary salts the double bond absorption band was only about two-thirds as intense as the carbonyl absorption band, and the two bands lay well within the range of 75 cm.⁻¹ of one another. On this basis one might qualitatively conclude that these compounds were also transoid. Finally, the bands in the 937–945-cm.⁻¹ range appearing in each spectrum indicated a *trans* arrangement about the double bond.

The ultraviolet spectra were obtained in 95% ethanol. Each spectrum exhibited a medium intensity band in the 206.5–208-mμ range. A large hypsochromic shift was observed when the spectra of the β-chlorovinyl ketones (Table II) were compared with the spectra of the β-acylvinyltrimethylammonium salts. In fact, the quaternary salts were found to absorb in the same wave-length range and with approximately the same intensities as do the unsubstituted vinyl ketones. A similar result has been observed in the case of aniline when compared with the anilinium cation.[37]

A fixed transoid β-chlorovinyl ketone, VIII, was prepared[38] for comparison with the labile systems and VIII gave an ultraviolet spectrum [λ_{max} 238 mμ (ε 13,500)] which compared favorably with I–VII. When VIII was treated with trimethylamine, a high conversion to tetramethylammonium chloride was found. Incidentally, VIII was inferred to be water sensitive.[38] However, it steam distilled in part along with toluene and was later recovered as unchanged VIII. The over-all reaction is given as the following.



Since trimethylamine gave complete retention of configuration when it replaced the chloride, it was desirable to determine whether this process was general for other nucleophiles (eq. 4).



(4)

The R group was held constant (as a methyl) and the X^- was represented by I^-, CN^-, ^-SCN, and $H\ddot{N}(CH_3)_2$. The results of this work also are given in Table III and show complete retention. The XVII is somewhat lower in its J_{AB} value than the other substituents (except for the XXI group, which is considered to lie in the *cis* configuration due to the added stability acquired through internal chelation). Although 8 c.p.s. is somewhat lower than the range expected for *trans* hydrogens (10–20 c.p.s.), only one isomer appeared to form and this compound is probably *trans*. This work is continuing.

(36) Unpublished results of W. R. Benson and A. E. Pohland.

(37) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Ed. Arnold, Ltd., London, 1954.

(38) A. W. Crossley and H. R. LeSeuer, *J. Chem. Soc.*, **83**, 110 (1903).

Experimental

Elemental analyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratory, 164 Banbury Road, Oxford, England. Melting points were taken on a Fisher-Johns melting point apparatus and were corrected. The refractive indices were obtained through use of a Bausch and Lomb refractometer. The Aerograph A110-C was used for all g.l.c. analyses; unless otherwise specified a silicone Dow 11 column was used. The n.m.r. spectra were measured on a Varian A-60 megacycle spectrometer. Infrared spectra were measured on a Beckman IR-5 spectrophotometer. The reported wave lengths were estimated to be within ± 1 cm.$^{-1}$ in the 1250–650-cm.$^{-1}$ range, ± 2 cm.$^{-1}$ in the 1250–1400-cm.$^{-1}$ region, ± 3 cm.$^{-1}$ in the 1400–1500-cm.$^{-1}$ range, ± 4 cm.$^{-1}$ in the 1600–1500-cm.$^{-1}$ region, ± 5 cm.$^{-1}$ in the 1600–3000-cm.$^{-1}$ region, and ± 10 in the 3500–3000-cm.$^{-1}$ region. All ultraviolet spectra were obtained using a Bausch and Lomb Spectronic 505 recording spectrophotometer.

Preparation of β-Chlorovinyl Ketones.—The preparation of β-chlorovinyl ketones generally involved the Friedel–Crafts addition of acid chlorides to acetylene. The acid chlorides were redistilled before use and were shown to be pure by gas chromatography. All the alkyl β-chlorovinyl ketones were unstable and decomposed slowly to brown liquids even when kept at low temperatures, except for the *t*-butyl derivative, which was quite stable. However, these brown liquids could still be redistilled before use. All were vesicants, the lower members being strongly lachrymatory. The phenyl β-chlorovinyl ketone was quite stable at room temperature.

Preparation of 1-Chlorobuten-3-one (I).—The method generally used here was that of Catch and co-workers.[39] In a 2-l. three-necked flask fitted with a gas inlet tube, Trubore stirrer, and condenser protected by a calcium chloride drying tube was placed 1.5 l. of carbon tetrachloride. The mixture was cooled to 0° in an ice–salt bath while acetylene was introduced over a period of *ca.* 15 min. The acetylene was dried and purified by passing it through a trap of concentrated sulfuric acid, protected on each side by an empty trap and by a mercury pressure release valve. The gas inlet tube was replaced by a dropping funnel and 333 g. (4.24 moles) of acetyl chloride was added dropwise over 15 min. The gas inlet tube was replaced and 650 g. (4.87 moles) of aluminum chloride was added in 50-g. lots each half hour through the neck containing the gas inlet tube. On completion of addition of the aluminum chloride, the mixture was stirred at room temperature an additional 6 hr. At the end of this time, the black viscous complex which had formed was hydrolyzed by pouring over chopped ice, the carbon tetrachloride layer separated, and the aqueous layer extracted with chloroform. The combined carbon tetrachloride–chloroform extracts were distilled at reduced pressure to yield 314.74 g. (71.8%) of crude product, b.p. 72–74° (95–100 mm.), which was shown to be slightly impure by gas chromatography. The mixture was refractionated to yield pure I, b.p. 76° (98 mm.), n^{20}D 1.4678 [lit.[42] b.p. 74° (100 mm.), n^{18}D 1.4649]. To the forerun of the initial distillation was added a 2 *M* solution of trimethylamine in toluene; 142.3 g. of β-acetylvinyltrimethylammonium chloride (X) was obtained, m.p. 142–146° dec. This corresponded to an additional 91.30 g. of I; thus the total yield was 406.04 g. or 92.7%. The other ketones were prepared similarly except for VI.

Preparation of 1-Chloro-4,4-dimethyl-1-penten-3-one (VI).—The procedure followed here was that of Kochetkov and co-workers.[41] The yield was 47.9% of hydroxymethylene pinacolone, b.p. 53–56° (25 mm.), n^{25}D 1.4503 [lit.[41] b.p. 53–56° (25 mm.), $n^{20.5}$D 1.4523]. This product was shown to be pure XXI by g.l.c.

In a 200-ml., single-necked flask fitted with a 60-ml. addition funnel protected by a calcium chloride drying tube, was placed 80 ml. of dry benzene and 16.4 g. (0.13 mole) of hydroxymethylenepinacolone. To this mixture was added dropwise with ice cooling 16.2 g. (0.14 mole) of thionyl chloride in 40 ml. of benzene. The mixture was allowed to warm to room temperature, after which it was refluxed for 8 hr. The solution was then fractionated to yield 5.42 g. of forerun, b.p. 68–72° (25 mm.), and 13.31 g. (71.1%) of VI, b.p. 72° (25 mm.), n^{24}D 1.4573 [lit.[41] b.p. 66–67.5° (27 mm.), n^{20}D 1.4593]. This product was shown to be pure by g.l.c.

Preparation of β-Acylvinyltrimethylammonium Chlorides.—Generally this involved the addition of a 2 *M* solution of trimethylamine (Rohm and Haas) in toluene to a solution of the chlorovinyl ketone in toluene. The solution immediately began to precipitate a white-tan solid and the solution warmed from the exothermic reaction. This solid was filtered and washed with toluene followed by absolutely dry ether. The melting point of this solid was usually 5 to 10° below the final melting point. In all cases the melting points varied depending upon how slowly the block was heated. The difficulty of identification by melting point in this case was overcome by the formation of the picrate derivative which easily gave a very pure, characteristic, reproducible melting point range without apparent decomposition. The substituted ammonium chloride salts were recrystallized from 1-butanol, acetonitrile, and/or 95% ethanol. The infrared spectrum of each picrate was taken and the new C=O and C=C bands were recorded in Table III. The yields were based on the crude products. A slight excess of the amine was used.

Preparation of β-Acetylvinyltrimethylammonium Chloride (X).—The method generally used here was that of Kochetkov and co-workers[28] and a typical experiment is given here in the preparation of compound X.

In a 500-ml. erlenmeyer flask was placed 36.36 g. (0.35 mole) of I and 200 ml. (0.40 mole) of a cold 2 *M* solution of trimethylamine in toluene. The reaction began immediately on mixing and was exothermic, yielding a light tan solid, 51.93 g. (90.5%), m.p. 143–145°. Recrystallization from 1-butanol yielded a product, m.p. 151–153° (dec.); recrystallization from acetonitrile yielded a product, m.p. 154–158° dec. (lit.[28] m.p. 150° dec., lit.[40] m.p. 135–136°). The picrate was prepared by dissolving 3.10 g. (0.014 mole) of X and 2.20 g. (0.014 mole) of picric acid in 75 ml. of 95% ethanol, heating to boiling, and then cooling to 0°. The product was filtered and recrystallized from 95% ethanol, m.p. 124.5–125°. The infrared spectrum of the picrate exhibited a carbonyl band at 1709 cm.$^{-1}$ and a double bond absorption band at 1689 cm.$^{-1}$. The other products and their physical properties are given in Table III.

Treatment of β-Isobutyrylvinyltrimethylammonium Chloride (XIII) with Bromine.—In a 125-ml. erlenmeyer flask were placed 3.84 g. (0.02 mole) of XIII and 50 ml. of chloroform. To this solution was added with stirring 3.20 g. (0.02 mole) of bromine in 10 ml. of chloroform. After *ca.* 15 min. all of the solid had disappeared; the mixture was stirred 24 hr. during which time a white solid slowly precipitated. Filtration yielded 3.18 g. of white solid, m.p. 131° dec. Evaporation of the filtrate yielded 3.80 g. of a second crop, m.p. 110–130° dec. Thus the total yield was 6.98 g. (99.3%). Recrystallization from methanol yielded a product, m.p. 133–134° dec. The dibromide of XIII is being studied further.

Anal. Calcd. for $C_{10}H_{29}Br_2ClNO$: C, 32.85; H, 5.51; N, 3.84. Found: C, 33.17; H, 5.43; N, 3.88.

Preparation of Methyl 2-Iodovinyl Ketone (XVII).—In a 250-ml., single-necked flask fitted with a condenser protected by a calcium chloride drying tube was placed 10.45 g. (0.10 mole) of I, 14.99 g. (0.10 mole) of sodium iodide, and 100 ml. of dry acetone. The mixture was refluxed 4 hr. and then cooled to room temperature. The white solid which had precipitated was filtered and washed with acetone to yield 5.43 g. (92.7%) of sodium chloride, m.p. >300°. The filtrate was flash evaporated to yield 19.72 g. of light yellow solid; recrystallization from petroleum ether (b.p. 30–60°) yielded 18.90 g. (96.4%) of XVII, m.p. 56–56.5° (lit.[41] m.p. 55–56°). This compound was highly vesicant and lachrymatory; it decomposed to a brown solid within an hour after drying and was, therefore, kept under petroleum ether until used. The infrared spectrum in Nujol exhibited strong carbonyl absorption at 1721 cm.$^{-1}$ and double bond absorption at 1629 cm.$^{-1}$. The ultraviolet spectrum in 95% ethanol exhibited maximal absorption at 203.5 mμ (ε 3960) and 259 (9860).

Preparation of Methyl 2-Thiocyanovinyl Ketone (XVIII).—In a 200-ml., single-necked flask fitted with a condenser was placed 8.00 g. (0.077 mole) of I in 140 ml. of acetone and 10.00 g. (0.103 mole) of potassium thiocyanate in 10 ml. of water. The mixture was refluxed 3 hr., whereupon 5.21 g. (77%) of potassium chloride was filtered off, washed with acetone, and dried, m.p. >300°.

(39) J. R. Catch, *et al.*, *J. Chem. Soc.*, 278 (1948).

(40) A. N. Nesmeyanov and M. T. Rubinskaya, *Dokl. Akad. Nauk SSSR*, **115**, 315 (1957).

(41) N. K. Kochetkov, *ibid.*, **82**, 593 (1952); *Chem. Abstr.*, **47** 2691 (1953).

The filtrate was flash evaporated to yield 8.22 g. (96.0%) of a yellow-orange solid, which was recrystallized from petroleum ether (b.p. 30–60°) to yield 8.15 g. of XVIII, m.p. 39–40° (lit.[41] m.p. 39–40°). This product also was a strong vesicant and lachrymator. Its infrared spectrum in Nujol exhibited absorption bands at 2410 (—SCN), 1672 (C=O), and 1550 (C=C) cm.$^{-1}$. The ultraviolet spectrum in 95% ethanol exhibited maximal absorption at 205 mμ (ε 1154) and 276.5 (9234).

Preparation of 1-(N,N-Dimethylamino)-1-buten-3-one (XIX).—In a 250-ml. erlenmeyer flask was placed 70 ml. (0.621 mole) of a 40% aqueous solution of dimethylamine. To this solution was added dropwise, with stirring and ice cooling, 16 g. (0.15 mole) of I. After 0.5 hr. at room temperature the mixture was saturated with solid potassium carbonate and continuously extracted with ether for 12 hr.: the ether extracts were dried over anhydrous magnesium sulfate and distilled to yield 8.17 g. (72%) of XIX, b.p. 132–133° (20 mm.), n^{20}D 1.5560 [lit.[42] b.p. 131–133° (20 mm.), n^{20}D 1.5562]. The infrared spectrum exhibited a strong carbonyl band at 1664 cm.$^{-1}$. A band at 960 cm.$^{-1}$ indicated a *trans* arrangement with the double bond. The ultraviolet spectrum 95% ethanol exhibited maximal absorption at 302 mμ (ε 24,900).

(42) N. K. Kochetkov, *Izvest. Akad. Nauk. SSSR Otdel. Khim. Nauk* 991 (1953); *Chem. Abstr.*, **49**, 2308 (1955).

Preparation of Methyl β-Cyanovinyl Ketone (XX).—In a 250-ml. erlenmeyer flask was placed 16.37 g. (0.10 mole) of X, 150 ml. of benzene, and 6.51 g. (0.10 mole) of potassium cyanide. To this solution was added 5.0 g. (0.052 mole) of trimethylamine hydrochloride in 5 ml. of water. The reaction mixture was heated to 50°, whereupon a solution of 3.25 g. (0.05 mole) of potassium cyanide in 15.0 ml. of water was added dropwise with stirring. Evolution of trimethylamine was observed. On cessation of trimethylamine evolution, the benzene layer was decanted and a new portion of benzene (100 ml.) added. The mixture was heated at 50° for 1 hr. with stirring, whereupon the benzene layer was decanted and a fresh portion of benzene added. The entire process was repeated twice more. The benzene extracts were combined, dried over anhydrous sodium sulfate, and distilled to yield 5.21 g. (54.9%) of XX, b.p. 71° (11 mm.), n^{20}D 1.4622 [lit.[40] b.p. 73° (11 mm.), n^{27}D 1.4590]. The infrared spectrum (neat) exhibited absorption bands at 2232 (C≡N), 1706 (C=O), and 1618 cm.$^{-1}$ (C=C). A strong band at 965 cm.$^{-1}$ indicated a *trans* arrangement about the double bond. The ultraviolet spectrum exhibited maximal absorption at 226 mμ (ε 8384).

Acknowledgment.—The authors wish to thank Dr. M. Hanna and Dr. C. DePuy for their kind advice

The Autoxidation of 4-Vinylcyclohexene[1a]

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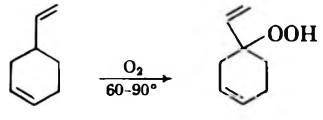
4-Vinylcyclohexene has been found to be autoxidized predominantly at the secondary allylic positions. All of the possible allylic hydroperoxides are formed to some extent. A similar product distribution is obtained from the attack on the olefin of *t*-butoxy radicals generated from *t*-butyl hydroperoxide–cobalt naphthenate and *t*-butyl peroxybenzoate–cuprous bromide.

The Diels–Alder dimer of butadiene, 4-vinylcyclohexene (**1**), has been reported[2] to be autoxidized in the liquid phase to yield the tertiary hydroperoxide **3b** exclusively. This result requires that the propagative species in the autoxidation chain, presumably a peroxy



1 **3b**

radical, removes a tertiary allylic hydrogen to the exclusion of the more abundant secondary. By contrast, our preliminary experiments with this system indicated that the oxidation produced a mixture of predominantly secondary hydroperoxides. Thus, the hydroperoxides could be catalytically hydrogenated and the resulting alcohols oxidized to a mixture of ketones in which the most abundant component would be 3-ethylcyclohexanone. A quantitative determination of the hydroperoxides produced in this autoxidation could provide valuable information regarding the selectivity of peroxy radicals toward attack on allylic carbon–hydrogen bonds of several types. Hence, our efforts were directed toward examining the isomer distribution obtained under differing conditions of temperature, solvent and initiation.

The autoxidation of **1** was effected by passing oxygen through the pure olefin or concentrated solutions of the olefin in *n*-decane, benzene, or *t*-butylbenzene at 60–80°. Most of the runs were terminated after sufficient oxygen was absorbed to oxidize 10–12% of **1**, but some cases were examined at conversion levels of 6 and 23%. Conversion level appeared to have no effect on isomer distribution. In a few instances, azobisisobutyronitrile (AIBN) initiation was employed. At low concentrations, AIBN had little effect, but at higher concentrations it eliminated a short induction period and increased the rate of oxygen absorption.

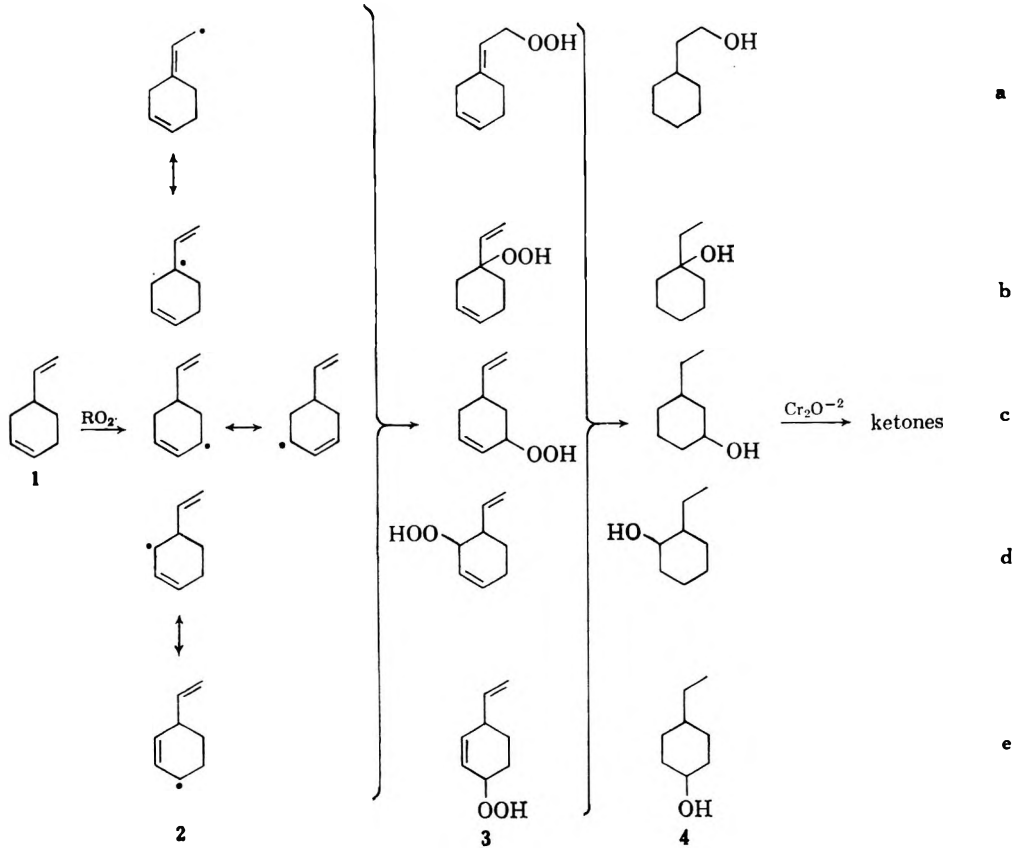
For low conversion runs, hydroperoxide of acceptable purity could be obtained by evaporation of the unoxidized olefin and evaporative distillation of the residue. The runs at higher conversions required extraction of the hydroperoxide with cold, dilute base and distillation to obtain hydroperoxide of satisfactory purity. Hydroperoxide with *ca.* 86% of the theoretical active oxygen could be obtained. It was feared that selective loss of secondary hydroperoxide by base-catalyzed decomposition[3] might occur during the extraction step, but a comparison of runs worked up by the two methods showed that these losses, if any, were not serious. That the distillation step (and the subsequent manipulations involved in analysis) did not change the isomer distribution was shown by analysis of the crude hydroperoxide by n.m.r. The secondary hydroperoxide fraction was estimated from a comparison of the area for the >CH-OO- hydrogen

(1) (a) Presented at the 18th Southwest Regional Meeting, American Chemical Society, Dallas, Tex., December 6, 1962; (b) The Carwin Company, Stiles Lane, North Haven, Conn.

(2) W. F. Brill, *J. Org. Chem.*, **24**, 257 (1959).

(3) N. Kornblum and H. E. De La Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951).

CHART I



with the area for the –OO–H hydrogen. Subsequent analysis by the scheme outlined below indicated 86.5% secondary, as compared with the 87% estimate by n.m.r.

The yield of hydroperoxide isolated by either of these procedures was only 55–65% based on oxygen uptake. No significant loss of active oxygen was apparent on heating a solution of the hydroperoxide in **1** under the reaction conditions; the active oxygen content dropped from 1.34% to 1.24% in 3 hr. at 80°. Some of the input oxygen is involved in formation of the polymeric peroxide which is always observed. In addition, the nonperoxidic fraction of the oxidation mixture contains alcohols and ketones derived from **1**. This portion of the oxidate was analyzed in the same manner as the hydroperoxide and shown to contain approximately the same isomer distribution. The hydroperoxide and ketone–alcohol fractions account for 90% of the input oxygen.

In order to determine the isomer distribution, the hydroperoxide mixture was hydrogenated to a mixture of ethylcyclohexanols, and the alcohols were oxidized to the corresponding ketones. Both alcohol and ketone mixtures were analyzed with gas–liquid partition chromatography (g.l.p.c.) by comparing retention times and peak areas with those for known mixtures of the expected components. In addition to the identification based on g.l.p.c. retention times, the major ketone component was isolated on a preparative-scale g.l.p.c. column and shown to be 3-ethylcyclohexanone by comparison of its semicarbazone with an authentic sample. The infrared spectrum of a known ketone mixture made up according to the g.l.p.c. analysis of an unknown, corresponded closely to the infrared spectrum of the unknown.

From peroxy radical attacks on **1** at the available allylic carbons, five hydroperoxide products might be anticipated as shown in Chart I. Hydrogenation produces a mixture of eight alcohols (including the *cis–trans* isomers of **4c**, **d**, and **e**) in which **4a** and **b** were determined by g.l.p.c. analysis on a packed column. The weight % of each component was obtained directly from calibration data. It was not possible to resolve completely the *cis–trans* pairs of the remaining secondary alcohols; so these were determined as the ketones. The only g.l.p.c. column available which achieved the necessary separation of all three ketone isomers was a 300-ft. capillary column coated with Carbowax 20M. A great deal of difficulty was experienced in obtaining reproducible areas for individual peaks, presumably due to variations in sample size. It was found that good reproducibility could be obtained for ratios of peak areas, and the ketones were analyzed on this basis. Results, normalized to 100%, are shown in Table I.

It is apparent from these data that the secondary allylic hydrogens are attacked preferentially and that the isomer distribution does not vary significantly over the limited ranges of temperature and diluents studied. Comparison of these results, in which peroxy radicals are the hydrogen-abstracting species, with those reported by Shelton and Henderson[4] for reaction of **1** with *t*-butyl hydroperoxide–cobalt naphthenate reveals an obvious discrepancy. For their system, in which *t*-butoxy radicals are the presumed hydrogen abstractors, a predominant secondary attack occurs also, but their analysis failed to reveal a product derivable from radical **2e** (Table II). In the interest of securing further information regarding the attack

(4) J. R. Shelton and J. N. Henderson, *J. Org. Chem.*, **26**, 2185 (1961).

TABLE I

ISOMER DISTRIBUTION IN AUTOXIDATION OF 4-VINYLCYCLOHEXENE

Diluent	AIBN init., g.,	Temp., °C.	% 4a	% 4b	% 4c	% 4d	% 4e
None		60	*b*	11.8 ± 0.7[a]	59.4 ± 2.6	11.9 ± 2.7	16.9 ± 0.7
None	0.1[c]	60	3.5	11.9	*b*	*b*	*b*
None	1.0[c]	60	2.0	10.6	*b*	*b*	*b*
None		75	*b*	10.2 ± 1.3	65.1 ± 1.6	8.3 ± 0.4	16.4 ± 0.1
t-BuC_6H_5[d]		75	3.3	10.0	63.4	7.9	15.4
C_6H_6[d]		82	*b*	9.0	65.1	7.2	18.7
n-Decane[d]		82	*b*	11.7	65.1	7.8	15.5

[a] Average deviation from the mean of duplicate runs. [b] Mixture not analyzed for this component. [c] For 100 ml. of olefin. [d] Fifty volume %.

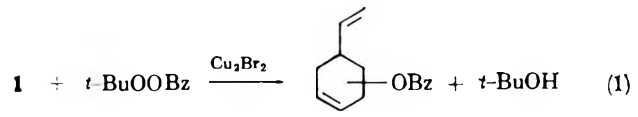
TABLE II

POSITION OF *t*-BUTOXY RADICAL ATTACK ON 4-VINYLCYCLOHEXENE

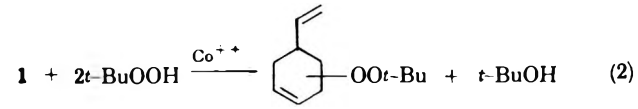
Radical source, temp., °C.	% 4b	% 4c	% 4d	% 4e
t-BuOOH–Co^{+2}, 45–55[a]	1–3	75–85	2–15	0
t-BuOOH–Co^{+2}, 50	3.4 ± 0.1[b]	63.2 ± 1.4	13.5 ± 0.6	18.8 ± 1.0
t-BuOOBz–Cu^{+}, 64–67	0[c]	56.0 ± 1.4[b]	19.4 ± 1.1	24.6 ± 0.3

[a] Data of Shelton and Henderson, ref. 4. [b] Average of two runs. [c] Less than 1%.

of *t*-butoxy radicals on **1** and in determining what effect, if any, metal ions might have on the isomer distribution, we have examined the reaction of **1** with *t*-butyl peroxybenzoate–cuprous bromide.[5,6] These results, along with our own data for the reaction of *t*-butyl hydroperoxide–cobalt naphthenate, are reported in Table II. As with the autoxidation experiments, attack at the secondary allylic hydrogens predominates.[7] The over-all reactions are outlined in eq. 1 and 2.



(1)



(2)

The reliability of the data in Table II is open to some question. Although the reaction of **1** with *t*-butyl peroxybenzoate proceeded readily, the yield and the purity of the product were low. After hydrogenation, the benzoate esters were saponified and the resultant alcohols analyzed as previously described. It is not known to what extent the saponification step may have affected the isomer distribution, or how much significance should be attached to the absence of **4b** from the product.

The hydroperoxide–cobalt reaction gave a much cleaner product. The analytical scheme followed the same pattern except that the mixed peroxide was hydrogenated directly to the saturated alcohols with a sponge nickel catalyst. The results are very similar to those reported by Shelton and Henderson if it is assumed that their analysis for **4c** also included **4e**.

(5) M. S. Kharasch, G. Sosnovsky, and N. C. Yang, *J. Am. Chem. Soc.*, **81**, 5819 (1959).

(6) J. K. Kochi, *Tetrahedron*, **18**, 483 (1962).

(7) The fact that the *t*-butoxy radical reacts with a surprising degree of selectivity may indicate a complex between the *t*-butoxy radical and the metal ion. Such a complex has been proposed to account for the abnormally high isotope effect for the hydrogen-abstraction step in a similar system [D. B. Denney, D. Z. Denney, and G. Feig, *Tetrahedron Letters*, **No. 15**, 19 (1959)].

In the cases examined, wherein **1** is subjected to attack by an oxy radical the tertiary hydrogen is decidedly less reactive than the secondary even allowing for the statistical factor of four secondary to one tertiary. This reversal of the normal relative reactivities appears in those cyclic olefins in which the tertiary allylic hydrogen and its associated double bond are not part of the same ring. In Table III are grouped a number of these along with some examples for which the usual reactivities apply.

TABLE III

AUTOXIDATION OF CYCLIC OLEFINS

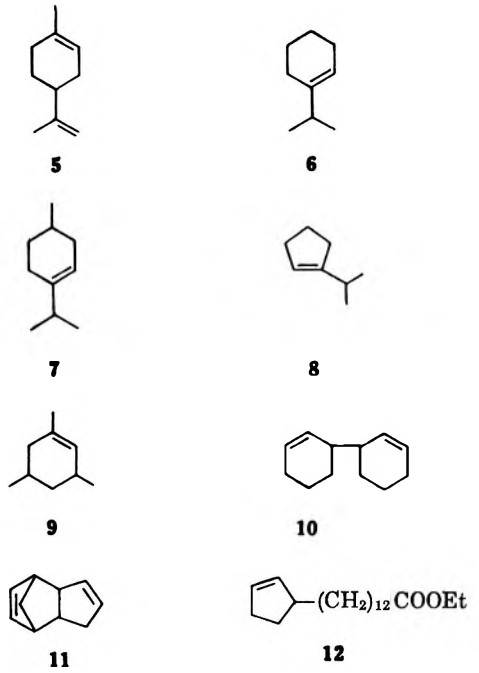
Secondary attack olefin	Tertiary attack olefin
1	9[a,b]
5[c]	
6[d]	10[a]
7[b,e]	11[f]
8[g]	12[h]

[a] L. Bateman, *Quart. Rev.* (London), **8**, 147 (1954). [b] J. L. Bolland, *Trans. Faraday Soc.*, **46**, 358 (1950). [c] A. Blumann and O. Zeitschel, *Ber.*, **47**, 2623 (1914); G. Widmark, *Arkiv Kemi*, **11**, 211 (1957); *Chem. Abstr.*, **52**, 1107 (1958); E. E. Royals and S. E. Horne, Jr., *J. Am. Chem. Soc.*, **77**, 187 (1955). [d] J. Moulines and R. Lalande, *Bull. soc. chim. France*, 1481 (1960). [e] H. Hock and S. Lang, *Ber.*, **75**, 300 (1942). [f] C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 409; H. Hock and F. Depke, *Ber.*, **84**, 356 (1951). [g] V. F. Belyaev and L. V. Kovalev, *Uch. Zap. Belorussk. Gos. Univ. Ser. Khim.*, **29**, 266 (1956); *Chem. Abstr.*, **54**, 7582, (1960). [h] A. G. Davies and J. E. Packer, *Chem. Ind.* (London), 1165 (1960).

These differences in reactivity may stem from the transition state requirement that, for maximum overlap of the developing radical with the π-orbitals of the double bond, the carbon–hydrogen bond to be broken be directed axially to the plane of the double bond. When the double bond and its allylic carbon are not part of the same ring this requirement results in loss of a degree of rotational freedom.[8] Hydrogen–hydrogen interactions between the vinyl hydrogens and those of the substituents on the allylic carbon are at a maximum in this conformation.[9] Both these factors would

(8) C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961).

(9) J. A. Meyer, V. Stannett, and M. Szwarc, *ibid.*, **83**, 25 (1961).



raise the energy of the transition state for abstraction of the tertiary hydrogen. For systems in which the double bond and its allylic carbon are part of the same ring, attainment of the transition state geometry results in no loss of rotational freedom and no large increase in nonbonded interactions.

Experimental

Materials.—Two samples of 4-vinylcyclohexene were used: Phillips Research grade for the initial experiments and a Humble sample of 99.7% purity for the succeeding runs. Both were percolated over silicic acid and stored under nitrogen prior to use. The solvents employed were *t*-butylbenzene, Phillips Petroleum Company pure grade; benzene, J. T. Baker analyzed reagent; *n*-decane, Matheson Coleman and Bell (b.p. 173–175°), percolated over alumina.

Calibration Compounds.—4-Ethylphenol was hydrogenated at 200° and 1500–1800 p.s.i.g. using Raney nickel catalyst to yield 4-ethylcyclohexanol, b.p. 192° at 768 mm., $n^{27}D$ 1.4601; lit.[10] b.p. 193–196° at 760 mm., $n^{20}D$ 1.4604. Oxidation of this alcohol with potassium dichromate in aqueous sulfuric acid gave 4-ethylcyclohexanone, which forms a semicarbazone, m.p. 171.5–174°, after recrystallization from methylcyclohexane.[11]

3-Ethylcyclohexanone was prepared from cyclohexenone by addition of the Grignard reagent from ethyl bromide and magnesium. It gave a semicarbazone, m.p. 167–174°, lit.[12] m.p. 175°.

2-Ethylcyclohexanone was obtained from Aldrich Chemical Company. It formed a semicarbazone which, after recrystallization from ethanol–water, had m.p. 155–157°, lit.[13] m.p. 163°.

1-Ethylcyclohexanol, prepared from cyclohexanone and the Grignard reagent from ethyl bromide and magnesium, had b.p. 67° at 10 mm.

2-Cyclohexylethanol was prepared by reduction of 4-(2-hydroxyethyl)cyclohexene and had b.p. 85.0° at 4.7 mm.

Oxidation Experiments.—The oxidation reactor consisted of a 500-ml. round-bottomed, four-necked, indented (Morton) flask, equipped with an efficient condenser, thermocouple well, gas inlet tube, and a Teflon-coated, high-speed stirrer. The coated stirrer was used to avoid the corrosion problems and consequent metal contamination observed in other oxidation systems. The apparatus was immersed in an oil bath maintained within ±1° of the desired temperature with a thermoregulating device. Oxygen entered the system through a wet-test meter, passed through the olefin condenser and a Dry Ice–isopropyl alcohol trap, and exited through another wet-test meter. The difference in readings between the inlet and the outlet wet-test meters was used as a measure of oxygen absorption. When the desired conversion had been attained (200 ml. of 1 requires 11 hr. at 60° for absorption of 4.22 l. of oxygen, 12% conversion), the oxygen input was stopped, and the reactor was cooled quickly in an ice–water bath. Conversions were usually *ca.* 12%, but ranged from 6–24%. The cooled oxidation mixture was transferred to a separatory funnel and was washed repeatedly with cold 5% sodium carbonate solution and then with cold 1 *N* sodium hydroxide solution. Acidification of the carbonate extracts produced a small amount (*ca.* 1 g.) of a viscous oil that was not further investigated. The sodium hydroxide extracts were acidified to pH 8.0–8.5 with gaseous carbon dioxide at 0°. The cold solution was extracted repeatedly with ether, the ether was dried with sodium sulfate, and the ether was evaporated. The strongly peroxidic yellow oil recovered (14.64 g., 0.105 mole) was evaporatively distilled at 47–49° and 0.03 mm. to give a nearly colorless oil of 86% purity based on active oxygen determination (iodometric).

In order to determine the isomer distribution in the hydroperoxide mixtures, samples were catalytically hydrogenated to a mixture of saturated alcohols. Thus, a sample of distilled hydroperoxide (1.6575 g., 0.0118 mole) dissolved in 30 ml. of absolute ethanol containing platinum oxide catalyst absorbed 679.8 cc. (0.0303 mole, 86%) of hydrogen. The catalyst was removed by filtration, and the solvent was distilled to yield 1.3352 g. of mixed alcohols. This sample was found to contain 8.9% 1-ethylcyclohexanol (4b) by g.l.p.c. analysis.

A sample of the alcohol mixture (1.0564 g., 0.0083 mole) was oxidized with potassium dichromate solution as described by Hussey and Baker[14] to yield 0.8720 g. (0.0069 mole, 83% yield) of mixed ketones and a tertiary alcohol.

Analysis of Ketone and Alcohol Mixtures.—The g.l.p.c. analyses were carried out in two steps. The alcohol mixtures were analyzed on a 2.5-m. column of 40% by weight polypentamethylene adipate on firebrick, operated at 140° and 70 cc./min. of helium. Known mixtures containing the tertiary alcohol were used to obtain calibration data of relative peak area to weight % tertiary alcohol. From this data, the per cent tertiary alcohol in the unknown samples was obtained graphically. Both known and unknown samples were run alternately, under identical conditions and on the same day, to minimize the effect of fluctuations in the operating characteristics of the column.

The ketone mixture was analyzed in much the same way, except that a Perkin-Elmer 300-ft. capillary column coated with Carbowax 20M was used at 130° and 25-lb. helium pressure. Under these conditions the peaks for 1-ethylcyclohexanol and 2-ethylcyclohexanone were sufficiently resolved to permit computation of the peak areas with reasonable accuracy. The remaining two peaks, corresponding to 3- and 4-ethylcyclohexanones, were resolved completely under these conditions. The absence of any other peaks of significant size suggests that the four compounds analyzed comprise the bulk of the sample.

In addition to their g.l.p.c. retention time, the compounds of the mixture were identified by comparing the infrared spectrum of the unknown with that of a synthetic mixture made up to match the g.l.p.c. analysis. The close correspondence of the spectra confirmed the g.l.p.c. assignments. Furthermore, a portion of the ketone mixture was separated by preparative g.l.p.c. Unfortunately, the resolution of the larger column was not sufficient to separate completely the 3- and 4-ethylcyclohexanones. However, the major component was concentrated and a semicarbazone, m.p. 162.5–164°, was prepared. The melting points of the semicarbazones of the isomeric ethylcyclohexanones and of the melting points of their mixtures with the unknown are as follows: 2-ethyl, 155–157°, 138.5–145°; 3-ethyl, 167–174°, 169–171°; 4-ethyl, 171.5–174°, 152–156.5°. Although the semicarbazone is probably not pure, it is evident that the 3-ethylcyclohexanone semicarbazone predominates, in agreement with the g.l.p.c. and infrared data.

Reaction of 1 with *t*-Butyl Hydroperoxide.—The procedure is essentially as described in ref. 4. To a stirred mixture of 108 g. (1 mole) of 1 and 10 g. (~0.1 mole) of *t*-butyl hydroperoxide at 0° was added, under nitrogen, a solution of 0.5 g. of 6% cobalt naphthenate in 0.5 ml. of 1. The mixture was allowed to warm to

(10) W. Ziegenbein, A. Schäffler, and R. Kaufhold, *Ber.*, **88**, 1906 (1955).

(11) G. I. Kiprianov and A. M. Veitsman [*Ukrain. Khim. Zhur.*, **19**, 662 (1953); *Chem. Abstr.*, **49**, 12320 (1955)] report m.p. 174–175°.

(12) G. F. Woods, P. H. Griswold, Jr., B. H. Armbrecht, D. I. Blumenthal, and R. Plepinger, *J. Am. Chem. Soc.* **71**, 2028 (1949).

(13) H. E. Ungnade and A. D. McLaren, *J. Org. Chem.*, **10**, 30 (1945).

(14) A. S. Hussey and E. H. Baker, *ibid.*, **25**, 1434 (1960).

room temperature and was heated to 50° for 4.5 hr. The reaction mixture was cooled, diluted with water, and was ether extracted. After having been washed with sodium bicarbonate solution and water and dried with magnesium sulfate, the ether solution was vacuum stripped to give 10.02 g. of crude product. Evaporative distillation at 48–58° and 0.03 mm. gave 4 ml. of colorless distillate and a thick, black residue. The distilled material in 25 ml. of ethanol was hydrogenated with a sponge nickel catalyst at 20° and 100 p.s.i.g. Filtration of catalyst and evaporation of solvent gave 2.78 g. (0.022 mole, ~22%) of a mixture of ethylcyclohexanols. The mixture was analyzed as described before.

Reaction of 1 with *t*-Butyl Peroxybenzoate.—A mixture of 1.004 g. of cuprous bromide and 50.0 ml. of 1 was stirred under helium at 70° while 2.39 g. (0.012 mole) of *t*-butyl peroxybenzoate was added over a 3.5-hr. period. Heating was continued an additional 16.5 hr., after which the mixture was cooled, filtered, washed with saturated sodium bicarbonate solution, then with water, and dried. Vacuum evaporation of unchanged olefin afforded 2.17 g. of residue.

A 2.01-g. sample was hydrogenated in ethanol with platinum oxide catalyst. This material apparently contained some unchanged olefin, since considerably more than the theoretical amount of hydrogen was absorbed (*ca.* 50% excess). The hydrogenation product was evaporatively distilled, then saponified in alcoholic sodium hydroxide. There was obtained 0.502 g. (4.0 mmoles, 36% based on total product) of ethylcyclohexanols. Analysis of the product by g.l.p.c. indicated the presence of small quantities of a number of other materials, as yet unidentified.

Acknowledgment.—The author is indebted to L. C. Jennings for much of the experimental work and to Professors W. E. Doering and R. Pettit for helpful discussions.

1-[*m*-(Ethoxydimethylsilyl)phenyl]-3-[*p*-(ethoxydimethylsilyl)phenyl]-hexafluoropropane and Its Cyclization to a Fluorinated Oxadisila-[3.3]metaparacyclophane

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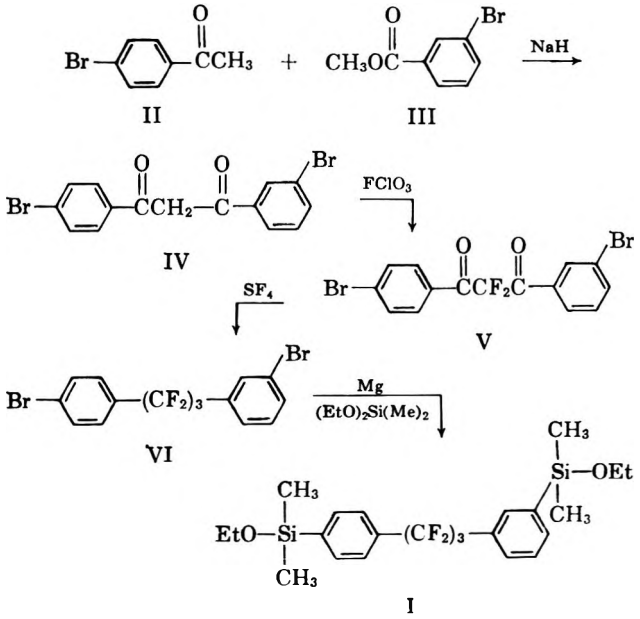
Treatment of a bifunctional Grignard compound, prepared from 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)hexafluoropropane (VI) with diethoxydimethylsilane, gave 1-[*m*-(ethoxydimethylsilyl)phenyl]-3-[*p*-(ethoxydimethylsilyl)phenyl]hexafluoropropane (I). A sublimate, obtained on heating the polymer of I, was shown to be a fluorinated oxadisila[3.3]metaparacyclophane (VII). To our knowledge, this is the first metaparacyclophane to be reported. Attempts to convert 1,3-bis(*p*-bromophenyl)hexafluoropropane (X) through the bifunctional Grignard compound to 1,3-bis[*p*-(ethoxydimethylsilyl)phenyl]hexafluoropropane (VIII) were not successful.

The synthesis of 1-[*m*-(ethoxydimethylsilyl)phenyl]-3-[*p*-(ethoxydimethylsilyl)phenyl]hexafluoropropane (I) was accomplished through the following sequence.



Condensation of *p*-bromoacetophenone (II) and methyl *m*-bromobenzoate (III) with sodium hydride in benzene gave a 43% yield of 1-(bromophenyl)-3-(*p*-bromophenyl)-1,3-propanedione (IV).

Treatment of IV in pyridine with perchloryl fluoride at −10 to 10° (hazardous!)[2] resulted in a 69% yield of 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)-2,2-difluoro-1,3-propanedione (V). A 53% yield of 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)hexafluoropropane (VI) was obtained on treatment of V with sulfur tetrafluoride.[3] Formation of a bifunctional Grignard compound from VI, followed by reaction with excess diethoxydimethylsilane, gave a 49% yield of I.

When a solution of I in benzene was refluxed with 50% sulfuric acid, and the benzene solution washed with water and concentrated, a clear tacky polymeric gum was obtained. On heating the gum at 145–155° (0.1 mm.) over a period of 12 hr., a white crystalline sublimate was obtained in 12% yield. Resublimation gave a product, m.p. 80–81.5°, that was homogeneous by v.p.c. The empirical formula $C_{19}H_{20}F_6OSi_2$ was derived from elemental analyses and from the parent peak 434 of the mass spectrum whose base peak 419 represented loss of a methyl group. The observed intensities of the parent +1 and the parent +2 peaks were in accord with those calculated[4] for the given empirical formula. The molecular weight in benzene solution by isothermal distillation was 436. Subsequent determinations gave values of 449 and 496, indicating some repolymerization. The infrared spectrum exhibited the characteristic $Si(CH_3)_2$ band at 7.95 μ, but lacked the ethoxy C–O–Si band at 10.55 μ. The n.m.r. spec-

(1) Deceased, September 2, 1963.

(2) Although this reaction has been carried out successfully ten times in the course of this work, it is considered to be very dangerous; all due precaution should be taken. The same procedure used in these laboratories for the fluorination of a similar compound, ethyl *p*-fluorobenzoylacetate, resulted in a violent explosion that completely demolished a 0.25-in. Plexiglas "safety" shield.

(3) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).

(4) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 9.

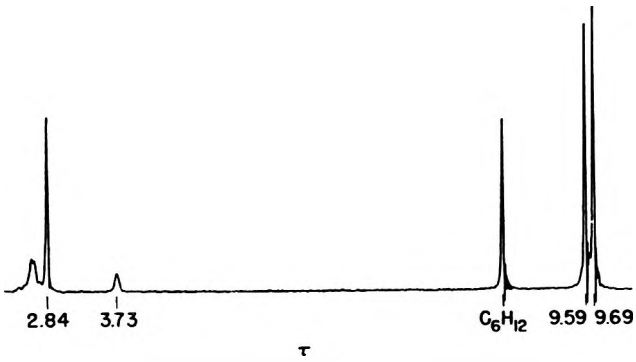
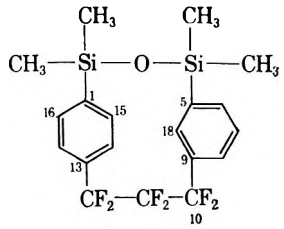


Fig. 1.—Proton n.m.r. spectrum of VII at 60 Mc.

trum (Fig. 1) showed an aromatic complex with a sharp peak at τ 2.84 ,a somewhat broadened resonance at 3.73, and two methylsilyl singlets at 9.59 and 9.69. The integrated areas for these three regions were 7.13:1.00:12.05, respectively.

From the foregoing data, the structure of a novel fluorinated oxadisila[3.3]metaparacyclophane[5] VII was assigned to this compound. To our knowledge, this is the first metaparacyclophane to be reported.[6]

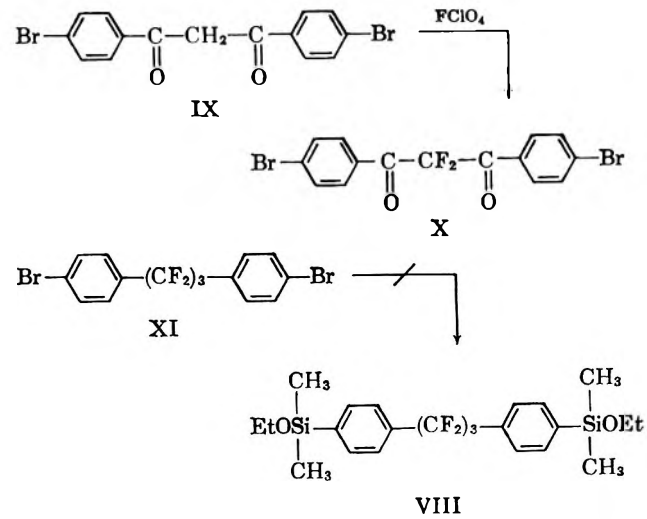


VII

Interpretation of the n.m.r. spectrum furnished convincing evidence for the proposed structure. The τ 3.73 peak (broadened by weak *meta* and *para* coupling) was assigned to the proton between the two ring substituents in the *meta*-substituted ring (C-18). Its relatively high field shift was ascribed to the ring-current shielding effect of the *para*-substituted ring. The magnitude of the shielding was not so great as in [2.2]metacyclophane (τ 5.75)[7] because of the larger size of our [3.3]cyclophane ring.

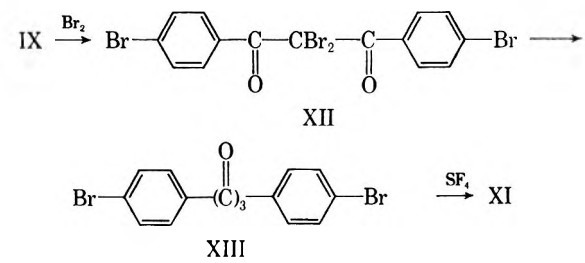
A Stuart–Briegleb model of VII clearly illustrated this shielding. The model was rigid with an angle of approximately 25° between the ring planes; the proton on C-18 was effectively positioned over the adjacent ring. The reason for two methyl shift positions was also apparent. All four methyl groups could freely rotate, but two *cis* groups were in more highly shielded positions than the other two. It is of interest to note that VII should exist as a pair of *dl* enantiomorphs.

A sequence of reactions analogous to reactions II → I was designed to synthesize 1,3-bis[*p*-(ethoxydimethylsilyl)phenyl]hexafluoropropane (VIII). Condensation of *p*-bromoacetophenone and methyl *p*-bromobenzoate gave 1,3-bis(*p*-bromophenyl)-1,3-propanedione (IX) in 50% yield. This was converted to 1,3-bis(*p*-bromophenyl)-2,2-difluoro-1,3-propanedione (X) in 53% yield with perchloryl fluoride. The latter compound on treatment with sulfur tetrafluoride gave a 73% yield of 1,3-bis(*p*-bromophenyl)hexafluoropropane (XI). Attempts to convert this compound through a Grignard reaction with diethoxydimethylsilane to VIII under the same conditions used for conversion of VI to I were unsuccessful.



IX X XI VIII

Alternative Routes.—Several other routes were explored to 1,3-bis[*p*-(ethoxydimethylsilyl)phenyl]hexafluoropropane (VIII). Bromination of 1,3-bis(*p*-bromophenyl)-1,3-propanedione (IX) by the procedure of Bigelow and Hanslick[8] gave a 79% yield of 1,3-bis(*p*-bromophenyl)-2,2-dibromo-1,3-propanedione (XII), which was hydrolyzed in 56% yield to 1,3-bis(*p*-bromophenyl)propanetrione (XIII). Fluorination of XIV with sulfur tetrafluoride gave only a 25% yield of 1,3-bis(*p*-bromophenyl)hexafluoropropane (XI)



XII XIII

The method of Inman, Oesterling, and Tyczkowski,[9] using perchloryl fluoride and sodium methoxide in methanol, gave only recovered starting material when applied to the conversion of IX to X. A modification of this method, using sodium methoxide in tetrahydrofuran, gave X in 82% yield on a 5-mmole scale. However, repetition of this procedure on a tenfold larger scale gave none of the desired product. The product isolated was methyl *p*-bromobenzoate, presumably from methoxide attack on the desired product (X). An attempt to prepare 1,3-bis(*p*-bromophenyl)-2,2-difluoro-1,3-propanedione (X) from 1,3-bis(*p*-bromophenyl)-propanetrione (XIII) with potassium fluoride in dimethylformamide was unsuccessful.

(5) Complete name by *Chemical Abstracts* nomenclature is 10,10,11,11,12,12-hexafluoro-2,2,4,4-tetramethyl-3-oxa-2,4-disilatricyclo[11.2.2.1^{5,9}]octadeca-5,7,9(18),13,15,16-hexaene.

(6) S. A. Fuqua and R. M. Silverstein, *Chem. Ind.* (London), 1591 (1963).

(7) D. J. Wilson, V. Boekelheide, and R. W. Griffin, *J. Am. Chem. Soc.*, **82**, 6302 (1960).

(8) L. A. Bigelow and R. S. Hanslick, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 244.

(9) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 6533 (1958).

Experimental

Melting points (Fisher-Johns apparatus) and boiling points are uncorrected.

Infrared spectra were recorded on either a Perkin-Elmer 221 or a Beckman IR-5; the mass spectrum on a CEC 21-103C spectrometer; the isothermal distillation molecular weight on a Mechro Labs osmometer 301.

The proton magnetic resonance spectra were obtained with a Varian HR-60 n.m.r. spectrometer operated at 60 Mc. For the silane monomers and polymers, solutions of 5–15% in carbon tetrachloride containing 1% cyclohexane were used. Shifts are reported in τ-values. A value of τ 8.56 was assigned to the cyclohexane resonance. Other proton spectra were taken in carbon tetrachloride containing 1% tetramethylsilane. The fluorine magnetic resonance spectra were obtained in trichlorofluoromethane solution and shifts are reported in parts per million from trichlorofluoromethane.

Vapor phase chromatographic analyses were performed with a 5 ft. × 0.25 in. column of 5% silicone SE-30 on Fluoropak in a Wilkens Aerograph Model A-110c. Flow rates were generally 75–85 ml./min. Retention volumes are not precisely reproducible on this instrument and are quoted only as an indication of relative peak positions.

1-(*m*-Bromophenyl)-3-(*p*-bromophenyl)-1,3-propanedione (IV).—To a stirred mixture of 430 g. (2.00 moles) of methyl *m*-bromobenzoate, 176 g. of 54.5% sodium hydride–oil dispersion (4.00 moles), and 2000 ml. of anhydrous benzene, maintained at 60° in a 12-l. flask, was added, from a dropping funnel, a solution of 398 g. (2.00 moles) of *p*-bromoacetophenone made up to 860 ml. with anhydrous benzene. One-third of the solution was added over a period of 1 hr. No reaction took place until 4 ml. of methanol was added as an initiator. Then, after an induction period of 3 hr., a brisk evolution of hydrogen started. The addition was continued over a period of 5 hr.; hydrogen evolution was monitored with a wet-test meter. Refluxing and stirring was continued overnight. The cooled mixture was treated with 60 ml. of methanol, then with a mixture of concentrated sulfuric acid and ice. Precipitated material was removed, dissolved in benzene, and added to the subsequently separated benzene layer. The benzene solution was distilled until all of the water was removed azeotropically, filtered, and cooled. Filtration gave 329 g. (43%) of crystalline material, m.p. 131–134°. Recrystallization from benzene yielded 258 g. of pure material, m.p. 138–139°; infrared, λ_{max}^{KBr} 5.95–6.25 (broad shoulder of enolized hydrogen-bonded carbonyl), 6.30 and 6.75 (aromatic C=C), 11.92, 13.00, and 13.88 μ (aromatic ring C—H).

Anal. Calcd. for $C_{15}H_{10}Br_2O_2$: C, 47.1; H, 2.64; Br, 41.8. Found: C, 47.1; H, 2.99; Br, 41.5.

1,3-(*m*-Bromophenyl)-3-(*p*-bromophenyl)-2,2-difluoro-1,3-propanedione (V).—The apparatus used to carry out the reaction with perchloryl fluoride (hazardous, see ref. 1) was a flat-bottomed 600-ml. cylinder, 2 in. in diameter. A 9-mm. gas inlet tube was fused through the wall, as close as possible to the bottom. A coarse-frit sintered glass plate was fused circumferentially 15 mm. above the bottom. In this way, gas could be introduced below the plate, and the solution above the plate could be stirred magnetically while the entire flask was held in an ice bath. A Dry Ice–acetone condenser was attached to the neck of the cylinder (standard taper joint), and a drying tube was fitted on the vent.

In the reactor, a stirred heterogeneous mixture of 75.0 g. (0.196 mole) of (*m*-bromobenzoyl)(*p*-bromobenzoyl)methane and 250 ml. of pyridine was cooled in an ice bath and treated with perchloryl fluoride for 5 hr. at such a rate that the perchloryl fluoride (b.p. −47°) refluxed slowly and smoothly off the tip of the condenser and the reaction temperature was held at −10 to 10°. In order to maintain these conditions, perchloryl fluoride was added only periodically. The reaction mixture was then allowed to warm to 30° over 7 hr. It was poured into water and extracted with benzene. The benzene solution was washed with dilute hydrochloric acid and water, dried, and the solvent was removed at reduced pressure. Crystallization of the residue from 800 ml. of petroleum ether (b.p. 65–110°) yielded 56.6 g. (69%) of light tan crystals, m.p. 66–67°. One more recrystallization gave an analytical sample, m.p. 67.2–68°.

Anal. Calcd. for $C_{15}H_8Br_2F_2O_2$: C, 43.09; H, 1.93; Br, 38.2; F, 9.09. Found: C, 43.21; H, 1.97; Br, 38.0; F, 9.40.

1-(*m*-Bromophenyl)-3-(*p*-bromophenyl)hexafluoropropane (VI).—A mixture of 270 g. of 90% sulfur tetrafluoride (2.23 moles) and 162 g. (0.386 mole) of 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)-2,2-difluoro-1,3-propanedione (V) in an 825-ml. high-pressure reactor was heated at 130° for 2 hr., at 150–170° for 12 hr., and at 225° for 7 hr. The cooled reaction mixture was dissolved in benzene and stirred with sodium fluoride. The benzene was removed, and the residue was recrystallized once from methanol–water to give 94.3 g. (53%) of light tan crystals, m.p. 53–56.5°. Fractional distillation through an 18-in. spinning-band column gave a cut, b.p. 123–125° (0.25 mm.). Recrystallization from pentane gave an analytical sample, m.p. 57–57.8°. The retention volume was 640 ml. at 180°. The proton n.m.r. spectrum consisted of an eleven-peak, complex aromatic multiplet centered at τ 2.53.

Anal. Calcd. for $C_{15}H_8Br_2F_6$: C, 39.0; H, 1.75; Br, 34.6. Found: C, 39.5; H, 1.81; Br, 34.3.

1-[*m*-(Ethoxydimethylsilyl)phenyl]-3-[*p*-(ethoxydimethylsilyl)-phenyl]hexafluoropropane (I).—Magnesium turnings (4.87 g., 0.260 g.-atom), prepared from sublimed magnesium (Dow Chemical Co.), were flame-dried in a stream of dry nitrogen in a flame-dried three-necked flask, fitted with a sealed stirrer, pressure-equalizing dropping funnel, and a condenser, connected through a drying tube to a nitrogen line. A small crystal of iodine was added to the warm flask, and the magnesium was stirred in the iodine vapor. Twenty milliliters of a solution of 46.20 g. (0.100 mole) of 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)hexafluoropropane (VI) in 450 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added to a refluxing mixture of the treated magnesium and 20 ml. of tetrahydrofuran. The reaction started after 10 min. The heat was removed, and the remainder of the solution of VI was added over a period of 30 min. The heat of reaction maintained reflux. Refluxing was continued for an additional hour. The homogeneous dark Grignard solution was transferred under nitrogen pressure to the dropping funnel of a similar dry apparatus, and was added over a period of 1 hr. to a refluxing mixture of 450 g. (3.03 moles) of diethoxydimethylsilane and 900 ml. of tetrahydrofuran. (Diethoxydimethylsilane was obtained from Peninsular Chemicals Research; the fraction that distilled at 113–114° through an 80-cm. helix-packed column was used.) Refluxing was continued for an additional 40 hr. Tetrahydrofuran and excess diethoxydimethylsilane were stripped and replaced with dry benzene. The precipitated salts were removed by filtration under nitrogen, and the residue was heated to 160° at 1 mm. The residue was distilled through an 8-in. spinning-band column. The desired product (27.74 g., 54.5%) distilled at 154.5–155° (0.04 mm.). V.p.c. (retention volume, 1960 ml. at 179°) showed a purity of 90%. Redistillation under the same conditions gave a product (11.85 g., $n^{25}D$ 1.4750) that was 99+% pure.

The proton n.m.r. spectrum showed a methylsilyl singlet at τ 9.65, a methyl triplet at 8.85 (J = 7 c.p.s.), a methylene quartet at 6.35 (J = 7 c.p.s.), and an aromatic multiplet which consisted of a sharp intense peak arising from a broad base, most of which was at a lower field.

Anal. Calcd. for $C_{23}H_{30}F_6O_2Si_2$: C, 54.3; H, 5.94; F, 22.4; Si, 11.04. Found: C, 53.5; H, 5.76; F, 22.2; Si, 11.46.

Fluorinated Oxadisila[3.3]metaparacyclophane (VII).—A solution of 14.312 g. (28.14 mmoles, 99.5 wt. %, 98.5 mole %) of 1-[*m*-(ethoxydimethylsilyl)phenyl]-3-[*p*-(ethoxydimethylsilyl)-phenyl]hexafluoropropane (I, 99 + mole % by v.p.c.) and 80.0 μl. (0.43 mmole, 0.5 wt. %, 1 5 mole %) of methylvinyldiethoxysilane (added to furnish cross-linking sites) in 50 ml. of benzene was prepared. To this solution was added a solution of 5 ml. of concentrated sulfuric acid and 10 ml. of water. The mixture was stirred and refluxed for 12 hr. Additional water and benzene were added and the benzene layer separated. The acid layer was extracted with benzene and the combined benzene solutions were consecutively washed three times with water. The solvent was removed at atmospheric pressure, then *in vacuo*. The residue was a tacky gum (ln η_r/c 0.23; c 1.1 g./dl., benzene) which weighed 12.33 g. (theoretical polymer, 12.26 g.). It was heated at 150° and 1-mm. pressure for 1 hr., during which time the viscosity increased and considerable bubbling was evident. The mixture was dissolved in benzene and transferred to another flask. The benzene was removed and the residue heated at 145–155° and 1-mm. pressure for 4 hr. During this time, white crystals sublimed into the neck of the flask. The residue in the flask was still a light amber gum. Upon removal of the sublimate and continued vacuum heating, additional white sublimate was formed. A total of 1.20 g. of crystalline white sublimate (m.p. 80–83°) was collected. The polymer residue weighed 10.99 g. Further heating of this residue yielded no more sublimate.

Resublimation gave an analytical sample, m.p. 80.0–81.5°, which was homogeneous by gas chromatography; infrared, λ_{max}^{film} 7.95 [$(CH_3)_2Si$], no ethoxy C–O–Si at 10.55 μ; n.m.r. (τ), 2.84 (complex with sharp peak, 7.13 protons, aromatic), 3.73 (singlet, slightly broadened, 1.00 proton, C-18), 9.59 and 9.69 (singlet, 12.05 protons, methylsilyl).

Mass spectrum. Calcd.[10] for $C_{19}H_{20}F_6OSi_2$: parent mass, 434; parent + 1 = 31.05% of parent peak ($C_{19}^{13}H_{20}^{2}$ = 20.85%, Si_2^{29} = 10.20%); parent + 2 = 8.98% of parent peak ($C_{19}^{13}H_{20}$ = 2.06%, O^{18} = 0.20%, Si_2^{30} = 6.72%). Found: parent + 1 = 31.2% of parent peak; parent + 2 = 10.4% of parent peak.

Anal. Calcd. for $C_{19}H_{20}F_6OSi_2$: C, 52.51; H, 4.64; F, 26.23; Si, 12.93. Found: C, 52.55, 52.62; H, 4.64, 4.75; F, 26.08; Si, 13.08.

1,3-Bis(*p*-bromophenyl)-1,3-propanedione (IX).—To a stirred mixture of 140 g. of 53.1% sodium hydride in oil dispersion (3.09 moles) and 323 g. (1.50 moles) of methyl *p*-bromobenzoate in 2500 ml. of dry benzene, maintained at 60°, was added, from a dropping funnel, a solution of 299 g. (1.50 moles) of *p*-bromoacetophenone made up to 500 ml. in dry benzene. Fifty milliliters of the *p*-bromoacetophenone solution was added to initiate the reaction; hydrogen evolution (wet-test meter) started in about 4 hr. The remainder of the solution was then added over a period of 4 hr., and stirring and heating were continued for an additional 10 hr. Work-up followed the procedure given for preparation of 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)-1,3-propanedione (IV). A 50% yield of the crude product (m.p. 193–194°) was obtained and used without further purification in the next step. An analytical sample was obtained by recrystallization from benzene, m.p. 197–198.5°.

Anal. Calcd. for $C_{15}H_{10}Br_2O_2$: C, 47.15; H, 2.64; Br, 41.83. Found: C, 46.86; H, 2.87; Br, 41.59.

1,3-Bis(*p*-bromophenyl)-2,2-difluoro-1,3-propanedione (X).—The apparatus described above was modified by removing the condenser. A stirred mixture of 100 g. (0.262 mole) of 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)1,3-propanedione (IV), and 400 ml. of pyridine was cooled to 0 to 10° (thermometer suspended in mixture) and perchloryl fluoride was slowly bubbled through for 11 hr. (hazard). The starting material slowly dissolved as the reaction proceeded. The mixture was poured into 4 l. of water, and the precipitate was removed by filtration, washed with water, and dried.

The total crude product from three runs was dissolved in hot petroleum ether (b.p. 65–110°) and filtered hot. On cooling the solution, 208 g. of product precipitated. Recrystallization from petroleum ether gave 187 g. (53%) of the desired product, m.p. 102–104°. An analytical sample obtained by an additional recrystallization melted at 105–107°. The petroleum ether-insoluble material (68.3 g.), on recrystallization from benzene, gave 42.8 g. of recovered starting material, m.p. 191–193.5°.

The infrared spectrum in a potassium bromide pellet showed the C=O absorption at 5.86, and sharp peaks at 8.62 and 8.75 μ ascribed to C—F absorption.

Anal. Calcd. for $C_{15}H_8Br_2O_3$: C, 45.5; H, 2.04. Found: C, 45.5; H, 2.16.

1,3-Bis(*p*-bromophenyl)hexafluoropropane (XI).—In an 825-ml. bomb, a mixture of 166 g. (0.396 mole) of bis(*p*-bromobenzoyl)difluoromethane and 269 g. of 90% sulfur tetrafluoride was heated at 100° for 2 hr., at 175° for 6 hr., and at 220–225° for 11 hr. Working up in the manner described for 1-(*m*-bromophenyl)-3-(*p*-bromophenyl)hexafluoropropane (VI) gave 202 g. of yellow solid which after two recrystallizations from 98% methanol yielded 133 g. (73%) of impure product (m.p. 119–123°). The high melting point of the material made distillation infeasible as a method of purification.

The product was successfully purified by column chromatography. A benzene solution of 89 g. of impure product was placed on a column of alumina 600 mm. long and 60 mm. in diameter. One fraction gave 68.1 g. of white needles (m.p. 125.0–126.0°). The fluorine n.m.r. spectrum of this material consisted of two singlets in 2:1 ratio. The larger peak, due to the four benzylic fluorine atoms, was at 109.2, and the smaller peak, due to the central CF_2, was at 122.0 p.p.m.

Anal. Calcd. for $C_{15}H_8Br_2F_6$: C, 38.99; H, 1.75; Br, 34.6. Found: C, 39.52; H, 1.81; Br, 35.5.

1,3-Bis(*p*-bromophenyl)-2,2-dibromo-1,3-propanedione (XII).—A solution of 19.2 g. (0.120 mole) of bromine in 50 ml. of chloroform was slowly added to an ice-cooled solution of 19.2 g. (0.0503 mole of 1,3-bis(*p*-bromophenyl)-1,3-propanedione (IX) in 150 ml. of chloroform at such a rate that the temperature did not exceed 15°. The hydrogen bromide evolved was removed with a stream of nitrogen. After addition of the bromine, the solution was stirred a few minutes longer. The solvent was removed at reduced pressure, and the residue was crystallized from alcohol to give 21.5 g. (79%) of white crystals (m.p. 84–88°). Three recrystallizations from absolute alcohol gave material melting at 92–94.7°; infrared, λ_{max}^{film} 5.92 μ.

Anal. Calcd. for $C_{15}H_8Br_4O_2$: C, 33.37; H, 1.49; Br, 59.21. Found: C, 33.72; H, 1.65; Br, 59.02.

1,3-Bis(*p*-bromophenyl)propanetrione (XIII).—A mixture of 5.4 g. (0.010 mole) of 1,3-bis(*p*-bromophenyl)-2,2-dibromo-1,3-propanedione (XII), 2.05 g. (0.025 mole) of sodium acetate, and 7.1 ml. of acetic acid was refluxed for 2 hr. The precipitate was stirred with 10 ml. of water, removed by filtration, and dried to give 4 g. of crude product. Sublimation in a vacuum and two recrystallizations from petroleum ether–benzene gave yellow needles, m.p. 145–147.5°; infrared, λ_{max}^{KBr} 5.92 μ.

Anal. Calcd. for $C_{15}H_8Br_2O_3$: C, 45.5; H, 2.04. Found: C, 45.5; H, 2.16.

1,3-Bis(*p*-bromophenyl)hexafluoropropane (XI) from the Triketone (XIII).—A mixture of 4.68 g. (11.8 mmoles) of 1,3-bis(*p*-bromophenyl)propanetrione (XIII) and 20 g. of 90% sulfur tetrafluoride was rocked and heated in a 100 ml. stainless steel bomb for 7 hr. at 50° and 8 hr. at 150° (250 p.s.i.). The product was dissolved in benzene and washed with dilute sodium bicarbonate solution. The benzene solution was filtered through a short alumina column and allowed to crystallize to give 1.38 g. (25%) of crude product (m.p. 114–121°). Several recrystallizations from benzene gave white crystals (m.p. 120–122°).

Anal. Calcd. for $C_{15}H_8F_6Br_2$: C, 38.99; H, 1.75. Found: C, 38.91; H, 1.87.

Acknowledgment.—This work was supported by Rock Island Arsenal under Contract No. DA-11-070-508-ORD-906. Mr. Z. T. Ossefort and Mr. R. F. Shaw were project monitors for Rock Island Arsenal. The n.m.r. spectra were obtained by Mr. W. R. Anderson, Jr., the mass spectrum by Mrs. L. Peters, and the isothermal distillation molecular weight by Mr. D. Tieszen.

(10) Silicon isotope abundances recalculated on basis Si^{28} = 100% from L. A. Koenig, J. H. E. Mattauck, and A. H. Wapstra, *Nucl. Phys.*, **31**, 18 (1962).

Alumina. Catalyst and Support. XXI.[1] Aromatization of 2,4-Dimethyl-3-methyl-C^{14}-pentane over Chromia–Alumina Catalyst. Contribution to the Mechanism of Aromatization[2]

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Received August 1, 1963

The aromatization of 2,4-dimethyl-3-methyl-C^{14}-pentane over "nonacidic" chromia–alumina was studied. The main aromatic products were *o*-, *m*-, and *p*-xylene, with the production of *m*-xylene dropping rapidly with the time. The radioactivity distribution in the xylenes supports the previously proposed cyclopropane- and cyclobutane-type intermediates for the dehydroisomerization and aromatization of branched hydrocarbons. In addition, this study has indicated that C_7- and C_8-membered ring intermediates must play at least a minor role in the aromatization of branched chain hydrocarbons.

The aromatization of methylpentanes must be preceded by some rearrangement to at least a C_6-chain intermediate and such a rearrangement presents an interesting mechanistic problem. Studies in our laboratory have shown that alumina has intrinsic acidic properties and that the strength of the acidic sites depends upon the method employed for the preparation of the aluminas.[3] It was found that chromia–alumina catalyst containing alumina prepared from aluminum isopropoxide has relatively strong acidic sites and that this catalyst may cause skeletal isomerization of the hydrocarbon *via* a carbonium ion mechanism.[4,5] However, chromia–alumina catalyst containing alumina prepared from potassium aluminate ("nonacidic" chromia–alumina) has relatively weak acidic sites and such cationic skeletal isomerization does not occur. This observation has been subsequently confirmed by others.[6]

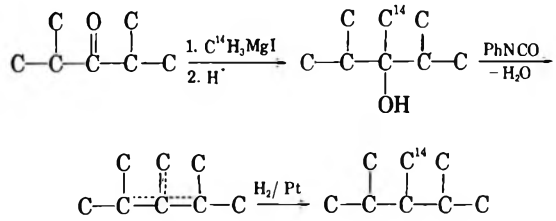
Large membered ring intermediates have been shown for the aromatization of *n*-heptane and *n*-octane[1,7,8] over "nonacidic" chromia–alumina catalyst. Further studies of the aromatization of branched C_6–C_8 hydrocarbons over "nonacidic" chromia–alumina catalyst have shown the existence of adsorbed cyclopropane intermediates and have indicated strongly the possibility of adsorbed cyclobutane intermediates prior to the aromatization reaction.[9,10]

In order to shed more light on the possible existence of cyclobutane intermediates, 2,4-dimethyl-3-methyl-C^{14}-pentane was synthesized and aromatized under conditions described previously.[9] The aromatic products of the reaction were mainly *o*-, *m*-, and *p*-xylene. The mechanism involving an adsorbed cyclopropane intermediate would produce *o*- and *p*-xylenes with 100% methyl-labeled *o*-xylene and 100% ring-labeled *p*-xylene (Scheme I). An adsorbed cyclobutane intermediate would give *m*-xylene with all the radioactivity in the ring (Scheme II). The production of *o*- and *p*-xylene are precluded by this mechanism.

The possibility of a combination of small and large membered ring intermediates cannot be excluded. Therefore, a mechanism combining an adsorbed cyclobutane intermediate followed by an adsorbed cycloheptane intermediate would predict 50–100% ring-labeled *o*- and *m*-xylene with 100% ring-labeled *p*-xylene (Scheme II, route b). However, a combination of cyclo-C_3, -C_4, and -C_8 adsorbed species would predict 75% ring-labeled *o*-, *m*-, and *p*-xylene (Scheme III). Therefore, ring label in *m*-xylene would give strong support for the existence of a cyclobutane intermediate.

Procedure

The 2,4-dimethyl-3-methyl-C^{14}-pentane was synthesized in greater than 99% purity by the following sequence of reactions.



The 2,4-dimethyl-3-methyl-C^{14}-pentane was dehydrogenated at 531° over "nonacidic" chromia–alumina catalyst by a previously described procedure.[8] Table I summarizes the reaction conditions and composition of the xylenes produced.

TABLE I

AROMATIZATION OF 2,4-DIMETHYL-3-METHYL-C^{14}-PENTANE OVER CHROMIA–ALUMINA CATALYST[a]

	Cut no. 1	2	3
Duration of experiment, min.	16	18	20
Total C_8H_{18} passed, ml.	3.9	4.5	5.0
Conversion of C_8H_{18} to xylenes, mole %	12	7.5	3.5
Conversion of C_8H_{18} to carbonaceous materials,[b] mole %.	←1.29%→		
Distribution of xylenes in the aromatic fraction, mole %			
o-Xylene	40.4	49.8	51.6
m-Xylene	33.0	21.5	18.8
p-Xylene	26.6	28.7	29.6

[a] The experiments were made at 531° and at an hourly liquid space velocity of 1.06. [b] The conversion to carbonaceous materials was determined at the end of the final experiment.

(1) For paper XX, see H. Pines, C. T. Goetschel, and S. M. Csicsery, *J. Org. Chem.*, **28**, 2713 (1963).

(2) (a) Paper XII of the series "Aromatization of Hydrocarbons"; for paper XI, see ref. 1; (b) this research was supported by the Atomic Energy Commission, Contract AT(11-1)-1046.

(3) H. Pines and W. O. Haag, *J. Am. Chem. Soc.*, **82**, 2471 (1960).

(4) H. Pines and C. T. Chen, *ibid.*, **82**, 3562 (1960).

(5) H. Pines and S. M. Csicsery, *ibid.*, **84**, 292 (1962).

(6) J. M. Bridges, C. T. Rymer, and D. S. MacIver, *J. Phys. Chem.*, **66**, 871 (1962).

(7) H. Pines and C. T. Chen, *J. Org. Chem.*, **26**, 1057 (1961).

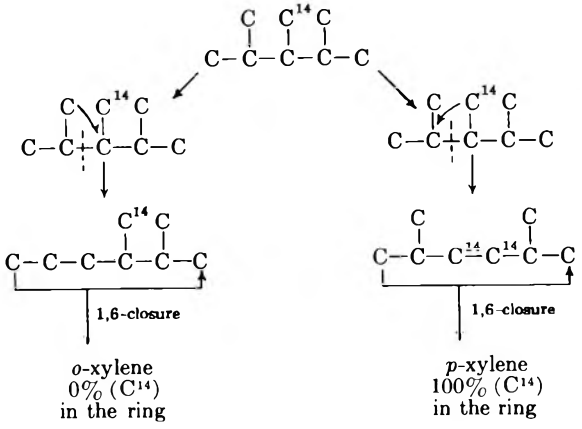
(8) H. Pines and C. T. Chen, *Actes Congr. Intern. Catolyse, 2e, Paris*, **I**, 367 (1960).

(9) H. Pines and S. M. Csicsery, *J. Catalysis*, **1**, 313 (1962).

(10) S. M. Csicsery and H. Pines, *J. Am. Chem. Soc.*, **84**, 3939 (1962).

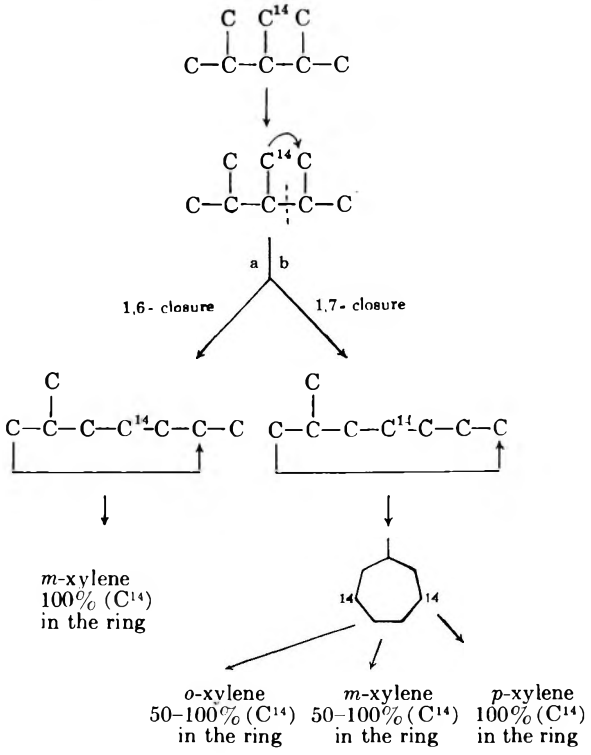
SCHEME I

AROMATIZATION OF 2,4-DIMETHYL-3-METHYL-C^{14}-PENTANE *via* CYCLOPROPANE INTERMEDIATES



SCHEME II

AROMATIZATION OF 2,4-DIMETHYL-3-METHYL-C^{14}-PENTANE *via* A CYCLOBUTANE INTERMEDIATE FOLLOWED BY 1,6-CLOSURE (ROUTE a) OR 1,7-CLOSURE (ROUTE b)



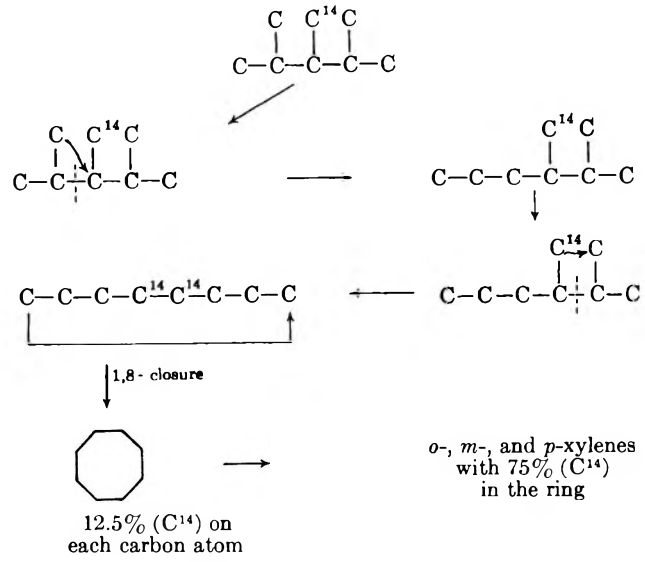
The reaction product was collected in three separate cuts. The xylenes in each cut were separated by preparative v.p.c.; the *m*- and *p*-xylene being collected together while the *o*-xylene was collected separately. The xylenes were diluted with their corresponding inactive compounds, then oxidized with alkaline potassium permanganate to their respective acids. The acids were then separated by the procedure described previously.[11]

The isophthalic and terephthalic acids thus produced were decarboxylated with boiling quinoline and copper oxide. The benzene and carbon dioxide produced were collected separately and analyzed for radioactivity. The *o*-xylene was decarboxylated by employing the Schmidt reaction and the products, anthranilic acid

(11) H. Pines and A. W. Shaw, *J. Am. Chem. Soc.*, **79**, 1474 (1957).

SCHEME III

AROMATIZATION OF 2,4-DIMETHYL-3-METHYL-C^{14}-PENTANE *via* A COMBINATION OF CYCLOPROPANE, CYCLOBUTANE, AND CYCLOOCTANE INTERMEDIATES



and carbon dioxide, collected separately and analyzed for radioactivity. Tables II and III summarize radioactivities of the aromatic acids and their decarboxylation products. The differences between the radioactivities of the acids and the sum of the radioactivities of their decarboxylation products were ±3% or less.

Discussion of Results

The radioactivity distribution of the xylenes produced from the aromatization of 2,4-dimethyl-3-methyl-C^{14}-pentane over "nonacidic" chromia–alumina catalyst is summarized in Table IV.

The fact that *m*- and *p*-xylene contain from 7–9% of their radioactivity in the side chain suggests that cyclopropane and cyclobutane intermediates cannot be the sole intermediate species participating in the aromatization reaction. This is substantiated further by the fact that *o*-xylene contains from 6–12% of the radioactivity in the ring. The inclusion of C_7- and/or C_8-membered intermediates appears necessary.

It cannot be determined from the present data whether cycloheptane or cyclooctane intermediate species are contributors or if, indeed, they both contribute. However, since over 90% of the radioactivity of *o*-xylene does, in fact, reside in the side chain, the contribution of such large membered ring intermediates is indicated to be only of minor importance. On the other hand, it can be seen that an adsorbed cyclobutane species must be involved in this aromatization process. The fact that *m*-xylene is formed at all suggests some sort of cyclobutane intermediate species, and also the fact that approximately 95% of the radioactivity of the *m*-xylene resides in the ring can be explained by assuming a cyclobutane intermediate. A strong support for the existence of a cyclobutane intermediate was the observation recorded before that 2,3-dimethylbutane isomerizes in the presence of a nonacidic chromia–alumina catalyst to 3-methylpentane.[9]

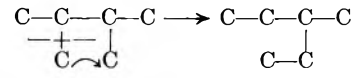


TABLE II

DECARBOXYLATIONS OF ACIDS DERIVED FROM *p*-XYLENE AND *m*-XYLENE PRODUCED BY THE AROMATIZATION OF 2,4-DIMETHYL-3-METHYL-C^{14}-PENTANE

	p-Xylene, cut no.			*m*-Xylene, cut no.		
	1	2	3	1	2	3
Acid decarboxylated,[a] mmoles	0.48	0.47	0.58	0.57	0.48	0.43
Barium carbonate obtained, mmoles	0.92	0.84	0.47	1.06	0.87	0.79
Benzene obtained, mmoles	0.24	0.21	0.09	0.24	0.26	0.17
Barium carbonate yield, mole %	97	88	41	94	90	92
Benzene yield, mole %	49	43	16	43	54	39
Radioactivities 10^{-3} μc./mmole						
Starting acid[a]	144	10.3	25.3	24.1	1.96	23.5
Barium carbonate	5.1	0.36	1.2	1.1	0.08	
Benzene	138	9.8	23.5	22.6	1.86	

[a] For *p*-xylene, terephthalic acid, and for *m*-xylene, isophthalic acid.

TABLE III

RADIOCHEMICAL ASSAY DATA

(Schmidt reaction on phthalic acid derived from *o*-xylene produced by aromatization of 2,4-dimethyl-3-methyl-C^{14}-pentane)

	Cut no.		
	1	2	3
Phthalic acid decarboxylated, mmoles	2.18	0.87	2.96
Barium carbonate obtained, mmoles	2.08	0.78	2.77
Anthranilic acid obtained, mmoles	0.33	0.04	0.08
Barium carbonate yield, mole %	96	90	94
Anthranilic acid yield, mole %	15	4	2.5
Radioactivities, 10^{-3} μc./mmole			
Phthalic acid	95.7	0.745	25.8
Barium carbonate	45.1	0.353	11.8
Anthranilic acid	50.8		14.8

TABLE IV

RADIOACTIVITY DISTRIBUTION FROM THE AROMATIZATION OF 2,4-DIMETHYL-3-METHYL-C^{14}-PENTANE

Compound and C^{14} location	Distribution in Cut no. 1	Cut no. 2	Cut no. 3
o-Xylene			
% side chain	94.2	96.1	91.4
% ring	6.0		11.6
Difference[a]	+0.2		+3.0
m-Xylene			
% side chain	9.1	8.1	
% ring	93.7	95.0	
Difference[a]	+2.8	+3.1	
p-Xylene			
% side chain	7.1	7.0	9.5
% ring	95.7	94.7	93.0
Difference[a]	+2.8	+1.7	+2.5

[a] Difference between the experimental value and 100% radioactivity recovery.

As of now, no mention has been made of the possibility of aromatization to occur from two simultaneous methyl injections *via* cyclopropane-type intermediates followed by either 1,6-closure to give *m*-xylene or 1,7-closure which yields *o*-, *m*-, and *p*-xylene. This mechanistic route would eliminate the need of a cyclobutane intermediate and still explain the production of *m*-xylene with the observed radioactivity distribution. However, it has been shown[9,10] that cyclopropane-type intermediates vary but little with time. Therefore, the fact that the *m*-xylene production is definitely a "time-dependent" reaction rules out the possibility of *m*-xylene formation by such a path.

Finally, since there is very little variation in the radioactivity distribution of the xylenes from cuts 1–3, little can be said about the possible change, with time, in the contributions of the various probable mechanisms for the formation of the xylenes.

Conclusion

This study has contributed and added support for the participation of cyclobutane-type intermediates in the aromatization of 2,3,4-trimethylpentane over chromia–alumina catalyst. Indeed, a cyclobutane-type intermediate must be involved to account for the *m*-xylene produced. As was to be expected, cyclopropane-type intermediates were also contributors. However, the participation of cyclopropane- and cyclobutane-type intermediates cannot be the only intermediate species in this reaction. It appears that C_7- and/or C_8-membered ring intermediates are participating to a minor extent.

Experimental

Synthesis of 2,4-Dimethyl-3-methyl-C^{14}-pentane. A. 2,4-Dimethyl-3-methyl-C^{14}-3-pentanol.—To a rapidly stirred mixture of 4.62 g. (0.19 g.-atom) of magnesium turnings in 80 ml. of absolute ether was added dropwise a solution of 24.2 g. (0.17 mol., 4.0 mc. C^{14}) of methyl iodide-C^{14} in 40 ml. of absolute ether over a period of 1.5–2.0 hr. Following the addition, the reaction mixture was stirred an additional hour at room temperature. Then a solution of 19.4 g. (0.17 mole) of 2,4-dimethyl-3-pentanone in 40 ml. of absolute ether was added dropwise over a 1.5–2.0-hr. period. Rapid stirring was continued at room temperature for 15 hr. after completion of the ketone addition. The reaction mixture was then poured over *ca.* 100 ml. of crushed ice and most of the precipitated hydroxide dissolved with 10% aqueous sulfuric acid (the pH always being kept on the basic side). The layers were separated and the water layer extracted with ether. The ether extracts and original organic layer were combined and washed with water, then 10% aqueous sodium bicarbonate, and finally dried with anhydrous sodium sulfate. The ether was removed by distilling from a small amount of anhydrous sodium carbonate. The residue (24 g.) contained 19.2 g. of 2,4-dimethyl-3-methyl-C^{14}-3-pentanol; yield, 87%.

B. 2,4-Dimethyl-3-methyl-C^{14}-pentenes.—The crude alcohol, prepared above, was dehydrated with 4.86 g. (0.06 mole) of dry pyridine and 40.0 g. (0.34 mole) of phenyl isocyanate, according to the procedure described in a previous paper.[9]

C. 2,4-Dimethyl-3-methyl-C^{14}-pentane.—The olefin (13.0 g.) was hydrogenated in a low-pressure shaking hydrogenation apparatus with platinum oxide catalyst. The product was chromatographed over 43 ml. of alumina (Merck, reagent grade). The 2,4-dimethyl-3-methyl-C^{14}-pentane thus obtained, 9.64 g., was 99.5% pure. Its radioactivity was 4.28 μc./mmole. Overall yield based on C^{14}H$_3$I used was 9.0%.

Catalyst.—The chromia–alumina catalyst was prepared according to a described procedure.[4] The alumina was precipitated from sodium aluminate and impregnated with chromic acid. The catalyst contained 13.8 wt.% of Cr_2O_3; its surface area was 89 m.^{2}/g.; and the average pellet weight was 0.022 g.

Apparatus and Procedure. A. Aromatization.—The apparatus and procedure for the aromatization was the same as described earlier.[9]

B. Separation of Aromatic Hydrocarbons from Reaction Product.—The separation was accomplished using an F & M Model 300 programmed temperature gas chromatograph[12] with an 11 mm. × 2.4 m. preparative v.p.c. column filled with 5% 7,8-benzoquinoline on 30–60-mesh Chromosorb. The column temperature used was 75° with a helium flow rate of 105–114 ml./min. The sample recovery was the same as described previously.[1]

C. Oxidation of the Xylenes.—The xylenes which were separated and collected from the preparative v.p.c. column were diluted from five–fifty times with their inactive xylenes and oxidized to the corresponding phthalic acids with hot alkaline potassium permanganate as described previously.[1]

D. Separation of the Phthalic Acids.—The separation and purification of the phthalic acids produced before was accomplished as described earlier.[11]

E. Radiochemical Assay.—The radiochemical assay of the resulting phthalic acids and their decarboxylation products was the same as previously described.[13]

(12) F & M Scientific Corp., Avondale, Pa.

(13) H. Pines and G. Benoy, *J. Am. Chem. Soc.*, **82**, 2483 (1960).

Kinetics of the Reaction of 2-Nitropropane with Methylenebisamines. A Study of the Mannich Reaction

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Received August 26, 1963

The Mannich reactions of 2-nitropropane with methylenebispiperidine and with methylenebismorpholine exhibit second-order kinetics, first order in each component. The 2-nitropropane reacts through the *aci* form. The rate increases with increasing dielectric constant, and decreases in basic media. Methylenebispiperidine exhibits a faster rate than methylenebismorpholine. The greater reactivity of the piperidine derivative is attributed to its greater base strength. Mechanisms are presented for media of low and high dielectric constant.

The Mannich reaction has been reviewed by Blicke[2] and Hellman,[3] and two excellent kinetic studies have been reported.[4,5] Alexander and Underhill studied the reaction of ethylmalonic acid as active hydrogen compound and dimethylamine as amine component. Cummings and Shelton used cyclohexanone and dimethylamine. Both of these studies employed aqueous solvents and both involved the over-all Mannich reaction of active hydrogen compound, formaldehyde, and amine.

$$Z-\underset{|}{\overset{|}{C}}-H + HCHO + HNR_2 \longrightarrow Z-\underset{|}{\overset{|}{C}}-CH_2NR_2 + H_2O \quad (1)$$

The present kinetic study was undertaken to investigate (1) the effect of amine basicity and (2) the effect of solvent dielectric constant.

Attempts to follow the rate of reaction of the mixture of reactants shown in eq. 1 necessarily leads to complex results because of the known initial reaction of amine and formaldehyde to form any of several intermediate species, *e.g.*, aminomethylol, methylenebisamine, and methyleneimmonium ion. The complexities of this reaction have been reviewed by Wagner.[6] The above mechanisms[4,5] are thus complicated by this initial reaction and further by the participation of water in the amine–formaldehyde equilibrium.[6]

$$R_2NH + HCHO \rightleftharpoons R_2NCH_2OH \xrightleftharpoons{R_2NH} R_2NCH_2NR_2 + H_2O$$

For these reasons, deductions about the intermediates (aminomethylol *vs.* methylenebisamine) and deductions based on activation parameters were prevented.

In the present work we studied the reaction of 2-nitropropane with two methylenebisamines. It is well-known that nitro alkanes react to form Mannich bases. Senkus[7] and Johnson[8] reported that the Mannich reaction of nitro alkanes proceeds through an intermediate formed by the condensation of the amine with formaldehyde. Butler[9] found that methylenebisamines react with 2-methyl-2-nitro-1-propanol (formed by the reaction of 2-nitropropane with formaldehyde) to form the usual Mannich bases. Another interesting feature of 2-nitropropane is its acidity which is intermediate between those of the active hydrogen compounds used in the kinetics studies discussed.[4,5]

The use of methylenebisamines in the present study can be explained on the following basis. Aminomethylols are not generally isolable,[6] thus they are difficult to study. It is known that methylenebisamines react with active hydrogen compounds to produce normal Mannich bases.[9–11] Fernandez and Butler[12] have demonstrated recently that the reaction of formaldehyde with secondary aliphatic amines produces primarily the methylenebisamine and only small proportions, if any, of the aminomethylol. While aminomethylols are not excluded as intermediates, evidence offered for their reactivity as intermediates is indirect and only recently was inferred[11] through a study of the reaction of α-amino ethers with β-naphthol to produce normal Mannich bases.

We have thus attempted to simplify the system at the risk of narrowing the scope of the results. Anhydrous solvents were employed in all runs to avoid formation of aminomethylol by hydrolysis of the methylenebisamines. We employed the methylenebisamines of piperidine and morpholine because of the rather large

(1) Student participant sponsored by National Science Foundation Undergraduate Science Education Grants No. G-21888 and GE-1210.

(2) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

(3) H. Hellman, *Angew. Chem.*, **65**, 473 (1953).

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(7) M. Senkus, *J. Am. Chem. Soc.*, **68**, 10 (1946).

(8) H. G. Johnson, *ibid.*, **68**, 12, 14 (1946).

(9) G. B. Butler, *ibid.*, **78**, 482 (1956).

(10) S. V. Liebermann and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

(11) J. E. Fernandez, C. Powell, and J. S. Fowler, *J. Chem. Eng. Data*, **8**, 600 (1963).

(12) J. E. Fernandez and G. B. Butler, *J. Org. Chem.*, **28**, 3258 (1963).

TABLE I

INITIAL RATES OF REACTION OF 2-NITROPROPANE WITH METHYLENEBISPIPERIDINE AT 78.6°

Run no.	Concn. of 2-nitropropane, *M*	Concn. of methylenebispiperidine, *M*	Initial rate, mole/l./hr.	k_1, hr.$^{-1}$	k_2, l./mole/hr.
1	2.50	0.125	0.205	0.714	0.295
2	2.50	0.250	0.393	0.747	0.286
					Av. = 0.290 ± 0.005
3	2.50	0.375	0.620	0.438	0.187
4	2.50	0.375		0.397	0.159
5	0.125	2.50	0.0175		
6	0.125	2.50	0.020	0.0614	0.0246
7	0.250	2.50	0.0425	0.0832	0.0361
8	0.375	2.50	0.062	0 0692	0.0286
					Av. = 0.0298 ± 0.0042

difference in basicity (pK_b 2.78 and 5.64 for piperidine and morpholine, respectively) and their nearly identical steric properties. The solvents used were dioxane, dimethylformamide, nitrobenzene, and triethylamine. Reaction rates were followed by the spectrophotometric analysis of the N–H overtone band[13] at 1.53 μ of the secondary amine produced.

$$(CH_3)_2\overset{NO_2}{\overset{|}{C}}H + R_2NCH_2NR_2 \longrightarrow (CH_3)_2\overset{NO_2}{\overset{|}{C}}CH_2NR_2 + HNR_2 \quad (2)$$

Experimental

Kinetics.—Kinetic runs were carried out using 2-nitropropane with methylenebispiperidine and with methylenebismorpholine. Eastman practical grade 2-nitropropane was redistilled through a Vigreux column and the fraction boiling at 119–120° retained. Methylenebispiperidine[14] and methylenebismorpholine[15] were prepared from the corresponding secondary amines and formaldehyde, b.p. 100–105° (3.5–4.0 mm.) and 107–109° (4.5 mm.), respectively. The near infrared spectra of these methylenebisamines showed no secondary N–H amine absorbance at 1.53 μ.[13]

Kinetic runs were carried out in dioxane, nitrobenzene, and dimethylformamide, and various mixtures of these solvents to determine the effect of dielectric constant on the reaction rate. Eastman practical grade *p*-dioxane was refluxed over sodium for 3 days, then distilled through a 25-plate sieve tray column. Eastman practical grade nitrobenzene was redistilled through a Vigreux column (b.p. 209°). Eastman Spectro Grade dimethylformamide was used as received.

Runs were made in constant temperature oil baths maintained at 78.60 ± 0.03°, 82.76 ± 0.03°, and 87.94 ± 0.04°. The reactants were mixed in a 50-ml. volumetric flask and quickly brought to temperature before immersing in the bath. The warm-up period normally took less than 1 min. Samples were withdrawn at recorded time intervals and the reaction quenched in a chilled glass tube. The progress of the reaction was followed by measuring spectrophotometrically the concentration of secondary amine produced (eq. 2). The 1.53-μ band due to the N–H overtone was convenient for this purpose since other bands did not interfere in this region.

All analyses were performed using a Perkin-Elmer Infracord Model 137-G spectrophotometer and 1-cm. silica cells. Beer's law for piperidine and morpholine was confirmed in all the solvents and solvent combinations used.

The order of the reaction of 2-nitropropane with methylenebispiperidine was determined by measuring the initial rate graphically when each component was in large excess. The linear variation of initial rate with concentration (Table I) shows that the reaction is first order with respect to each component. The second-order rate constants were determined by using low concentrations of each reactant and plotting the second-order function $C_t/C_i(C_0 - C_t)$ against time where C_0 = initial concentration of reactants, C_t = amount of reactants consumed at time t. The slope (rate constant) was obtained by the method of least squares. Most runs were carried out to more than 50% completion (Table II).

The second-order rate constants for the reaction of methylenebismorpholine with 2-nitropropane were also determined at three temperatures (Table III).

Kinetic Runs in Basic Media.—An effect due to excess basicity was suspected from the low values of k_2 obtained in runs 3–8. Reactions were, therefore, run in mixtures of dioxane and triethylamine (Table II). The triethylamine was redistilled through a Vigreux column after refluxing for 2 days over solid potassium hydroxide (b.p. 89°). This material showed no absorption at 1.53 μ. These runs were carried out only to *ca.* 35% completion because evaporation of triethylamine during analysis became increasingly important during the later stages of each run.

Runs in the Absence of 2-Nitropropane.—These runs were carried out to determine the extent of hydrolysis of methylene bisamine during the course of a kinetic run. A mixture of equal volumes of dimethylformamide and methylenebispiperidine was allowed to stand in the 78.60° bath for 71 hr. At the end of this time the mixture was analyzed for piperidine. The concentration was 0.06 *M* corresponding to a loss of 1% of the methylenebisamine. Runs carried out under similar conditions using 2-nitropropane were virtually complete (80%) in 1 hr. A similar run of methylenebispiperidine in dioxane yielded no measurable amount of secondary amine after 50 hr.

Interpretation

From the previous data the following deductions can be made. (1) The reaction is first order in 2-nitropropane and first order in methylenebisamine. (2) The rate is decreased when an excess of methylenebisamine is used or when triethylamine is added. (3) Reactions of methylenebispiperidine exhibit a faster rate than those of methylenebismorpholine. (4) The reaction rate increases with an increase in the dielectric constant of the medium. (5) Reactions employing excess 2-nitropropane exhibit faster rates than can be explained on the basis of dielectric effects alone.

The order of the reaction was confirmed by the linear variation of initial rate with concentration of each reactant. In addition to this, all second-order plots were linear.

The effect of a basic medium on the reaction can be shown by the rates of reaction determined in triethylamine (runs 19–22, 27, 28), and in excess methylenebispiperidine (runs 5–8). The 2-nitropropane anion is the predominant species in these basic media,[16] and the

(13) W. Kaye, *Spectrochim. Acta*, **6**, 257 (1954).

(14) Schmidt and Kohler, *Arch. Pharm.*, **240**, 232 (1902).

(15) U. S. Patent 2,388,058 (October 30, 1945).

(16) The equilibrium constant for the neutralization $(CH_3)_2CHNO_2 + ET_3N \rightleftharpoons [(CH_3)_2CNO_2]^-[ET_3NH]^+$ is given by the relation $K = K_aK_o/K_w \cong 10^6$.

TABLE II

KINETIC DATA FOR THE REACTION OF 2-NITROPROPANE WITH METHYLENEBISPIPERIDINE

Run no.	Concn. of 2-nitropropane, *M*	Concn. of methylenebispiperidine, *M*	k_2, l./mole/hr.	Solvent[a]	Dielectric[b] constant
			Temp. = 78.60 ± 0.03°		
9	0.500	0.125	0.0897	Dioxane	2.12[c]
10	0.250	0.250	0.0848		2.12
11	0.250	0.250	0.0797		2.12
12	0.125	0.125	0.0909		2.12
			Av. = 0.0863 ± 0.0047		
13	0.250	0.250	0.354	28.95% DMF in dioxane	11.77
14	0.250	0.250	0.354		11.77
			Av. = 0.354 ± 0.0		
15	0.250	0.250	0.820	62.0% DMF in dioxane	19.47
16	0.250	0.250	0.700		19.47
			Av. = 0.760 ± 0.060		
17	0.250	0.250	1.64	100% DMF	27.5
18	0.250	0.250	1.48		27.5
			Av. = 1.56 ± 0.08		
19	0.250	0.250	0.0177	56.4% TEA in dioxane	1.82[d]
20	0.250	0.250	0.0182		1.82
21	0.250	0.250	0.0196		1.82
22	0.250	0.250	0.0257		1.82
			Av. = 0.0204 ± 0.0027		
23	0.250	0.250	0.167	21.3% $PhNO_2$ in dioxane	6.45[c]
24	0.250	0.250	0.194		6.45
			Av. = 0.181 ± 0.014		
25	5.57	0.250	0.505	49.7% 2-NP in dioxane	11.1
26	5.57	0.250	0.417		11.1
			Av. = 0.461 ± 0.044		
27	0.250	0.250	0.220	50% TEA in DMF	
28	0.250	0.250	0.225		
			Av. = 0.223 ± 0.003		
			Temp. = 82.76 ± 0.03°		
29	0.250	0.250	0.113	Dioxane	
30	0.250	0.250	0.114		
			Av. = 0.1135 ± 0.0005		
31	0.250	0.250	2.13	DMF	
32	0.250	0.250	2.00	DMF	
			Av. = 2.065 ± 0.065		
			Temp. = 87.94 ± 0.04°		
33	0.250	0.250	0.160	Dioxane	
34	0.250	0.250	0.155		
			Av. = 0.158 ± 0.003		
35	0.250	0.250	3.30	DMF	
36	0.250	0.250	3.06	DMF	
			Av. = 3.18 ± 0.12		

[a] Concentrations are in mole %; DMF = dimethylformamide, TEA = triethylamine, 2-NP = 2-nitropropane, $PhNO_2$ = nitrobenzene. [b] The dielectric constant of DMF at this temperature was obtained by a linear extrapolation of the data of G. R. Leader and J. F. Gormley [*J. Am. Chem. Soc.*, **73**, 5731 (1951)]. The dielectric constants for the mixtures were calculated from the equation

$$\epsilon_{\text{solution}} = \text{mole fraction } A(\epsilon_A) + \text{mole fraction } B(\epsilon_B)$$

The dielectric constant of 2-nitropropane was obtained from "Lange's Handbook of Chemistry," 9th Ed., Handbook Publishers, Inc., Sandusky, Ohio, p. 1224 [ϵ (30°) = 25.5, α = 0.109]. [c] "Handbook of Physics and Chemistry," Chemical Rubber Publishing Co., 41st Ed., Cleveland, Ohio, 1960. [d] "International Critical Tables," Vol. VI, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p. 82.

low rates observed can be explained by the reaction of this anion to produce the very reactive amide ion R_2N^-. (See p. 405, col. 2.)

Methylenebismorpholine, which has a basic dissociation constant *ca.* 1/800th as great as that of methylenebispiperidine,[17] is considerably less reactive toward 2-nitropropane (Table III). Since these amines are nearly identical sterically, difference in reactivity can be attributed only to difference in basic strength.

A plausible mechanism in media of low dielectric constant involves the union of one molecule of 2-nitropro-

(17) H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5441 (1957).

TABLE III

KINETIC DATA FOR THE REACTION OF 2-NITROPROPANE WITH METHYLENEBISMORPHOLINE

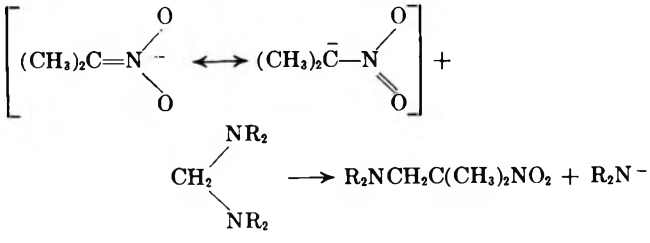
Run no.	Concn. of 2-nitropropane, M	Concn. of methylenebismorpholine, M	k_2, l./mole/hr.	Solvent
		Temp. = 78.60 ± 0.03°		
37	0.250	0.250	0.0097	Dioxane
38	0.250	0.250	0.0067	
39	0.250	0.250	0.00979	
40	0.250	0.250	0.00784	
			Av. = 0.0085 ± 0.0013	
41	0.250	2.50	0.00222	
42	0.250	2.50	0.00167	
			Av. = 0.00195 ± 0.00027	
43	0.250	0.250	0.0525	DMF
44	0.250	0.250	0.0457	DMF
			Av. = 0.0491 ± 0.0034	
		Temp. = 82.76 ± 0.03°		
45	0.250	0.250	0.00785	Dioxane
46	0.250	0.250	0.00945	
			Av. = 0.00865 ± 0.0008	
47	0.250	0.250	0.0532	DMF
48	0.250	0.250	0.0703	DMF
			Av. = 0.0617 ± 0.0086	
		Temp. = 87.94 ± 0.04°		
49	0.250	0.250	0.0127	Dioxane
50	0.250	0.250	0.0120	
			Av. = 0.0124 ± 0.0004	
51	0.250	0.250	0.0773	DMF
52	0.250	0.250	0.0865	DMF
			Av. = 0.0819 ± 0.0046	

TABLE IV

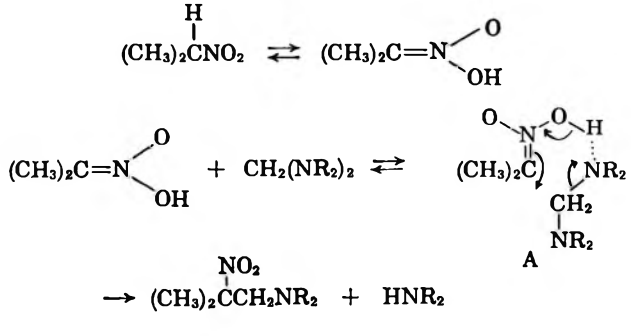
ACTIVATION PARAMETERS[a]

Amine	Solvent	E^{*b}	ΔH^{*b}	ΔF^{*b}	ΔS^{*b}
Methylenebispiperidine	Dioxane	16.32	15.63	21.81	−17.35
Methylenebispiperidine	DMF	20.30	19.61	19.73	−0.33
Methylenebismorpholine	Dioxane	11.40	10.71	23.52	−35.98
Methylenebismorpholine	DMF	14.53	13.84	22.26	−23.61

[a] The values of E^* were determined from plots of log k_2 *vs.* $1/T$ (Fig. 3); $\Delta H^* = E^* - RT$; $\Delta F^* = \Delta H^* - T\Delta S^*$; and ΔS^* was determined from $k_2 = \kappa(k_B T/h)\exp(\Delta S^*/R - E^*/RT)$, κ assumed to be unity (S. Glasstone, K. J. Laidler, and H. Eyring, "Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 21). [b] The values for E, H, and F are in kcal./mole; values for S are in cal./mole/deg.



pane in the *aci* form with one molecule of methylenebisamine to form a hydrogen-bonded complex which can rearrange to form the Mannich base and a molecule of secondary amine.



Such a complex avoids formation of the amide ion R_2N^- and is consistent with the entropy of activation observed for this reaction (Table IV).

The enhanced reactivity of the piperidine derivative compared with that of the morpholine derivative can be attributed to its greater basicity which results in a greater electron shift to the α carbon atom in the transition state. The higher values of ΔS^* for the morpholine reaction can be explained best by assuming that the morpholine transition state A is associated with more solvent molecules than the piperidine species.

The results of reactions carried out in solvent mixtures of varying dielectric constant are pictured in Fig. 1. In all the solvent combinations except excess 2-nitropropane and excess amine, the dependence of rate constant on dielectric constant follows a smooth curve. It is of interest that the logarithm of the rate constant is a nearly linear function of dielectric constant (Fig. 2). This implies a nearly linear dependence of ΔF^* on dielectric constant. A consideration of the activation parameters listed in Table IV leads one to the conclusion that in a medium of high dielectric constant the mechanism changes to one which involves a slightly higher enthalpy of activation and a lower entropy of

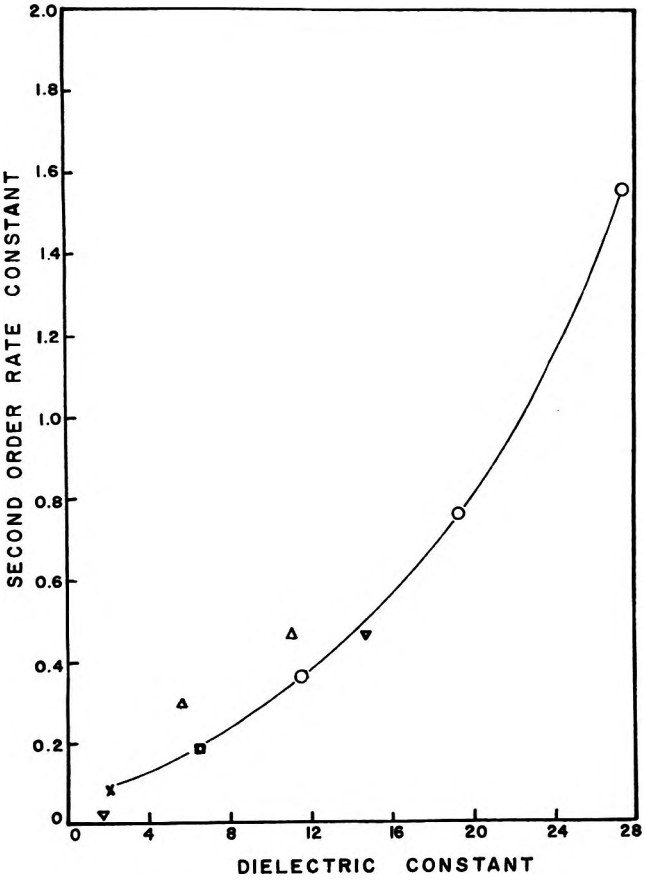


Fig. 1.—Effect of dielectric constant on rate constant: O, DMF–dioxane mixtures; □, nitrobenzene–dioxane; ▽, triethylamine–dioxane; △, excess 2-nitropropane; X, dioxane.

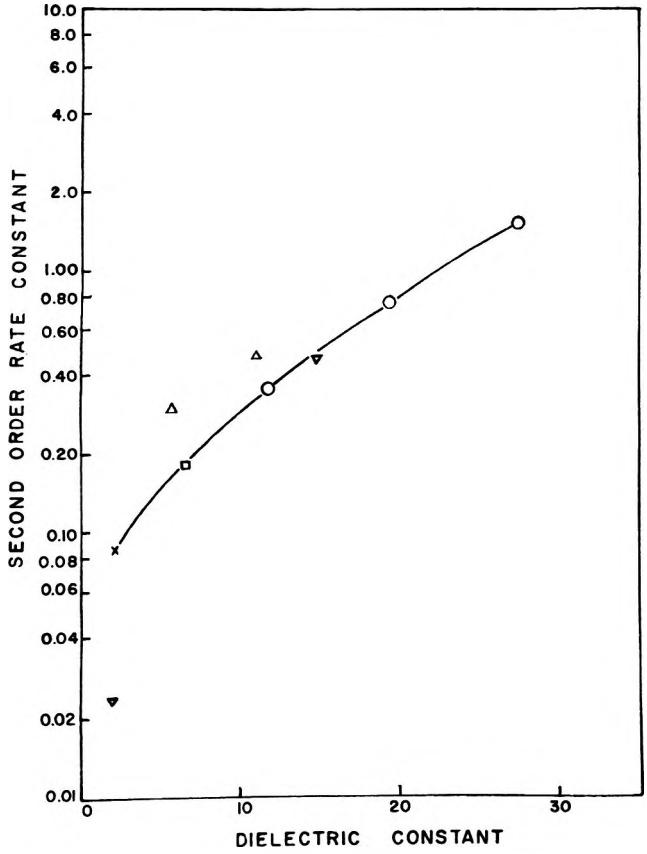


Fig. 2.—Effect of dielectric constant on log k_2 (the points are the same as in Fig. 1).

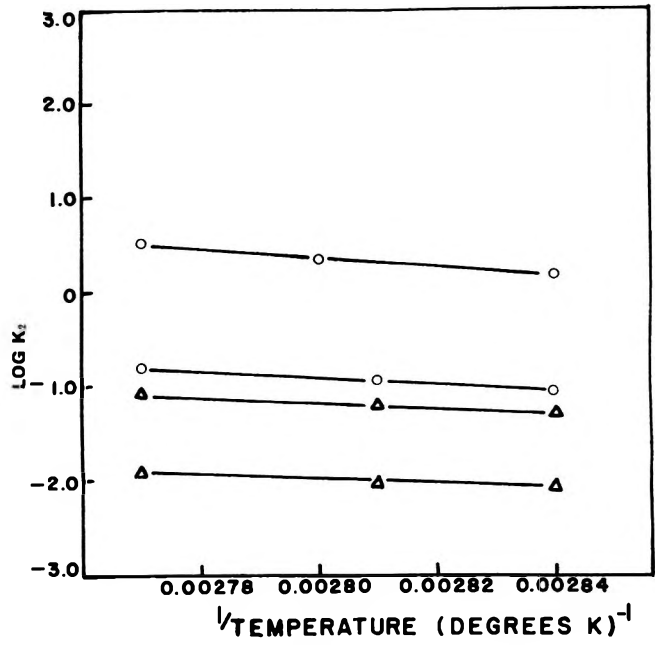
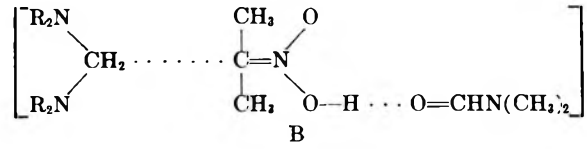


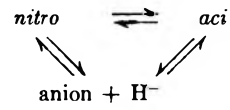
Fig. 3.—Arrhenius plots of the reaction of 2-nitropropane with methylene bispiperidine (O) and with methylenebismorpholine (△). In each case the upper curve represents the reaction in DMF; the lower one represents the reaction in dioxane.

activation (see Fig. 3). This effect is readily explained if one considers that the above transition state A involves replacing at least one solvent molecule in the "solvent shell" of the nitro alkane by a molecule of methylenebisamine before the transition state is formed. In the more polar solvent the transition state can be represented by B. This species does not require so great a ΔS^* as does A, although it requires a greater E^* because of the transitory formation of R_2N^-. The more polar solvent in this case reduces the energy of this ion.



B

The accelerating effect of excess 2-nitropropane on the rate constant (runs 1–4) could be due to the following two factors. (1) At high concentrations of 2-nitropropane there is a larger amount of *aci* form and



(2) nitropropane has a rather large dielectric constant. Runs in which 2-nitropropane was in excess exhibited larger rate constants than can be explained on the basis of dielectric effects alone. This is demonstrated in Fig. 1 and 2 in which the points corresponding to runs using excess 2-nitropropane are considerably above the curve. Hence the accelerating effect of excess 2-nitropropane must be in part due to the larger

concentration of *aci* form present in these mixtures and the rate equation should be expressed in the form

$$\text{rate} = k_2[aci][\text{methylenebisamine}]$$

or

$$\text{rate} = k_2K_e[\text{nitro}][\text{methylenebisamine}]$$

where K_e is the equilibrium constant for the nitro–*aci* interconversion. That the inhibiting effect of base is not due entirely to dielectric effects is shown by the runs in excess triethylamine which fell below the curve in Fig. 1 and 2.

Synthesis and Study of Mannich Bases from 2-Naphthol and Primary Amines[1]

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Several 1-alkylaminomethyl-2-naphthols (III) were prepared from the corresponding naphthoxazines (I). These new Mannich bases (III) were found to undergo self-condensation with great ease in warm ethanol to form mainly either *N,N*-bis(2-hydroxy-1-naphthylmethyl)alkylamines (II) or the original naphthoxazine along with bis(2-hydroxy-1-naphthyl)methane. The course of the reaction depended largely on the structure of the primary amine used in the synthesis of I.

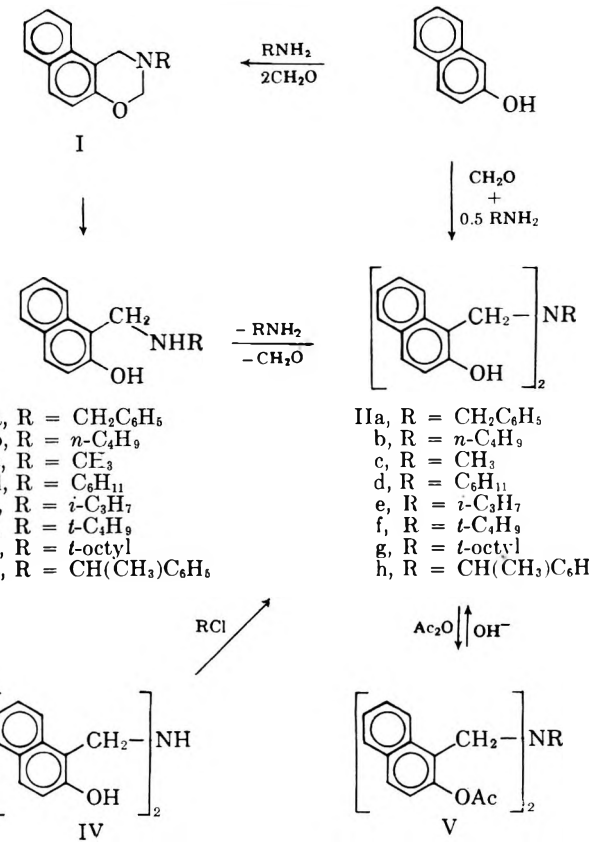
Mannich bases have been used widely as synthetic intermediates.[4,5] Work in this laboratory[6,7] on phenolic Mannich bases derived from primary amines has shown the importance of several reaction variables on the course of the condensation. These included the nature and position of substituents on the phenol, reactant ratios, temperature, and the basicity of the amine.

Marked differences in behavior also were found between phenols and naphthols. For example, phenols having a free *ortho* or *para* position reacted readily with equimolar quantities of formaldehyde and primary amines to form Mannich bases. However, use of 2-naphthol in place of the phenol led to a 2-suhstituted 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (I) or the corresponding *N,N*-bis(2-hydroxy-1-naphthylmethyl)-amine (II) depending on the particular amine and temperature employed.[6]

Hydrochlorides of Mannich bases (III) from 2-naphthols and primary amines were obtained indirectly, however, by the acidic hydrolysis of naphth[1,3]oxazines.[6] In the present study, neutralization of the Mannich base (IIIa) hydrochloride from benzylamine resulted in a solid product which upon recrystallization from warm ethanol did not give the corresponding free base but rather a good yield of *N,N*-bis(2-hydroxy-1-naphthylmethyl)benzylamine. This result was of particular interest since earlier attempts[6] to prepare the latter compound (IIa) by direct condensation of 2-naphthol with formaldehyde and benzylamine in the calculated 2:2:1 molar ratio led to an 86% yield of the corresponding naphthoxazine (Ia).

The structure of IIa was confirmed by an independent synthesis involving the condensation of benzyl chloride with *N,N*-bis(2-hydroxy-1-naphthylmethyl)amine (IV) and also by the synthesis of a diacetate (V). The latter was reconverted to IIa upon saponification.

The ease with which the self-condensation of IIIa occurs is rather surprising in view of the comparative stability of naphtholic Mannich bases from secondary amines although the structure of the latter would, of course, preclude an analogous reaction.



It was found possible to prepare the crystalline free Mannich base (IIIa) in high yield (94%), however, by neutralizing an aqueous suspension of the corresponding hydrochloride with 2-aminoethanol in the presence of ether at 0° and removing the ether under reduced pressure with cooling. The free base (IIIa) was readily converted to *N,N*-bis(2-hydroxy-1-naphthyl)benzylamine (IIa) in 83% yield when an ethanol solution was warmed to 60° for 5 min.

(1) Supported in part by a research grant CY-5211 from the National Cancer Institute of the Public Health Service and a grant from Miles Laboratories.

(2) Department of Chemistry, Arizona State University, Tempe, Ariz.

(3) Abstracted in part from a thesis submitted by W. A. Nasutavicus to the Graduate School of the University of Utah in partial fulfillment of the requirements for the degree of Master of Arts.

(4) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

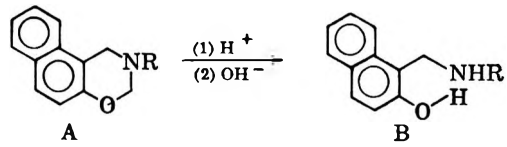
(5) J. H. Brewster and E. L. Eliel, *ibid.*, **7**, 99 (1953).

(6) W. J. Burke, M. J. Kolbezen, and C. W. Stephens, *J. Am. Chem. Soc.*, **74**, 3601 (1952).

(7) W. J. Burke, R. P. Smith, and C. Weatherbee, *ibid.*, **74**, 602 (1952); W. J. Burke, K. C. Murdock, and Grace Ek, *ibid.*, **76**, 1677 (1954); W. J. Burke, C. R. Hammer, and C. Weatherbee, *J. Org. Chem.*, **26**, 4403 (1961).

TABLE I

3-SUBSTITUTED 1*H*-2,3-DIHYDRONAPHTH[1,2-*e*][1,3]OXAZINES AND 1-SUBSTITUTED AMINOMETHYL-2-NAPHTHOLS



Structure	R	Yield, %	M.p., °C	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Amine·HCl M.p., °C.	Chlorine, % Calcd.	Chlorine, % Found
A	$CH(CH_3)_2$	70		$C_{15}H_{17}NO$					183–184[a,b]	13.44	13.40
A	$C(CH_3)_3$	97	75–76[c]	$C_{16}H_{19}NO$	79.63	79.59	7.94	7.75	204–205[d]	12.76	12.75
A	$CH(CH_3)C_6H_5$	90	75–76[e]	$C_{20}H_{19}NO$	83.00	82.84	6.62	6.66	180–182[b]	10.88	10.82
A	C_6H_{11}	64[f]	43–44[c]	$C_{18}H_{21}NO$	80.86	80.90	7.92	8.26	178–179[l]		
A	*t*-Octyl	85	84–85[d]	$C_{20}H_{27}NO$	80.76	80.99	9.15	9.07			
B	$CH_2C_6H_5$	94	55–56[g]	$C_{18}H_{17}NO$	82.10	82.59	6.51	6.65			
B	C_6H_{11}	100	82–84[g]	$C_{17}H_{21}NO$	79.96	80.00	8.29	8.43	192–193[m]		
B	$C(CH_3)_3$	90	71–73[g]	$C_{15}H_{19}NO$	(6.11% N)	(5.92% N)			202–205[h]	13.34	13.18
B	$CH(CH_3)_2$	90		$C_{14}H_{17}NO$	(4.91% N)	(5.06% N)			180–181[a,i]	14.08	14.22
B	*t*-Octyl	98	83–84[c]	$C_{19}H_{27}NO$	79.94	79.95	9.53	9.12	185–187[j]	11.02	11.05
B	$CH(CH_3)C_6H_5$	100	Oil	$C_{18}H_{19}NO$	81.47	82.15	7.22	7.24	135–137[k]	11.30	11.11

[a] Isolated and characterized as the hydrochloride. [b] Washed with acetone. [c] Recrystallized from methanol. [d] Recrystallized from 95% ethanol. [e] Recrystallized from dimethylformamide–methanol (1:5). [f] This compound had been reported as an oil. Calcd., for neut. equiv.: 267.4. Found, 270.4. [g] Obtained by treatment of hydrochloride with 2-aminoethanol, not recrystallized. [h] Recrystallized from propanol-1. [i] Recrystallized from ethanol–acetone. [j] Recrystallized from butanol-1–acetone. [k] Recrystallized from acetone containing a trace of water. [l] Lit.[6] m.p. 178–179. [m] Lit.[6] m.p. 192–193.

In view of these results, a study of the stability of other related naphtholic Mannich bases was undertaken. Neutralization of 1-*n*-butylaminomethyl-2-naphthol (IIIb) hydrochloride with 2-aminoethanol at room temperature readily gave the corresponding, previously reported *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)-*n*-butylamine (IIb) in 70% yield. Under similar conditions the Mannich base from methylamine (IIIc) gave an oil which upon treatment with warm methanol deposited the known[6] *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)methylamine (IIc).

1-Cyclohexylaminomethyl-2-naphthol (IIId) was readily obtained in 85% yield upon neutralization of the corresponding hydrochloride at 0°. The product was characterized as the *N*,*O*-diacetyl derivative. When the free base was warmed in ethanol at 35° for several minutes a 65% yield of *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)cyclohexylamine (IId) was obtained along with small amounts of bis(2-hydroxy-1-naphthyl)methane (8%) and 2-cyclohexyl-2,3-dihydro-1*H*-naphth[1,2-*e*]-[1,3]oxazine (18%). The last compound, previously reported[6] as oil, was obtained as a low melting, crystalline solid. Similar results were obtained at 65° except that the yield of the bisamine (IId) was only 37%.

Four new naphthoxazines and the corresponding Mannich base hydrochlorides were prepared by procedures similar to those used earlier[6] in order to study the influence of substituents on the α carbon of the amine on the stability and decomposition path of the free Mannich bases. The condensation of 2-naphthol and formaldehyde with isopropylamine, α-methylbenzylamine, *t*-butylamine, and *t*-octylamine gave the expected naphthoxazines in high yields. These were readily hydrolyzed to the corresponding Mannich base hydrochlorides. Data on these compounds are given in Table I.

Neutralization of 1-isopropylaminomethyl-2-naphthol (IIIe) hydrochloride in the cold led to a low melting solid, which upon treatment with warm ethanol gave an 80% yield of the corresponding tertiary amine (IIe). In another run, addition of concentrated hydrochloric acid to the cold solution shortly after neutralization resulted in a 90% recovery of the Mannich base (IIIe) hydrochloride. This indicates that the low melting solid initially obtained upon neutralization was probably the unstable free Mannich base (IIIe).

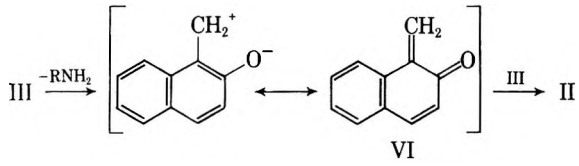
In contrast to the results with IIIe, the free base (IIIg) obtained from the neutralization of 1-*t*-octylaminomethyl-2-naphthol hydrochloride was sufficiently stable to withstand several recrystallizations at room temperature from dimethylformamide to which methanol was added. Moreover, when base IIIg was warmed in ethanol for 5 min. at 55°, no *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)-*t*-octylamine (IIg) was isolated. Instead, bis(2-hydroxy-1-naphthyl)methane (73%) and 2-*t*-octyl-1*H*-2,3-dihydronaphth[1,2-*e*][1,3]-oxazine (34%) were obtained in the indicated yields, based on IIIg. The results obtained when the *t*-butyl Mannich base (IIIf) was warmed in ethanol at 55° were analogous to those obtained with the *t*-octyl compound (IIIg) in that bis(2-hydroxy-1-naphthyl)methane and 3-*t*-butyl-2*H*-1,3-dihydronaphth[1,3]oxazine were formed in high yields, and no *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)-*t*-butylamine was isolated. A somewhat smaller amount of oxazine was obtained when IIIg was heated at 50–60° for 24 hr.

When the Mannich base 1-α-methylbenzylaminomethyl-2-naphthol (IIIh) was warmed in ethanol and treated with formaldehyde, the corresponding naphthoxazine and bis(2-hydroxy-1-naphthyl)methane were obtained, but there was no evidence for the formation of *N*,*N*-bis(2-hydroxynaphthylmethyl)-α-methylbenzylamine (IIh).

In carbon alkylations with phenolic Mannich bases derived from secondary amines, methylene quinones have been postulated as intermediates[5] and *o*-quinone methide recently has been prepared.[8] The addition of

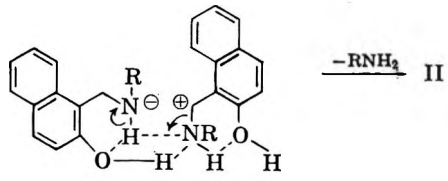
(8) P. D. Gardner, H. Sarrafizadeh, and R. Brandon, *J. Am. Chem. Soc.*, 81, 5515 (1959).

a Mannich base (III) to an analogous *o*-methylene naphthoquinone intermediate (VI), formed by the elimination of a mole of primary amine from III, would offer a possible route to the formation of *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)amines (II).



VI

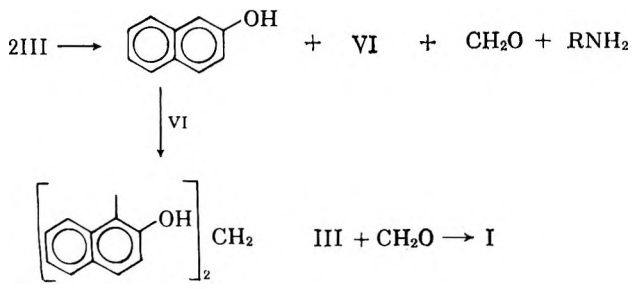
Study of molecular models indicated the excellent opportunities for inter- as well as intramolecular hydrogen bonding of the naphtholic Mannich bases (III). The formation of a dimeric intermediate such as VII would appear to provide an opportunity to facilitate both amine elimination and tertiary amine (II) formation. The possibility of reaction between two molecules of Mannich base with one acting as an acid and another as a base has been pointed out by Brewster and Eliel.[5]



VII

The failure to convert the Mannich bases (III) to the corresponding tertiary amines (II) when R was *t*-butyl, *t*-octyl, or *α*-methylbenzyl would be consistent with either of the above mechanisms. Bulky R substituents could be expected to discourage either intermolecular hydrogen bonding or the addition of the Mannich base to the *o*-methylene naphthoquinone intermediate (VI).

Phenolic Mannich bases from secondary amines have long been known to undergo self-condensation to form bis(hydroxyaryl)methanes[9] and recently Mannich bases from lawsone were shown to undergo an analogous reaction.[10] It was proposed that the Mannich base reacted first to form lawsone, an *o*-methylene quinone, formaldehyde, and the secondary amine. A similar reaction path with the naphtholic Mannich bases (III) with bulky R substituents would account readily for the formation of bis(2-hydroxy-1-naphthyl)methane and a naphthoxazine.



Since *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)-*t*-octylamine (IIg) was not obtained from the Mannich base (IIIg) the possibility of preparing this compound directly by reaction of *t*-octylamine, formaldehyde, and 2-naphthol in a molar ratio of 1:2:2 at 0° was explored. Even at this low temperature, known to be favorable to the formation of bis(hydroxynaphthyl)amines,[6] a high yield (88%) of the naphthoxazine (I) was obtained. Replacement of *t*-octylamine with *t*-butylamine also led to naphthoxazine formation (47% based on *t*-butylamine), but in addition a high yield of bis(2-hydroxy-1-naphthyl)methane (88% based on available 2-naphthol) was obtained. In neither case was any of the *N*,*N*-bis(hydroxynaphthyl)amine (II) isolated.

Experimental[11]

1-Benzylaminomethyl-2-naphthol (IIIa).—2-Aminoethanol (8 ml.) was added to an agitated suspension of 12.0 g. of IIIa hydrochloride in 200 ml. of water and 300 ml. of ether at 0°. The mixture was stirred at 0° for 10 min. and the small amount of undissolved solid removed by filtration. The ether layer was separated and the aqueous layer extracted with two 100-ml. portions of ether at 0°. The combined ether extracts were concentrated under reduced pressure at 0° and the resulting solid (9.9 g., 94% yield) quickly removed by filtration, washed with ethanol at 0°, and dried at room temperature at 0.1-mm. pressure, m.p. 54–57°

A similar procedure was used to prepare 1-cyclohexylaminomethyl-2-naphthol.

N,*N*-**Bis(2-hydroxy-1-naphthylmethyl)benzylamine (IIa). Procedure A.**—Ethyl ether (300 ml.) and 25 ml. of 2-aminoethanol were added to a suspension of 36 g. of IIIa hydrochloride in 1 l. of water at room temperature. The solid dissolved upon agitation and the ether layer separated. The aqueous layer was extracted twice with ether. Removal of solvent from the combined ether extracts left an oil which was dissolved in 100 ml. of ethanol. Within 15 min. crystallization occurred to yield 14.5 g. (60% yield), m.p. 125–128°; after recrystallization from ethanol, the melting point was 135°.

Procedure B.—1-Benzylaminomethyl-2-naphthol (IIIa, 7 g.) in 75 ml. of 95% ethanol was warmed at 60° for 5 min. and kept at room temperature for 2 days. The white solid (4.52 g., 81% yield) which separated was removed by filtration and washed with cold ethanol, m.p. 131–134°; after recrystallization from ethanol, the melting point was 135–136°.

Procedure C.—Benzyl chloride (2 ml., 0.017 mole) was added to a solution of 2 g. of *N*,*N*-bis(2-hydroxy-1-naphthylmethyl)-amine (0.0057 mole) in 75 ml. of pyridine. After 16 hr. at room temperature the reaction mixture was added with stirring to distilled water. The resulting product (2.5 g., 96% yield) melted at 135–136° after recrystallization from ethanol and did not depress the melting point of the product from procedure A.

N,*N*-**Bis(2-acetoxy-1-naphthylmethyl)benzylamine.**—Acetic anhydride (2.5 g., 0.03 mole) was added to a solution of 4 g. of IIa (0.013 mole) in 20 ml. of pyridine. After 16 hr. at room temperature, the reaction mixture was poured slowly with agitation into ice and water. The yield of the resulting solid was essentially quantitative; after recrystallization from methanol, the melting point was 170–172°.

Anal. Calcd. for $C_{33}H_{29}NO_4$: C, 78.70; H, 5.80. Found: C, 78.52; H, 5.67.

Treatment of the above ester with a 1% solution of sodium hydroxide in aqueous ethanol at 25° for 3 hr. gave a product which melted at 133–135° and did not depress the melting point of IIa.

N,*N*-**Bis(2-hydroxy-1-naphthylmethyl)amines (II).**—The following tertiary amines (II) were prepared from the corresponding Mannich bases by a method similar to that described in procedure A for IIa above. The compounds used in the mixture melting point determinations were prepared directly from 2-naphthol as described earlier.[6]

N,*N*-**Bis(2-hydroxy-1-naphthylmethyl)-*n*-butylamine** (IIb).—The yield was 70%, m.p. and m.m.p. 136–138°, lit.[6] m.p. 137–138°. The **hydrochloride** melted at 135–137°, lit.[6] m.p. 135–137°.

N,*N*-**Bis(2-hydroxy-1-naphthylmethyl)methylamine** (IIc).—The yield was 59%, m.p. and m.m.p. 146–148°, lit.[6] m.p. 147–

(9) K. Auwers and A. Dumbrowski, *Ann.*, **344**, 280 (1906).

(10) W. R. Vaughn, M. S. Habib, R. S. McElhinney, N. Takahashi, and J. A. Waters, *J. Org. Chem.*, **26**, 2394 (1961).

(11) All melting points are uncorrected.

148°. The **hydrochloride** melted at 149–151°, lit.[6] m.p. 148–151°.

N,N-**Bis(2-hydroxy-1-naphthylmethyl)isopropylamine (IIe).**—The yield was 83%, m.p. 125–126°, after recrystallization from methanol–1-dimethylformamide (6:1).

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.75. Found: C, 80.53; H, 6.95.

The **hydrochloride** melted at 163–164°, after recrystallization from methanol.

Anal. Calcd. for $C_{25}H_{26}ClNO_2$: Cl^-, 8.69. Found: Cl^-, 8.73.

Treatment of 1-*t*-Octylaminomethyl-2-naphthol (IIIg) with Hot Ethanol.—1-*t*-Octylaminomethyl-2-naphthol (2.5 g.) was warmed to 50–55° in 30 ml. of 95% ethanol for 5 min. and then kept at room temperature for 2 days. Removal of the solvents under reduced pressure gave an oil which was dissolved in 100 ml. of ether. The resulting solution was extracted with 100 ml. of water containing 2 g. of sodium hydroxide. The ether extract was washed with water and dried over sodium sulfate. Evaporation of the ether gave a solid, m.p. 78–80°. It was recrystallized from 95% ethanol to yield 0.45 g. (34%), m.p. 82–83°; mixture melting point with an authentic sample of 2-*t*-octyl-1*H*-2,3-dihydronaphth[1,2-*e*][1,3]oxazine, m.p. 83–84°, gave no depression.

The aqueous extracts were washed with ether. Upon adding 37% hydrochloric acid to pH 1, a white solid separated. It readily dissolved in ether. Removal of the ether gave 0.95 g. (73% yield) of bis(2-hydroxy-1-naphthyl)methane; melting point and mixture melting point with authentic specimen was 200–202°, lit.[12] m.p. 200°.

The aqueous extracts were neutralized with potassium bicarbonate and extracted with ether. Removal of the ether gave only a trace of oil.

N-**Cyclohexyl-*N*-(2-acetoxy-1-naphthylmethyl)acetamide.**—Acetic anhydride (10 g., 0.12 mole) was added to a solution of 4 g. of 1-cyclohexylaminomethyl-2-naphthol (0.016 mole) in 20 ml. of pyridine cooled on an ice bath. After 24 hr. at room temperature, 70 ml. of water was added. Upon cooling 4.8 g. (88% yield) of solid, m.p. 107–108°, separated. The product was recrystallized twice from methanol containing a trace of water, m.p. 108–109°.

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.32; H, 7.42. Found: C, 74.43; H, 7.37.

N-*α*-**Methylbenzyl-*N*-(2-acetoxy-1-naphthylmethyl)acetamide** was prepared from Mannich base by above procedure, 61% yield, m.p. 119–121°, from methanol.

Anal. Calcd. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41. Found: C, 76.30; H, 7.00.

N-*α*-**Methylbenzyl-*N*-(2-hydroxy-1-naphthylmethyl)acetamide.**—Hydrolysis of the above ester in 2% potassium hydroxide in 95% ethanol at 25° for 3 hr. gave a product, m.p. 160–160.5°, after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.96; H, 6.63. Found: C, 78.77; H, 6.59.

Acknowledgment.—We wish to express our appreciation to Dr. C. W. Stephens, Mr. Joe E. Brown, and Mr. George Van Lear for technical assistance.

(12) O. Manasse, *Ber.*, **27** 2409 (1894).

Amine Exchange Reactions. Mannich Bases from Aromatic Amines[1]

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An exchange reaction occurs readily between tertiary Mannich bases (I) and primary and secondary arylamines, making accessible the monosubstituted arylamine Mannich bases (II and IV) in good yield. The arylamines used include polycyclic and heterocyclic bases as well as diamines. Experiments suggest that the overall amine-exchange reaction may proceed both by a substitution as well as by an elimination–addition mechanism.

A survey of the literature[2] concerning the Mannich reaction, using ketones as the acidic entity, reveals that, although the range of aliphatic amines used is virtually unlimited, the only reported successful condensation using an arylamine is the synthesis, in unstated yield, of 1,2,6-triphenyl-4-piperidone[3] from acetone, benzaldehyde, and aniline. Attempted Mannich reaction[4] between acetophenone, formaldehyde, and aniline hydrochloride failed to give the required *β*-anilinopropiophenone (IIa), leading instead to the formation of polymeric products derived from the aldehyde and amine.

Only a few isolated examples[5–9] of such condensations have appeared since that observation, and Mannich bases of type II are not readily available and cannot be prepared by the standard Mannich reaction. A number of syntheses of *β*-arylamino ketones (II) by other routes appear in the literature[10–12] but the methods are usually complex, the starting materials difficultly accessible, and the preparations confined to specific examples and not general in scope.

R–$COCH_2CH_2$–NR'_2	I	a	R = Ph; Ar = Ph
R–$COCH_2CH_2$–NHAr	II	b	R = Me; R′ = Et
R–$COCH_2CH_2$–NHR′	III	e	R = Me; Ar = Ph
		d	R = Ph; R′ = Et
R–$COCH_2CH_2$–NMeAr	IV	e	R = R′ = Me
Ph–$COCHMeCH_2NEt_2$	V	f	R = Ph; Ar = *p*-ClC_6H_4
Ph–$COCHMeCH_2NHC_6H_4$-*p*-Cl	VI	g	R = Ph; R′ = Me

It was shown recently[13] that the exchange reaction between tertiary Mannich bases (I) and primary alkyl-

(1) This work was partially supported by a grant (HE 5881) from the National Institutes of Health, U. S. Public Health Service.

(2) (a) F. F. Blicke, "Organic Reactions," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303; (b) "Methoden der Organischen Chemie," (Houben-Weyl), Georg Thieme Verlag, Stuttgart, 1957, p. 731; (c) B. Reichert, "Die Mannich Reaktion," Springer Verlag, Berlin, 1960.

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(6) H. G. Johnson, *ibid.*, **68**, 14 (1946).

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(11) I. Vavrecka, *Collection Czech. Chem. Commun.*, **14**, 399 (1949).

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(13) J. C. Craig, S. R. Johns, and M. Moyle, *J. Org. Chem.*, **28**, 2779 (1963).

TABLE I

β-ARYLAMINOPROPIOPHENONES[a] $PhCOCH_2CH_2NHAr$

Ar	Reaction time, hr.	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5	1	90	113–114					
p-MeC_6H_4	1	87	114–115	[b]				
p-$MeOC_6H_4$	1	89	111–112	[c]				
p-ClC_6H_4	1	88	134–135	[d]				
p-$C_6H_5COC_6H_4$	4	90	131–132	$C_{22}H_{19}NO_2$	80.26	80.22	5.91	5.81
p-$MeCOC_6H_4$	16	79	178–180	$C_{17}H_{17}NO_2$	76.38	76.21	6.41	6.50
p-$NO_2C_6H_4$	30	67	173–175	$C_{15}H_{14}N_2O_3$	66.65	66.48	5.22	5.39
p-$MeCONHC_6H_4$	12	80	144–145	$C_{17}H_{18}N_2O_2$	72.32	72.28	6.43	6.45
p-$HOOCC_6H_4$	1	84	210–211	$C_{16}H_{15}NO_3$	71.36	71.06	5.61	5.58
1-Pyrenyl	15	50	156–157	$C_{25}H_{19}NO$	85.93	85.72	5.48	5.54
2-Naphthyl	12	81	150–151	$C_{19}H_{17}NO$	82.87	82.71	6.23	6.42
2-Pyridyl	4	74	88–89	$C_{14}H_{14}N_2O$	74.30	74.27	6.24	6.19
3-Pyridyl	2	85	98–99	$C_{14}H_{14}N_2O$	74.30	73.99	6.24	6.27
3-Quinolyl	1	76	151–152	$C_{18}H_{16}N_2O$	78.23	77.96	5.84	5.83

[a] Prepared by method B. [b] Lit.[15] m.p. 113–114°. [c] Lit.[15] m.p. 114–115°. [d] Lit.[15] m.p. 136–138°.

amines gives the monosubstituted secondary Mannich bases (III), *e.g.*, reaction 1. Since Mannich bases from arylamines were required for other work, the application of this exchange reaction to aromatic amines was next investigated. We now report a method by which these compounds can be readily obtained in good yield.[14]

Equimolar quantities of the tertiary aliphatic Mannich base 1-diethylamino-3-butanone (Ib) and aniline hydrochloride reacted exothermally at room temperature; the mixture first became homogeneous, then crystals of diethylamine hydrochloride separated. The required 1-anilinobutan-3-one (IIc) was isolated in 70% yield. When the reactants were refluxed in 50% ethanol for a short time, the yield was increased to 86%. The reaction could be carried out using either the Mannich base and an arylamine salt, or the Mannich base hydrochloride and an arylamine, or a mixture of the two bases with the addition of a molar proportion of hydrochloric acid.

By this means the required 1-arylamino-3-butanones (II, R = Me) were prepared from a range of p-substituted anilines $RC_6H_4NH_2$ in which R = H, Me, OMe, Cl, and Ph, as well as with β-naphthylamine. The aromatic tertiary Mannich base β-diethylaminopropiophenone (Id) could be used under the same experimental conditions and readily underwent amine exchange with a variety of primary aromatic amines to give the β-arylaminopropiophenones (II, R = Ph) shown in Table I. The arylamines used include polycyclic and heterocyclic bases, as well as diamines. When methylaniline was employed as the arylamine moiety, amine exchange took place readily with both Ie and Ig to give, respectively, 1-(N-methylanilino)-3-butanone (IVc) and β-(N-methylanilino)propiophenone (IVa), both in 45% yield. The amine-exchange method, therefore, appears to be applicable to secondary arylamines also.

Since this work was completed, a recent publication[15] has appeared giving the preparation of several β-arylaminopropiophenones (IIa) in 37 to 62% yield by prolonged refluxing of β-dialkylaminopropiophenone hydrochloride and an aromatic primary amine. However, the results reported in the present study show that the reaction proceeds under milder conditions and has a wider range of applicability than was indicated by these authors.[15]

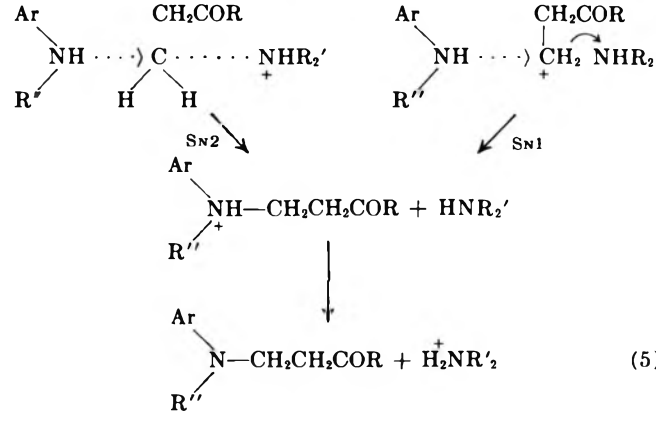
$$PhCOCH_2CH_2NEt_2 + C_6H_{11}NH_2 \longrightarrow PhCOCH_2CH_2NHC_6H_{11} + Et_2NH \quad (1)$$

$$RCOCH_2CH_2\overset{+}{N}HR_2' + ArNHR'' \longrightarrow RCOCH_2CH_2NR''Ar + R_2'\overset{+}{N}H_2 \quad (2)$$

$$RCOCH(H)CH_2\overset{+}{N}HR_2' \underset{3b}{\overset{3a}{\rightleftharpoons}} RCOCH{=}CH_2 + H_2\overset{+}{N}R_2' \quad (3)$$

$$RCOCH{=}CH_2 + Ar\,NHR'' \longrightarrow RCOCH_2CH_2NR''Ar \quad (4)$$

IV



(5)

Using aniline or methylaniline as the arylamine, the over-all amine exchange (eq. 2) may proceed either by an elimination reaction (eq. 3a) followed by a Michael addition (eq. 4) with the arylamine to give the product (IV) or alternatively by a direct substitution (reaction 5) which may be either concerted (SN2) or may occur *via* an intermediate carbonium ion (SN1) with identical results. Application of the amine exchange reaction to the branched-chain Mannich base β-diethylamino-α-methylpropiophenone (V) and p-chloroaniline resulted in a 20% yield of β-(p-chloroanilino)-α-methylpropiophenone (VI), compared with a 90% yield of the corresponding unbranched β-(p-chloroanilino)-propiophenone (IIf). If the N-deuterioarylamine were used, in the form of its deuteriochloride salt, and reaction (eq. 2) carried out in deuterium oxide as solvent,

(14) A preliminary publication has appeared in *Chem. Ind.* (London), 690 (1963).

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then (following the instantaneous proton transfer to the stronger base) the elimination–addition mechanism (reactions 3 and 4) would result in the incorporation of one atom of deuterium into the α-methylene group (C-2) in the products 1-anilino-3-butanone (IIc) and 1-(N-methylanilino)-3-butanone (IVc), while, if the direct substitution (reaction 5) operated, no deuterium due to this substitution reaction would appear in that position.

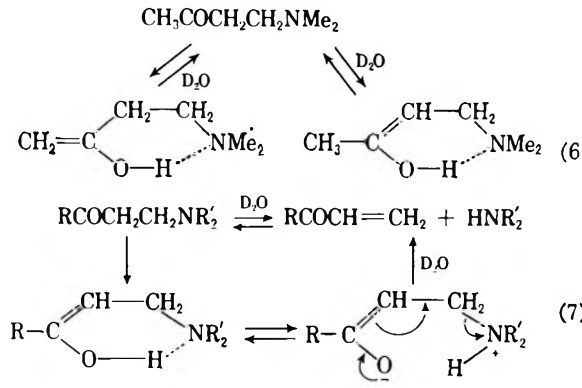
The use of n.m.r. spectroscopy offers a highly sensitive method for the location and estimation of deuterium substitution in a molecule.[16] To simplify the n.m.r. spectra, methylaniline was initially used as the arylamine and 1-dimethylamino-3-butanone (Ie) as the Mannich base.

In 1-dimethylamino-3-butanone, the methyl and dimethyl group appeared as singlets at δ 1.93 and 2.00 p.p.m., respectively, and the methylene groups as a multiplet at δ 2.36 p.p.m. In 1-(N-methylanilino)-3-butanone (IVc), the C-methyl and N-methyl singlets were found at δ 1.85 and 2.70 p.p.m., respectively, and the methylene groups as two separate triplets, δ 2.37 (C-2) and 3.47 (C-1) p.p.m. (shifted by the adjacent phenyl group), both with J = 7 c.p.s. The aromatic multiplet was at δ 6.94. The n.m.r. spectrum of 1-anilino-3-butanone (IIc) showed the methyl group and the aminohydrogen as singlets at δ 1.86 and 4.08 p.p.m., respectively, and the methylene groups as well-separated triplets, δ 2.39 (C-2) and 3.18 (C-1) p.p.m., with J = 7 c.p.s. in both cases. The aromatic multiplet was located at δ 6.95 p.p.m.

N-Deuteriomethylaniline and N-deuterioaniline deuteriochlorides were prepared by repeated treatment of the respective hydrochlorides with deuterium oxide until the infrared spectrum of the product showed no further change. Deuteration could be followed by a decrease in the absorption bands at 2920 and 2820 cm.$^{-1}$ ($\overset{+}{N}H_2$),[17] and a corresponding increase in bands at 2220 and 2120 cm.$^{-1}$ ($\overset{+}{N}D_2$).

Before carrying out the reaction using the deuterated arylamine salts, it was necessary to ascertain the extent of self-deuteration of 1-dimethylamino-3-butanone (Ie) under the reaction conditions used. It is well-known[18] that, *e.g.*, acetone undergoes rapid deuteration in the presence of alkali, but the occurrence of deuteration as a result of self-enolization under the sole influence of the basic group in the same molecule does not seem to have been observed previously.

When Ie alone was treated under the constant experimental conditions, the product was indeed found to contain, from the integrated n.m.r. spectrum, 1.66 and 2.27 D in positions 2 and 4, respectively, of 1-dimethylamino-3-butanone (Ie), the hydrogen content of the rest of the molecule being unchanged. The deuterium may be due to reversible self-enolization to the two enol forms stabilized by hydrogen bonding (reaction 6) and to some elimination–recombination (reaction 7); the figures found are in the ratio 2.28:3. Treatment of the deuteriochloride of Ie alone under the same condition gave a base (liberated at 0° using sodium ethoxide) which contained 1.22 and 1.60 D at positions 2 and 4; the rest of the molecule remained



unchanged. Although the total deuterium incorporation in the salt was less (as expected since the nitrogen was protonated), these figures are again in almost the same ratio 2.30:3. From the experimentally found deuterium content, the relative rates of deuterium exchange at C-2 and C-4 in Ie and its deuteriochloride may be calculated. In every experiment 15 moles of deuterium oxide per mole of Ie were used. Employing the following more accurate second-order equation

$$kt = \log \frac{a}{a - x} - \log \frac{b}{b - x}$$

which takes into account the change in the concentration of deuterium oxide during the time t, then for the base (Ie) at C-2, a = 2, b = 15, and x = 1.66, giving $(k_2)t$ = 0.7186. Similarly from C-4, a = 3, b = 15, and x = 2.27 gives $(k_4)t$ = 0.5425, and k_2/k_4 = 1.325. For the deuteriochloride of Ie, the same method of calculation yields $(k_2)t$ = 0.3720 and $(k_4)t$ = 0.2820, whence k_2/k_4 = 1.320. Thus, although the extent of deuteration in the salt is less, the ratio of the rates of deuteration at C-2 and C-4 is unchanged. It is clear that the rate of deuterium exchange in Ie is determined by the acid–base interaction (self-enolization, reaction 6) occurring initially as formation of a hydrogen bond and proceeding to a complete transfer of a proton and resultant ionization. In view of the very weak nature of, *e.g.*, acetone as an acid[19] in water (pK_a 20), this rate is surprisingly rapid.

Reaction of deuterioaniline deuteriochloride with Ie in deuterium oxide and isolation of the product (IIe) by extraction with anhydrous ether gave a material, the integrated n.m.r. spectrum of which showed incorporation of 1.7 D at C-2 and 2.2 D at C-4 in the 1-anilinobutan-3-one (IIc), as well as the expected deuteration of the amino group.

Since the nature of the amine exchange reaction as either elimination–addition or substitution can only affect the extent of deuteration at C-2 but not that at C-4, it is seen that, using the previously determined

(16) N.m.r. spectra were determined on the neat liquids at 60 Mc. using a Varian HR-60 instrument, with chemical shifts given in p.p.m. from a trace of dissolved tetramethylsilane. Deuterium content at the various molecular sites was determined from proton count data obtained using the electronic integrator. Each determination was the mean of five runs; the standard deviation of the average value was about 2%.

(17) P. J. Stone, J. C. Craig, and H. W. Thompson, *J. Chem. Soc.*, 52 (1958).

(18) (a) K. F. Bonhöffer, K. H. Geib, and O. Reitz, *J. Chem. Phys.*, **7**, 664 (1939); (b) S. K. Hsu, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938); C. L. Wilson, *ibid.*, 1550 (1936).

(19) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).

ratio[20a] $k_2/k_4 = 1.32$ and the figure of 2.2 D (found) at C-4 in the product (IIc), the calculated amount of deuteration (x) at C-2 in IIc due to the self-enolization may be found from the expression that follows

$$\frac{k_2}{k_4} = 1.32 = \frac{\log \frac{2}{2-x} - \log \frac{15}{15-x}}{\log \frac{3}{3-2.2} - \log \frac{15}{15-2.2}}$$

whence $x = 1.61$ D. The experimentally found deuterium content at C-2 is 1.7 D, and it appears that only very little additional deuterium is present at C-2, suggesting that the amine exchange reaction occurs substantially (90%) as substitution (reaction 5) and only to an extent of 10% as elimination–addition (reactions 3 and 4) in the case of aniline as the arylamine, since the substitution mechanism would contribute no deuterium at C-2, while the elimination–addition would introduce one deuterium into that position.

When the reaction was repeated using deuteriomethylaniline deuteriochloride and Ie in deuterium oxide, the product (IVc) was found to contain 1.36 D at C-2 and 1.30 D at C-4. Using the same calculation as before, the ratio $k_2/k_4 = 1.32$ and the figure 1.30 D at C-4 gives 1.01 D as the calculated amount of deuteration expected at C-2 due to self-enolization.[20b] The value found (1.36 D) thus represents a substantial proportion (up to *ca.* 35%) of the elimination–addition, with a corresponding reduction in the substitution pathway to *ca.* 65%. Since methylaniline reacts more slowly than aniline in the over-all amine-exchange reaction, it might be expected that the product (IVc) from methylaniline would contain more deuterium than the product (IIc) from aniline, due to the greater possibility for deuteration of the molecules of aliphatic Mannich base (Ie) by reactions 3, 6, and 7, *before* they undergo reaction 2. However, the total deuterium content of IVc at C-2 and C-4 was only 2.66 D compared with 3.9 D for IIc at the same positions.

The unexpectedly large amount of deuteration at C-2 and C-4 in the product (IIc) from aniline may be due to the small, but significant, water solubility of this product (IIc), resulting in some deuterium–hydrogen exchange by reaction 6 in both the C-2 and C-4 positions *after* the formation of IIc. This should not occur in the case of the product (IVc) which is substantially insoluble in water. This hypothesis was checked by submitting both IIc and IVc to deuterium oxide under the exact conditions of the amine-exchange reaction, followed by removal of the heavy water *in vacuo* when it was found that there was indeed no detectable deuterium in the recovered 1-(N-methylanilino)-3-butanone (IVc), while the recovered 1-anilino-3-butanone (IIc) showed (apart from complete deuteration of the NH group) incorporation of 0.41 D at C-2 and 0.53 D at C-4. The increased amount of deuterium in IIc is thus explicable.

(20) (a) If the ratio found for the self-deuteration of IIc, $k_2/k_4 = 1.28$ (following), is used for this calculation, then $x = 1.59$ D, *i.e.*, not significantly different from the above. (b) If pseudounimolecular kinetics[19c] are employed as a first approximation in view of the large molar excess of deuterium oxide used, the simplified expression $kt = \log a/a - x$ gives $k_2/k_4 = 1.25$ and 1.24 for Ie and its deuteriochloride, respectively, and thence the values $x = 1.61$ D for IIc and $x = 1.01$ D for IVc, *i.e.*, identical with those obtained by the more exact bimolecular equation. (c) A. I. Shatenshtein, "Isotopic Exchange and the Replacement of Hydrogen in Organic Compounds," Consultants Bureau, New York, N. Y., 1962, p. 23.

It is interesting that the ratio k_2/k_4 for the deuterium incorporation in IIc, calculated as before in the case of Ie, gives $k_2/k_4 = 1.28$ for IIc. The arylamine Mannich bases of type IIa and IVa showed greatly enhanced stability. They have been found to be stable to heat, even distilling unchanged at temperatures up to 200° *in vacuo*, *i.e.*, under conditions in which any incipient fragmentation would readily go to completion as it does in the case of their aliphatic analogs. This increased stability is presumably due to their low basic strength (pK_a *ca.* 4.5) and the resultant decrease in reactions 6 and 7.

When methylaniline was refluxed with the tertiary Mannich base (Ig) in 50% aqueous alcohol under the previous conditions, but in the *absence of acid*, the product (IVa) was obtained in reduced (31%) yield. Since the dimethylamino moiety is a poor leaving group, this would indicate that, under these conditions, elimination–addition predominates. In order to test the speed of the addition reaction itself, phenyl vinyl ketone was treated with either dimethylamine or its hydrochloride and afforded 85% of Ig after 5 min. in each case. The same ketone when treated with methylaniline gave 57% of the product (IVa) in that time, or 66% after 2 hr.

The finding that the yield of IVa (45%) from the over-all exchange reaction of methylaniline hydrochloride and Ig after 2 hr. is not further increased by extending the reaction time to 5 hr. indicates the existence of an equilibrium, as does the fact that equimolar amounts of phenyl vinyl ketone, methylaniline, and dimethylamine hydrochloride gave an identical yield (44%) of IVa after 2 hr.

A possible interpretation of these results would be that the exchange reaction (5) occurs, probably by an SN1 mechanism in the highly polar medium employed, to give IVa and dimethylamine hydrochloride which accumulates. At the same time, reaction 3 also is taking place, forming the vinyl ketone and more dimethylamine salt. Initially some vinyl ketone reacts by addition with the arylamine present, but, as more and more dimethylamine salt is produced, this will compete increasingly with the methylaniline for any vinyl ketone formed, and thus reaction 3b will be promoted at the expense of reaction 4. After 2 hr., this equilibrium appears to be entirely in favor of reaction 3b.

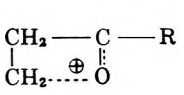
With the equimolar amounts of phenyl vinyl ketone, methylaniline, and dimethylamine hydrochloride, no SN1 reaction can occur until reaction 3b has produced some Ig hydrochloride. Since reaction 3b is faster than reaction 4, only a small amount of addition will take place in that time, after which the SN1 reaction will give the same (44%) yield of IVa.

Using the Mannich base (Ig) and methylaniline only, no proton is present to turn the dimethylamino moiety into a leaving group, and reaction 5 cannot take place. Only reactions 6 and 7 occur, and only the latter produces vinyl ketone and dimethylamine. Since no dimethylamine salt is formed from reaction 5, reaction 4 will be promoted and reaction 3 retarded by the presence of a molar amount of methylaniline, resulting in a higher (31%) yield of IVa by addition compared with that (*ca.* one-third of 44% total yield) obtained previously.

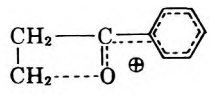
Using aniline as the arylamine, the SN1 reaction ap-

pears to predominate and to be markedly faster than with methylaniline (86% yield as against 45% under the same conditions). The reason may well be steric, since it is known that nucleophilic attack on carbon is usually more subject to steric hindrance than is coordination with a proton,[21] and this steric effect may destroy the usual correlation between the rate of nucleophilic substitution and the basicity of the reagent.

It is possible that the facile SN1 process represented by the over-all reaction 2 is dependent upon, and substantially promoted by, powerful neighboring group assistance from the carbonyl function in I and by the formation of the resonating bridged carbonium–oxonium ion (VII). The presence of R = C_6H_5 would



VII



VIII

further assist in dispersing the positive charge and thereby aid in the formation of the bridged ion (VIII). This type of anchimeric assistance may account for the numerous cases of amine exchange observed to occur in Mannich bases.[22]

Experimental

1-Anilino-3-butanone (IIc). A.—Thirteen grams (0.10 mole) of aniline hydrochloride and 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone were mixed at room temperature. The reaction was exothermic and initially became homogeneous, then large leaflets separated after *ca.* 30 min. The mixture was kept overnight at room temperature, then distributed between ether and water. Distillation of the dried (sodium sulfate) ether layer gave a small forerun of unchanged aniline, then 11.3 g. (70%) of 1-anilino-3-butanone, b.p. 100–102° (0.25 mm.), $n^{17}D$ 1.5640, m.p. 34–36°. The semicarbazone crystallized from ethanol as needles, m.p. 165–166°; lit.[11] b.p. 138–148° (7 mm.), $n^{20}D$ 1.5615, m.p. 35–36° for the ketone and m.p. 166° for the semicarbazone.

B.—A solution of 13.0 g. (0.10 mole) of aniline hydrochloride and 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone in 50 ml. of ethanol and 50 ml. of water was heated under reflux for 1 hr. The solvent was removed *in vacuo;* then the reaction worked up as in A. The product was 13.9 g. (86%) of 1-anilino-3-butanone, identical with that obtained in A.

1-(*p*-Anisidino)-3-butanone.—A mixture of 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone, 12.3 g. (0.10 mole) of *p*-anisidine, 10 ml. of 10 *N* hydrochloric acid, 50 ml. of ethanol, and 50 ml. of water was heated under reflux for 1 hr. The solvent was evaporated *in vacuo;* the residue was distributed between ether and water. Distillation of the dried (sodium sulfate) ether layer gave 16.2 g. (84%) of 1-*p*-anisidino-3-butanone, b.p. 128–130° (0.1 mm.), $n^{16}D$ 1.5603.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.01; H, 7.88.

The semicarbazone crystallized from ethanol as needles, m.p. 151–152°, lit.[12] m.p. 151°.

1-(*p*-Toluidino)-3-butanone.—A mixture of 14.4 g. (0.10 mole) of *p*-toluidine hydrochloride, 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone, 50 ml. of ethanol, and 50 ml. of water was treated as in B. The product was 14.0 g. (80%) of 1-(*p*-toluidino)-3-butanone, b.p. 118–120° (1.0 mm.), m.p. 42–43°. The semicarbazone crystallized from ethanol as needles, m.p. 162–164°; lit.[12] m.p. 41–43° for the ketone and m.p. 163° for the semicarbazone.

1-(*p*-Chloroanilino)-3-butanone.—A mixture of 7.2 g. (0.05 mole) of 1-diethylamino-3-butanone, 8.3 g. (0.05 mole) of *p*-chloroaniline hydrochloride, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. On cooling, the product was filtered and crystallized from methanol, giving 7.8 g. (77%) of 1-(*p*-chloroanilino)-3-butanone, m.p. 74–75°.

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.74; H, 6.12. Found: C, 60.66; H, 5.98.

The semicarbazone crystallized from ethanol as needles, m.p. 173–174°.

Anal. Calcd. for $C_{11}H_{15}ClN_4O$: C, 51.87; H, 5.94. Found: C, 51.60; H, 5.76.

1-(β-Naphthylamino)-3-butanone.—A mixture of 9.0 g. (0.05 mole) of β-naphthylamine, 7.15 g. (0.05 mole) of 1-diethylamino-3-butanone, 5 ml. of 10 *N* hydrochloric acid, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. On cooling, the product was collected by filtration. Crystallization from methanol gave 8.2 g. (76%) of 1-(β-naphthylamino)-3-butanone, m.p. 72–74°.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.82; H, 7.10. Found: C, 78.61; H, 7.15.

1-(4′-Phenylanilino)-3-butanone.—A mixture of 7.2 g. (0.05 mole) of 1-diethylamino-3-butanone, 10.3 g. (0.05 mole) of 4-phenylaniline hydrochloride, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 4 hr. On cooling, the product was filtered and crystallized from methanol. The product was 9.9 g. (82%) of 1-(4′-phenylanilino)-3-butanone, m.p. 87–88°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.02; H, 6.99.

β-Anilinopropiophenone (IIa). Method A.—A mixture of 6.5 g. (0.05 mole) of aniline hydrochloride and 10.3 g. (0.05 mole) of β-diethylaminopropiophenone was kept overnight at room temperature. Initially, an exothermic reaction set in, the mixture became homogeneous, then set to a crystalline mass. Water was added and the product was isolated with chloroform. Evaporation of the dried (sodium sulfate) chloroform extract and crystallization from ethanol gave 8.5 g. (75%) of β-anilinopropiophenone, m.p. 113–114°, lit.[23] m.p. 111–112°.

Method B.—A mixture of 4.7 g. (0.05 mole) of aniline, 10.3 g. (0.05 mole) of β-diethylaminopropiophenone, 25 ml. of ethanol, 25 ml. of water, and 5 ml. of 10 *N* hydrochloric acid was heated under reflux. A solid separated after a few minutes, and after 1 hr. the mixture was cooled and the product was filtered. Crystallization from ethanol gave 10.1 g. (90%) of β-anilinopropiophenone, m.p. and m.m.p. 113–114°.

β-(*p*-Chloroanilino)-α-methylpropiophenone (VI).—A mixture of 8.2 g. (0.05 mole) of *p*-chloroaniline hydrochloride, 11.0 g. (0.05 mole) of β-diethylamino-α-methylpropiophenone, 25 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. The solvent was evaporated *in vacuo*, water was added, and the product was isolated with ether. Distillation gave 4.1 g. (64%) of unchanged *p*-chloroaniline, b.p. 85–90° (0.1 mm.), m.p. and m.m.p. 73–75°. Crystallization of the residue from petroleum ether (b.p. 60–90°) gave 2.6 g. (20%) of β-(*p*-chloroanilino)-α-methylpropiophenone as plates, m.p. 70–71°.

Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89. Found: C, 70.18; H, 5.82.

N,N′-Bis(β-benzoylethyl)-*o*-phenylenediamine.—A mixture of 5.4 g. (0.05 mole) of *o*-phenylenediamine, 12.1 g. (0.05 mole) of β-diethylaminopropiophenone hydrochloride, and 50 ml. of ethanol was heated under reflux for 1 hr. On cooling, the product was filtered, taken up in benzene, and percolated through a short column of neutral alumina. Crystallization from ethanol gave 7.8 g. (42%) of N,N′-bis(β-benzoylethyl)-*o*-phenylenediamine as needles, m.p. 139–140°.

Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.40; H, 6.49. Found: C, 77.55; H, 6.62.

N,N′-Bis(β-benzoylethyl)-*p*-phenylenediamine.—A mixture of 5.4 g. (0.05 mole) of *p*-phenylenediamine, 12.1 g. (0.05 mole) of β-diethylaminopropiophenone hydrochloride, and 50 ml. of ethanol was heated under reflux for 1 hr. under nitrogen. Crystallization (charcoal) of the product from chloroform gave 14 g. (76%) of buff leaflets, m.p. 179–181°.

Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.40; H, 6.49; N, 7.52. Found: C, 76.95; H, 6.41; N, 7.32.

1-(N-Methylanilino)-3-butanone (IVc). A.—A mixture of 10.7 g. (0.10 mole) of N-methylaniline, 15.2 g. (0.10 mole) of 1-dimethylamino-3-butanone hydrochloride, 50 ml. of ethanol, and 50 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo*, water was added, and the product was isolated with ether. Distillation of the dried (sodium sulfate)

(21) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 159.

(22) J. H. Brewster and E. L. Eliel, "Organic Reactions," Coll. Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 138.

(23) J. Kenner and F. S. Statham, *J. Chem. Soc.*, 299 (1935).

ether extract gave unchanged N-methylaniline, then 7.6 g. (43%) of 1-(N-methylanilino)-3-butanone, b.p. 95–96° (1.0 mm.), $n^{25}D$ 1.5495.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.39; H, 8.67.

The semicarbazone crystallized from ethanol as needles, m.p. 169–171°; lit.[12] b.p. 153–161° (14 mm.) for the ketone and m.p. 163° for the semicarbazone.

Anal. Calcd. for $C_{12}H_{18}N_4O$: C, 61.51; H, 7.74. Found: C, 61.31; H, 7.41.

B.—A mixture of 10.7 g. (0.10 mole) of N-methylaniline, 15.2 g. (0.10 mole) of 1-dimethylamino-3-butanone hydrochloride, and 30 ml. of water was heated on the steam bath for 2 hr., and then worked up as in A. The product was 5.1 g. (30%) of 1-(N-methylanilino)-3-butanone, b.p. 95–96° (1.0 mm.), $n^{25}D$ 1.5495.

Deuterated 1-(N-Methylanilino)-3-butanone.—A solution of 4.3 g. (0.03 mole) of N-methylaniline hydrochloride in 6 ml. of deuterium oxide was evaporated to dryness *in vacuo* at 25°. This procedure was repeated six times, after which a constant infrared spectrum was obtained. The deuterated salt was heated on the steam bath for 2 hr. with 3.45 g. (0.03 mole) of 1-dimethylamino-3-butanone and 9 ml. of deuterium oxide; then the cooled reaction mixture was extracted with anhydrous ether. Distillation of the ether extract gave a forerun of deuterated N-methylaniline then deuterated 1-(N-methylanilino)-3-butanone, b.p. 81–82° (0.1 mm.), $n^{24}D$ 1.5475.

Deuterated 1-Anilino-3-butanone.—Treatment of 4.0 g. (0.03 mole) of aniline hydrochloride as above gave deuterated 1-anilino-3-butanone, b.p. 94–95° (2 mm.), $n^{24}D$ 1.5530.

Self-Deuteration of 1-Dimethylamino-3-butanone.—A mixture of 3.45 g. (0.03 mole) of 1-dimethylamino-3-butanone and 9 ml. of deuterium oxide was heated on the steam bath for 2 hr., and then the cooled mixture was extracted with anhydrous ether. Distillation of the ether gave deuterated 1-dimethylamino-3-butanone, b.p. 60–62° (25 mm.), $n^{25}D$ 1.4425.

β-(N-Methylanilino)propiophenone (IVa). **A.**—A mixture of 3.21 g. (0.03 mole) of N-methylaniline, 6.42 g. (0.03 mole) of β-dimethylaminopropiophenone hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo*, the residue was distributed between ether and water, and the dried (sodium sulfate) ether layer was evaporated finally at 100° (1.0 mm.) Crystallization of the residue from ethanol gave 3.2 g. (45%) of β-(N-methylanilino)-propiophenone as needles, m.p. 60–61°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.41; H, 6.86.

B.—An ice-cold solution of 1.5 g. of sodium hydroxide in 50 ml. of water was added to 6.42 g. (0.03 mole) of β-dimethylaminopropiophenone hydrochloride, and the liberated base was extracted with ether. The ether was washed with water, dried (sodium sulfate), and evaporated. The resulting β-dimethylaminopropiophenone was heated under reflux for 2 hr. with 3.21 g. (0.03 mole) of N-methylaniline, 20 ml. of ethanol, and 10 ml. of water; then the solvent was evaporated *in vacuo*. The residue was taken up in 75 ml. of ice-cold 1 *N* hydrochloric acid, the solution was washed with ether, then was brought to pH 7.5 with sodium hydrogen carbonate. The liberated bases were isolated with ether; the ether was dried (sodium sulfate) and evaporated finally at 100° (1.0 mm.). Crystallization of the residue from ethanol gave 2.2 g. (31%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

C.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 3.21 g. (0.03 mole) of N-methylaniline, 2.45 g. (0.03 mole) of dimethylamine hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr. The solvent was evaporated *in vacuo*, water was added, and the product was isolated with ether. Evaporation of the dried (sodium sulfate) ether extracts finally at 100° (1.0 mm.) and crystallization of the residue from ethanol gave 3.1 g. (43%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

D.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 3.21 g. (0.03 mole) of N-methylaniline, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 2 hr., and then the solvent was evaporated *in vacuo*. The residue was taken up in 40 ml. of 1 *N* hydrochloric acid; the solution was washed with ether, then was brought to pH 7.5 with sodium hydrogen carbonate. The liberated bases were extracted with ether and the dried (sodium sulfate) ether extracts were evaporated finally at 100° (1 mm.). Crystallization of the residue from ethanol gave 4.7 g. (66%) of β-(N-methylanilino)-propiophenone, m.p. and m.m.p. 60–61°.

E.—The same reactants were heated for 5 min. then worked up as before. The product was 4.1 g. (57%) of β-(N-methylanilino)propiophenone, m.p. and m.m.p. 60–61°.

β-Dimethylaminopropiophenone (Ig). **A.**—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 1.35 g. (0.03 mole) of dimethylamine, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 5 min.; then the solvent was evaporated *in vacuo*. The residue was taken up in 40 ml. of ice-cold 1 *N* hydrochloric acid; the solution was washed with ether and then was brought to pH 14 with ice-cold 3 *N* sodium hydroxide. The product, isolated with ether, was 4.6 g. (86%) of β-dimethylaminopropiophenone, $n^{25}D$ 1.5240, m.p. 30–32°.

B.—A mixture of 3.96 g. (0.03 mole) of freshly prepared phenyl vinyl ketone, 2.45 g. (0.03 mole) of dimethylamine hydrochloride, 20 ml. of ethanol, and 10 ml. of water was heated under reflux for 5 min.; then the solvent was evaporated *in vacuo*. The residue was distributed between ether and ice–water, and the aqueous layer was made basic with ice-cold 3 *N* sodium hydroxide. Isolation with ether gave 4.4 g. (84%) of β-dimethylaminopropiophenone, identical with that obtained in A.

Isomerism in the Direct Chlorination of 2-Methylpyrazine[1a]

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The product of the direct chlorination of 2-methylpyrazine is shown to be a mixture of 2-chloro-3-methylpyrazine and 2-chloro-6-methylpyrazine.

The direct nuclear chlorination of alkylpyrazines recently reported[2,3] has greatly expedited the study of the pyrazine ring system. The alkylchloropyrazines obtained by this method are also available, though less conveniently, by the chlorination of the corresponding alkylhydroxypyrazines with a phosphorus halide. The alkylhydroxypyrazines are obtained *via* the condensation of amino acid amides with α-dicarbonyl compounds.[4] The commercial availability of the three alkylchloropyrazines Ia–c[5] prompted us to prepare a number of dialkylamino derivatives and related compounds for exploratory pharmacological screening.

When commercial Ia was treated with excess piperidine either alone or in the presence of aqueous base the product was shown by gas–liquid chromatography

(1) (a) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963; (b) Chemistry Department, Manchester College, North Manchester, Ind.

(2) H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

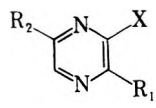
(3) A. Hirschberg and P. E. Spoerri, *ibid.*, **26**, 2356 (1961); see also R. A. Pages and P. E. Spoerri, *ibid.*, **28**, 1702 (1963).

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1580 (1952).

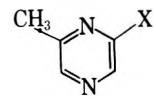
(5) These compounds were generously supplied by the Wyandotte Chemicals Corp., the method of preparation being as described in ref. 1.

(g.l.c.) to be a mixture of two components in a ratio of about 70:30. With hydrogen chloride, a mixture of bright yellow salts was obtained which could be separated by fractional crystallization. The less soluble, higher melting compound was present in smaller amount. Both had the same per cent composition. The compounds could be separated for analytical purposes by paper ionophoresis, the higher melting compound having the greater mobility. This isomer was also slightly more basic. Its pK_a in water was found to be 3.51 compared to 3.10 for the lower melting isomer. It was assumed that if one of the two compounds had the expected structure Ie then the other must be IIc or IIIc. Expansion or contraction of the pyrazine ring was ruled out on the basis of the similar spectral and chemical properties of the two compounds. Compound IVb was not considered a likely possibility but was nevertheless prepared by treating 2-chloromethylpyrazine[3] (IVa) with piperidine. IVb formed *colorless* salts and could, therefore, be eliminated.

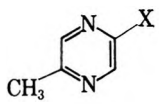
In order to prepare authentic IIc and/or IIIc the corresponding chloro compounds were desired. Both IIa and IIIa have been prepared by chlorination of the corresponding pyrazinols IIb and IIIb, which were in



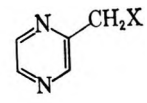
Ia, R_1 = CH_3; R_2 = H; X = Cl
b, R_1 = CH_3; R_2 = CH_3; X = Cl
c, R_1 = C_2H_5; R_2 = C_2H_5; X = Cl
d, R_1 = CH_3; R_2 = H; X = OH
e, R_1 = CH_3; R_2 = H; X = 1-piperidyl
f, R_1 = CH_3; R_2 = H; X = $N(CH_3)_2$



IIIa, X = Cl
b, X = OH
c, X = 1-piperidyl
d, X = $N(CH_3)_2$



IIa, X = Cl
b, X = OH
c, X = 1-piperidyl



IVa, X = Cl
b, X = 1-piperidyl

turn prepared by the condensation of pyruvaldehyde and glycinamide. Karmas and Spoerri[4] report that this reaction gives a separable mixture of 2,5- and 2,6-methylpyrazinols whereas Jones[6] appears to have obtained only the former. In this laboratory, when pyruvaldehyde was used as the bisulfite addition compound[7] the 2,6 isomer (IIIb) was the only compound which could be isolated. The IIIb obtained was easily purified and converted to the chloro compound (IIIa). All of the strong infrared bands of IIIa were found to be present in the spectrum of commercial Ia. With piperidine, IIIa gave a base which afforded a yellow hydrochloride. This salt was found to be identical in all respects with the less abundant higher melting hydrochloride. The identity of the by-product was thus established as the 2,6 isomer (IIIc).

A sample of pure 2-chloro-3-methylpyrazine (Ia) was then prepared from the commercial material by a three-step sequence.[8] Ammonolysis[3] gave a mixture of aminomethylpyrazines. Since the 2,3 isomer is less soluble and higher melting, purification by recrystallization was relatively easy. Treatment of the pure amino compound with nitrous acid then gave pure 2-hydroxy-3-methylpyrazine (Id) which was converted by phosphorus oxychloride to Ia. The infrared spectrum of this material was identical with the spectrum of a sample[9] of pure Ia prepared by the procedure of Karmas and Spoerri. *The only difference between the spectra of pure Ia and commercial Ia was that, in the former, the bands characteristic of IIIa were absent.*[10] Very small amounts of the 2,5 isomer (IIa) would, of course, not be detected by infrared spectroscopy. Hirschberg and Spoerri[3] conclude from ammonolysis studies of their chlorinated methylpyrazine that at least 5% of IIa is present. In addition to 60% of 2-amino-3-methylpyrazine melting at 166–167°, they were able to isolate about 5% of a solid melting at 111–112° which they assumed to be 2-amino-5-methylpyrazine. Since the literature[4,11] records a melting point of 116–118° for the 2,5 isomer and 124–125° and 127–128° for the 2,6 isomer, it is possible that Hirschberg and Spoerri isolated an impure form of the latter compound. Our results would support this conclusion, particularly in view of the similarity in reaction conditions employed by the two groups[2,3] for the chlorination of methylpyrazine.

The reaction of commercial Ia with other primary and secondary amines also gave mixtures which were separable by a combination of fractional distillation of the bases and fractional crystallization of the salts. Since the content of 2,6 isomer generally ranged up to 25–30% it follows that caution must be used in assigning structures to compounds derived from commercial Ia in less than 25–30% yield. Similarly, compounds obtained in yields above 70–75% are likely to contain the 2,6 isomer as an impurity. The techniques which have been found useful for differentiating between the 2,3 and 2,6 isomers in a large number of compounds prepared in our laboratories include the following.

A. Comparison with material obtained from a chloropyrazine of known structure and purity.

B. Yield of *pure* compound if in the range 40–70%.

C. In four cases examined, the crude bases were readily separated by g.l.c. The larger peak was assigned the 2,3 structure. The bases could then be individually purified and the relative retention times correlated with those obtained for the crude mixture. This method appears to be useful even when conversions are as low as 50–60% (see ref. 8).

(6) R. G. Jones, U. S. Patent 2,520,088 (August 22, 1950); *Chem. Abstr.*, **44**, 10,740 (1950).

(7) F. Muehlmann and A. R. Day, *J. Am. Chem. Soc.*, **78**, 242 (1956).

(8) Several attempts to purify 2-chloro-3-methylpyrazine by taking advantage of the slightly greater reactivity of the 2,6 isomer toward amines were unsuccessful. Infrared analysis of methylchloropyrazine recovered from reactions in which the commercial material was subjected to partial reaction with various amines showed that the purification achieved was not sufficient to be useful. Somewhat better results were obtained by partial quaternization with dimethyl sulfate but again a pure product could not be obtained.

(9) This material was generously supplied by Dr. Bernard Klein, Veterans Administration Hospital, Bronx, N. Y.

(10) E. A. Wipert (personal communication from Wyandotte Chemicals Corp.) reports that some 2-chloro-6-methylpyrazine can be separated from commercial Ia when its hexane solution is cooled to −20° and that it constitutes about 25% of the total. Separation of the isomers by g.l.c. is extremely difficult. After an intensive search for adequate columns and conditions, a partial but still very incomplete resolution of isomers was achieved.

(11) J. Weijlard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945).

TABLE I

Substituent	Salt[a]	M.p., °C.	Recrystn. solvent	Reaction time, hr. (temp., °C.)[b]	Yield, %	Formula	Anal.	C	H	N	Ultraviolet spectra[c] λ_{max}, mμ (log ε)
3-Substituted 2-methylpyrazines											
$NH(CH_3)$	C	53–55	Ether	18 (130)		$C_6H_9N_3$	Calcd.	58.51	7.37	34.12	239 (4.06)
							Found	58.24	7.52	34.32	321 (3.75)
	A	238–240[f]	Ethanol								
						$C_6H_9N_3 \cdot HCl$					239 (4.06)
											321 (3.75)
$N(CH_3)_2$[d]	A	142–144	Ethanol–ether	210 (18)	20	$C_7H_{11}N_3 \cdot HCl$	Calcd.	48.42	6.97	24.20	
							Found	48.52	7.24	23.98	
1-Piperidyl	A	112–114	2-Propanol–ethyl acetate	96 (reflux)	31	$C_{10}H_{16}N_3 \cdot HCl$	Calcd.	56.20	7.55	19.66	239 (3.74)
							Found	56.43	7.40	19.78	257 (3.79)
											317 (3.62)
	B	131–133	2-Propanol–ethyl acetate			$C_{10}H_{16}N_3 \cdot H_2SO_4$	Calcd.	43.62	6.23	15.26	
							Found	43.56	6.50	15.10	
1-Pyrrolidinyl	A	197–200	Dichloromethane–ethyl acetate	241 (reflux)	23	$C_9H_{13}N_3 \cdot HCl$	Calcd.	54.13	7.07	21.04	255 (4.02)
							Found	54.34	7.33	20.89	336 (3.68)
Morpholino	A	168–172	Acetonitrile	26 (reflux, 25% KOH)	7	$C_9H_{13}N_3O \cdot HCl$	Calcd.	50.11	6.54	19.48	235 (3.75)
							Found	50.25	6.34	19.72	248 (3.77)
											314 (3.64)
1-Piperazinyl	D	160–163	Ethyl acetate–acetonitrile	120 reflux, ethanol)		$C_9H_{14}N \cdot C_7H_8O_3S$	Calcd.	54.83	6.33	15.99	244 (3.78)
							Found	55.01	6.50	15.70	312 (3.70)
6-Substituted 2-methylpyrazines											
$NHCH_3$	C	63–66	[g]	336 (20)		$C_6H_9N_3$	Calcd.	58.51	7.37	34.12	242 (4.38)
							Found	58.33	7.13	34.24	330 (3.76)
$N(CH_3)_2$	A	222–225	Methanol–ether	200 (20)[e]	13	$C_7H_{11}N_3 \cdot HCl$	Calcd.	48.42	6.97	24.20	247 (4.04)
							Found	48.20	7.02	24.25	339 (3.68)
1-Piperidyl	A	171–172	Benzene	24 (reflux)	10	$C_{10}H_{16}N_3 \cdot HCl$	Calcd.	56.20	7.55	16.59	227 (3.73)
							Found	56.25	7.71	16.57	256 (4.18)
											350 (3.76)
1-Pyrrolidinyl	A	112–113	Dichloromethane–ethyl acetate–ether	18 (reflux)	3	$C_9H_{13}N_3 \cdot HCl$	Calcd.	54.13	7.06	21.05	251 (4.15)
							Found	54.28	7.24	20.89	350 (3.80)
Morpholino	A	172–174	Ethyl acetate	26 (reflux, 25% KOH)	<1	$C_9H_{13}N_3O \cdot HCl$	Calcd.	50.11	6.54	19.48	250 (4.04)
							Found	50.34	6.79	19.29	333 (3.70)
1-Piperazinyl	D	198–199	Ethyl acetate	120 (reflux, ethanol)		$C_9H_{14}N_4 \cdot C_7H_8O_3S$	Calcd.	54.83	6.33	15.99	246 (4.10)
							Found	54.96	6.62	16.00	327 (3.77)

[a] A, hydrochloride; B, sulfate; C, free base; D, *p*-toluenesulfonate. [b] Some reactions were carried out in the presence of aqueous base or inert solvent as indicated. [c] Prepared by dissolving the base or hydrochloride in water (see ref. 12). [d] The compound described in the literature[2] as having this structure is probably the 2,6 isomer (see text). [e] The amine was used as a 25% aqueous solution. [f] Lit.[2] m.p. 236–240°. [g] Purified for analysis by sublimation at 63° (0.04 mm.).

D. When the bases can be separated by paper ionophoresis, the 2,6 isomer has the greater mobility, fluoresces more brightly, and forms a darker iodoplatinate.

E. The hydrochlorides of 2-dialkylamino-3-methylpyrazines show little or no absorption in the 1600–1900-cm.$^{-1}$ region, but occasionally show a *very weak band* at 1620 cm.$^{-1}$. The 2,6 isomers show a medium to strong band at 1620 cm.$^{-1}$ (all Nujol mulls).

F. Both series of dialkylaminomethylpyrazines have a band at 355–375 mμ in 1 *M* hydrochloric acid which is responsible for the yellow color of the salts. In neutral solution, the band shifts to 317–337 mμ for the 2,3 isomers and to 333–350 mμ for the 2,6 isomers. For a given isomeric pair, the 2,6 isomer absorbs at a longer wave length than the 2,3 isomer with respect to this band.[12]

Gainer, *et al.*,[2] described the preparation in 7% yield of 2-dimethylamino-3-methylpyrazine hydrochloride which melted at 224–230°. A repetition of this experiment in our laboratory afforded a mixture of products which was partially separated by fractional distillation.[13] The hydrochlorides of the higher and lower boiling fractions were then prepared and purified to constant melting point. Thus, from one run there was obtained a salt melting at 222–225° and about three times as much of another salt melting at 142–143°. These compounds were assigned the 2,6 and 2,3 structures, respectively, on the basis of D, E, and F. The higher melting product, therefore, has the 2,6 orientation rather than the 2,3 orientation as stated in the literature It is probable that a number of compounds described as being 2-substituted 3-methylpyrazines contain appreciable quantities of 2,6 isomers[14] (see Table I).

Experimental[15]

Aminolysis of Chloropyrazines.—In the preferred method, a mixture of the chloropyrazine and two or more equivalents of amine was heated in a suitable vessel under conditions commensurate with the reactivity of the components. In earlier experiments water or aqueous alkali was sometimes added, but it is doubtful if the reaction was aided thereby.

When commercial 2-chloro-3-methylpyrazine was the starting material the isomeric products were separated by fractional recrystallization of a suitable salt (or the free base if crystalline) aided in some cases by prior fractional distillation of the crude mixed bases. Partial separations are possible by the latter method since at water pump pressure (*ca.* 15 mm.) the 2,6 iso-

(12) The spectra obtained for neutral solutions were obtained by dissolving the hydrochlorides in water and making the necessary dilution. The salts are so extensively dissociated that the addition of sodium hydroxide had a negligible effect on the spectrum.

(13) In all cases so far examined the boiling point of the 2,6 isomer is slightly higher than that of the 2,3 isomer.

(14) J. Behun, P. Kan, P. Gibson, C. Lenk, and E. Fujiwara, *J. Org. Chem.*, **26**, 4981 (1961).

(15) Infrared spectra were run on a Baird 455 spectrograph, ultraviolet spectra were run on a Beckman DK-1, and gas–liquid chromatography was performed on a Perkin-Elmer 254 and a Research Specialties 600. Melting points were taken in capillaries using Anschutz thermometers in a Hershberg apparatus. Ionophoreses were run in 5 *M* acetic acid on Whatman No. 1 paper at *ca.* 30 v./cm.

mers usually boil about 5–10° higher than the 2,3 isomers. The difficulty of separating the isomers is reflected in the low yields reported in some cases.

2-Piperidino-3-methylpyrazine Hydrochloride and 2-Piperidino-6-methylpyrazine Hydrochloride.—A mixture of 10 g. (0.078 mole) of commercial 2-chloro-3-methylpyrazine, 15.4 ml. (0.16 mole) of piperidine, and 15 ml. of water was maintained at reflux for 4 days. The reaction mixture was made strongly basic and extracted with ether. The ether layer was separated, dried over potassium carbonate, and evaporated on a rotating evaporator at *ca.* 1 mm. Two 5-ml. portions of toluene were successively added and evaporated leaving 12.5 g. (90%) of the mixed bases. A solution of the mixed bases in 100 ml. of ethyl acetate was then treated with *ca.* 0.07 mole of hydrogen chloride in 90 ml. of ether in five roughly equal portions, the precipitated solids being removed by filtration after each addition. The first fraction, 3.7 g. (22.5%) of a yellow solid melting at 164–166°, was mostly the 2,6 isomer. The other fractions all melted in the range 98–112° and were combined to give a total of 9.2 g. (56%) of crude 2,3 isomer. Recrystallization from dichloromethane–ether afforded 5.0 g. (31%) of yellow crystals, m.p. 112–114°.

The first (high melting) fraction was recrystallized from acetonitrile–benzene to give 1.6 g. (10%) of yellow crystals, m.p. 169–171°. An additional recrystallization from benzene raised the melting point to 170–172°.

2-Methylamino-3-methylpyrazine.—A mixture of 64.3 g. (0.5 mole) of commercial 2-chloro-3-methylpyrazine and 60 ml. of liquid dimethylamine was heated for 18 hr. at 130° in a steel bomb. Excess dimethylamine was vented from the bomb and the residue dissolved in 100 ml. of water. Potassium carbonate (52 g.) was then added and the solution extracted with 800 ml. of ether. The extract was dried over potassium carbonate and concentrated on a steam bath. Distillation at 0.25 mm. gave only a single fraction boiling at 65° which weighed 41.1 g. (67%) and which partly crystallized. The solid was separated by filtration and washed with ether. This was compared with the total distillate by means of g.l.c. on Apiezon L at 137°. The distillate exhibited two fairly well-resolved peaks with retention times of 9.0 and 11.5 min. with areas under the curves corresponding to approximately 84% and 16%, respectively, of the weight of the material. Since the solid had a retention time of 9.3 min. under the same conditions, it is concluded that it is the 2,3 isomer. Conversion to the hydrochloride gave a white solid melting at 238–240° in close agreement with that reported by Gainer, *et al.*[2]

2-Hydroxy-3-methylpyrazine and 2-Chloro-3-methylpyrazine.—To a magnetically stirred solution of 2.0 g. (0.0183 mole) of 2-amino-3-methylpyrazine[3] in a mixture of 6.3 ml. of sulfuric acid and 17 ml. of acetic acid cooled to 0°, was added 2.3 g. (33.5 mmoles) of sodium nitrite in small portions during 10 min. The mixture was then stirred at 0° for an additional 1.5 hr. and permitted to warm to room temperature during 18 hr. with continuous stirring. The mixture was diluted with water, made basic with 10 *M* potassium hydroxide, and adjusted to pH 6 with hydrochloric acid. The solvent was then removed by evaporation at reduced pressure on a rotary evaporator and the residue purified by sublimation at 0.05 mm. (130°). The product, 1.8 g., melted at 139–148°. Recrystallization from ethyl acetate gave 1.35 g. (64%) of pale yellow crystals, m.p. 149–152°. The literature[4,16] records m.p. 151–152° and 150–152°.

(16) M. E. Hultquist, U. S. Patent 2,805,223; *Chem. Abstr.*, **52**, 2931 (1958).

Conversion to 2-chloro-3-methylpyrazine was carried out by the Karmas–Spoerri procedure.[4] Although the ultraviolet spectra of the 2,3 and 2,6 isomers were almost identical, the infrared spectra were quite different. The principal differences are listed, all bands being medium to very strong in intensity: 2,6 isomer ($cm.^{-1}$), 1260, 1178, 1015, 895, 740 (carbon disulfide solution); 2,3 isomer ($cm.^{-1}$), 1210, 1195, 1090, 1070, 855 (neat).

2-Hydroxy-6-methylpyrazine.—To 24 g. (0.1 mole) of commercial 30% aqueous pyruvaldehyde was added 19 g. (0.1 mole) of sodium metabisulfite (equivalent to 0.2 mole of sodium bisulfite) and the mixture stirred for 1 hr. at room temperature. The addition compound was precipitated as a gummy solid on addition of 60 ml. of methanol and 20 ml. of ethanol.

This solid was dissolved in 10 ml. of water and 5.5 g. (0.05 mole) of glycineamide hydrochloride was added. The pH was then adjusted to 8 with 10 *M* potassium hydroxide and the mixture maintained at 60–80° for 2 hr. The pH was adjusted to 10 and kept at 50–60° (spontaneous heating) for 30 min. The mixture was cooled and adjusted to pH 6 with concentrated hydrochloric acid, cooled to 0°, and filtered to give 3.2 g. (58%) of solid, m.p. 247° dec. Recrystallization from 35 ml. of water afforded 1.1 g. (20%) of light tan platelets, m.p. 246–248°, lit.[4] m.p. 250–251°.

2-Chloro-6-methylpyrazine.—A mixture of 1.1 g. of 2-hydroxy-6-methylpyrazine, 4 ml. of phosphorus oxychloride and a small drop of dimethylformamide was maintained at reflux for 40 min. The brown mixture was cooled, poured into 100 ml. of ice and water, and shaken vigorously. The mixture was then extracted twice with 25-ml. portions of ether and the extract washed with water and saturated sodium sulfate solution. After drying over calcium chloride the ether was removed by distillation through a short column packed with glass helices. Removal of the last traces of solvent at 15 mm. left 1.0 g. (78%) of a colorless crystalline residue, m.p. 49–51°, lit.[4] m.p. 50–51°.

2-Piperidino-6-methylpyrazine from Pure 2-Chloro-6-methylpyrazine.—A solution of 1.0 g. of the above chloro compound and 5 ml. of piperidine was maintained at reflux for 30 min. The cooled mixture was diluted with 10 ml. of ether, the precipitated piperidine hydrochloride removed by filtration, and the filtrate concentrated to a brown oil. Two small portions of toluene were added and evaporated. The residual oil was taken up in 10 ml. of ethyl acetate and the solution was treated with excess hydrogen chloride to give 0.57 g. (41%) of yellow solid, m.p. 168–169°. The melting point was raised to 169–172° by sublimation at 90° (0.05 mm.). On admixture of this material with the high melting by-product from the piperidinolysis of commercial 2-chloro-3-methylpyrazine, the melting point was 169–172°. The infrared spectra and ionophoretic mobilities of the substances were identical.

Acknowledgment.—We wish to acknowledge the services of the Analytical and Physical Chemistry Section, under the supervision of Mr. Arnold D. Lewis for physical–analytical data. In particular we want to thank Mr. Thomas Wildeman, Mrs. Unni Zeek, and Miss Awilda Calenti for microanalyses; Mrs. Barbara Kane, Mr. Robert Puchalski, and Mr. Joseph Brooks for infrared and ultraviolet spectra and interpretations; and Miss Marianne Garofalo for gas–liquid chromatograms. The technical assistance of Mr. Jerry Cetenko and Mr. George Conrad is also gratefully acknowledged.

Methanesulfenyl Chloride. IV. The Reaction of Sulfenyl Chlorides with Alkyl Xanthates and Trimethyl Thionophosphate[1]

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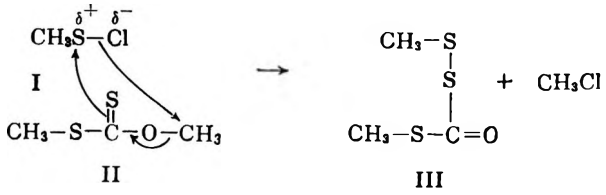
Methanesulfenyl chloride (I) reacts with O,S-dimethyl xanthate (II) by a mechanism which is apparently an electrophilic attack at the thiocarbonyl sulfur atom to form 2,3,5-trithiahexanone-4 (III) and methyl chloride. I also reacts with S-methyl O-*n*-propyl xanthate to form III and *n*-propyl chloride. Benzenesulfenyl chloride and trichloromethanesulfenyl chloride react with II to form methyl chloride and, respectively, 1-phenyl-1,2,4-trithiapentanone-3 and 1,1,1-trichloro-2,3,5-trithiahexanone-4. I reacts with trimethyl thionophosphate to liberate methyl chloride and to form S-methylsulfenyl O,O-dimethyl thiolphosphate.

The ability of methanesulfenyl chloride (I) to react with various types of organic molecules in a manner suggesting electrophilic attack has been reported in previous publications.[3] In considering other types of molecules to use as substrates for reaction with I, O,S-dimethyl xanthate (II), $CH_3OC(=S)SCH_3$, seemed of interest since it has three different sites at which electrophilic attack might occur—the alkoxy oxygen, the thiono sulfur, and the thiol sulfur.

Reaction between I and II took place readily with the liberation of methyl chloride and the formation of a yellow oil. Purification of the latter gave a colorless product, the analysis of which corresponded to 2,3,5-trithiahexanone-4 (III), $CH_3SSC(=O)SCH_3$, suggesting that attack had occurred at the thiono sulfur atom, according to the following equation.



The reaction between I and S-methyl O-*n*-propyl xanthate also took place readily with the formation of III and 1-chloropropane. There seems little doubt concerning the structure of III since it shows a strong infrared absorption in the carbonyl region whereas the spectra of both II and S-methyl O-*n*-propyl xanthate showed none. In addition, both xanthate esters show strong absorption in the 1220-cm.$^{-1}$ region indicative, according to Bellamy,[4] of a thiocarbonyl in dimethyl thiocarbonate and dithioacetic acid. This thiocarbonyl absorption band is missing in III and in the trithia ketones formed when trichloromethanesulfenyl and benzenesulfenyl chlorides react with II.

Special mention should be made of the absence of a carbonyl absorption band in the xanthate esters studied, for II was found to isomerize readily into S,S-dimethyl dithiolcarbonate in the presence of methyl sulfate. Preparations of II made with the latter reagent showed carbonyl adsorption. The conversion of xanthate esters to dithiolcarbonates had been reported previously,[5] but no reference has been found to the problem the isomerization causes in preparing pure xanthate esters.

Benzenesulfenyl chloride and trichloromethanesulfenyl chloride react with II in an analogous manner forming methyl chloride and, respectively, 1-phenyl-1,2,4-trithiapentanone-3, $C_6H_5SSC(=O)SCH_3$, and 1,1,1-trichloro-2,3,5-trithiahexanone-4, $Cl_3CSSC(=O)SCH_3$. The latter compound is isomeric with the product prepared by the reaction of trichloromethanesulfenyl chloride with an alkali salt of methyl xanthate.[6,7]

One extension of the reaction to other types of thiono esters was carried out. Trimethyl thionophosphate reacted readily with I to yield methyl chloride and a product the analysis of which corresponded to O,O-dimethyl S-methylsulfenyl thiolphosphate, $CH_3SSP(=O)(OCH_3)_2$.

The reaction of sulfenyl chlorides with compounds containing thiocarbonyl groups to form disulfido products is not entirely new. Margot and Gysin[8] treated benzenesulfonylthioureas with trichloromethanesulfenyl chloride (V) and obtained compounds of the type $RSO_2NHC(SSCCl_3)NR'$. In an analogous reaction, Harris[9] found that alkyl thionocarbamate esters react with sulfenyl chlorides to split out alkyl chlorides and form alkyl or aryl carbamoyl disulfides of the type $RNHC(=O)SSR'$. When the reaction was carried out in the presence of a tertiary amine, like pyridine, the product was a dithioformamidic ester, $RN{=}C(OR')SSR$.''

Experimental

Preparation of Xanthate Esters.—O,S-Dimethyl xanthate (II) was prepared by treating a methanol solution of potassium methyl xanthate with methyl iodide below 40°. After standing overnight the reaction mixture was diluted with water and the crude xanthate ester was separated, dried, and distilled. The purified

(1) Taken from the Master's thesis of William J. Evers, 1962.

(2) National Defense Education Act, Title IV Fellow, 1960–1962.

(3) I. B. Douglass and D. A. Koop, *J. Org. Chem.*, **27**, 1398 (1962), and prior publications.

(4) L. J. Bellamy in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, London, 1961, p. 52.

(5) E. Billmann and J. Bjerrum, *Ber.*, **50**, 503 (1917).

(6) R. S. Hawley and A. R. Kittleson, U. S. Patent 2,553,777 (May 22, 1951); *Chem. Abstr.*, **45**, 7742i (1951).

(7) V. Ettel and M. Zbirovsky, *Chem. Listy*, **50**, 670 (1956); *Chem. Abstr.*, **50**, 8513*f* (1956).

(8) A. Margot and H. Gysin, U. S. Patent 2,813,902 (November 19, 1957); *Chem. Abstr.*, **52**, 7349*f* (1958).

(9) J. F. Harris, Jr., *J. Am. Chem. Soc.*, **82**, 155 (1960).

product boiled at 66–68° (21 mm.) and had $n^{25}D$ 1.5655 and d^{0}_{4} 1.2045, d^{24}_{4} 1.1804. The compound showed no infrared absorption in the carbonyl region but absorbed strongly at 1070, 1090, 1160, 1220, and 1435 cm.$^{-1}$, and more weakly at 975 cm.$^{-1}$. Earlier attempts to prepare the compound from equivalent amounts of methyl sulfate and potassium methyl xanthate led to a product contaminated with unchanged methyl sulfate from which it could not be separated by distillation. The methyl sulfate also catalyzed the conversion of the xanthate to the isomeric S,S-dimethyl dithiolcarbonate. Such preparations always showed infrared absorption in the carbonyl region and slowly formed glistening crystals on standing.

A preparation of II containing residual methyl sulfate was refluxed for 28 hr. at atmospheric pressure and was completely converted to S,S-dimethyl dithiolcarbonate boiling at 169° (760 mm.) or 75–76° (29 mm.) and having $n^{24}D$ 1.5461 and d^{0}_{4} 1.2128, d^{24}_{4} 1.1878 [lit.[10] b.p. 169° (760 mm.), $n^{17.5}D$ 1.5504, and $d^{17.5}_{4}$ 1.1913]. Its infrared spectrum showed strong absorption at 870, 970, and 1640 cm.$^{-1}$ and moderately strong absorption at 1045, 1310, 1420, 1740, and 2900 cm.$^{-1}$. The spectrum was identical with that of a specimen prepared by the reaction of methyl chlorothiolformate with methyl mercaptan.

S-Methyl O-*n*-propyl xanthate was prepared by the action of methyl iodide on a solution of potassium *n*-propyl xanthate. The product boiled at 92–94° (15 mm.) and had $n^{20}D$ 1.5375 [lit.[11] b.p. 201–203° (760 mm.), $n^{20}D$ 1.53789]. Its infrared spectrum showed strong absorption peaks at 1065 and 1220 cm.$^{-1}$ and weak absorption at 925, 970, 1110, 1145, 1320, 1345, 1380, 1420, 1465, and 2950 cm.$^{-1}$, but no absorption in the region 1500–2000 cm.$^{-1}$.

Methanesulfenyl chloride was prepared by the method previously described.[12]

Benzenesulfenyl chloride was prepared by the method of Morrison.[13] The trichloromethanesulfenyl chloride was a sample of "perchloromethyl mercaptan," obtained from the Stauffer Chemical Company, and was used as received.

Reaction of Sulfenyl Chlorides with Xanthate Esters.—A pure sample of O,S-dimethyl xanthate (II, 48.4 g., 0.4 mole), contained in a three-necked reaction flask equipped for stirring and fitted with reflux condenser and outlet leading to a Dry Ice trap, was treated slowly with I (34.2 g., 0.4 mole) at −40° to −50°. When addition was complete, the mixture was allowed to warm to room temperature and was then heated to 80° to drive off volatile matter. The residue consisted of 41 g. of yellow liquid. From the cold trap 19 g. of colorless liquid was recovered which, after bubbling through sodium hydroxide solution and recondensing, gave an infrared spectrum identical with that of methyl chloride. The recovered yield was 95%.

A thin layer chromatograph of the yellow residue in the reaction flask indicated three substances were present. Two, which moved more rapidly on the plate, were present only in minor proportions and remain unidentified. The principal product was isolated by column chromatography on silicic acid using *n*-hexane as eluent. Chromatography of a 6.0-g. portion of the yellow liquid residue gave 4.2 g. (46% over-all yield) of 2,3,5-trithia-

hexanone-4, $CH_3SSCSCH_3$, having $n^{28}D$ 1.5934.

Anal. Calcd. for $C_3H_6OS_3$: C, 23.36; H, 3.92; S, 62.36. Found: C, 23.62; H, 3.95; S, 62.46.

The infrared spectrum showed strong absorption of 840, 885, 1640, and 1705 cm.$^{-1}$ and moderate absorption at 960, 1310, and 1415 cm.$^{-1}$.

In similar manner the reaction between I and S-methyl O-*n*-propyl xanthate yielded *n*-propyl chloride (identified by its boiling point, refractive index, and infrared spectrum, which was identical with Sadtler Standard Spectrogram 193) and 30 g. of a yellow, liquid residue. Chromatography of a 3.5-g. portion of the latter gave 1.6 g. of colorless product having $n^{24}D$ 1.5914 and an infrared spectrum identical with that of the 2,3,5-trithiahexanone-4 previously obtained.

Benzenesulfenyl chloride (14.5 g., 0.1 mole) was added dropwise with stirring to 12.2 g. (0.1 mole) of O,S-dimethyl xanthate at −20°. Further treatment, as previously described, led to the recovery and identification of methyl chloride in 57% yield and 21.6 g. of a liquid residue. Chromatography of a 4.0-g. portion of the latter gave 3.06 g. of colorless product, which after rechromatographing had $n^{25}D$ 1.6478, d^{0}_{4} 1.315, and d^{25}_{4} 1.294, and showed strong absorption peaks at 685, 745, 835, 885, 1640, and 1705 cm.$^{-1}$ and weaker absorption peaks at 975, 1025, 1315, 1440, and 1480 cm.$^{-1}$. The over-all yield was 76%.

Anal. Calcd. for $C_3H_5OS_3$: C, 44.41; H, 3.72; S, 44.47. Found: C, 44.73; H, 4.24; S, 44.53.

Trichloromethanesulfenyl chloride (18.6 g., 0.1 mole) reacted with II (12.2 g., 0.1 mole) at 30° over a 30-min. period to yield methyl chloride (3.4 g., 67%), isolated and identified as described above, and 25.8 g. of liquid residue. Chromatography of 4.0 g. of residue yielded 3.5 g. of material which thin layer chromatography indicated to be a single component. The recovered pure product corresponded to an 87% over-all yield. Rechromatographing gave an analytical sample having $n^{25}D$ 1.6118, d^{0}_{4} 1.563 and d^{25}_{4} 1.532, and showing strong infrared absorption at 750, 770, 790, 830, 880, 1650, and 1720 cm.$^{-1}$ and much weaker bands at 970, 1315, and 2350 cm.$^{-1}$. The analysis corresponds to 1,1,1-trichloro-2,3,5-trithiahexanone-4.

Anal. Calcd. for $C_3H_3Cl_3S_3O$: C, 13.98; H, 1.17; S, 37.34; Cl, 41.29. Found: C, 14.30; H, 1.43; S, 37.50; Cl, 41.20.

The Reaction of I with Trimethyl Thionophosphate.—Trimethyl thionophosphate (31.2 g., 0.2 mole), prepared by the reaction of trimethyl phosphite with sulfur after the method of Pistschimuka,[14] was treated with I (17.1 g., 0.2 mole) in the usual manner at −20°. Methyl chloride in 53% yield was isolated and identified as described, and the residue was chromatographed on silicic acid, using 2:1 petroleum ether–benzene as eluent. When the fast-moving yellow band had been removed from the column the main product was purified, using as eluent a mixture of 8% ether in benzene. Rechromatographing gave an analytical sample having $n^{30}D$ 1.5103 and corresponding on analysis to S-methylsulfenyl O,O-dimethyl thiolphosphate.

Anal. Calcd. for $C_3H_9O_3PS_2$: C, 19.15; H, 4.82; S, 34.07; P, 16.46. Found: C, 19.32; H, 4.75; S, 34.08; P, 16.52.

Acknowledgment.—The authors gratefully acknowledge a grant from the Petroleum Research Fund, administered by the American Chemical Society, which partially supported this research.

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Reaction of Cycloalkylmethyl Chlorides with Sodium. Fused Cyclopropanes from Cycloalkylcarbenes

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Reactions of sodium with cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, and cyclopropylmethyl chlorides have been studied. Bicyclic hydrocarbons containing fused cyclopropane rings, presumably formed through intramolecular insertions of cycloalkylcarbenes into C–H bonds, were found in the products of all reactions except those with cyclopropylmethyl chloride. Cyclopentene and cyclobutene, also observed as products, must have formed by rearrangements of cyclobutylcarbene and cyclopropylcarbene, respectively.

To study the reactions of cycloalkylcarbenes, we have investigated the products obtained from treating cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, and cyclopropylmethyl chlorides with sodium in hydrocarbon solutions. In the reaction of an alkyl chloride with sodium, a portion of the chloride is converted to an alkylsodium which then reacts rapidly with additional chloride to produce a carbene (α-elimination), olefin (β-elimination), or coupling product (Wurtz reaction).[1] A number of subsequent reactions are known for carbenes. Rearrangement to olefin (by carbon or hydrogen migration) or cyclopropane (by intramolecular C—H insertion) will produce monomeric products. Reaction with more metal alkyl or with any of the C—H, C—Cl, or C=C bonds present in other molecules in the reaction mixture will lead to products of higher molecular weight. Only monomeric products were examined in this study. As expected from the stoichiometry of the reaction, the elimination products, C_nH_{2n-2}, in any run were found to be somewhat less than one-half of the monomeric product, with products arising from the base, C_nH_{2n}, comprising the remainder.

For example, the reaction of cyclohexylmethyl chloride with sodium led to a mixture of C_7 hydrocarbons (Table I) containing methylcyclohexane as the only C_nH_{2n} product and bicyclo[4.1.0]heptane and methylenecyclohexane as the only C_nH_{2n-2} products. Methylcyclohexane presumably arises from reaction of cyclohexylmethylsodium as a base and bicyclo[4.1.0]heptane from an intramolecular insertion reaction of cyclohexylcarbene. Though methylenecyclohexane could form either from the chloride by β-elimination or from cyclohexylcarbene by hydrogen migration, it probably formed mostly from the carbene since α-elimination has been shown[1] to predominate over β-elimination in similar reactions of other primary chlorides.

Cyclopentylmethyl chloride and sodium reacted to give a similar mixture containing methylcyclopentane as the only C_nH_{2n} product, and bicyclo[3.1.0]hexane, methylenecyclopentane, and cyclohexene as C_nH_{2n-2} products. The chloride contained 6% of cyclohexyl chloride which could have been responsible for the cyclohexene observed.

A similar reaction of cyclobutylmethyl chloride gave a mixture of C_5 hydrocarbons containing methylcyclobutane and 1-pentene as C_nH_{2n} products, and bicyclo[2.1.0]pentane, methylenecyclobutane, and cyclopentene as C_nH_{2n-2} products. A control reaction of sodium with a mixture of cyclopentyl chloride and cyclohexylmethyl chloride led to substantial amounts of cyclopentane as well as cyclopentene. Therefore, in the reaction with cyclobutylmethyl chloride, the cyclopentene formed most reasonably by carbon migration in the cyclobutylcarbene intermediate and not by a β-elimination reaction of cyclopentyl chloride, which conceivably might have formed from cyclobutylmethyl chloride under the reaction conditions.

Addition of cyclopropylmethyl chloride to a phenylsodium solution led to a mixture of C_2 and C_4 hydrocarbons composed principally of 1-butene, cyclobutene, butadiene, and ethylene. Reaction of the chloride with sodium produced the same C_4 compounds, but 1-butene comprised 59% of the product. The products which apparently formed from the carbene were cyclobutene, butadiene, and ethylene. The same products plus acetylene were obtained by Friedman and Shechter[2] from the reaction of cyclopropanecarboxaldehyde tosylhydrazone with base, and the relative proportions of the products were similar despite the difference of almost 150° in reaction temperature and the different precursor of cyclopropylcarbene. Acetylene presumably formed along with ethylene in our reactions but would have remained in the reaction flask as the sodium salt.

Ring opening of the alkylsodium compounds to isomers is postulated to account for the formation of 1-pentene from cyclobutylmethyl chloride and 1-butene from cyclopropylmethyl chloride. This type of interconversion has been reported for the cyclopropylmethyl and 3-butenyl Grignard and lithium reagents,[3] and we have observed the corresponding ring cleavage of cyclobutylmethyllithium and of a cyclobutylmethyl Grignard reagent.[4] Since ring cleavages of cyclobutylmethyllithium and the corresponding Grignard reagent proceed nearly to completion,[4] the relative yields of 1-pentene and methylcyclobutane in the reaction product from cyclobutylmethyl chloride probably do not

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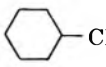
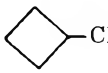
(2) L. Friedman and H. Shechter, *ibid.*, **82**, 1002 (1960).

(3) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Rüchardt, and J. D. Roberts, *ibid.*, **82**, 2646 (1960); P. T. Lansbury and V. T. Pattison, *ibid.*, **85**, 1886 (1963).

(4) E. A. Hill, H. G. Richey, Jr., and T. C. Rees, *J. Org. Chem.*, **28**, 2161 (1963).

TABLE I

HYDROCARBON PRODUCTS FROM REACTIONS OF CYCLOALKYLMETHYL CHLORIDES

Reactants	Yield of monomeric product, %	Components in product mixture, mole %: C_nH_{2n} components: Methylcycloalkane	C_nH_{2n} components: 1-Alkene	C_nH_{2n-2} components: Bicycloalkane	C_nH_{2n-2} components: Methylenecycloalkane	C_nH_{2n-2} components: Cycloalkene
 $CH_2Cl + Na$	69	61		3	36[a]	
 $CH_2Cl + Na$	68	54		34	10	2
 $CH_2Cl + Na$	40	6	59	10	8	17
 $CH_2Cl + PhNa$	8[b]		17	*c*		47

[a] Slightly contaminated with an unidentified component. [b] This was the yield of $C_2 + C_4$ hydrocarbons. [c] Other products were butadiene (15%, contaminated with an impurity that probably was methylcyclopropane), ethylene (19%), and an unidentified component (1.5%).

reflect the composition of an equilibrium mixture of the two sodium derivatives; the presence of methylcyclobutane suggests that the rate of reaction of cyclobutylmethylsodium in the elimination reactions is comparable to its rate of ring opening. The related open-chain olefins (1-heptene and 1-hexene) were not found in the products from reactions with cyclohexylmethyl and cyclopentylmethyl chlorides.

The maximum yield of fused cyclopropane relative to isomeric olefins was found with cyclopentylmethyl chloride suggesting that a nearly coplanar arrangement of the bivalent carbon, the ring carbon to which it is attached, and the C–H bond may be favorable for insertion. With cyclobutylcarbene and cyclopropylcarbene, competition from ring expansion by carbon migration becomes important; in addition, as the ring size decreases, the bivalent carbon becomes increasingly further from the C–H bond on an adjacent carbon. The decrease in insertion by the carbene from cyclohexylmethyl chloride may be ascribed to the strain introduced in attaining a nearly eclipsed conformation. Moore, Ward, and Merritt have reported the formation in good yield of tricyclic insertion products from the reaction of 7,7-dibromobicyclo[4.1.0]heptane with methyllithium.[5] In this reaction, however, hydrogen migration is probably minimized since it would lead to a highly strained fused cyclopropene.

Experimental

Cycloalkylmethyl Chlorides.—Cyclohexylmethyl Chloride, b.p. 58–60° (18 mm.), lit.[6] 54–55° (19 mm.), was prepared from reaction of cyclohexylmethanol with thionyl chloride and pyridine as described by Kice.[6]

Cyclopentylmethyl chloride, b.p. 136–138° (731 mm.), lit.[7] 72° (25 mm.) and 60 (50), was prepared from cyclopentylmethanol in a similar manner but with a shorter reaction time and at a lower temperature. The lower layer (pyridinium salts) of the reaction mixture crystallized, facilitating the isolation of the chloride. This chloride sample was found to contain about 6% of cyclohexyl chloride by g.l.p.c. using a 100-ft. capillary column coated with SE-30 methyl silicone gum rubber (General Electric).

Cyclobutylmethyl chloride, apparently not reported previously was prepared by treating cyclobutylmethanol with thionyl chloride and tri-*n*-butylamine in ether solution using a modification of a procedure[8] used to prepare cyclopropylmethyl chloride. The ether was distilled from the reaction mixture at slightly reduced pressure. Then over 1.5 hr. the temperature was raised to 90° and the pressure was reduced to about 20 mm.; the product distilled from the reaction mixture as it formed. Redistillation gave cyclobutylmethyl chloride, b.p. 109.5–110.5° (740 mm.), that was shown by n.m.r. analysis (comparison of areas of the doublet due to the hydrogens of the chloromethyl group of cyclobutylmethyl chloride and the complex peak due to the methine hydrogen of cyclopentyl chloride) to contain less than 1% of cyclopentyl chloride. A sample prepared by a procedure similar to that used for cyclopentylmethyl chloride contained 15% of cyclopentyl chloride.

Anal. Calcd. for C_5H_9Cl: C, 57.42; H, 8.67. Found: C, 57.13; H, 8.83.

Cyclopropylmethyl chloride, b.p. 83.5–85° (719 mm.), lit.[8] 85.5° (748 mm.), was prepared as described by Caserio, Graham, and Roberts.[8] The infrared spectrum of the sample was identical with a published one.[9]

Separation and Identification of Products.—Reaction products were separated by g.l.p.c. in instruments with thermal conductivity detectors and using helium as the carrier gas. The columns used were column A, 5-ft., 25% Apiezon J (Metropolitan Vickers Co.) on firebrick; column B, 10-ft., silver nitrate in diethylene glycol on firebrick; column C, 2-ft., SE-30 methyl silicone gum rubber (General Electric) on firebrick; column D, 20-ft., 30% dipropylene glycol dibenzoate on firebrick. Fractions were collected in traps cooled in liquid nitrogen and then transferred to a vacuum line. The weights of fractions were assumed to be proportional to the peak areas on the gas chromatograms.[10,11] Identification of each fraction is described subsequently.

Reaction of Cyclohexylmethyl Chloride with Sodium.—The chloride (5.0 g.) was added over 90 min. to 1.1 g. of sodium cut into small pieces in 5 ml. of cyclohexane. The reaction mixture warmed considerably. The reaction flask was heated at 75° for 1 hr. and then was connected to a trap cooled in liquid nitrogen, and the volatile materials were transferred to the trap using a vacuum pump. Chromatography of the reaction mixture over column A gave, in order of elution, cyclohexane, a mixture of methylcyclohexane and methylenecyclohexane, followed closely by a small amount of an unknown component, and bicyclo[4.1.0]heptane. Using column B, methylenecyclohexane was eluted after methylcyclohexane, and their relative amounts were determined. The yield of C_7 hydrocarbons was calculated by subtracting the large amount of solvent present (estimated by comparing areas of the cyclohexane peak with the areas due to C_7

(5) W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Am. Chem. Soc.*, **83**, 2019 (1961).

(6) J. L. Kice, *ibid.*, **80**, 348 (1958).

(7) M. Mousseron, *Bull. soc. chim. France*, [5] **15**, 84 (1948); J. von Braun and E. Anton, *Ber.*, **66**, 1373 (1933); N. Turkiewicz, *ibid.*, **72**, 1060 (1939).

(8) M. C. Caserio, W. H. Graham, and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960).

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(11) G. L. Tingey, Ph.D. thesis, The Pennsylvania State University, June, 1963.

components) and the small amount of unchanged chloride (estimated from comparing areas of the chloride peak and the peak due to cyclohexane and C_7 components in a chromatogram with column C) from the weight of the crude product. Methylcyclohexane and bicyclo[4.1.0]heptane were identified by comparison of their infrared spectra with those of authentic samples. Methylenecyclohexane was identified by a comparison of the infrared spectrum of the gas with that reported for a liquid sample.[12] A reaction run in the same manner using *n*-tetradecane as solvent gave very similar results.

Reaction of Cyclopentylmethyl Chloride with Sodium.—In a similar manner, 5.0 g. of chloride was added over 75 min. to 1.4 g. of sodium in 4 ml. of isooctane, and the reaction mixture then was heated gradually to 100° over 1 hr. The yield of C_6 hydrocarbons was calculated by correcting the weight of the crude product by the same procedure described for the reaction with cyclohexylmethyl chloride. Chromatography of the reaction mixture over column D gave, in order of elution, methylcyclopentane, methylenecyclopentane, and a mixture of bicyclo[3.1.0]hexane and cyclohexene. Methylcyclopentane was identified by comparison of its infrared spectrum with API 14,[13] and methylenecyclopentane by comparison of the spectrum of the gas with that reported for a liquid sample[14]; cyclohexane has the same retention time but the infrared spectrum indicates that it could not be present in significant amount. Bicyclo[3.1.0]hexane was identified by the n.m.r. spectrum of a carbon tetrachloride solution which had complex absorption from τ 8.2 to 9.0.[15] Cyclohexene has the same retention time as bicyclo[3.1.0]hexane, and its presence was detected and its amount was estimated by the presence of weak absorption at τ 4.4 (identical in position with the absorption of authentic cyclohexene). A reaction run in the same manner in *n*-tetradecane gave similar results.

Reaction of Cyclobutylmethyl Chloride with Sodium.—In a similar manner, 2.1 g. of cyclobutylmethyl chloride was added over 1 hr. to 1.1 g. of sodium in 1.4 ml. of *n*-tetradecane. Chromatography of the reaction mixture over column D gave, in order of elution, 1-pentene, methylcyclobutane, methylenecyclobutane, cyclopentene, and bicyclo[2.1.0]pentane. Cyclopentene and 1-pentene were identified by comparison of their infrared spectra with those of authentic samples. Methylcyclobutane and methylenecyclobutane were identified by comparison of their spectra with API 890 and 561, respectively.[13] Bicyclo[2.1.0]pentane was identified by the close comparison of the infrared spectrum of a carbon tetrachloride solution with that reported for the pure liquid[16] and also by comparison of its n.m.r. spectrum with one reported.[17] Cyclopentane has the same retention time as methylenecyclobutane but was shown to be absent by examination of the n.m.r. spectrum. In a similar reaction with chloride containing 15% of cyclopentyl chloride, cyclopentane (identified by comparison of its infrared spectrum with API 446)[13] was shown to comprise 14% of the product by rechromatographing the "methylenecyclobutane" fraction over column B which eluted cyclopentane before methylenecyclobutane. A reaction with 1.2 g. of cyclopentyl chloride and 4.0 g. of cyclohexylmethyl chloride led to cyclopentane (32%) and cyclopentene (68%) as the only detected C_5 products.

Reactions of Cyclopropylmethyl Chloride with Phenylsodium and Sodium.—Phenylsodium was prepared in 12 ml. of isooctane from 7.5 g. (0.067 mole) of chlorobenzene and a dispersion of 2.2 g. (0.096 g.-atom) of sodium in 4.2 g. of mineral oil. Then a solution of 1.99 g. (0.022 mole) of cyclopropylmethyl chloride in 5 ml. of isooctane was added over 45 min. Nitrogen was passed continually over the reaction mixture, and the exit gases were passed through a trap cooled in liquid nitrogen. The reaction mixture was stirred for an additional 90 min. Then the material in the trap was transferred to a vacuum line and was fractionated crudely by two distillations through a Dry Ice trap to remove less volatile components. Chromatography over column D gave, in order of elution, ethylene, 1-butene, butadiene, cyclobutene, and an unidentified peak. Ethylene was identified by its retention time. Butadiene and 1-butene were identified by comparison of their infrared spectra with API 917 and 901, respectively,[13] and cyclobutene by comparison with a published spectrum.[18] The butadiene peak had a shoulder slightly before the main peak of about one-fifth of the total peak area. The retention time of this shoulder corresponded to that of methylcyclopropane,[11] and some weak bands in the infrared spectrum corresponded to those in the infrared spectrum of methylcyclopropane.[19] Another reaction carried out by adding the chloride to sodium in cyclohexane gave in 5% yield a mixture of 1-butene (59%), butadiene (11%, with a small shoulder preceding the main peak), and cyclobutene (30%); Dry Ice was used in the trap so that ethylene would not have been collected.

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(15) Spectra were taken at 60 Mc. Chemical shifts are in parts per million relative to tetramethylsilane as 10.0.
(16) R. Criegee and A. Rimmelin, *Ber.*, **90**, 414 (1957).
(17) J. P. Chesick, *J. Am. Chem. Soc.*, **84**, 3250 (1960).
(18) J. D. Roberts and C. W. Sauer, *ibid.*, **74**, 3192 (1952).
(19) F. E. Condon and D. E. Smith, *ibid.*, **69**, 965 (1947).

Condensation of Dimethyl Acetylenedicarboxylate with Malononitrile, Ethyl Cyanoacetate, and Malonate Esters

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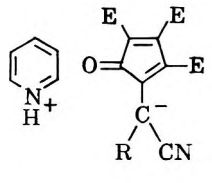
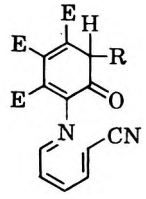
In the presence of a mixture of pyridine and acetic acid, dimethyl acetylenedicarboxylate condenses with malononitrile and with ethyl cyanoacetate to give, respectively, pyridinium salts II and III. Under the same conditions dimethyl acetylenedicarboxylate and malonate esters yield two isomeric 1,1,2,3,4,5,6,7-octacarboalkoxycycloheptadienes. Aqueous potassium acetate converts these cycloheptadienes into the potassium salt of the strongly acidic 1,2,3,4,5-pentacarboalkoxycyclopentadiene.

In his classical studies of the chemistry of acetylenic esters Diels has shown that, in the presence of pyridine and acetic acid, dimethyl acetylenedicarboxylate readily condenses with malononitrile, ethyl cyanoacetate, dimethyl, and diethyl malonate to form a multitude of products.[1] While careful experimental work led to the isolation of a variety of products, disturbing features in several structural assignments prompted our

(1) (a) O. Diels, *Chem. Ber.*, **75**, 1452 (1942); (b) O. Diels and U. Kock, *Ann.*, **556**, 38 (1944).

reinvestigation of some of these interesting reactions. As previously reported,[1] dimethyl acetylenedicarboxylate (I) and malononitrile react with equimolar quantities of pyridine and acetic acid to give a blue-black crystalline compound (A), m.p. 205–206°, while I and ethyl cyanoacetate give a deep blue crystalline compound (B), m.p. 171–172°. In accord with Diels we find that A and B result from the condensation of 2 moles of I, 1 mole each of the nitrile and pyridine, less the elements of 1 mole of methanol. However, the strong absorption band in the visible spectrum (668 mμ for A and 625 mμ for B) is wholly incompatible with the unlikely structures IV and V which Diels[1b] suggested for A and B. We propose that the formulations for A and B of II and III are in complete agreement with the chemical and physical properties of the substances. Compound II shows a broad absorption in the visible at 668 mμ. In the infrared nitrile (4.53 μ), ester (5.76 μ), cyclopentadienone carbonyl (5.89, 5.98 μ), and pyridinium cation (6.15, 6.76 μ)[2] are evident.





II, R = CN; E = CO_2Me IV, R = CN; E = CO_2Me
III, R = $CO_2C_2H_5$; E = CO_2Me V, R = $CO_2C_2H_5$; E = CO_2Me

The p.m.r. spectrum of II (Table I) shows a complex multiplet at τ 0.94–2.1 (protonated pyridine) and singlets at τ 6.20, 6.40, 6.41 (methoxy). Compound III exhibits an absorption band in the visible at 625 mμ. The infrared spectrum shows the presence of the nitrile (4.55 μ), ester (5.74 μ), cyclopentadienone carbonyl (5.83, 5.96 μ), and pyridinium (6.12, 6.75 μ).[2] The p.m.r. spectrum of III has a complex multiplet at τ 1.0–2.1 (protonated pyridine), a quartet at τ 5.86 (J = 7 c.p.s., —CH_2—O— of ethoxy group), three singlets at τ 6.25, 6.49, 6.54 (CH_3—O—), and a triplet at τ 8.81 (J = 7 c.p.s., CH_3— of ethoxy). A possible mechanism for the formation of II and III may be envisaged as follows (col. 2).

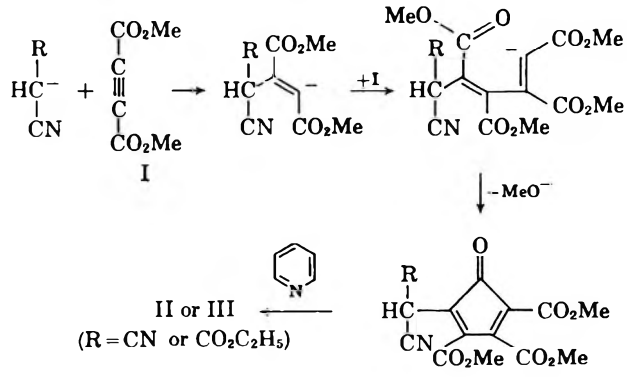
TABLE I

PROTON MAGNETIC SPECTRA[a]

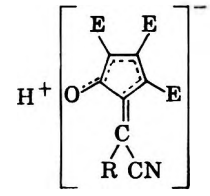
Compound	τ-Values	Multiplicity[b]	Assignment
II[c]	0.94 to 2.1	Complex	Protonated pyridine
	6.20	s	CH_3O—
	6.40	s	CH_3O—
	6.41	s	CH_3O—
III[c]	1.0 to 2.1	Complex	Protonated pyridine
	5.86	q (J = 7 c.p.s.)	—CH_2O— of ethoxy
	6.25	s	CH_3O—
	6.49	s	CH_3O—
	6.54	s	CH_3O—
	8.81	t (J = 7 c.p.s.)	CH_3— of ethoxy

[a] Spectra were obtained on a Varian A-60 spectrometer using chloroform-d as solvent (except where noted) and tetramethylsilane as internal standard. [b] s = singlet, d = doublet, t = triplet, q = quartet. [c] Dimethyl sulfoxide-d_6 used as solvent.

(2) G. M. Barrow, *J. Am. Chem. Soc.*, **78**, 5802 (1956).

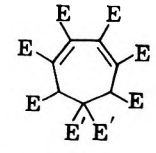


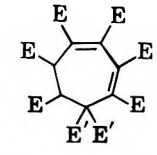
The acids corresponding to these deep blue stabilized carbanions are colorless and quite strong. Spectrophotometric determination of the pK_a gave a value of 1.98 for VI and 2.4 for VII.



VI, R = CN; E = CO_2Me
VII, R = $CO_2C_2H_5$; E = CO_2Me

In marked contrast to the above reactions, dimethyl acetylenedicarboxylate condenses with dimethyl malonate in the presence of pyridine and acetic acid to give two colorless, pyridine-free isomeric products C, m.p. 225–226°, and D, m.p. 185–187°, as previously reported.[3] While Cookson[4] reported that C was derived from 1 mole of dimethyl malonate and 2 moles of dimethyl acetylenedicarboxylate, the data which we present here, show that C as well as D are derived from 1 mole of malonate ester and 3 moles of dimethyl acetylenedicarboxylate. We propose that C be assigned structure VIII and D be assigned the isomeric structure IX. In accord with these structures are the elemental analyses and molecular weight determina-





VIII, E = E′ = CO_2Me IX, E = E′ = CO_2Me
XII, E = CO_2Me; XI, E = CO_2Me;
E′ = $CO_2C_2H_5$ E′ = $CO_2C_2H_5$

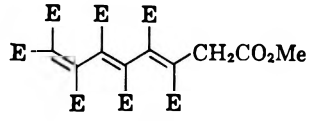
tions, which establishes the composition of these isomers as $C_{23}H_{26}O_{16}$. Spectral data on VIII show the presence of ester carbonyl (5.74 μ) and a conjugated diene system (6.17 μ and 284 mμ). The p.m.r. spectrum of VIII (Table II) indicates the presence of the allylic ring proton and four different carbomethoxy groups. In the case of IX spectral data establishes the presence of ester carbonyl (5.75 μ) and a conjugated diene

(3) While Diels[1a] reported the isolation of both compounds, Cookson and co-workers[4] could not obtain the lower melting isomer. They rationalized their inability to find this substance on the basis that Diels' material was a mixture of esters derived from dimethyl and ethyl methyl malonates which appeared unlikely in view of the 1° melting range reported by Diels.

(4) R. C. Cookson, J. Hudec, and B. Whitear, *Proc. Chem. Soc.*, 117 (1961).

system (6.15 μ and 264 mμ). The p.m.r. spectrum of IX (Table II) indicates the presence of eight carbomethoxy groups in addition to an AX pattern arising from the two different vicinal protons.

While the p.m.r. spectrum of IX establishes the cyclic system proposed, the data for VIII are also consistent with an acyclic formulation X. That VIII is the correct structure is demonstrated by partially exchanging the allylic ring protons with deuterium. By following



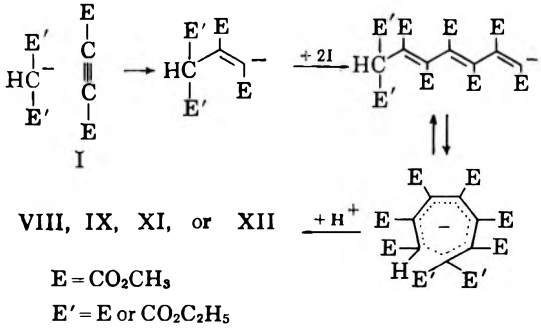
X, E = CO_2Me

this slow exchange in the n.m.r., it was found that the singlet due to the ring proton is not replaced by a triplet as would be expected for the geminal protons of X, but is slowly washed out of the spectrum. Under the same conditions IX isomerized to VIII in a few minutes.

VIII proved quite unreactive toward a number of reagents (NBS, bromine, mercuric acetate, selenium dioxide, CH_3CO_2I, tetracyanoethylene, benzyne, hydrogen peroxide–acetonitrile).

Diethyl malonate also forms two isomeric condensation products with dimethyl acetylenedicarboxylate. The lower melting isomer, m.p. 155–156°, previously isolated by Diels,[1a] has been assigned the structure XI. In addition, careful chromatographic work-up of the residues remaining from the isolation of XI gave the higher melting isomer, m.p. 162–163°, which has been assigned the structure XII. These structural assignments are supported by elemental analyses and molecular weight determinations.[5]

It is apparent that the formation of VIII, IX, XI, and XII involves a mechanism which is rather different from that involved in the formation of II and III.



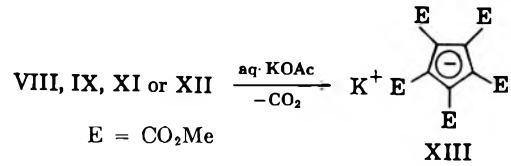
VIII, IX, XI, or XII

E = CO_2CH_3

E′ = E or $CO_2C_2H_5$

One may speculate that replacement of the nitrile function by carboalkoxy subtly alters the character of the intermediates, either by electronic or steric interactions, to enable addition of a third molecule of the acetylenic ester.

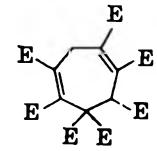
Substantiating earlier findings,[1a] we observed formation of a yellow crystalline compound (E) when VIII and IX are refluxed with aqueous potassium acetate. Furthermore, we find that during this transformation carbon dioxide is evolved (1 mole of carbon dioxide per mole of VIII). Recrystallization of E removes the bright yellow color to give a white crystalline solid, m.p. 219–220°. Elemental analysis established the structure of this compound as XIII, the potassium salt of 1,2,3,4,5-pentacarbomethoxycyclopentadiene.



VIII, IX, XI or XII; E = CO_2Me

XIII

In addition to E and carbon dioxide, a moderate quantity of an intractable water-soluble oil can be isolated whose infrared spectrum possessed a broad band in the carbonyl region, plus a trace of a water-insoluble crystalline solid, m.p. 128–129°, which is assigned structure XIV. This assignment is supported by the elemental analysis, molecular weight, infrared



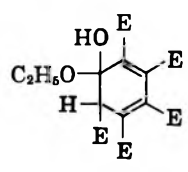
XIV, E = CO_2Me

spectrum (ester carbonyl and carbon–carbon double bond), ultraviolet spectrum (end absorption with shoulder at 235 mμ), and p.m.r. (Table II) spectrum, which shows the presence of seven different carbomethoxy groups, an allylic ring proton, and an AB quartet arising from the geminal ring protons.

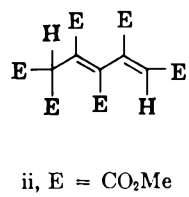
A clue to the mechanism of this reaction (VIII and IX → XIII) is revealed in our observation that both isomers derived from diethyl malonate, XI and XII, also afforded good yields of potassium salt XIII.[6] It is clear from these results that the fragment lost in this reaction includes the moiety that began as malonate ester. One plausible mechanism suggested by these data involves the removal of a ring proton by base (acetate), an internal Michael reaction followed by rearrangement and cleavage to XIII and tricarboalkoxyethylene. Hydrolysis and decarboxylation of the triester would account for the carbon dioxide observed.

Treatment of the potassium salt (XIII) with hydrochloric acid, gives good yields of the acidic compound 1,2,3,4,5-pentacarbomethoxycyclopentadiene (XV), m.p. 149–150°.[1,3] Elemental analysis and neutralization equivalent are in accord with the formula $C_{15}H_{16}O_{10}$. The infrared spectrum indicates the presence of ester carbonyls (5.80 μ) as well as carbon–carbon unsaturation (6.27 μ). The p.m.r. spectrum consists of a sharp singlet at τ 6.07 indicating the equivalence of the carbomethoxy groups. The singlet expected for the acidic proton in XIII has eluded detection in a

(5) The low values obtained by Diels[1a] for the molecular weight of XI led him to formulate 1:2 malonate–acetylenic ester condensation products with the general structure (i). Cookson and co-workers[4] have assumed that these low values were correct and thus, formulate VIII as ii.



i, E = CO_2Me



ii, E = CO_2Me

(6) Diels reported that, in contrast to VIII and IX, XI upon refluxing with aqueous potassium acetate gave malonate ester.

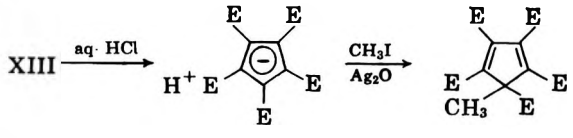
TABLE II

PROTON MAGNETIC SPECTRA[a]

Compound	τ-Values	Multiplicity[b]	Relative area (no. of protons)	Assignment
VIII	4.95	s	1.8	Allylic proton
	6.12	s	6.0	CH_3—O—
	6.26	s		CH_3—O—
	6.30	s	18.0	CH_3—O—
	6.32	s		CH_3—O—
IX	4.88	d (J = 1.5 c.p.s.)	2.2	Allylic proton
	5.31	d (J = 1.5 c.p.s.)		Proton on satd. C
	6.17	s	2.8	CH_3—O—
	6.23	s	5.9	CH_3—O—
	6.29	s		CH_3—O—
	6.32	s	15.0	CH_3—O—
XI	4.88	d (J = 1.6 c.p.s.)	1.2	Allylic proton
	5.33	d (J = 1.6 c.p.s.)	1.2	Proton on satd. C
	5.5–6.1	Complex[c]		—CH_2—O— of ethoxy
	6.17	s		CH_3—O—
	6.23	s	22.2	CH_3—O—
	6.28	s		CH_3—O—
	6.32	s		CH_3—O—
	8.69	t (J = 7.1 c.p.s.)	6.0	CH_3— of ethoxy
	8.73	t (J = 7.1 c.p.s.)		CH_3— of ethoxy
XII	4.95	s	2.0	Allylic proton
	5.82	q (J = 3.7 c.p.s.)	4.1	—CH_2—O— of ethoxy
	5.84	q (J = 3.6 c.p.s.)		
	6.12	s	6.0	CH_3—O—
	6.26	s	6.1	CH_3—O—
	6.32	s	6.0	CH_3—O—
	8.80	t (J = 7.1 c.p.s.)	6.0	CH_3—of ethoxy
XIV	5.13	s	0.8	Allylic proton
	5.78	q (J = 10.6 c.p.s.)	1.8	Allylic geminal protons
	6.17	s	2.9	CH_3—O—
	6.25	s		CH_3—O—
	6.23	s		CH_3—O—
	6.27	s	18.0	CH_3—O—
	6.28	s		CH_3—O—
	6.30	s		CH_3—O—
	6.33	s		CH_3—O—
XV	6.07[d]	s		CH_3—O—
XVI	6.23	s	12.0	CH_3—O—
	6.28	s		CH_3—O
	6.37	s	2.8	CH_3—O
	8.32	s	2.6	CH_3—C

[a] Spectra were obtained on a Varian A-60 spectrometer using chloroform-*d* as solvent and tetramethylsilane as internal standard. [b] s = singlet, d = doublet, t = triplet, q = quartet. [c] Barely discernable are two closely spaced quartets having slightly different coupling constants. [d] In deuterium oxide this singlet was slightly sharper and occurred at τ 6.2.

number of solvents (chloroform-*d*, deuterium oxide, benzene, and nitrobenzene). Presumably, it is either obscured by the methoxy proton absorption or, more likely, it is very broad.



XV XVI

Methyl iodide and silver oxide convert XV into the C-methyl derivative (XVI), m.p. 101–102°. The preparation of XVI from XV with diazomethane as previously reported[4] could not be repeated. This structural assignment is substantiated by the elemental analysis and molecular weight determination as well as the infrared, ultraviolet, and p.m.r. spectra (Table II).

Experimental[7]

Preparation of II.—This salt was prepared according to the method of Diels.[1b] A 60% yield of this blue-black crystalline solid was obtained; m.p. 205–206° (from acetonitrile), lit.[1b] m.p. 201–202°; λ_{max}^{KBr} 3.38, 4.53, 5.76, 5.89, 5.98, 6.15, 6.47, 6.60, 6.72, 6.75, 6.90 μ; λ_{max}^{EtOH} 227 sh mμ (log ε 3.93), 257 (4.35), 262 sh (4.33), 313 (4.40), 401 sh (3.68), 668 (3.68).

Anal. Calcd. for $C_{19}H_{15}O_7N_3$: N, 10.58. Found: N, 10.79; pK_a 1.98.

Preparation of III.—Following the method of Diels[1a] there was obtained a 68% yield of the dark blue crystalline salt, III.

(7) Melting points are corrected. Analyses and molecular weight determinations were carried out in the Mellon Institute microanalytical laboratories and at various commercial laboratories. Molecular weight determinations were made using the thermoelectric osmometer.

Recrystallization from acetonitrile gave analytically pure material; m.p. 171–172°, lit.[1a] 173–174°; λ_{max}^{KBr} 3.28, 3.35, 4.55, 5.72, 5.79, 5.92, 6.09, 6.35, 6.55 μ; λ_{max}^{EtOH} 252 sh mμ (log ϵ 4.29), 257 (4.29), 262 sh (4.25), 317 (4.36), 625 (3.28).

Anal. Calcd. for $C_{21}H_{20}O_9N_2$: C, 56.75; H, 4.54; N, 6.30. Found: C, 57.05; H, 4.63; N, 6.35; pK_a 2.4.

1,1,2,3,4,5,6,7-Octacarbomethoxy-3,5-cycloheptadiene (VIII).—Portionwise addition of 2.5 ml. of equal parts (by weight) of pyridine and acetic acid to a stirred solution of 38 g. (0.27 mole) of dimethyl acetylenedicarboxylate and 11.7 g. (0.09 mole) of dimethyl malonate in 60 ml. of absolute ether resulted in an exothermic reaction. After the vigorous reaction had subsided the dark red mixture was refluxed for 2 hr. (It was necessary to break up the reaction product which formed a solid mass at the bottom of the reaction flask.) This solid was collected, washed with ether, and dried. Most of this material was dissolved in a minimum volume of methanol. The insoluble portion (2 g.), which is impure IX, was collected and worked up according to the description in the next experiment. Chilling the filtrate gave a white crystalline solid 25.9 g., m.p. 225–226°, lit.[1a] m.p. 226°. Further cooling afforded a second crop of 5.0 g., m.p. 223–225° (total yield, 63%). Recrystallization from methanol gave an analytical sample; m.p. 226–227°; λ_{max}^{Nujol} 3.33, 3.40, 3.54, 5.74, 6.17 μ; λ_{max}^{MeOH} 211 mμ (log ϵ 3.94), 284 (3.62).

Anal. Calcd. for $C_{23}H_{26}O_{16}$: C, 49.47; H, 4.70; mol. wt., 558.4. Found: C, 49.48; H, 4.71; mol. wt., 536.

Deuterium exchange was carried out by warming a solution of VIII in acetic acid-*d* containing a trace of pyridine.

1,1,2,3,4,5,6,7-Octacarbomethoxy-4,6-cycloheptadiene (IX).—The 2 g. (4% yield) of insoluble material from the preceding experiment, m.p. 185–187°, was recrystallized from a large volume of methanol with no change in its melting point; lit.[1a] m.p. 182–183°; $\lambda_{max}^{HCCl_3}$ 3.33, 3.40, 5.75, 6.15, 6.96 μ; λ_{max}^{MeOH} 228 mμ (log ϵ 3.94), 264 (3.60).

Anal. Calcd. for $C_{23}H_{26}O_{16}$: C, 49.47; H, 4.70; mol. wt., 558.4. Found: C, 49.72; H, 4.88; mol. wt., 556.

1,1-Dicarboethoxy-2,3,4,5,6,7-hexacarbomethoxy-4,6-cycloheptadiene (XI).—To a stirred solution of 6.08 g. (38 mmoles) of diethyl malonate and 16.19 g. (144 mmoles) of dimethyl acetylenedicarboxylate in 25 ml. of ether was added 1 ml. of a solution containing equal volumes of pyridine and acetic acid. A red color formed and an exothermic reaction began. After 15 min. the reaction had subsided. The mixture was refluxed for 1.25 hr., then allowed to stand at room temperature overnight. The solid, which precipitated (~16 g.), was collected, dried, and stirred with a solution of 50 ml. of ether and 10 ml. of dioxane. The residual material was filtered from the solution (this solution contains XII) and crystallized from methanol to give 3.2 g. (14%) of a white crystalline solid, m.p. 150–152°. Four recrystallizations from methanol gave 1.5 g. of analytically pure material; m.p. 155–156°, lit.[1a] m.p. 154–155°; $\lambda_{max}^{HCCl_3}$ 3.40, 5.75, 6.15, 6.95 μ; λ_{max}^{EtOH} 215 sh mμ (log ϵ 4.08), 275 sh (3.67), 263 (3.77).

Anal. Calcd. for $C_{25}H_{30}O_{16}$: C, 51.20; H, 5.16; mol. wt., 586.4. Found: C, 51.43; H, 5.26; mol. wt., 574.

1,1-Dicarboethoxy-2,3,4,5,6,7-hexacarbomethoxy-3,5-cycloheptadiene (XII).—The dioxane–ether solution and the various mother liquor from the recrystallizations of XI were combined, concentrated, and chromatographed two times on silicic acid (chloroform eluent). An oil resulted, which was crystallized from methanol. A second recrystallization gave 6.45 g. (29%) of white crystals, m.p. 161–162°. A further recrystallization gave an analytical sample; m.p. 162–163°; $\lambda_{max}^{HCCl_3}$ 3.40, 5.75, 6.14, 6.96 μ; λ_{max}^{EtOH} 215 sh mμ (log ϵ 3.96), 285 (3.61).

Anal. Calcd. for $C_{25}H_{30}O_{16}$: C, 51.20; H, 5.16; mol. wt., 586.5. Found: C, 50.91; H 5.22; mol. wt., 543.

1,2,3,4,5-Pentacarbomethoxycyclopentadienyl Potassium (XIII).—A mixture of 100 g. (0.18 mole) of VIII and 500 ml. of water containing 165 g. of potassium acetate was refluxed for 2 hr. with vigorous stirring. Carbon dioxide was evolved and a clear yellow solution was obtained. This hot solution was filtered and then allowed to cool. A yellow crystalline solid formed (62 g.) which may be converted to the free acid (XV) as described in the next experiment. Thorough washing of the crude yellow solid affords 50 g. (62%) of a pale yellow crystalline solid, m.p. 217–218°. A white crystalline analytical sample was prepared by crystallizing this material from ethanol, m.p. 219–220°.

Anal. Calcd. for $C_{15}H_{15}O_{10}K$: C, 45.68; H, 3.84. Found: C, 45.78; H, 3.85.

A second white crystalline form, m.p 185–186°, was obtained when chloroform–acetonitrile mixture was used for crystallization.

1,2,3,4,5-Pentacarbomethoxycyclopentadiene (XV).—A solution of 5 g. (0.013 mole) of the potassium salt (XIII) in 25 ml. of water was filtered[8] and concentrated hydrochloric acid added until precipitation of the white solid was complete. This material was collected and dried overnight *in vacuo* to give 4.0 g. (90%) of a white solid, m.p. 148–150°, lit.[1a] m.p. 147–148°. An analytical sample was prepared by crystallizing this material from methanol; m.p 149–150°; $\lambda_{max}^{HCCl_3}$ 5.80, 6.27 μ; λ_{max}^{MeOH} 262 mμ (log ϵ 4.69), 295 (4.16).

Anal. Calcd. for $C_{15}H_{16}O_{10}$: C, 50.56; H, 4.53; neut. equiv., 356. Found: C, 50.54; H, 4.47; neut. equiv., 365.

Both XI and XII gave clear yellow solutions after refluxing and stirring with an aqueous solution of potassium acetate for 2 and 8 hr., respectively. The cooled solutions deposited XIII, which afforded, in both cases, a 69% yield of XV, m.p. 149–151° (mixture melting point with XV obtained from VIII was not depressed and infrared spectra were identical).

1-Methyl-1,2,3,4,5-pentacarbomethoxycyclopentadiene (XVI).—A mixture of 250 mg. (0.70 mmole) of XV, 250 mg. of silver oxide, 0.25 ml. of methyl iodide in 10 ml. of methanol was refluxed for 24 hr. The precipitate was removed and the filtrate refluxed for 12 hr. with a second portion of 250 mg. of silver oxide and 0.25 ml. of methyl iodide. This was repeated a third time. Evaporation of the filtrate left a solid residue which was crystallized from methanol, to give 170 mg. (66%) of a white crystalline solid, m.p. 100–101°. An analytical sample was prepared by an additional recrystallization from methanol; m.p. 101–102°, lit.[3] m.p. 102–103°; $\lambda_{max}^{HCCl_3}$ 3.31, 3.37, 5.73, 6.13, 6.33, 6.93 μ; λ_{max}^{MeOH} 220 mμ (log ϵ 3.95), 292 (3.80).

Anal. Calcd. for $C_{16}H_{18}O_{10}$: C, 51.89; H, 4.90; mol. wt., 370.3. Found: C, 51.79; H, 4.88; mol. wt., 360.

(8) The insoluble residue (220 mg.), which was collected, was crystallized from methanol to give a white crystalline solid, XIV; m.p. 128–129°; $\lambda_{max}^{HCCl_3}$ 3.33, 3.42, 5.74, 6.06, 6.94 μ; the ultraviolet spectrum showed only end adsorption with a shoulder at 235 mμ (log ϵ 3.95). *Anal.* Calcd. for $C_{24}H_{24}O_{14}$: C, 50.39; H, 4.83; mol. wt., 500. Found: C, 50.52; H, 4.77; mol. wt., 508.

Anodic Decarboxylation of Carboxylic Acids[1]

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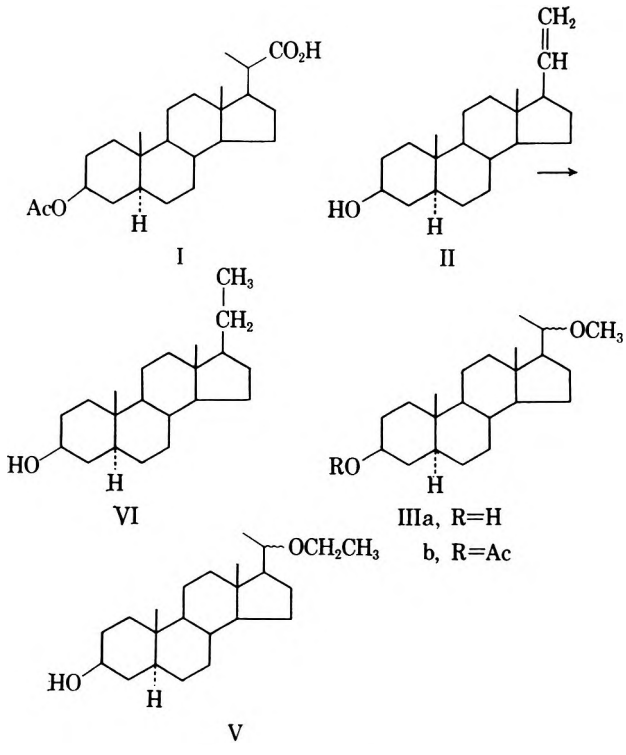
The electrolytic oxidation of 3β-acetoxybisnorallocholanic acid (I) in methanol at pH 11.3, 8.6, and 5.7 is described. The reaction in ethanol and 2-propanol also is discussed. The various reaction products, *i.e.*, pregnane derivatives II–V, indicate a carbonium ion intermediate is involved.

Recent investigations[2,3] have shown that the electrolysis of carboxylic acids in methanol yielded methyl ethers, apparently from attack of solvent on a carbonium ion intermediate. The free radical evidently undergoes further oxidation at the platinum anode. We subsequently have reported[1] similar ether formation as well as olefin production (β-elimination) in the electrolytic decarboxylation of isostevic acid. An extension of the study of the anodic reaction with 3β-acetoxybisnorallocholanic acid (I) at various pH with different alcohols is the subject of this paper.

The anodic reaction of I in methanol at pH 11.3[4] gave a neutral mixture in 68% yield. The reaction was carried out at 11.5–12.5° and at 130–133 ma. The neutral material consisted of three major compounds, II, IIIa, and IV (11%, 42%, and 14% yields, respectively). Compound II, m.p. 131–133°, gave a positive tetranitromethane test and the infrared spectrum showed bands at 1640 and 912 cm.$^{-1}$, indicative of a vinyl-type olefin. This observation was supported by n.m.r., the spectrum showing multiplets centered at τ 5.05 (2 protons) and 4.46 (1 proton), the typical absorption for an olefin of this type (CH_2=CH—). Hydrogenation of II with palladium on charcoal in ethanol–dioxane under a pressure of 24 p.s.i. gave 5α-pregnan-3β-ol (VI). Its infrared spectrum showed the absence of bands at 1640 and 912 cm.$^{-1}$. Compound IIIa, m.p. 242–243°, was identified as 20ξ-methoxy-5α-pregnan-3β-ol. The compound gave a positive Zeisel test and the infrared spectrum showed a broad band at 1093 cm.$^{-1}$ (methoxyl). The n.m.r. spectrum showed a singlet at τ 6.71 (methoxyl) and an asymmetric doublet centered at τ 8.85 (J = 7 c.p.s.), to which was assigned the C-21 methyl absorption coupled to a proton on an adjacent carbon to which is attached oxygen (CH_3–CH–O–). Preliminary infrared and n.m.r. data on the third isolated compound (IV), m.p. 218–220°, indicated a second methoxy compound, possibly the C-20 methoxy epimer of IIIa.[5] The 3β-acetoxy group of I was shown to be hydrolyzed at pH 11.3 (10.5–12°) and hence the C-3 hydroxyl group did not arise from the electrolytic process, *i.e.*, cathodic reduction.

The electrolysis was then performed at other base concentrations in order to study the effect on neutral fraction yields as well as to illustrate that the olefin–methoxy ratio is base independent. Anodic reaction of I at pH 8.6 gave a neutral mixture in 68% yield, equivalent to the experiment conducted at pH 11.3. The mixture consisted of two previously described compounds, II and IIIa (8% and 7% yields, respectively), plus a less polar compound, IIIb, in 40% yield. The infrared spectrum of IIIb showed bands at 1730 (3β-acetoxy) and 1075 cm.$^{-1}$ (methoxyl). The n.m.r. spectrum, that is similar to IIIa with the exception of a band at τ 7.96 (acetate methyl), showed the presence of a singlet at τ 6.70 (methoxyl) and a doublet at τ 8.81 and 8.90 (CH_3CH–O–). The hydrolysis of the 3-acetoxy group was thus greatly decreased at this pH. Acetylation of IIIa gave IIIb, identical with the product obtained directly from the electrolysis (mixture melting point, infrared, and gas chromatography). The olefin–methoxy ratio did not change significantly in comparison to the electrolysis at pH 11.3. The yield of neutral material was greatly reduced to 13% when the reaction was carried out at pH 5.7. Gas and thin layer chromatography showed the presence of at least six compounds in this mixture, including II–IV.



Attention was then directed to the reaction of I in ethanol and 2-propanol. Assuming an attack of solvent on a carbonium ion, an increase in the olefin–alkoxy ratio *via* a decrease in alkoxy formation was expected because of the greater bulk of these alcohols in comparison to methanol. Anodic reaction of I

(1) Paper II concerning electrolytic reactions. For paper I, see J. A. Waters, E. D. Becker, and E. Mosettig, *J. Org. Chem.*, **27**, 4689 (1962).

(2) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *J. Am. Chem. Soc.*, **82**, 2645 (1960).

(3) W. B. Smith and H.-G. Gilde, *ibid.*, **83**, 1355 (1961).

(4) The pH values recorded in this paper are those readings observed on a Beckman pH meter, Model G, immediately after preparing the solutions prior to electrolysis. These readings were taken for comparative purposes and no exact significance can be attributed to the stated values.

(5) A shift of the carbonium ion to the more stable C-17 position and subsequent nucleophilic attack cannot be ruled out.

in ethanol under basic conditions gave a neutral mixture in 81% yield, consisting of two major products, Δ^{20}-5α-pregnen-3β-ol (II) in 30% yield and 20ξ-ethoxy-5α-pregnan-3β-ol (V) in 27% yield. The olefin–alkoxy ratio was increased *ca.* fivefold in this reaction over that in methanol (pH 11.3). The reaction of I in 2-propanol gave a neutral fraction in poor yield (16%), which was a mixture of at least ten compounds. The reaction was not further investigated.

The anodic oxidation of carboxylic acid I appears to proceed through a free-radical intermediate to a carbonium ion from which II (β-elimination) or IIIa, IIIb, and V (attack by solvent) may result. Products of this nature arising from a free-radical reaction are more difficult to interpret.[6] These results are in accord with former observations.[1-3]

The anodic decarboxylation reaction may be a useful approach to biological intermediates, *e.g.*, pregnane derivatives, such as described in this paper.

Experimental[7]

Description of the Electrolysis Apparatus.—The apparatus consisted of two smooth platinum electrodes (sheet), 9 mm. wide and 40 mm. long. The electrodes, placed parallel to each other 3–4 mm. apart, were immersed 25–30 mm. into the magnetically stirred solutions. Glass beakers (30 ml.) were used as electrolysis vessels.

Anodic Reaction of 3β-Acetoxybisnorallocholanic Acid (I) in Methanol at pH 11.3.—To a solution of 505 mg. of 3β-acetoxybisnorallocholanic acid (I) in 30 ml. of absolute methanol was added 133 mg. of metallic sodium. The pH of the resulting solution was 11.3. The solution was electrolyzed at 133 ma. and 7–8 v. for 8 hr. Methanol was added periodically to maintain the original volume. The temperature of the solution was maintained at 11–12.5° by use of an evaporating acetone bath. On completion of the electrolysis, the solvent was removed under reduced pressure and the residue dissolved in chloroform and extracted three times with 5% sodium hydroxide. After washing the chloroform extract two times with water and drying over sodium sulfate, the solvent was removed under reduced pressure. The neutral mixture, 277 mg. (*ca.* 68%) of thick oil, was subjected to preparative thin layer chromatography (silica gel G) developed continuously[8] with dichloromethane–ether (95:5) as solvent for 3.5 hr. Inspection of the plate under short wave ultraviolet light indicated three distinct bands. Elution of each band[9] with acetone gave 31 mg. (11%) of white solid (upper band), 128 mg. (42%) of white solid (middle band), and 43 mg. (14%) of white solid (lower band). These per cents were in good agreement with those obtained from a gas chromatogram of the neutral mixture. Crystallization of the upper band product (31 mg.) from dilute methanol gave 14 mg. of white needles, m.p. 131–133°. The product gave a positive tetranitromethane test. The infrared spectrum showed bands at 3600 (–OH), 1640, and 912 cm.$^{-1}$ (CH_2=CH—). The n.m.r. spectrum showed multiplets centered at τ 5.05 and 4.46. Analysis of the product indicated Δ^{20}-5α-pregnen-3β-ol (II), $[\alpha]^{20}D$ 0 ±2° (*c* 0.53, chloroform).

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.44; H, 11.56.

Crystallization of the product from the middle band (133 mg.) from dilute methanol gave 71 mg. of crystalline product, m.p. 129–229°. Two additional recrystallizations from methanol–ether gave a sharp melting compound, m.p. 242–243° (dried at 100° under high vacuum). The compound gave a positive Zeisel test and the infrared spectrum showed a broad band at 1093 cm.$^{-1}$ (methoxyl). The n.m.r. spectrum showed the following bands: singlet at τ 6.71 (–OCH_3) and doublet centered at 8.85 (J = 7 c.p.s., CH_3–CH(–O–)–). Analysis of the product indicated 20ξ-methoxy-5α-pregnan-3β-ol (IIIa); $[\alpha]^{20}D$ −14.0 ±3° (*c* 0.35, chloroform).

Anal. Calcd. for $C_{22}H_{38}O_2$, C, 78.98; H, 11.45; OCH_3, 9.31. Found: C, 79.23; H, 11.73; OCH_3, 9.62.

Crystallization of the product from the lower band from dilute methanol gave 14 mg. of white crystals, m.p. 200–210°. A second recrystallization raised the melting point to 218–220°, white needles. The infrared spectrum showed a band at 1070 cm.$^{-1}$. The n.m.r. spectrum on a small amount of sample showed absorption similar to that of IIIa. The analytical data supported a $C_{22}H_{38}O_2$ methoxy compound (IV).

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.98; H, 11.45. Found: C, 79.01; H, 11.79.

Hydrolysis of I at pH 11.3.—A solution of 98 mg. of 3β-acetoxybisnorallocholanic acid (I) in 6 ml. of methanol containing 26 mg. of metallic sodium was set at 10.5–12° for 8 hr. Approximately one-half of the solvent was then evaporated under an air stream. The solution was acidified with 5% hydrochloric acid to congo red. The white solid was removed by suction filtration, washed repeatedly with water, and air-dried. Recrystallization from a large amount of ethanol gave 51 mg. of white, crystalline compound, m.p. 273–275°. An additional recrystallization raised the melting point to 277–278°. The analytical data indicated 3β-hydroxybisnorallocholanic acid, $[\alpha]^{20}D$ 0 ± 1.5° (*c* 0.6, ethanol), lit.[10] m.p. 270°.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.59; H, 10.67.

Anodic Reaction of I in Methanol at pH 8.6.—A solution of 505 mg. of I in 30 ml. of absolute methanol containing 69 mg. of sodium methoxide (pH 8.6) was electrolyzed for 8 hr. at 130 ma. and 12 v. Methanol was added periodically to maintain original volume. The temperature of the solution was maintained at 21–23.5°. Work-up of the reaction in the usual manner gave 291 mg. of neutral mixture (*ca.* 68%) as a thick oil. The material was subjected to preparative thin layer chromatography (silica gel G) with dichloromethane–ether (4:1) as solvent. Inspection of the plate under short wave ultraviolet light showed three definite bands. The products of the two lower bands corresponded to compounds II and IIIa by gas and thin layer chromatography. A yield of 24 mg. (8%) of II and 24 mg. (7%) of IIIa was obtained. The product of the uppermost band, 157 mg. of white solid, was further purified to remove a trace impurity using preparative thin layer chromatography (dichloromethane–ether, 95:5). Elution of the major band with acetone gave 128 mg. of white solid. Crystallization of 63 mg. of this product from methanol gave 25 mg. of white flakes, m.p. 108–118°. A second recrystallization gave 11 mg. of pure product, m.p. 122–125°. The infrared spectrum showed bands at 1730 (3β-AcO) and 1075 cm.$^{-1}$ (methoxyl). The n.m.r. spectrum showed the following bands: singlet at τ 7.96 (acetate methyl), singlet at 6.70 (OCH_3), doublet at 8.81 and 8.90 (CH_3–CH(–O–)–). Analytical data indicated 20ξ-methoxy-5α-pregnan-3β-ol acetate (IIIb), $[\alpha]^{20}D$ +12.0 ± 3.0° (*c* 0.33, chloroform).

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.81; H, 10.92.

Anodic Reaction of I in Methanol at pH 5.7.—To 484 mg. of carboxylic acid I in 30 ml. of absolute methanol was added *ca.* 0.6 mg. of metallic sodium. A small amount of heating was necessary to bring about solution. The cooled solution (pH 5.7) was then electrolyzed for 9 hr. at 100–110 ma. and 125 v. at a temperature of 35–38°. Work-up in the usual manner gave a low yield of neutral material, 54 mg. (*ca.* 13%), as a thick oil. Preparative thin layer (silica gel G, dichloromethane–ether, 98:2) gave six products, four of which corresponded to compounds II–IV as shown by gas and thin layer chromatography.

Anodic Reaction of I in Ethanol at pH 10.0.—To 522 mg. of I in 30 ml. of absolute ethanol was added 130 mg. of metallic sodium (pH 10.0). The solution was electrolyzed for 8 hr. at

(6) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 581.

(7) Melting points were taken on a Kofler block and are uncorrected. Analyses and rotations were performed by the Analytical Services Unit, NIAMD, under the direction of Mr. H. G. McCann. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer through the cooperation of Mr. H. K. Miller and Mrs. A. H. Wright. N.m.r. spectra were obtained with a Varian HR-60 spectrophotometer. Deuteriochloroform was used as an internal reference. Gas chromatograms were obtained through the cooperation of Dr. D. F. Johnson on a Chromalab chromatograph, Model 210, using a 4-ft. column (4-mm. i.d.) of 1% SE-30 on Gaschrom P (100–120 mesh) at 215° and 30 p.s.i.

(8) R. D. Bennett and E. Heftmann, *J. Chromatog.*, **12**, 245 (1963). The author thanks Dr. Bennett for advice concerning this technique.

(9) The product eluted from each band was rechecked for homogeneity by regular thin layer chromatography in all cases throughout this paper.

(10) E. Fernholz, *Ann.*, **507**, 128 (1933).

130 ma. and 12–20 v. at a temperature of 14–17°. Work-up of the solution in the usual manner gave 330 mg. of neutral material (*ca.* 81%). The mixture was subjected to preparative thin layer chromatography developed continuously for 2.5 hr., using dichloromethane–ether (98:2) as solvent. Two distinct bands were shown under short wave ultraviolet light. Elution of these bands with acetone gave 96 mg. of II (30%) and 103 mg. of V (27%). These per cents were in good agreement with those obtained from a gas chromatogram of the neutral mixture. Compound II was recrystallized from methanol, m.p. 130–132°, identical with II previously described (mixture melting point, infrared, and gas chromatography). The second product (V), was recrystallized from acetone to give a white crystalline compound, m.p. 127–130°. A second recrystallization gave raised m.p. 137.5–139°; *trans* crystallization, m.p. 160–164°. The infrared spectrum showed a broad band at 1075 cm.$^{-1}$ (ethoxyl). Analytical data indicated 20ξ-ethoxy-5α-pregnan-3β-ol, $[\alpha]^{20}D$ 11.0 ± 3.0° (c 0.6, chloroform).

Anal. Calcd. for $C_{23}H_{40}O_2$: C, 79.25; H, 11.57. Found: C, 79.17; H, 11.81.

Attempted Anodic Reaction of I in 2-propanol.—To a solution of 457 mg. of I in 50 ml. of 2-propanol was added 28 mg. of sodium (pH of cloudy solution 8.4). The solution was electrolyzed for 10 hr. at 30–35 ma. and 135–150 v. at 18.5–23°. Work-up in the usual manner gave 60 mg. of neutral material (*ca.* 16%). A thin layer chromatogram (dichloromethane–ether, 4:1) showed a mixture of at least ten compounds. The reaction was not further investigated.

20ξ-Methoxy-5α-pregnan-3β-ol Acetate (IIIb).—A solution of 70 mg. of crude 20ξ-methoxy-5α-pregnan-3β-ol (IIIa) in 4 ml. of pyridine containing 0.5 ml. of acetic anhydride was refluxed for 2 hr. The cooled solution was poured into ice–water (10 ml.) and the mixture extracted with 3–5 ml. portions of chloroform. Evaporation of the solvent gave a brown crystalline solid. Recrystallization from methanol gave 21 mg. of white flakes, m.p. 111–118°. Two additional recrystallizations raised the melting point to 123–126°. A mixture melting point with IIIb obtained from the anodic reaction (methanol, pH 8.6) was 122–125°. The gas chromatographic retention times and infrared spectra of both samples were identical.

5α-Pregnan-3β-ol (IV).—To a solution of 27 mg. of Δ^{20}-5α-pregnen-3β-ol (II) in 6 ml. of ethanol–dioxane (1:1) was added 96 mg. of palladium on charcoal (10%). The mixture was hydrogenated for 6 hr. at room temperature and under a pressure of 24 p.s.i., using the Parr apparatus. Removal of the catalyst by filtration and evaporation of the solvent gave a gum. The product was subjected to preparative thin layer chromatography developed continuously for 2 hr. (silica gel G; dichloromethane–ether, 95:5). Elution of the major band with acetone gave 11 mg. of white solid, m.p. 118–128°. Recrystallization from methanol gave 2.7 mg. of 5α-pregnan-3β-ol (VI) as shiny white flakes, m.p. 138–139.5°, lit.[11] m.p. 138–138.4°. The infrared spectrum showed the absence of bands at 1640 and 912 cm.$^{-1}$.

Acknowledgment.—The author wishes to thank Mr. R. B. Bradley of this Institute for the n.m.r. spectral determinations.

(11) E. P. Oliveto, L. Weber, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 4482 (1954).

Kolbe Electrolyses of 3-Phenyl- and 3,3-Diphenylpropanoic Acids

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The question of phenyl 1,2-migration of free radicals during Kolbe electrolyses has been examined by electrolyzing 3,3-diphenylpropanoic acid (1) in acetic acid containing acetate ion and (2) in methanol, and (3) by electrolyzing 3-phenylpropanoic acid in acetic acid containing acetate ion. The electrolysis products from 1 consisted of 1,1-diphenylpropane (IV), 3-phenyl-3,4-dihydrocoumarin (V), and 1,2-diphenylethyl acetate (VIII), along with smaller quantities of phenyl cinnamate (VI), 2-*O*-acetyl-1,1-diphenylethylene glycol (IX), and phenyl 3-acetoxy-3-phenylpropanoate (VII). The identified electrolysis products from 2 were 1,1,4,4-tetraphenylbutane (XIII) and methyl 1,2-diphenylethyl ether (XVIII). VIII and XVIII represent products of phenyl 1,2-migration. The electrolysis products from 3 consisted of *n*-propylbenzene and 2-phenylethyl acetate. Arguments are presented supporting the hypothesis that the unrearranged hydrocarbon products (IV and XIII) arose by coupling of free radicals prior to rearrangement and that the rearranged acetate and ether products (VIII and XVIII) resulted from anodic oxidation of unrearranged 2,2-diphenylethyl radicals to 2,2-diphenylethyl carbonium ions, followed by rearrangement of the latter to more stable benzylic 1,2-diphenylethyl carbonium ions which ultimately solvolyzed to the observed oxygenated products.

Recently, with the intention of developing a system in which the possibility of bridged radical intermediates could be critically evaluated, we have succeeded[2] in generating the 1,2,2-triphenylethyl-1-C^{14} radical (I)

$Ph_2CH—\dot{C}^{14}HPh$ (I) $\quad Ph_2\dot{C}HCH_2Ph$ (II) $\quad Ph\dot{C}HCH_2Ph$ (III)

by the decarbonylation of 2,3,3-triphenylpropionaldehyde-2-C^{14}. The label redistribution in the monomeric decarbonylation product, 1,1,2-triphenylethane, indicated that radical I had undergone phenyl 1,2-rearrangement to the extent of 5–14% during its transitory existence. In considering methods by which radical intermediates might be produced to broaden the above studies, the Kolbe electrolysis reaction appeared potentially applicable. While phenyl 1,2-shifts are observed frequently and are well-documented for radical intermediates produced by a variety of other techniques,[2] the situation regarding such rearrangements during Kolbe electrolyses is less straightforward. Urry[3] has reported the formation of rearranged products (isobutylbenzene, 2-methyl-3-phenyl-1-propene, and 1-phenyl-2-methyl-1-propene) along with unrearranged products (*t*-butylbenzene, ethyl β-phenylisovalerate, 2,2-dimethyl-2,2-diphenylhexane, and neophyl β-phenylisovalerate) during the Kolbe electrolysis (*ca.* 2 ma./cm.^{2}) of β-phenylisovaleric acid in ethanol. More recently, on the other hand, Breederveld and Kooyman[4] noted specifically the absence of rearranged products on Kolbe electrolysis of β-phenylisovaleric acid under slightly different conditions (methanol and methanol–acetic acid solvents, *ca.* 150 ma./cm.^{2}). Accordingly, it appeared initially pertinent to ascertain if Kolbe electrolysis would lead

(1) The authors are grateful to the National Science Foundation for a grant (G9479) which supported part of this study.

(2) W. A. Bonner and F. D. Mango, *J. Org. Chem.*, **29**, 29 (1964).

(3) W. H. Urry, Abstracts of Papers, 12th National Organic Chemistry Symposium of the American Chemical Society, Denver, Colo., 1951, p. 36.

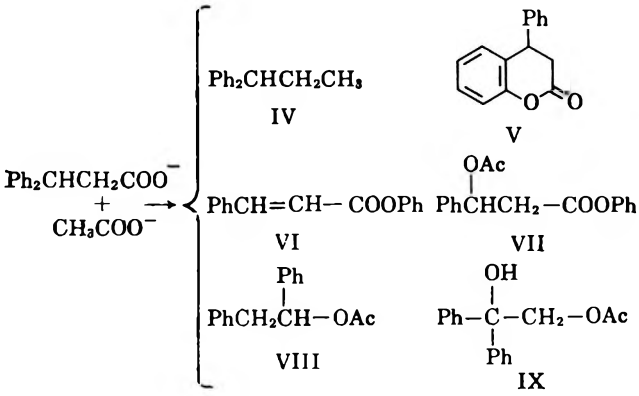
(4) H. Breederveld and E. C. Kooyman, *Rec. trav. chim.*, **76**, 297 (1957).

to phenyl 1,2-rearrangement in radical systems somewhat analogous to I. We, therefore, undertook to study the electrolysis of 3,3-diphenylpropanoic acid, rearrangement of whose initial 2,2-diphenylethyl primary radical (II) into the more stable secondary benzyl radical (III) might be readily detected by ordinary (*i.e.*, nonlabeling) techniques.

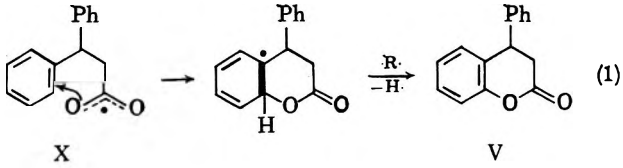
Sodium 3,3-diphenylpropanoate was electrolyzed in glacial acetic acid solution containing sodium acetate (whose concomitant electrolysis might provide methyl radicals[4] to couple with II or III), and the crude product was chromatographed on acid-washed alumina. Seven fractions resulted, which afforded the six discrete products summarized in Chart I.

CHART I

PRODUCTS FROM ELECTROLYSIS OF $Ph_2CHCH_2COO^-$ AND CH_3COO^- IN ACETIC ACID

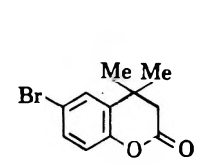


The only hydrocarbon product recovered, 1,1-diphenylpropane (IV), could be accounted for by the coupling at or near the electrode surface of unrearranged 2,2-diphenylethyl radicals (II) with methyl radicals. No rearranged hydrocarbon [*e.g.*, (a) the dimer of III or (b) 1,2-diphenylpropane, the coupling product of III with $CH_3\cdot$] was observed. The absence of such products indicates either that radical II does not here rearrange to III or, if it does, that III follows a path other than coupling. The formation of 4-phenyl-3,4-dihydrocoumarin (V) presumably results from the homolytic cyclization of the initially produced propionoxy radical (X, eq. 1) prior to its de-

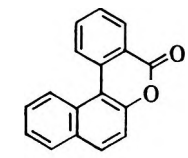


(1)

carboxylation. Analogous radical cyclizations have been reported in the Hunsdiecker decarboxylations of silver β-phenylisovalerate to produce the lactone (XI)[5a] and of silver 3,3-diphenylpropanoate to produce the lactone (V),[5b] as well as in the thermal decomposition of *t*-butyl *o*-(1-naphthyl)perbenzoate to produce the lactone (XII).[6] The presence of unrearranged 2-*O*-acetyl-1,1-diphenylethylene glycol (IX) in the crude electrolysis product seemed possibly due to the intermediate formation of 1,1-diphenylethylene,



XI



XII

since it has been reported[7] that ethylene results in good yield during the electrolysis of sodium propionate. The possibility that such a mechanism was responsible for formation of IX was strengthened by our observation that the electrolysis of sodium acetate in acetic acid in the presence of 1,1-diphenylethylene afforded the monoacetate (IX) in good yield.[8] The remaining oxygenated substances (VI, VII, and VIII) in Chart I represent rearrangement products. The phenyl cinnamate (VI) and phenyl 3-acetoxy-3-phenylpropanoate (VII) products clearly have arisen from a phenyl 1,4-migration, though it is not clear at present if this migration involved radical or carbonium ion intermediates (see below). Similar phenyl 1,4-migrations have been observed during the Hunsdiecker decarboxylation of silver 3,3,3-triphenylpropanoate,[9,10] as well as during the Kolbe electrolysis of the same acid.[4] The 1,2-diphenylethyl acetate (VIII) derivative in Chart I represents the only observed product of phenyl 1,2-migration. It was unaccompanied by detectible amounts of unrearranged 2,2-diphenylethyl acetate.

Three paths, as summarized in eq. 2, 3, and 4, appeared possible *a priori* for the formation of the rearranged acetate (VIII). The Hofer–Moest oxidations

$$\underset{\text{II}}{Ph_2CHCH_2\cdot} \xrightarrow{Ph\sim} \underset{\text{III}}{PhCHCH_2Ph} \xrightarrow{AcO\cdot} \underset{\text{VIII}}{\overset{OAc}{\overset{|}{PhCHCH_2Ph}}} \quad (2)$$

$$\text{II} \xrightarrow{Ph\sim} \text{III} \xrightarrow[-e^-]{\text{anode}} \overset{+}{PhCHCH_3Ph} \xrightarrow{AcO^-} \text{VIII} \quad (3)$$

$$\text{II} \xrightarrow[-e^-]{\text{anode}} Ph_2CHCH_2^+ \xrightarrow{Ph\sim} \overset{+}{PhCHCH_2Ph} \xrightarrow{AcO^-} \text{VIII} \quad (4)$$

postulated in eq. 3 and 4 are analogous to those described by Corey,[11] who found that electrolytically generated aliphatic radicals readily undergo further oxidation to carbonium ions, especially when the latter can be resonance-stabilized. Benzylic radicals apparently oxidize with even greater ease, since the electrolyses of mono-, di-, and triphenylacetic acids afford progressively decreasing amounts of coupling products and increasing amounts of solvolysis products.[12,13] Similarly, our present attempts to electrolyze the sodium salt of 2,3,3-triphenylpropanoic acid in methanol yielded no coupling product, but only methyl 1,2,2-triphenylethyl ether in 53% yield.

It would appear that the coupling mechanism (eq. 2) is incapable of explaining the formation of the rear-

(5) (a) C. E. Berr, Dissertation, University of California at Los Angeles, 1952; (b) U. K. Pandit and I. P. Dirk, *Tetrahedron Letters*, **14**, 891 (1963).

(6) D. F. DeTar and C. C. Chu, *J. Am. Chem. Soc.*, **82**, 4969 (1960).

(7) C. L. Wilson and W. J. Lippincott, *ibid.*, **78**, 4290 (1956).

(8) This novel electrolytic hydroxylation of alkenes has been explored in greater detail and will be described fully in a forthcoming communication.

(9) J. W. Wilt and D. Oathoudt, *J. Org. Chem.*, **21**, 1550 (1956); **23**, 218 (1958).

(10) J. W. Wilt and J. L. Finnerty, *ibid.*, **26**, 2173 (1961).

(11) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *J. Am. Chem. Soc.*, **82**, 2645 (1960).

(12) R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, *J. Chem. Soc.*, 3624 (1952).

(13) B. Wladislaw and A. M. J. Ayres, *J. Org. Chem.*, **27**, 281 (1962).

ranged acetate (VIII). Should mechanism 2 have intervened, one would certainly anticipate recovering as well unrearranged 2,2-diphenylethyl acetate—perhaps even as the predominant isomer—since the less stable radical II should be more reactive than the more stable III in such a process. Unrearranged acetate, however, was not detected. Furthermore, Swarc[14] has estimated the lifetime of the acetoxy radical to be only 10^{-9}–10^{-10} sec., and has suggested that such radicals can react only in their original "cage" and not in the surrounding solution. To confirm these conclusions regarding mechanism 2, 3,3-diphenylpropanoic acid was electrolyzed in methanol solvent rather than acetic acid. Should mechanism 2 prevail, one would expect in methanol the coupling products 1,1,4,4-tetraphenylbutane (XIII, from II), 1,2,3,4-tetraphenylbutane (XIV, from III), and 1,1,3,4-tetraphenylbutane (XV, from II + III), as well as the esters XVI and XVII (from $Ph_2CHCH_2COO\cdot$ with II and III). If the oxidation–solvolysis paths 3 or 4 prevailed, however, the anticipated solvolysis products should be methyl 1,2-diphenylethyl ether (XVIII), with possibly a small amount of methyl 2,2-diphenylethyl ether (XIX, if path 4). The principal products from the above electrolysis in methanol, on chromatographic separation, proved to be the unrearranged coupling product (XIII) and the rearranged ether (XVIII). Small amounts of the lactone (V) and the 1,4-migration product, phenyl 3-methoxy-3-phenylpropanoate (XX), were also obtained. None of the unrearranged ether (XIX) nor the other coupling products (XIV–XVII) could be recovered from the crude electrolysis product. These results appear to confirm the above conclusion that the rearranged acetate (VIII) resulting from phenyl 1,2-migration is formed by solvolysis of a cationic intermediate (eq. 3 or 4) and not by the radical coupling path (eq. 2).

$Ph_2CHCH_2CH_2CHPh_2$ (XIII)

$PhCH_2\underset{Ph}{\underset{|}{C}}H—\underset{Ph}{\underset{|}{C}}HCH_2Ph$ (XIV)

$Ph_2CHCH_2\underset{Ph}{\underset{|}{C}}HCH_2Ph$ (XV)

$Ph_2CHCH_2COOCH_2CHPh_2$ (XVI)

$Ph_2CHCH_2COO\underset{Ph}{\underset{|}{C}}HCH_2Ph$ (XVII)

$PhCH_2\underset{Ph}{\underset{|}{C}}H—OCH_3$ (XVIII)

$Ph_2CHCH_2—OCH_3$ (XIX)

$PhC\underset{OCH_3}{\underset{|}{H}}CH_2COOPh$ (XX)

Solvolysis path 3 for the formation of rearranged acetate (VIII) involves phenyl 1,2-rearrangement of the initial 2,2-diphenylethyl radical (II), prior to anodic oxidation of the rearranged radical (III) to the rearranged 1,2-triphenylethyl carbonium ion. Solvolysis path 4 entails anodic oxidation of the initial radical II to the unrearranged 2,2-triphenylethyl carbonium ion, followed by a phenyl 1,2-shift to the rearranged carbonium ion. One might anticipate a preference for path 3, since this involves not only the rearrangement of an unstable primary aliphatic radical (II) to a more stable secondary benzyl radical (III), but also the relief of perhaps appreciable B-strain at C-2 in II. Furthermore, the benzylic radical III should presumably undergo anodic oxidation more readily than the primary radical II.[12,13] Against path 3, however, was our failure to detect either the dimer of III from electrolysis in methanol, or the $CH_3\cdot$ + III coupling product, 1,2-diphenylpropane, from electrolysis in acetic acid. In favor of path 4 was our exclusive isolation of XIII, the dimeric coupling product of II, from electrolysis in methanol, and of the unrearranged $CH_3\cdot$ + II coupling product (IV) from electrolysis in acetic acid.

While the preponderence of evidence thus appeared to favor the solvolysis mechanism 4, it seemed desirable to establish experimentally the fact that anodic oxidation and subsequent solvolysis could in fact occur on a primary alkyl radical in the present system. To this end sodium 3-phenylpropanoate was electrolyzed with sodium acetate in acetic acid. Here, after initial decarboxylation, the primary 2-phenylethyl radical cannot rearrange to a more stable secondary benzylic radical (*i.e.*, no hydrogen 1,2-shift should occur[15]), no coupling with the acetoxy radical should take place (see above), and any acetate product must arise by anodic oxidation of the 2-phenylethyl radical to the 2-phenylethyl carbonium ion, followed by solvolysis. Chromatographic separation of the crude electrolysis product from sodium 3-phenylpropanoate afforded the unrearranged $CH_3\cdot$ coupling product, *n*-propylbenzene, and the solvolysis product, 2-phenylethyl acetate. The isolation of the latter acetate appears to confirm the supposition that the anodic oxidation of the primary radical in path 4 can occur, and to render this path as the more probable mechanism in the present case. We plan to test this conclusion experimentally by electrolysis studies with C^{14}-labeled analogs. The finding of Muhs[16] that, in the Kolbe electrolysis of aliphatic acids, the rearranged products appear exclusively monomeric while the dimeric products prove to be unrearranged, supports our suggestion that rearranged products arise *via* cationic intermediates which cannot undergo self-coupling.

To test for possible anchimeric assistance by the β-phenyl group in the above production of the 2-phenylethyl acetate solvolysis product, sodium propionate itself was electrolyzed under similar conditions. β-Phenyl participation has been proposed as occurring during several solvolysis reactions of 2-phenylethyl derivatives.[17] The electrolysis product was examined by vapor–liquid partition chromatography and found to be primarily ethyl acetate. The isolation of ethyl acetate indicates that phenyl participation need not intervene in the above anodic oxidations of 2-phenylethyl or 2,2-diphenylethyl radicals and, specifically, that bridged phenonium ions (eq. 5) are not prerequisites in these instances.

$$PhCHCH_2\cdot \xrightarrow{-e} \underset{\oplus}{CH_2—CH_2} \xrightarrow{OAc^-} PhCH_2CH_2OAc \quad (5)$$

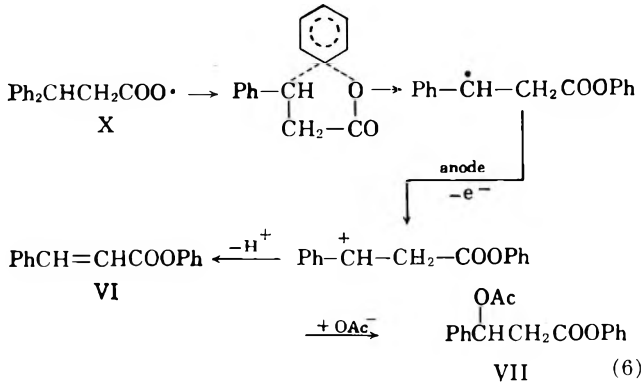
(14) L. Herk, M. Feld, and M. Swarc, *J. Am. Chem. Soc.*, **83**, 2998 (1961).

(15) D. Y. Curtin and V. C. Kauer, *J. Org. Chem.*, **25**, 880 (1960); L. H. Slaugh, *J. Am. Chem. Soc.*, **81**, 2262 (1959).

(16) M. A. Muhs, *Dissertation Abstr.*, **14**, 765 (1954).

(17) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 575 ff.

One possible rationalization for the formation of the phenyl 1,4-migration products (VI and VII) in the 3,3-diphenylpropanoate system (Chart I) is shown in eq. 6. We have no direct experimental evidence, however, bearing on the validity of this suggestion.



(6)

Experimental

3,3-Diphenylpropanoic acid was prepared by the aluminum chloride-catalyzed alkylation of benzene with cinnamic acid according to the procedure of Homes and Hill.[18] The purified product had m.p. 154–155°, in agreement with the reported value.[18]

Electrolysis of 3,3-Diphenylpropanoic Acid in Acetic Acid.—The electrode unit consisted of two platinum foil electrodes (1.25 × 1.25 cm.) spaced approximately 2 mm. apart and joined to wires sealed into a tapered glass head (⅋ 29/42, female) equipped with a gas exit tube. The cell compartment (30 ml.), fitted to receive the electrode unit, was equipped with a water jacket for thermostating. The electrolysis apparatus was energized by a 12-v. Heathkit battery eliminator.

The solution of 3,3-diphenylpropanoic acid (5.37 g.) and sodium acetate (1.59 g.) in acetic acid (30 ml.) was electrolyzed (0.2-amp. current) in the above cell for 38 hr. (12 f./mole), with continual magnetic stirring and external cooling (cell contents, 32–38°). The majority of solvent was then removed by evaporation at reduced pressure, and the residue was dissolved in ether. The ether solution was extracted twice with 5% aqueous ammonium hydroxide (discard), then was washed with water, dried (magnesium sulfate), filtered, and evaporated, affording 3.85 g. of thick, amber oil. A portion (1.98 g.) of the crude product was chromatographed on silicic acid using hexane–benzene mixtures gradually enriched in benzene, then benzene and finally ether as eluent, collecting 50-ml. portions of eluate. Residues from the evaporation of each portion were examined by infrared spectroscopy and thin layer chromatography (t.l.c.), and similar residues were combined yielding a total of seven fractions (fractions 1–7, in order of appearance) which totaled 1.73 g. (87.4%).

Fraction 1 (66 mg.) was rechromatographed [silica–(hexane–ether), 100:1] to give 63 mg. of clear oil, homogeneous by t.l.c. and having an R_f value and infrared spectrum identical with those of authentic 1,1-diphenylpropane (IV), prepared independently. A spot during t.l.c. corresponding to 1,2-diphenylpropane was absent, as were infrared bands at 1005 and 2849 cm.$^{-1}$ which proved characteristic of the latter hydrocarbon. Fraction 2 (50 mg.) solidified and was recrystallized from ethanol, m.p. 73–75°. It showed t.l.c. behavior identical with that of phenyl cinnamate (VI, m.p. 74–76°), showed no mixture melting point depression (74–76°) with this ester, and displayed an infrared spectrum superimposable on that of an authentic sample. Fraction 3 (oil, 107 mg.) had an R_f value by t.l.c. identical with that of authentic 1,2-diphenylethyl acetate (VIII) and different from that of 2,2-diphenylethyl acetate. Its infrared spectrum was identical with the spectrum of 1,2-diphenylethyl acetate, with the exception of three very weak bands (1198, 1169, 738 cm.$^{-1}$) not present in the spectrum of the authentic sample. Its retention time in gas chromatography (180°) on a silicone rubber column was identical with the retention time of authentic 1,2-diphenylethyl acetate. The identity of fraction 3 was confirmed by treatment of a portion (56 mg.) with an ether solution containing an excess of lithium aluminum hydride. The mixture was heated under reflux for 1 hr., then processed as usual to produce 40 mg. of oil which solidified. Recrystallization from hexane–benzene gave a sample of 1,2-diphenylethano., m.p. 63–66°, which showed no mixture melting point depression (64–66°) with an authentic sample and gave an infrared spectrum identical with that of the authentic sample. Fraction 4 (oil, 168 mg.) showed two spots by t.l.c. The lower R_f spot was identical in position and hue to one of authentic 4-phenyl-3,4-dihydrocoumarin (V), while the faster travelling spot corresponded to 1,2-diphenylethyl acetate (VIII). A portion of fraction 4 was gas chromatographed (200°) on a silicone rubber column, and the presence of 4-phenyl-3,4-dihydrocoumarin (55%) was confirmed by peak enhancement with an authentic sample. Fraction 5 (solid, 253 mg.) was recrystallized from ethanol, m.p. 81.5–83.5°. It showed similar t.l.c. behavior, an identical infrared spectrum, and no mixture melting point depression (81.5–83.5°) with authentic 4-phenyl-3,4-dihydrocoumarin (m.p. 83–84°). Fraction 6 (oil, 471 mg.) displayed a strong carbonyl stretching frequency at 1750 cm.$^{-1}$ as well as ester C—O stretching bands[19] at 1140, 1163, 1196, and 1231 cm.$^{-1}$. The n.m.r. spectrum (tetramethylsilane internal standard taken as zero, deuteriochloroform, Varian A60 n.m.r. spectrometer) of a distilled portion of fraction 6 was consistent with the structure, phenyl 3-acetoxy-3-phenylpropanoate (VII). The benzylic methynyl proton, coupled to the two nonequivalent methylene protons (6.0 and 8.5 c.p.s.), appeared as a quartet centered at 6.3 p.p.m. The spectrum displayed another quartet centered at 3.08 and a sharp acetate methyl band at 2.01 p.p.m. Several bands appeared in the aromatic region of the spectrum between 6.8 and 7.5 p.p.m. The integrated band intensities from low to high field were in the ratio 10:1:2:3. Fraction 6 (169 mg.) was purified by rechromatographing on silicic acid (20 g.) using ether–hexane (1:10) as eluent. The first 100 ml. of eluate was discarded and the next 25 ml. was evaporated to yield 90 mg. of clear oil, homogeneous by t.l.c.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.98; H, 5.81.

Confirmation of the identity of fraction 6 as phenyl 3-acetoxy-3-phenylpropanoate (VII) was obtained by pyrolysis of a 90 mg. sample for 5 min. at 400° (Woods metal bath). The crude product, a dark oil, was chromatographed on silicic acid (benzene eluent) to yield an amber oil which solidified. Recrystallization from ethanol gave a sample of solid, m.p. 70.5–76°, which was shown by its mixture melting point (73.5–76°) and the identity of its t.l.c. behavior and infrared spectrum with those of an authentic sample, to consist of phenyl cinnamate (VI) (m.p. 76–78°). Fraction 7 showed the presence of four components by t.l.c., and its infrared spectrum showed the presence of both ester and hydroxylic compounds. A portion (115 mg.) of the crude fraction was dissolved in ethanol (6 ml.) and treated with water (4 ml.) containing potassium hydroxide (1.7 g.). The mixture was heated under reflux for 5 hr. and allowed to stand at 25° for 4 days, then was evaporated to about half its volume at reduced pressure. The aqueous residue (A) was extracted with ether, and the extracts were washed with water, dried, and stripped of solvent to give 58 mg. of viscous, amber oil which solidified. This was chromatographed on silicic acid (5 g.) using benzene, gradually enriched with ether, as eluent. Evaporation of the first 250 ml. of eluent afforded 12 mg. of pale oil which crystallized. The solid was treated with a few drops of benzene and the supernatant solution was separated and treated with a little hexane, affording white needles, m.p. 119–120.5°. The infrared spectrum of these was identical with that of authentic 1,1-diphenylethylene glycol (m.p. 120–122°), and a mixture melting point gave no depression. The aqueous alkaline residue (A) above was acidified and extracted with ether, yielding ultimately 73 mg. of dark, acidic oil from which no crystalline material could be recovered chromatographically. Another portion (227 mg.) of fraction 7 was chromatographed on silicic acid (25 g.) using benzene as eluent. Evaporation of the first 150 ml. yielded 196 mg. of thick oil which proved to contain four components by t.l.c. Its infrared spectrum showed O—H, C=O, and C—O stretching frequencies. One of the spots by t.l.c. corresponded both in position and color under ultraviolet illumination to the spot corresponding to authentic 2-*O*-acetyl-1,1-diphenylethylene glycol (IX).

(18) R. B. Homes and A. J. Hill (to American Cynamid Co.), U. S. Patent 2,423,025 (June 24, 1947).

(19) A. D. Cross, "Introduction to Practical Infrared Spectroscopy," Butterworths Scientific Publications, London, 1960, p. 64.

The authentic samples used for t.l.c., melting point, and infrared comparisons with the products from the previous electrolysis were prepared in the following ways.

1,2-Diphenylethyl Acetate (VIII).—This compound (VIII) was prepared by acetylation of authentic 1,2-diphenylethanol (4 g.) with acetic anhydride (3 ml.) in refluxing acetic acid (40 ml.) during 4 hr. Solvent evaporation, followed by chromatographic purification (silicic acid) of the residue afforded the pure oily ester, which was t.l.c. homogeneous and had infrared stretching bands for C=O and C—O at 1740 and 1230 cm.$^{-1}$, respectively.[19] Its reduction with lithium aluminum hydride regenerated 1,2-diphenylethanol. **2,2-Diphenylethyl acetate** was prepared by lithium aluminum hydride reduction of 2,2-diphenylacetic acid, followed by acetylation, as described above, of the resulting 2,2-diphenylethanol. The crude, solid acetate was recrystallized from ethanol to give white crystals, m.p. 55.5–57°, C=O infrared band at 1725 cm.$^{-1}$ and C—O band at 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.78; H, 6.64.

1,1-Diphenylpropane (IV) was prepared by the reduction of 3,3-diphenylpropanoic acid with excess lithium aluminum hydride in ether. The crude, oily 3,3-diphenyl-1-propanol product, showing no carbonyl absorption in the infrared, was converted to its tosylate by the procedure of Cram.[20] The latter in turn was reduced with lithium aluminum hydride in ether solution, affording a clear, oily product. This was purified by chromatographing on neutral alumina (grade II), using hexane as eluent. The purified oil was homogeneous by t.l.c. and showed an n.m.r. spectrum consistent with that of 1,1-diphenylpropane. The aromatic protons appeared at 7.1 p.p.m. The benzylic methynyl proton, split by the two adjacent methylene protons (8.5 c.p.s.), appeared as a triplet centered at 3.7 p.p.m. The three methyl protons, also coupled to the two methylene protons (7.5 c.p.s.), showed as a triplet centered at 0.9 p.p.m. The two methylene protons, coupled to both the adjacent methynyl and three methyl protons, appeared as a quintuplet centered at 2.1 p.p.m. The material had b.p. 281°, in agreement with the recorded boiling point (278.5–280.5°)[21] for 1,1-diphenylpropane. **1,2-Diphenylpropane** was prepared by the dehydroxylation of 1,2-diphenyl-1-propanol[22] with Raney nickel[23] in refluxing ethanol. The crude product, whose t.l.c. behavior revealed the presence of some unchanged starting material, was purified by chromatographing twice on neutral alumina. The n.m.r. spectrum of the t.l.c. homogeneous oily product was consistent with 1,2-diphenylpropane. The three methyl protons, coupled to the adjacent methynyl proton (5.5 c.p.s.), appeared as a doublet centered at 1.1 p.p.m. A multiplet, centered at 2.7 p.p.m., represented the benzylic methylene and methynyl protons. The aromatic protons appeared around 7.5 p.p.m. The oil had b.p. 275°, in agreement with the reported value[21] of 280–282°.

4-Phenyl-3,4-dihydrocoumarin (V), m.p. 83–84°, was prepared from phenol and cinnamic acid after the procedure of Simpson and Stephen.[24] **1,1-Diphenylethylene glycol** was prepared by the permanganate hydroxylation of 1,1-diphenylethylene after the method of Clark and Owen,[25] the purified sample having m.p. 120–122°.[26] A portion of this glycol was converted into **2-*O*-acetyl-1,1-diphenylethylene glycol (IX)** by treatment with excess acetic anhydride in pyridine (1:1). The crude solid product crystallized from hexane–benzene as white needles, m.p. 93–93.5°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.97; H, 6.32.

Electrolysis of Sodium 3,3-Diphenylpropanoate in Methanol.—A solution of 3,3-diphenylpropanoic acid (2.67 g.) in absolute methanol (25 ml.) containing sodium (27 mg.) was electrolyzed in the manner described above. It was not possible to maintain a constant current since a white precipitate, which obstructed the current flow, formed at the anode. This difficulty was largely overcome by reversing the electrode polarity every 5 min. The electrolysis was continued for a period of 20 hr., whereupon the mixture was processed as before to yield 1.56 g. of crude sirup. This was chromatographed on 200 g. of silicic acid, using benzene–hexane mixtures gradually enriched in benzene, and finally ether as eluents. Residues from eluate evaporation, combined as before, afforded 5 fractions totalling 97.3% of the charge. These are described below in order of their appearance in the column eluates. Fraction 1 (13%) solidified and was recrystallized from hexane as white needles, m.p. 119–122°. The infrared and n.m.r. spectra of the product were consistent with 1,1,4,4-tetraphenylbutane (XIII), whose reported[27] melting point is 122°. The aromatic protons appeared as a multiplet centered at 7.2, the methynyl protons as a multiplet around 4.1, and the methylene protons as a triplet (4.0 c.p.s.) centered around 2.02 p.p.m. The integrated band intensities for each proton type, respectively, were 10:1:2. Fraction 2 (4.5%) was an oil whose small quantity precluded further purification and characterization. Its t.l.c. behavior suggested the presence of one major component along with one or more minor ones. Fraction 3 (1.1%) crystallized and was recrystallized from hexane–benzene to provide a few milligrams of white solid, m.p. 137–139°. Its infrared spectrum was quite similar to that of 1,1,4,4-tetraphenylbutane, showing no absorption bands attributable to functional groups. The reported melting point for 1,1,3,3-tetraphenylpropane is 139°, but sufficient material was not available for further characterization. Fraction 4 (12.7%) proved to be a clear oil which was homogeneous on t.l.c. Its infrared spectrum and t.l.c. R_f value were identical with those of authentic methyl 1,2-diphenylethyl ether (XVIII) described below and distinctly different from those of authentic methyl 2,2-diphenylethyl ether. Fraction 5 (68.8%) was a crude oil whose t.l.c. behavior suggested the presence of at least four components. One of the t.l.c. spots was identical in position and hue with that of 4-phenyl-3,4-dihydrocoumarin (V). Further attempts at column chromatographic separation of fraction 5 led to no further identifiable products.

Methyl 1,2-Diphenylethyl Ether (XVIII).—1,2-Diphenylethanol (1 g.) was methylated by dissolving in methyl iodide (25 ml.) and stirring in the presence of silver oxide (10 g.), Drierite (10 g.) and glass beads[28] for a period of 30 hr. The crude product was a thick oil (1 g.), which was chromatographed on silicic acid (100 g.) using benzene as eluent. Evaporation of the first 100 ml. of eluate left a pale oil, which was rechromatographed in the same way. Its infrared spectrum showed no OH absorption, and its n.m.r. spectrum was consistent with the structure of the desired ether. The aromatic protons appeared from 6.9–7.3 p.p.m. The benzylic methynyl proton, coupled to two nonequivalent methylene protons (7.0 and 7.5 c.p.s.) revealed a quartet centered at 4.2 p.p.m. A sharp peak at 3.09 p.p.m. was superimposed on a sextet centered at 2.9 p.p.m. The integrated band intensities from low to high field were 10:1:5.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.94; H, 7.56.

Methyl 2,2-diphenylethyl ether, an oil, was prepared from 2,2-diphenylethanol in the manner described before, then purified twice by similar column chromatography. The n.m.r. spectrum showed a quartet around 4.19 p.p.m., corresponding to the methynyl proton coupled to two nonequivalent methylene protons (6.0 and 8.0 c.p.s.). The methylene protons appeared as a triplet centered at 3.75, and the methyl protons as a sharp singlet at 3.12 p.p.m. The integrated band intensities were 10:1:2:3.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.94; H, 7.56.

Electrolysis of 3-Phenylpropanoic Acid in Acetic Acid.—A solution of 3-phenylpropanoic acid (2.89 g.) and sodium acetate (1.43 g.) in acetic acid (25 ml.) was electrolyzed as above for 21 hr. (0.2 amp., 8 f./mole). The mixture was treated with excess ammonium hydroxide and the basic solution was extracted thoroughly with ether. The extracts were washed, dried, and evaporated to yield 534 mg. of neutral, amber oil. This was chromatographed on 50 g. of silicic acid, with ether as eluent, affording 411 mg. of clear oil, which was examined by gas chromatography on diethylene glycol succinate (150°) and silicone rubber (120°) columns. Authentic samples of *n*-propylbenzene, 2-phenylethyl acetate, and 3,4-dihydrocoumarin were used for identification purposes. The observed retention times showed that *n*-propylbenzene and 2-phenylethyl acetate were present but that 3,4-dihydrocoumarin was absent. In a duplication of

(20) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 2863 (1949).

(21) P. Sabatier and M. Murat, *Compt. rend.* **155**, 385 (1912); *Ann. chim.* (Paris), [9] **4**, 287 (1915).

(22) M. Tiffeneau, *ibid.*, [8] **10**, 192, 353 (1907); M. F. Kayser, *ibid.*, [11] **6**, 145 (1936).

(23) J. A. Zderic, W. A. Bonner, and T. W. Greenlee, *J. Am. Chem. Soc.*, **79**, 1696 (1957).

(24) D. Simpson and J. Stephen, *J. Chem. Soc.*, 1382 (1956).

(25) M. F. Clark and L. N. Owen, *ibid.*, 315 (1949).

(26) P. Weidenkoff, *Ber.*, **39**, 2063 (1906).

(27) K. Ziegler, H. Colonius, and O. Schäfer, *Ann.*, **473**, 56 (1929).

(28) W. A. Bonner, *J. Am. Chem. Soc.*, **73**, 3126 (1951).

the above electrolysis the two products were separated by column chromatography and their identities were confirmed by comparison of their infrared spectra with those of authentic samples.

Electrolysis of Propionic and Acetic Acids.—A mixture of propionic acid (6.8 g.), acetic acid (20 g.), and sodium acetate (2.1 g.) was electrolyzed as above (0.3 amp.) for a period of 6 hr. All material boiling below 120° was distilled directly from the reaction mixture, and the distillate was examined by gas chromatography using three different column packings. Peak enhancement, using authentic ethyl acetate, confirmed the presence of this ester, which was calculated to have been formed in about 13% yield from the propionic acid precursor.

Electrolysis of 2,3,3-Triphenylpropanoic Acid. A. In Methanol.—2,3,3-Triphenylpropanoic acid[28] (685 mg.) in methanol (20 ml.) containing sodium (26 mg.) was electrolyzed as above for a period of 17 min., after which the crude product was recovered by solvent evaporation. The residue was dissolved in ether, and the solution was extracted with dilute aqueous sodium hydroxide. Ether extraction of the acidified aqueous layer afforded 290 mg. of unchanged acid. Evaporation of the original ether layer yielded 351 mg. of crude product. This was chromatographed on acid-washed alumina (grade III, benzene–hexane eluent) to provide 172 mg. of white solid, m.p. 67.5–68°, after recrystallization from dilute methanol. The sample gave no mixture melting point depression, and displayed an infrared spectrum identical with that of authentic methyl 1,2,2-triphenylethyl ether. The latter sample, m.p. 66.5–68°, was prepared by the methylation of 1,2,2-triphenylethanol, as described before,[28] using methyl iodide and silver oxide.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 86.82; H, 6.87.

B. In Acetic Acid.—A mixture of 2,3,3-triphenylpropanoic acid (450 mg.) and sodium acetate (200 mg.) in acetic acid (20 ml.) was electrolyzed as described above (8 f./mole). The mixture was evaporated to dryness, dissolved in ether and extracted with ammonium hydroxide solution (discard). Evaporation of the ether solvent yielded 370 mg. of crude product which was chromatographed on acid-washed alumina (grade III, benzene–hexane eluent), affording 260 mg. of white solid. This was recrystallized from ethanol, m.p. 147–149°. The product showed no mixture melting point depression and had an infrared spectrum superimposible on that of authentic 1,2,2-triphenylethyl acetate, m.p. 155–156°.[29]

(29) W. A. Bonner and C. J. Collins, *J. Am. Chem. Soc.*, **75**, 5372 (1953).

Wheat Bran Phenols[1]

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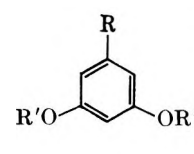
A mixture of 5-*n*-alkylresorcinols is found to be present in the nonsaponifiable fraction of wheat bran. The structures of two phenols are shown to be 5-*n*-nonadecylresorcinol and 5-*n*-heneicosylresorcinol by analysis and synthesis.

While much effort has been expended in the past on investigations of the chemical constitution of wheat, only little is known about the composition of the nonsaponifiable portion of wheat bran.[2] On undertaking an investigation of the latter and initially carrying out alumina chromatography, we encountered the presence of hydrocarbons, steroids, and a phenolic material. The unusual presence of a phenolic constituent, designated at first as substance A, in the nonsaponifiable fraction of a plant extract aroused our attention and led to a structure analysis which constitutes the major portion of this communication.

Early elemental analyses of crystalline substance A, m.p. 84–85°, pointed to a $C_{13}H_{24}O$ formula. Its infrared spectrum showed hydroxyl and aromatic absorption bands and its ultraviolet spectrum was characteristic of a phenolic compound. Its phenolic character was confirmed by the preparation of a crystalline methyl ether and acetate. The infrared spectrum of the ester revealed no hydroxyl peaks and only a 5.65-μ band in the carbonyl region. Inspection of the n.m.r. spectra of substance A and its two derivatives indicated the presence of aromatic hydrogens. The ratio (2:1) of the intensities of the O-methyl signal *vs.* the aromatic hydrogen signal in the methyl ether as well as the same ratio of the acetyl methyl signal *vs.* the aromatic hydrogen signal in the ester showed that A was a monoalkylated dihydric phenol of a $C_{26}H_{48}O$ formula. A positive mercuric nitrate test[3] suggested it was an alkylresorcinol. An n.m.r. analysis of the six dimethoxytoluenes (*vide infra*) and comparison of their spectra with the spectrum of the dimethyl ether of substance A established that A was a 5-alkylresorcinol.

The resistance of A to hydrogenation over palladium–charcoal and the absence of olefinic hydrogen signals in its n.m.r. spectrum indicated that the alkyl side chain was saturated. The n.m.r. signal of the side chain was composed of a benzylic two-proton multiplet at 2.33–2.75 p.p.m. (deuterioacetone solution with an internal tetramethylsilane standard), a broad methylene *ca.* 36-proton singlet at 1.32 p.p.m., and a methyl three-proton multiplet at 0.82–1.05 p.p.m. Thus substance A appeared to be 5-*n*-eicosylresorcinol (Ia).



Ia, R = $(CH_2)_{19}CH_3$; R′ = H
b, R = $(CH_2)_{18}CH_3$; R′ = Me
c, R = $(CH_2)_{20}CH_3$; R′ = Me
d, R = $(CH_2)_{18}CH_3$; R′ = H
e, R = $(CH_2)_{20}CH_3$; R′ = H
f, R = $(CH_2)_{16}CH_3$; R′ = Me
g, R = $(CH_2)_{22}CH_3$; R′ = Me
h, R = $(CH_2)_{24}CH_3$; R′ = Me

In view of the fact that all previously reported naturally occurring *n*-alkylphenols have been shown to possess side chains containing odd numbers of carbon atoms in agreement with biosynthetic arguments (*vide infra*), the structure Ia was anomalous. The first indication of the heterogeneity of substance A was the wide melting ranges of its diacetate and dimethyl ether. As a consequence the vapor phase chromato-

(1) This work was carried out under contracts with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contracts were supervised by the Northern Utilization Research Branch and the Western Utilization Research and Development Division of the Agricultural Research Service.

(2) M. T. Ellis, *Biochem. J.*, **12**, 160 (1918); R. J. Anderson and F. P. Nabenhauer, *J. Am. Chem. Soc.*, **46**, 1717 (1924); M. Gažo and V. Špringer, *Poľnohospodárstvo*, **7**, 807 (1960); *Chem. Abstr.*, **55**, 8694*b* (1961).

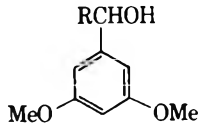
(3) A. Butenandt and F. H. Stodola, *Ann.*, **539**, 40 (1939).

TABLE I
CHEMICAL SHIFTS
(in parts per million, singlets unless otherwise noted)

	Aldehydes			Toluenes		
Methoxy substitution	Aromatic hydrogens	Methoxy hydrogens	Aldehyde hydrogens	Aromatic hydrogens	Methoxy hydrogens	Methyl hydrogens
2,3	7.05–7.50 multiplet	3.90, 3.98	10.40	6.58–7.05 multiplet	3.77, 3.80	2.26
2,4	6.35–6.58, 7.62–7.80 multiplets	3.83, 3.86	10.20	6.22–6.43, 6.83–7.08 multiplets	3.73, 3.75	2.14
2,5	6.80–7.35 multiplet	3.78, 3.87	10.47	6.68 broad singlet	3.72, 3.75	2.21
2,6	6.47–6.65, 7.28–7.58 multiplets	3.87, 3.87	10.47	6.35–6.53, 6.88–7.21 multiplets	3.77, 3.77	2.11
3,4	6.84–7.02, 7.32–7.52 multiplets	3.91, 3.94	9.80	6.69 broad singlet	3.79, 3.81	2.27
3,5	6.62–6.72, 6.92–7.02 multiplets	3.83, 3.83	9.87	6.37 broad singlet	3.77, 3.77	2.30

graphic behavior of the ether was investigated. It revealed the presence of five constituents of which the two with longest retention times and the one with the shortest were decidedly minor components. The presence of two major constituents (82% of the total), the previous analyses of substance A, and biosynthetic speculations made the possibility of these two chromatographic fractions representing resorcinol dimethyl ethers with C_{19} and C_{21} side chains (Ib and Ic, respectively) an attractive working hypothesis. Therefore, the synthesis of these compounds was undertaken.

Treatment of 3,5-dimethoxybenzaldehyde with *n*-octadecylmagnesium bromide as well as with *n*-eicosylmagnesium bromide led to the carbinols IIa and IIb, respectively, whose hydrogenolysis over palladium–charcoal yielded Ib and Ic, respectively. Conversion of Ib and Ic to their respective resorcinols, Id and Ie, was accomplished by heating in refluxing pyridine hydrochloride.



IIa, R = $(CH_2)_{17}CH_3$
b, R = $(CH_2)_{19}CH_3$

The two major components of the v.p.c. fractionation of A-dimethyl ether were isolated. The one with the shorter retention time proved to be identical in all respects with Ib and the one with the longer retention time was shown to be Ic. Repeated crystallization of A-dimethyl ether also afforded Ic. The three minor components of the vapor phase chromatogram were isolated in moderate states of purity but in exceedingly low yields. Their ultraviolet spectra were identical with those of Ib and Ic. A plot of retention times of the chromatographic fractions *vs.* homologous molecular formulas suggested that the three minor constituents possessed C_{17}, C_{23}, and C_{25} side chains (If, Ig, and Ih, respectively). Unfortunately insufficient quantities of these compounds prevented a rigorous proof of their structure.

As already indicated above, the structure analysis of the wheat bran phenols required an inspection of the n.m.r. spectra of dimethoxytoluene model compounds. Table I lists the n.m.r. signals of all six toluenes and the dimethoxybenzaldehydes from which the toluenes were derived. While the chemical shift (3.72–3.81 p.p.m.) of the methoxy hydrogens in the toluenes appears to be essentially independent of their position in the aromatic nucleus, the chemical shift of the methyl hydrogens varies with their relationship to the methoxy groups. Substitution in the *ortho* and *para* position leads to as much as a 0.2-p.p.m. upfield shift of the methyl hydrogen signal with respect to *meta* substitution. In the aldehyde series *ortho* substitution moves the aldehyde hydrogen signal 0.4–0.5 p.p.m. downfield, while *para* substitution shifts it 0.1–0.2 p.p.m. upfield.

The wheat bran phenols now take their place alongside a growing group of naturally occurring phenols of polyacetate biosynthetic origin[4] containing *meta*-oriented, long, unbranched, odd-numbered, and sometimes unsaturated carbon chains. Their closest structural relatives are the 5-*n*-alkylresorcinols of the Anacardium, Ginkgo, and Grevillea species.[5]

Experimental[6]

Nonsaponifiable Portion of Wheat Bran.—Wheat bran (22.7 kg.) was extracted in a Soxhlet apparatus with hexane for 24 hr.

(4) A. J. Birch and F. W. Donovan, *Australian J. Chem.*, **6**, 360 (1953), and references cited therein. In a letter of July 3, 1945 to Professor Roger Adams, Professor Marvin Carmack pointed to the Collie hypothesis as a possible route of biosynthesis of the natural 5-*n*-alkylresorcinols found among the depsides, in cashew nut oil, and as part of the skeleta of the marihuana principles. While these comments appear to represent the first modern expression of the polyacetate biosynthesis of certain phenolic natural products, they were never published.

(5) S. Furukawa, *Sci. Papers Inst. Phys. Chem. Res.* (Tokyo), **26**, 178 (1935); H. J. Backer and N. H. Haack, *Rec. trav. chim.*, **60**, 661 (1941); W. F. Symes and C. R. Dawson, *Nature*, **171**, 841 (1953); J. L. Occolowitz and A. S. Wright, *Australian J. Chem.*, **15**, 858 (1962).

(6) Melting points were determined on a Kofler hot stage and are uncorrected. Ultraviolet spectra were determined for ethanol solutions using a Cary recording spectrophotometer Model 14. Infrared spectra were measured using a Perkin-Elmer Infracord spectrophotometer Model 137 and, unless otherwise stated, were for Nujol mulls. N.m.r. spectra were obtained using a Varian A-60 spectrometer; the positions of the peaks were measured relative to tetramethylsilane as the internal reference; unless otherwise stated the solvent was deuteriochloroform. Gas phase chromatography (g.p.c.) was carried out using a F & M Model 500 programmed temperature gas chromatograph; all gas chromatograms were obtained using a 2-ft. column of 5% silicone gum rubber on Chromasorb P, with a carrier gas (helium) flow rate of 135 ml. per min. Thin layer chromatography (t.l.c.) was conducted using silica as the absorbant, 95:5 chloroform–ethyl acetate as the developing solvent, and iodine as the visualizing agent; R_f values reported are only reproducible to ±0.05. Optical rotations were determined using a Rudolph polarimeter Model 80. Microanalyses were preformed by Dr. A. Bernhardt, Mulheim, Germany. Wheat bran was supplied by Pillsbury Mills, Inc., Minneapolis 14, Minn. Unless otherwise stated, alumina was 80–200 mesh, as supplied by the Chicago Apparatus Co. Solvents were removed *in vacuo* on the steam bath.

The solvent was eliminated from the extract leaving a dark oil (785 g.). This oil was added to a mixture of 50% aqueous potassium hydroxide solution (1.5 l.) and 5% ethanolic pyrogallol (3.0 l.), and the mixture was boiled under reflux for 90 min. The cooled solution was diluted with water (27 l.), and extracted continuously with ether for 4 days. The ether extract (6 l.) was washed with two 1-l. portions of water and brine (1 l.), then dried over sodium sulfate. The solvent was removed from this dried extract, leaving a brown solid (87.0 g., 0.38% of wheat bran).

Chromatography of the Nonsaponifiable Portion of Wheat Bran.—The nonsaponifiable portion of wheat bran (87.0 g.) was chromatographed over a column of alumina (4.8 kg., 180 × 10 cm.), and five main fractions were obtained. Hexane eluted a colorless semisolid (2.7 g., 3.1%), the hydrocarbon fraction; 1:1 hexane–benzene eluted a yellow oil (4.0 g., 4.6%), the middle fraction; benzene eluted a colorless crystalline solid, m.p. 128–138° (13.1 g., 15.0%), the steroid fraction; 1:1 benzene–ether eluted a colorless crystalline solid, m.p. 81–84° (9.6 g., 11.0%), substance A; ether eluted a yellow oil (27.6 g., 31.6%), the end fraction.

Chromatography of the Hydrocarbon Fraction.—A portion of the hydrocarbon fraction (100 mg.) was chromatographed over a column of alumina (200 g., 30 × 5 cm.), and successive fractions (100 ml.) of eluate were examined. Fractions 8–15 (hexane) contained a colorless semisolid (total, 92 mg.) which could not be induced to crystallize. Its infrared and ultraviolet spectra indicated the absence of functional groups, but it gave a positive unsaturation test with tetranitromethane. G.p.c. examination of this fraction, programming the temperature from 125–300°, then keeping the temperature at 300°, revealed the presence of at least thirty-two constituents.

Chromatography of the Middle Fraction.—A portion of the middle fraction (2.14 g.) was chromatographed over a column of alumina (200 g., 30 × 5 cm.), and successive fractions (100 ml.) of eluate were examined. Fractions 3–11 (hexane) contained colorless semisolid hydrocarbon(s) (total, 0.14 g.). Fractions 18–25 (3:1 hexane–benzene) contained a colorless oil (total 0.18 g.); ultraviolet spectrum, no absorption above 220 mμ; infrared spectrum, $\mu_{max}^{CHCl_3}$ 5.85, 6.25. Fractions 34–43 (1:1 hexane–benzene) contained a colorless solid (total 0.09 g.), m.p. 55–66°; ultraviolet spectrum, λ_{max} 285 mμ; infrared spectrum, $\mu_{max}^{CHCl_3}$ 5.89 (m), 6.07 (s), 6.17 (s), 6.30 (m). Fractions 50–55 (1:3 hexane–benzene) and 56–66 (benzene) contained a colorless crystalline solid (total, 0.94 g.), m.p. 130–135° (β-sitosterol mixture). Fractions 74–86 (3:1 benzene–ether) contained a colorless solid (total, 0.14 g.), m.p. 71–78° (impure substance A).

Chromatography of the Steroid Fraction.—A portion of the steroid fraction (5.80 g.) was chromatographed over a column of alumina (330 g., 50 × 5 cm.), and successive fractions (200 ml.) of the eluate were examined. Fractions 4–11 (hexane) contained a colorless oil (total 0.06 g.); fractions 22–26 (benzene) and 27–41 (9:1 benzene–ether) contained colorless crystalline materials (total 4.42 g.) whose melting points rose steadily from 128–131° (fraction 22) to 135–138° (fraction 41) and whose optical rotations (chloroform) varied steadily from $[\alpha]^{28}D$ +5° (fraction 22) to −30° (fraction 41).

β-Sitosterol has m.p. 139–140°, $[\alpha]D$ −36° (chloroform).

Substance A.—Repeated crystallization from hexane afforded substance A as silvery flakes, m.p. 84–85°. This material showed the following properties: t.l.c., R_f 0.20; $[\alpha]^{22}D$ 0° (*c* 1.02% in ethanol); ultraviolet spectrum, λ_{max} 275, 281.5 mμ; infrared spectrum, μ_{max} 3.05 (s, hydroxyl), 6.15 (m), 6.25 (s, aromatic ring); n.m.r. spectrum (deuterioacetone), 3-proton multiplet between 0.82 and 1.05 p.p.m. (C–CH_3), *ca.* 36-proton broad singlet at 1.32 p.p.m. (–$(CH_2)_{ca\ 18}$–), 2-proton multiplet between 2.33 and 2.75 p.p.m. (benzylic protons), 3-proton broad singlet at 6.23 p.p.m. (aromatic protons), and 2 singlets, total 2 protons, at 3.17 and 7.97 p.p.m. (hydroxylic protons, *vide infra* for orcinol); a ferric chloride test in ethanol was negative; a mercuric nitrate test for resorcinols was positive.[3]

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 80.14; H, 11.96; O, 7.90; 1C–CH_3, 4.20. Calcd. for $C_{25}H_{44}O_2$: C, 79.73; H, 11.78; O, 8.49; 1C–CH_3, 4.51. Found: C, 80.05; H, 11.87; H, 7.79; C–CH_3, 2.50.

A-Dimethyl Ether.—A (1.30 g.) and dimethyl sulfate (6.1 g.) were added to a mixture of dry acetone (100 ml.) and anhydrous potassium carbonate (36 g.), and the mixture was boiled under gentle reflux for 50 hr. The mixture was cooled and filtered, and the solvent was eliminated from the filtrate, leaving a pale yellow solid (1.39 g.). T.l.c. showed a single spot (R_f 0.94). This material was crystallized from hexane (3 ml.) giving colorless crystals (1.10 g.), m.p. 43–50°; ultraviolet spectrum, λ_{max} 273, 280 mμ; infrared spectrum, no hydroxyl absorption; n.m r. spectrum, 3-proton multiplet between 0.82 and 1.05 p.p.m. (C–CH_3), *ca.* 40-proton broad singlet at 1.28 p.p.m. (–$(CH_2)_{ca\ 20}$–), 2-proton multiplet between 2.30 and 2.80 p.p.m. (benzylic protons), 6-proton singlet at 3.78 p.p.m. (aromatic methoxys), 3-proton broad singlet at 6.38 p.p.m. (aromatic protons).

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11; O, 7.40. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96; O, 7.91. Found: C, 80.54; H, 11.93; O, 7.42.

A-Dimethyl ether (839 mg.) was recrystallized five times from hexane, giving colorless crystals (62 mg.), m.p. 61–63°. A mixture melting point with Ic was 61–63°; the ultraviolet and infrared spectra were identical with those of Ic; the n.m.r. spectrum was identical with that of Ic, except that the broad singlet at 1.28 p.p.m. contained *ca.* 41 protons.

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11; O, 7.40. Found: C, 80.70; H, 12.14; O, 7.28.

A-Diacetate.—A (402 mg.) was dissolved in a mixture of pyridine (5 ml.) and acetic anhydride (10 ml.), and this solution was stirred and heated (steam bath) for 3 hr. The solution was cooled, then poured into ice–water (20 ml.), and extracted with four 50-ml. portions of hexane. The hexane extract was washed with water (50 ml.) and brine (50 ml.), then dried over sodium sulfate. The solvent was eliminated from the dried extract, leaving a colorless solid (454 mg.). T.l.c. showed a single spot (R_f 0.80). This material was recrystallized four times from ethanol, giving colorless needles (238 mg.), m.p. 60–66°; t.l.c., R_f 0.80; ultraviolet spectrum, λ_{max} 261 mμ; infrared spectrum, no hydroxyl absorption, μ_{max} 5.65 (s, phenol acetate); n.m.r. spectrum, 3-proton multiplet between 0.78 and 1.05 p.p.m. (C–CH_3), *ca.* 38-proton broad singlet at 1.28 p.p.m. (–$(CH_2)_{ca\ 19}$–), 6-proton singlet at 2.26 p.p.m. (phenolic acetates), 2-proton multiplet between 2.40 and 2.85 p.p.m. (benzylic protons), 3-proton broad singlet at 6.83 p.p.m. (aromatic protons).

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72; O, 13.10. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50; O, 13.89. Found: C, 76.37; H, 10.46; O, 13.12.

Attempted Reduction of A.—A (201 mg.) was dissolved in ethanol (150 ml.) and was subjected to hydrogenation at 50° and 40 p.s.i. in the presence of 10% palladium on charcoal (20 mg.). After 4 hr. the mixture was filtered through Celite to remove the catalyst, and the solvent was removed from the filtrate leaving a colorless solid (192 mg.). This material was crystallized from hexane, and the resulting crystals (167 mg.) were shown to be identical with A (melting point, mixture melting point, infrared spectrum, t.l.c.).

3,5-Dimethoxybenzyl Alcohol.—3,5-Dimethoxybenzoic acid (25.0 g., R_f 0.04) was dissolved in warm, dry tetrahydrofuran (400 ml.), and this warm solution was added continuously over 90 min. to a gently refluxing suspension of lithium aluminum hydride (10 g.) in tetrahydrofuran (100 ml.). When the addition was complete the mixture was boiled under gentle reflux for 4 hr., then cooled (ice–water bath). The excess hydride and the complex were decomposed by cautious addition of ethyl acetate (60 ml.), water (60 ml.), and 2 *N* aqueous hydrochloric acid (100 ml.). The volume of the resulting suspension was reduced to 150 ml. (rotatory evaporator, bath temperature of 40°), diluted by addition of water (200 ml.), and extracted with six 500-ml. portions of ether. The ether extract was washed with water (1 l.), 2 *N* aqueous sodium hydroxide (1 l.), water (1 l.), and brine (1 l.), then dried over sodium sulfate. The solvent was eliminated from this dried extract, leaving a colorless solid (22.9 g.), which was crystallized from hexane, giving 3,5-dimethoxybenzyl alcohol as needles (21.8 g., 94%), m.p. 46.5–47° (lit.[7], m.p. 47–48°); t.l.c., R_f 0.14; infrared spectrum, μ_{max} 2.95 (m, hydroxyl), no carbonyl absorption; n.m.r. spectrum, 1-proton broad singlet at 2.25 p.p.m. (hydroxyl proton), 6-proton singlet at 3.77 p.p.m. (aromatic methoxys), 2-proton broad singlet at 4.61 p.p.m. (benzylic protons), 3-proton, 5-line multiplet between 6.30 and 6.60 p.p.m. (aromatic protons).

3,5-Dimethoxybenzaldehyde.—Freshly prepared "active" manganese dioxide[8] (201 g.) was added to a solution of 3,5-di-

(7) R. Adams, S. MacKenzie, Jr., and S. Loewe, *J. Am. Chem. Soc.*, **70**, 664 (1948).

(8) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

methoxybenzyl alcohol (17.8 g.) in dry, ethanol-free chloroform (2 l.), and the mixture was stirred in an atmosphere of nitrogen for 24 hr. at room temperature. The mixture was filtered, and the residue was washed with six 500-ml. portions of boiling chloroform. The solvent was eliminated from the combined filtrate and washings, leaving a colorless crystalline solid (13.9 g.), m.p. 43–45°. This was crystallized from pentane, giving 3,5-dimethoxybenzaldehyde as prisms (12.8 g., 72%), m.p. 45–45.5° (lit.[9] m.p. 48°); t.l.c., R_f 0.57; infrared spectrum, no hydroxyl absorption, μ_{max} 5.93 (s, aldehyde carbonyl); n.m.r. spectrum, 6-proton singlet at 3.83 p.p.m. (aromatic methoxys), 1-proton, 2-line multiplet between 6.60 and 6.75 p.p.m., and a 2-proton, 2-line multiplet between 6.92 and 7.05 p.p.m., (aromatic protons), 1-proton singlet at 9.87 p.p.m. (aldehydic protons).

***n*-Eicosyl Bromide.**—1-Eicosanol (19.1 g.) was powdered and added to concentrated sulfuric acid (7 g.) and 48% aqueous hydrobromic acid (22 g.), and this solution was stirred and heated at 140° (bath temperature) for 5 hr. The resulting dark solution was cooled, diluted by the addition of water (30 ml.), and extracted with two 80-ml. portions of ether. The ether extract was washed with water (50 ml.), two 50-ml. portions of saturated aqueous sodium bicarbonate, water (50 ml.), and brine (50 ml.), then dried over sodium sulfate. The solvent was eliminated from the dried extract, leaving a very dark brown solid (23.4 g.). This was dissolved in hexane (150 ml.), and this solution was applied to a column of alumina (Guilini, neutral, activity I, 200 g., 18 × 3.8 cm.). Hexane (1 l.) eluted *n*-eicosyl bromide as a colorless solid (18.7 g., 82%), m.p. 33–34°, lit.[10] 30–31°; t.l.c., R_f 0.87; infrared spectrum, no hydroxyl absorption. G.p.c. showed that this material was 90% pure (retention time for *n*-eicosyl bromide, 3.4 min. with a column temperature of 250°).

***n*-Octadecyl Bromide.**—The commercially available *n*-octadecyl bromide was a very pale yellow semisolid. A 20.0-g. sample was dissolved in hexane (100 ml.) and this solution was applied to a column of alumina (Guilini, neutral, activity I, 200 g., 18 × 3.8 cm.). Hexane (600 ml.) eluted the bromide as a colorless solid (18.7 g.), m.p. 26–27°, lit.[11] m.p. 25.5–26°; t.l.c., R_f 0.87; infrared spectrum, no hydroxyl absorption. G.p.c. showed that this material was 87% pure (retention time for *n*-octadecyl bromide, 4.7 min. with a column temperature of 215°).

α-(3,5-Dimethoxyphenyl)-*n*-heneicosanol (IIb).—In a 100-ml. two-necked flask fitted with a dropping funnel and condenser, and containing a magnetic stirring bar, were placed dry magnesium turnings (1.16 g., 0.048 g.-atom), and these were covered with absolute ether (20 ml.). A few drops of a solution of *n*-eicosyl bromide (16.71 g., 0.046 mole) in absolute ether (30 ml.) were added, and, other less drastic methods having failed, the reaction was initiated by the addition of 2 small drops of methyl iodide. The rate of reaction was slow, and the mixture was heated under gentle reflux with rapid stirring while the remainder of the solution of *n*-eicosyl bromide was added dropwise over a period of 1 hr. Heating and stirring were continued for a further 5 hr. to complete formation of the Grignard reagent.

The heating bath was removed and an ice–water bath substituted. A solution of 3,5-dimethoxybenzaldehyde (6.15 g., 0.037 mole) in absolute ether (15 ml.) was added dropwise over a period of 45 min. to the rapidly stirred Grignard suspension. When this addition was complete, the heating bath was reintroduced, and the stirred mixture was boiled under gentle reflux for 4 hr. to complete the reaction. Excess magnesium was removed from the cooled reaction mixture by filtration, and the complex salt present in the filtrate was decomposed by the portionwise addition of powdered ice. Thereafter the mixture was extracted with two 50-ml. portions of 2 *N* aqueous sulfuric acid, washed with saturated aqueous sodium bicarbonate solution (30 ml.), water (30 ml.), and brine (30 ml.), then dried over sodium sulfate. The solvent was eliminated from this dried solution, leaving a pale yellow solid (17.90 g.), which was crystallized from hexane (400 ml.) giving IIb as colorless crystals (13.96 g., 85%), m.p. 75–75.5°; t.l.c., R_f 0.39; ultraviolet spectrum, λ_{max} 274 mμ (ε 1900), 280 (1930); infrared spectrum, μ_{max} 3.05 (m, hydroxyl), no carbonyl absorption; n.m.r. spectrum, 3-proton multiplet between 0.78 and 1.05 p.p.m. ($C-CH_3$), *ca.* 40-proton broad singlet at 1.27 p.p.m. ($-(CH_2)_{ca\ 20}-$), 1-proton broad singlet at 2.03 p.p.m. (hydroxylic proton), 6-proton singlet at 3.77 p.p.m. (aromatic methoxys), 1-proton multiplet between 4.40 and 4.75 p.p.m. (benzylic proton), 3-proton, 5-line multiplet between 6.25 and 6.55 p p.m. (aromatic protons). Recrystallization of a sample for elemental analysis did not raise the melting point.

Anal. Calcd. for $C_{29}H_{52}O_3$: C, 77.62; H, 11.68; O, 10.70. Found: C, 77.58; H, 11.61; O, 10.81.

α-(3,5-Dimethoxyphenyl)-*n*-nonadecanol (IIa).—This preparation was identical with that described above except that *n*-octadecyl bromide (15.43 g., 0.046 mole) was used. This procedure afforded IIa as colorless crystals (12.08 g., 77%), m.p. 71–71.5°; t.l.c., R_f 0.38; ultraviolet spectrum, λ_{max} 274 mμ (ε 1860), 280 (1880); infrared spectrum, μ_{max} 3.04 (m, hydroxyl), no carbonyl absorption; n.m.r. spectrum, identical with that of IIb, except that the broad singlet at 1.27 p.p.m. contained *ca.* 37 protons. Recrystallization of a sample for elemental analysis did not raise the melting point.

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50; O, 11.41. Found: C, 77.23; H, 11.40; O, 11.16.

5-*n*-Heneicosylresorcinol Dimethyl Ether (Ic).—IIb (12.68 g.) was dissolved in warm ethyl acetate (200 ml.) containing concentrated sulfuric acid (10 drops), and the mixture was subjected to hydrogenation at 55° and 40 p.s.i. in the presence of 10% palladium on charcoal (1.27 g.). After 4 hr. the mixture was filtered through Celite to remove the catalyst, and the volume of the filtrate was reduced to 80 ml. (rotatory evaporator, bath temperature 40°). The concentrate was kept at 0° for 1 hr., and the resulting precipitate was collected, giving Ic as colorless crystals (11.70 g., 96%), m.p. 62–64°; t.l.c., R_f 0.94; ultraviolet spectrum, λ_{max} 273 mμ (ε 1590), 280 (1610); infrared spectrum, no hydroxyl absorption; n.m.r. spectrum, 3-proton multiplet between 0.75 and 1.05 p.p.m. ($C-CH_3$), *ca.* 40-proton broad singlet at 1.28 p.p.m. ($-(CH_2)_{ca\ 20}-$), 2-proton multiplet between 2.33 and 2.75 p.p.m. (benzylic protons), 6-proton singlet at 3.76 p.p.m. (aromatic methoxys), 3-proton broad singlet at 6.33 p.p.m. (aromatic protons). Recrystallization of a sample for elemental analysis gave fine needles, m.p. 63.5–64.5°.

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11; O, 7.40. Found: C, 80.41; H, 12.05; O, 7.49.

5-*n*-Nonadecylresorcinol Dimethyl Ether (Ib).—This preparation was similar to that described before. Hydrogenolysis of IIa (9.86 g.) afforded Ib as colorless crystals (8.93 g., 94%), m.p. 55–57°; t.l.c., R_f, 0.94; ultraviolet spectrum, λ_{max} 273 mμ (ε 1550), 280 (1570); infrared spectrum, no hydroxyl absorption; n.m.r. spectrum, identical with that of Ic, except that the broad singlet at 1.28 p.p.m. contained *ca.* 36 protons. Recrystallization of a sample for elemental analysis gave fine needles, m.p. 56.5–57.5°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96; O, 7.91. Found: C, 79.93; H, 12.02; O, 7.91.

Anhydrous Pyridine Hydrochloride.—Dry hydrogen chloride was bubbled through a rapidly stirred solution of dry pyridine (60 g.) in absolute ether (500 ml.) contained in a cooled (ice-water bath) flask. After 3 hr. the gas flow was stopped and most of the solvent was decanted, the remainder being pumped off *in vacuo* at room temperature, leaving colorless crystals of pyridine hydrochloride (84 g., 96%), m.p. 143–144°. This salt was very hygroscopic and was stored *in vacuo* over concentrated sulfuric acid.

5-*n*-Heneicosylresorcinol (Ie).—Ic (4.65 g.) was mixed with anhydrous pyridine hydrochloride (37.5 g.) in a 100-ml. flask fitted with a short air condenser. This mixture was heated in an atmosphere of nitrogen until the pyridine hydrochloride refluxed freely (bath temperature, 265°). (Preliminary experiments had established that with a bath temperature of 220° no reaction occurred although orcinol dimethyl ether was efficiently demethylated under these conditions.) The mixture was maintained at this elevated temperature for 8 hr., then the flask was allowed to cool. The solidified contents were removed and shaken with a mixture of 2 *N* aqueous sodium hydroxide solution (500 ml.) and ether (1 l.). The pale yellow ether layer was combined with the three 1-l. portions of further ether extracts of the red basic aqueous layer, and the resulting ether solution was washed with two 1-l. portions of 2 *N* aqueous hydrochloric acid to remove pyridine, then with water (1 l.), and brine (1 l.), then dried over sodium sulfate. The solvent was eliminated from this dried solution, leaving a solid neutral material (3.87 g.), which was crystallized from hexane (75 ml.) giving a fawn ma-

(9) J. P. Lambooy, *J. Am. Chem. Soc.*, **76**, 133 (1954).
(10) G. Jacini, *Chim. e ind.* (Milan), **34**, 137 (1952).
(11) R. Lukeš and M. Černý, *Chem. listy*, **51**, 1327 (1957).

terial (3.15 g.), m.p. 98–100°, t.l.c. of which revealed only 1 spot (R_f 0.20). This material was distilled at 1 μ and 160° (bath temperature) using a cold-finger sublimator, giving colorless material (2.54 g.), m.p. 99.5–100.5°, which was crystallized from hexane, giving Ie as plates (2.34 g., 54%), m.p. 99.5–100.5°; t.l.c., R_f 0.20; ultraviolet spectrum, λ_{max} 275 mμ (ϵ 1740), 281.5 (1730); infrared spectrum, identical with that of A; n.m.r. spectrum (deuterioacetone), identical with that of A, except that the broad singlet at 1.32 p.p.m. contained *ca.* 35 protons, and the 2 peaks, total of 2 (hydroxyl) protons, appeared at 2.97 and 7.97 p.p.m.; a ferric chloride test in ethanol was negative; a mercuric nitrate test for resorcinols was positive.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96; O, 7.90; 1C–CH_3, 4.20. Found: C, 80.01; H, 12.06; O, 7.99; C–CH_3, 2.94.

5-*n*-Nonadecylresorcinol (Id).—The demethylation of Ib was carried out in a manner very similar to that described above for Ic. Heating a mixture of Ib (3.81 g.) and anhydrous pyridine hydrochloride (31.0 g.) at 265° (bath temperature) for 8 hr., followed by the above work-up, gave a solid neutral material (3.21 g.), which was crystallized from hexane (45 ml.) giving fawn material (2.68 g.), m.p. 94–96°, t.l.c. of which revealed only 1 spot (R_f 0.20). This material was distilled at 1 μ and 160° (bath temperature) using a cold-finger sublimator, giving colorless material (2.19 g.), m.p. 96.5–97.5°, which was crystallized from hexane, giving Id as plates (2.03 g., 57%), m.p. 96.5–97.5°; t.l.c., R_f 0.20; ultraviolet spectrum, λ_{max} 275 mμ (ϵ 1780), 281.5 (1740); infrared spectrum, identical with that of A in the 2.5–12-μ region, very slight differences from that of A in the 12–15-μ region; n.m.r. spectrum (deuterioacetone), identical with that of A, except that the broad singlet at 1.32 p.p.m. contained *ca.* 31 protons, and the 2 peaks, total of 2 (hydroxyl) protons, appeared at 3.05 and 7.97 p.p.m.; a ferric chloride test in ethanol was negative; a mercuric nitrate test for resorcinols was positive.

Anal. Calcd. for $C_{25}H_{44}O_2$: C, 79.73; H, 11.78; O, 8.49; 1C–CH_3, 4.51. Found: C, 79.71; H, 11.76; O, 8.48; C–CH_3, 2.94.

Methylation of Ie.—Ie (150 mg.) and dimethyl sulfate (0.8 g.) were added to a mixture of dry acetone (10 ml.) and anhydrous potassium carbonate (4 g.) and the mixture was boiled under gentle reflux for 48 hr. The mixture was cooled and filtered, and the solvent was eliminated from the filtrate, leaving a pale yellow solid (161 mg.). This material was crystallized from hexane (1 ml.) and the resulting colorless crystals (112 mg.) were shown to be identical with Ic (melting point, mixture melting point, infrared spectrum, t.l.c.). This confirmed that no rearrangement of the side chain of Ic had occurred during its demethylation.

Methylation of Id.—The methylation of Id (148 mg.) was conducted exactly as described above for Ie and furnished a pale yellow solid (160 mg.). This material was crystallized from hexane (1 ml.) and the resulting colorless crystals (92 mg.) were shown to be identical with Ib (melting point, mixture melting point, infrared spectrum, t.l.c.). This confirmed that no rearrangement of the side chain of Ib had occurred during its demethylation.

5-*n*-Heneicosylresorcinol Diacetate.—Ie (200 mg.) was acetylated in exactly the same way as described for A above. Regular work-up afforded a very pale yellow crystalline solid (227 mg.), t.l.c. of which showed 1 spot (R_f 0.80). This material was crystallized twice from ethanol, giving colorless plates (176 mg.), 72.5–73°; t.l.c., R_f 0.80; ultraviolet spectrum, λ_{max} 261.5 mμ (ϵ 305); infrared spectrum, no hydroxyl absorption, μ_{max} 5.64 (s, phenol acetate); n.m.r. spectrum, identical with that of A-diacetate, except that the broad singlet at 1.28 p.p.m. contained *ca.* 36 protons.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72; O, 13.10. Found: C, 76.27; H, 10.45; O, 13.10.

5-*n*-Nonadecylresorcinol Diacetate.—Id (199 mg.) was acetylated in exactly the same way as described for A above. Standard work-up afforded a very pale yellow crystalline solid (227 mg.), t.l.c. of which showed only 1 spot (R_f 0.80). This material was crystallized twice from ethanol, giving colorless needles (163 mg.), m.p. 67.5–68°; t.l.c., R_f 0.80; ultraviolet spectrum, λ_{max} 261 mμ (ϵ 291); infrared spectrum, no hydroxyl absorption, μ_{max} 5.65 (s, phenol acetate); n.m.r. spectrum, identical with that of A-diacetate except that the broad singlet at 1.28 p.p.m. contained *ca.* 32 protons.

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50; O, 13.89. Found: C, 75.83; H, 10.31; O, 14.01.

Gas Phase Chromatography of A-Dimethyl Ether, Ib, and Ic.—Since the methylation of A was essentially quantitative, any method which reveals the number and relative amounts of the components in this dimethyl ether also reflects the number and relative amounts of the components in A. G.p.c. (with the column maintained at 300°) of the reaction product from the methylation of A revealed the presence of five constituents, whose retention times and per cent of total area were as follows: (i) 2.5 min., 4%; (ii) 4.2 min., 34%; (iii) 7.2 min., 48%; (iv) 11.0 min., 9%; (v) 16.8 min., 5%. Under the same conditions Ib had the same retention time as ii, and Ic had the same retention time as iii. When successive retention times were plotted against equal increments on the other coordinate axis the points fell on a smooth curve, suggesting that i, iv, and v were similar to Ib and Ic with side chains $-C_{17}H_{35}$, $-C_{23}H_{47}$, $-C_{25}H_{51}$, respectively.

The gas chromatograph was used as a preparative instrument. Because of the small capacity of the column, 3 mg. was the largest amount of sample which could be injected at a time. In this way 60 mg. of A-dimethyl ether was separated into five fractions, each of which was rechromatographed leading finally to five components of varying degrees of homogeneity (the numbering corresponds to that used above): (i) <1 mg. of a colorless solid, m.p. 50–52°, 95% purity (g.p.c.), ultraviolet spectrum, λ_{max} 273 and 280 mμ; (ii) 10 mg. of a colorless solid, m.p. 57–58.5°, 98% purity (g.p.c.), identified as Ib by mixture melting point and infrared spectrum; (iii) 14 mg. of a colorless solid, m.p. 63–64°, 98% purity (g.p.c.), identified as Ic by mixture melting point and infrared spectrum; (iv) 2 mg. of a colorless solid, m.p. 66–69°, 90% purity (g.p.c.), ultraviolet spectrum, λ_{max} 273 and 280 mμ; (v) <1 mg. of a colorless solid, m.p. 69–72°, 92% purity (g.p.c.), ultraviolet spectrum, λ_{max} 273 and 280 mμ.

Orcinol.—Commercial orcinol (pink, m.p. 106–108°) was sublimed at 1 μ and 100° (bath temperature), and the colorless sublimate was crystallized from benzene, giving needles, m.p. 107.5–108.5°; t.l.c., R_f 0.07; ultraviolet spectrum, λ_{max} 275 mμ (ϵ 1680), 281.5 (1660); infrared spectrum, μ_{max} 3.05 (s, hydroxyl); n.m.r. spectrum (deuterioacetone), 3-proton singlet at 2.18 p.p.m. (aromatic C–CH_3), 3-proton broad singlet at 6.25 p.p.m. (aromatic protons), and two singlets, approximate total 2 protons, one singlet at 8.10 p.p.m., independent of concentration, intensity increasing with increasing concentration, the other singlet appearing between 2 and 5 p.p.m., dependent on concentration (high-field position at low concentration), intensity decreasing with increasing concentration (hydroxylic protons).

2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-Dimethoxytoluenes.—The above toluenes were prepared by reduction and hydrogenolysis of the corresponding aldehydes. The aldehyde (1.00 g.) was dissolved in ethanol (100 ml.) containing concentrated hydrochloric acid (5 drops), and the mixture was subjected to hydrogenation at room temperature and 40 p.s.i. in the presence of 30% palladium on charcoal (0.10 g.). After 2 hr. the mixture was filtered through Celite to remove the catalyst, and the solvent eliminated from the filtrate leaving a residue which was distilled *in vacuo* to give the toluene. The yields are given in Table II.

TABLE II

YIELDS OF DIMETHOXYTOLUENES

Dimethoxytoluene	B.p. (bath temp. at 0.5 mm.), °C.	Yield, g.
2,3	90	0.84
2,4	85	0.83
2,5	90	0.86
2,6	110	0.83
3,4	90	0.85
3,5	90	0.88

Acknowledgment.—The authors are indebted to Mr. J. W. Chamberlin for valuable technical assistance.

Reaction of Triphenylbenzoylmethylenephosphorane with Benzoyl Peroxide

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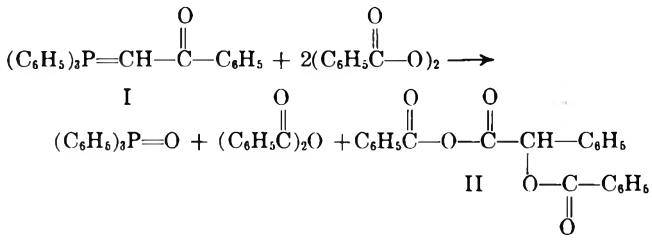
Triphenylbenzoylmethylenephosphorane reacts with benzoyl peroxide at room temperature to give triphenylphosphine oxide and a mixture of benzoic anhydride and benzoic benzoylmandelic anhydride. The formation of these products is rationalized mechanistically.

Several recent papers have described the reactions of phosphoranes with various oxidizing agents.[3] It was the purpose of the work now being reported to study the reactions of phosphoranes with benzoyl peroxide. Triphenylbenzoylmethylenephosphorane (I)



was taken as a representative of the more stable resonance stabilized phosphoranes. It was found that I reacts readily with benzoyl peroxide at room temperature in solvents such as carbon tetrachloride and chloroform. By a combination of analytical methods it was demonstrated that 2 moles of peroxide were required to consume 1 mole of phosphorane. The infrared spectra of several reaction mixtures had carbonyl bands which indicated that an ester as well as anhydrides had been formed. For example the infrared spectra of reaction mixtures in ethanol-free chloroform exhibited bands at 5.50, 5.55, 5.65, and 5.80 μ. Although the presence of these peaks does not prove that anhydrides and an ester were formed, their positions are in agreement with this postulate.[4] The formation of triphenylphosphine oxide also was indicated.

The reaction mixture from a reaction conducted in pure chloroform was treated with an aqueous solution of sodium bicarbonate and triethylamine. The basic hydrolysate yielded a mixture of acids on acidification. Spectral evidence, infrared and n.m.r., as well as evidence from other experiments to be cited indicated that this was a mixture of benzoic and benzoylmandelic acid. The nonhydrolyzed neutral material was found to be triphenylphosphine oxide contaminated with N,N-diethylbenzamide.[5]

When the reaction was conducted in commercial chloroform, *i.e.*, containing *ca.* 1% ethanol, and its course was followed by periodic inspection in the n.m.r., it was easily seen that some substance was being formed which was reacting with the ethanol. From such a reaction mixture there was isolated, after hydrolysis with sodium bicarbonate and triethylamine, ethyl benzoylmandelate. Another major product was triphenylphosphine oxide. From the basic extracts there was isolated a mixture of acids, whose spectral characteristics indicated benzoic and benzoylmandelic acids.

Periodic examination of the n.m.r. spectrum of a reaction mixture in pure chloroform showed that initially a peak at τ 3.60 appears and reaches a maximum but then diminishes in intensity and a new peak at τ 3.75 appears. On standing 7 days there was no further change in intensity or position of these peaks. The τ 3.60 peak was always considerably more intense than the τ 3.75 peak.

On the basis of the infrared data, the n.m.r. data, and the formation of ethyl benzoylmandelate, it seemed reasonable to suggest that the products of the reaction were benzoic anhydride and benzoic benzoylmandelic anhydride. In order to test this hypothesis mandelic acid was treated with benzoyl chloride in pyridine. This should lead to the initial formation of benzoic benzoylmandelic anhydride. The material obtained after a standard purification sequence had in the n.m.r. two general absorptions for aromatic protons and also peaks at τ 3.70 and 3.88 (carbon tetrachloride solvent). The τ 3.70 peak was by far the most intense of the two. After standing 1 year, the sample had solidified and the n.m.r. was investigated again. The τ 3.70 peak had disappeared and the τ 3.88 peak had grown much larger. A reaction conducted in carbon tetrachloride also had peaks at τ 3.70 and 3.88; the former being the most intense. The infrared spectra of the reaction mixture and the synthetic material were very similar in the carbonyl region. It was obvious though that the synthetic mixture contained much less benzoic anhydride. The band at 5.55 μ was considerably less intense than that of the reaction mixture. The 5.8-μ band was quite intense but this is undoubtedly due to the contribution of the ester carbonyl.

Although it was not possible to isolate the primary products from this reaction and it was necessary to resort to a second chemical reaction before isolation, the data point strongly to the equation illustrated. The τ 3.60 (chloroform) and 3.75 (carbon tetrachloride) peaks are assigned to the benzylic hydrogen of II.

(1) Rutgers Research Council Faculty Fellow, 1963–1964.

(2) National Defense Education Act Fellow, 1959–1962; Public Health Service Fellow, 1962–1963.

(3) (a) D. B. Denney, L. C. Smith, J. Song, C. J. Rossi, and C. D. Hall, *J. Org. Chem.*, **28**, 778 (1963); (b) D. B. Denney and S. T. Ross, *ibid.*, **27**, 998 (1962); (c) G. Maerkl, *Ber.*, **95**, 3003 (1962); (d) F. Ramirez, R. B. Mitra, and N. B. Desai, *J. Am. Chem. Soc.*, **82**, 5763 (1960).

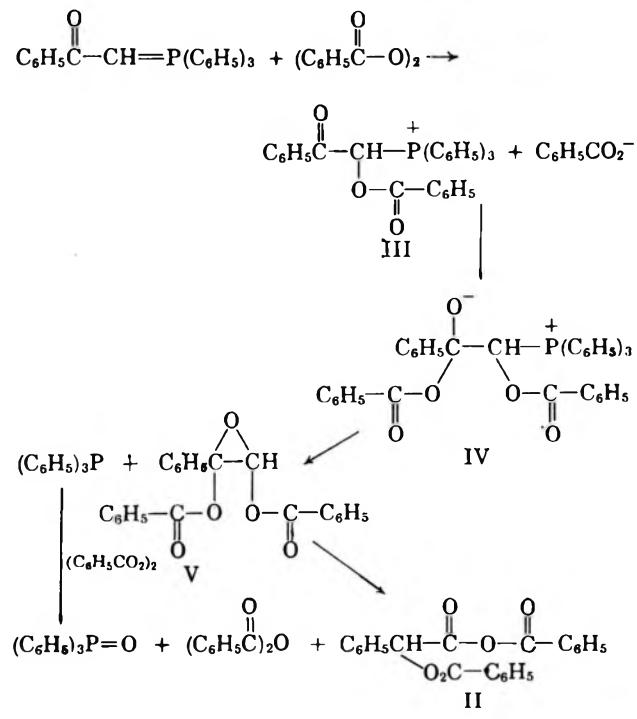
(4) L. J. Bellamy ["The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, New York, N. Y., 1958, Chap. 8] reports 5.59 and 5.79 μ for benzoic anhydride and *ca.* 5.50 and 5.72 μ for aliphatic and mixed aliphatic aromatic anhydrides. Benzoates (Chap. 11) absorb at *ca.* 5.80 μ.

(5) Several reaction mixtures were hydrolyzed by this technique. Invariably small amounts of N,N-diethylbenzamide were found in the neutral products. Initially it was thought that diethylamine, present as a contaminant in the triethylamine, was reacting with benzoic anhydride to give the amide. When triethylamine which was absolutely free of diethylamine was used, N,N-diethylbenzamide was still formed. A most likely explanation for this behavior is that small amounts of benzoyl peroxide present in the reaction mixture react with triethylamine to give diethylamine. This is a well-known reaction; see, for example, A. G. Davies, "Organic Peroxides," Butterworth and Co., London, England, 1961, pp. 135–136. The diethylamine then reacts with benzoic anhydride to give the amide.

Ethanolysis or hydrolysis by adventitious water gives rise to the τ 3.75 (chloroform) and 3.88 (carbon tetrachloride) peaks which are assigned to benzoylmandelic acid.[6] The concordance between the n.m.r. spectra of the synthetic material and that of the reaction mixture strongly supports this postulate. The formation of ethyl benzoylmandelate when ethanol is present in the reaction mixture is in complete accord with the formation of II. The mixed anhydride would be expected to react preferentially at the aliphatic carbonyl carbon atom and also it would react more rapidly than benzoic anhydride.[7] It should be noted that the n.m.r. spectrum of a reaction mixture run in chloroform containing ethanol did indicate that a small amount of ethyl benzoate was formed.

The nature of the reaction products, the relatively low temperatures required to effect the reaction, and the lack of attack on solvent suggest that the reaction is ionic in nature. In order to establish whether the reaction proceeds by an ionic or radical path it was conducted in the presence of three well-known inhibitors: galvinoxyl,[8] *trans*-stilbene,[9] and 2,6-di-*t*-butyl-4-methylphenol.[10] The course of the reactions were observed by comparing infrared spectra with those obtained from a reaction mixture which did not contain an inhibitor. In no case was there any noticeable effect on the course or rate of the reaction. It was noted that the galvinoxyl was destroyed (loss of color). This could well be due to its reaction with intermediates formed during the reaction, since it is quite a reactive substance.[8] The results of the experiments in the presence of inhibitors indicate that the reaction does not follow a radical path although there may be some radicals formed by side reactions.

The formation of the products can be rationalized by the mechanism in col 2. It is suggested that the phosphorane acts as a nucleophile and displaces on one of the peroxidic oxygens to give the ion pair (III). Nucleophilic displacements of this type are well-known.[11] Addition of benzoate ion to the carbonyl carbon to give IV followed by displacement of triphenylphosphine leads to V. The reaction of triphenylphosphine with benzoyl peroxide to give benzoic anhydride and triphenylphosphine oxide is well-known.[12] The sequence from III to V is reasonable and is supported by the observations that nucleophiles often add to the carbonyl carbon atom of α-halo ketones to give an intermediate alkoxide ion which displaces halide to yield a substituted epoxide similar to V.[13] Rearrangement of the epoxide leads directly to the mixed anhydride (II). The epoxide (V) should be particularly susceptible to rearrangement because development of a partial positive charge on either carbon of the epoxide ring is enhanced by the benzoyloxy and phenyl groups. It is interesting to note that the same product is obtained irrespective of whether phenyl or hydrogen migrates.



Other mechanisms can be written for the reaction; in particular, several ways can be devised for proceeding from III to II. It also is interesting to note that other phosphoranes will probably react with benzoyl peroxide to give intermediates similar to III. There seems to be no reason for predicting that the following reactions should be similar.

Experimental[14]

Benzoylmethylenetriphenylphosphorane (I).—The modified procedure of Ramirez and Dershowitz[15] gave yields of *ca.* 75%, m.p. 185–187°, lit.[15b] m.p. 186–188°.

Stoichiometry of the Reaction.—To a solution of 7.6 g. (0.02 mole) of I in 60 ml. of chloroform was added with stirring over 45 min. 4.84 g. (0.02 mole) of benzoyl peroxide in 40 ml. of chloroform. Titration of an aliquot for phosphorane[16] concentration and another for peroxide[17] concentration showed that all of the peroxide had reacted and *ca.* 50% of the phosphorane had reacted. Additional increments of benzoyl peroxide were added until a total of 2 moles of peroxide per mole of phosphorane had been added. At this point there was no phosphorane left and only a small amount of benzoyl peroxide was present.

Reaction of I with Benzoyl Peroxide in Stock Chloroform.—Benzoyl peroxide (43.7 g., 0.181 mole) in 300 ml. of chloroform was added with stirring to 34.3 g. (0.0903 mole) of I in 200 ml. of chloroform. A portion of the reaction mixture, 425 ml., was extracted with 400 ml. of 5% sodium bicarbonate solution. Acidification gave a solid which was taken up in ether. Evaporation of the dried (magnesium sulfate) ether solution gave 13.4 g. of material. The infrared spectrum of this material had typical

(6) In view of the isolation and structure proof of ethyl benzoylmandelate, it did not seem necessary to characterize more fully the mixture of acids obtained on hydrolysis. These all had the τ 3.75 (chloroform) and 3.88 (carbon tetrachloride) peaks.

(7) (a) P. S. Bailey and Y. G. Chang [*J. Org. Chem.*, **27**, 1192 (1962)] have shown that benzoic acetic anhydride reacts with ethanol to give 85% attack at the acetic carbonyl; (b) C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960).

(8) F. D. Greene, W. Adam, and J. E. Cantrill, *J. Am. Chem. Soc.*, **83**, 3461 (1961).

(9) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *ibid.*, **72**, 5426 (1950).

(10) K. U. Ingold, *Chem. Rev.*, **61**, 577 (1961).

(11) A. G. Davies, "Organic Peroxides," Butterworths and Co., London, England, 1961, Chap. 9.

(12) L. Horner and W. Jurgeleit, *Ann.*, **591**, 138 (1955).

(13) (a) T. I. Temnikova and N. I. Almashi, *Zh. Obshch. Khim.*, **23**, 1338 (1953); *Chem. Abstr.*, **48**, 12025 (1954); (b) R. Justoni, *Gazz. chim. ital.*, **69**, 378 (1939).

(14) Analyses were performed by G. Robertson, Florham Park, N. J. Melting points are corrected. N.m.r. spectra were obtained with a Varian A-60 spectrometer; τ-values are relative to tetramethylsilane as internal standard. G.l.p.c. analyses were conducted with an F & M Model 500 chromatograph using the conditions specified.

(15) (a) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957); (b) D. B. Denney and S. T. Ross, *ibid.*, **27**, 998 (1962).

(16) S. T. Ross and D. B. Denney, *Anal. Chem.*, **32**, 1896 (1960).

(17) L. S. Silbert and D. Swern, *ibid.*, **30**, 385 (1958).

acid absorption and two carbonyl peaks at 5.83 and 5.93 μ. The n.m.r. spectrum in trifluoroacetic acid had a peak at τ 3.70 and two sets of complex multiplets centered at *ca.* τ 1.96 and 2.52. The n.m.r. spectrum in chloroform had aromatic absorptions and a peak at τ 3.76 and in carbon tetrachloride this absorption was found at τ 3.85.

The extracted chloroform solution was stirred at room temperature for 45 hr. with a mixture of 350 ml. of 5% sodium bicarbonate solution and 50 ml. of triethylamine. Acidification of the bicarbonate extract yielded 18 g. of material whose infrared spectrum was identical with that of benzoic acid. The chloroform solution was extracted with four 300-ml. portions of 5% hydrochloric acid, 300 ml. of 5% sodium bicarbonate solution, 450 ml. of water, and then dried with magnesium sulfate. Removal of the solvent afforded an oil which was triturated with ether to give 19.6 g. of triphenylphosphine oxide, which gave no depression of melting point with an authentic sample. The infrared spectrum of this material was identical with that of an authentic sample. Evaporation of the ether triturant gave 19.7 g. of oil which was molecularly distilled. A number of fractions were collected. Two major fractions, 2.3 g. and 3.7 g., b.p. 100–122° (block) at 0.01 mm., were analyzed by g.l.p.c. on a 2-ft. silicone gum rubber column, programmed from 100–350° at 15°/min. The first fraction had two major components with retention times of 4.6 and 7.9 min. A sample of the 4.6-min. component was collected and shown to be N,N-diethylbenzamide. Its infrared spectrum and g.l.p.c. retention time were identical with that of an authentic sample. The second fraction showed one major component, retention time 8.0 min. A sample of this material was collected. Its n.m.r. and infrared spectra were identical with that of an authentic sample of ethyl benzoylmandelate. The total distillate, 14.4 g., consisted of these two components with ethyl benzoylmandelate constituting by far the major amount.

Ethyl Benzoylmandelate.[18]—This compound was prepared by acid-catalyzed esterification with ethanol followed by benzoylation with benzoyl chloride in pyridine. The infrared spectrum had two carbonyl bands at 5.7 and 5.8 μ. The n.m.r. spectrum in carbon tetrachloride had two multiplets of aromatic protons centered at τ 2.0 and 2.6, benzylic proton at τ 3.97, quartet of methylene protons at τ 5.82, and a triplet (methyl) at τ 8.78. The integrated ratio was 2:8:1:2:3. The n.m.r. spectrum in chloroform showed slight shifts, *ca.* τ 0.03, of all peaks except for the benzylic proton which was found at τ 3.85.

Reaction of I with Benzoyl Peroxide in Ethanol-Free Chloroform.—In this reaction the molar ratio of 2:1 peroxide–phosphorane was used. The conditions and quantities were essentially as before. After the extraction with triethylamine and sodium bicarbonate solution, there was obtained 75% of mixed benzoic and benzoylmandelic acids. The neutral residue consisted of triphenylphosphine oxide, N,N-diethylbenzamide, and most probably some benzoic anhydride, since more benzoic acid was obtained on further extractions with bicarbonate solutions.

Spectral Measurements on Reaction Mixtures.—A reaction mixture A in ethanol-free chloroform showed after 2 hr. two complex multiplets at τ 1.8 and 2.5 and a single peak at τ 3.60. After 6 hr. a small peak appeared at τ 3.75; at 25 hr. the peak at τ 3.60 had decreased in intensity and that at τ 3.75 had increased, although it was still less intense than the τ 3.60 peak. Little further change was noted. The infrared spectrum showed carbonyl absorption at 5.50, 5.55, 5.65, and 5.80 μ.

A similar reaction mixture B in ethanol containing chloroform after 2 hr. had τ 1.8 and 2.5 complex multiplets and two single peaks at τ 3.58 and 3.85, also methylene and methyl protons. After 25 hr. the peak at τ 3.58 had decreased in intensity and a new peak appeared at τ 3.75. The τ 3.85 peak had increased in intensity. After 7 days the τ 3.58 peak was gone. A small peak at τ 3.75 remained. The τ 3.85 peak had increased and was by far the major absorption in this region. Two quartets of methylene protons centered at τ 5.65 and 5.85 and two triplets of methyl protons at τ 8.67 and 8.85 were present. The n.m.r. spectrum of ethyl benzoate had a quartet at τ 5.65 and triplet at τ. 8.65 The other ethyl group agrees well with that of ethyl benzoylmandelate.

A reaction mixture in carbon tetrachloride had after 20 hr. two sets of complex multiplets at τ 1.9 and 2.7 and two single peaks at τ 3.68 and 3.90. The τ 3.68 peak was considerably more intense than the τ 3.90 peak.

Reaction of Mandelic Acid and Benzoyl Chloride.—To a solution of 1.52 g. (0.01 mole) of mandelic acid and 1.58 g. (0.02 mole) of pyridine in 25 ml. of ethanol-free chloroform was added 2.82 g. (0.02 mole) of benzoyl chloride in 10 ml. of chloroform. After 30 min. the solution was extracted with 12 ml. of 1% hydrochloric acid, 20 ml. of 5% sodium bicarbonate solution, and 25 ml. of water. The dried (magnesium sulfate) solution was evaporated to give 3.30 g. of clear oil. The infrared spectrum had bands in the carbonyl region at 5.50, 5.60, 5.75 and 5.80 μ. The n.m.r. spectrum in carbon tetrachloride had two sets of complex multiplets at *ca.* τ 1.9 and 2.6 and two single peaks at 3.70, most intense, and 3.88. After standing 1 year the oil had solidified. The τ 3.70 peak had disappeared and the τ 3.88 peak had greatly increased in intensity. The bands at 5.50 and 5.60 μ had disappeared and there remained one strong band at 5.75 μ with a shoulder at 5.80 μ. Typical acid absorption in the 3–4-μ region was present.

Reaction of Benzoylmethylenetriphenylphosphorane with Benzoyl Peroxide in the Presence of Galvinoxyl.—A solution of 0.39 g. (0.001 mole) of I and 0.04 g. (0.0001 mole) of galvinoxyl in 10 ml. of stock chloroform at room temperature showed no visible color change after standing 30 min. Benzoyl peroxide (0.49 g., 0.002 mole) was added. The infrared spectrum was taken five times over 1 hr. and at the end of 2, 4, and 8 hr. Comparison with spectra taken on a solution of the same composition but without galvinoxyl showed them to be essentially identical. The deeply colored solution faded rapidly and after 100 min. it was light yellow. No further color change was noted.

Reaction of Benzoylmethylenetriphenylphosphorane with Benzoyl Peroxide in the Presence of *trans*-Stilbene.—A solution of the same composition as that described before except for the inclusion of 0.36 g. (0.002 mole) of *trans*-stilbene was subjected to periodic infrared examination. Comparison with the spectra of the control showed that the rate of disappearance of the benzoyl peroxide was the same in both cases. The characteristic 10.36-μ band of *trans*-stilbene did not alter in intensity.

Reaction of Benzoylmethylenetriphenylphosphorane with Benzoyl Peroxide in the Presence of 2,6-Di-*t*-butyl-4-methylphenol.—A solution of the same composition as used above except for the addition of 0.08 g. (0.0004 mole) of 2,5-di-*t*-butyl-4-methylphenol was subjected to periodic infrared examination. Comparison with the spectra of the control showed that the rate of disappearance of the benzoyl peroxide was the same in both cases. The characteristic 2.7-μ band of the phenol did not diminish in intensity.

Acknowledgment.—Funds for the purchase of the n.m.r. spectrometer were provided in part by the National Science Foundation.

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2,4-Dinitrophenylhydrazones. V. The Formation of 1-(2,4-Dinitrophenyl)pyrazolines from Methylol Ketones[1,2]

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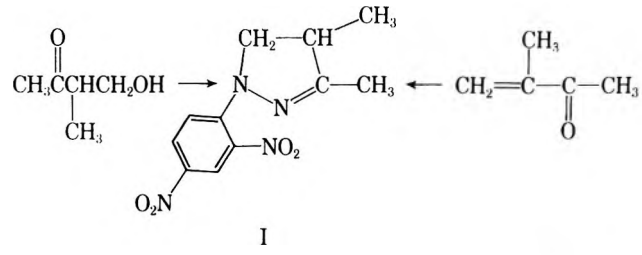
It is found that the reaction of 2,4-dinitrophenylhydrazine with 3-methyl-4-hydroxybutanone and 3-hydroxymethyl-4-heptanone gives the 2,4-dinitrophenylhydrazones of the dehydrated ketones rather than the isomeric 2,4-dinitrophenylpyrazolines. The authentic pyrazolines and 3-(2-methyl-3-oxobutyl)-6-nitrobenzotriazole 1-oxide are reported. It appears that, in contrast to general belief, the reaction of methylol ketones with 2,4-dinitrophenylhydrazine does not lead to 1-(2,4-dinitrophenyl)-2-pyrazolines.

Until n.m.r. spectroscopy became available as an analytical tool it was not easy to distinguish unsaturated 2,4-dinitrophenylhydrazones from the isomeric 1-(2,4-dinitrophenyl)-2-pyrazolines. Although it is thought that the reaction of 2,4-dinitrophenylhydrazine with an α,β-unsaturated carbonyl compound gives the 2,4-dinitrophenylhydrazone rather than the pyrazoline, reaction with some types of β-substituted carbonyl compounds is regarded as a method of synthesizing the corresponding pyrazolines.[3] Among these are β-hydroxy ketones. In the previous paper[4] it was shown that the reaction of some β-alkoxy ketones with 2,4-dinitrophenylhydrazine resulted in the formation of some new compounds, the 3-(3-oxoalkyl)-6-nitrobenzotriazole 1-oxides. We were able to distinguish among the isomeric 2,4-dinitrophenylhydrazones, pyrazolines, and benzotriazole oxides by absorption and n.m.r. spectroscopy. It also was found that 4-hydroxybutanone reacted similarly to give 3-(3-oxobutyl)-6-nitrobenzotriazole 1-oxide. It was noted that this result contrasted with reports that the reaction of β-hydroxy ketones with 2,4-dinitrophenylhydrazine gave the 2,4-dinitrophenylpyrazolines.[5-8] In order to clarify this phase of pyrazoline chemistry we have re-examined some of the cases in the literature and find that the products reported appear to be not the pyrazolines but the unsaturated 2,4-dinitrophenylhydrazones and, in one case, the isomeric benzotriazole oxide.

Results and Discussion

3-Methyl-4-hydroxybutanone.—It is reported[5] that the boiling of this ketone for several hours with 2,4-dinitrophenylhydrazine in an acidic ethyl alcohol solution gave 1-(2,4-dinitrophenyl)-3,4-dimethylpyrazoline (I). Similar treatment of methyl isopropenyl ketone also gave I.

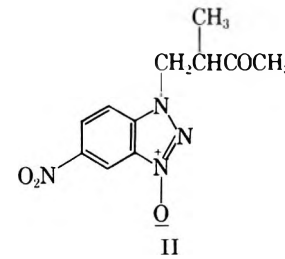
The melting point of the product was 191°. We have repeated these experiments. Preparation of the 2,4-dinitrophenylhydrazone of methyl isopropenyl ketone by the diglyme method[9] for α,β-unsaturated ketones



I

gave the red derivative, m.p. 192.7–193.7°, λ_{max}^{EtOH} 369 mμ. An identical product was obtained by treating the methylol ketone as described.[5] Authentic I was made from 3,4-dimethylpyrazoline by the method of Chambers and Willard.[10] The product had m.p. 108.5–110.5°, λ_{max}^{EtOH} 392 mμ. The 2,4-dinitrophenylhydrazone of methyl isopropenyl ketone is reported by Martin[11] as having m.p. 190°, λ_{max}^{EtOH} 371 mμ. The ultraviolet absorption maximum for authentic I is consistent with 391 mμ for the 3-methyl- and 394 mμ for the 3-ethyl-1-(2,4-dinitrophenyl)pyrazolines described in our last paper.[4]

Because we had found that 4-hydroxybutanone in similar circumstances gave a ketoalkyl benzotriazole oxide we were interested in preparing the analogous compound in the present case. This was achieved by the reaction of 6-nitrobenzotriazole oxide with methyl isopropenyl ketone. The product (II) had m.p. 181.3–181.8°, λ_{max}^{EtOH} 263 and 349 mμ, and showed a strong carbonyl absorption at 1730 cm.$^{-1}$.



II

It also is reported elsewhere[6] that the reaction of 3-methyl-4-hydroxybutanone with 2,4-dinitrophenylhydrazine gives the pyrazoline (I), but the melting point is given as 180–181.5°. It appears that the product may have been II rather than the pyrazoline.

We report also the 2,4-dinitrophenylhydrazone of the 3-methyl-4-hydroxybutanone, prepared by the diglyme method[9] and having the m.p. 107–109°, λ_{max}^{EtOH} 361 mμ.

(1) Taken from the M. S. degree thesis of Miss Julie Y.-F. Tsai, Texas Technological College, August, 1963.

(2) This work was supported by Grant No. 1603-AD(2) and by the Institute of Science and Engineering, Texas Technological College.

(3) T. L. Jacobs, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 64–68.

(4) H. J. Shine, L.-T. Fang, H. E. Mallory, N. F. Chamberlain, and F. Stehling, *J. Org. Chem.*, **28**, 2326 (1963).

(5) G. T. Morgan and E. L. Holmes, *J. Chem. Soc.*, 2667 (1932).

(6) K. Koeda, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **72**, 1022 (1951); *Chem. Abstr.*, **47**, 3239 (1953).

(7) R. L. Wear, *J. Am. Chem. Soc.*, **73**, 2390 (1951).

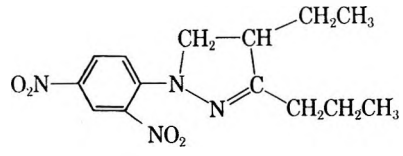
(8) A. S. Spriggs, C. M. Hill, an ' G. W. Senter, *ibid.*, **74**, 1555 (1952).

(9) H. J. Shine, *J. Org. Chem.*, **24**, 1790 (1959).

(10) W. L. Chambers and M. L. Willard, *J. Am. Chem. Soc.*, **82**, 3373 (1960).

(11) G. Martin, *Ann. chim.* (Paris), [13]**4**, 541 (1959).

3-Hydroxymethyl-4-heptanone.—The product of reaction of this ketone with 2,4-dinitrophenylhydrazine is described[7] as 1-(2,4-dinitrophenyl)-3-propyl-4-ethylpyrazoline (III), m.p. 118–119.5°. This is actually the



III

2,4-dinitrophenylhydrazone of 2-ethyl-1-hexen-3-one, m.p. 119.5–120.5°, λ_{max}^{EtOH} 370 mμ, which we have made from the methylol ketone and directly by the diglyme method from the unsaturated ketone.

The authentic III was made and has m.p. 73.7–76.2°, λ_{max}^{EtOH} 393 mμ.

We were unable to prepare the corresponding 6-nitrobenzotriazole oxide or the 2,4-dinitrophenylhydrazone of the methylol ketone.

Thus, it is found in these examples that the reaction of 2,4-dinitrophenylhydrazine with β-hydroxy ketones does not lead to the pyrazolines. By analogy, it seems probable that the three pyrazolines reported by Spriggs, Hill, and Senter[8] are the 2,4-dinitrophenylhydrazones of the corresponding unsaturated ketones. These examples[8] were not reinvestigated by us.

Experimental[12]

Reaction with 3-Methyl-4-hydroxybutanone.—This compound was prepared as described by Morgan and Holmes,[5] and had b.p. 82–87° (11 mm.), $n^{20}D$ 1.4319. The 2,4-dinitrophenylhydrazone was prepared in diglyme[9] and recrystallized from methanol, m.p. 107–109°.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 47.01; H, 5.12; N, 19.66.

Three grams of the ketone was boiled for 6 hr. (to complete solution) with 3 g. of 2,4-dinitrophenylhydrazine and 0.5 ml. of concentrated hydrochloric acid in 20 ml. of ethyl alcohol. The red precipitate which formed on cooling was recrystallized from ethyl acetate and had m.p. 195.5–196°. The infrared spectrum (potassium bromide pellet) was identical with that of the 2,4-dinitrophenylhydrazone of methyl isopropenyl ketone.

Methyl isopropenyl ketone was prepared from the commercially available dimer (Chemical Intermediates and Research Laboratories, Cuyahoga Falls, Ohio). After fractional distillation, the product had b.p. 89–92° (680 mm.), $n^{20}D$ 1.4230; lit.[11] b.p. 98° (760 mm.), $n^{20}D$ 1.4232. The 2,4-dinitrophenylhydrazone had m.p. 192.7–193.7° (ethyl acetate); lit.[11] m.p. 190°.

Anal. Calcd. for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.95; H, 4.52; N, 20.81.

3-(2-Methyl-3-oxobutyl)-6-nitrobenzotriazole 1-Oxide (II).—A solution containing 0.5 g. of methyl isopropenyl ketone and 5 drops of concentrated hydrochloric acid was shaken overnight with 0.5 g. of 6-nitrobenzotriazole 1-oxide. Bright yellow crystals had formed and most of the 6-nitrobenzotriazole oxide had disappeared. The filtered solids were washed with hot water, and the residue was crystallized from hot ethyl alcohol–acetone. Yellow needles, m.p. 181.3–181.8°, formed. The infrared spectrum (potassium bromide pellet) was very similar to the spectra of the oxobutyl and oxopentyl analogs.[4]

Anal. Calcd. for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.69; H, 4.56; N, 21.40.

1-(2,4-Dinitrophenyl)-3,4-dimethylpyrazoline (I).—Methyl isopropenyl ketone and hydrazine hydrate were used to prepare 3,4-dimethylpyrazoline. The method of Beech, Turnbull, and Wilson[13] was used. The preparation was carried out under nitrogen, and the product was distilled under nitrogen. The crude product, b.p. 40–60° (3 mm.), was used for reaction in ether with 1-bromo-2,4-dinitrobenzene as described by Chambers and Willard.[10] The yellow product was crystallized from ether–petroleum ether (b.p. 30–60°) and had m.p. 108.5–110.5°.

Anal. Calcd. for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.91; H, 4.55; N, 20.94.

Reactions with 3-Hydroxymethyl-4-heptanone.—This compound was prepared from ethyl ketene dimer as described by Wear.[7] The product had b.p. 94–99° (5 mm.), $n^{20}D$ 1.4426; lit.[7] b.p. 75° (1.5 mm.), $n^{23}D$ 1.4389.

Three grams of the ketone, 4 g. of 2,4-dinitrophenylhydrazine, and 0.5 ml. of concentrated hydrochloric acid were boiled for 3 hr. The red precipitate obtained on cooling was crystallized from ethyl alcohol–ethyl acetate, petroleum ether–ethyl acetate, and finally ethyl alcohol, to give red needles, m.p. 120.5–121°.

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 55.03; H, 6.09; N, 18.53.

Treating the methylol ketone with 2,4-dinitrophenylhydrazine by a standard method for making 2,4-dinitrophenylhydrazones[14] gave red needles (ethyl alcohol), m.p. 120.5–121°. This had an infrared spectrum (potassium bromide pellet) identical with the product, m.p. 120.5–121°, reported above and with the 2,4-dinitrophenylhydrazone of the unsaturated ketone, below.

2-Ethyl-1-hepten-3-one.—This was prepared in poor yield by the *p*-toluenesulfonic acid-catalyzed dehydration of the methylol ketone. The product had b.p. 95° (95 mm.), $n^{20}D$ 1.4356. A better yield of the ketone was obtained by the longer chloromethylation and dehydrohalogenation procedure described by Colonge.[15] The product had b.p. 70–74° (40 mm.), $n^{20}D$ 1.4344; lit.[15] b.p. 157–159° (742 mm.), $n^{18}D$ 1.4408.

The 2,4-dinitrophenylhydrazone, prepared in diglyme,[9] had m.p. 119.5–120.5°.

An attempt to convert the unsaturated ketone to the substituted 6-nitrobenzotriazole oxide by reaction with 6-nitrobenzotriazole 1-oxide in acidic ethyl alcohol was unsuccessful.

1-(2,4-Dinitrophenyl)-3-propyl-4-ethylpyrazoline.—The 2-ethyl-1-hexen-3-one was converted to 3-propyl-4-ethylpyrazoline by the standard method.[13] The crude product, b.p. 86–91° (7 mm.), was used directly to prepare the 1-(2,4-dinitrophenyl)-pyrazoline.[10] The product was an oily solid which was recrystallized only with difficulty several times from petroleum ether and finally from *n*-hexane to give a product with m.p. 73.7–76.2°.

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.66; H, 6.24; N, 18.03.

(12) Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(13) S. G. Beech, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 4686 (1952).

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(15) J. Colonge, *Bull. soc. chim. France*, [5]3, 2116 (1936).

Rearrangement and Cleavage of 2-Aryliodoniobenzoates. Trapping Agents for Benzyne[1-3]

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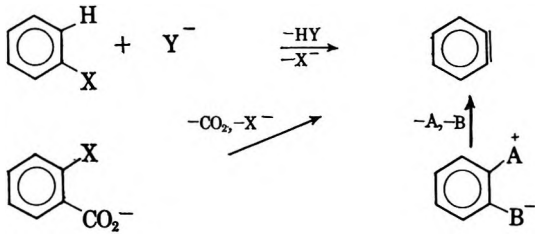
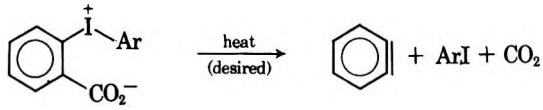
Acid-catalyzed condensation of 2-iodosobenzoic acid with benzene, mesitylene, and cyclohexylbenzene has given 2-carboxydiphenyliodonium salts, which were converted by base to the corresponding betaines, 2-aryliodoniobenzoates. On heating, these betaines rearrange in part to aryl 2-iodobenzoates. A competitive thermal reaction of the betaines, favored at higher temperatures, is cleavage to aryl iodides, carbon dioxide, benzyne, and other reactive intermediates, whose structure and further reactions are discussed. The efficiency of benzyne-trapping reagents increases in the order: anthracene < 1,3-diphenylisobenzofuran < 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone) < 2,5-bis(*p*-dimethylaminophenyl)-3,4-diphenylcyclopentadienone < 2,5-di-*p*-anisyl-3,4-diphenylcyclopentadienone.

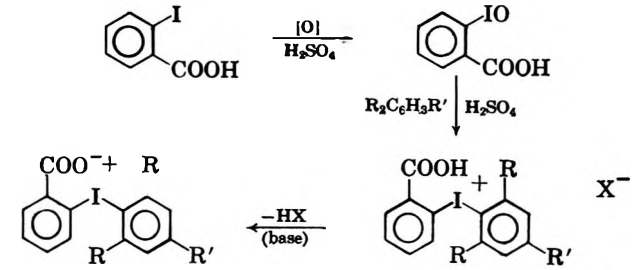
The reactive, highly unsaturated benzyne[5] is prepared by the removal of two *ortho* substituents from substituted benzenes in three ways: removal of hydrogen and an *ortho* substituent by strong base,[5] loss of carbon dioxide and halide ion (pyrolysis of an *o*-halobenzoate ion[6]), and loss of two *ortho* substituents as stable molecules.[5,7,8]



In previous examples of the third method $-A^+$ has been the diazonio group ($-N_2^+$) while $-B^-$ has been the carboxylate ion[7] ($-CO_2^-$) or the sulfinate ion[8] ($-SO_2^-$). An aim of the present work was to investigate the possibility that the decomposition of the stable betaine 2-phenyliodoniobenzoate[3] (diphenyliodonium-2-carboxylate) might provide an additional route to benzyne.



Preparation of Betaines.—Previously, 2-phenyliodoniobenzoate was prepared by the oxidation of 2-iodobenzoic acid to 2-iodosobenzoic acid in sulfuric acid, followed by addition of benzene to allow condensation to an iodonium salt.[3] In the present work it was found preferable to isolate 2-iodosobenzoic acid[9] and effect separately its condensation with benzene, mesitylene, and cyclohexylbenzene.



I, R = R′ = H
II, R = R′ = CH_3
III, R = H; R′ = cyclohexyl

$X^- = HSO_4^-$ or I^-

In aprotic solvents the solubilities of the betaines, formed by treatment of the iodonium salts with base, increased with alkylation of the phenyl group. The importance of such solubility lies in the fact that reaction of betaines in solution is more rapid than those of betaines in the solid state.[10]

Thermal Reactions of Betaines.—Exploratory work showed that betaine I and II dissolved in halobenzenes and γ-butyrolactone at about 100° and in diglyme (β-methoxyethyl ether) at about 120°; betaine III, from cyclohexylbenzene, was more soluble. Slow carbon dioxide evolution began above 130° and increased in rate and total amount with temperature.

TABLE I

PRODUCTS FROM 2-ARYLIODONIOBENZOATES ON HEATING IN THE ABSENCE OF BENZYNE-TRAPPING REAGENTS

Betaine	Solvent	Temp., °C.	Hours	Yield, % IV	V	VI	VII
I	C_6H_5I	100	150	*a*	100[b]		
		130	20	*a*	54	10	*a*
		150	4	*a*	30	12	15
	Diglyme	162	2	42	20	13	10
	Lactone[c]	204	2	44	6	30	6
II	Triglyme	175	2	72	5	4	*a*
III	Xylene	138	2	33	25	4	*a*
	C_6H_5Br	155	2	29	20	10	*a*

[a] Not determined. [b] In 5% conversion. [c] γ-Butyrolactone.

(1) This article is taken from the dissertation of Samuel J. Huang, submitted in partial fulfillment of the requirement of the degree of Doctor of Philosophy (Chemistry).

(2) Diaryliodonium Salts. XX. Preceding article: F. M. Beringer and P. S. Forgione, *Tetrahedron*, **19**, 739 (1963).

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(6) E. McNelis, *J. Org. Chem.*, **28**, 3188 (1963). This work makes unlikely the formation of xanthone by decomposition of halobenzoate through a disalicylide intermediate.

(7) (a) M. Stiles and R. G. Miller, *J. Am. Chem. Soc.*, **82**, 3802 (1960); M. S. Barry, G. N. Spokes, and M. Stiles, *ibid.*, **82**, 5240 (1960); M. Stiles, R. G. Miller, and U. Burckhardt, *ibid.*, **85**, 1792 (1963); R. G. Miller and M. Stiles, *ibid.*, **85**, 1798 (1963); (b) L. Friedman and F. M. Loguilo, *ibid.*, **85**, 1549 (1963).

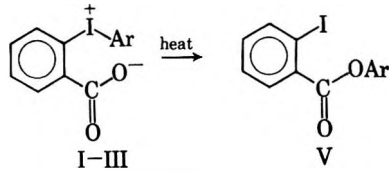
(8) G. Wittig and R. W. Hoffmann, *Angew. Chem.*, **73**, 435 (1961).

(9) (a) V. Meyer and W. Wachter, *Ber.*, **25**, 2632 (1892); P. Askenasy and V. Meyer, *ibid.*, **26**, 1354 (1893); (b) D. Twiss and R. V. Heinzelmann, *J. Org. Chem.*, **15**, 496 (1950).

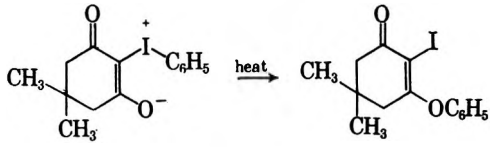
(10) It has long been known that diphenyliodonium iodide dissolved in iodobenzene decomposes faster than the same salt in the solid state: C. J. Fletcher and C. N. Hinshelwood, *J. Chem. Soc.*, 596 (1935).

In the absence of added benzyne-trapping reagents the other main products were aryl iodides (IV), aryl 2-iodobenzoates (V), xanthone (VI), and 3,4-benzocoumarin (VII), as summarized in Table I.

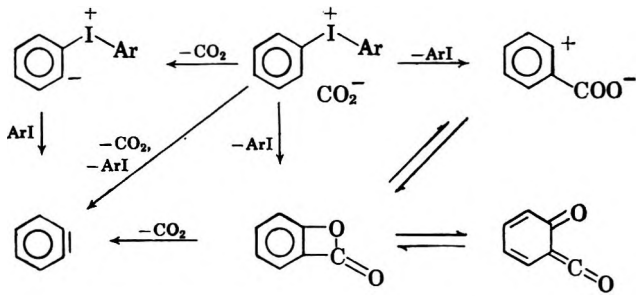
Rearrangement.—At the low end of the temperature range for thermal reaction of the betaines the predominant path is rearrangement to aryl 2-iodobenzoates (V), possibly by intramolecular nucleophilic displacement. Indeed when betaine I was heated in iodobenzene at 100° for 7 days, the only product found was phenyl 2-iodobenzoate, in 5% conversion.



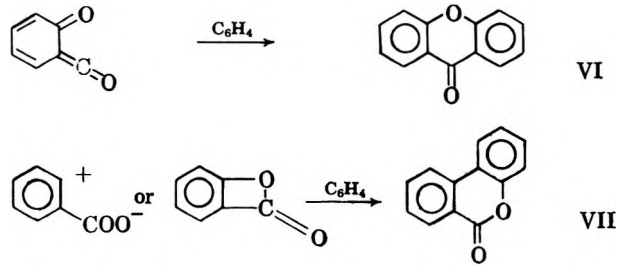
Such a rearrangement is closely relatedly to that of a betaine from dimedone.[11]



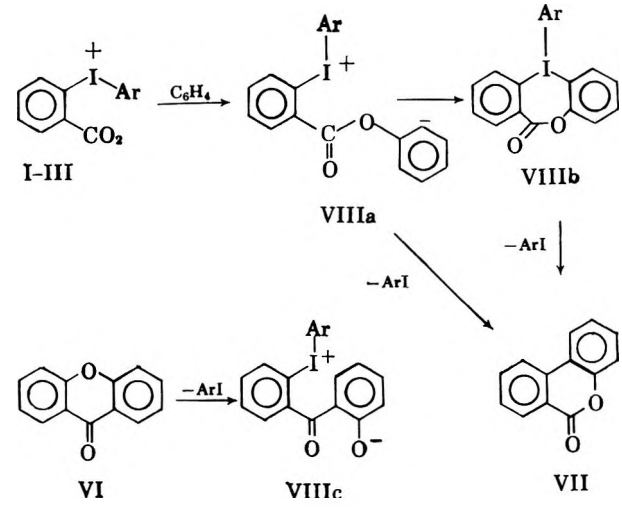
Thermal Cleavage Reactions.—To facilitate discussion, a schematic chart is now given to summarize other possible competitive modes of "decomposition" proceeding by cleavage of the betaines. In the absence of benzyne-trapping reagents these intermediates



may react to give xanthone (VI) and the isomeric lactone 3,4-benzocoumarin (VII). The structures of the products suggest the natures of the intermediates.

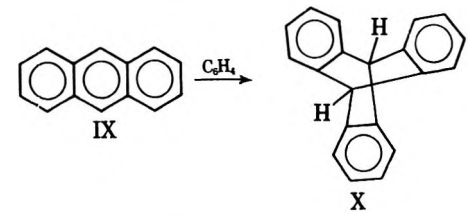


The formation of xanthone[6] and 3,4-benzocoumarin also can be rationalized as arising from the addition of benzyne to betaine,[5] giving intermediates VIIIa[6] and/or VIIIb[12] which undergo ring closure with loss of iodobenzene to give 3,4-benzocoumarin (VII). The intermediate VIIIa also may rearrange to VIIIc which undergoes ring closure with loss of iodobenzene to give xanthone (VI).



While the intermediacy of benzyne seems highly probable (and is confirmed by trapping experiments, which follow), a choice between the various reaction paths for forming or utilizing benzyne is not now possible.

Trapping of Benzyne with Anthracene.—When analytically pure betaine I was heated at 222° with an equivalent of anthracene (IX) in triglyme, 22% of triptycene (X) was formed.[13] When the reaction was run with four equivalents of I, 90% of triptycene was isolated. However, when the same reaction was run



in diglyme at 162°, no triptycene was isolated. Rather, the main products were phenyl 2-iodobenzoate, iodobenzene, carbon dioxide, xanthone, and a compound of unknown structure, $C_{28}H_{18}O_4$, m.p. 270–272°. Subsequently, it was found that catalytic amounts of cupric sulfate, silver acetate, molecular iodine, or the unknown impurities in crude betaine[14] allow the formation of 16–30% of triptycene under the same conditions (Table II). The origin of the catalytic effects is not known.

Other Trapping Reagents for Benzyne.—When betaine I was heated at 162° in diglyme containing 1,3-diphenylisobenzofuran (XI), 21% of 9,10-diphenylanthracene (XIII) was formed. The intermediate 9,10-epoxy-9,10-diphenyl-9,10-dihydroanthracene[15] (XII) was isolated when the reaction was run in triglyme

(11) O. Neilands, G. Vanags, and E. Gudriniece, *J. Gen. Chem., USSR*, **28**, 1258 (1958).

(12) (a) F. M. Beringer, J. W. Dehn, Jr., and M. Winicov, *J. Am. Chem. Soc.*, **82**, 2548 (1960); (b) K. Clauss, *Ber.*, **88**, 268 (1955).

(13) (a) The isolation of triptycene from the thermal decomposition of 2-phenyliodoniobenzoate in the presence of anthracene, carried out in this laboratory, has been reported by F. A. Weinstein (B. S. thesis, Polytechnic Institute of Brooklyn, 1961). (b) While the present work was in progress, a communication was published reporting the same reaction: E. LeGoff, *J. Am. Chem. Soc.*, **84**, 3786 (1962).

(14) Betaine prepared according to the procedures of 13a and 13b was found to contain 1–2% of uncombustible impurities.

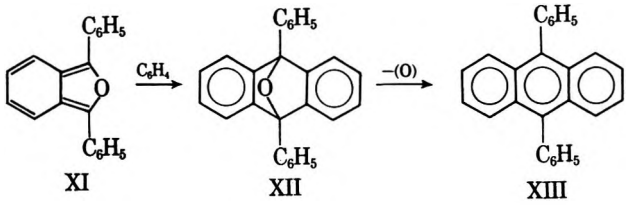
(15) G. Wittig, E. Knauss, and K. Niethammer, *Ann.*, **630**, 16 (1960).

TABLE II

TRIPTYCENE FORMED BY HEATING BETAINE I IN THE PRESENCE OF ANTHRACENE[a]

Solvent	Temp., °C.	Hours	Catalyst[b]	Yield triptycene, %
Diglyme	162	2	None	0
			I_2	30
			$CuSO_4$	24
			AgOAc	16
			c	18
			Others[d]	0
C_6H_5X[e]	132	3	I_2	Trace
C_6H_5Br	155	3	I_2	14
C_6H_5I	189	3	I_2	23
Triglyme	222	2	None	22, 90[f]

[a] One equivalent of anthracene. [b] One-tenth equivalent of catalyst. [c] Unidentified impurities in crude betaine. [d] Copper powder, potassium *t*-butoxide, potassium persulfate, and sodium hydroxide. [e] Chlorobenzene and iodobenzene, separately. [f] One-fourth equivalent of anthracene.



XI XII XIII

at 222° for 15 min. The conversion of XII to XIII could be achieved by heating in diglyme at 162° for 2 hr. or by reduction with zinc dust in acetic acid.

Decomposition of betaine I in the presence of tetracyclone[16] (XIVa) gave 1,2,3,4-tetraphenylnaphthalene (XVa) in 36–57% yield depending on solvent and reaction temperature (Table III).

TABLE III

DECOMPOSITION OF BETAINE I IN THE PRESENCE OF VARIOUS BENZYNE-TRAPPING REAGENTS[a]

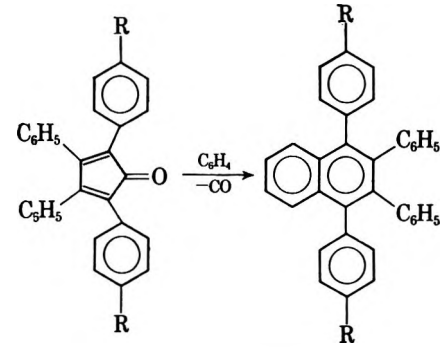
Reagent	Solvent	Temp., °C.	Hours	Yield product, %
IX	Diglyme	162	2	0 (X)
	Triglyme	222	2	22
XI	Diglyme	162	2	21 (XIII)
XIVa	Diglyme	162	2	36 (XVa)
	Lactone[b]	204	0.25	56
	Triglyme	222	0.25	57
XIVb	Lactone[b]	204	0.5	79 (XVb)
XIVc	Lactone[b]	204	0.5	65 (XVc)

[a] Equivalent amounts of reagent and betaine I. [b] γ-Butyrolactone.

2,5-Di-*p*-anisyl-3,4-diphenylcyclopentadienone (XIVb) was found to be the most effective benzyne-trapping reagent among those studied. In a reaction of betaine I with XIVb (1:1 molar ratio) in γ-butyrolactone at 204°, 79% of 1,4-di-*p*-anisyl-2,3-diphenylnaphthalene (XVb) was isolated. This suggests that addition reactions of benzyne are favored by increased electron density in the diene. These results are in agreement with the observation of Romanelli and Becker[17] that the reaction of methyl phenylpropiolate with substituted tetracylones is speeded by high electron density in the tetracyclone.

(16) This reaction, mentioned in ref. 13b, also has been studied by Professor L. F. Fieser (private communication).

(17) M. G. Romanelli and E. I. Becker, *J. Org. Chem.*, **27**, 662 (1960).



XIVa, R = H
b, R = OCH_3
c, R = $N(CH_3)_2$

XVa, R = H
b, R = OCH_3
c, R = $N(CH_3)_2$

Experimental[18]

Starting Materials.—Solvents were purified by passage through alumina columns and distillation. Reagent grade chemicals were distilled or recrystallized before used.

2-Iodosobenzoic Acid.—2-Iodobenzoic acid (148.8 g., 0.6 mole) in 200 ml. of concentrated sulfuric acid and 100 ml. of fuming nitric acid was heated at 100° for 1 hr. The mixture after cooling was poured into ice–water, and the resulting yellow precipitate was filtered, washed with water, and dried to give 144 g. (0.55 mole, 92%) of 2-iodosobenzoic acid. Recrystallization from water gave white crystals, m.p. 200° dec., lit.[9] m.p. 200° dec.

2-Phenyliodoniobenzoate (I).—To a solution of 26.4 g. (0.1 mole) of 2-iodosobenzoic acid in 100 ml. of concentrated sulfuric acid at 0–5° there was added 100 ml. of benzene. The mixture was stirred for 4 hr. at room temperature and then poured into ice–water. Crystalline 2-carboxydiphenyliodonium bisulfate was collected. Addition to the filtrate of 40 ml. of saturated potassium iodide solution gave pale yellow crystals of 2-carboxydiphenyliodonium iodide, which were also collected. The combined iodonium salts were stirred vigorously with 100 ml. of 5 *N* sodium hydroxide to give a tan precipitate. This was collected, washed with water, and dried to give 29.2 g. (0.09 mole, 90%) of 2-phenyliodoniobenzoate (I). Recrystallization from chloroform–methanol (30/70 by volume) gave colorless crystals, m.p. 205° dec.; ultraviolet absorption maxima, $\lambda_{max}^{H_2O}$ 205 mμ (log ε 4.43), 266 (4.02); principal bands in infrared spectrum (potassium bromide), 3005 (w), 1630 (s), 1524 (s), 1400 (m), 1335 (s), 1005 (w), 995 (w), 817 (m), 738 (s), 720 (s), and 685 cm.$^{-1}$ (m). The n.m.r. spectrum showed absorption bands with fine structures for ring hydrogens from τ 1.46 to 3.28.

Anal. Calcd. for $C_{13}H_9IO_2$: C, 48.14; H, 2.78; I, 39.19. Found: C, 48.13; H, 2.92; I, 39.58.

Recrystallization from methanol–water (50/50 by volume) gave colorless crystals of **2-phenyliodoniobenzoate monohydrate**, m.p. 220° dec.

Anal. Calcd. for $C_{13}H_{11}IO_3$: C, 45.61; H, 3.21; I, 37.13. Found: C, 45.87; H, 3.35; I, 37.37.

2-Mesityliodoniobenzoate (II).—To a solution of 105.6 g. (0.4 mole) of 2-iodosobenzoic acid and 150 ml. of mesitylene in 300 ml. of acetic anhydride at 0–5° there was added slowly 50 ml. of concentrated sulfuric acid. After the dark blue mixture had been stirred at room temperature for 6 hr. and cooled to 0°, 100 ml. of 30% ammonia was added. The ammonium sulfate that formed was filtered, and the filtrate was evaporated to dryness *in vacuo*. Trituration of the solid with 250 ml. of ether gave tan crystals which were washed with water and dried to give 117.1 g. (0.32 mole, 80%) of 2-mesityliodoniobenzoate (II). Recrystallization from chloroform–methanol (30/70 by volume) gave colorless crystals, m.p. 213–214° dec.

Anal. Calcd. for $C_{16}H_{15}IO_2$: C, 52.48; H, 4.13; I, 34.66. Found: C, 52.70; H, 4.10; I, 34.88.

(18) Analyses were performed by Schwarzkopf Microanalytical Laboratory, 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 14 recording spectrophotometer. N.m.r. spectra were taken on a Varian A-60 high resolution n.m.r. spectrometer by Mr. H. Talts. Melting points were taken in capillary tubes and were corrected.

2-(*p*-Cyclohexylphenyl)iodoniobenzoate (III).—Compound III was prepared as before in 82% yield. Recrystallization from chloroform–methanol gave colorless crystals, m.p. 208° dec.

Anal. Calcd. for $C_{19}H_{19}IO_2$: C, 56.17; H, 4.69; I, 31.24. Found: C, 56.00; H, 4.51; I, 30.90.

Reactions of Betaines.—Typical procedures are described below. Products are listed in Tables I–III. Known compounds were identified by ultraviolet and infrared spectra, melting points and mixture melting points, and refractive indices. Only the properties of the previously unknown compounds are given below.

Decomposition of Betaines (Table I).—Solutions of betaines I–III were heated under nitrogen until the carbon dioxide evolution ceased. The solvent was removed by distillation *in vacuo* or by extraction with water. The residue was chromatographed on a Florisil column (substance–absorbent, $^1/_{40}$ to $^1/_{30}$ by weight) prepared in hexane. The column was eluted successively with hexane, benzene, methylene chloride, acetone, and methanol. Products were obtained from the column in the following order: **aryl iodides, xanthone, 3,4-benzocoumarin**, and then **aryl 2-iodobenzoates.** The esters were hydrolyzed to 2-iodobenzoic acid and the corresponding phenols by acid or base.

2-Phenyliodoniobenzoate (I) with Anthracene (IX) (Table II).—One equivalent of 2-phenyliodoniobenzoate was added to a solution of one equivalent of anthracene (and in some cases one-tenth equivalent of catalyst) at the desired temperature. The mixture was heated under nitrogen for 2–3 hr., and the solvent was removed by distillation *in vacuo* or by extraction with water. The residue and 3 equiv. of maleic anhydride were heated at reflux in xylene for 30 min. After cooling, the anthracene–maleic anhydride adduct was collected, and the filtrate was hydrolyzed with 1 *N* sodium hydroxide at 100° for 1 hr. The organic layer was separated, washed with water, and concentrated *in vacuo*. Trituration of the residue with methanol gave pale yellow crystals of **triptycene (X).** Recrystallization from ethanol gave colorless crystals, m.p. 254°, lit.[19] m.p. 255–256°; principal bands of infrared spectrum, 3040 (w), 2960 (w), 1470 (s), 1195 (doublet, w); 1165 (w), 1120 (doublet, w), 795 (m), 755 (w), 748 (m), and 740 cm.$^{-1}$ (s). The n.m.r. spectrum showed ring hydrogen absorption bands at τ 2.75 to 3.52 and bridgehead hydrogen absorption, band at τ 4.82.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.70; H, 5.52.

When the reaction of 2-phenyliodoniobenzoate with anthracene was run in diglyme at 162° for 2 hr., no triptycene was isolated. A compound which melted at 270–272°, with an empirical formula of $C_{28}H_{18}O_4$, was found, but its structure has not been established.

2-Phenyliodoniobenzoate (I) with 1,3-Diphenylisobenzofuran (XI).—To a solution of 2.70 g. (10 mmoles) of 1,3-diphenylisobenzofuran in 75 ml. of diglyme at 162° there was added 3.24 g. (10 mmoles) of 2-phenyliodoniobenzoate. After the mixture had been heated to reflux (nitrogen) for 2 hr., the mixture was concentrated *in vacuo*. The residue was chromatographed on a 200-g. Florisil column prepared in hexane and was eluted successively with hexane and carbon tetrachloride.

The hexane eluate after evaporation of solvent gave 0.69 g. (2.1 mmoles, 21%) of **9,10-diphenylanthracene (XIII)** as fluorescent crystals, m.p. 246–247°, after recrystallization from ethanol, lit.[15] m.p. 245–247°. The n.m.r. spectrum showed anthracene ring hydrogen absorption bands at τ 2.38 and 2.97 and a single band for hydrogens on the phenyl rings at τ 2.59.

Anal. Calcd. for $C_{26}H_{18}$: C, 94.59; H, 5.41. Found: C, 94.34; H, 5.38.

When the above reaction was run with three equivalents of I in triglyme at 222° for 15 min., **9,10-epoxy-9,10-diphenyl-9,10-dihydroanthracene (XII)** was isolated. Recrystallization from ether–methanol gave white crystals, m.p. 188–188.5°, lit.[15] m.p. 188–188.5°.

Anal. Calcd. for $C_{26}H_{18}O$: C, 90.14; H, 5.24. Found: C, 89.89; H, 5.18.

2-Phenyliodoniobenzoate (I) with 2,3,4,5-Tetraphenylcyclopentadienone (XIVa) (Table III).—To a refluxing solution of 1.92 g. (5 mmoles) of 2,3,4,5-tetraphenylcyclopentadienone in 15 ml. of solvent (diglyme, γ-butyrolactone, and triglyme, separately) there was added 1.62 g. (5 mmoles) of 2-phenyliodoniobenzoate. The mixture was heated to reflux (nitrogen) until the evolution of carbon dioxide ceased and concentrated *in vacuo*. The residue was chromatographed on a 200-g. Florisil column prepared in hexane and was eluted successively with hexane and carbon tetrachloride.

The hexane eluate after evaporation of solvent gave 36 to 57% of **1,2,3,4-tetraphenylnaphthalene (XVa).** A sample was recrystallized from ethanol and distilled at 225° (0.05 mm.), m.p. 204°, lit.[16] m.p. 203–204°. The n.m.r. spectrum showed naphthalene ring hydrogen absorption bands at τ 2.49 and 2.68 and phenyl ring hydrogen absorption bands at τ 2.83 and 3.22.

Anal. Calcd. for $C_{34}H_{24}$: C, 94.43; H, 5.57. Found: C, 94.14; H, 5.59.

2-Phenyliodoniobenzoate (I) with 2,5-Di-*p*-anisyl-3,4-diphenylcyclopentadienone[17] (XIVb).—Reaction of 2.5 mmoles each of I and XIVb in 7.5 ml. of γ-butyrolactone at 204° for 30 min. was followed by removal of solvent and chromatographing largely as described before. The hexane eluate gave 0.97 g. (1.97 mmoles, 79%) of **1,4-di-*p*-anisyl-2,3-diphenylnaphthalene (XVb)**, m.p. 221.5–222°, unchanged by recrystallization from ethanol–carbon tetrachloride.

Anal. Calcd. for $C_{36}H_{28}O_2$: C, 87.77; H, 5.73. Found: C, 87.67; H, 5.67.

2-Phenyliodoniobenzoate (I) with 2,5-Bis(*p*-dimethylaminophenyl)-3,4-diphenylcyclopentadienone[18] (XIVc).—The reaction was run and worked up as before to give 65% of **1,4-bis(*p*-dimethylaminophenyl)-2,3-diphenylnaphthalene (XVc)**, m.p. 246–248°, raised to 247–248° by recrystallization from acetone.

Anal. Calcd. for $C_{38}H_{34}N_2$: C, 87.99; H, 6.59; N, 5.42. Found: C, 87.91; H, 6.47; N, 5.42.

Acknowledgment.—Samples of tetracyclones provided by Mr. M. Ogliaruso and Mr. M. Romanelli are gratefully acknowledged.

(19) G. Wittig, *Org. Syn.*, **39**, 75 (1959).

The Light-Catalyzed Oxidation of Starch with Aqueous Chlorine

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Products of relatively high carbonyl content (to 25 mole %) were prepared in good yield by the oxidation of cornstarch with aqueous chlorine in the presence of ultraviolet radiation. The rate of this oxidation is greatly affected by illumination. In certain cases, oxidations which require 5–8 days in the dark can be accomplished in a matter of hours when illuminated. The light-catalyzed oxidation also is affected significantly by pH. Comparative experiments (at both room temperature and ice-bath temperature) indicate that the reaction rate is three times as fast at pH 4 as at pH 0.5. Under comparable conditions of illumination, chloric acid was shown to be unreactive with starch. Product yields (recovered by simple filtration) varied considerably from 97% at pH 0.5 and ice-bath temperature to 30% at pH 4 and room temperature. At pH 4 and low temperature, products of 25 mole % carbonyl content were isolated in 91% yield. In general, about 17 mole % carbonyl is introduced for each equivalent of chlorine consumed. Under certain conditions products are obtained in which more than half of the observed carbonyl content is due to the presence of aldehyde groups.

In earlier publications,[1] we reported that the aqueous chlorine oxidation of cornstarch was strongly catalyzed by light. Although the chemical action of chlorine on starch was recognized as early as 1829,[2] it is surprising that this rather drastic effect of light had not been reported. In the many references to chlorine–water oxidation of carbohydrates,[3] we have found only one mention[4] of the effect of light on the reaction rate. The authors of this work noted that ultraviolet radiation caused fiftyfold increases in the rate of oxidation of D-mannitol (to D-mannose and D-fructose) by aqueous chlorine. Evidently, no additional work has been done to exploit this rather drastic effect of light on aqueous chlorine oxidation.[5]

Perhaps, the well-known fact that chlorine water can be decomposed by light was the reason that most previous investigators performed their experiments in the dark. This light-catalyzed decomposition of chlorine water has been investigated in considerable detail by Allmand[6] and co-workers who have demonstrated that ultraviolet radiation can completely decompose chlorine water to chloric acid, hydrochloric acid, and oxygen. In our work, we noted that the decomposition of chlorine water, under identical conditions of illumination, proceeded many times more slowly than the starch oxidation.

Working with nongelatinized cornstarch to simplify product recovery, we observed that, in the dark, the consumption of one equivalent of chlorine per anhydroglucose unit (A.G.U.) of starch requires about 8 days at room temperature (using approximately 0.1 *N* chlorine water). A similar experiment in a clear glass vessel exposed to indirect sunlight required only 6 hr. for the complete consumption of the chlorine.

Gelatinization of the starch causes a further increase in the reaction rate. In comparative experiments, using nearly identical conditions of illumination, temperature, and reagent concentrations, gelatinized starch is oxidized about four times as fast as nongelatinized starch (Fig. 1).

In the dark, gelatinized starch is oxidized only about 1.7 times as fast as nongelatinized starch (Fig. 2). Therefore, in the illuminated experiments, the predominant reason that the gelatinized starch is more rapidly oxidized is probably the fact that the gelatinized reaction mixture is more transparent. Note that in the illuminated experiments, the oxidation is complete in a matter of hours, not days.

It is well-known that the pH of the chlorine–water solution influences the rate of starch oxidation in the dark. As might be expected, the light-catalyzed oxidation is affected similarly. At room temperature, the oxidation is about three times as fast at pH 4 as at pH 0.5. A similar rate relationship was noted when the experiments were performed at ice-bath temperature (Fig. 3). In these experiments, the starch was not gelatinized, chlorine–starch ratio was 1.5 equivalents/A.G.U., and the products were isolated by filtration. At ice-bath temperature the yields were above 90%, but at room temperature, the yields dropped considerably (Table I).

TABLE I

THE EFFECT OF REACTION pH AND REACTION TEMPERATURE ON YIELD AND PRODUCT COMPOSITION

	pH 4		pH 0.5	
	25°	0°	25°	0°
Yield (%)	30	91	47	97
Carboxylic acid content (mole %)		12.9		4.1
Carbonyl content (mole %)		24.6		13.2
Aldehyde content (mole %)		13.3		4.4

It has been shown[7] that, in aqueous chlorine at pH 4, the species present is almost exclusively hypochlorous acid. Conversely, at pH 0.5 the reagent consists almost entirely of molecular chlorine. Thus, the rate data indicate that both reagents are capable of oxidizing starch and that hypochlorous acid reacts about three times as fast as molecular chlorine. It should be noted, however, that these findings do not

(1) (a) A. F. Meiners and F. V. Morriss, Abstracts, Thirteenth Annual Kansas City Chemistry Conference, paper 17, published in "The Kansas City Chemist," November, 1961; (b) A. F. Meiners and F. V. Morriss, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 20.

(2) J. Liebig, *Poggendorff's Ann. Phys. Chem.*, **15**, 541 (1829). This publication and other early observations are discussed by J. A. Radley, *Mfg. Chemist*, **13**, 104 (1942).

(3) See, for example, the work on starch oxidation by (a) M. E. McKillican and C. B. Purves, *Can. J. Chem.*, **32**, 312 (1954); (b) C. H. Hullinger and R. L. Whistler, *Cereal Chem.*, **28**, 153 (1951); and (c) R. L. Whistler and R. Schweiger, *J. Am. Chem. Soc.*, **79**, 6460 (1957). (d) See also, a review on the oxidation of glycosides and cellulose by O. Theander, *Svensk Kem. Tidskr.*, **71**, 1 (1959).

(4) R. Bognar and L. Somogyi, *Acta. Chim. Acad. Sci. Hung.*, **14**, 407 (1958).

(5) N. Uchino and R. L. Whistler [*Cereal Chem.*, **39**, 477 (1962)] recently reported that visible light caused a slight acceleration of the reaction of chlorine gas with moist wheat starch.

(6) K. W. Young and A. J. Allmand, *Can. J. Research*, **27B**, 318 (1949).

(7) B. P. Ridge and A. H. Little, *J. Textile Inst. Trans.*, **33**, T33 (1942).

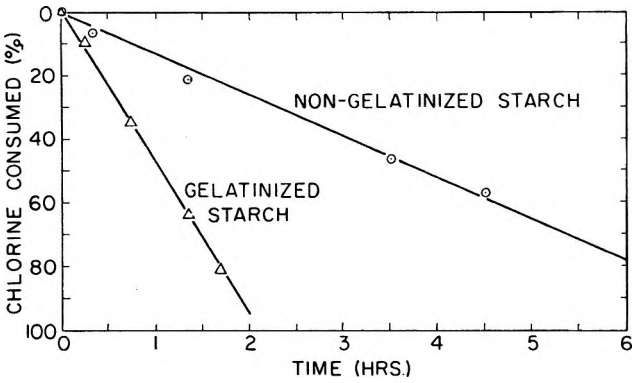

Fig. 1.—The ultraviolet-catalyzed chlorine oxidation of starch (1.5 equiv./A.G.U.).

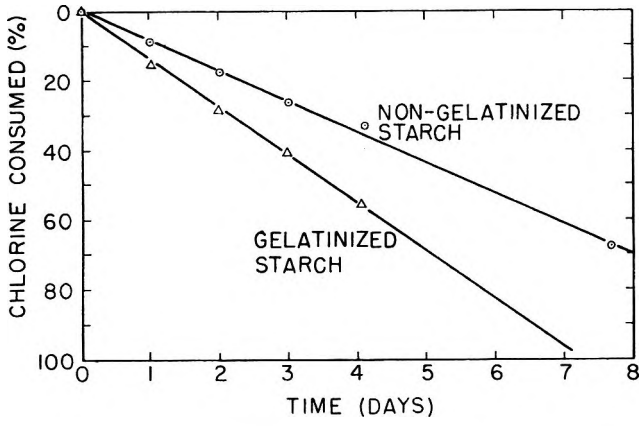

Fig. 2.—The chlorine oxidation of starch in the dark (0.77 equiv./A.G.U.).

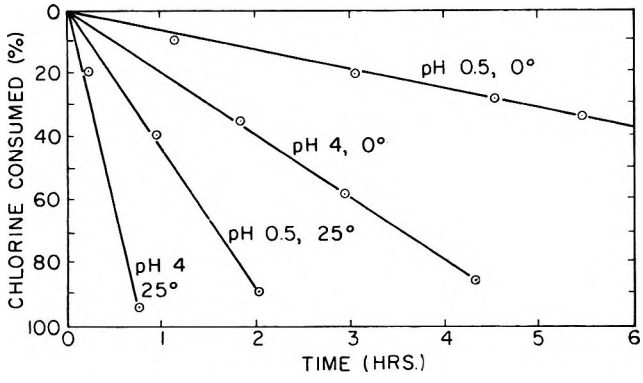

Fig. 3.—The influence of pH and temperature on rate of the ultraviolet-catalyzed chlorine oxidation of nongelatinized starch (1.5 equiv./A.G.U.).

demonstrate that either the chlorine molecule or the hypochlorous acid molecule is the actual reacting species. A comparable relationship between reaction rate and pH was observed in the oxidation of ethanol by bromine[8]; above pH 3, the reaction rate increases markedly with increasing pH. However, subsequent work[9] demonstrated conclusively that bromine and *not* hypobromous acid was the reactive species.

Chloric acid was initially suspected of being an intermediate in the starch oxidation, since chloric acid can be produced in significant quantities by the photolysis of chlorine water.[6] Although it is known that chloric acid will not oxidize aldoses,[10] it was necessary to demonstrate that chloric acid would not oxidize starch in the presence of strong illumination. In a suitable experiment, it was shown that only small amounts of chloric acid were consumed when starch was treated with two equivalents of chloric acid per A.G.U. It also was demonstrated that only relatively small amounts of chloric acid are generated when chlorine water is illuminated similarly. Thus chloric acid cannot be a significant intermediate in the light-catalyzed chlorine–starch oxidation.

A series of oxidized starches was prepared in order to observe the effect of the chlorine–starch ratio on the yields and carbonyl contents of the products (Table II). These experiments were performed at 10–12° using untreated chlorine water, which has a pH of about 2.5. In each case about 17 mole % of carbonyl content was introduced for each equivalent of chlorine consumed. The products were recovered by filtration and again it was observed that the yields decreased as the extent of oxidation increased.

TABLE II

THE EFFECT OF REACTANT RATIO

	Reactant ratio (equiv. of Cl_2/A.G.U.)		
	0.33	0.67	1.0
Weight of starch (g.)	250	250	165
Chlorine concentration (N)	0.014	0.032	0.032
Reaction time (hr.)	5.0	7.0	7.0
Equiv. of chlorine consumed/A.G.U.	0.25	0.58	0.87
Yield (%)	95	94	85
Carbonyl content of product (mole %)	4.7	10.0	14.8

These oxidized starches were not much different visibly from the starting materials. Microscopic examination showed that the starch granules are intact and are indistinguishable from the original product. All of the products contained some carboxylic acid, but the amounts were fairly low, usually being less than one-third of the observed carbonyl content. The products were 95–99% dispersible in water, but formed dispersions of much lower paste viscosity than ordinary cornstarch. As might be expected, the paste viscosity decreases as the extent of oxidation increases. When heated in mild alkali, for example at pH 9, the oxidized starches evidently decomposed producing dark brown solutions.

Experimental evidence indicates that a significant portion (usually about one-half) of the observed carbonyl content in the oxidized starches consists of aldehyde groups. Also, the results of previous investigators indicate that a majority of the aldehyde groups are located at the 6-position in the anhydroglucose unit. For example, McKillican and Purves,[3a] in a study of the hypochlorous acid oxidation of wheat starch in the dark, concluded that 65 to 80% of the carbonyl groups in their products were aldehyde groups in the 6-position. Also Olof Theander[3d] isolated and identified products from the oxidation of methyl β-glucoside with hypochlorous acid at pH 4. He observed the formation of all four of the theoretically possible oxoglucosides. His results indicated that the product having the alde-

(8) L. Farkas, B. Perlmutter, and O. Schächter, *J. Am. Chem. Soc.*, **71**, 2829 (1949).

(9) B. Perlmutter-Hayman and Y. Weissman, *ibid.*, **86**, 2323 (1962).

(10) A. Jeanes and H. S. Isbell, *J. Res. Natl. Bur. Std.*, **27**, 131 (1941).

hyde group in the 6-position represents about half of the total yield of carbonyl-containing products.

Aldehyde contents were determined using some analytical methods developed for chlorine-oxidized starch by Ellington and Purves.[11] One method involves determining the carbonyl content of the product before and after treatment with chlorous acid. The observed decrease in carbonyl content represents the aldehyde content, since chlorous acid does not oxidize ketone groups under the conditions prescribed.

Another method is based on the fact that, under certain conditions, alkaline hypoiodite oxidizes aldehyde groups, but not ketone groups. By measuring the uptake of hypoiodite, the aldehyde content can be calculated.

The results of our analytical studies using both methods are in fair agreement. For example, analysis of an oxidized starch prepared by a light-catalyzed oxidation at pH 0.5 (1.5 equivalents of chlorine/A.G.U., 7.25 hr. reaction time, 97% yield, total carbonyl content of 17.7%) showed an aldehyde content of 8.6 mole % according to the chlorous acid procedure and in the range 7.6 to 9.8 mole % according to the hypoiodite procedure.

Experimental

The Oxidation of Starch with Aqueous Chlorine in the Dark.—Ordinary cornstarch[12] (10.0 g., 0.056 A.G.U.) was gelatinized in 250 ml. of water by heating and stirring constantly until the temperature of the water reached 96°. After cooling, the dispersion was diluted to 900 ml. with water and chlorine water so that the final mixture contained 0.044 equiv. of chlorine. In a similar experiment, performed simultaneously, the starch was not gelatinized. The reaction vessels were brown, screw-capped bottles and the mixtures were stirred by means of magnetic stirrers. Insulation was placed between the bottles and the stirrer to minimize heating, and both experiments were placed in a hood so that a constant stream of air at room temperature passed over the bottles and the stirrers. At intervals, 50-ml. aliquots of each reaction mixture were taken and the chlorine concentration determined. Potassium iodide was added to acidified aliquots and the liberated iodine was titrated with 0.1 *N* thiosulfate. Since it required several minutes to remove the iodine color from particles of nongelatinized starch, these end points were difficult to see. Therefore, an excess of thiosulfate was added and, when the iodine color had disappeared, the excess thiosulfate was back-titrated with 0.05 *N* iodine. A plot of % chlorine reacted *vs.* time (Fig. 1) indicates that the rate of oxidation of gelatinized starch is 1.7 times as fast as the rate of oxidation of nongelatinized starch.

The Light-Catalyzed Oxidation. A. The Effect of Gelatinization.—Cornstarch (30 g., 0.167 A.G.U.) was gelatinized as before in 400 ml. of water. The starch gel was cooled in ice, mixed with 2.2 l. of a cold aqueous solution containing 0.237 equiv. of chlorine, and the mixture was diluted to 3.0 l. The reaction mixture was irradiated with a 100-w. mercury flood lamp (General Electric-H4JM) and stirred by means of a magnetic stirrer. An ice bath was used to hold the temperature of the reaction mixture between 10–12° and the progress of the reaction was followed as before. In a second experiment, conditions were duplicated except that the starch was not gelatinized. The gelatinized starch was oxidized 3.6 times as fast as the nongelatinized starch (Fig. 2) and both of the light-catalyzed reactions were many times as fast as comparable oxidations in the dark (note that the time scale in Fig. 2 is in hours, not days).

B. The Effect of pH and Temperature.—Two sets of duplicate experiments were performed in which the incident illumination and the pH of the solutions were accurately controlled. In the low pH experiments, the chlorine water was acidified with concentrated hydrochloric acid (50 ml./l.) to pH 0.5. In the other runs, the pH was adjusted to pH 4.0 with sodium dihydrogen phosphate and sodium hydroxide. During the runs, the pH was observed continuously and additional sodium hydroxide was added at intervals to maintain pH 4.0. The previously described ultraviolet lamp was placed in exactly the same position for each run.

The concentration of cornstarch in the reaction mixtures was 1% by weight, and the chlorine concentration, 0.9 *N*, provided a chlorine–starch ratio of 1.5 equiv./A.G.U.

Two sets of experiments were run, one at room temperature and one at ice-bath temperature. The progress of the reactions was followed as before. A comparison of the rates is presented in Fig. 3. The products were recovered by filtration, washed with methanol, and air-dried. The yields and product compositions are presented in Table I.

C. The Effect of Reactant Ratio.—A series of larger-scale reactions were performed in which the chlorine–starch ratio was varied. The reaction vessel was a 30-l. Pyrex resin kettle illuminated by three ultraviolet lamps. The experiments were performed at 10°, using an efficient stirrer and an ice-bath to maintain this temperature (±1°) during the reaction. Table II summarizes the reaction conditions and typical results. The products were recovered as before.

Functional Group Analyses.—Carbonyl contents were determined using a modification of the procedure described by Gladding and Purves.[13] Starch samples (1–5 g.) were adjusted to pH 5.0, allowed to stir for several hours, and then adjusted back to pH 5.0, if necessary. Reagent grade hydroxylamine hydrochloride solution (5% by weight) was adjusted to pH 5.0 and 100 ml. of the freshly prepared solution was pipeted into the starch suspensions. The mixtures were placed in brown bottles and shaken mechanically overnight. Samples and blanks (usually in duplicate) were then titrated to pH 3.2.

Carboxylic acid determinations were done by the calcium acetate procedure described by Yackel and Kenyon[14] and by the paste titration procedure of Mattisson and Legendre.[15] The products obtained from an acid environment showed little difference between the original and de-ashed samples.

Aldehyde determinations were done using modifications of the methods described by Ellington and Purves.[11]

A. Chlorous Acid Procedure.—In a typical analysis, a starch sample (6–7 g.) was treated with 150 ml. of 4% sodium chlorite (analytical reagent grade) in 30% acetic acid at room temperature for exactly 1 hr. Anhydrous methanol (400 ml.) was added and the mixture was filtered. The product was washed successively with (1) 70% methanol that had been made 0.5 *N* with hydrochloric acid, (2) 70% methanol, and (3) absolute methanol. After vacuum drying at 50° overnight, the product was obtained in yields of 84–89%. A carbonyl analysis of the product was obtained (using the hydroxylamine procedure) and the difference between this figure and the original carbonyl content was taken as the aldehyde content.

B. Hypoiodite Procedure.—In a typical analysis, duplicate samples (1.7–2.6 g.) of oxidized starch were placed in a solution consisting of 50.0 ml. of carbonate–bicarbonate buffer (pH 11.2) and 25.0 ml. of 0.05 *N* iodine. The pH of the resulting mixture was 9.7. Duplicate blank runs were made on the oxidized starch at pH 5.6 by employing identical amounts of buffer and iodine to which 20.0 ml. of 0.33 *N* sulfuric acid was added. The samples were shaken vigorously for 2.5 hr. at room temperature. An identical amount of acid was added to the alkaline samples and a slight excess (15.0 ml.) of 0.1 *N* thiosulfate was added to all four mixtures. Shaking was continued until all of the solutions became colorless and each was titrated to the iodine end point with 0.05 *N* iodine. The aldehyde contents were calculated as the difference in iodine uptake between the alkaline oxidation and the acid oxidation.

The Treatment of Starch with Chloric Acid in the Presence of Ultraviolet Radiation.—Cornstarch (30 g., 0.167 A.G.U.) was added to 3 l. of 0.02 *M* potassium chlorate which had been acidified to pH 1.5 with dilute sulfuric acid. The reaction vessel was identical to the one used in the light-catalyzed oxidation study. The mixture was cooled to 10° and the ultraviolet lamp (the same as used previously) was positioned as before. At intervals, aliquots were withdrawn and analyzed for chlorate.

(11) A. C. Ellington and C. B. Purves, *Can. J. Chem.*, **31**, 801 (1953).

(12) The cornstarch used in all of the experiments was the variety prepared for domestic use and contained 9.5–10.5% moisture.

(13) E. K. Gladding and C. B. Purves, *Paper Trade J.*, **116**, 26 (1943).

(14) E. C. Yackel and W. O. Kenyon, *J. Am. Chem. Soc.*, **64**, 121 (1942).

(15) M. F. Mattisson and K. A. Legendre, *Anal. Chem.*, **24**, 1942 (1952).

Chlorate analyses were done by the following procedure. An aliquot (20 ml.) was transferred to a beaker containing excess (50 ml.) 0.1 *N* ferrous ammonium sulfate. The mixture was heated to boiling in an atmosphere of carbon dioxide. On cooling, the mixture was titrated with 0.1 *N* permanganate. The end point was determined electrometrically using a Beckman portable pH meter with a silver indicator electrode.

After 4 hr. of illumination, only 5% of the available chloric acid had been consumed. The original concentration of chloric acid (2 equiv./A.G.U.) was considerably greater than the chloric acid concentration that would be generated by comparable illumination of chlorine water (only 0.0034 mole of chloric acid was produced when 3.0 l. of 0.103 *N* chlorine water was illuminated for 5 hr. at pH 1.5 and 10°). These observations indicate that chloric acid is not a significant intermediate in the light-catalyzed chlorine–starch oxidation.

Acknowledgment.—This work was supported by the Nebraska Agricultural Products Research Fund Committee of the Nebraska Department of Agriculture and Inspection.

Acridizinium Ion Chemistry. IV.[1] Oxidation with Nitric Acid

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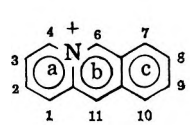
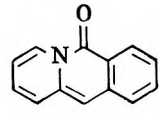
Oxidation of the acridizinium nucleus by nitric acid results in attack at ring b when no strong activating groups are present, yielding 2-(2-carboxy-4-nitrobenzoyl)pyridines. Oxidation with nitric acid of an acridizinium salt containing one or more hydroxyl or methoxyl groups in ring c, results in degradation of ring c, and the formation of a betaine of 2,3-dicarboxyquinolizinium hydroxide.

Although the acridizinium, or benzo[*b*]quinolizinium ion (I) has been known since 1954,[3] little is known about its behavior on oxidation. It has been stated[3] that oxidation of the ion (I) in alkaline permanganate yielded phthalic acid, while more recently Paquette[4] has shown that alkaline ferricyanide solution can convert the



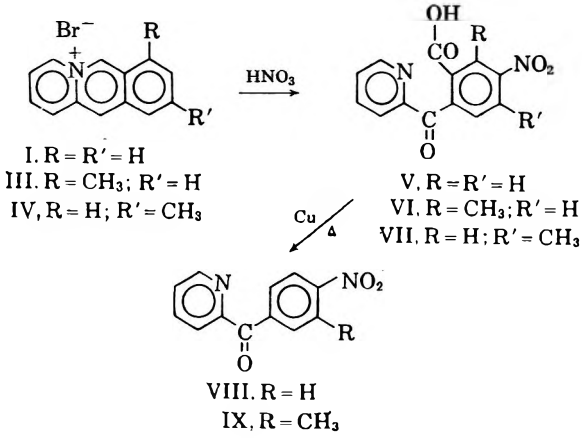
I



II

acridizinium ion to an amide (II). Since it is known[1,5] that the acridizinium ion in alkaline solution exists almost entirely as the pseudobase, both of the previous oxidation attempts could probably best be described as oxidation of the pseudobase.

It was felt that oxidations carried out in an *acidic* medium might lead to new and interesting results, and in this paper are described our experiments using nitric acid. When acridizinium bromide (I) was heated for 3 hr. at 100° with 12 *M* nitric acid, the product was an acid, the composition of which suggested that nitration as well as oxidation had occurred. Decarboxylation of the acid gave the known 2-(4-nitrobenzoyl)pyridine (VIII) and established the structure of the acid as V.

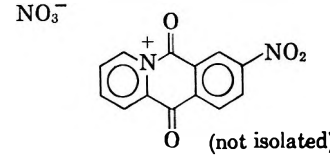


I. R = R′ = H
III. R = CH_3; R′ = H
IV, R = H; R′ = CH_3

V, R = R′ = H
VI, R = CH_3; R′ = H
VII, R = H; R′ = CH_3

VIII. R = H
IX, R = CH_3

The oxidation may be considered to be similar to that of the attack of nitric acid on anthracene to yield anthraquinone. The intermediate acylammonium salt (X) would be expected to hydrolyze rapidly to the keto acid V. The same nitroketo acid was obtained (25% yield) with even quite dilute (3 *M*) nitric acid. It is not certain whether nitration precedes oxidation, but it is perhaps significant that nitration has occurred in what corresponds to position 8, theoretically one of the least electron-deficient of the acridizinium nucleus.[6]



X

The oxidation of the 7-methyl- (III) and 9-methylacridizinium (IV) salts[3] likewise afforded nitroketo acids which by analogy were assigned structures VI and VII. That the assumption concerning the location of the nitro group was correct was shown by the fact that both acids afforded the same nitro ketone (IX) on decarboxylation.

This demonstration of the vulnerability of ring b to nitric acid oxidation made it of interest to try similar experiments in which ring c would be highly activated, and, hence, more likely to be oxidized. When 7,10-dimethoxyacridizinium picrate[7] (XI) was oxidized with 8 *M* nitric acid a very insoluble product was formed. This new substance had a composition indicating the loss of four carbon atoms, and a neutral equivalent cor-

(1) For the preceding communication of this series, see C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **81**, 1938 (1959).

(2) This research was supported by a research grant NSF-G19901 of the National Science Foundation.

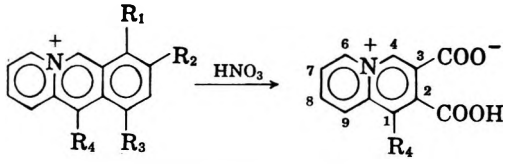
(3) C. K. Bradsher and L. E. Beavers, *Chem. Ind.* (London), 1394 (1954); C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

(4) L. A. Paquette, *Chem. Ind.* (London), 1292 (1962).

(5) J. H. Saylor and J. G. Frost, unpublished spectrographic data.

(6) Position 8 is remote from the charged nitrogen atom and, unlike neighboring positions 7 and 9, cannot (by charge delocalization) become the site of a positive charge.

(7) C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, **29**, 61 (1964).



XI, $R_1 = R_3 = OCH_3$; $R_2 = R_4 = H$
XII, $R_1 = R_2 = OCH_3$; $R_3 = R_4 = H$
XIII, $R_2 = OH$; $R_2 = R_3 = R_4 = H$
XIV, $R_1 = R_3 = OCH_3$; $R_2 = H$; $R_4 = C_6H_5$
XV, $R_4 = H$
XVI, $R_4 = C_6H_5$

responding to one acidic hydrogen. The ultraviolet absorption spectrum is remarkably like that reported for quinolizinium salts[8] and gives one every reason to believe that the new product is the betaine (XV)[9] of 2,3-dicarboxyquinolizinium hydroxide. The same product XV was obtained by oxidation of 7,8-dimethoxyacridizinium (XII) picrate[10] and 8-hydroxyacridizinium (XIII) bromide.[8]

Although the new betaine (XV) melted with gas evolution, no conditions were found for decarboxylation under conditions leading to the isolation of a product. It was found that 48% hydrobromic acid afforded a salt believed to be 2,3-dicarboxyquinolizinium bromide. The salt obtained by action of concentrated sulfuric acid gave a neutral equivalent indicating that it was 2,3-dicarboxyquinolizinium bisulfate, but was hydrolyzed in solution to yield the betaine (XV).

In order to afford further analytical evidence concerning the terminal ring oxidation, 7,10-dimethoxy-11-phenylacridizinium (XIV) perchlorate was synthesized by extension of a previously described[11] method. The oxidation product had the properties expected for the betaine (XVI) of 1-phenyl-2,3-dicarboxyquinolizinium hydroxide. The oxidation of these activated systems is important in that it has provided the first example of the transformation of an acridizinium derivative into a quinolizinium derivative.

Experimental

All analyses were by Dr. Ing. A. Schoeller, Mikoranalytisches Laboratorium, Kronach, West Germany. Melting points were determined using a Laboratory Devices Mel-Temp block and are uncorrected. Infrared spectra were measured in potassium bromide pellets using the Perkin-Elmer Model 21 spectrophotometer. The ultraviolet absorption spectra were recorded using a Cary Model 14 recording spectrophotometer with methanol as the solvent. Wave lengths are recorded in mμ and shoulders are indicated by an asterisk (*).

2-(2-Carboxy-4-nitrobenzoyl)pyridine (V).—To 4 g. of acridizinium bromide (I),[12] 40 ml. of 12 *M* nitric acid was added in one portion. After the vigorous reaction (red-brown fumes) had subsided, the mixture was heated on the steam bath for 3 hr. The acid was removed under reduced pressure (aspirator) leaving a yellow residue which was crystallized from acetic acid–water, 1.76 g. (43%), m.p. 218.5–221° dec. Recrystallization afforded colorless needles, m.p. 225–227° dec. The infrared spectrum showed a band in the carbonyl region at 5.95 μ.

Anal. Calcd. for $C_{13}H_8N_2O_5$: C, 57.36; H, 2.96; N, 10.29; neut. equiv., 272. Found: C, 56.93; H, 2.96; N, 10.02; neut. equiv., 266.

Oxidation of 4 g. of acridizinium bromide (I) with 40 ml. of 3 *M* nitric acid gave the same acid (V) in 25% yield.

2-(4-Nitrobenzoyl)pyridine (VIII).—A mixture of the acid (0.5 g.) and copper powder (0.5 g.) was heated for 2 hr. at 220°. The residue was vacuum distilled and the distillate crystallized from ethanol, 0.16 g. (35%), m.p. 96–98°. Recrystallization gave the pure product as colorless needles, m.p. 99–99.5° (lit.[13] m.p. 99–100°).

Anal. Calcd. for $C_{12}H_8N_2O_3$: C, 63.15; H, 3.53. Found: C, 63.14; H, 3.59.

The phenylhydrazone was prepared according to the method of Koenigs, Mensching, and Kirsch[13] as short red needles, m.p. 170–172° (lit.[13] m.p. 171°).

2-(2-Carboxy-3-methyl-4-nitrobenzoyl)pyridine (VI).—The oxidation of 4 g. of 7-methylacridizinium bromide (III)[3] was carried out as in the case of the lower homolog (I) except that the crude product was taken up in ether and the ethereal solution extracted with 3% sodium hydroxide in three portions. The basic solution was acidified to pH 6 with hydrochloric acid. The acidified solution was then extracted with ether and the ethereal solution washed with water and dried. Concentration of the ether solution gave 1.2 g. (29%) of solid, m.p. 176–180°. Recrystallization of the product from ether gave colorless needles, m.p. 190.5–192°.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; N, 9.79. Found: C, 58.94; H, 3.50; N, 9.57.

Phenylhydrazone of 2-(3-Methyl-4-nitrobenzoyl)pyridine (IX).—Acid VI (0.4 g.) was heated for 3.5 hr. at 185° with an equal weight of copper powder. On vacuum distillation of the residue too little of ketone IX was obtained for satisfactory isolation as such, and the crude product in acetic acid was converted to the phenylhydrazone. Recrystallization of the phenylhydrazone from ethanol gave yellow needles, m.p. 149–151°, with loss of solvent at 130°.

Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.46; H, 4.80; N, 16.51.

2-(2-Carboxy-4-nitro-5-methylbenzoyl)pyridine (VII).—The oxidation of 4 g. of 9-methylacridizinium bromide (IV)[3] was carried out exactly as in the case of the lower homolog (I). A colorless powder, 2 g. (46%), was obtained, m.p. 203–206° dec. Recrystallization of the product from dilute acetic acid afforded colorless needles, m.p. 220.5–221° dec.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; neut. equiv., 286. Found: C, 58.53; H, 3.53; neut. equiv., 283.

2-(3-Methyl-4-nitrobenzoyl)pyridine (IX).—The decarboxylation of acid VII (0.5 g.) was carried out as in the previous cases and the distillate crystallized from ethanol as colorless needles, 0.06 g. (15%), m.p. 89–90°.

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.65; H, 4.11; N, 11.67.

The phenylhydrazone was identical with that obtained from the decarboxylation product of VI (mixture melting point).

Betaine (XV) of 2,3-Dicarboxyquinolizinium Hydroxide. A. By Oxidation of 7,10-Dimethoxyacridizinium (XI) Picrate.[7]—To 8.7 g. of 7,10-dimethoxyacridizinium picrate, 120 ml. of 8 *M* nitric acid was added in one portion. After the initial reaction had subsided (about 1 min.), the solution was heated on the steam bath for 3 hr. The nitric acid was removed under reduced pressure (aspirator), and the residue crystallized from a large volume of acetic acid, 2.86 g. (71%), 260° dec. (gas evolution).

B. Oxidation of 7,8-Dimethoxyacridizinium (XII) Picrate.—Oxidation of 0.45 g. of 7,8-dimethoxyacridizinium picrate as described in A yielded 0.1 g. (50%) of product, 260.5° dec. (with gas evolution). The infrared spectrum was identical with that of the product XV obtained from XI.

C. By Oxidation of 8-Hydroxyacridizinium (XIII) Bromide.—The oxidation of 6 g. of 8-hydroxyacridizinium bromide was carried out as in A and B except that 12 *M* nitric acid was used, 0.58 g. (12%), 261° dec. (gas evolution). The infrared absorption spectrum was identical with spectra obtained for products from A and B. The analytical sample was a colorless microcrystalline powder, λ_{max} 327* mμ (log ε 4.04) and 337 (4.15) (trifluoroacetic acid).

Anal. Calcd. for $C_{11}H_7NO_4 \cdot 0.25\ H_2O$: C, 59.60; H, 3.41; N, 6.32; neut. equiv., 221.5. Found: C, 59.72; H, 3.58; N, 6.04; neut. equiv., 208.

2,3-Dicarboxyquinolizinium Bromide.—In an attempted decarboxylation, a sample of the betaine (XV) was refluxed for 24

(8) R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 1691 (1960).

(9) The formulation of the betaine as XV, with the 3-carboxyl rather than the 2-carboxyl ionized, is based upon minimum charge separation, but is not supported by experimental evidence.

(10) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

(11) C. K. Bradsher and T. W. G. Solomons, *ibid.*, **81**, 2550 (1959).

(12) C. K. Bradsher, T. W. G. Solomons, and F. R. Vaughan, *J. Org. Chem.*, **25**, 757 (1960).

(13) E. Koenigs, H. Mensching, and P. Kirsch, *Ber.*, **59**, 1717 (1926).

hr. with 48% hydrobromic acid. At the end of this period the acid was removed and the residue digested with ethanol. Filtration of the suspension removed some unchanged starting material, but concentration of the filtrate afforded a small amount of a new compound, m.p. 300° dec. Recrystallization of this substance from ethanol–ethyl acetate afforded a colorless microcrystalline powder, m.p. 301.5° dec.

Anal. Calcd. for $C_{11}H_8BrNO_4 \cdot 0.5\ H_2O$: C, 43.01; H, 2.95; N, 4.59. Found: C, 42.73; H, 3.09; N, 4.62.

2,3-Dicarboxyquinolizinium Bisulfate.—A solution of the betaine (XV, 0.1 g.) in concentrated sulfuric acid (6 ml.) was heated for 1 hr. at 170°. The solution was cooled and slowly added to 30 ml. of cold ether. Collection of the colorless precipitate gave 0.1 g. (71%) of a very hygroscopic material, m.p. 234–235° dec.

Anal. Calcd. for $C_{11}H_9NSO_8$: neut. equiv., 105. Found: neut. equiv., 104.

When the bisulfate was washed with water or barium chloride solution (colorless precipitate), the betaine (XV) was recovered.

7,10-Dimethoxy-11-phenylacridizinium (XIV) Perchlorate.—A solution of 2,5-dimethoxybenzyl bromide[14] (15 g.) and 2-benzoylpyridine (12.8 g.) in dimethylformamide (15 ml.) was allowed to stand for 5 days at room temperature. When ether was added an oil separated. The ether was decanted and the oil transferred to a round bottom flask by use of methanol. After evaporation of the methanol, 90 g. of polyphosphoric acid was added, and the mixture stirred and heated at 90–100° for an hour. The acid was cooled and hydrolyzed by addition of ice. To the filtered phosphoric acid solution, an excess of 35% perchloric acid was added. The precipitate was collected and recrystallized from ethanol as orange needles, 9.6 g. (36%), m.p. 254–255° dec.; λ_{max} 250 mμ (log ε 5.08), 323* (3.31), 409 (4.02), and 455* (3.84).

Anal. Calcd. for $C_{21}H_{18}ClNO_6$: C, 60.65; H, 4.36; N, 3.37 Found: C, 60.64; H, 4.45; N, 3.51.

The picrate crystallized from ethanol as orange needles, m.p. 197–198° dec.

Anal. Calcd. for $C_{27}H_{20}N_4O_9$: C, 59.55; H, 3.73; N, 10.29. Found: C, 59.60; H, 3.64; N, 10.29.

Betaine (XVI) of 1-Phenyl-2,3-dicarboxyquinolizinium Hydroxide.—Five grams of 7,10-dimethoxy-11-phenylquinolizinium (XIV) perchlorate was oxidized in the usual way with 8 *M* nitric acid. The residue left by removal of most of the nitric acid was taken up in 50 ml. of water and the water evaporated *in vacuo*. After repetition of the process several times the product was allowed to crystallize from about 20 ml. of water, 1.78 g. (51%), 203° dec. (with gas evolution). Recrystallization of the product from methanol gave colorless needles, 210.5° dec. (gas evolution); λ_{max} 227 mμ (log ε 4.26), 255 (4.22), 332* (3.96), and 342 (4.12).

Anal. Calcd. for $C_{17}H_{11}NO_4$: C, 69.61; H, 3.78; N, 4.78. Found: C, 69.72; H, 3.86; N, 5.10.

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Hexofuranosyl Nucleosides from Sugar Dithioacetals[1]

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Improved procedures were found for the partial hydrolysis of the diethyl dithioacetals of D-glucose and D-galactose (I) to their tetra-*O*-acetyl-1-thio-α-D-glycofuranosides (IIa and II). The acetylated thioglycoside of D-glucofuranose (IIa) was converted with bromine to tetra-*O*-acetyl-D-glucofuranosyl bromide (sirup) which was condensed with the chloromercuri derivative of 2,6-diacetamidopurine (IV) to give the acetylated nucleoside and this on partial deacetylation yielded 2-acetamido-9-β-D-glucofuranosyladenine (VIa). Tetra-*O*-acetyl-β-D-galactofuranosyl chloride (III), similarly prepared from the dithioacetal (I), was transformed to 9-β-D-galactofuranosyladenine (VIII, dimorphous), 2-acetamido-9-β-D-galactofuranosyladenine (VI), and 2,6-diamino-9-β-D-galactofuranosylpurine (VII).

In the pentose series, a sugar may be forced into its furanose form by suitable blocking of the terminal position. This procedure is not applicable in the hexose series and special methods are required to obtain furanoside derivatives. Haworth[4] and associates utilized carbonate esters in several successful syntheses of hexofuranosides. In the galactose structure, a furanose pentaacetate is obtainable by direct acetylation of the sugar and is separable from the pyranose pentaacetate by laborious fractional crystallization methods.[5] Todd and co-workers[6] have reported a crude picrate of 9-β-D-galactofuranosyl-2-methylthioadenine, prepared by using tetra-*O*-acetyl-β-D-galactofuranose derived from such an acetylation of D-galactose.

In the glucose series, the isopropylidene cyclic acetals (1,2 and 1,2:5,6)[7] possess a furanose ring and have been utilized in the synthesis of 9-β-D-glucofuranosyladenine[8] as well as 6-deoxy-D-glucofuranosyl[9] and 6-deoxy-6-iodo-L-iodofuranosyl[10] nucleosides. The nucleosides of L-rhamnofuranose,[11] 6-deoxy-D-allofuranose,[12] and 6-deoxy-L-talofuranose[13] were likewise synthesized utilizing 2,3-*O*-isopropylidene-L-rhamnofuranose[14] as the initial source of the hexofuranose.

Most aldose dithioacetals undergo partial demercaptalation under suitable conditions to form thioglycofuranosides.[15] Ethyl 1-thio-α-D-glucofuranoside has been obtained in 63% yield[16] from D-glucose diethyl dithioacetal by partial demercaptalation with aqueous mercuric chloride and mercuric oxide and it undergoes

(1) Preliminary communication, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 7D.

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(3) Fellow under support of the National Science Foundation Grant NSF-G14629 (Ohio State University Research Foundation Project 1178).

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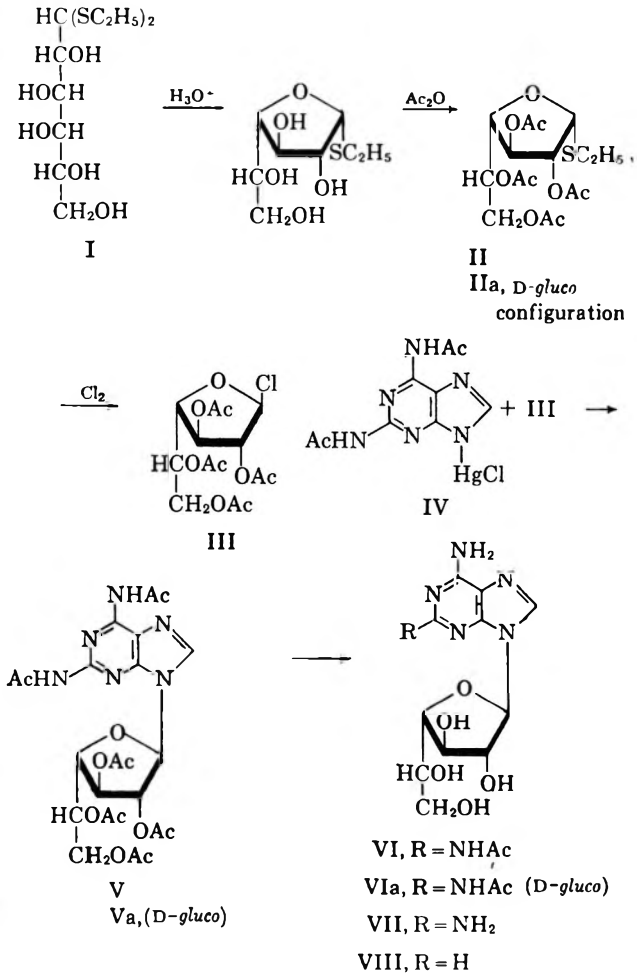
conversion to ethyl 1-thio-β-D-glucofuranoside and ethyl 1-thio-α- and β-D-glucopyranoside under mild acidic conditions. Acetylation of ethyl 1-thio-α-D-glucofuranoside gives the crystalline tetraacetate.[15] Partial demercaptalation of D-galactose diethyl dithioacetal similarly[17] yields ethyl 1-thio-α-D-galactofuranoside, isolated in 43% yield as the 2,3,5,6-tetraacetate by chromatographic techniques.

The present work describes the conversion of D-glucose diethyl dithioacetal and D-galactose diethyl dithioacetal into the corresponding ethyl tetra-*O*-acetyl-1-thio-α-D-furanosides (II and IIa) by partial demercaptalation with dilute hydrochloric acid and mercuric oxide followed by acetylation. These furanose intermediates were then utilized in the synthesis of hexofuranosyl nucleosides.

An acetylated thioglycoside is convertible with bromine to the acetylated glycosyl bromide in a reaction established by Bonner[18] and extended by Weygand and associates.[19] This reaction was utilized in the present work for the conversion of ethyl tetra-*O*-acetyl-1-thio-α-D-glucofuranoside (IIa) to the sirupy tetra-*O*-acetyl-D-glucofuranosyl bromide.[20] Extension of this reaction to the synthesis of the crystalline tetra-*O*-acetyl-β-D-galactofuranosyl chloride (III) of Hudson and Johnson[5] has been made by Wolfrom and Groebke.[21]



The chloride III was converted to a nucleoside by coupling with 2,6-diacetamido-9-chloromercuripurine (IV), by the general method of Davoll and Lowy,[22a] to give, after deacetylation, the crystalline 2,6-diamino-9-β-D-galactofuranosylpurine (VII). Partial deacetylation led to the crystalline 2-acetamido-9-β-D-galactofuranosyladenine (VI). Coupling of tetra-*O*-acetyl-β-D-galactofuranosyl chloride with 6-benzamido-9-chloromercuripurine, followed by deacylation, gave the crystalline 9-β-D-galactofuranosyladenine (VIII).

In our experience, the employment of the tetra-*O*-acetylglycosyl chloride is perferable to the use of the corresponding bromide in this relatively high temperature reaction. Judged by its rotation, the tetra-*O*-acetyl-D-galactofuranosyl chloride possessed the β-D anomeric structure which in turn gave rise to a β-D nucleoside. An anomerization of the β-D chloride may have occurred prior to reaction as the β-D-halo derivatives of the *gluco* and *galacto* series are known to be unstable and readily anomerize in solution. An alternative explanation has been given by Baker and associates[22b] who postulated the formation, from either anomeric halide, of a transient 1,2-ortho ester carbonium ion which would then form the 1,2-*trans* glycoside on attack by the nitrogen heterocycle.

The sirupy tetra-*O*-acetyl-D-glucofuranosyl bromide was likewise condensed with 2,6-diacetamido-9-chloromercuripurine (IV) to give an amorphous 2,6-diacetamido-9-(tetra-*O*-acetyl-β-D-glucofuranosyl)purine (Va) which on partial deacetylation yielded the crystalline 2-acetamido-9-β-D-glucofuranosyladenine (VIa).

Experimental[23]

Improved Preparation of Ethyl Tetra-*O*-acetyl-1-thio-α-D-galactofuranoside (II).—D-Galactose diethyl dithioacetal (I), 28.6 g. (0.13 mole), 600 ml. of water, and 8.5 ml. (0.1 mole) of concentrated hydrochloric acid were stirred vigorously 20 hr. at 20°. Yellow mercuric oxide, 32.9 g. (1.5 moles), was added and stirring was continued for 5 hr. After cooling in iced water, the suspension was filtered and the colorless filtrate was concentrated under reduced pressure to a thin sirup. A white precipitate, 0.1 g., formed during the concentration and was discarded. The aqueous sirup was dissolved in absolute methanol and thrice evaporated. Crystalline D-galactose was recovered by successive treatments of the residue with absolute methanol and absolute ethanol and standing at 0°, 8.07 g. (44.5%), m.p. 167–170°. The alcoholic mother liquor was concentrated under reduced pressure and dried to a nonreducing glass, 11.8 g. (56%). The glass was suspended in 40 ml. of pyridine, treated with 75 ml. of acetic anhydride, the mixture allowed to stand 21 hr. at room temperature, and then poured with stirring into iced water. The product was extracted with chloroform, the extract washed with several portions of water, dried (anhydrous sodium sulfate), and evaporated under reduced pressure. Anhydrous ether was added and evaporated to give a colorless sirup which crystallized on storage in an evacuated desiccator over phosphorus pentaoxide

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(23) The ultraviolet absorption analyses were made on a Cary recording spectrophotometer, Model 10, Applied Physics Corp., Pasadena, Calif. The infrared spectral data were obtained with an infrared recording spectrophotometer, Model B, Baird Associates, Inc., Cambridge, Mass. Structural assignments were made essentially according to W. B. Neely [*Adran. Carbohydrate Chem.*, **12**, 13 (1957)] and B. R. Baker and K. Hewson [*J. Org. Chem.*, **22**, 959 (1957)]. Chromatographic data refer to descending chromatograms on Whatman No. 1 paper with 1-butanol–ethanol–water (40:11:19 v./v.) with indication by ultraviolet light and by sodium metaperiodate and ammoniacal silver nitrate sprays according to L. Hough and J. K. N. Jones ["Methods in Carbohydrate Chemistry," Vol. I., R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1963, p. 28].

and sodium hydroxide, 19.0 g. (48.5%), m.p. 43.5–47°, $[\alpha]^{29}D$ +104° (*c* 1.14, chloroform). The ethyl tetra-*O*-acetyl-1-thio-α-galactofuranoside[17] so obtained was of sufficient purity for use in the next step.

2,6-Diacetamido-9-(tetra-*O*-acetyl-β-D-galactofuranosyl)purine (V).—Tetra-*O*-acetyl-β-D-galactofuranosyl chloride[21] (III, 2.0 g.) was added to an azeotropically dried mixture of 2,6-diacetamido-9-chloromercuripurine[22] (IV, 2.8 g.), Celite[24] (1 g.), cadmium carbonate (1.8 g.), and toluene (100 ml.). The suspension was stirred 4 hr. under reflux, the hot mixture filtered, the filter cake extracted with warm chloroform, and the combined filtrate and chloroform solution evaporated under reduced pressure to a sirup. The sirup was extracted with chloroform. The chloroform solution was washed with 30% aqueous potassium iodide, then with water, and dried (magnesium sulfate). Evaporation of the chloroform solution under reduced pressure yielded a white amorphous solid, 1.24 g. (40.4%), m.p. 100–112°, $[\alpha]^{20}D$ −28.5 ± 3° (*c* 0.3, chloroform); absorption spectra data[23]: $\lambda_{max}^{95\%\ EtOH}$ 236.2, 273.5, 279.5 mμ; λ_{max}^{KBr} 3.15, 3.25 (NH), 5.75 (ester carbonyl), 5.95 (amide carbonyl), 6.15, 6.25, 6.75 (NH and purine ring), 7.30 (methyl hydrogen), 9.04, 9.25, 9.60, 9.82 μ (C–O–C).

Anal. Calcd. for $C_{23}H_{28}O_{11}N_6$: C, 48.92; H, 5.06; N, 14.89. Found: C, 49.12; H, 5.01; N, 15.80.

Attempts to crystallize V were unsuccessful.

2-Acetamido-9-β-D-galactofuranosyladenine (VI).—The partial deacetylation of V was effected with boiling methanolic *n*-butylamine.[25] Amorphous V (700 mg.) was dissolved in methanol (25 ml.) containing *n*-butylamine (1.0 ml.) and heated 6 hr. under reflux, during which time precipitation of a colorless crystalline solid resulted. After partial evaporation and cooling, the crystalline material was removed by filtration, 340 mg. (88%), m.p. 212–213°. The crude crystalline material was decolorized (activated carbon) in water and recrystallized from aqueous ethanol to give analytically pure material, m.p. 240–241°, $[\alpha]^{23}D$ −53 ± 5° (*c* 0.18, water); absorption spectra data[23]: $\lambda_{max}^{H_2O}$ 226.0, 268.0 mμ; λ_{max}^{KBr} 2.95, 3.15 (OH, NH), 5.88 (amide), 6.10, 6.24, 6.44, 6.80 (NH_2, NH, and purine ring), 8.90, 9.08, 9.30, 9.55 μ (C–O–C, C–OH); X-ray powder diffraction data[26]: 10.40 s, 8.27 vs (1), 5.95 vw, 5.34 m, 4.58 m, 4.24 m, 3.97 vs (2), 3.65 vs (3), 3.43 vw, 3.19 vw, 2.96 w.

Anal. Calcd. for $C_{13}H_{18}N_6O_6$: C, 44.05; H, 5.12; N, 23.73. Found: C, 43.85; H, 5.17; N, 23.90.

Compound VI moved on paper chromatography[23] as a single zone, R_{Ad} 0.49.

2,6-Diamino-9-β-D-galactofuranosylpurine (VII).—Crystalline VI, 170 mg., was suspended in 10 ml. of absolute methanol, treated with a solution of sodium methoxide made by dissolving two freshly cut pea size pellets of sodium metal in 20 ml. of absolute methanol and the mixture refluxed 5.5 hr. The solution was cooled, neutralized with glacial acetic acid, and treated with 5 ml. of 10% methanolic picric acid. Precipitation resulted immediately. The yellow picrate was cooled, separated by filtration, and washed with absolute methanol, 180 mg., m.p. 220–228° dec. The picrate was dissolved in boiling water and regenerated with Dowex-1 (CO_3^{-2}) anion-exchange resin. The colorless solution was concentrated under reduced pressure to give a sirup which crystallized on evaporation from absolute ethanol, 65 mg. (43.5%), m.p. 224–225°, $[\alpha]^{20}D$ −64° (*c* 0.23, water); absorption spectra data[23]: λ_{max}^{water} 258, 281 mμ; λ_{max}^{KBr} 3.04 (OH, NH), 6.04, 6.30, 6.88 (NH and purine ring), 9.14, 9.70 μ (C–OH); X-ray powder diffraction data[26]: 7.53 m, 6.07 w, 5.74 m, 5.22 m, 4.82 m, 4.46 m, 4.26 s (3), 3.81 s (1), 3.48 s (2), 3.25 w, 3.07 vw, 2.95 vw, 2.76 vw. The material moved as a single spot, R_{Ad} 0.31, on paper chromatography.[23]

Anal. Calcd. for $C_{11}H_{16}N_6O_5$: C, 42.30; H, 5.17; N, 26.91. Found: C, 42.13; H, 5.74; N, 26.22.

The complete deacetylation of V with boiling methanolic sodium methoxide in 6 hr. gave 33.4% VII while deacetylation with boiling methanolic *n*-butylamine produced 68% VI and 14% VII.

9-β-D-Galactofuranosyladenine (Dimorphous) (VIII).—Crystalline tetra-*O*-acetyl-β-D-galactofuranosyl chloride[21] (III, 1.6 g.) was added to an azeotropically dried mixture of 6-benzamido-9-chloromercuripurine[27] (2.07 g.), Celite[24] (1 g.), cadmium carbonate (1.8 g.), and toluene (150 ml.). The suspension was stirred 4.25 hr. under reflux, the hot mixture filtered, the filtrate extracted with warm chloroform, and the combined extracts evaporated under reduced pressure to a sirup. The sirup was extracted with chloroform, washed with 30% aqueous potassium iodide, then with water, and dried (magnesium sulfate). Evaporation of the chloroform under reduced pressure gave a white amorphous solid, 1.71 g. (69.0%), m.p. (range) 67–87°, $[\alpha]^{20}D$ −15° (*c* 1.25, chloroform); absorption spectra data[23]: λ_{max}^{KBr} 2.8–3.0 (broad, NH), 3.33 (C–H), 5.65 (ester carbonyl), 5.82 (amide carbonyl), 6.05, 6.18, 6.28, 6.6, 6.7, 6.86 (NH, purine ring, benzene ring), 7.29 (methyl hydrogen), 8.15 (C–O–C, acetate), 9.4–9.7 μ (broad, C–O–C).

Deacetylation and debenzoylation of 6-benzamido-9-(tetra-*O*-acetyl-β-D-galactofuranosyl)purine was effected with boiling methanolic *n*-butylamine.[25] The acylated nucleoside (0.26 g.) was dissolved in methanol (20 ml.) containing *n*-butylamine (0.5 ml.) and the solution was refluxed 6 hr. The sirup obtained on solvent removal, under reduced pressure, was dissolved in methanol, and ether added to incipient turbidity. Crystals formed on standing in the refrigerator. Filtration of the fine white crystals was effected in a drybox because of their extremely hygroscopic nature, 0.05 g. (37%), m.p. 209–212° dec., $[\alpha]^{24}D$ −52 ± 3° (*c* 0.3, water); absorption spectra data[23]: $\lambda_{max}^{H_2O}$ 262.5 mμ; λ_{max}^{KBr} 3.05, 3.15 (OH, NH), 6.15, 6.25, 6.40, 6.85 (NH_2, NH, and purine ring), 9.15, 9.45, 9.70, 9.95 μ (C–O–C, C–OH); X-ray powder diffraction data[26]: 9.35 m, 6.63 m, 5.77 m, 5.47 s (3), 5.13 s (2), 4.60 m, 4.20 w, 3.88 m, 3.63 s (1), 3.39 s, 3.27 m, 3.12 w, 2.98 vw, 2.81 w, 2.74 w, 2.41 m, 2.29 w, 2.19 w.

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.43; H, 5.09; N, 23.54. Found: C, 44.13; H, 5.42; N, 22.50.

Crude 6-benzamido-9-(tetra-*O*-acetyl-β-D-galactofuranosyl)-purine (0.5 g.) was dissolved in 10 ml. of absolute ethanol, and 2 ml. of a 10% ethanolic picric acid solution added. The mixture was boiled 4 min. during which time yellow crystals separated from the solution and were removed by filtration of the hot solution, 0.33 g. This product was recrystallized three times from ethanol, m.p. 208–209°; X-ray powder diffraction data[26]: 8.89 vw, 8.01 w, 7.41 m, 6.44 vw, 6.09 m, 5.70 vw, 5.28 w, 5.01 w, 4.60 vw, 4.44 m (3), 4.05 w, 3.87 w, 3.34 m (1), 3.21 m (2). Removal of the picrate anion[27] by stirring, in an aqueous acetone solution, the *O*-acetylated picrate (0.134 g.) with Dowex-1 (CO_3^{-2}) anion-exchange resin[28] gave a white gummy material which failed to crystallize from common solvents. The gummy 9-(tetra-*O*-acetyl-β-D-galactofuranosyl)adenine was deacetylated with boiling methanolic *n*-butylamine as described above. A white crystalline solid precipitated from the hot solution. Upon cooling and filtering, pure 9-β-D-galactofuranosyladenine (VIII) was obtained, 0.043 g. (75%), m.p. 224–225°, $[\alpha]^{24}D$ −52 ± 2° (*c* 0.3, water), spectral and X-ray powder diffraction data identical with those cited before. A recrystallization of the previously prepared hygroscopic VIII (m.p. 209–212° dec.), utilizing the higher melting VIII (m.p. 224–225°) as nucleating agent, yielded white crystals, m.p. 224–225°.

Ethyl Tetra-*O*-acetyl-1-thio-α-D-glucofuranoside (IIa).—D-Glucose diethyl dithioacetal was partially demercaptalated to ethyl 1-thio-α-D-glucofuranoside by a modification of the procedure of Pacsu and co-workers[15,16] and Wolfrom and co-workers.[17] D-Glucose diethyl dithioacetal, 28.0 g. (0.10 mole), was stirred 1 hr. at room temperature with 600 ml. of water containing 8.0 ml. of concentrated hydrochloric acid. The suspension was neutralized with 32.9 g. (0.05 mole excess) of yellow mercuric oxide. The heavy suspension was stirred 1 hr., then cooled in iced water, and filtered. The colorless filtrate was evaporated under reduced pressure to 75 ml. and maintained at 0°. Crystallization of a nonreducing solid resulted, 18.8 g. (84%), m.p. 143–146°. Recrystallization from hot methanol gave ethyl 1-thio-α-D-glucofuranoside,[16,29] m.p. 151–153°, $[\alpha]^{24}D$ +121° (*c* 1.23, water). Acetylation of 5.0 g. of the thiofuranoside with 18 ml. of pyridine and 25 ml. of acetic anhydride at room temperature for 24 hr. gave a neutral sirup which crystallized from 50% aqueous ethanol on evaporation under reduced pressure, 9.5 g., m.p. 62–64°.[29]

(24) A silicous filter aid. Johns-Manville Co., New York, N. Y.

(25) L. Goldman, J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, **78**, 4173 (1956); E. J. Reist and B. R. Baker, *J. Org. Chem.*, **23**, 1083 (1958); B. R. Baker and K. Hewson, *ibid.*, **22**, 959 (1957).

(26) Interplanar spacing, Å., Cu K_α radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very; three strongest lines numbered (1, strongest).

(27) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Am. Chem. Soc.*, **79**, 2778 (1957).

(28) A product of the Dow Chemical Co., Midland, Mich.

(29) M. L. Wolfrom, D. I. Weisblat, and A. R. Hanze, *J. Am. Chem. Soc.*, **66**, 2065 (1944).

2,6-Diacetamido-9-(tetra-*O*-acetyl-β-D-glucofuranosyl)purine.—Ethyl tetra-*O*-acetyl-1-thio-α-D-glucofuranoside (IIa) was converted to a sirupy tetra-*O*-acetyl-D-glucofuranosyl bromide by the method of Weygand and co-workers[19] and this derivative was converted to a nucleoside by the general method of Davoll and Lowy.[22] Crystalline ethyl tetra-*O*-acetyl-1-thio-α-D-glucofuranoside (IIa, 8.5 g.) was dissolved in absolute ether (90 ml.) and treated under magnetic stirring at room temperature with bromine (1.25 ml.). After 7 min. stirring, the amber solution was evaporated under reduced pressure; petroleum ether (b.p. 30–60°) was added and the mixture was twice evaporated to a dry sirup, 9.9 g. This product, dissolved in dry toluene, was added to an azeotropically dried mixture of 2,6-diacetamido-9-chloromercuripurine (10.1 g.),[22] cadmium carbonate (10 g.), Celite (5 g.),[24] and toluene (275 ml.), and the suspension was heated 2.5 hr. at reflux. Filtration of the hot suspension and collection of the material soluble in hot chloroform, followed by washing of the chloroform extract with 30% aqueous potassium iodide, then with water, and drying (sodium sulfate), gave a sirup, 13.63 g. (quantitative). Solid material was obtained by the addition of absolute ether to a concentrated ethanolic solution, m.p. 107–116°, $[\alpha]^{29}D$ +30 ± 3° (*c* 0.37, chloroform); absorption spectra data[23]: λ_{max}^{EtOH} 237, 264, 288 mμ; λ_{max}^{KBr} 3.15, 3.25, 3.35 (NH), 5.70–5.95 (ester carbonyl, amide carbonyl), 6.10–6.25, 6.60–6.90 (NH and purine ring), 7.25–7.35 (methyl hydrogen), 9.24–9.80 μ (C–O–C). This amorphous substance could not be obtained in analytical purity

Anal. Calcd. for $C_{23}H_{28}O_{11}N_6$: C, 48.92; H, 5.00; N, 14.89. Found: C, 48.26; H, 5.10; N, 12.74.

2-Acetamido-9-β-D-glucofuranosyladenine (VIa).—Partial deacetylation of 2,6-diacetamido-9-(tetra-*O*-acetyl-β-D-glucofuranosyl)purine (Va, 850 mg.) in absolute methanol (50 ml.) and *n*-butylamine (1.5 ml.)[25] by refluxing 5 hr. resulted in crystallization from the hot mixture. Pink needles separated at 0°, 380 mg. (81%). Recrystallization (carbon) from water gave colorless needles, m.p. 241–242° dec., $[\alpha]^{28}D$ −77 ± 8° (*c* 0.13, water); absorption spectra data[23]: $\lambda_{max}^{H_2O}$ 226, 269 mμ; λ_{max}^{KBr} 2.98, 3.18 (OH, NH), 5.90 (amide), 6.10, 6.25, 6.38, 6.85 (NH_2, NH, and purine ring), 9.00, 9.15, 9.40, 9.60 μ (C–O–C, C–OH); X-ray powder diffraction data[26]: 8.85 s (3), 7.90 s (2), 4.93 m, 4.51 m, 3.97 s (1), 3.88 vw, 3.60 w, 3.48 vw, 3.38 w, 3.03 m, 2.92 vw, 2.85 vw, 2.69 vw, 2.61 vw, 2.45 vw, 2.36 vw, 2.32 vw, 2.18 vw, 1.95 w. This material moved as a single zone on paper chromatography,[23] R_{Ad} 0.61.

Anal. Calcd. for $C_{13}H_{18}N_6O_6$: C, 44.05; H, 5.12; N, 23.73. Found: C, 43.83; H, 5.19; N, 23.85.

Structural Investigations of Acetylated Sugar Phenylhydrazine Derivatives

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The n.m.r. spectra of the following compounds were investigated to ascertain the utility of this technique in assigning cyclic or acyclic structures to such derivatives: D-*arabino*-3,4,5,6-tetraacetoxy-1-phenylazo-*trans*-1-hexene (I), D-*arabino*-3,4,5,6-tetraacetoxy-1-(*p*-bromophenyl)azo-*trans*-1-hexene (II), D-*lyxo*-3,4,5,6-tetraacetoxy-1-phenylazo-*trans*-1-hexene (III), penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone (IV), penta-*O*-acetyl-*aldehydo*-D-galactose *p*-nitrophenylhydrazone (V), penta-*O*-acetyl-D-mannose *p*-nitrophenylhydrazone (VI), D-glucose "α"-phenylhydrazone pentaacetate (VII), tetra-*O*-acetyl-D-*arabino*-hexose phenylosazone (VIII), and tetra-*O*-acetyl-D-*lyxo*-hexose phenylosazone (IX). It was found that the presence of a low field signal, due to a formyl proton on C-1, is indicative of an acyclic structure in sugar derivatives. Fischer's D-glucose "α"-phenylhydrazone pentaacetate has been so found to be 1-acetyl-1-phenyl-2-(tetra-*O*-acetyl-β-D-glucopyranosyl)-hydrazine. Definitive evidence for the chelate structure of phenylosazones has been obtained. Three striking examples of magnetic nonequivalence of two apparently equivalent protons due to asymmetry at an adjacent center have been found, all occurring in acyclic galactose derivatives. Optical rotatory dispersions of III, IV, V, VI, and VIII have been determined and analyzed.

The structure of the crystalline tetra-*O*-acetyl derivative isolated by Wolfrom and Blair[3] from the acetylation of D-mannose phenylhydrazone has been shown to be D-*arabino*-3,4,5,6-tetraacetoxy-1-phenylazo-*trans*-1-hexene (I) by means of n.m.r. spectroscopy[4] as applied to the *p*-bromophenyl analog, D-*arabino*-3,4,5,6-tetraacetoxy-1-(*p*-bromophenyl)azo-*trans*-1-hexene (II). The analysis of the n.m.r. spectrum of I (Fig. 1) itself is now reported (Table I), along with that of II for comparative purposes. In the spectrum of I, the quartet at τ 2.68, half buried in the phenyl multiplet, shows a coupling constant in common with the quartet at τ 3.25. The low field quartet is assigned to the C-1 proton, which is coupled with the C-2 and C-3 protons. The quartet at higher field is due to the C-2 proton, coupled with its adjacent protons. The allylic C-3 proton, coupled with the protons on C-1, C-2, and C-4, gives an octet at τ 4.08. The quartet at τ 4.37 is assigned to the C-4 proton and the multiplet centered at τ 4.78 to the C-5 proton. The C-6 protons give the multiplet centered at τ 5.80. The complexity of this multiplet is probably due to slight nonequivalence of the C-6 protons due to asymmetry at C-5.

It has been shown that D-*lyxo*-3,4,5,6-tetraacetoxy-1-phenylazo-*trans*-1-hexene (III), an analog of I and II, may be prepared[4] through elimination of 1 mole of acetic acid from penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone[5] (IV) by heating in aqueous ethanol solution. The analysis of the n.m.r. spectrum of III is tabulated in Table I. A doublet at τ 2.70 and a quartet at τ 3.29 were assigned to the C-1 and C-2 protons, respectively. Two masses of lines centered at τ 4.50 and 5.86 of relative areas 2:3 are due to the protons on C-3 and C-4 and those on C-5 and C-6, respectively. This spectrum differs from those of the previously discussed *arabino* analogs in that the C-3 and C-5 proton signals are shifted upfield and there is no observable coupling between the C-1 and C-3 protons. In general, however, this spectrum substantiates the previous assignments, as one may expect such differences as noted due to the difference in configuration.

The analysis of the n.m.r. spectrum (Fig. 2) of penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone (IV), of proven acyclic structure,[5,6] is given in Table II.

(1) Fellow of the Corn Industries Research Foundation.

(2) National Science Foundation Cooperative Graduate Fellow.

(3) M. L. Wolfrom and M. G. Blair, *J. Am. Chem. Soc.*, **68**, 2110 (1946).

(4) M. L. Wolfrom, A. Thompson, and D. R. Lineback, *J. Org. Chem.*, **27**, 2563 (1962).

(5) M. L. Wolfrom and C. C. Christman, *J. Am. Chem. Soc.*, **53**, 3413 (1931).

(6) J. Compton and M. L. Wolfrom, *ibid.*, 1157 (1934).

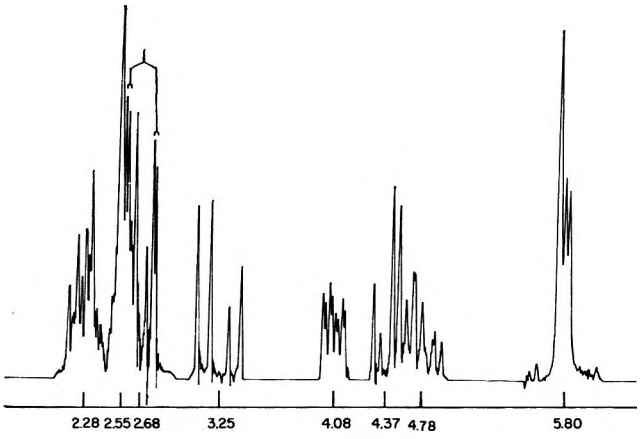

Fig. 1.—N.m.r. spectrum (τ) of D-*arabino*-3,4,5,6-tetraacetoxy-1-phenylazo-*trans*-1-hexene (I).

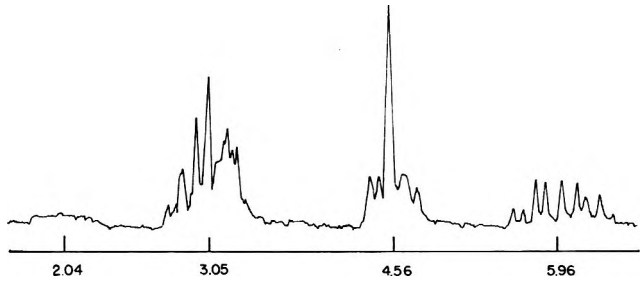

Fig. 2.—N.m.r. spectrum (τ) of penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone (IV).

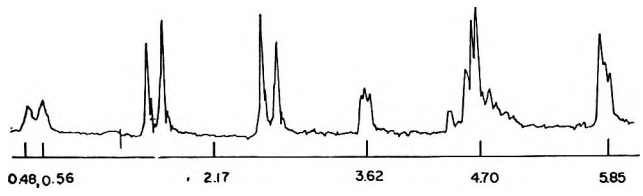

Fig. 3.—N.m.r. spectrum (τ) of penta-*O*-acetyl-*aldehydo*-D-mannose *p*-nitrophenylhydrazone (VI).

The N–H signal, broadened by the nitrogen quadrupole, is a very low broad line at τ 2.04. The complex multiplet at τ 3.05, of relative area six, includes the signals due to the aromatic protons and the C-1 proton. The C-2, C-3, C-4, and C-5 protons give a multiplet of relative area four at τ 4.56. The grouping of eight lines at τ 5.96 is the AB portion, the C-6 protons, of an ABX multiplet, the X proton, that on C-5, being buried in the multiplet at τ 4.56. The nonequivalence of the protons at C-6 arises from the asymmetry at C-5[7] and the imbalance of the populations of the possible rotamers about the C-5–C-6 bond. Analysis of this multiplet yields, in absolute magnitudes, $\delta_{6,6'} = 0.337$ p.p.m., $J_{6,6'} = 11.1$ c.p.s., $J_{5,6} = 5.2$ c.p.s., and $J_{5,6'} = 7.4$ c.p.s.[8]

Because of its insolubility in deuteriochloroform, difficulties were encountered in obtaining a suitable n.m.r. spectrum of penta-*O*-acetyl-*aldehyde*-D-galactose *p*-nitrophenylhydrazone (V), of proven[5] acyclic structure. A spectrum taken at high gain showed a fine structure very similar to the spectrum of IV, differing only slightly in chemical shifts of the multiplets and in the aromatic region. The C-1 aldehydic proton, coupled with the C-2 proton, gave a doublet at τ 3.00, $J_{1,2} = 4.0$ c.p.s. The aromatic protons gave a symmetrical A_2B_2 spectrum centered at τ 2.42. The C-2, C-3, C-4, and C-5 protons gave a multiplet at τ 4.50, very similar to the corresponding multiplet in the spectrum of IV. The C-6 protons were nonequivalent in this case also, giving a multiplet with several lines.

Mild acetylation of D-mannose *p*-nitrophenylhydrazone yielded a crystalline product whose analysis showed it to be the penta-*O*-acetyl derivative (VI). An analysis (Table II) of the n.m.r. spectrum (Fig. 3) of this crystalline substance conclusively proved that it was penta-*O*-acetyl-*aldehydo*-D-mannose *p*-nitrophenylhydrazone (VI). The two broad lines at τ 0.56 and 0.48 are assigned to the C-1 proton and the imino proton, respectively, since the latter line was found to disappear when VI was exchanged by deuterium in deuterium oxide–deuteriochloroform. The aromatic protons gave an A_2B_2 spectrum centered at τ 2.17. The multiplet at τ 3.62 is due to the C-2 proton, and that at 5.85, the C-6 protons, which again seem slightly nonequivalent due to asymmetry at C-5. The C-3, C-4, and C-5 protons give the complex multiplet centered at τ 4.70.

In the n.m.r. spectra of aldehydes,[9] their semicarbazones,[10] 2,4-dinitrophenylhydrazones,[10] and oximes,[11] the formyl proton gives a signal at low field which is usually readily distinguished from the rest of the spectrum. The presence of such a low field signal in the spectra of sugar phenylhydrazones is indicative of a Schiff base structure, as in the spectra of V and VI. However, in some cases, as that of IV, the formyl proton signal is buried in the aromatic multiplet. In such a case, the presence or absence of an acyclic structure must be determined by other methods or by comparing the fine structure of the signals from the protons on the carbohydrate portion of the molecule to the corresponding signals in the spectra of a proven cyclic or acyclic structure of the same conformation.

Fischer[12] first prepared D-glucose "α"-phenylhydrazone. A cyclic structure for this compound was indicated by the isolation of 1-acetyl-1-phenylhydrazine from a hydrolyzate of its pentaacetate[13] and its inability to undergo the formazan reaction.[14] The n.m.r. spectrum of D-glucose "α"-phenylhydrazone was accordingly determined (Fig. 4, curve A) for comparison with proven acyclic analogs. The spectrum was quite similar to that of cyclic β-D-glucopyranose pentaacetate in corresponding regions. The phenyl group gave a signal at τ 2.75 of relative area five and two sharp lines at τ 8.01 and 8.06 were assigned to the methyl protons of the acetyl groups. A mass of lines centered at τ 5.09 comprised the signals attributed to protons on C-2, C-3, and C-4. The anomeric proton gave a broad line at τ 5.60, overlapping the signal attributed to the

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(12) (a) E. Fischer, *Ber.*, **20**, 821 (1887); (b) G. H. Stempel, Jr., *J. Am. Chem. Soc.*, **56**, 1351 (1934).

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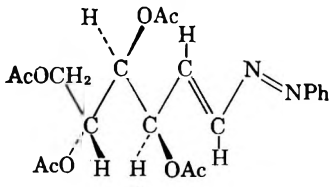
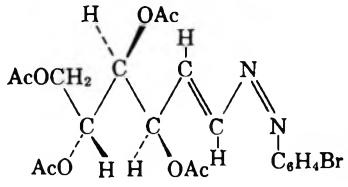
(14) G. Zemplén and L. Mester, *Acta Chim. Acad. Sci. Hung.*, **2**, 9 (1952).

TABLE I

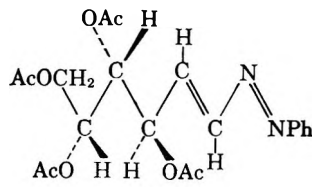
NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA FOR TETRAACETOXY-1-PHENYLAZO-*trans*-1-HEXENES



I



II

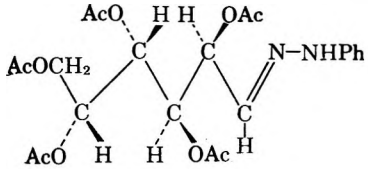


III

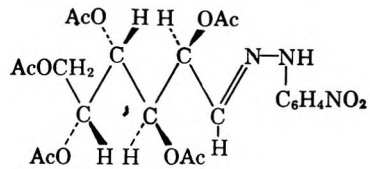
Protons on	I Chemical shift, τ	I Coupling constant, c.p.s.	II Chemical shift, τ	II Coupling constant, c.p.s.	III Chemical shift, τ	III Coupling constant, c.p.s.
Aromatic ring	2.28, 2.55		2.73	...	2.33, 2.75	...
C-1	2.68	$J_{1,2}$ = 13.5	2.99	$J_{1,2}$ = 12.0	2.70	$J_{1,2}$ = 10.5
C-2	3.25	$J_{1,3}$ = 1.0	3.50	$J_{1,3}$ = 1.0	3.29	$J_{2,3}$ = 6.0
C-3	4.08	$J_{2,3}$ = 6.0	4.23	$J_{2,3}$ = 5.0	...	
C-4	4.37	$J_{3,4}$ = 3.0		$J_{3,4}$ = 2.5	4.50	
C-5	4.78	$J_{4,6}$ = 9.0	4.70			
C-6	5.80		5.70		5.86	
Acetyl groups	7.87, 7.93, 7.97		7.92		8.09, 8.13, 8.14	

TABLE II

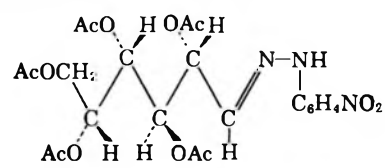
NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA FOR ACYCLIC PHENYLHYDRAZONE PENTAACETATES



IV



V



VI

Protons on	IV, chemical shift, τ	V, chemical shift, τ	VI, chemical shift, τ
Aromatic Ring	3.05		2.17
N	2.04	1.74	0.48
C-1	...	3.00	0.56
C-2			3.62
C-3, C-4, C-5	4.56	4.50	4.70
C-6	5.96	..	5.85
Acetyl Groups	7.92, 7.96, 7.98, 8.03	8.03, 8.05, 8.06, 8.07, 8.08	7.52, 7.99, 8.03

C-6 protons at τ 6.08. The C-5 proton gave a multiplet at τ 6.44 and the imino hydrogen gave a low broad line at τ 3.88. To confirm the assignment of this line to the imino hydrogen, a deuteriochloroform solution of VII was shaken overnight with a few drops of deuterium oxide, thus exchanging the imino hydrogen with deuterium. The spectrum of the resulting two-phase mixture (Fig. 4, curve B) had no signal at τ 3.88, the line assigned to the imino hydrogen. Further, the signal due to the C-1 proton was simplified to a doublet at τ 5.80, $J_{1,2}$ = 7.8 c.p.s. This is due to exchange of the *N*-deuterium atom in the wet solution or possibly because replacing the *N*-proton with deuterium reduces the spin coupling constant by the ratio of the gyromagnetic ratios of deuterium and hydrogen, about $^1/_7$. The magnitude of $J_{1,2}$ indicates that D-glucose "α"-phenylhydrazone exists in the β-D-pyranose form.[15] This VII may now be designated 1-acetyl-1-phenyl-2-(tetra-*O*-acetyl-β-D-glucopyranosyl)hydrazine.

It has been reported that hydrazones of simple aldehydes rearrange to a phenylazo structure on heating in alcohol solution.[16] It accordingly would appear possible that sugar osazones might have this type of structure since they are prepared in hot buffered acetic acid solutions. A phenylazo structure, in equilibrium with the classic Fischer structure, has indeed been proposed by Zerner and Waltuch[17] to account for the mutarotation of osazones. Engel,[18] however, found the ultraviolet spectra not in accord with such a situation. An analysis (Table III) of the n.m.r. spectrum of tetra-*O*-acetyl-D-*arabino*-hexose phenylosazone (VIII)[18-20] proves the presence of a formyl proton and a strongly hydrogen-bonded proton, thus confirming the chelate structure first proposed by Fieser and Fieser[21] and supported by chemical evidence adduced by Mester.[22] An isolated singlet far downfield at τ −2.32 is assignable to the chelated proton, and a singlet at τ 1.62 to the C-1 aldehydic proton. A multiplet centered at τ 2.80 comprised the aromatic proton signals. Complex multiplets at τ 4.25 and 4.70 are assigned to the C-3, C-4, and C-5 protons and the C-6 methylene group gives a multiplet at τ 5.70. Three sharp lines at τ 7.92, 7.96,

(15) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **79**, 1005 (1957); ref. 8, p. 395.

(16) R. O'Connor, *J. Org. Chem.*, **26**, 4375 (1961).

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(18) L. L. Engel, *J. Am. Chem. Soc.*, **57**, 2419 (1935).

(19) K. Maurer and B. Schiedt, *Ber.*, **68**, 2187 (1935).

(20) M. L. Wolfrom, M. Konigsberg, and S. Soltzberg, *J. Am. Chem. Soc.*, **58**, 490 (1936).

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(22) L. Mester, *J. Am. Chem. Soc.*, **77**, 4301 (1955).

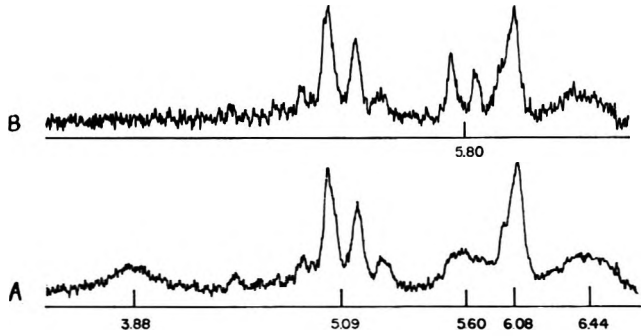


Fig. 4.—N.m.r. spectra (τ) of 1-acetyl-1-phenyl-2-(tetra-*O*-acetyl-β-D-glucopyranosyl)hydrazine (glucose "α"-phenylhydrazone pentaacetate, VII): A, deuteriochloroform solvent; B, deuteriochloroform–deuterium oxide solvent.

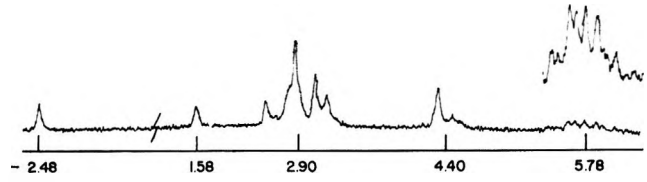


Fig. 5.—N.m.r. spectrum (τ) of tetra-*O*-acetyl-D-*lyxo*-hexose phenylosazone (X).

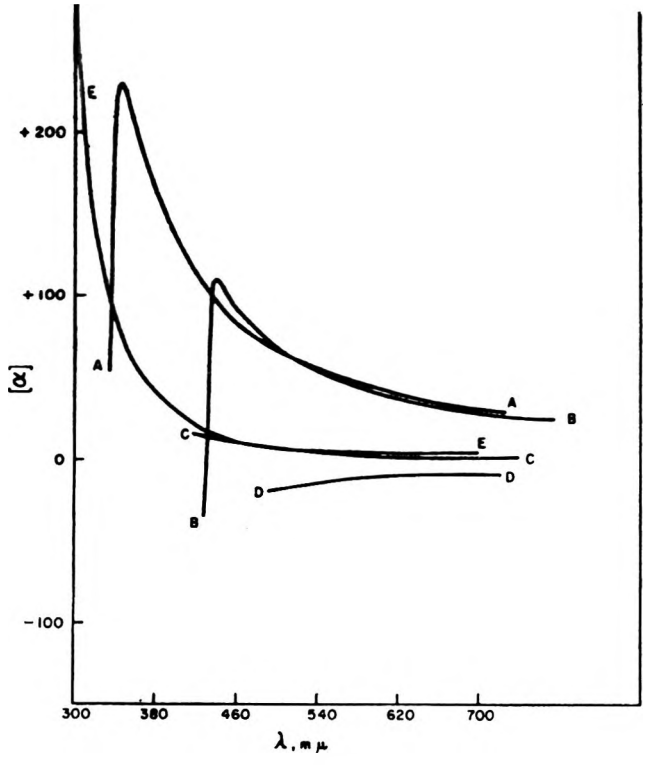
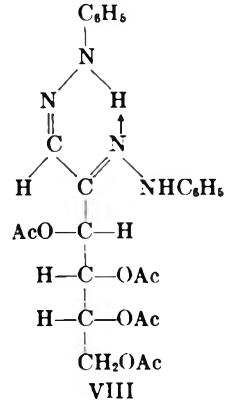


Fig. 6.—Optical rotatory dispersions at 28–29°, in acetonitrile (*c* 1.0), of penta-*O*-acetyl-*aldehydo*-D-galactose phenylhydrazone (IV, curve A), penta-*O*-acetyl-*aldehydo*-D-mannose *p*-nitrophenylhydrazone (VI, curve C), penta-*O*-acetyl-*aldehydo*-D-galactose *p*-nitrophenylhydrazone (V, curve B), D-*lyxo*-3,4,5,6-tetraacetoxy-1-phenylazo-*trans*-1-hexene (III, curve D) (*c* 0.5), and D-glucose "α"-phenylhydrazone pentaacetate (VII, curve E); Rudolph automatic recording spectropolarimeter, Model No. 260/655/850/810-614, Rudolph Instruments Engineering Co., Little Falls, N. J.

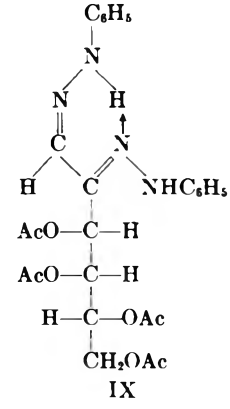
and 8.00 are assigned to the acetate methyl protons. The chelate structure also is indicated clearly by the n.m.r. spectrum (Fig. 5) of tetra-*O*-acetyl-D-*lyxo*-hexose phenylosazone (IX) (Table III).[20] As in two of the other galactose derivatives discussed in this paper, IV and V, the C-6 protons are magnetically nonequivalent. Calculations yield $\delta_{6,6'} = 0.372$ p.p.m., $J_{5,6} = 3.7$ c.p.s., $J_{5,6'} = 6.8$ c.p.s., and $J_{6,6'} = 11.9$ c.p.s. The apparently common occurrence of this phenomenon in acyclic galactose derivatives is worthy of note.

TABLE III

NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA FOR PHENYL OSAZONE TETRAACETATES



VIII



IX

Protons on	VIII, chemical shift, τ	IX, chemical shift, τ
N (chelated)	−2.32	−2.48
Aromatic rings	2.80	2.90
C-1	1.62	1.58
C-3, C-4, C-5	4.25, 4.70	4.40
C-6	5.70	5.78
Acetyl groups	7.92, 7.96, 8.00	7.90, 7.95, 8.05

The optical rotatory dispersion curves for III, IV, V, VI, and VII in acetonitrile are shown in Fig. 6. A simple negative curve (D) and a simple positive curve (C), both referable to single Drude factors, were obtained for III and VI, respectively. Biot–Lowry plots of $1/[\alpha]$ against λ^2 yielded straight lines from which there can be located the optically active absorption bands at 312 mμ for III and 363 mμ for VI. These results compare with ultraviolet absorption at 303 mμ for III[4] and 370 mμ for VI. The curve obtained for VII (E) was complex but normal[23]; a Biot–Lowry plot was nonlinear. The curves for IV (A) and V (B) were complex and anomalous, not referable to single Drude factors.

Experimental

N.m.r. Spectra.—All spectra were taken at 60 Mc. in deuteriochloroform solution with a tetramethylsilane internal reference standard. The spectra of I, II, and VII were taken by Varian Associates. The spectra of III, IV, V, and VI were obtained on a Varian Associates HR-60 spectrometer and calibrated by the usual side-band technique. All other spectra were taken on a Varian Associates A-60 spectrometer and were calibrated by obtaining a second spectrum in chloroform and interpolating between the tetramethylsilane and chloroform lines. For purposes of brevity, the acetate methyl group protons are not shown in the figures.

Penta-*O*-acetyl-*aldehydo*-D-galactose Phenylhydrazone.—This substance was prepared by the acetylation of D-galactose phenylhydrazone as described by Wolfrom and Christman[5], $[\alpha]^{24}D$ +46° (*c* 2, acetonitrile, optical rotatory dispersion shown in Fig. 6, curve A); λ_{max}^{EtOH} 280, 302.5 (shoulder), 372.5, 550 mμ (ϵ_{max} 1.82×10^4, 1.135×10^4, 339, 234, respectively); n.m.r. spectrum shown in Fig. 2; X-ray powder diffraction pattern[24]: 8.65 m,

(23) T. M. Lowry, "Optical Rotatory Power," Longmans Green and Co., New York, N. Y., 1935, p 142.

(24) Interplanar spacing, Å., Cu Kα radiation. Relative intensities, estimated visually: s, strong; m, medium; w, weak; v, very. Strongest lines numbered, 1 strongest.

7.99 w, 6.81 s, 6.03 vs (1), 5.36 s (2), 4.79 w, 4.57 m, 4.01 w, 3.59 m, 3.43 s (3), 3.11 vw, 3.02 vw, 2.92 w, 2.82 w.

Penta-*O*-acetyl-*aldehydo*-D-galactose *p*-Nitrophenylhydrazone.—This substance was prepared by the acetylation of D-galactose *p*-nitrophenylhydrazone[25] as described by Wolfrom and Christman,[5] $[\alpha]^{24}D$ +41° (*c* 2, acetonitrile, optical rotatory disper ion in Fig. 6, curve B); λ_{max}^{EtOH} 375 and 550 mμ (ϵ_{max} 2.34 × 10^4 and 266, respectively); X-ray powder diffraction pattern[24]: 12.63 w, 9.41 s (2), 7.20 w, 6.33 vs (1), 5.75 w, 5.40 w, 5.15 w, 4.65 w, 4.15 m, 3.92 s (3), 3.68 m, 3.53 vw, 3.40 w, 3.27 vw, 2.73 vw.

Penta-*O*-acetyl-*aldehydo*-D-mannose *p*-Nitrophenylhydrazone.—This substance was prepared by the acetylation of D-mannose *p*-nitrophenylhydrazone[25] according to the procedure of Wolfrom and Christman.[5] The sirupy product was dissolved in 50 ml. of benzene and chromatographed, in equal portions, on two columns (75 × 240 mm.) filled with Magnesol-Celite[26] (5:1 by weight) and developed with 1400 ml. of benzene–2-methyl-2-propanol (100:1 by volume). Extrusion and streaking with alkaline permanganate solution revealed the presence of two zones 90–175 and 220–230 mm. from the column top. The zones were excised, twice extracted with acetone, filtered; the solvent was removed under reduced pressure and the resulting sirups were crystallized from ethanol. Both zones gave the same bright yellow crystalline material as identified by melting point and mixture melting point, 3.47 g., m.p. 130–131°, $[\alpha]^{27}D$ −16.0° (*c* 4, pyridine), +4.5° (*c* 2, acetonitrile, optical rotatory dispersion shown in Fig. 6 curve C); λ_{max}^{EtOH} 370 (shoulder) and 540 mμ (ϵ_{max} 1100 and 166, respectively); n.m.r. spectrum shown in Fig. 3; X-ray powder diffraction pattern[24]: 12.40 w, 9.85 m, 8.12 m, 6.58 s (2), 6.13 vw, 5.36 vs (1), 5.01 w, 4.70 s (3), 4.33 w, 3.99 m, 3.73 m, 3.47 w, 3.25 w, 3.09 vw, 2.88 m, 1.98 vw.

Anal. Calcd. for $C_{12}H_{12}O_7N_3(CH_3CO)_5$: C, 50.29; H, 5.14; N, 8.00; CH_3CO, 10.74 ml. of 0.1 *N* NaOH for 100 mg. Found: C, 50.57; H, 5.50; N, 7.71; CH_3CO (as *O*-Ac),[20] 10.25 ml.

1-Acetyl-1-phenyl-2-(tetra-*O*-acetyl-β-D-glucopyranosyl)hydrazine.—D-Glucose "α"-phenylhydrazone was prepared according to the method of Stempel,[12b] m.p. 145–150°. This hydrazone was then acetylated in the manner described by Behrend and Reinsberg,[13] m.p. 151–153°, $[\alpha]^{32}D$ +20° (*c* 2.0, chloroform), +9.0° (*c* 2.0, pyridine), +2.0° (*c*, 2.0, acetonitrile, optical rotatory dispersion shown in Fig. 6, curve E); n.m.r. spectrum shown in Fig. 4; λ_{max}^{EtOH} no absorption between 285 and 600 mμ; λ_{max}^{KBr} 3.1, 3.4, 5.7 (carbonyl), 6.1, 6.3, 6.5, 6.7, 7.0, 7.3, 7.9, 8.1–8.3 (acetate), 9.1, 9.4, 9.6, 10.2, 11.0, 11.9, 12.5, 13.1, 13.9, 14.3, 15.5 μ; X-ray powder diffraction pattern[24]: 10.78 w, 9.61 m (3), 8.85 m, 6.71 vw, 5.40 s (1), 4.82 w, 4.51 m, 4.23 w, 3.87 s (2), 3.56 vw. Hofmann[27] reported m.p. 152–153° and $[\alpha]D$ +11.97° (pyridine) for this material while Behrend and Reinsberg[13] reported m.p. 151° and $[\alpha]D$ +17.5° (pyridine).

Acknowledgment.—Acknowledgment is made to Dr. Leroy F. Johnson of Varian Associates, Palo Alto, California, in obtaining and interpreting one of the n.m.r. spectra. Certain other spectra were obtained by Byron Bossenbroek and the optical rotatory dispersion measurements were carried out by Neal Franks. Stimulating discussions with Dr. R. D. Guthrie, University of Leicester, are acknowledged.

(25) W. Alberda van Ekenstein and J. J. Blanksma, *Rec. trav. chim.*, **22**, 434 (1903).

(26) W. H. McNeely, W. W. Binkley, and M. L. Wolfrom, *J. Am. Chem. Soc.*, **67**, 527 (1945).

(27) A. Hofmann, *Ann.*, **366**, 306 (1909).

The Synthesis of the *t*-Butyl 1-Thio-D-glucosides and of 2,4-Dinitrophenyl 1-Thio-β-D-glucopyranoside. The Reaction of Some 1-Thio-D-glucosides with Mercury Salts of Carboxylic Acids

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Both anomeric *t*-butyl 1-thio-D-glucopyranosides and *t*-butyl 1-thio-D-glucofuranosides, as well as 2,4-dinitrophenyl 1-thio-β-D-glucopyranoside, have been synthesized. The behavior of some of these thioglucosides with mercury salts of carboxylic acids has been investigated and a tentative mechanism of the formation of 1-*O*-acylaldoses by this pathway is proposed.

Earlier investigations in this laboratory[1-4] have shown that various 1-thioaldose derivatives (dithioacetals and alkyl 1-thioglycosides) undergo metathetical reactions with silver and mercury salts. Thus, ethyl 1-thio-β-D-glucopyranoside is converted into a mixture of the anomeric 1-*O*-mesitoyl-D-glucopyranoses when treated with silver mesitoate[1] (silver 2,4,6-trimethylbenzoate), and the condensation of 5-*O*-benzoyl-2-deoxy-D-*erythro*-pentose diisopropyl dithioacetal with chloromercuri-6-benzamidopurine leads (after the removal of masking groups) to a mixture of the anomeric 9-(2-deoxy-D-*erythro*-pentofuranosyl)adenines. In the studies of the behavior of ethyl 1-thioaldosides with silver salts of carboxylic acids,[1,4] prolonged boiling in acetonitrile was found necessary to effect complete reaction, although an ethyl 1-thioaldofuranoside[4] obviously reacted more readily than did an ethyl 1-thioaldopyranoside.[1] Under these conditions, acyl migrations (for example, conversion of 1-*O*-benzoyl-α-D-glucopyranose to 2-*O*-benzoyl-D-glucose) take place and the procedure is obviously less than ideal for inserting labile substituents at C-1 in an aldose. Pedersen and Fletcher[4] noted that mercuric acetate reacts with ethyl 5-*O*-benzoyl-1-thio-β-L-arabinofuranoside more readily than does silver benzoate. In seeking methods whereby this reaction can be carried out under comparatively mild conditions, we have, therefore, now turned our attention to some mercury salts of carboxylic acids, and, for glycosides, have used *t*-butyl 1-thio-β-D-glucopyranoside (II), *t*-butyl 1-thio-α-D-glucofuranoside (X), and 2,4-dinitrophenyl 1-thio-β-D-glucopyranoside (XIV) in the hope of revealing any influence of the electronegativity of the aglucon on the nature of the reaction.

Although 2-methyl-2-propanethiol (*t*-butyl mercaptan) is a readily available substance, no *t*-butyl thioglycosides appear to have been reported in the litera-

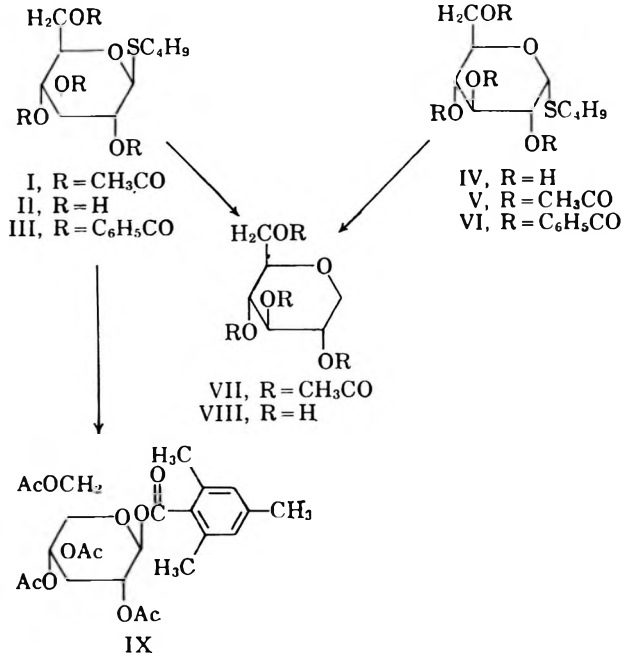
(1) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3215 (1960).

(2) C. Pedersen, H. W. Diehl, and H. G. Fletcher, Jr., *ibid.*, **82**, 3425 (1960).

(3) C. Pedersen and H. G. Fletcher, Jr., *ibid.*, **82**, 5210 (1960).

(4) C. Pedersen and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 1255 (1961).

ture. However, the thiol was found to react readily with β-D-glucopyranose pentaacetate in ether solution in the presence of zinc chloride to give *t*-butyl 1-thio-β-D-glucopyranoside tetraacetate (I) in 69% yield; deacetylation afforded the parent glucoside (II). The reaction was repeated using benzene in place of ether, and *t*-butyl 1-thio-β-D-glucopyranoside tetraacetate (I) was obtained in 24% yield. Deacetylation of the material remaining in the mother liquor gave *t*-butyl 1-thio-α-D-glucopyranoside (IV) in 38% yield. Reductive desulfurization of I with Raney nickel gave 1,5-anhydro-D-glucitol tetraacetate (VII), whereas desulfurization of IV yielded the unsubstituted anhydride (VIII), demonstrating that both substances are 1-thio-D-glucopyranosides. Anomeric configurations were assigned to the 1-thio-D-glucopyranosides on the basis of their optical rotations.

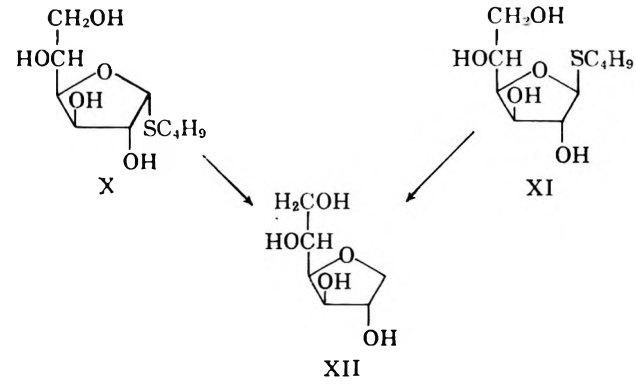


t-Butyl 1-thio-β-D-glucopyranoside (II) reacts readily with mercury mesitoate in acetonitrile solution at room temperature, giving, after acetylation, 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucopyranose (IX)[5] in 38% yield.

Condensation of β-D-glucofuranose pentabenzoate with 2-methyl-2-propanethiol in ethereal solution in the presence of zinc chloride gave, after debenzoylation, *t*-butyl 1-thio-α-D-glucofuranoside (X) in 48% yield. In a similar preparation, the crude *t*-butyl 1-thio-D-glucofuranoside tetrabenzoate was chromatographed, and a levorotatory fraction debenzoylated to give *t*-butyl 1-thio-β-D-glucofuranoside (XI). Both X and XI gave 1,4-anhydro-D-glucitol (XII) on reductive desulfurization with Raney nickel, confirming their furanoside structures; again, anomeric configurations were assigned on the basis of optical rotations.

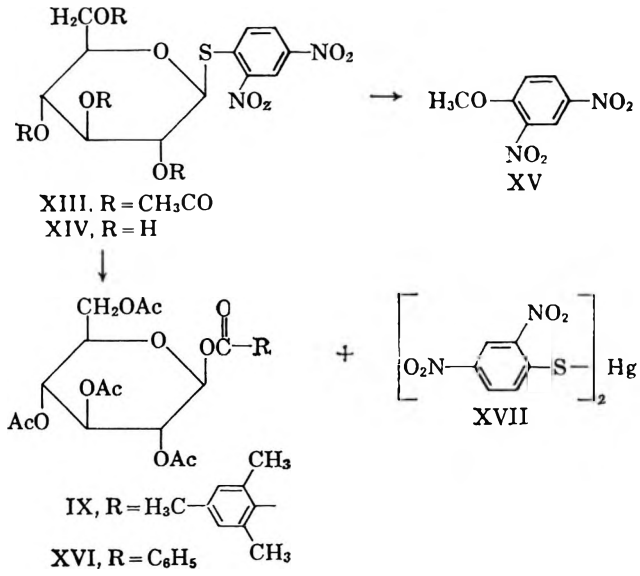
The behavior of *t*-butyl 1-thio-α-D-glucofuranoside (the only anomer available in sufficient quantity for testing) with mercury mesitoate in acetonitrile solution proved unique in our experience, inasmuch as the only crystalline product recoverable was mesitoic anhydride, a readily isolable and identifiable substance. The

(5) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 207 (1956).



mechanism of the formation of this unexpected substance must at this juncture remain a matter for speculation.

2,4-Dinitrophenyl 1-thio-β-D-glucopyranoside tetraacetate (XIII) was synthesized through condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with 2,4-dinitrobenzenethiol in the presence of ethanolic potassium hydroxide. Some difficulty was encountered in the deacetylation of XIII, since the two nitro groups labilize the S-aryl bond. Thus, barium methoxide gave only a poor yield of the deacetylated glucoside (XIV), but a considerable amount of 2,4-dinitroanisole (XV) was isolated and chromatographic evidence for the presence of di(β-D-glucopyranosyl) disulfide was obtained. On the other hand, deacetylation of XIII with methanolic ammonia gave XIV in good yield. Treatment of XIV in acetonitrile solution with either

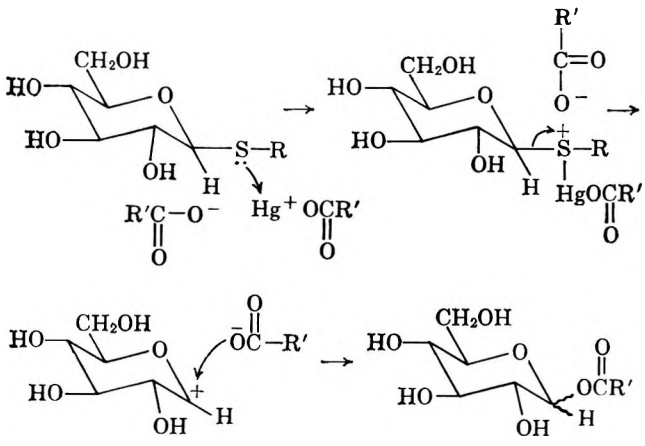


mercuric benzoate or mercuric mesitoate at room temperature gave 1-*O*-benzoyl-β-D-glucopyranose or 1-*O*-mesitoyl-β-D-glucopyranose (isolated as their tetraacetates XVI and IX in low yield). In both cases, di(2,4-dinitrophenylthio)mercury (XVII), the other expected product, was isolated in substantial yield.

Discussion

The condensation of 1-thioglycosides in acetonitrile solution with silver salts of carboxylic acids is a non-stereospecific reaction, giving a mixture of the anomeric 1-*O*-acylaldoses.[1] With both mercury and silver salts of carboxylic acids, 1-thioglycosides usually give, quite promptly, a precipitate which changes in appearance

as the reaction proceeds. This observation suggests that a complex is initially formed between the two components[6] and subsequently breaks down to the 1-*O*-acylaldose and a di(alkylthio)mercury. Such a transformation may be rationalized in the following fashion.



In this mechanism, the electronegativity of the aglucon would be expected to play a greater or lesser role by diminishing or increasing the electron density around the sulfur atom. The observation that *t*-butyl 1-thio-β-D-glucopyranoside gives a higher yield of 1-*O*-mesitoyl-β-D-glucopyranose than does 2,4-dinitrophenyl 1-thio-β-D-glucopyranoside may be regarded as supporting this concept.[7] However, in such apparently complex and often heterogeneous reactions, where a large proportion of the products are as yet unidentified, such a mechanism must at this point remain purely speculative. Irrespective of mechanistic considerations, the reaction appears to offer some potential utility as a synthetic method.

A simple technique for minimizing the dispersion of the vapors of volatile thiols during some typical manipulations is described in the Experimental section.

Experimental[8]

A Technique for Handling Volatile Thiols.—Dispersion of the objectionable vapors of volatile thiols may be minimized in several ways. In this work, evaporation of the thiols was always carried out as a codistillation (usually with carbon tetrachloride) *in vacuo*, the distillate being retained in the trap shown in Fig. 1. Dry Ice and acetone were used to cool the trap, and the distillate collected in the spherical flask was promptly treated with an excess of concentrated, aqueous calcium hypochlorite at the conclusion of the distillation. Alternatively, the calcium hypochlorite solution may be placed in the flask prior to the distillation.

In filtering solids contaminated with volatile thiols, the filter may be covered with a large conical funnel attached to the vacuum system through the trap shown in Fig. 1.

***t*-Butyl 1-Thio-β-D-glucopyranoside Tetraacetate (I).**—A mixture of 25 ml. of anhydrous ether and 5 g. of powdered, freshly fused zinc chloride in a glass-stoppered flask was stirred at room temperature until the solid had changed to an oil. 2-Methyl-2-propanethiol[9] (15 ml.) and β-D-glucopyranose pentaacetate (10 g.) were then added, and the reaction mixture was stirred at room temperature. After 2.5 hr., the pink reaction mixture was nearly homogeneous; shortly thereafter, the product began to crystallize as fine, silky needles. After a total of 12 hr., the mixture was a deep purple. Carbon tetrachloride (25 ml.) was added, the flask was attached to the trap described (Fig. 1), and the major part of the solvent and unchanged thiol was distilled into the trap under reduced pressure. Water (100 ml.) and carbon tetrachloride (100 ml.) were added to the residue, the mixture was filtered, and the solid was washed with carbon tetrachloride. The aqueous layer was separated, run directly into concentrated, aqueous calcium hypochlorite, and discarded; the carbon tetrachloride solution was dried (magnesium sulfate), filtered, and concentrated *in vacuo* to a thick sirup. Two 50-ml. batches of carbon tetrachloride were successively evaporated from this sirup to remove most of the thiol. The thick, colorless sirup was dissolved in 50 ml. of ethyl acetate and reconcentrated *in vacuo*, the residue was dissolved in 20 ml. of warm ethyl acetate, and the solution was filtered through a thin layer of decolorizing carbon, reheated, and diluted with 2–3 volumes of pentane. Crystallization was completed at 5° to give 5.8 g. of product, m.p. 144–145°. A second crop (1.62 g., slightly less pure) raised the total crude yield to 7.42 g. (69%). One recrystallization from ethanol–pentane gave pure I, m.p. 145–146°, $[\alpha]^{20}D$ −5.9° (*c* 0.65, chloroform).

Anal. Calcd. for $C_{18}H_{28}O_9S$ (420.46): C, 51.41; H, 6.71; S, 7.62. Found: C, 51.57; H, 6.83; S, 7.51.

2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol (VII) from I.—A solution of I (0.5 g.) in 20 ml. of 70% aqueous ethanol was treated with 4 teaspoonfuls of freshly prepared Raney nickel (under ethanol). After being boiled under reflux for 3 hr., the suspension was cooled and filtered, and the filtrate was concentrated (*in vacuo*) at 40° to a colorless sirup which from 4 ml. of ether and 3 ml. of pentane gave a nearly quantitative yield of crystals, m.p. 70–74°, $[\alpha]^{20}D$ +38.8° (*c* 1.0, chloroform); lit.[10] m.p. 73–74°, $[\alpha]^{20}D$ +38.9° (chloroform).

***t*-Butyl 1-Thio-β-D-glucopyranoside (II).**—I (2 g.) was catalytically deacetylated with barium methoxide in methanol. The deacetylated product, crystallized from acetone–pentane and dried *in vacuo* at 40°, weighed 0.95 g. (76%), m.p. 113–115°. Recrystallized from acetone–pentane, the pure II had m.p. 115–116°, $[\alpha]^{20}D$ −52.8° (*c* 0.55, water).

Anal. Calcd. for $C_{10}H_{20}O_5S \cdot 0.5H_2O$ (261.33): C, 45.96; H, 8.10; S, 12.27. Found: C, 46.03; H, 7.95; S, 12.46.

Attempts to obtain anhydrous material failed. Acetylation (acetic anhydride–pyridine) gave I, 93% yield, m.p. 145–146°, $[\alpha]^{20}D$ −5.9° (*c* 1.0, chloroform). A mixture melting point with the original ester was not depressed.

***t*-Butyl 1-Thio-β-D-glucopyranoside Tetrabenzoate (III).**—II (0.15 g.) was benzoylated (benzoyl chloride–pyridine) and the product crystallized on adding water. Recrystallized from 5

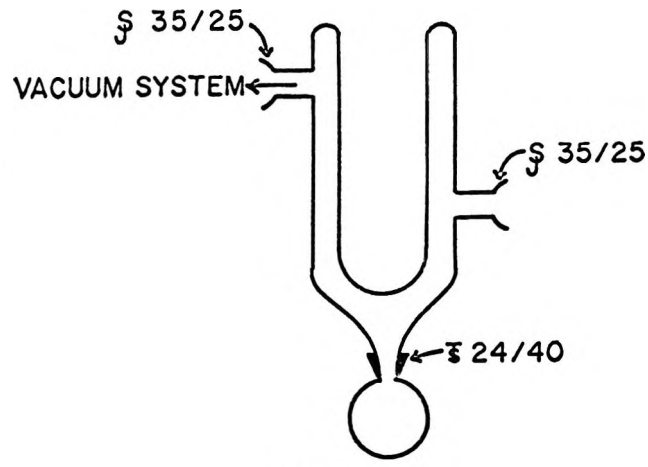


Figure 1.

(6) E. Hardegger, E. Schreier, and Z. El Heweihi [*Helv. Chim. Acta*, **33**, 1159 (1950)] described several addition compounds of aldose dithioacetals with mercuric chloride.

(7) It may be noted that no fully acylated 1-thioglycosides have yet been found to undergo displacements with mercury or silver salts, ref. 1, footnote 11. In the course of the present work, *t*-butyl 1-thio-β-D-glucopyranoside tetraacetate in acetonitrile solution was found to be unaffected by mercury mesitoate.

(8) Melting points are corrected. Selected absorption maxima, together with probable assignments, are given for infrared spectra, intensities being indicated as s (strong), m (medium), w (weak). Ar indicates a substituted benzene ring.

(9) A sample (*t*-butyl mercaptan) obtained from Phillips Petroleum Co., Special Products Division, Bartlesville, Okla., was found to be of high purity and was employed throughout this research.

(10) N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, **65**, 64 (1943).

ml. of hot ethanol, III (0.33 g., 86%) had m.p. 183–184°, $[\alpha]^{20}D$ +32.2° (*c* 1.1, chloroform).

Anal. Calcd. for $C_{29}H_{36}O_9S$ (668.73): C, 68.24; H, 5.43; S, 4.79. Found: C, 68.26; H, 5.55; S, 4.76.

t-Butyl 1-Thio-α-D-glucopyranoside (IV).—A mixture of 5 g. of freshly fused zinc chloride, 15 ml. of 2-methyl-2-propanethiol, 20 ml. of dry benzene, and 10 g. of β-D-glucopyranose pentaacetate was stirred at room temperature for 20 hr. and then processed as for I. The resulting sirup, dissolved in ethyl acetate–pentane, gave 2.6 g. (24%) of I, m.p. 144–145°. Solvent was removed from the mother liquor and the sirupy residue was deacetylated with barium methoxide in methanol. After the solution had been neutralized with carbon dioxide, the methanol was removed *in vacuo*, the residue was dissolved in 50 ml. of water, and the solution was filtered from a trace of flocculent material and deionized with ion-exchange resins. Concentration gave a sirup which was dissolved in a mixture of 5 ml. of ethyl acetate and 10 ml. of pentane to give 2.54 g. (38%) of product, m.p. 139–141°. Recrystallized from the same solvent mixture, IV had m.p. 142–143°, $[\alpha]^{20}D$ +233° (*c* 0.78, water).

Anal. Calcd. for $C_{10}H_{20}O_5S{\cdot}0.5H_2O$ (261.33): C, 45.96; H, 8.10; S, 12.27. Found: C, 45.81; H, 8.22; S, 12.01.

1,5-Anhydro-D-glucitol (VIII) from IV.—IV (0.5 g.) was desulfurized by boiling with a suspension of 2 teaspoonfuls of freshly prepared Raney nickel in 10 ml. of 70% aqueous ethanol. After filtration, the solution was concentrated *in vacuo* and the product crystallized from methanol, 0.13 g. (41%), m.p. 142–143°, $[\alpha]^{20}D$ −42.7° (*c* 1.0, water). A mixture melting point with an authentic sample of VIII[10] was not depressed.

t-Butyl 1-Thio-α-D-glucopyranoside Tetraacetate (V).—IV (0.15 g.) was acetylated (acetic anhydride–pyridine) to give a clear, colorless sirup which, from ethyl acetate–pentane, gave 0.19 g. (79%) of crystals, m.p. 63–65°. Recrystallization from warm hexane afforded pure V, m.p. 62–64°, $[\alpha]^{20}D$ +185° (*c* 0.6, chloroform).

Anal. Calcd. for $C_{18}H_{28}O_9S$ (420.46): C, 51.41; H, 6.71; S, 7.62. Found: C, 51.53; H, 6.92; S, 7.41.

t-Butyl 1-Thio-α-D-glucopyranoside Tetrabenzoate (VI).—IV (0.22 g.) was benzoylated (benzoyl chloride–pyridine) to give a sirup which, from 5 ml. of ethanol, gave 0.55 g. (96%) of product, m.p. 167–168°. Recrystallization from ethanol afforded needles which were dried *in vacuo* at 110°, m.p. 168–169°, $[\alpha]^{20}D$ +96.8° (*c* 0.85, chloroform).

Anal. Calcd. for $C_{38}H_{36}O_9S{\cdot}0.5H_2O$ (677.74): C, 67.33; H, 5.55; S, 4.73. Found: C, 67.53; H, 5.92; S, 4.58.

Attempts to dehydrate this compound completely were unsuccessful.

Mercuric 2,4,6-Trimethylbenzoate (Mesitoate.)—The following procedure for the preparation of mercuric mesitoate proved convenient. A suspension of mesitoic acid[11] (30 g.) in 150 ml. of water was nearly neutralized by the cautious addition of 6 *N* ammonium hydroxide. Care was taken to avoid an excess of base, and a trace of the acid was filtered off (decolorizing carbon). A solution of 60 g. of mercuric nitrate monohydrate in 18 ml. of water was added, the solution was heated (until the salt had dissolved) and cooled to room temperature; after 10 min. the crystals were filtered off, washed thoroughly with water, and dried *in vacuo* at 60° to yield 40.2 g. of fine needles (84%). This salt is adequate for most purposes; it may be recrystallized from acetonitrile or 2-ethoxyethanol with considerable loss. The above product was recrystallized from hot 2-ethoxyethanol (5 ml./g.) to give 15.4 g. of pure salt; a second crop (10 g.) was obtained from the mother liquor. A sample of the first crop, dried *in vacuo* at 100°, was used for analysis.

Anal. Calcd. for $C_{20}H_{22}HgO_4$ (526.99): C, 45.58; H, 4.21. Found: C, 45.63; H, 4.40.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucopyranose (IX) from II.—II (1 g.) was dissolved in 100 ml. of dry acetonitrile, and 5.0 g. of mercuric mesitoate was added. The mixture was stirred at room temperature overnight and filtered through a layer of decolorizing carbon. Solvent was removed from the filtrate *in vacuo* at 40°, and the residue was dissolved in water–methanol (10:1) and treated with hydrogen sulfide to remove mercuric ions. After being filtered through a thin layer of decolorizing carbon, the solution was concentrated *in vacuo*, and the resulting sirup was dried by evaporation therefrom *in vacuo* of several portions of benzene. Acetylation with 10 ml. of dry pyridine and 8 ml. of acetic anhydride afforded a clear, colorless sirup. From absolute ethanol, 0.45 g. (38%) of material was obtained, m.p. 139–140°, $[\alpha]^{20}D$ +9.5° (*c* 3.9, chloroform). Recrystallization from benzene–hexane gave pure IX, m.p. 141–142°, $[\alpha]^{20}D$ +4.2° (chloroform). A mixture melting point with authentic material[5] was undepressed.

t-Butyl 1-Thio-α-D-glucofuranoside (X).—Freshly fused zinc chloride (5 g.) was added to 50 ml. of anhydrous ether, and the mixture was stirred until the solid had been converted to an oil. 2-Methyl-2-propanethiol (15 ml.) and 10 g. of β-D-glucofuranose pentabenzoate[12] (m.p. 141–143°, $[\alpha]^{20}D$ −56.8° in chloroform) were added, and the mixture was stirred at room temperature (20 hr.). The solvent, zinc chloride, and unchanged mercaptan were removed as for I to give a sirup which was debenzoylated with barium methoxide in methanol. The methanolic solution was neutralized with carbon dioxide and concentrated *in vacuo*, and the semisolid residue was diluted with 10 ml. of water. Methyl benzoate was removed by extraction with two 3-ml. portions of cyclohexane and the aqueous phase, after being filtered through a thin bed of decolorizing carbon, was concentrated to a sirup. From methanol–isopropyl ether, the product (0.9 g., 48%) was obtained in crystalline form, m.p. 135–136°. Recrystallization from the same solvent mixture gave pure X, m.p. 139–140°, $[\alpha]^{20}D$ +84.9° (*c* 0.5, water).

Anal. Calcd. for $C_{10}H_{20}O_5S{\cdot}0.5H_2O$ (261.33): C, 45.96; H, 8.10; S, 12.27. Found: C, 45.85; H, 8.16; S, 12.25.

1,4-Anhydro-D-glucitol (XII) from X.—(0.5 g.) was desulfurized by boiling for 3 hr. in 10 ml. of 70% aqueous ethanol containing 2 teaspoonfuls of freshly prepared Raney nickel. The suspension was cooled and filtered, the filtrate was concentrated *in vacuo*, and the resulting sirup was dissolved in 0.5 ml. of isopropyl alcohol to give 0.1 g. (32%) of crystals, m.p. 105–110°. A second recrystallization afforded pure XII, $[\alpha]^{20}D$ −21.7° (*c* 1.0, water); its m.p. 114–115° was not depressed on admixture with an authentic sample; lit.[13] m.p. 115–116°, $[\alpha]^{20}D$ −21.9° (water).

t-Butyl 1-Thio-β-D-glucofuranoside (XI).—Freshly fused zinc chloride (5 g.) was stirred at room temperature with 50 ml. of anhydrous ether for 15 min. 2-Methyl-2-propanethiol (15 ml.), chloroform (15 ml., U.S.P.), and β-D-glucofuranose pentabenzoate (10 g.) were added, and the mixture was stirred at room temperature. After 10 min., dissolution was not complete, and 55 ml. of methylene chloride was added to give a solution. After being kept for 16 hr. at room temperature, the mixture was filtered to remove 0.45 g. of material, m.p. >300°. The filtrate was concentrated to about one-third of its volume, and was diluted with methylene chloride (50 ml.) and water (50 ml.). After being shaken, the aqueous layer was discarded, and the organic layer was washed with water (50 ml.) and with saturated aqueous bicarbonate, dried (anhydrous magnesium sulfate), and concentrated *in vacuo* to a sirup. This sirup (8 g.) was chromatographed on a column of 300 g. of alumina (acid-washed Alcoa, equilibrated with atmospheric moisture). Elution with 200-ml. portions of benzene led to the collection of a substantial peak of levorotatory material, $[\alpha]^{20}D$ *ca.* −65° (chloroform). Efforts to obtain this material crystalline being unsuccessful, it was debenzoylated (barium methoxide in methanol) in the usual way to yield, from ether, fine needles (0.57 g.), m.p. 89–90°. Recrystallized from ethyl acetate and dried at 56° *in vacuo*, the product had m.p. 89–90°, $[\alpha]^{20}D$ −140° (*c* 0.38, water).

Anal. Calcd. for $C_9H_{20}O_5S$ (252.32): C, 47.60; H, 7.99. Found: C, 47.68; H, 8.01.

Desulfurization of 0.40 g. of XI with Raney nickel was performed as for the α-D anomer to give 0.0656 g. (25%) of crystals, m.p. 106–110°; on recrystallization from isopropyl alcohol, m.p. 112–114°, undepressed by admixture with authentic XII. XII had $[\alpha]^{20}D$ −21.1° (*c* 0.83, water).

Reaction of X with Mercuric Mesitoate.—X (1 g., 3.83 mmoles) was dissolved in 200 ml. of acetonitrile, half of the acetonitrile was removed by boiling, and the solution was cooled to room temperature, treated with 5 g. of mercuric mesitoate (9.49 mmoles), and stirred overnight. A trace of a fine precipitate was removed by filtration (decolorizing carbon), and the clear, colorless solution was concentrated *in vacuo* to a thin sirup which crystallized spontaneously. The crystals were removed and washed with 1 ml. of methanol, 0.44 g., m.p. 92–100°; a second crop (0.10 g., m.p. 96–100°) formed on standing; total yield, 0.54 g., 1.74 mmoles. After recrystallization from acetone, the

(11) K & K Laboratories, Inc., 177-10 93rd Avenue, Jamaica 33, N. Y.

(12) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **76**, 513 (1928).

(13) S. Soltzberg, R. M. Goepp, Jr., and W. Freudenberg, *J. Am. Chem. Soc.*, **68**, 919 (1946).

product was obtained as prisms, m.p. 102–103°, mixed with authentic mesitoic anhydride,[14] m.p. 102–103° and had infrared spectrum identical with that of an authentic sample.

A blank run, in which mercury mesitoate in acetonitrile was boiled for an extended period, failed to yield detectable amounts of mesitoic anhydride.

2,4-Dinitrophenyl 1-Thio-β-D-glucopyranoside Tetraacetate (XIII).—A solution of 12 g. of potassium hydroxide in 325 ml. of 95% ethanol was mixed with 48 g. of 2,4-dinitrobenzenethiol, and the resulting, dark red suspension was treated with a solution of 81.55 g. of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in 400 ml. of chloroform. After being boiled under reflux for 2 hr., the reaction mixture was cooled, diluted with 100 ml. of chloroform, and washed with 1/3-saturated, aqueous sodium bicarbonate. A small quantity of insoluble, yellow powder was filtered from the organic layer, which was then washed four times with dilute, aqueous sodium bicarbonate and twice with water. The dark red chloroform solution was filtered through a thick layer of decolorizing carbon on Filter-Cel, and was concentrated to a small volume. From its solution in chloroform–acetone–pentane, the product was obtained as pale yellow needles which were dried at 60° for 1 hr., 67.1 g. (64% based on the bromide), m.p. 199–200°. Successive recrystallizations from acetone–ethanol and from hot 2-methoxyethanol afforded pure XIII, m.p. 199–200°, $[\alpha]^{20}D$ −98.0° (*c* 0.80, chloroform); ν_{max}^{Nujol} 1762 s and 1747 s (OAc), 1604 m (Ar), 1530 m ($ArNO_2$) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{22}N_2O_{13}S$ (530.46): C, 45.28; H, 4.18; N, 5.28; S, 6.04. Found: C, 45.08; H, 4.19; N, 5.48; S, 6.47.

Deacetylation of XIII. A. With Methanolic Ammonia.—XIII (10 g.) was suspended in 300 ml. of methanol, the suspension cooled in ice, and dry ammonia gas passed in for 2 hr. The mixture was then stirred at 0° for 1.5 hr. and at room temperature for 1.5 hr., and concentrated to a brown sirup. Most of the acetamide was removed at 100° *in vacuo*, the residue was dissolved in hot acetone, and the red solution passed through a pad of Darco X. On being cooled, the solution deposited pale yellow needles of the acetone solvate of XIV which were dried at 60°, 5.6 g. (71%, based on the solvate), m.p. 184–185° (sintering at 113°). Recrystallization from acetone–ethanol–benzene and then from acetone containing a little methanol gave pure XIV containing acetone of crystallization, m.p. 117–119° (foaming), $[\alpha]^{20}D$ −207° (*c* 0.57, methanol); ν_{max}^{Nujol} 3300 s (OH), 1680 s (acetone), 1593 s (Ar), 1530 s, shoulder ($ArNO_2$), 1516 s (Ar) cm.$^{-1}$. Drying *in vacuo* at 120° for 1 hr. gave the solvent-free compound (weight loss, 13.3%; theoretical, 13.82%).

Anal. Calcd. for $C_{12}H_{14}N_2O_9S \cdot C_3H_6O$ (420.39): C, 42.85; H, 4.79; N, 6.67; S, 7.63. Found: C, 42.55; H, 4.75; N, 6.51; S, 7.66.

Anal. Calcd. for $C_{12}H_{14}N_2O_9S$ (362.31): C, 39.78; H, 3.89. Found: C, 39.86; H, 4.07.

Crystallization of XIV from hot water or from water containing a little ethanol yielded pale yellow tufts of needles which were dried overnight at 60°, m.p. 184–186° dec. (sintering from 108°), $[\alpha]^{20}D$ −249° (*c* 0.74, methanol); ν_{max}^{Nujol} 3550 s, 3400 s, and 3300 s (OH), 1650 w (H_2O), 1600 s (Ar), 1526 s ($ArNO_2$) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}N_2O_9S \cdot 0.5H_2O$ (371.32): C, 38.81; H, 4.07; N, 7.55; S, 8.63. Found: C, 38.91; H, 4.19; N, 7.52; S, 8.57.

B. With Barium Methoxide.—Deacetylation of XIII (9.18 g.) in a mixture of 200 ml. of methanol and 200 ml. of dichloromethane, using 10 ml. of 1.5 *N* barium methoxide, was allowed to proceed for 22 hr. at room temperature. The pale orange suspension was diluted with methanol (1 l.) and the solution was deionized by passage through Amberlite IR-120 (H^+), 5 × 12 cm. and Amberlite IR-45(OH^-), 5 × 15 cm. Concentration of the solution gave a bright yellow residue which crystallized from aqueous ethanol as pale yellow needles, 0.77 g. (22%), m.p. 85–87°. Recrystallization from ethanol–isopropyl ether gave nearly colorless needles of 2,4-dinitroanisole, m.p. 88–89°, $[\alpha]^{20}D$ 0° (*c* 1.05, chloroform). The infrared spectrum of the material (potassium bromide disk) was identical with that of an authentic specimen; a mixture melting point was undepressed.

The material remaining in the mother liquor was crystallized from acetone containing a little ethanol, to give the acetone solvate of XIV, 2.45 g. (34%).

Examination of the mother liquor by paper chromatography, using ethyl acetate–acetic acid–water (9:2:2, v./v.) and a periodate–silver nitrate spray, revealed that, in addition to XIV ($R_{glucose}$ 3.33), a second compound ($R_{glucose}$ 0.73) was present. The latter substance cochromatographed with di(β-D-glucopyranosyl) disulfide, prepared by catalytic deacetylation of its octaacetate.[15]

The Reaction of XIV with Mercuric Benzoate.—A mixture of 0.61 g. of the acetone solvent of XIV, 0.71 g. (1.1 molar equiv.) of dried mercuric benzoate, and 100 ml. of dry acetonitrile was stirred at room temperature for 21 hr. The pale yellow opalescent solution was evaporated to dryness, and the residue was treated with 20 ml. of methanol. A pale yellow solid was filtered off, washed thoroughly with methanol, and dried at 60°, 0.232 g. (53%), m.p. 256.5–257° dec. Recrystallized from boiling acetonitrile, this product was obtained as pale yellow needles, m.p. 258.5°; mixed with an authentic sample of bis(2,4-dinitrophenylthio)mercury (prepared as described later), the material melted at 257° dec.

Anal. Calcd. for $C_{12}H_6HgN_4O_8S_2$ (598.93): C, 24.06; H, 1.01; Hg, 33.49; N, 9.35; S, 10.71. Found: C, 24.35; H, 1.29; Hg, 32.8; N, 9.99; S, 10.88.

The pale yellow mother liquor was saturated with hydrogen sulfide and was evaporated to dryness to coagulate the precipitated mercuric sulfide. Methanol (15 ml.) and dichloromethane (15 ml.) were added, and the suspension was centrifuged; the decantate was concentrated to a yellow sirup which crystallized from water, yielding 40 mg. of impure XIV. The mother liquor was extracted twice with ether to remove benzoic acid, concentrated to dryness, the acetylated (acetic anhydride–pyridine). Crystallization of the resulting sirup from ethanol afforded 120 mg. of pale yellow needles, m.p. 193–198°, undepressed on admixture with XIII, $[\alpha]^{20}D$ −93° (*c* 1.37, chloroform). On standing, the aqueous ethanolic mother liquor afforded clusters of colorless needles, 0.063 g. (10%), m.p. 139–141°. Recrystallization from aqueous ethanol gave XVI, $[\alpha]^{20}D$ −31.4° (*c* 0.74, chloroform), m.p. 142–145°, m.m.p. 142–146° with authentic material.

Bis(2,4-dinitrophenylthio)mercury (XVII).—2,4-Dinitrobenzenethiol (0.17 g.) was shaken with 10 ml. of dry acetonitrile, contaminating disulfide was removed by centrifugation, the residue being washed with 10 ml. of acetonitrile. The combined solution and washing was treated with a solution of 0.348 g. of mercuric benzoate in 30 ml. of acetonitrile, and the pale yellow mixture was kept at room temperature for 20 hr. Concentration gave a dark yellow solid which was triturated with methanol; the yellow crystals were removed by filtration, 0.145 g., m.p. 255–256° dec. Recrystallization from hot acetonitrile gave pale yellow needles, 0.083 g., m.p. 257.5° dec.

Anal. Calcd. for $C_{12}H_6HgN_4O_8S_2$ (598.93): C, 24.06; H, 1.01; Hg, 33.49; N, 9.35; S, 10.71. Found: C, 24.42; H, 1.26; Hg, 32.6; N, 9.78; S, 10.51.

The Reaction of XIV with Mercuric Mesitoate.—A mixture of 525 mg. of the monoacetone solvate of XIV, 1.314 g. of mercuric mesitoate (2 molar equiv.), and 40 ml. of dry acetonitrile was stirred at room temperature for 24 hr. during which time the suspended solid dissolved, yielding a pale yellow, opalescent solution. Concentration of the solution to dryness gave a bright yellow sirup to which 20 ml. of methanol was added. After *ca.* 1 min., yellow crystals started separating from the mixture, which was kept at 0° for 1 hr.; washed with methanol and dried, XVII (165 mg., 44%) had m.p. 257.5–258.5° dec.

The combined filtrate and washings were diluted with 60 ml. of dichloromethane, saturated with hydrogen sulfide, and evaporated to dryness to coagulate the mercuric sulfide. The black residue was extracted with 100 ml. of 1:1 (v./v.) methanol–dichloromethane, and the extracts were filtered through a layer of charcoal on Filter-Cel. Concentration of the filtrate gave an orange mass which was treated with 50 ml. of water and then was extracted with two 30-ml. portions of dichloromethane to remove mesitoic acid. Evaporation of the aqueous layer afforded a sirup which, on trituration with ether–ethanol, deposited some yellow amorphous powder. After filtration, removal of the solvent gave a pale yellow sirup which was acetylated (acetic anhydride–pyridine). Crystallization from ethanol–pentane yielded 40 mg. (6%) of square prisms of 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucopyranose, m.p. 137–138°. Recrystallization from ben-

(14) R. C. Fuson, J. Corse, and N. Rabjohn, *J. Am. Chem. Soc.*, **63**, 2852 (1941).

(15) N. K. Richtmyer and C. S. Hudson, *ibid.*, **65**, 1477 (1943).

zene–hexane gave material with m.p. 139–140°, undepressed on admixture with an authentic specimen.[5] Dissolution of the material remaining in the original mother liquor led to the isolation of 30 mg. of crystalline material, m.p. 110–140°; this was not further investigated.

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Greenheart Alkaloids. II. Isolation and Characterization of Seven Alkaloids[1,2]

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Seven alkaloid hydrochlorides were isolated from the ether-soluble alkaloids of the bark of greenheart (*Ocotea rodiaei*). These alkaloids fall into two groups with properties pointing to bisbenzylisoquinoline structures with one diphenyl ether linkage and two diphenyl ether linkages, respectively. The first group includes rodiasine, which previously had been isolated as the methiodide, and also norrodiasine and dirosine. The second group includes ocoteamine, otocamine, demerarine, and ocodemerine. None of these alkaloids has the properties of chondrodendrine, commonly called "bebeerine," which has been believed to be the predominant alkaloid in greenheart bark.

The ether-soluble alkaloids from greenheart bark (*Ocotea rodiaei*) generally have been believed to consist predominantly of the well characterized alkaloid chondrodendrine, commonly called "bebeerine."[3] However, this belief was based on an old comparison of the amorphous alkaloids from greenheart with alkaloids from other sources, and it was not found possible to isolate chondrodendrine from greenheart by previously reported methods.[1] Rodiasine dimethiodide, which was obtained by the treatment of the ether-soluble alkaloids with methyl iodide, appears to be the first pure alkaloid isolated from greenheart. This compound had the characteristics of a bisbenzylisoquinoline alkaloid (or biscoclaurine alkaloid) with one diphenyl ether linkage.[1]

Preliminary investigations showed that the ether-soluble alkaloids consisted of many components rather than of one predominant alkaloid. Attempted fractional crystallization from organic solvents gave only amorphous products and showed evidence of some decomposition of the alkaloids in organic solvents. Crystalline alkaloid hydrochlorides were obtained from dilute hydrochloric acid solutions of the ether-soluble alkaloid mixtures, but such crystallizations were very slow. Additional crystalline hydrochlorides were obtained by countercurrent distribution of the alkaloids with acetate buffer and chloroform; further additional alkaloid hydrochlorides were obtained by conventional chromatography on alumina, employing the stepwise addition of more polar solvents. However, better separation was obtained by gradient elution chromatography.

Chromatography of the ether-soluble alkaloids on neutral alumina with a gradient eluent consisting of methylene chloride and methanol gave the curve shown in Fig. 1. The composition of the eluent was changed in an exponential manner, as shown in Fig. 1, by adding to a constant volume mixer[4] methylene chloride containing geometrically increasing proportions of methanol. To minimize decomposition, the chromatograms were run as rapidly and with as little solvent as appeared practical.

From the majority of the chromatography fractions, crystalline alkaloid hydrochlorides were obtained. Fractional crystallization gave eight alkaloid hydrochlorides which were purified to constant specific rotation.[2a] Distribution coefficients were determined for the various batches of hydrochlorides obtained in the crystallization scheme, because in some cases the specific rotations were quite similar and the decomposition points were not only similar but also depended on the rate of heating and were not depressed in mixtures.

The eight products obtained were tentatively designated alkaloids C, D, E, F, G, H, I, and J hydrochlorides. The specific rotations and distribution coefficients of these hydrochlorides are listed in Table I.

TABLE I

ALKALOIDS FROM GREENHEART

Name of alkaloid	Original designation	$[\alpha]_D$,[a] deg.	K[b]	R_f[c,d]	Phenolic peak,[d] cm.$^{-1}$	Functional groups[d,e] OH	NH
			Group A				
Rodiasine	D	+74	0.7	0.46	3385	1	0
Norrodiasine	C	+74	2.3	0.42	3365	1	1
Dirosine	E	+97	2.8	0.40	3360	1	1
			Group B				
Ocoteamine	G	+250	10.5	0.33	3555	1	1
Otocamine	H	+268	0.4	0.34	None	(0)	(1)
Demerarine	F	−181	11.5	0.33	3545	1	1
Ocodemerine	J[f]	−170	0.5	(0.33)	(None)	(0)	(1)
			Mixtures				
	I	+148	0.5	0.35 0.48	3380	1/2	1/2
	J	−38	1.4	0.33 0.43	3350		

[a] Specific rotation of the hydrochloride (c 1.0, water). [b] Distribution coefficient of the hydrochloride in 0.5 *M* acetate buffer, pH 4.17, chloroform. [c] For amyl alcohol, pyridine, water (110:110:90) on buffered paper. [d] Values in parentheses were not obtained directly but are indicated by various considerations, as indicated in the text. [e] As deduced from the absorption peaks of the acetylated alkaloids, 0 = none. [f] Originally a component of this mixture of hydrochlorides.

(1) A previous paper was H. McKennis, Jr., P. J. Hearst, R. W. Drisko, T. Roe, Jr., and R. L. Alumbaugh, *J. Am. Chem. Soc.*, **78**, 245 (1956).

(2) Presented in part by P. J. Hearst and H. Hochman, before the Organic Chemistry Division of the American Chemical Society (a) at Dallas, Tex., April, 1956, and (b) at Miami, Fla., April, 1957.

(3) T. A. Henry, "The Plant Alkaloids," 4th Ed., The Blakiston Co., Inc., New York, N. Y., 1949, p. 363; M. Kulka, "The Alkaloids," Vol. IV, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, Inc., New York, N. Y., 1954, p. 227 (also Vol. VII, 1960, p. 439).

(4) R. M. Bock and N. S. Ling, *Anal. Chem.*, **26**, 1451 (1954).

In view of the previous work with rodiasine dimethiodide,[1] it appeared likely that the alkaloids might be biscoclaurine alkaloids with one diphenyl ether linkage. Equivalent weight determinations for most of these alkaloids gave values close to the calculated values of 298, 305, 312, and 319 of a homologous series of such alkaloids; and, on the basis of the experimental equivalent weights of 306 and 320, respectively, for alkaloid E and for its O-methylated derivative, this type of structure with two free phenolic groups and two N-methyl groups was tentatively proposed for alkaloid E.[2b] However, the results of microanalyses subsequently showed that the equivalent weights were somewhat in error because of the hydration of the hydrochlorides. Furthermore, the experimental equivalent weights of most of the alkaloids, except for that of O-methylated alkaloid E, were also close to the calculated values of 297, 304, and 311 for a homologous series of biscoclaurine alkaloids with two diphenyl ether linkages.

The purified alkaloids were divided into two groups by paper chromatography. The system employed was amyl alcohol, pyridine, and water on paper impregnated with potassium dihydrogen phosphate.[5] One group of alkaloids, group A, had R_f values of 0.40 to 0.46. Another group, group B, had R_f values of 0.31 to 0.35. Two of the hydrochlorides, which had been recrystallized to constant specific rotation, each gave two distinct spots and were thus shown to be mixtures. These groupings are indicated in Table I.

Individual alkaloids within each group could not be differentiated by paper partition chromatography. Neither could this differentiation be made with multibuffer paper chromatography,[6] which had previously been employed to separate the two diasterioisomeric biscoclaurine alkaloids, oxyacanthine and repandine.[7] The pH of the zone of farthest advance was found to be less reproducible than the R_f values.

Infrared spectra of the alkaloid hydrochlorides in potassium bromide disks again showed similarities in the alkaloids of group A and similarities in the alkaloids of group B. Neither the small differences between the spectra of individual alkaloids within each group, nor the differences between the groups appeared to be of immediate significance.

Characteristic differences between the alkaloids of groups A and B were found in the infrared absorption peaks attributable to the phenolic groups of the alkaloids. These peaks, in the region near 3 μ, could not be studied in potassium bromide pellets because of strong interference by a peak at about 2.9 μ. This interference peak was somewhat dependent on the preparation of the pellet but could not be eliminated. A similar peak has been observed by others.[8,9] The spectrum in this region was, therefore, studied with chloroform solutions of the free alkaloids. The alkaloids in group A had phenolic peaks at approximately 3375 cm.$^{-1}$, whereas those of group B had phenolic peaks at approximately 3550 cm.$^{-1}$, as indicated in Table I. The position of phenolic peaks of mixtures I and J indicated

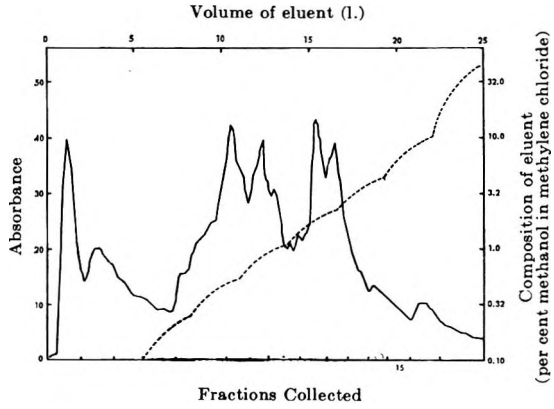
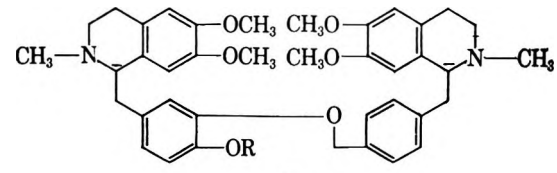


Fig. 1.—Chromatography of greenheart alkaloids: ———, absorbance of eluate; ———, composition of eluent.

that in each mixture, the component from group A was phenolic and the component from group B was nonphenolic.

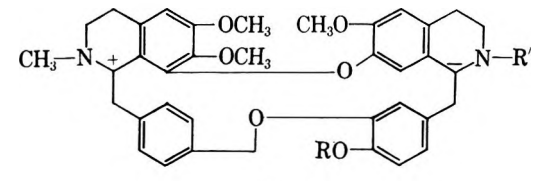
The sharp phenolic peaks at 3550 cm.$^{-1}$, given by group B alkaloids, appear to be characteristic of phenols substituted by ether groups in the *ortho* position. The broader lower peaks near 3375 cm.$^{-1}$, given by the group A alkaloids, appear to be characteristic of phenolic groups with strong internal hydrogen bonding. Flett,[10] who assigned these positions, studied hydroxy compounds in carbon tetrachloride solution. However, the relative positions of the peaks obtained with chloroform solutions and with carbon tetrachloride solutions of the alkaloids were similar, although the actual positions were shifted to somewhat lower wave numbers when chloroform was employed. The effect of the solvent appears to be greater for phenols with strong internal bonding (3360 *vs.* 3451 cm.$^{-1}$ for alkaloid E) than for phenols which do not have strong internal hydrogen bonding (3555 *vs.* 3560 cm.$^{-1}$ for alkaloid G).

The above results pointing to phenols with strong internal hydrogen bonding for the alkaloids in group A might be expected for biscoclaurine alkaloids with one diphenyl ether linkage. Such a molecule, as exemplified by daurricine (I, R = H) would be quite flexible and the hydrogen atom of the phenolic group could easily approach some of the other oxygen atoms of the molecule.



I

On the other hand, biscoclaurine alkaloids with two diphenyl ether linkages, as exemplified by oxyacanthine (II, R = H, R′ = CH_3), would not be sufficiently flexible to give strong internal hydrogen bonding.



II

(5) D. A. A. Kidd and J. Walker, *J. Chem. Soc.*, 669 (1954).
(6) M. Schmall, E. G. Wollish, and E. G. E. Shafer, *Anal. Chem.*, **28**, 1373 (1956).
(7) Y. Watanabe and M. Uchiyama, *Yakugaku Zasshi*, **78**, 96 (1958).
(8) G. Roberts, *Anal. Chem.*, **29**, 911 (1957).
(9) A. Baker, *J. Phys. Chem.*, **61**, 450 (1957).
(10) M. St. C. Flett, *Spectrochim. Acta*, **10**, 21 (1957).

Phenolic biscoclaurine alkaloids with two diphenyl ether linkages might, therefore, be expected to give the peak characteristic of phenols substituted by ether groups in the *ortho* position, such as those observed for the phenolic alkaloids in Group B.

The comparative flexibility of the alkaloids in group A and the comparative rigidity of the alkaloids in group B may also be responsible for the low specific rotations of the former alkaloids as compared with those of the latter alkaloids. Known biscoclaurine alkaloids with one diphenyl ether linkage commonly have specific rotations below 140°, whereas the corresponding alkaloids with two diphenyl ether linkages may have specific rotations of twice this value.[11]

Alkaloid H had no peak attributable to a phenolic group but did have a weak peak at 3300 cm.$^{-1}$ which could be attributed to the presence of a secondary amino group. Alkaloid G gave the same peak but in the spectrum of alkaloid E this peak was lacking or was masked by the broad phenolic peak. In hexachlorobutadiene mulls, both alkaloids E and G gave weak peaks at 3285 and 3319 cm.$^{-1}$, respectively. Very weak peaks of secondary amino groups have been observed for other alkaloids.[12]

The presence and number of phenolic and secondary amino groups could be ascertained from the infrared absorption peaks of the acetylated alkaloids. The O-acetyl peaks of the various acetylated pure alkaloids, at 1765 cm.$^{-1}$, had the same absorbance values, and similarly, the N-acetyl peaks, at 1630 cm.$^{-1}$, had the same absorbance values. It was, therefore, assumed that a maximum of one hydroxyl and one secondary amino group was present in the original alkaloids. The presence or absence of phenolic and secondary amino groups thus determined, and as listed in Table I, was consistent with the microanalytical results.

Microanalytical results were consistent with the postulated structures for the alkaloids of groups A and B, of biscoclaurine alkaloids with one diphenyl ether linkage and two diphenyl ether linkages, respectively. Alkaloid E, with four methoxyl groups, on treatment with diazomethane gave an O-methyl derivative with five methoxyl groups, as expected for a biscoclaurine alkaloid with one diphenyl ether linkage. Similarly, alkaloid G, with three methoxyl groups, gave an O-methyl derivative with four methoxyl groups, as expected for a fully methylated biscoclaurine alkaloid with two diphenyl ether linkages.

Two of the three alkaloids in group A gave rodiasine dimethiodide[1] on treatment with methyl iodide. These alkaloids could, therefore, differ only in degree of methylation of the amino groups. Alkaloid D, with one phenolic group and no secondary amino group, as noted in Table I, and with two N-methyl groups, according to microanalyses, was thus the ditertiary precursor of rodiasine dimethiodide, and it was named rodiasine. Alkaloid C, with only one N-methyl group and a secondary amino group, was named norrodiasine.

The remaining alkaloid in group A, alkaloid E, was the most abundant of the alkaloids and was obtained in an 11% yield. It apparently had the same number and types of functional groups as norrodiasine, but it did not give rodiasine dimethiodide. It was designated dirosine.

Two of the four alkaloids in group B had positive optical rotations. One of these, alkaloid G, which had one phenolic group and one secondary amino group, was named ocoteamine. The other, alkaloid H, which was nonphenolic but also had one secondary amino group, was named otocamine.

The other two alkaloids in group B, which had negative optical rotations, were alkaloid F and a component isolated from mixture J. These alkaloids apparently had the same number and types of functional groups as did ocoteamine and otocamine, respectively, and they were designated demerarine and ocodemerine.

None of these alkaloids can be chondrodendrine, or "bebeerine," because chondrodendrine has two phenolic groups and no secondary amino groups.

In two recent publications, Grundon and McGarvey[13] described the isolation of three alkaloids from greenheart, which they designated sepeerine, ocotine, and rodiasine. The first of these was assigned the structure II (R = R′ = H). There were some differences in the reported physical properties of sepeerine and those observed for ocoteamine. However, a sample of Dr. Grundon's sepeerine had an infrared spectrum indistinguishable from that of ocoteamine, and structure II (R = R′ = H) was shown also to be that of ocoteamine.[14,15] For rodiasine no direct comparisons could be made; the reported physical properties were similar but not identical. Ocotine which was obtained in only one of Dr. Grundon's two reported extractions apparently was not obtained in the present study.

Experimental

Ether-Soluble Greenheart Bark Alkaloids.—The preparation was a modification of a previously reported procedure.[1] Fifty kilograms of ground bark was extracted with six 80-l. portions of 0.1 *N* sulfuric acid. The extracts were made alkaline to pH 9 and the precipitate was collected and dried to give a 2.0% yield of crude bases. The latter were extracted with ether for 3 days to give the "ether-soluble" alkaloids in an over-all yield of approximately 0.6%.

Gradient Elution Chromatography.—Thirty grams of ether-soluble alkaloids was chromatographed on a 7.5 × 18 cm. column of approximately 750 g. of neutral alumina of activity III.[16] (The alumina had been prepared by treating with sulfuric acid at pH 3 for 1 hr., washing with water, treating with ammonia at pH 9 for 0.5 hr., washing with water and alcohol, drying at 210° for 2 hr., and re-exposing to the atmosphere to obtain the desired activity.) The eluent employed consisted of 2.75 l. of methylene chloride, followed by 22 l. of gradient eluent having the composition shown in Fig. 1.

The gradient eluent was produced in a constant volume mixer made with a 5-l. three-necked flask. At the bottom of this mixer, which initially contained 5.5 l. of well-stirred methylene chloride, were added successive 2.75-l. portions of 0.25, 0.5, 1, 2, 4, 8, and 20% methanol in methylene chloride and then 100% methanol. The composition of the overflow from an efficiently stirred mixer was calculated from the equation $y = 1 - e^{-x}$, where x is the volume of new solvent added, expressed as a portion of the mixer capacity, and y is the partial volume of new solvent present in

(11) Based on specific rotations reported in ref. 2 and in other literature.

(12) L. H. Briggs, L. D. Colebrook H. K. Miller, and Y. Sato, *J. Chem. Soc.*, 3417 (1960).

(13) M. F. Grundon and J. E. B. McGarvey, *J. Chem. Soc.*, 2739 (1960); *ibid.*, 2077 (1962); and a preliminary report, M. F. Grundon, *Chem. Ind.* (London), 1772 (1955).

(14) P. J. Hearst, in press.

(15) Because the physical properties of the alkaloids and their derivatives indicated a higher degree of purity for ocoteamine, and because the name "sipeerine" had been used previously for the ether-insoluble alkaloids of greenheart bark, the name ocoteamine appears more desirable for this ether-soluble alkaloid.

(16) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

the reservoir, and, therefore, the portion of new solvent present in the overflow.

The chromatography was completed in about 8 hr. At 250-ml. intervals, eluent samples were taken and diluted 1:100, and the absorbances of these solutions were determined at 283 mμ. For a typical run, the observed absorbances multiplied by 100 are plotted in Fig. 1.

Three runs carried out under similar conditions gave curves which were quite similar. The fractions from these runs were cut in like manner, employing as guides the shapes of the curves, as well as the cumulative absorbances and the cumulative volumes of the eluates. The fractions were evaporated to small volumes, water and a slight excess of hydrochloric acid were added; the remaining methylene chloride was removed by flushing the warmed solution with a stream of nitrogen, and the solutions were freeze-dried. The seventeen corresponding fractions from each of the three runs were combined. Since the equivalent weight of the 90 g. of starting material was about 315, the theoretical yield of hydrochlorides was 100 g., and the over-all yield of 91 g. was a 91% recovery. The properties of the fractions are listed in Table II.

TABLE II

CHROMATOGRAPHY OF GREENHEART ALKALOIDS

Fraction	Yield, %	$[\alpha]_D$, deg.	K^a	Cryst. hydrochlorides isolated
1	6.4	+176	0.12	
2	6.1	+210	0.13	
3	3.1	+228	0.17	
4	2.9	+232	0.19	D
5	4.9	+202	0.32	D
6	5.4	+127	0.62	D, I, E
7	11.3	+69	1.1	E, H, J
8	9.5	+41	1.6	E, J, H
9	6.7	+62	1.3	E, C
10	4.3	+47	1.2	C
11	8.3	+68	2.4	G, F
12	7.9	+17	3.3	G, F
13	5.1	+20	2.5	G, F
14	3.0	+47	2.6	F
15	2.3	+47	2.7	
16	2.4	+51	2.8	
17	2.1	+53	2.3	

[a] Distribution coefficient in 0.5 *M* acetate buffer, pH 4.17, chloroform.

In a subsequent set of chromatographic separations, 200 g. of ether-soluble alkaloids were chromatographed in four 50-g. portions. Woehlm alumina, nonalkaline, was employed in 1800-g. portions, deactivated with 40.5 ml. of water to give an activity somewhat greater than II. The columns were approximately 9.4 × 28.5 cm. The 40 l. of gradient eluent employed in each chromatography was prepared with 2-l. solvent portions whose initial 0.25% methanol content was successively multiplied by a factor of the fifth root of four. The eluate from the column was run through a flow cell of 0.15-mm. path length, in a recording spectrophotometer. The fractions yielded a total of 191 g. (86%) of alkaloid hydrochlorides.

Crystalline hydrochlorides were obtained from eleven of the seventeen chromatography fractions described before, as listed in Table II. The crystalline products were obtained by dissolving the crude fractions in water, adding various amounts of hydrochloric acid, and letting the solutions cool. In the initial isolation of alkaloid F hydrochloride, crystallization was induced by the addition of a few drops of chloroform to the aqueous solution from which alkaloid G hydrochloride previously had been allowed to crystallize. The total yields of the reasonably pure hydrochlorides are listed in Table III.

The alkaloid hydrochlorides were purified to constant rotation by fractional crystallization from aqueous solutions containing 0.25% to 2.5% hydrochloric acid. The various mother liquors were worked into the crystallization scheme and the compositions of the various fractions were followed by measurements of the specific rotations and the distribution coefficients.

From the second set of large-scale chromatographic runs, the hydrochlorides of alkaloids C, D, E, F, and G were obtained in somewhat lower yields than before. The hydrochlorides of alkaloids H, I, and J were not obtained from these chromatographic runs.

TABLE III

ADDITIONAL PROPERTIES OF THE ALKALOIDS

Alkaloid	Yield, %	M.p. of the hydrochloride, °C.	Equiv. wt.[a]	M.b.p.c.[b]	Absorbance[c] at— 1765 cm.$^{-1}$	1630 cm.$^{-1}$
C	0.9	282		5.4	0.39	0.62
D	1.8	292	324	5.0	0.40	None
E	10.7	303	307	5.2	0.40	0.63
F	6.5	278	297	5.8	0.41	0.60
G	2.7	290	298	5.6	0.43	0.65
H	1.0	281	313	5.2		
I	0.8	286	313	5.6, 5.2	0.25	0.40
J	4.2	275	307	5.6, 5.2		

[a] Equivalent weight derived from that of the hydrochloride. [b] Multibuffer paper chromatography, pH of farthest advance. [c] For the acetylated derivative, as described in the text.

Alkaloid J hydrochloride, which was later shown to be a mixture, was crystallized from ethanol to give alkaloid E hydrochloride and the residue, crystallized from aqueous hydrochloric acid at 50°, gave a new alkaloid hydrochloride, designated ocodemerine hydrochloride.

Properties of the Alkaloid Hydrochlorides.—Melting points of the hydrochlorides, which occurred with decomposition, were determined in evacuated capillaries at rates of heating of 5° per min. The values, which are listed in Table III, were not depressed by mixing but were affected by the rate of heating. The specific rotations of aqueous solutions are given in Table I.

Distribution coefficients were determined as follows. A solution of a 1-mg. sample of the alkaloid hydrochloride in 20 ml. of 0.5 *M* acetate buffer at pH 4.17 was diluted with buffer to give an absorbance reading, A_0, of about 0.4 in. a 1-cm. cell at 283 mμ when compared with the buffer solvent. To a 10-ml. aliquot was added 10 ml. of chloroform (containing 1.0% alcohol). The resultant mixture was maintained at 25°, thoroughly shaken, and allowed to separate into two layers. The absorbance of the equilibrated buffer solution, A_f, was determined by comparison with similarly treated buffer solvent. The distribution coefficient was calculated according to the equation, $K = A_f/(A_0 - A_f)$.

The distribution coefficients varied strongly with pH ($\Delta \log K/\Delta pH$ = approx. 0.6), and critical comparisons were always made with the same buffer solutions and in the same set of three determinations. Values obtained are listed in Table I.

For equivalent weight determinations, 125-mg. quantities of alkaloid hydrochloride were titrated with 0.1 *N* sodium hydroxide. The alkaloids began to precipitate at pH 7. The inflection of the titration curve and the maximum rate of pH change were at pH 9.3, and duplicate determinations agreed within 0.5%. From the values obtained, 36.5 was subtracted to give the equivalent weights of the free alkaloids, as listed in Table III.

Microanalyses were performed by Dr. W. Zimmermann, University of Melbourne, Australia. The results are given in Table IV.

Paper Chromatography.—Small quantities of the hydrochlorides in water were treated with ammonia and the resultant precipitates were collected by centrifuging, washed with water, and dried under vacuum. The alkaloids were chromatographed with amyl alcohol, pyridine, water (110:110:90) on paper impregnated with potassium dihydrogen phosphate.[5] The chromatograms were developed by exposure to iodine vapors. Iodoplatinate reagent[17] was equally effective when the excess reagent was washed out to reduce the background color, but Draggendorff reagent[17] gave very weak spots. The R_f values obtained are listed in Table I.

Multibuffer paper chromatographies were run essentially as described before,[7] but with 1.5-cm. spaces between the 2-cm. buffer zones of pH 6.4, 6.2, ..., 4.2. (A zone of pH 7.6 was applied to the origin of some papers so that the hydrochlorides could be employed directly.) The eluent employed was chloro-

(17) R. Meunier and M. Macheboeuf, *Bull. soc. chim. biol.*, **31**, 1141 (1949).

TABLE IV

MICROANALYTICAL RESULTS FOR ALKALOIDS FROM GREENHEART

Alkaloid hydrochloride	Empirical formula	Values	Composition, % C	H	O	Cl	CH_3O	N-CH_3
		Group A						
Rodiasine	$C_{38}H_{41}O_6N_2 \cdot 2HCl \cdot 2^1/_2H_2O$	Calcd.	61.6	6.93	18.3	9.55	(4) 16.75	(2) 4.05
		Found	61.2	6.82	17.8	10.0	16.44	3.8
Norrodiasine	$C_{37}H_{42}O_6N_2 \cdot 2HCl \cdot 2H_2O$	Calcd.	61.8	6.73	17.8	9.86	(4) 17.28	(1) 2.1
		Found	61.4	6.51	18.1	10.6	16.95	1.8
Dirosine	$C_{37}H_{42}O_6N_2 \cdot 2HCl \cdot 1^1/_2H_2O$	Calcd.	62.4	6.66	16.9		(4) 17.50	(1) 2.11
		Found	62.0	6.50	16.3		17.30	2.0
		Group B						
Ocoteamine	$C_{36}H_{38}O_6N_2 \cdot 2HCl \cdot H_2O$	Calcd.	63.1	6.17	16.3		(3) 13.59	(1) 2.19
		Found	63.2	6.29	15.6		13.47	2.2
Otocamine	$C_{37}H_{40}O_6N_2 \cdot 2HCl \cdot H_2O$	Calcd.	63.5	6.34	16.0	10.14	(4) 17.78	(1) 2.14
		Found	63.9	6.39	16.8	10.5	17.27	1.9
Demerarine	$C_{36}H_{38}O_6N_2 \cdot 2HCl \cdot H_2O$	Calcd.	63.1	6.17	16.3	10.4	(3) 13.59	(1) 2.19
		Found	63.2	6.19	16.8	10.4	13.57	1.9
Ocodemerine	$C_{37}H_{40}O_6N_2 \cdot 2HCl \cdot 1^1/_2H_2O$	Calcd.	62.7	6.40	16.9		(4) 17.54	(1) 2.12
		Found	62.8	6.64	16.1		17.60	2.1
		O-Methyl derivatives						
O-Methyldirosine	$C_{38}H_{44}O_6H_2 \cdot 2HCl \cdot 1^1/_2H_2O$	Calcd.	63.0	6.82	16.6		(5) 21.4	
		Found	62.8	6.66	16.5		21.24	
O-Methylocoteamine	$C_{37}H_{40}O_6N_2 \cdot 2HCl \cdot H_2O$	Calcd.	63.5	6.34	16.0		(4) 17.8	
		Found	63.4	6.34	16.4		17.58	

form. The dried paper strips were developed with iodoplatinate reagent, washed with water, and dried; they were then exposed to iodine fumes to further bring out the spots. Direct treatment of the dried but unwashed buffered strips with iodine fumes was not effective. The zones of farthest advance of the V-shaped spots are listed in Table III.

Infrared Spectra.—Spectra of 2-mg. portions of the hydrochlorides in 0.75-in. pellets of 1.5 g. of potassium bromide were determined with a Beckman IR-7 spectrophotometer. Absorptions of approximately 35% were obtained in the 3400-cm.$^{-1}$ (2.9-μ) region.

Solution spectra of 2-mg. portions of the free alkaloids, prepared as described earlier, in 3 ml. of Spectro Grade chloroform were determined with a Beckman DK-2 spectrophotometer. The positions of the peaks obtained were converted to wave numbers and are listed in Table I. Additional slight peaks at 3300 cm.$^{-1}$ were obtained for alkaloids G and H. The broad peaks of the group A alkaloids and of the mixtures I and J had half-band widths of approximately 125 cm.$^{-1}$, and absorbances of about 0.08, the sharper peaks of alkaloids F and G had half-band widths of approximately 45 cm.$^{-1}$, and absorbances of about 0.16. In spectrograde carbon tetrachloride, the peaks of alkaloids E and G were at 3450 and 3560 cm.$^{-1}$, respectively.

Spectra of hexachlorobutadiene mulls of alkaloids E and G were obtained with the IR-7 using the expanded 90–100% T scale. Weak bands at 3285 and 3319 cm.$^{-1}$, respectively, were obtained.

Acetylated Alkaloids.—A 15-mg. portion of the alkaloid or its hydrochloride was dissolved in 0.4 ml. of pyridine and 0.3 ml. of acetic anhydride and the mixture was held at 60° for 1 hr. The cooled reaction mixture was treated with 4 ml. of water and, after further cooling, was treated with ammonia to precipitate the product. The latter was collected by centrifuging, washed twice with water, and dried at reduced pressure.

The infrared spectra of solutions of 7.5 mg. of the acetylated alkaloids in 0.25 ml. of chloroform were determined with the IR-7 spectrophotometer. The O-acetyl peaks appeared at 1765 and the N-acetyl peaks at 1630 cm.$^{-1}$. The original alkaloids had much weaker bands at 1610 and no bands near 1765 cm.$^{-1}$. The absorbances obtained with 0.2-mm. cells are listed in Table III.

Quaternary Derivatives.—Small samples of the hydrochlorides of alkaloids C, D, and E were converted to the free bases. The latter were dissolved in methanol and were treated with methyl iodide. Alkaloids C and D each gave the methanol-insoluble, crystalline rodiasine dimethiodide, m.p. 320° dec. Alkaloid E did not give a methanol-insoluble methiodide.

O-Methyl Derivatives.—Amorphous alkaloid E was crystallized from methanol and a methanol solution was treated with excess diazomethane for 1 day. The product was extracted with hydrochloric acid and was recrystallized as the hydrochloride. The product was converted to the amorphous alkaloid and the diazomethane methylation was repeated. The final product, recrystallized to constant specific rotation, gave O-methyldirosine hydrochloride, $[\alpha]_D$ +107° (*c* 1.03, water). Microanalyses are listed in Table IV.

Alkaloid G was similarly O-methylated, except that one 2-day reaction was employed. Recrystallization from dilute hydrochloric acid solution gave O-methylocoteamine hydrochloride, $[\alpha]_D$ +254° (*c* 1.00, water). Microanalyses are listed in Table IV.

Acknowledgment.—The author wishes to express his appreciation to Dr. H. Hochman, for many stimulating discussions; to Mr. Thorndyke Roe, Jr., for the isolation of the crude alkaloids; to Mr. Frank Curry and Miss Mary Jane Noonan, for assistance in the purification of the alkaloids; and to the Greenhart and Wallaba Timber Company, now Greenhart (Demerara), Inc., and the Willems Timber and Trading Company, for generous supplies of greenhart bark.

Alkaloids of *Cassia* Species. I. Cassine[1]

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A crystalline alkaloid, $C_{19}H_{37}NO_2$, has been isolated from *Cassia excelsa* Shrad. and named cassine. The functional groups are identified as a hydroxyl group, a secondary amine, and a methyl ketone. Dehydrogenation of cassine produces a 2,6-dialkyl-3-hydroxypyridine, and cleavage of ketone VI by a second-order Beckmann rearrangement demonstrates the 2-alkyl group to be methyl. These observations and deductions from the n.m.r. spectrum show III to be the structure of cassine.

The presence of alkaloids in the American tropical legume *Cassia excelsa* Shrad. has been noted by investigators of the U. S. Department of Agriculture,[2] and an alkaloid characterized by crystalline salts has been isolated by Brazilian workers.[3]

Extracting the leaves and twigs of *C. excelsa*[4] by conventional procedures yields a mixture of basic materials amounting to 2.9% of the dry weight. A fraction of this proved to be soluble in hot hexane; concentrating the solutions under reduced pressure left a clear oil. An ethanolic solution of this material was acidified by hydrochloric acid and crystallized to provide a mixture of hydrochlorides. Repeated chromatography of the free bases eventually produced pure samples of two alkaloids, cassine and casselsine. Selected fractions were recrystallized as the hydrochlorides and the pure bases regenerated and distilled.

Pure cassine melted at 57–58.5° and possessed a small but reproducible optical activity, $[\alpha]^{25}D$ −0.6°.[5] Analysis showed the empirical formula of $C_{19}H_{37}NO_2$, at least two C-methyl groups, no methoxyl groups, and an N-methyl group; this last result, however, was eventually shown to be spurious (following). The infrared spectrum showed carbonyl absorption (1720 cm.$^{-1}$) appropriate to a ketone, and a peak (3530 cm.$^{-1}$) in the NH or OH region. The CH stretching region was free of any absorption not attributable to aliphatic groups, and the compound showed no intense absorption in the ultraviolet region.

Acetylation of the base provided an O,N-diacetyl derivative as a neutral oil, $C_{23}H_{41}NO_4$, with infrared absorption at 1725 and 1630 cm.$^{-1}$, and without OH or NH peaks. Sodium borohydride reduced the base to a dihydro derivative, m.p. 53–57°. These derivatives and spectra identify the functional groups of the molecule as a secondary amine, a hydroxyl, and a ketone. Attempts to demonstrate the presence of a double bond failed. The molecule failed to absorb hydrogen when stirred with palladized charcoal, and the diacetyl derivative was not affected by potassium permanganate in acetone. Evidently cassine contains a cyclic system.

The n.m.r. spectrum of cassine (see Fig. 1) shows no protons with resonance at low field, and confirms the absence of aldehydic or olefinic protons. The peak at τ 6.55 corresponds to a single carbinol proton, showing the alcohol to be secondary. The peak at τ 7.95 might originate with a methyl ketone or an N-methyl group; the observations below demonstrate that the former possibility is correct. The only other methyl group visible is represented by a doublet centered at τ 8.98; it is, therefore, coupled with a single proton, and occurs in the group $>CHCH_3$.

Treating the base with hypoiodite solution produced iodoform and demonstrated the presence of a methyl ketone or carbinol. The ketone could be condensed with piperonal in the presence of alkali to give a piperonylidine ketone, m.p. 106–107.5°, $C_{27}H_{41}NO_4$, ν_{max} 1700 cm.$^{-1}$. Since a Kuhn–Roth determination on this product showed reduced C-methyl content, it seemed likely that cassine contained a methyl ketone, rather than a methyl carbinol. The peak at τ 7.95 in the n.m.r. spectrum and that at 1360 cm.$^{-1}$ in the infrared spectrum are consistent with this conclusion. In an attempt to condense the ketone with 2 moles of an aldehyde, cassine was heated in hydrochloric acid with benzaldehyde at 120° to produce a compound whose ultraviolet spectrum corresponds to the monobenzylidine derivative; no absorption at longer wave lengths characteristic of the bisbenzylidine derivative could be detected. This result implies branching at the α-carbon of the methyl ketone, which was substantiated by deuteration experiments. When cassine was equilibrated with deuteriomethanol in the presence of sodium methoxide, removed from the base, and re-equilibrated with water, the product contained 3.7 atoms of deuterium, consistent with the existence of a group, $-CHCOCH_3$.

When cassine was heated at 220° under nitrogen with palladized charcoal, it was converted to the optically inactive dehydro derivative, $C_{19}H_{31}NO_2$, m.p. 104–105°. This compound shows the characteristic ultraviolet spectra of a 3-hydroxypyridine[6] in neutral, acidic, and basic solutions, and retains the carbonyl absorption of the methyl ketone. The n.m.r. spectrum confirms the retention of the methyl ketone, and shows

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) M. E. Wall, C. R. Eddy, J. J. Wallaman, D. S. Correll, B. G. Schubert, and H. S. Gentry, "Steroidal Sapogenins. XXVI," ARS-73-4, U. S. Department of Agriculture, Philadelphia, Pa., 1954.

(3) O. Goncalves de Lima, I. L. d'Albuquerque, M. P. Machado, and G. P. Pinto, *Rev. Inst. Antibiot. Univ. Recife*, **1**, 23 (1958); *Chem. Abstr.*, **53**, 22212 (1959). This material, named cassilisin, formed a hydrochloride of m.p. 155.8–157.5° and a hydrosulfate of m.p. 271°. It has not been encountered in this study.

(4) The author is indebted to Dr. Quentin Jones of the U. S. Department of Agriculture Plant Introduction Station, Beltsville, Md., for supplying this material from the department's garden in Miami, Fla.

(5) Because the optical activity of the parent alkaloid is very small, the possibility must be considered that the activity arises from an impurity. However, N-methylcassine has a considerably greater activity ($[\alpha]D$ 6.5°) and the methiodide yet more ($[\alpha]D$ 15.8°). It seems unlikely that an impurity could be retained in these transformations to the extent these values imply.

(6) 3-Hydroxypyridines are unusual among phenols in showing a bathochromic shift in both acid and base. In particular, this phenomenon is not exhibited by 2- and 4-hydroxypyridines; *cf.* H. S. Mosher, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 442.

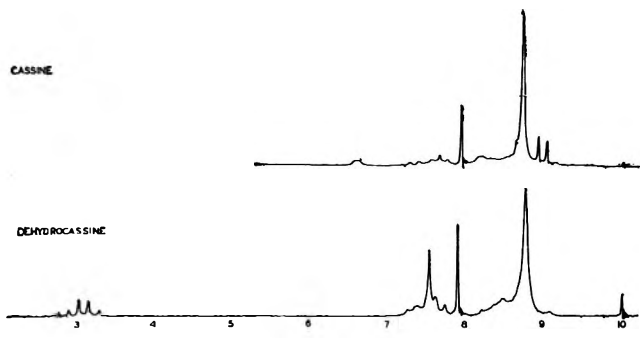
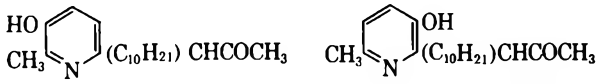


Figure 1.

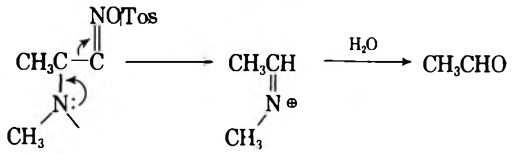
a new peak at τ 7.50 corresponding to an aromatic methyl group. As the doublet at τ 8.98 is absent, it is clear that dehydrogenation has converted a methylpiperidine into the corresponding methylpyridine. At low field the spectrum shows a quartet of two protons, β and γ on the pyridine ring. Thus the dehydrogenation product must be represented by one of the two alternative structures, Ia or Ib.



Ia Ib

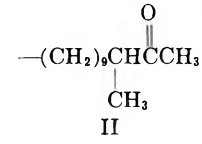
Analysis of cassine had shown the presence of an N-methyl group, and the n.m.r. spectrum with a peak at τ 7.95 is not inconsistent with this. However, the ready dehydrogenation to a pyridine without loss of a carbon atom, nor loss of the τ 7.95 peak in the n.m.r. spectrum, renders the presence of an N-methyl group in the original base impossible.[7] This conclusion was confirmed by a study of N-methyl derivatives of cassine. Treatment of cassine with methyl iodide or under Eschweiler–Clark conditions provided only impure products or starting material, but the base could be converted to the tertiary N-methyl derivative, $C_{20}H_{39}NO_2$, by stirring an ethanolic solution of the base and formaldehyde under hydrogen, in the presence of palladized charcoal. The oily N-methyl derivative formed a crystalline hydrochloride, m.p. 110–111°, $[\alpha]^{26}D$ 6.5°, and a methiodide, m.p. 91–93°, $[\alpha]^{26}D$ 15.8°, whose analyses showed but one and two N-methyl groups, respectively.

A method was now sought to reveal the substituent at the α-position of the piperidine ring between the hydroxyl group and the nitrogen atom of cassine by cleaving the molecule to recognizable products. When treatment by sodium periodate and by lead tetraacetate failed to effect a cleavage, a second-order Beckmann rearrangement was chosen, for recent studies[8] have shown this to be an effective method of cleaving α-amino oximes. The existing carbonyl group was eliminated by a Wolff–Kishner reduction of N-methylcassine to produce a base which formed a crystalline hydrochloride, m.p. 127–129°. Chromic acid oxidation of the material provided a ketone, isolated as the crystalline oxime, m.p. 166–168°, which was treated by pyridine and *p*-toluenesulfonyl chloride and the mixture refluxed with water to produce acetaldehyde, identified as its dinitrophenylhydrazone by paper chromatography in two systems. The α-amino oxime must, therefore, bear a methyl group to produce the acetaldehyde.



Structure Ia can now be recognized as the correct alternative.

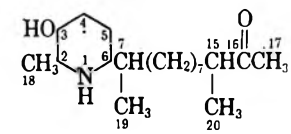
The structure of the side chain may be inferred from the following arguments. (1) The methylene group α to the ketone has been shown to be substituted, and the empirical formula precludes a ring structure. (2) The side chain is, therefore, branched and dehydrocassine must possess an asymmetric center. However, dehydrocassine is optically inactive. It is most likely, then, that the branching is α to the ketone or to the piperidine ring, for such centers might well be racemized under dehydrogenation conditions. (3) The n.m.r. spectrum of cassine shows no methyl group other than the group on the ring and that of the ketone. Any other methyl groups must be obscured by the strong peaks of the methylene resonance. To possess a chemical shift near τ 8.7 the methyl protons must be β to an unsaturated group or a hetero atom. The only such position common to cassine and dehydrocassine is α to the ketone, and the side chain most likely possesses the structure II,[9] and cassine is III. The product of dehydrogenation must be represented by IV, while V and VI represent the Wolff–Kishner product and its oxidation product.



II

Recently, Tichy and Sicher have demonstrated that the stereochemistry of 2,6-dialkyl-3-hydroxypiperidine systems is reflected in the infrared spectrum by the OH

(9) In particular, the n.m.r. spectrum eliminates the possibility of *gem*-dimethyl groups, which would produce an unmistakable sharp peak at high field. The possibility of a methyl group β to the nitrogen, such as at C-19 in structure i, might be supported by the following arguments. A methyl group α to a nitrogen atom (*i.e.*, C-18), as well as that α to a carbonyl group (C-20) may well be obscured by the broad methylene peak,



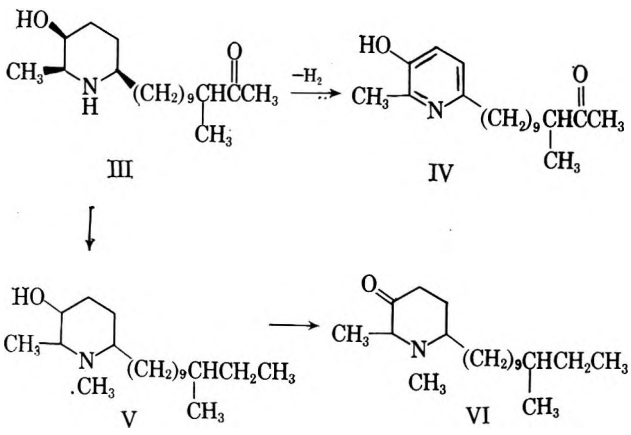
i

the methyl doublet arising from the methyl group β to the nitrogen (C-19). In dehydrocassine, the ring methyl (C-18) produces the peak at τ 7.50 while the methyl groups α to the carbonyl (C-20) and α to the aromatic system (C-19) are obscured. Both asymmetric centers (C-7 and C-15) are capable of racemization during dehydrogenation. However, the possibility of a C-19 methyl may be excluded, since the chemical shift of a methyl group β to a nitrogen atom is actually near τ 8.9–9.0[10] and C-19 of i could not be obscured by the methylene resonance.

(10) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectra No. 92, 296 and 302.

(7) Analysis of 3-hydroxypiperidine itself under standard conditions produced an N-methyl value of 5% ($C_5H_{11}NO$ would require 15%).

(8) *Cf.* (a) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958); (b) R. K. Hill and R. T. Conley, *ibid.*, **82**, 645 (1960); (c) C. A. Grob, H. P. Fischer, N. Link, and E. Renk, *Helv. Chim. Acta*, **46**, 1190 (1963).



III IV V VI

stretching frequency.[11a] In the all-*cis* systems, the most favorable configuration possesses the hydroxy group in the axial configuration (*cf.* VII) favorable to hydrogen bonding. As a result, the hydroxyl absorbs at a single frequency, about 100 cm.$^{-1}$ below the characteristic absorption of secondary hydroxyls, 3630 cm.$^{-1}$. Other configurations show absorption from both free and hydrogen-bonded hydroxyl. The sole peak from the hydroxyl of N-methylcassine occurs at 3530 cm.$^{-1}$, and that of the Wolff–Kishner product (V) appears at 3535 cm.$^{-1}$, revealing the all-*cis* configuration. The stereochemistry of cassine, then, is that represented by III or its mirror image.

VII VIII

Derivatives of 3-hydroxypiperidines occur rather seldom in nature, but cassine is obviously closely related to carpaine (VIII). The stereochemistry of carpaine has been demonstrated to be all-*cis* also.[11] The carbon skeleton of cassine contains the straight fourteen-carbon system of carpaine, with the addition of the group C–C–C–C. It seems reasonable to speculate that the former system arises in nature from the condensation of acetic acid units and the latter from a mevalonic unit.[11b]

Experimental[12]

Isolation.—Leaves of *Cassia excelsa* Shrad. (2.8 kg.) were extracted with 24 l. of 1% ethanolic tartaric acid at 50–60°. The extracts were filtered and concentrated under reduced pressure to 3 l., diluted with 6 l. of water, and treated with 300 ml. of 2 *N* sulfuric acid. The acid solution was filtered, washed with trichloroethylene, and made basic with ammonia. This solution was extracted with chloroform and the organic layers distilled to dryness to leave 81.3 g., 2.9%. For more convenient handling this material was dissolved in ethanol and diluted to 150 ml.

A 50-ml. aliquot of this solution, corresponding to 27 g. of the crude extract, was diluted to 300 ml. with 1 *N* hydrochloric acid and extracted twice with benzene. The aqueous solution was made basic by 25 ml. of 50% sodium hydroxide solution and extracted three times with chloroform; the extracts were washed with water and concentrated to dryness to leave a residue of 19.6 g. This was digested repeatedly with boiling hexane, leaving an insoluble residue of 6.5 g. The hexane solution was filtered and concentrated to dryness to yield 13.4 g. of a clear yellow oil. This material was dissolved in 100 ml. of ethanol and made acid by concentrated hydrochloric acid, diluted with 100 ml. of ethyl acetate, and scratched and chilled until a crystalline precipitate formed. Further crops could be obtained by concentrating the filtrates and adding ethyl acetate. Thus a total of 6.0 g. of crystalline hydrochlorides was obtained. The free base, obtained by dissolving the hydrochlorides in ethanol, diluting with chloroform, adding ammonia, and washing the organic phase with water, was chromatographed over 150 g. of silicic acid, eluting with chloroform with increasing concentration of methanol. The alkaloids were eluted chiefly by 3% and 5% methanol–chloroform solutions. Fractions were converted to hydrochlorides and identified by infrared spectra in Nujol. Casselsine appeared first and could be recognized by peaks at 1010 and 950 cm.$^{-1}$; cassine followed, showing peaks at 1012 and 990 cm.$^{-1}$. Material melting above 165° was collected as pure, the intermediate cuts being rechromatographed until pure materials were obtained. Thus, by repeated chromatography, 0.62 g. (0.06% of dry plant weight) of cassine hydrochloride and 0.56 g. (0.05%) of casselsine hydrochloride were obtained.[13]

Cassine hydrochloride crystallized from ethanol as clustered needles, m.p. 173–175°; ν_{max}^{nujol} 3290, 1715, 1530, 1170, 1160, 1010, and 990 cm.$^{-1}$; λ_{max} 276 mμ (ε 33). Repeated attempts to obtain satisfactory carbon analyses on carefully purified materials failed.

Anal. Calcd. for $C_{19}H_{38}NO_2Cl$: C, 65.60; H, 11.03; neut. equiv., 347.9. Found: C, 64.83, 64.87; H, 10.91, 10.84; neut. equiv., 349, 351.

Cassine was obtained by treating an aqueous suspension of the hydrochloride with ammonia and extracting with chloroform. Analytical material was obtained by distillation at 90° (0.001 mm.), m.p. 57–58°, unchanged by further chromatography; $[\alpha]^{25}_{589}$ −0.6°, $[\alpha]^{25}_{436}$ −1.7°, $[\alpha]^{25}_{380}$ −3.0° (c 8.0); $\nu_{max}^{CCl_4}$ 3530, 2930, 2860, 2810 (sh), 1720, 1360, and 690 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{37}NO_2$: C, 73.26; H, 11.97; N-CH_3, 4.85; C-CH_3, 9.64 for two; neut. equiv., 311.5. Found: C, 73.37, 73.34; H, 11.76, 11.84; N-CH_3, 2.99; C-CH_3, 8.70; neut. equiv., 306.

Cassine hydronitrate precipitated from dilute aqueous nitric acid and was recrystallized from ethyl acetate, m.p. 116–117°.

Anal. Calcd. for $C_{19}H_{38}N_2O_5$: C, 60.93; H, 10.23; N, 7.48. Found: C, 61.12; H, 9.91; N, 7.58.

Diacetyl Cassine.—Cassine (92 mg.) was heated with 10 ml. of acetic anhydride and 0.1 g. of sodium acetate on a steam bath for 1 hr., then added to 300 ml. of 1 *N* potassium bicarbonate, and stirred until no odor of the anhydride could be detected. The suspension was extracted with chloroform; the extract was washed with water, 1 *N* hydrochloric acid and water, and was distilled to dryness to leave a clear oil of 125 mg. This was chromatographed over silicic acid, eluting with chloroform. The center fractions of the eluate were distilled at 110° (0.002 mm.); ν_{max} 1725 (broad), 1630, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{41}NO_4$: C, 69.83; H, 10.45. Found: C, 69.67; H, 10.61.

Piperonylidinecassine was prepared in a centrifuge tube by treating a solution of 157 mg. of cassine and 180 mg. of piperonal in 1 ml. of ethanol with 1 ml. of 6 *N* sodium hydroxide at room temperature. After 15 min., the solution was scratched and diluted with water until the product crystallized. It was centri-

(11)(a) M. Tichy and J. Sicher, *Tetrahedron Letters*, 511 (1962). (b) NOTE ADDED IN PROOF.—Mass spectrometric studies of cassine and dehydrocassine have shown no peaks of *m/e* values greater than 297 and 291, respectively; if these values represent the true molecular weights, structures III–VI must be altered by changing the number of methylene groups in the side chain from 9 to 8.

(12) All melting points were observed on a Kofler microscope hot stage and are corrected. The author is indebted to Mrs. K. S. Warren for polarimetric and spectrophotometric data and to Mr. David Rogerson for extractions of plant material. Rotations were measured in ethanolic solution on a Rudolph photoelectric spectropolarimeter with a 1-dm. tube. Ultraviolet spectra were recorded in absolute ethanol on a Cary Model 11 MS recording spectrophotometer. Infrared spectra were observed either on a Perkin-Elmer Model 21 or a Beckmann IR-7 double-beam spectrophotometer in chloroform solution, unless otherwise specified. We are indebted to Dr. E. D. Becker and Mr. R. B. Bradley of the National Institute of Arthritis and Metabolic Diseases for the n.m.r. spectra, which were obtained on a Varian-V-4300-2 n.m.r. spectrometer operating at 60 Mc. Frequencies were obtained relative to tetramethylsilane as an internal standard by interpolation using the audio side-band technique. Analyses were performed by W. Manser of Zurich, Switzerland, by J. F. Alicino of Metuchen, N. J., and by Micro-Tech Laboratories of Skokie, Ill.

(13) The characterization of casselsine will be described in a later publication.

fuged and the precipitate dried and crystallized from ethyl acetate to yield 101 mg. of m.p. 97–101°. Several recrystallizations provided material of m.p. 106–107.5°; ν_{max}^{Nujol} 3350, 1700, 1620, 1600, 1035, 1000, and 630 cm.$^{-1}$; λ_{max} 247 mμ (ε 10,000), 297 (10,300), and 338 (18,800).

Anal. Calcd. for $C_{27}H_{41}NO_4$: C, 73.10; H, 9.32; C-CH_3, 3.39. Found: C, 72.63; H, 9.10; C-CH_3, 3.46.

Vigorous Condensation of Cassine with Benzaldehyde.—Cassine (6.1 mg.) was sealed in a tube with 27 mg. of benzaldehyde and 13.5 mg. of a 10% sodium hydroxide solution, and 0.2 ml. of ethanol, and heated 22 hr. at 120°. After cooling, the tube was opened, and the contents acidified with dilute hydrochloric acid and extracted with ether. The aqueous layer was made basic with ammonia and extracted with chloroform; the extract was washed with water and distilled to dryness to leave a residue of 6 mg. The ultraviolet spectrum showed only a peak at 287 mμ.

Tetradeuteriocassine was prepared by dissolving 9 mg. of cassine in 0.5 ml. of CH_3OD and treating with a drop of 0.1 *N* sodium methoxide in CH_3OD. After 30 min. the solution was distilled to dryness under reduced pressure, and the residue dissolved in ether, centrifuged, and the clear centrifugate distilled to dryness under reduced pressure. The infrared spectrum showed peaks at 2260, 2220 and 2180 cm.$^{-1}$, with minor changes about 1360 cm.$^{-1}$; m.p. 57–59°. The material was distilled at 100° (0.001 mm.).

Anal. Calcd. for $C_{19}H_{33}D_4NO_2$: 10.8% atom excess deuterium. Found: 9.91%.[14]

Dihydrocassine.—Cassine (112 mg.) was dissolved in 3 ml. of methanol and treated with 100 mg. of sodium borohydride in four portions. After the solution had stood 0.5 hr. it was made acid with hydrochloric acid, extracted twice with ether, made basic with 10% sodium hydroxide, and extracted twice with chloroform and twice with 4:1 chloroform–ethanol. The organic layers were concentrated to dryness and the residue acidified with hydrochloric acid and dried under reduced pressure, to leave 115 mg. of m.p. 161–170°. Recrystallization from ethanol–ethyl acetate gave material of m.p. 173–176°; admixture of cassine hydrochloride lowered the melting point to 168–173°. The infrared spectrum (potassium bromide) showed a sharp peak at 3400, broad absorption from 3000–2400 and no carbonyl absorption, and significant peaks at 1540, 1380, and 1000 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{40}NO_2Cl$: C, 65.20; H, 11.52; Cl, 10.13; neut. equiv., 350.5. Found: C, 64.97; H, 11.20; Cl, 10.57; neut. equiv., 346.

N-Methylcassine was prepared by stirring 0.415 g. of cassine, 117 mg. of 10% palladized charcoal, and 5 ml. of 30% formaldehyde in 30 ml. of ethanol under hydrogen for 4 hr. The solution absorbed 11 ml. of hydrogen. It was filtered, concentrated to 3 ml., diluted with water, and made acid with 6 *N* hydrochloric acid. This solution was extracted with ether, made basic with ammonia and extracted twice with chloroform; the extracts were washed with water and concentrated to dryness under reduced pressure. The residue (403 mg.) was converted to its hydrochloride by concentrated acid. Drying provided a residue of 470 mg. of material of m.p. 107.5–109.5°. Recrystallization from ethyl acetate produced material of m.p. 110.5–111.5°. The infrared spectrum resembled that of cassine hydrochloride, with increased absorption at 2700 cm.$^{-1}$, lacking the bands at 1530 and 1015 cm.$^{-1}$, but retaining those at 3290, 1720 and 988 cm.$^{-1}$; $[\alpha]^{26}_{589}$ 6.5°, $[\alpha]^{26}_{436}$ 14°, $[\alpha]^{26}_{350}$ 26° (*c* 0.92).

Anal. Calcd. for $C_{20}H_{40}NO_2Cl$: C, 66.36; H, 11.06; Cl, 9.80; NCH_3, 4.15; neut. equiv., 362. Found: C, 66.03; H, 11.43; Cl, 9.74; NCH_3, 4.34; neut. equiv., 363.

N-Methylcassine methiodide was prepared by allowing 230 mg. of N-methylcassine in ethanol solution to stand with 2 ml. of methyl iodide overnight. Evaporation of the solvents left a residue of 330 mg., which crystallized on trituration with ethyl acetate, m.p. 87–89°. Crystallization from the same solvent produced material of m.p. 91–93°; $[\alpha]^{26}_{589}$ 15.8°, $[\alpha]^{26}_{436}$ 31.4°, $[\alpha]^{26}_{380}$ 42.6°, $[\alpha]^{26}_{320}$ 69.7°, (*c* 1.015); ν_{max}^{KBr} 3330, 1710 and 990 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{42}NO_2I$: C, 53.96; H, 9.06; I, 27.14; NCH_3, 6.44 for two. Found: C, 54.06; H, 8.70; I, 26.9; NCH_3, 7.45.

Dehydrocassine.—Cassine (0.84 g.) was heated with 278 mg. of 10% palladized charcoal under nitrogen for 30 min. at 220°. The waxy product was dissolved in ethanol, centrifuged, and the supernatant diluted with water, acidified with hydrochloric acid, and extracted three times with benzene; the extract was washed with water and distilled to dryness under reduced pressure to leave a residue of 83 mg. The aqueous raffinate was made basic with ammonia and extracted twice with 4:1 chloroform–ethanol solution, which was washed with water and distilled to dryness under reduced pressure, leaving a residue of 577 mg. This was chromatographed over a column of silicic acid; eluting with 1% methanol in chloroform produced 297 mg. of dehydrocassine, m.p. 97°. Recrystallization from aqueous methanol provided material of m.p. 104–105°; $\nu_{max}^{CCl_4}$ 3611 cm.$^{-1}$; ν_{max}^{Nujol} 2600 (broad), 1722, 1590, 1508, 1285 and 833 cm.$^{-1}$; λ_{max} 224 mμ (ε 9180), 288 (6500); on addition of alkali the peaks shifted to 245 (12,600) and 311 (8600). An acid solution showed λ_{max} 230 mμ (ε 7450) and 301 (10,200). The material exhibited no optical activity between 589 and 370 mμ with a maximum $[\alpha]$ <0.5° (*c* 1.02).

Anal. Calcd. for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23. Found: C, 74.35; H, 9.91; OCH_3, 0.0; N-CH_3, 0.0.

Wolff–Kishner Reduction of N-Methylcassine.—A 300-mg. sample of N-methylcassine, 175 mg. of potassium hydroxide, and 0.6 ml. of 85% hydrazine hydrate were warmed on a steam bath in 5 ml. of ethylene glycol for 1 hr. The flask was then provided with a downward condenser and the volatile components distilled to a temperature of 204°. The solution was refluxed 4 hr., cooled, diluted with water, made acid with dilute hydrochloric acid, and washed twice with ether. The aqueous layers were made basic by ammonia and extracted twice with chloroform, and the extracts were washed with water and concentrated under reduced pressure to a residue of 225 mg. This material was dissolved in ethanol, made acid by dilute hydrochloric acid, and concentrated to dryness. Crystallization from ethyl acetate provided 140 mg., m.p. 125–129°. Repeated crystallization provided material of m.p. 127–129°. The infrared spectrum showed no absorption between 1600 and 2000 cm.$^{-1}$; $[\alpha]^{24}D$ 9.0°, $[\alpha]^{24}_{456}$ 13.5°, $[\alpha]^{24}_{370}$ 18.5°, $[\alpha]^{24}_{300}$ 38° (*c* 0.54). In dilute carbon tetrachloride solution, the hydroxyl peak occurred at 3535 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{42}NOCl$: C, 69.02; H, 12.17. Found: C, 68.96; H, 12.26.

Oxidation and Cleavage.—The base regenerated from 150 mg. of the above salt was dissolved in acetone and treated with 0.21 ml. of Kiliani reagent[15] for 20 min. The solution was diluted with water, extracted twice with ether, made basic by ammonia, and extracted twice with chloroform; the extracts were washed with water and concentrated to dryness. The 48-mg. residue was converted to the oxime by warming with 100 mg. of hydroxylamine hydrochloride and dilute ammonia in ethanol. It was concentrated to dryness under reduced pressure and the residue crystallized from ethyl acetate and benzene to yield 29 mg., m.p. 164–167°.

A 7-mg. sample of this material was sealed in a test tube with 1 ml. of pyridine and 12 mg. of *p*-toluenesulfonyl chloride and the tube heated 3 hr. in a steam bath and 1 hr. at 130°. The tube was cooled, the contents treated with 1 ml. of water and refluxed 1 hr. The mixture was diluted with water, extracted twice with ether, and treated with a sulfuric acid solution of 2,4-dinitrophenylhydrazine. A precipitate formed which amounted to 5 mg. It was chromatographed on paper impregnated with dimethylformamide. Elution by cyclohexane gave an R_f value of 0.39, identical with that of known acetaldehyde dinitrophenylhydrazone. The derivative of acetone had an R_f value of 0.54 when run simultaneously.[16] On untreated paper, eluting by methanol–saturated heptane,[17] the precipitate and known acetaldehyde dinitrophenylhydrazone had an R_f value of 0.43; acetone dinitrophenylhydrazone, R_f 0.61.

Iodoform Test.—Cassine (14 mg.) was dissolved in 0.5 ml. of purified dioxane and treated with 0.1 ml. of 10% sodium hydroxide and 0.35 ml. of *ca.* 1 *N* iodine solution in 20% potassium iodide, and heated at 60° for 2 min.[18] Filtering the precipitate provided 1.7 mg. of iodoform, m.p. 120–122°, undepressed by admixture of authentic material.

(14) Performed by Mr. Joseph Nemeth, Urbana, Ill.

(15) *Cf.* K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. P. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(16) L. Horner and W. Kirmse, *Ann.*, **597**, 48 (1955).

(17) D. F. Meigh, *Nature*, **170**, 579 (1952).

(18) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 156.

Notes

The Structure of the Phloroglucinol Dianion

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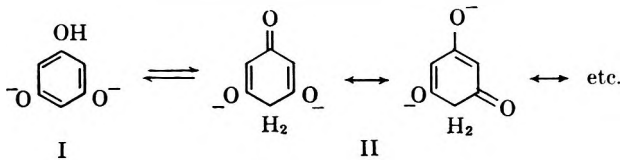
It has long been known that phloroglucinol reacts readily in the keto form.[1] Baeyer observed in 1886 that the compound forms a trioxime with hydroxylamine,[2] and alkylation in alkali gives either C- or O-alkylation, according to the specific conditions.[3] Recently, Fray has made the interesting observation that sodium borohydride reduces phloroglucinol to resorcinol.[4] The occurrence of a peak at 350 mμ in the ultraviolet spectrum of an alkaline solution has been repeatedly observed and cited as support for the existence of a keto form by its resemblance to that of dihydroresorcinol or filicinic acid.[5] In particular, the careful work of Scheibe and Kohler[5d] has shown that the dianion exists much more in tautomeric form II than the other ionic forms exist in corresponding forms. However, none of these observations can reveal ac-



I II

curately the extent to which the equilibrium of the various anions favors keto structures, for the equilibrium is displaced by subsequent irreversible reactions to form the products observed, while ignorance of the extinction coefficient expected of such structures as II prevents assay by spectrophotometric means.

This question has now been investigated by examining the n.m.r. spectrum of aqueous solutions of phloroglucinol and its sodium salts.

Experimental

Commercial phloroglucinol (The Matheson Co.), m.p. 217–219° (lit.[6] 217–218°), was treated with the appropriate quantity of 50% sodium hydroxide and was diluted to provide the solutions described in Table I. Spectra were determined in a Varian A-60 n.m.r. spectrometer equipped with a variable temperature probe. To distinguish the resonance peaks of the carbon-bound protons from the spinning side bands of the solvent, each spectrum was run at two different spin speeds; the peaks reported are those whose positions were not affected by this procedure. Positions are noted relative to the position of the main peak of sodium trimethylsilyl propanesulfonate (Eastman Kodak Co.), added in approximately 1% concentration.[7] Temperatures were measured by noting the difference in chemical shift of the two peaks of ethylene glycol, and were determined from a graph of the equation, $T = 188 - 1.66\ \Delta$, in which Δ is expressed in c.p.s.[8]

Table I

Nuclear Magnetic Resonance Spectra of Phloroglucinol Solutions

	Aromatic, τ	Olefinic τ,	Width[a]	Alicyclic τ,	Width[a]	Temp., ±2°C.
Phloroglucinol, 0.062 *M*	3.95					35
Monosodium phloroglucinolate, 0.2 *M*	3.98					35
Disodium phloroglucinolate, 1.0 *M*		4.92	2.4	6.95	2.8	35
1.0 *M*		4.95	2.6	6.97	4.6	50
1.0 *M*		4.93	3.6	6.95	7.0	61
0.2 *M*		4.97	1.4	7.00	1.2	35
0.05 *M*		4.98		7.03	0.9	35
Trisodium phloroglucinol,[b] 0.20 *M*		4.92		6.95	5.5	35

[a] Width of the peak at half height in c.p.s. [b] *I.e.*, a solution of phloroglucinol treated with 3 equiv. of sodium hydroxide and diluted to the specified molarity.

The rapid exchange between the salts and the solvent made it impossible to determine their spectra in deuterium oxide solution; the only peak observed was that of water. The insolubility of the salts in organic solvents precluded use of the other solvents common in n.m.r. spectroscopy.

Disodium phloroglucinolate was prepared for the infrared spectrum by evaporating the aqueous solution to dryness and holding the solid under high vacuum for several hours. The spectra of Nujol mulls were determined on a Perkin-Elmer Model 21 infrared spectrometer by Mrs. K. S. Warren.

Discussion

The n.m.r. spectrum of an aqueous solution of phloroglucinol shows a single peak for the aromatic protons at τ 3.95, which is slightly shifted by the addition of one mole of sodium hydroxide to τ 3.98. However, addition of 2 equiv. of sodium hydroxide produces a solution whose spectrum shows no aromatic peak, but contains an olefinic peak at τ 4.97, and a peak at τ 7.00 corresponding to the methylene group between two carbonyl groups. Integration of the two peaks by tracing, cutting, and weighing showed them to be of equal area, while an equimolar mixture of sodium

(1) *Cf.* W. J. Hickinbottom, "The Chemistry of Carbon Compounds," Vol. IIIA, E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1954, pp. 483–484.

(2) A. Baeyer, *Ber.*, **19**, 159 (1886).

(3) A. Spitzer, *Monatsh.*, **11**, 104, 287 (1890); J. Herzig and F. Wenzel, *ibid.*, **27**, 786 (1906).

(4) G. I. Fray, *Tetrahedron*, **3**, 316 (1958).

(5) (a) A. Lambrechts, *Compt. rend.*, **198**, 1852 (1934); (b) N. A. Valyasko and E. M. Voroshin, *Trudy Kharkov Khim. Tekhnol. Inst. in. S. M. Kirova*, **5**, 15 (1945); *Chem. Abstr.*, **43**, 2598 (1949); (c) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **73**, 2708 (1951); (d) H. Köhler and H. Scheibe, *Z. anorg. allgem. Ch m.*, **285**, 221 (1956).

(6) A. Baeyer, *Ber.*, **19**, 2187 (1886).

(7) G. V. D. Tiers and A. Kowalsky, Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, p. 17R.

(8) "Preliminary Instruction Manual, V-6057, Variable Temperature System for A-60 Analytical Spectrometers," Varian Associates, Palo Alto, Calif., p. 29.

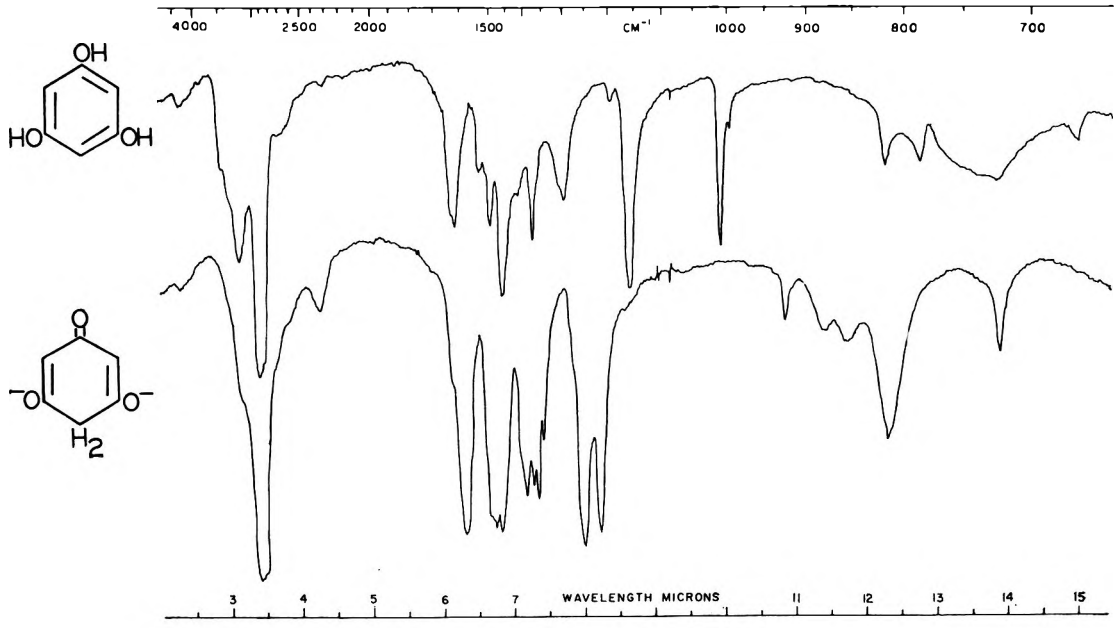


Figure 1.

benzoate and disodium phloroglucinolate shows peaks near τ 2.5 and 6.93 in the anticipated ratio of 5:2.

The chemical shift of the observed peaks is relatively insensitive to changes in concentration and temperature. Warming, however, produced the broadening to be expected of the increased rate of exchange, with the eventual disappearance of the separate peaks into the solvent peak at about 75°.[9] Addition of further sodium hydroxide increased the rate of exchange at room temperature, with the eventual disappearance of the C–H proton peak.

TABLE II

DISSOCIATION CONSTANTS OF SELECTED DIBASIC PHENOLS[a]

	$K_1 \times 10^9$	$K_2 \times 10^{12}$
Phloroglucinol	3.56	1320
Pyrogallol	9.67	2.30
Resorcinol	0.71	4.78
Catechol	0.75	0.84
Hydroquinone	0.12	0.92

[a] C. T. Abichandani and S. K. Jatkar, *J. Indian Inst. Sci.*, A21, 417 (1938).

These observations demonstrate clearly that phloroglucinol and its monosodium salt exist in an aromatic structure, while the disodium salt exists as the alicyclic tautomer (II).

The infrared spectra of Nujol mulls of phloroglucinol and the disodium salt both show strong absorption near 1600 cm.$^{-1}$ but differ markedly at lower frequencies (see Fig. 1). The strong aromatic oxygen peaks of the phloroglucinol are absent in the spectrum of the disalt, which evidently also exists in the alicyclic form (II) in the solid state.

The unusual structure of the dianion is associated with unusual acidity. As Table II shows, the second dissociation constant of resorcinol is approximately 300 times smaller than that of phloroglucinol, while those of other polyphenols are even smaller.

(9) *Cf.* J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 218.

The Ionization Constants, Ultraviolet and Infrared Spectra of Some Substituted Benzimidazoles

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The benzimidazole ring is of considerable chemical and biological interest and has been the subject of many papers. Review articles on benzimidazoles may be consulted for leading references in this field.[1a–c] A considerable amount of work on benzimidazole chemistry has been carried out in this laboratory by several workers. This interest in benzimidazole chemistry has prompted us to start a systematic study of various physical properties of substituted benzimidazoles in order to observe the effect of substituents on the physical properties of the ring. Because of the importance of the benzimidazole ring, more data on the ionization constants and spectroscopic characteristics of substituted benzimidazoles appeared desirable.

Experimental and Results

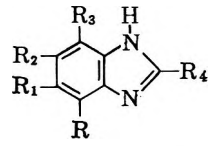
The benzimidazoles used in this study were either available commercially or prepared by well-known procedures. All compounds were recrystallized from the appropriate solvents to constant melting points. All melting points are uncorrected. Melting points and appropriate references are shown in Table I. The ionization constants of various substituted benzimidazoles are also listed in Table I.

The pK_a values shown in Table I were determined by potentiometric titration. A Leeds and Northrup pH meter equipped with glass and saturated calomel electrodes was used to follow the pH of each solution during its titration. The pH meter was calibrated against two buffers: (1) 0.05 *M* potassium phthalate

(1) (a) J. B. Wright, *Chem. Rev.*, **48**, 437 (1951); (b) K. Hofmann, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1953, p. 379; (c) E. S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. 5, Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 194.

TABLE I

IONIZATION CONSTANTS AND MELTING POINTS OF SUBSTITUTED BENZIMIDAZOLES



R	R_1	R_2	R_3	R_4	pK_a, in 5:95 ethanol–water (0.1 M in NaCl) at 30 ± 0.5°C.	Lit. pK_a In water	Lit. pK_a In 50% ethanol	M.p., °C.	Lit. m.p., °C.
H	H	H	H	H	5.52	5.53[a]	4.98[b]	169–170	170–172[b]
H	CH_3	H	H	H	5.65	5.81[b]	5.32[b]	116–118	114[b]
H	OCH_3	H	H	H	5.72		5.07[b]	123–124	123[b]
H	OC_2H_5	H	H	H	5.70			117–118	118–119[b]
H	NO_2	H	H	H	4.50	3.80[c]	2.68[b]	205	204–206[d]
H	H	H	NO_2	H	4.55	3.80[c]		247–248	248–249[d]
H	H	H	H	CH_3	6.10	6.19[b]	5.77[b]	175–176	178.5 179[b]
H	H	H	H	C_2H_5	6.15	6.20[b]	5.69[b]	172–173	177[b]
H	H	H	H	i-C_3H_7	6.08	6.23[b]	5.79[b]	232–233	225–226[e]
H	H	H	H	$CH(OH)CH_3$	5.55			178–180	178.5–179.5[f]
H	H	H	H	$CH_2C_6H_5$	5.70			187	189[b]
H	H	H	H	C_6H_5	5.33		4.51[b]	290	290[b]
H	H	H	H	$COCH_3$	4.61			190–193	188–189[g]
H	H	H	H	CF_3	4.51			209–210	210–210.5[h]
H	CH_3	CH_3	H	H	5.99	5.98[b]	5.48[b]	203–204	204–205[b]
OCH_3	H	H	OCH_3	H	5.63			228	218–222[i]
H	OCH_3	OCH_3	H	H	5.81			183–185	179–183[i]
H	Cl	Cl	H	H	4.74		3.26[b]	204–205	204–205[j]
H	NO_2	H	OCH_3	H	4.65			265–266	258–260[k]
H	Cl	H	H	CH_3	5.68			208–209	215–218[l]
H	Cl	H	NO_2	H	4.60			228–229	229–230[m]
H	CH_3	H	H	$CH(OH)CH_3$	5.70			183–184	183–184[f]
H	OCH_3	H	H	$CH(OH)CH_3$	5.59			160–161[n]	
H	NO_2	H	H	$CH(OH)CH_3$	4.65			200–202	204–205[f]
H	Cl	H	H	$CH(OH)CH_3$	5.08			175–176	178–179[f]
OCH_3	H	H	OCH_3	$CH(OH)CH_3$	5.10			171–172[o]	
H	CH_3	CH_3	H	CH_3	6.26		6.29[b]	233–234	233–234[b]
H	CH_3	CH_3	H	C_2H_5	6.39			223–224	223–224[p]
H	CH_3	CH_3	H	i-C_3H_7	6.35			206–207	206–207[p]
H	CH_3	CH_3	H	$CH_2C_6H_5$	6.07			104–105[q]	
H	OCH_3	NO_2	H	CH_3	4.88			172–173	172–174[r]
H	OCH_3	H	NO_2	CH_3	4.90			203–204	204–205[r]
OCH_3	Br	H	OCH_3	CH_3	5.18			176–177	177–181[i]

[a] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940); A. Albert, R. J. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948). [b] K. Hofmann, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers Inc., New York, N. Y., 1953. p. 379. [c] J. L. Rabinowitz and E. C. Wagner, *J. Am. Chem. Soc.*, **73**, 3030 (1951). [d] E. C. Fisher and M. M. Joullié, *J. Org. Chem.*, **23**, 1944 (1958). [e] D. Jerchel, H. Fischer, and M. Kracht, *Ann.*, **575**, 162 (1952). [f] W. R. Siegart and A. R. Day, *J. Am. Chem. Soc.* **79**, 4391 (1957). [g] H. Matrick, Ph.D. thesis, University of Pennsylvania, 1960, p. 93. [h] W. T. Smith, Jr., and E. C. Steinle, Jr., *J. Am. Chem. Soc.*, **75**, 1292 (1953). [i] L. Weinberger and A. R. Day, *J. Org. Chem.*, **24**, 1451 (1959). [j] M. T. Davies, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, **3**, 420 (1951). [k] H. B. Gillespie, M. Engelman, and S. Graff, *J. Am. Chem. Soc.*, **76**, 3531 (1954). [l] E. J. VanLare, U. S. Patent 2,739,149 (March 20, 1956). [m] J. R. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **77**, 4324 (1955). [n] *Anal.* Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25; N, 14.58. Found: C, 62.67; H, 6.07; N, 14.38. [o] *Anal.* Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.46; H, 6.31; N, 12.61. Found: C, 59.25; H, 6.39; N, 12.42. [p] Personal communication from Aldrich Chemical Co., Inc., Milwaukee 10, Wis. [q] *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 76.60; H, 8.51; N, 14.89. Found: C, 76.38; H, 8.36; N, 14.84. [r] H. B. Gillespie, M. Engelman, F. Spano, and S. Graff, *J. Am. Chem. Soc.*, **79**, 2245 (1957).

(pH 4.00 at 30°) and (2) 0.025 M potassium dihydrogen phosphate and 0.025 M disodium hydrogen phosphate (pH 6.85 at 30°). The solutions to be titrated were prepared by dissolving 1×10^{-5} mole of compound in 5 ml. of distilled water and 5 ml. of absolute ethanol to make 10 ml. of solution. This solution was then mixed with 25 ml. of 0.4 M sodium chloride solution and 65 ml. of distilled water. The resulting solution (100 ml.) was 1×10^{-4} M with respect to the compound analyzed and was titrated with 1×10^{-3} M of hydrochloric acid which had been standardized against sodium carbonate using methyl purple as the indicator. The sodium chloride was used to keep the ionic strength of the solution constant during the titrations.[2]

(2) J. L. Irwin and E. M. Irwin, *J. Am. Chem. Soc.*, **69**, 1091 (1947).

The ultraviolet spectra were obtained on a Beckman DU spectrophotometer modified by Process and Instruments Co. with an attached Leeds and Northrup Speedomax Type G recorder with 1-cm. quartz cells.

Solutions which were 1×10^{-4} M in absolute ethanol, 0.01 N hydrochloric acid (pH 2.02), and 0.01 N sodium hydroxide (pH 12.12) were prepared for each compound. The 0.01 N hydrochloric acid was prepared from 0.1 N hydrochloric acid purchased from Arthur H. Thomas Co. The 0.01 N sodium hydroxide was prepared accurately, and its normality was checked by titration with 0.01 N hydrochloric acid, using phenolphthalein as the indicator.

The optical densities used to calculate the molecular extinction coefficients were uncorrected values. The characteristic bands

TABLE II

CHARACTERISTIC BANDS IN THE ULTRAVIOLET SPECTRA OF SOME SUBSTITUTED BENZIMIDAZOLES

R	R_1	R_2	R_3	R_4	λ_{max}^{EtOH} (log ϵ), mμ	λ_{max}^{HCl} (log ϵ), mμ[a]	λ_{max}^{NaOH} (log ϵ), mμ[a]
H	H	H	H	C_2H_5	280 (3.89), 272 (3.91), 243 (3.80)	274 (3.91), 268 (3.92), 235 (3.61)	277 (3.75), 271 (3.74), 240 (3.63)
H	H	H	H	$CH(CH_3)_2$	280 (3.84), 272 (3.86), 241 (3.73)	274 (3.85), 267 (3.87)	278 (3.65), 270 (3.63), 240 (3.49)
H	CH_3	CH_3	H	C_2H_5	287 (3.78), 281 (3.85), 244 (3.65)	283 (3.93), 274 (3.93)	286 [3.71],[b] 280 [3.79], 243 [3.52]
H	CH_3	CH_3	H	$CH(CH_3)_2$	286 (3.81), 282 (3.88), 246 (3.71)	283 (3.91), 274 (3.92)	286 [3.68], 281 [3.75], 243 [3.41]
H	CH_3	CH_3	H	$CH_2C_6H_5$	287 (3.83), 283 (3.89), 246 (3.73)	285 (3.96), 277 (3.97)	286 [3.40]
H	H	H	H	$COCH_3$	300 (3.92), 235 (3.65)	300 (3.76), 275 (3.83), 267 (3.77), 234 (3.64)	320 (3.97), 237 (3.74)
H	H	H	H	CF_3	281 (3.72), 274 (3.79), 266 (3.76) 246–252 (3.71)		
H	Cl	H	H	CH_3	287 (3.76), 281 (3.86), 246 (3.74)	283 (3.86), 275 (3.89), 234–238 (3.56)	285 (3.70), 280 (3.69), 243 (3.42)
H	Cl	Cl	H	H	293 (3.70), 284 (3.80), 252 (3.61)	289 (3.74), 281 (3.84), 243–246 (3.50)	290 (3.55)
H	OC_2H_5	H	H	H	290 (3.71), 286 (3.74), 243 (3.58)	283 (3.84)	283 (3.76), 241 (3.49)
H	OCH_3	OCH_3	H	H	289 (3.84), 243 (3.48)		
OCH_3	H	H	OCH_3	H	251 (3.77)	263–266 (3.79)	249 (3.58)
OCH_3	Br	H	OCH_3	CH_3	251 (3.70)	260 (3.75)	251 (3.58)
OCH_3	NO_2	H	H	H	300 (3.81), 234 (3.97)	277 (3.88), 243 (3.91)	360–380 (3.89), 243–246 (3.91)
NO_2	OCH_3	H	H	H	366–372 (3.83), 306–309 (3.67)	349–352 (3.54), 280 (3.90)	380–400 [3.60]
NO_2	Cl	H	H	H	303–312 (3.74)	277 (3.87)	368–380 (3.88), 234 (3.83)
H	OCH_3	NO_2	H	CH_3	340 (3.57), 295 (3.60), 251–254 (3.90), 237 (3.94)	340 (3.40), 246–249 (3.90), 234–237 (3.87)	368–380 (3.94), 254–257 (3.79)
NO_2	OCH_3	H	H	CH_3	308–311 (3.76)	342–352 (3.56), 288–291 (3.76), 247 (3.67)	360–380 (3.78)
H	H	H	H	H	279 (3.81), 272 (3.82), 243 (3.68)	274 (3.88), 266 (3.90)	278 (3.67), 272 (3.66), 241 (3.40)
H	CH_3	H	H	H	284 (3.89), 278 (3.91), 244 (3.75)	280 (3.89), 272 (3.91)	283 (3.79), 277 (3.79), 243 (3.53)
H	Cl	H	H	H	286 (3.83). 281 (3.92), 246 (3.76)	284 (3.90), 275 (3.93), 240 (3.59)	286 (3.69)
H	NO_2	H	H	H	306 (3.89), 234–237 (3.99)	280 (3.95), 226–229 (3.95)	360–366 (3.94), 249 (3.93)
H	OCH_3	H	H	H	286–289 (3.79), 243–246 (3.57)	284 (3.93)	286–289 (3.71)
OCH_3	H	OCH_3	H	H	254 (3.80)	266 (3.79)	254 (3.47)

[a] The hydrochloric acid and sodium hydroxide were 0.01N. [b] The values in brackets are approximate due to insufficient solubility.

in the ultraviolet spectra of the substituted benzimidazoles studied are shown in Table II.

All infrared measurements were made on a Perkin-Elmer Model 421 spectrophotometer. The machine was calibrated against a polystyrene film and all values were corrected. All compounds were studied as potassium bromide disks. The characteristic bands in the infrared spectra of the substituted benzimidazoles studied are shown in Tables III, IV, V and VI.

Discussion

The pK_a values of various substituted benzimidazoles under various conditions have been reported in the literature. The most complete study of ionization constants of substituted benzimidazoles has been carried out by Davies, Mamalis, Petrow, and Sturgeon, who determined the pK_a values of a large number of substituted benzimidazoles both in water and 50% aqueous ethanol.[3] It is apparent from the literature that pK_a values obtained under different conditions vary considerably. In order to establish any correlation among various substituted benzimidazoles the same conditions must be used. The choice of water as a solvent is satisfactory, but too few benzimidazoles are sufficiently soluble in water. Although 50% aqueous ethanol is a good solvent for most benzimidazoles, pK_a determinations in organic solvents are not too accurate. To overcome this difficulty we have used just enough ethanol to dissolve all of the benzimidazoles studied, and the same small amount was used in all cases. These solutions were then diluted carefully with water to the same volume. The values obtained under these conditions appeared to be in good agreement with values previously determined in aqueous medium. Since our values were determined under identical conditions, they may be compared among themselves. Electron-donating groups such as alkyl groups and alkoxyl groups increase the basic character of the benzimidazole ring. Electron-withdrawing groups such as the nitro, trifluoromethyl, phenyl, and acetyl groups decrease the basicity of benzimidazole. Position is an important factor in determining basicity,

(3) M. T. Davies, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, **3**, 420 (1951).

TABLE III

CHARACTERISTIC BANDS IN THE SPECTRA OF SOME MONOSUBSTITUTED BENZIMIDAZOLES[a]

R = NO_2	R_1 = OCH_3	R_1 = OC_2H_5	R_1 = NO_2	R_4 = $CH_2C_6H_5$	R_4 = C_6H_5	R_4 = $COCH_3$[b]
1637 m	1633 s	1629 s	1625 m	1628 m	1624 m	1620 m
1585 m	1595 s	1593 m	1593 m	1605 w	1606 w	1584 m
1526 s	1509 m	1518 s	1514 s	1590 m	1595 ms	1509 s
1483 s	1473 s	1476 s	1480 w	1538 s	1543 m	1491 s
1416 s	1463 s	1461 s	1451 s	1498 s	1498 s	1445 s
1360 s	1428 w	1429 s	1406 s	1489 m	1480 s	1424 s
1335 s	1398 s	1398 m	1374 m	1459 s	1463 s	1389 s
1294 s	1350 s	1368 w	1349 s	1430 s	1444 s	1379 s
1259 s	1295 s	1350 m	1316 w	1389 m	1408 s	1358 s
1229 w	1285 s	1306 s	1300 m	1328 m	1378 s	1316 s
1210 w	1275 w	1291 s	1265 m	1319 m	1346 s	1283 m
1186 m	1245 s	1255 s	1244 m	1275 s	1318 s	1233 s
1164 m	1197 s	1202 s	1198 w	1228 m	1280 s	1148 s
1121 s	1190 s	1174 s	1182 w	1197 w	1231 s	1133 m
1066 m	1153 s	1110 s	1134 w	1177 w	1189 m	1123 m
1000 w	1132 m	1089 w	1108 w	1161 w	1161 w	1016 m
935 s	1116 w	1041 s	1068 s	1150 m	1150 m	1007 m
882 w	1027 s	962 s	953 s	1110 w	1121 s	990 m
857 m	950 s	952 s	897 m	1077 w	1115 s	956 m
808 m	917 w	905 m	839 m	1025 s	1075 w	903 w
798 m	880 m	810 s	829 m	1014 s	1028 m	856 w
728 s	832 s	764 w	817 s	1002 ms	1007 m	812 m
	792 s	748 w	794 s	990 w	969 s	772 m
	748 m		762 w	966 w	927 m	747 s
			740 s	928 ms	889 m	
				890 m	849 w	
				849 m	811 m	
				830 w	781 m	
				768 s	766 s	
				747 s	738 s	
				722 s	703 s	

[a] Bands are in cm.$^{-1}$. [b] ν_{max} 1664 cm.$^{-1}$ (C=O for the ketone group).

TABLE IV

CHARACTERISTIC BANDS IN THE SPECTRA OF SOME SUBSTITUTED 2-(1-HYDROXYMETHYL)BENZIMIDAZOLES[a]

R = H	R_1 = CH_3	R_1 = Cl	R_1 = NO_2	R_1 = OCH_3	R = R_4 = OCH_3
1625 m	1632 m	1624 m	1628 s	1629 s	1632 w
1593 m	1596 m	1588 m	1598 m	1598 m	1528 s
1535 m	1533 m	1530 m	1540 m	1530 m	1450 m
1488 m	1456 s	1473 s	1510 s	1491 s	1424 s
1458 s	1443 s	1447 s	1468 s	1460 s	1405 m
1439 s	1421 m	1424 s	1413 s	1429 s	1371 m
1372 s	1375 m	1414 s	1378 w	1376 m	1349 w
1321 s	1314 s	1378 m	1335 s	1309 s	1310 w
1305 s	1301 s	1316 s	1304 s	1279 s	1270 m
1274 s	1282 m	1296 m	1245 m	1239 m	1255 s
1224 m	1232 m	1279 m	1218 m	1202 s	1230 m
1146 m	1145 s	1243 w	1106 m	1149 s	1192 w
1122 s	1132 m	1219 m	1079 s	1109 s	1172 m
1111 s	1102 s	1106 s	1064 m	1086 m	1119 m
1088 s	1086 s	1086 m	1028 m	1029 s	1092 s
1044 m	1049 w	1061 m	990 m	997 m	1072 m
1009 m	1040 m	992 s	948 m	954 m	1053 m
990 s	993 s	927 m	895 m	912 m	994 w
971 w	948 m	902 m	845 m	835 m	984 m
916 m	907 m	856 m	825 m	801 s	898 w
814 s	869 m	798 s	755 m	768 w	787 m
766 m	831 m	755 w	735 m	724 w	723 m
737 s	791 s	706 m			
	759 m				
	728 w				
	703 w				

[a] Bands are in cm.$^{-1}$.

particularly in the case of substituents which act predominantly through an inductive effect. Since the effect of a substituent on the basicity of benzimidazole is stronger the closer this group is to the nitrogen atom, groups in the 2-position are more effective in modifying the basic nature of the imidazole ring than similar groups in the 5(6)-position. This is illustrated by the fact that 2-methylbenzimidazole is more basic than either 5(6)-methyl- or 5,6-dimethylbenzimidazole.

4,7-Dimethoxybenzimidazole is more basic than benzimidazole but less basic than 5(6)-methoxy- and 5(6)-ethoxybenzimidazoles. The 2-(1-hydroxyethyl)-benzimidazoles follow the expected changes by introduction of substituents in the 5(6)-position. However, 4,7-dimethoxy-2-(1-hydroxyethyl)benzimidazole is less basic than either 2-(1-hydroxyethyl)benzimidazole or 4,7-dimethoxybenzimidazole. All 2,5,6-trialkylbenzimidazoles show approximately the same basicity and are more basic than the mono- or disubstituted compounds. The other trisubstituted benzimidazoles have pK_a values which are in agreement with the expected effects of the substituents involved.

The ultraviolet spectra of many substituted benzimidazoles, measured under a variety of conditions, have been reported in the literature. The most comprehensive study of ultraviolet spectra of substituted benzimidazoles has been carried out by Leandri, Mangini, Montanari, and Passerini.[4] The ultraviolet spec-

(4) G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazz. chim. ital.*, **85**, 769 (1955).

TABLE V

CHARACTERISTIC BANDS IN THE SPECTRA OF SOME DISUBSTITUTED BENZIMIDAZOLES[a]

$R_1 = R_2 = Cl$	$R_1 = Cl$, $R_4 = CH_3$	$R_1 = Cl$, $R_3 = NO_2$	$R = R_3 = OCH_3$	$R_1 = R_2 = OCH_3$	$R_1 = OCH_3$, $R_3 = NO_2$	$R_1 = NO_2$, $R_2 = OCH_3$
1633 m	1629 m	1639 m	1634 m	1632 m	1649 w, br	1632 m
1581 m	1588 m	1575 m	1628 w	1598 m	1589 m	1614 m
1489 s	1550 m	1521 s	1549 s	1511 s	1534 s	1520 s
1478 s	1470 s	1490 s	1531 s	1489 s	1474 s	1452 m
1449 s	1450 s	1457 s	1511 s	1464 s	1429 s	1419 m
1392 s	1441 s	1401 m	1463 s	1442 s	1362 s	1394 m
1327 s	1394 s	1350 s	1448 s	1415 s	1336 s	1340 s
1283 s	1342 m	1339 s	1429 s	1363 w	1309 s	1310 s
1267 s	1297 s	1269 s	1418 s	1322 s	1287 s	1290 m
1186 w	1282 s	1213 w	1391 s	1269 s	1226 m	1275 m
1156 w	1241 m	1192 w	1334 s	1247 s	1200 m	1238 w
1151 w	1228 s	1123 s	1287 m	1217 s	1191 m	1210 m
1099 s	1186 w	1089 m	1273 m	1197 s	1150 s	1172 w
960 s	1128 w	1081 m	1252 s	1167 s	1122 m	1106 s
948 s	1058 s	1011 m	1212 m	1156 s	1032 m	1066 m
865 s	1025 s	941 s	1166 s	1113 s	1019 w	974 m
852 s	920 s	894 s	1156 w	1034 m	948 m	961 m
819 s	850 s	873 s	1094 s	999 s	929 ms	859 m
751 w	804 s	806 s	1024 s	953 s	871 w	833 w
734 w	755 w	762 m	990 s	932 w	838 m	754 m
	727 w	741 m	971 m	861 s	820 w	739 m
	706 m		920 w	849 s	781 w	
	702 m		782 s	819 s	762 w	
			774 s	796 s		
			716 s	780 s		
				737 w		
				704 w		

[a] Bands are in cm.$^{-1}$.

TABLE VI

CHARACTERISTIC BANDS[a] IN THE SPECTRA OF SOME TRISUBSTITUTED[b] BENZIMIDAZOLES

$R_1 = R_2$, $R_4 = CH_3$	$R_1 = R_2 = CH_3$, $R_4 = C_2H_5$	$R_1 = R_2 = CH_3$, $R_4 = CH(CH_3)_2$	$R_1 = R_2 = CH_3$, $R_4 = CH_2C_6H_5$	$R = NO_2$, $R_1 = OCH_3$, $R_4 = CH_3$	$R_1 = NO_2$, $R_2 = OCH_3$, $R_4 = CH_3$
1651 s	1637 m	1630 m	1635 m	1630 s	1630 s
1594 m	1589 w	1589 m	1608 w	1581 s	1591 m
1541 m	1544 s	1543 m	1589 w	1547 w	1551 w
1520 m	1469 s	1464 s	1538 m	1499 s	1514 s
1467 s	1444 s, br	1454 s	1499 m	1451 m	1468 s
1452 s	1410 s	1441 s	1463 s	1430 w	1440 m
1434 s	1385 s	1420 m	1444 s	1380 s	1409 s
1392 s	1370 m	1381 m	1422 s	1342 s	1364 m
1310 s	1311 s	1371 m	1387 w	1324 s	1340 s
1267 m	1238 m	1312 s	1377 w	1299 s	1332 s
1249 w	1222 w	1290 m	1359 w	1274 s	1284 s
1236 m	1192 w	1260 w	1313 s	1233 s	1240 w
1164 m	1165 ms	1243 m	1281 w	1197 ms	1205 s
1104 w	1107 ms	1220 w	1230 w	1176 w	1171 m
1022 m	1071 ms	1168 m	1197 w	1153 w	1065 m
1002 m	1038 s	1111 m	1181 w	1086 s	1044 w
869 m	1026 s	1089 m	1167 m	1076 s	1027 w
857 m	1001 s	1073 m	1144 m	1029 m	1002 m
775 w	968 m	1028 m	1103 w	1013 w	904 w
751 w	859 s	1007 s	1076 w	952 w	880 w
739 w	797 m	898 w	1034 m	822 s	831 m
		852 m	1017 m	813 s	762 w
		776 w	1002 m	777 w	
		738 w	923 w	716 w	
			856 m		
			806 w		
			781 m		
			757 w		
			738 m		
			721 s		

[a] Bands are in cm.$^{-1}$. [b] One tetrasubstituted benzimidazole was studied, 2-methyl-5(6)-bromo-4,7-dimethoxybenzimidazole. The characteristic bands in the spectrum of this compound are 1624 m, 1539 m, 1500 s, 1484 m, 1464 m, 1424 s, 1383 m, 1363 m, 1329 m, 1292 s, 1262 s, 1227 s, 1183 m, 1149 s, 1077 s, 1028 m, 971 m, 816 s, 773 w, 749 m, and 709 m cm.$^{-1}$.

trum of benzimidazole resembles that of a substituted benzene. The band of shorter wave length has been related to excitations whose site is the amidine ring and the bands of longer wave length have been related to excitations involving the benzene ring. Some transitions may arise from excitations which include both rings, and in those cases it may be expected that they would produce bands of greater intensity at longer wave lengths. Substitution of simple alkyl groups in the benzimidazole ring causes small bathochromic wave length displacements for all bands. The ultraviolet spectra of 2-ethyl- and 2-isopropylbenzimidazole are very similar to the spectrum of benzimidazole. All the 2,5,6-trialkylbenzimidazole show increased bathochromic displacements of all bands. An electron-withdrawing group such as the acetyl group when in the 2-position modifies the ultraviolet spectrum of the benzimidazole ring considerably. An intense band around 300 mμ replaces the fine structure bands and the band at 240 mμ shows a hypsochromic displacement. The trifluoromethyl group is also an electron-withdrawing group, but it can only act through an inductive effect. When in the 2-position this substituent increases the degree of resolution of the fine structure and causes broadening and a bathochromic displacement of the 240-mμ band. Alkoxyl groups are well-known electron-donating groups and may be expected to cause bathochromic shifts. The spectrum of 5,6-dimethoxybenzimidazole shows loss of fine structure, but the bands present are similar in position to those of the monosubstituted compounds. The ultraviolet spectrum of the 4,7-dimethoxy compound has completely lost the fundamental character of the benzimidazole spectrum. A similar change has been reported in the ultraviolet spectrum of 4(7)-methoxybenzimidazole.[4]

The ultraviolet spectra of 5(6)- and 4(7)-nitrobenzimidazoles have been reported by other investigators. The nitro group causes a regression of the shorter wave length band, disappearance of the fine structure, and appearance of a new band at around 300 mμ. In contrast with the behavior of the other substituents, a larger bathochromic displacement is noted for the 4(7) isomer. For methyl-substituted benzimidazoles, the greater bathochromic displacement of the 5(6) isomers is considered characteristic of substitution in this position.[5] The behavior of 4(7)-nitrobenzimidazole was first ascribed to chelation.[6] Although chelation may be important in the ground state, Leandri, *et al.*,[4] have shown that it cannot be used to explain the ultraviolet data. The 315-mμ band of 4(7)-nitrobenzimidazole shifts to a shorter wave length in acid solution but undergoes a further bathochromic displacement in alkaline solution. Chelation would not be possible under these conditions. Further support against chelation is given by the fact that the methylated products obtained by methylation of the 4(7) isomer have an almost identical spectrum with that of the original 4(7) isomer. Leandri, *et al.*,[4] associate the band in the 300-mμ region with the nitro group and consider the nitrobenzimidazoles as a nitrobenzene system slightly modified by the amidine chain. The large bathochromic shift in alkali is attributed to the increased acidity of the N–H bond since this shift is not nearly so pronounced in the methylated products. The ultraviolet spectra of the various nitro substituted benzimidazoles studied resemble those of the parent nitro compounds. A methyl group in the 2-position increases the resolution of the fine structure bands. The ultraviolet spectra of substituted 2-(1-hydroxyethyl)benzimidazoles resemble the spectra of similarly substituted benzimidazoles except for slight bathochromic shifts due to the presence of the hydroxyethyl group.

In dilute acid solution the benzimidazole ring is protonated, and this reaction immobilizes the unshared pair of electrons on the basic nitrogen, making it less available for resonance and forming a benzimidazolium ion which is best represented as a symmetrical resonance hybrid. The ultraviolet spectra of the compounds studied in 0.01 *N* hydrochloric acid showed shifts towards shorter wave lengths, as compared with their spectra in ethanol. The only shift towards longer wave lengths observed in dilute acid solution was in the case of 4,7-dimethoxybenzimidazole and its derivatives.

In dilute basic solution salt formation should occur, and since resonance should be greater in the salt, bathochromic displacements should be expected. This has not been found to be the case for several compounds. Loss of fine structure is sometimes observed. The ultraviolet spectra of substituted 4(7)- and 5(6)-nitrobenzimidazoles and 2-acetylbenzimidazole show bathochromic displacements in alkali. In these cases, a salt is certainly formed, and the greater mobility of electrons in the salt facilitates the formation of an electronic excited state.

Although some infrared absorption values for substituted benzimidazoles may be found in the literature, little systematic work has been done in this field until a recent study of the infrared spectra of simple alkyl- and perfluoroalkylbenzimidazoles.[7]

The infrared spectra of benzimidazoles are very complex. Benzimidazoles are not very soluble in the common solvents used in infrared work, and their spectra are best determined as potassium bromide disks. Because of the low solubility of the compounds studied in suitable solvents, all spectra were determined as potassium bromide disks in spite of the fact that in this medium certain bands originate from some type of crystal interaction rather than from a vibration of the molecule itself.

Benzimidazoles are known to be strongly associated through intermolecular hydrogen bonding. The spectra of all compounds studied show strong broad bands from 3300 to 2800 cm.$^{-1}$ which indicate polymeric association through intermolecular hydrogen bonding. The CH stretching vibrations of the ring also occur in this range (3300–3100 cm.$^{-1}$) and cannot be distinguished from the NH stretching frequencies.

Bands derived primarily from aromatic C=C and C=N stretching modes are found in the same region and cannot be distinguished. The C=C skeletal in-plane vibrations of benzene give rise to four bands near 1600, 1580, 1500, and 1450 cm.$^{-1}$. The infrared spectrum of benzimidazole has two bands of medium intensity at 1622 and 1591 cm.$^{-1}$ and a weak band at 1604 cm.$^{-1}$. The 1650–1500-cm.$^{-1}$ region is a very

(5) G. H. Beaven, E. R. Holiday, and E. A. Johnson, *Spectrochim. Acta*, **4**, 338 (1951).

(6) J. L. Rabinowitz and E. C. Wagner, *J. Am. Chem. Soc.*, **73**, 3030 (1951).

(7) K. J. Morgan, *J. Chem. Soc.*, 2343 (1961).

characteristic region of the benzimidazole spectrum. All substituted benzimidazoles have bands in this region which vary in position and intensity with the nature and position of the substituent. The spectra of most substituted benzimidazoles only have two bands, one around 1620 cm.$^{-1}$ and the other around 1590 cm.$^{-1}$. The band around 1590 cm.$^{-1}$ is in general fairly intense because of the conjugation between the benzene and imidazole rings. In the infrared spectrum of 4,7-dimethoxybenzimidazole and its 2-(1-hydroxyethyl) analog this band is absent. The frequencies of these bands also vary with the electronegativity of the substituent. The 2-substituted benzimidazoles show the least variation in frequency for these two bands since groups in this position are less apt to influence the vibrations of the benzene ring. Substitution in the 2-position is accompanied by the appearance of a rather intense band around 1550 cm.$^{-1}$. This band has been reported to be characteristic of 2-substitution.[7] Our data appears to support this although the band is absent in the infrared spectrum of 2-acetylbenzimidazole.

All benzimidazoles show strong bands in the 1500–1400-cm.$^{-1}$ region which could be attributed to skeletal in-plane vibrations. 5(6)- and 4(7)-substituted benzimidazoles show intense and sometimes broad bands around 1480, 1450, and 1420 cm.$^{-1}$. Similar bands are observed for the 2-substituted compounds. In the 1400–1300-cm.$^{-1}$ region, 5(6)-substituted benzimidazoles usually show two bands around 1370 and 1350 cm.$^{-1}$. The spectra of the 2-substituted benzimidazoles have a strong band around 1320 cm.$^{-1}$, and a medium to strong band around 1380 cm.$^{-1}$. In the case of the nitro substituted benzimidazoles, it is difficult to distinguish the bands in the 1570–1500- and 1370–1300-cm.$^{-1}$ regions from the nitro group absorptions.

Heterocyclic compounds also show a series of characteristic bands in the 1250–1000-cm.$^{-1}$ region which may be assigned to in-plane CH deformations and ring-breathing modes. The position of these bands is reported to be similar for compounds with the same number of hydrogen atoms in the same orientation. Similarly, substituted benzimidazoles also show a number of bands in this region which are similarly located. The C–O vibrations of aralkyl ethers are reported to cause strong absorption around 1250 and 1150 cm.$^{-1}$. Strong bands in these regions are noted when alkoxy groups are present.

Bands which appear regularly in the spectra of the simple benzimidazoles near 1000 and 960 cm.$^{-1}$ may be associated with benzenoid ring-breathing modes, and bands near 760 and 880 cm.$^{-1}$ with the heterocyclic ring-breathing modes.[7] Out-of-plane CH deformations and in-plane ring deformations cause absorption in the 1000–650-cm.$^{-1}$ region. The out-of-plane CH bending frequencies of substituted benzenes also fall in this region. The spectra of all 5(6)- and 4(7)-substituted compounds have an intense band around 950 cm.$^{-1}$ which is the strongest band in the region. The pattern found in the spectra of 2-substituted benzimidazoles is less constant although a band of medium intensity is sometimes present around 960 cm.$^{-1}$.

The out-of-plane CH bending frequencies of some substituted benzimidazoles have been assigned[8] as follows: 735 cm.$^{-1}$ for 2-methylbenzimidazole; 870, 812, and 800 cm.$^{-1}$ for 5(6)-methylbenzimidazole; 900, 830, and 820 cm.$^{-1}$ for 5(6)-nitrobenzimidazole. These values were derived by considering the 2-position as that of an *o*-disubstituted benzene (770–735 cm.$^{-1}$) and the 5(6)-position as having one isolated pair of hydrogens and one isolated hydrogen (850–800 cm.$^{-1}$, 900–830 cm.$^{-1}$). All bands were strong, although there were medium bands of doubtful identity.[8]

The spectra of 5(6)-substituted benzimidazoles show broad strong bands in the 900–800-cm.$^{-1}$ region and it is hard to make specific assignments. The spectra of 2-substituted benzimidazoles show a fairly constant band around 850 cm.$^{-1}$ of variable intensity. The spectra of all 2-substituted benzimidazoles have a very intense band between 747–733 cm.$^{-1}$. This band is the most intense in this region and one of the most intense in the spectra. It may be ascribed to the out-of-plane CH bending frequency. A medium to weak band is also present around 760 cm.$^{-1}$. The spectra of the 5(6)-substituted compounds show two intense bands around 790 and 740 cm.$^{-1}$. The out-of-plane CH bending frequencies of 4(7)-substituted benzimidazoles should cause absorption in the 800–700- and 720–685-cm.$^{-1}$ regions. The infrared spectrum of the 4(7)-nitrobenzimidazole shows two intense bands at 798 and 728 cm.$^{-1}$ which could be ascribed to the out-of-plane bending frequencies of a 4(7)-substituted benzimidazole.

In addition to vibrations typical of the benzimidazole ring, the vibrations typical of the groups attached to the ring must be considered. In general, substituents show the same characteristic bands regardless of whether they are attached to a benzene or benzimidazole ring. However, some of these vibrations may be modified by the heterocyclic nucleus if a strong electronic interaction occurs between the ring and the substituent. For instance, in the case of 2-acetylbenzimidazole, conjugation of the keto group with the heterocyclic ring is evidenced by its absorption at 1664 cm.$^{-1}$, typical of α,β-unsaturated ketones.

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Reactions of Free Radicals with Olefins. Thermal Decomposition of *t*-Butyl Peracetate in the Presence of 4-Vinylcyclohexene

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To obtain additional information on free radicals and their reactions with specific olefins, a study was undertaken complementing work previously published from this laboratory.[1,2] These earlier studies involved

(1) J. R. Shelton and J. N. Henderson, *J. Org. Chem.*, **26**, 2185 (1961).
(2) J. R. Shelton and A. Champ, *ibid.*, **28**, 1393 (1963).

reactions of *t*-butoxy and *t*-butylperoxy radicals with 4-vinylcyclohexene, conducted in the presence of cobalt or cupric ions. In a reaction of 4-vinylcyclohexene with *t*-butyl hydroperoxide in the presence of cobalt ions, the olefin was peroxidated mainly in the 6-position and to a minor extent in position 3, with only traces of product attributed to reaction at the tertiary C–H in the 4-position. It was further concluded that this distribution of isomers is probably due to steric factors.

To determine the generality of these reactions as well as the preference of radicals toward substitution *vs.* addition, research was extended to methyl and acetoxy free radicals. These radicals were generated by thermal decomposition of *t*-butyl peracetate.

$$CH_3CO_2OC(CH_3)_3 \xrightarrow{130^\circ} CH_3CO_2\cdot + \cdot OC(CH_3)_3$$

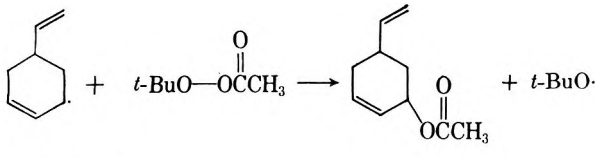
$$CH_3CO_2\cdot \longrightarrow CH_3\cdot + CO_2$$

It was shown by Bartlett and Hiatt[3] that the thermal decomposition of *t*-butyl peracetate involves the rupture of the O–O bond in the primary step, followed by loss of carbon dioxide. Thus, *t*-butoxy, acetoxy, and methyl radicals were made available.

Some possible products which might be formed by thermal decomposition of *t*-butyl peracetate in the presence of 4-vinylcyclohexene are given in Chart I. After removal of excess 4-vinylcyclohexene, the reaction mixture was hydrogenated and then reduced with lithium aluminum hydride in order to simplify the analysis. V.p.c. and infrared analysis of the reaction mixture showed that compounds **1**, **2**, **3**, **4**, **7**, and **10** were absent. Compound **8** was found to be present in 2.6% and compound **6** in 1.3%. V.p.c. further indicated that 2-ethylcyclohexanol was present (<0.4%); however, this was not substantiated unequivocally by infrared. It was shown that *n*-propylcyclohexane (compound **9**) was a product. A large amount of dehydro dimer of 4-vinylcyclohexene also was isolated. Although *t*-butyl alcohol and methane were found in large amounts, neither acetic acid nor ethane could be detected.

The formation of *t*-butyl alcohol and methane supports the supposition that *t*-butoxy radicals and methyl radicals remove an allylic hydrogen from 4-vinylcyclohexene to yield 4-vinylcyclohexenyl radicals A, B, C (Chart I). These radicals can then combine to form dehydro dimer, and/or couple with $CH_3\cdot$ or $CH_3CO_2\cdot$ to give substitution products.

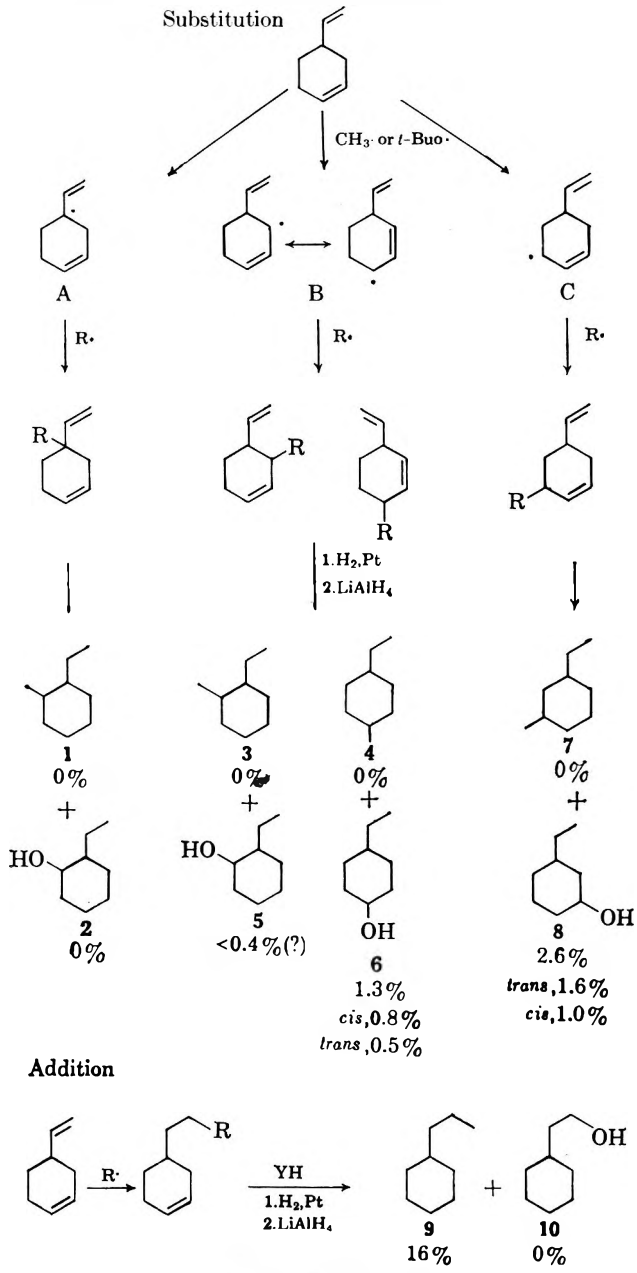
Alternatively, in view of the instability of acetoxy radicals, the radicals derived from 4-vinylcyclohexene might attack the perester directly to form the observed products. While peresters are not so subject to radical-induced decomposition as diacyl and diaroyl peroxides, the relatively small amount of acetate esters obtained (approximately 5% based on perester) could result from reactions of the following type.



(3) P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958).

CHART I

SOME POSSIBLE PRODUCTS OF THE THERMAL DECOMPOSITION OF *t*-BUTYL PERACETATE IN 4-VINYLCYCLOHEXENE



R· = $CH_3\cdot$ or $CH_3CO_2\cdot$

YH = some H source, such as 4-vinylcyclohexene

The isomer distribution indicates that the less sterically hindered position 6 is the preferred one for hydrogen abstraction leading to products derived from radical C. This is in keeping with previous findings.[1] The formation of the 4 isomer (compound **6**) probably arises from attack of $CH_3\cdot$ and/or *t*-BuO· on 4-vinylcyclohexene in the 2-position to form B which, being resonance stabilized, yields the sterically favored compound. Supporting this contention is the fact that a small amount of the 2 isomer (compound **5**) seems to be present. If compounds **6** and **8** resulted from addition of acetate radicals to the internal double bond with subsequent removal of hydrogen, equal amounts would be expected, and, as seen from Chart I, such was not the case. Furthermore, if addition of acetoxy radicals occurred, it should have taken place preferentially at

the vinyl double bond.[4] However, addition of CH_3· evidently did occur; and (see Chart I), after hydrogenation of the product, *n*-propylcyclohexane was identified.

The major product was the relatively nonvolatile dehydro dimer, formed probably by self-coupling and combination of radicals B and C. Since a large excess of 4-vinylcyclohexene was used and considerable amounts of methane and *t*-butyl alcohol were found, the concentration of the 4-vinylcyclohexenyl radicals must have been sufficient to produce these dimers.

Infrared analysis of the residue gave a spectrum which showed both vinyl and internal unsaturation and resembled the dehydro dimer with the exception that additional bands characteristic of acetate were present. Thin layer chromatography resulted in two poorly resolved spots which were not further analyzed or identified. It seems reasonable, however, to assume that the residue contained rather low molecular weight telomers (probably dimeric and trimeric) terminated by acetoxy and/or 4-vinylcyclohexenyl radicals.

The relative amounts of the various products of the reaction of radicals derived from *t*-butyl peracetate with 4-vinylcyclohexene are compared in Table I.

TABLE I

RELATIVE AMOUNTS OF PRODUCTS

Original perester	21.0 g.	0.159 mole	
t-Butyl alcohol	9.2	0.124	78% based on weight of perester
n-Propylcyclohexane	3.2	0.029	
Cyclo esters	1.3	0.008	
Dehydro dimer	14.5	0.068	
		0.105	66%
Residue	18.5		

These reactions in 4-vinylcyclohexene demonstrated that abstraction of allylic hydrogen is the preferred path with a combination of methyl and oxy radicals derived from *t*-butyl peracetate leading to formation of dehydro dimer and substitution products. Addition of methyl radical to the vinyl double bond also occurred, as evidenced by the addition product (compound **9**) and the formation of what appeared to be telomers of 4-vinylcyclohexene.

Experimental

Reagents.—The 4-vinylcyclohexene[5] was purified by pouring the required amount through a column of activated alumina immediately before reaction, $n^{24}D$ 1.4613, lit.[6] $n^{20}D$ 1.4624. The *t*-butyl peracetate (Lupersol No. 7) was supplied[7] as a 75% solution in benzene which was washed once with dilute sodium carbonate solution and dried over magnesium sulfate. Slow distillation removed all the benzene; the ester distilled at b.p. 27–28° (0.9 mm.), lit.[8] b.p. 23–24° (0.5 mm.).

Reaction of *t*-Butyl Peracetate with 4-Vinylcyclohexene.—In a typical reaction 172 g. (1.59 moles) of 4-vinylcyclohexene was placed in a round-bottomed flask with 21.0 g. (0.159 mole) of *t*-butyl peracetate under nitrogen at atmospheric pressure and heated at reflux temperature with magnetic stirring. The evolution of carbon dioxide was checked from time to time by bubbling the effluent gas through a freshly prepared barium hydroxide solution. Analysis of the evolved gas through a 24-ft. column (silicone grease on Chromosorb) at Dry Ice temperature gave evidence for carbon dioxide and methane. No ethane was detected. After approximately 12–14 hr. (24 to 28 half-lives), the carbon dioxide evolution had stopped and the reaction was terminated.

The clear but faintly yellow reaction mixture was very slowly distilled under nitrogen through a 10-in. column packed with glass helices. Fractions collected were (1) b.p. 79–83°, 9.2 g.; (2) b.p. 118–128°, 133.4 g.; (3) b.p. 57–65° (30 mm.), 3.7 g.; (4) b.p. 92–97° (12 mm.), 1.3 g.; and residue, 33 g.

Analysis of the Reaction Products.—By means of infrared and v.p.c. analysis of the fraction, cut 1 was shown to be essentially pure *t*-butyl alcohol. The infrared spectrum was in agreement with the literature.[9a] A 3,5-dinitrobenzoate derivative melted at 141.8°, lit.[10] 142°. Cut 2 consisted of unchanged 4-vinylcyclohexene. Cut 3 was essentially a hydrocarbon mixture. Cut 4 showed strong acetate absorption.

Identification of the Hydrocarbon.—V.p.c. analysis of cut 3 showed that it was composed of essentially two components. Hydrogenation of this material over Adams' catalyst in acetic acid produced the saturated hydrocarbon which was a mixture of 13% ethylcyclohexane[9b] and 84% *n*-propylcyclohexane.[9c] A trace impurity which had been detected in 4-vinylcyclohexene prior to its use in the reaction had concentrated during the fractionation so that several extraneous infrared bands were found in the mixture. After hydrogenation this impurity is converted to cyclooctane which was identified by means of an authentic sample and the literature infrared spectrum.[11]

A specific search was made for 2-methyl-1-ethylcyclohexane, 3-methyl-1-ethylcyclohexane, and 4-methyl-1-ethylcyclohexane with negative results.

Identification of Ester— Fraction 4 gave a positive ester test.[10] Infrared of this material gave evidence of acetate ester (1250–1230 cm.$^{-1}$), vinyl (3080, 1640, 997, 910 cm.$^{-1}$), and internal unsaturation (3030 cm.$^{-1}$). To ease the analysis of this material, this fraction was hydrogenated over Adams' catalyst in acetic acid. Following the usual work-up procedure, the reduced material was treated subsequently with 0.5 g. of lithium aluminum hydride in 75 ml. of ether. The reaction mixture, after stirring for several hours was treated with approximately 10 ml. of sodium carbonate solution, and extracted with ether. The combined ether extracts were dried over magnesium sulfate and evaporated to give a residue of 0.4 ml. Examination of this material by v.p.c. (Carbowax on Chromosorb column, at 100° and 50 ml./min. He flow) produced a chromatogram with six bands having retention times of 12, 16, 18, 20.5, 23.5, and 26.5 min., respectively. A comparison of the retention times and infrared spectra with the isomeric ethylcyclohexanols gave evidence for the following compounds (see Table II).

For the *cis*,*trans*-3-ethylcyclohexanol and the *cis*-4-ethylcyclohexanol, the absorbance–concentration plots were linear at 840, 815, and 990 cm.$^{-1}$, respectively. Considerable difficulty was encountered with the *trans*-4-ethylcyclohexanol since the 1090 cm.$^{-1}$ band is the only one that is free from interference; unfortunately, this band is very small.

The absence of 1-ethylcyclohexanol and 2-cyclohexylethanol was established by a comparison with reported infrared spectra.[1,12]

The v.p.c. bands (Table II) 3 and 4 corresponded to a mixture of *cis*- and *trans*-2-ethylcyclohexanol, but the presence of these compounds in the final product could not be established unequivocally by infrared.

Although routine infrared spectra were obtained on a Perkin-Elmer 237B spectrophotometer, the infrared spectra used in the identification of the ethylcyclohexanols were obtained on Beckman IR-7 and IR-8 spectrometer. The per cent composition of this mixture was obtained by selecting the characteristic peaks that showed least interference with those of other isomers and applying the base line technique.[13]

Comparison Compounds.—The following compounds were prepared so that their v.p.c. and infrared spectra could be compared with the products of the reaction: *cis*,*trans*-3-ethylcyclo-

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(5) Cities Service Research and Development Co., New York, N. Y.
(6) O. Aschan, *Ber.*, **57** 1959 (1924).
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(8) J. K. Kochi, *J. Am. Chem. Soc.*, **84**, 774 (1962).
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TABLE II

VAPOR PHASE CHROMATOGRAPHY RETENTION TIMES AND INFRARED SPECTRA FOR ETHYLCYCLOHEXANOLS

V.p.c. band	Retention time, min.	%	Compound	Characteristic absorption bands, cm.$^{-1}$
1	12	3		
2	16	4		
3	18	1	2-Ethylcyclohexanol (*cis*- and *trans*-)	880, 845, 820
4	20.5	7		
5	23.5	44	*trans*-3-Ethylcyclohexanol	1036, 1014, 968, 857, 815
			cis-4-Ethylcyclohexanol	1144, 990, 952, 897
6	26.5	41	*trans*-4-Ethylcyclohexanol	1090, 1052, 965, 897
			cis-3-Ethylcyclohexanol	1111, 1049, 957, 839

hexanol, *cis,trans*-4-ethylcyclohexanol, *cis,trans*-2-ethylcyclohexanol, 2-methyl-1-ethylcyclohexane, 3-methyl-1-ethylcyclohexane, 4-methyl-1-ethylcyclohexane, and ethylcyclohexane. Each was obtained by a method reported in the literature. The physical properties were in agreement with the reported values.

Analysis of the Residue.—Approximately 25 g. of the residue was placed in the bulb of a small modified retort and heated in a 60° oil bath for 24 hr. under vacuum (0.5 mm.). The volatile material (5.6 g.) was trapped in a second bulb contained in a Dry Ice–acetone bath. When the volatile material was chromatographed it gave two peaks with only minor impurities (less than 3%). This material was identified by means of infrared as the dehydro dimer.[2]

The remaining viscous residue was chromatographed using the thin layer technique (t.l.c.). The adsorbant was silica gel g and the eluent benzene (or petroleum ether, b.p. 30–60°). Two spots were observed when the plate was treated with iodine. One of these had an R_f value identical with that of the dehydro dimer. By v.p.c. it was shown that this viscous residue still contained 5.3 g. of dehydro dimer. The original 33 g. of residue, therefore, was composed of 14.5 g. (0.068 mole based on perester) of dehydro dimer and 18.5 g. of higher molecular weight material. Infrared of the entire residue showed it to be very much like the dehydro dimer but contaminated with acetate esters.

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The Isomerization of 1,2-Di-*n*-octylcyclopropene with Alumina

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The fatty acids that contain a cyclopropene ring, sterculic acid and malvalic acid, are formed as triglycerides in *Sterculia foetida* oil and in cottonseed oil and are remarkable both for their unique chemical structure and for the physiological effects that have been observed when they are included in poultry diets.[1-4] Because destruction of the cyclopropene ring by hydrogenation,[2] rearrangement,[5] or reaction with gaseous hydrogen chloride or sulfur dioxide[6] eliminates the biological effects, we have been interested in the structures of the products that are formed by these procedures.

This paper concerns the nature of the products formed when the cyclopropene ring is destroyed by rearrangement with alumina. The simplicity of sterculene (I, 1,2-di-*n*-octylcyclopropene) together with its ready availability[7a] led to its choice as a model compound for the isomerization.

Sterculene was stirred at room temperature under nitrogen with an equal weight of activated alumina in ten volumes of petroleum ether (b.p. 30–60°). During the reaction its characteristic cyclopropene infrared bands at 5.38 and 9.92 μ[7b] gradually diminished in size and were replaced by bands at 6.13 and 11.15 μ (unsymmetrical disubstituted olefin) and 10.37 μ (*trans* double bond).

After 35 hr. the cyclopropene infrared bands had disappeared and the reaction mixture no longer gave the Halphen test,[8] an empirical test for sterculic and malvalic acid derivatives. The solution was filtered and distilled to give a 72% yield of a clear colorless oil having the same boiling point as I; redistillation showed the same boiling point and did not yield any residue.

A portion (12%) of the product polymerized during the isomerization, and the remainder (16%) could not be extracted from the alumina with petroleum ether.

The isomerized material smoothly consumed 1.7 moles of hydrogen per $C_{19}H_{36}$, which suggested that it is a mixture of compounds, 30% of the material containing one double bond and 70% containing two double bonds. Under the same conditions, I consumed 0.95 mole of hydrogen per $C_{19}H_{36}$.

The ultraviolet spectrum of the isomerized material showed an absorption peak with a maximum at 232 mμ. By assuming a molar extinction coefficient of 22,000[9] the material was calculated to contain 64% of compounds having conjugated double bonds.

The isomerized material reacted with maleic anhydride in refluxing xylene. After removal of solvent and saponification, 36% of the starting material was ex-

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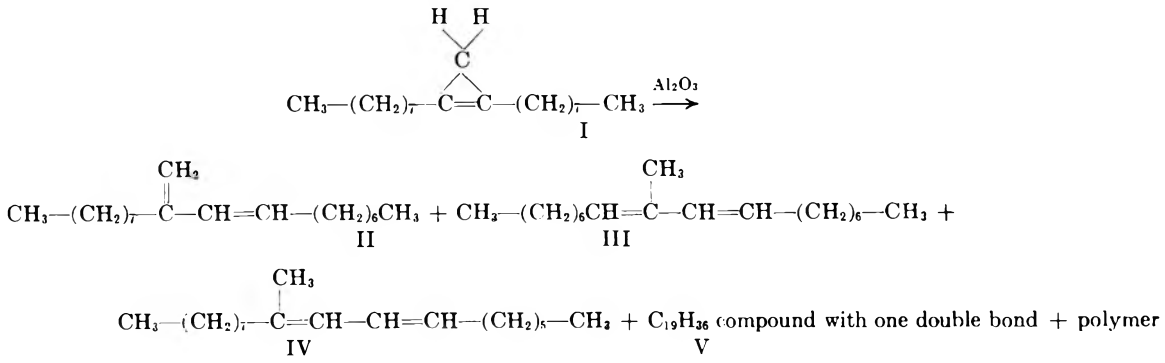


tracted from the alkaline saponification liquors. This suggested that 64% of the isomerized sterculene contained conjugated double bonds. The infrared spectrum of the material not reacting with maleic anhydride showed no characteristic bands for unsaturation.

A portion of the isomerized material was ozonized in methylene chloride at −50°. The ozonide was decomposed with zinc and aqueous acetic acid and separated into water-soluble, acidic, and neutral components. Formaldehyde was identified in the aqueous solution by its dimedone derivative.

The acid fraction, comprising 35% of the isomerized material ozonized, was methylated with 7% boron trifluoride in methanol and the methyl esters separated into three fractions by distillation. The fractions were analyzed by gas–liquid chromatography (g.l.c.) and the relative amount of methyl enanthate, caprylate, and pelargonate in each estimated from the areas under the peaks of the chromatogram and are given in Table I. The pure esters were separated on a preparative column, saponified, and the three acids positively identified as their crystalline *p*-toluidides.

TABLE I

PRODUCTS OBTAINED FROM OZONOLYSIS OF ISOMERIZED STERCULENE

Acidic		Neutral	
Compound	Yield,[a] %	Compound	Yield,[a] %
Methyl enanthate	2[b]	Enanthaldehyde	1[b]
Methyl caprylate	11[b]	Caprylaldehyde	21[b]
Methyl pelargonate	16[b]	2-Decanone	2[b]
Distillation residue	6	C_{19} compounds	6
		Distillation residue	19

[a] Expressed as per cent of the isomerized sterculene ozonized. [b] Calculated from g.l.c. data.

The neutral fraction comprised 49% of the isomerized sterculene ozonized and was separated into four fractions by distillation. Enanthaldehyde, caprylaldehyde, and 2-decanone were recognized by g.l.c.; the amounts of each were estimated from the chromatograms and are given in Table I. The latter two compounds were identified by their crystalline 2,4-dinitrophenylhydrazones.

From the spectral, hydrogenation, maleic anhydride adduction, and ozonolysis data, the scheme, at the top of this page, for the isomerization of I is suggested.

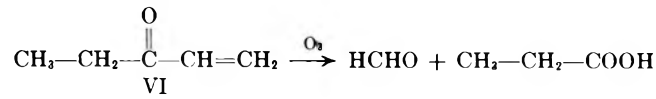
Under the conditions of the reaction about 28% of I or its isomerization products polymerize or cannot be removed from the alumina for other reasons. About 20–25% of I rearranges to substances whose structure is unknown. Presumably this is the portion of the distillate that absorbs 1 mole of hydrogen, does not react with maleic anhydride, and forms high molecular weight compounds on ozonolysis. At the present time, no further work is contemplated on this fraction.

The remaining 50–55% of I isomerizes to 9-methylene-10-octadecene (II), 9-methyl-8,10-octadecadiene (III), and 9-methyl-9,11-octadecadiene (IV). The latter is formed only to a small extent, 2–3%, for only that quantity of enanthaldehyde, enanthic acid, and 2-decanone were found in the ozonolysis mixture (Table I).

The relative quantities of the major isomerization products II and III can be calculated from the ratios of the C_8 and C_9 compounds obtained by ozonolysis. Compound II should give 1 mole each of C_8 and C_9 compounds and compound III should give 2 moles of C_8. It was observed (Table I) that twice as much C_8 as C_9 material is obtained; therefore, twice as much II is present in the isomerization mixture as III.

Theoretically, ozonolysis of structure II should give α-ketodecanoic acid or α-ketodecanal. Neither of these compounds were observed. The large quantity of pelargonic acid obtained arose from overoxidation of the primary ozonolysis products of II.

To test this theory, ethyl vinyl ketone (VI) was ozonized and the ozonide decomposed with zinc and acetic acid. Formaldehyde was identified as its dimedone derivative and propionic acid was the only other fragment found.



Experimental

Sterculene (I) was prepared as described previously,[7a] b.p. 99–104° (0.05 mm.), $n^{20}D$ 1.4543, infrared at 5.38, 9.92 μ; lit.[7b] b.p. 102° (0.04 mm.), $n^{20}D$ 1.4540, infrared at 5.38, 9.92 μ. The alumina (Aluminum Company of America, Alcoa, grade F-6, mesh 8-14) was activated at 200 to 220° under nitrogen. Gas–liquid chromatography (g.l.c.) was performed with the Aerograph A-90-C apparatus. Ten-foot analytical columns with 30% diethylene glycol succinate or with 10% ethylene glycol succinate, and a 5-ft. preparative column with 20% diethylene glycol succinate were used.

Isomerization Reaction.—I (48.2 g.) was dissolved in 500 ml. of petroleum ether (b.p. 30–60°) and added to the activated alumina (50 g.). The mixture was stirred under nitrogen at room temperature for 35 hr. The mixture was filtered, the alumina extracted several times with fresh petroleum ether, and the combined filtrates evaporated *in vacuo* to leave 40.7 g. (84%) of an oil. The product was distilled, b.p. 100–118° (0.07 mm.), to give 35.1 g. (72.3% of I) of a colorless oil. This distillate was used for all further characterization studies.

Hydrogenation.—Two samples of 0.2881 g. and 0.2736 g. of the distillate were hydrogenated in absolute ethanol (15 ml.) over 5% palladium on charcoal (0.1 g.) at atmospheric pressure

and room temperature in a standard Hershberg apparatus; 1.71 and 1.72 moles of hydrogen per $C_{19}H_{36}$ were consumed, respectively.

Maleic Anhydride Addition.—The distillate (2.5 g.) was refluxed for 5 hr. with maleic anhydride (3.0 g.) in xylene (10 ml.). After cooling, petroleum ether was added and the mixture extracted with water to remove unchanged maleic anhydride. The residue after removal of solvent (3.08 g.) was refluxed with sodium hydroxide (2.0 g.) in methanol (25 ml.) overnight. Water was added and the alkaline solution extracted with petroleum ether to yield an oil (0.9 g.) representing 36% of the distillate used in the experiment.

In a second run, the distillate (2.18 g.) was refluxed with maleic anhydride (2.00 g.) in xylene (10 ml.) overnight. Petroleum ether was added and the unchanged maleic anhydride extracted with water. Evaporation of the solvent left an oil (2.66 g.) which was distilled. A product (0.77 g., 35% of starting material) was obtained at 107° (0.05 mm.) whose infrared spectrum was the same as the neutral fraction obtained from the first run.

Ozonolysis.—The distillate (33.0 g.) of isomerized sterculene in dry methylene chloride (250 ml.) was cooled to −50° and ozone (3.36 g./hr.) was passed through the solution for 7 hr. The solution was allowed to warm to room temperature and was added to a suspension of zinc dust (16.0 g.) in 50% aqueous acetic acid (150 ml.) in a 1-l. flask fitted with stirrer, dropping funnel, and Vigreux condenser. Considerable heat was evolved during the addition, enough to distil most of the methylene chloride. The mixture was stirred overnight, refluxed an hour, filtered, and extracted three times with petroleum ether.

A portion of the aqueous layer was added to a solution of 10% dimedone in ethanol. White crystals were obtained, m.p. 190–191°, unchanged on admixture with an authentic sample of the dimedone derivative of formaldehyde, lit.[10] m.p. 187°.

The petroleum ether solution was extracted twice with 5% aqueous sodium hydroxide, dried over sodium sulfate, and evaporated to leave the neutral oxidation products (16.2 g.). G.l.c. showed four peaks and three of them corresponded to enanthaldehyde, caprylaldehyde, and 2-decanone. The aqueous solution was acidified and extracted to yield the acidic oxidation products (11.5 g.). These were esterified with a solution (80 ml.) of 7% boron trifluoride in methanol. G.l.c. showed three peaks corresponding to methyl enanthate, caprylate, and pelargonate. The neutral fraction was distilled. Four fractions were obtained: N-1, 5.50 g., b.p. 90–120° (45 mm.); N-2, 1.85 g., b.p. 60–100° (0.10 mm.); N-3, 2.62 g., b.p. 100–148° (0.10 mm.); N-4, residue, 6.20 g.

The methyl esters of the acidic fraction were distilled to yield three fractions: A-1, 8.45 g., b.p. 110–124° (45 mm.); A-2, 1.00 g., b.p. 60° (0.05 mm.); A-3, residue, 2.00 g.

Identification of Neutral Constituents.—A sample (0.6 g.) of N-1 was treated with 2,4-dinitrophenylhydrazine (0.4 g.) in ethanol (20 ml.). Yellow crystals were obtained, m.p. 104–105°, unchanged upon admixture with an authentic sample of caprylaldehyde 2,4-dinitrophenylhydrazone, lit.[11] m.p. 106°.

Fraction N-2 on similar treatment yielded the 2,4-dinitrophenylhydrazone of 2-decanone, m.p. and m.m.p. 73–74°, lit.[12] m.p. 73–74°.

Fraction N-3 on g.l.c. showed a small peak corresponding to 2-decanone and a large peak of long retention time, similar to that observed for 9,11-nonadecadione obtained by ozonolysis of sterculene (see below). It did not yield any crystalline carbonyl derivatives or a chelate with cupric acetate. It is presumed to be a dicarbonyl compound arising from structure V.

9,11-Nonadecadione.—I (10.0 g.) was ozonized as were the rearrangement products above and worked up in the same way. The product was distilled, b.p. 130–140° (0.10 mm.), to give 7.9 g. (70% of I) of a pale yellow sirup.

Anal. Calcd. for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found: C, 76.85; H, 12.39.

A sample of this compound yielded readily a bluish precipitate, m.p. 104–105°, on treatment with cupric acetate in ethanol.

Anal. Calcd. for $Cu(C_{19}H_{35}O_2)_2$: C, 69.74; H, 10.78. Found: C, 69.83; H, 11.05.

Identification of Acidic Constituents.—Fraction A-1 showed peaks on g.l.c. corresponding to the methyl esters of enanthic, caprylic, and pelargonic acid. Fraction A-2 contained only methyl pelargonate. Fraction A-1 was separated on a preparative g.l.c. column into its constituents.

Each was saponified and the *p*-toluidides of the acids prepared by the method given in Shriner and Fuson.[13] In this way, the *p*-toluidides of enanthic acid (m.p. 79–80°, lit.[13] m.p. 80°), caprylic acid (m.p. 69°, lit.[13] m.p. 70°), and pelargonic acid (m.p. 82°, lit.[13] m.p. 84°) were obtained. The melting points of the derivatives were not depressed upon admixture with authentic samples.

Ozonolysis of Ethyl Vinyl Ketone (VI).—A solution of ketone VI (10.5 g.) in methylene chloride (200 ml.) was cooled to −50° and ozone (2.88 g./hr.) was passed through it for 5.5 hr. The solution was allowed to warm to room temperature and added to zinc dust (11 g.) in 50% acetic acid (60 ml.).

The mixture was extracted with petroleum ether to yield an acid that was esterified with the 7% boron trifluoride in methanol reagent (70 ml.). Methylene chloride was added to the esterification medium and the solution washed several times with water, dried, and distilled. When about 30 ml. of material were left in the distillation flask, 20 ml. of bromobenzene were added and the distillation resumed. A fraction was collected, b.p. 75–78° (3.5 g.). It was saponified and its *p*-toluidide prepared. The melting point of the derivative, 123°, was unchanged on admixture with the *p*-toluidide of propionic acid, lit.[13] m.p. 124°.

The dimedone derivative of formaldehyde was obtained from the aqueous layer as before, m.p. and m.m.p. 190–191°, lit.[10] m.p. 187°.

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Steric Hindrance to Halogenation and Oxidation at the Tertiary Carbon of o-Carbophenoxytriphenylmethane

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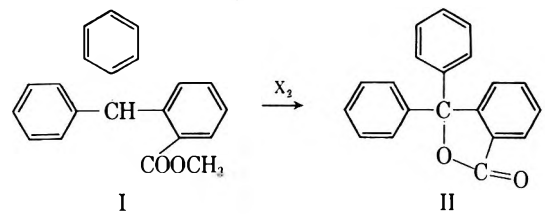
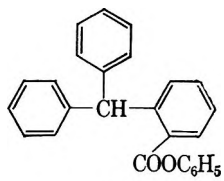
In connection with another investigation, various substituted trityl halides have been prepared by free-radical halogenation of the corresponding triphenylmethanes. An interesting example of the steric protection of the tertiary position of the triphenylmethane molecule by a bulky *ortho* substituent has been encountered in the course of this synthetic work. Generally, trityl halides can be prepared in good quantity from the corresponding triphenylmethanes by photochemical methods or by reaction with N-bromosuccinimide. For example, a pure sample of trityl chloride itself has been obtained in 67% yield through photochlorination of triphenylmethane. Methyl *o*-benzhydrylbenzoate readily undergoes radical-type halogenation to give 3,3-diphenylphthalide (eq. 1). Presumably the tertiary halide derived from the ester is highly unstable with respect to lactone formation. No reaction occurs, however, when phenyl *o*-benz-

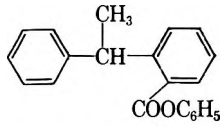


I II (1)



III

hydrylbenzoate (III) is treated with molecular chlorine or bromine under conditions which lead to the reaction of the methyl ester.[1] The carbophenoxy group must constitute a formidable steric barrier to tertiary hydrogen atom extraction. It is interesting to note that 1-phenyl-1-(*o*-carbophenoxyphenyl)ethane (IV) is much less easily photochlorinated than is the corresponding methyl ester.[2]



IV

The *o*-carbophenoxy group also screens the tertiary carbon of triphenylmethane against attack by an oxidizing agent. Under conditions which promote the reaction of tri-*p*-nitrophenylmethane with chromium trioxide in acetic acid to form the corresponding carbinol,[3] III is unreactive. The methyl ester (I) reacts under these same conditions to produce a mixture of products in which 3,3-diphenylphthalide again appears to be the major component.

Experimental

The Methyl (I) and Phenyl (III) Esters of *o*-Benzhydrylbenzoic Acid.—A sample of *o*-benzhydrylbenzoic acid was prepared by the aluminum chloride-catalyzed reaction of 3-phenylphthalide and benzene.[4] The acid was converted to the acid chloride by refluxing in carbon tetrachloride, with an equimolar quantity of phosphorus pentachloride. When the reaction was complete, the solvent was removed and the residue was refluxed with methanol for several hours. The methyl ester, m.p. 94–96° (lit.[5] m.p. 98°), was isolated in 52% yield from the methanol solution. The phenyl ester was prepared by refluxing a mixture of crude samples of the acid chloride, phenol, and pyridine (in equimolar amounts) in carbon tetrachloride for 2 hr. The product was isolated in 71% yield (9.0 g. from 10.0 g. of starting acid), m.p. 89–90.5°, after recrystallization from petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{26}H_{20}O_2$: C, 85.60; H, 5.55. Found: C, 85.90; H, 5.26.

Photochlorination. A. Triphenylmethane.—A solution of 4.0 g. (0.016 mole) of triphenylmethane in 150 ml. of carbon tetrachloride was irradiated with a tungsten lamp as it was treated dropwise with a solution of 1.2 g. (0.015 mole) of chlorine in 100 ml. of the same solvent. After the reaction was complete, the solvent was removed and the crude trityl chloride was recrystallized from petroleum ether to provide 3.0 g. (67% yield) of pure material, m.p. 111–112° (lit.[6] m.p. 112°).

B. Methyl *o*-Benzhydrylbenzoate.—A 2.0-g. sample of this ester was photochlorinated with an equimolar quantity of chlorine by essentially the same procedure as was used for the reaction of triphenylmethane. From the product a sample of 3,3-diphenylphthalide was obtained. This was crystallized from petroleum ether to provide 1.0 g. (56% yield) of pure material of m.p. 115° (lit.[7] m.p. 116°) and equiv. wt., 284 (calcd. for $C_{20}H_{14}O_2$, 286).

C. Phenyl *o*-Benzhydrylbenzoate.—A 1.0-g. (0.004 mole) sample of this ester was treated with 3.0 g. (0.04 mole) of chlorine, again by essentially the same procedure as has been described for the preparation of trityl chloride. The crude product was crystallized from petroleum ether to provide 0.8 g. of a solid of m.p. 88–90°. The melting point of this material was not depressed by mixing with a sample of the starting ester.

Photobrominations. A. Methyl *o*-Benzhydrylbenzoate.—A 5.0-g. sample of this ester was photobrominated by the general procedure described previously.[1] From the reaction product 3.0 g. (62%) of 3,3-diphenylphthalide, m.p. 116–118°, was isolated. This material had an infrared spectrum identical with that of the product of photochlorination of the starting ester.

B. Phenyl *o*-Benzhydrylbenzoate.—A 10.0-g. sample of the phenyl ester was treated with an equimolar amount of bromine in carbon tetrachloride and irradiated under the same conditions, which lead to rapid photobromination of diphenylmethane derivatives and also of methyl *o*-benzhydrylbenzoate.[1] After 1 hr. the reaction mixture still had an intense bromine color. The solvent and unchanged bromine were removed by evaporation. In this fashion 9.5 g. (crystallized from petroleum ether) of unchanged phenyl *o*-benzhydrylbenzoate was obtained, m.p. 87–90°. The melting point of this material was not depressed by mixing with a sample of the starting ester.

Oxidation of the Esters.—A 1.0-g. sample of methyl *o*-benzhydrylbenzoate was oxidized by refluxing for 3 hr. in a solution of 0.2 g. of chromium trioxide in 50 ml. of acetic acid. The solution turned green during this period. The crude product was isolated by the procedure reported by Fischer and Fischer.[3] This was an oil (0.6 g.) which could not be induced to crystallize. On the basis of its infrared spectrum it was concluded that this material was predominantly 3,3-diphenylphthalide.

An attempt was made to oxidize a 1.0-g. sample of phenyl *o*-benzhydrylbenzoate by the same procedure used in oxidizing the corresponding methyl ester. After it was refluxed for 3 hr., the reaction mixture was still purple. From the acetic acid solution 0.8 g. (after crystallization from petroleum ether) of the starting phenyl ester, m.p. 85–87°, was obtained. The infrared spectrum of this material was identical with that of phenyl *o*-benzhydrylbenzoate.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

(1) In an earlier investigation [A. Singh, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 1179 (1962)], it was found that methyl *o*-benzylbenzoate also underwent photobromination to yield a lactone. 3-phenylphthalide. The corresponding phenyl ester, however, reacts with bromine under irradiation to provide *o*-carbophenoxybenzhydryl bromide in excellent yield.

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The Preparation of N,N,N′N′-Tetramethyl-*p*-phenylenediamine[1]

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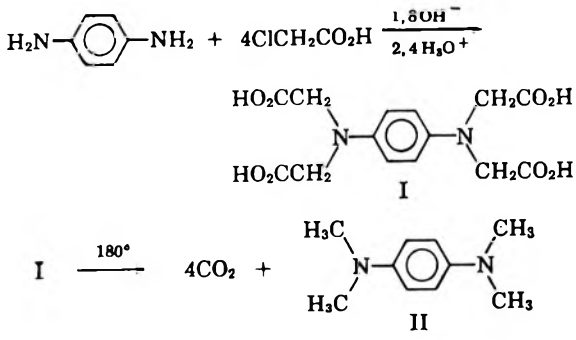
The N-methylation of *p*-phenylenediamine by heating its dihydrochloride with methanol in a sealed tube was first described by R. Meyer.[2] Although this procedure gives low yields and purification of the

(1) This work was supported by a grant, NSF-G18894, from the National Science Foundation.

(2) R. Meyer, *Ber.*, **36**, 2979 (1903).

product is tedious, it is apparently the most satisfactory synthesis of N,N,N′N′-tetramethyl-*p*-phenylenediamine (II) yet reported. Application of the Eschweiler–Clark modification of the Leuckart Reaction[3] to *p*-phenylenediamine fails, apparently due to condensation of formaldehyde with the activated ring.[4] Although the decarboxylation of phenyliminodiacetic acid to N,N-dimethylaniline has been reported,[5] this type of reaction seems not to have been applied very frequently to the methylation of anilines. We wish to report a facile example of this reaction (eq. 2), which affords a ready synthesis of II.



Although the mechanism of the decarboxylation is presently unknown, the reported catalysis by ferric ion[5b] and the induction period occasionally observed in the present work are suggestive of a homolytic process.

Experimental

***p*-Phenylenediiminotetraacetic Acid (I).**—*p*-Phenylenediamine, 10.8 g. (0.1 mole), chloroacetic acid, 37.8 g. (0.4 mole), sodium hydroxide, 32.0 g. (0.8 mole), and potassium iodide, 5.0 g. (0.03 mole), were dissolved in 500 ml. of water and boiled under reflux for 1 hr. To the hot solution there was added cautiously 40 ml. of concentrated hydrochloric acid. The precipitate which formed upon cooling the solution in ice was filtered with suction and dried under vacuum at room temperature. The nearly colorless crystals melted at 165° with decomposition (lit.[6] m.p. 165° dec.) and weighed 18.9 g. (55%).

Decarboxylation of I to N,N,N′,N′-Tetramethyl-*p*-phenylenediamine (II).—I (17.0 g., 0.05 mole) was placed in a large vacuum sublimation apparatus which was then evacuated by means of an aspirator to approximately 20 mm. A Wood's Metal bath which had been preheated to 180° was cautiously applied to the sublimer. Melting of the solid was accompanied by evolution of gas, and the product sublimed on the cold finger.

In order to remove colored impurities the product was dissolved in petroleum ether (b.p. 30–60°) and passed through a short column of basic activated alumina. Evaporation of the solvent, followed by one additional vacuum sublimation, afforded colorless crystals (4.3 g., 52%), m.p. 51–52° (lit.[2] m.p. 51°). Recrystallization from petroleum ether afforded glistening platelets of the same melting point. The visible absorption spectrum of the radical cation, "Wurster's Blue," formed on oxidation of the amine was in quantitative agreement with that reported.[7] Several samples of the purified amine have remained colorless in contact with air, but with exclusion of light and moisture, for periods of up to 3 years.

(3) M. L. Moore, *Org. Reactions*, **5**, 301 (1949); H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).
(4) J. R. Cox, Jr., unpublished results.
(5) (a) A. Hausdörfer, *Ber.*, **22**, 1798 (1889); (b) Kalle and Co., German Patent 375463, abstracted in P. Friedländer, *Fortsch. Teerfarbenfabrik.*, **14**, 400 (1926).
(6) L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, **106**, 331 (1934).
(7) L. Michaelis, M. P. Schubert, and S. Granick, *J. Am. Chem. Soc.*, **61**, 1981 (1939).

Arylation Reactions of Anthraquinones. The Preparation of 1-Aryl-4-aminoanthraquinones

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Nesmeyanow and co-workers[1] have studied the decomposition of the simpler diazonium fluoroborates in organic solvents; low yields of arylated products are always obtained.[2] In intramolecular arylations (Pschorr synthesis), fluoroborates are good sources of radicals; for example, benzofluorenone is obtained in 66% yield.[3] The thermal decomposition of a number of anthraquinone diazonium fluoroborates, for example, anthraquinone-1-diazonium fluoroborate and -1,5-bis-diazonium fluoroborate, in aromatic solvents gives the corresponding fluorinated anthraquinones[4] in high yield; however, the diazonium fluoroborates derived from 1-amino-4-chloro- and 1-amino-4-nitroanthraquinone under similar conditions proved to be effective sources of anthraquinyl radicals. These compounds, when decomposed by heating a suspension in an aromatic solvent, form 1-aryl-4-chloro- and 1-aryl-4-nitroanthraquinones in yields of 40–65%.

The yields reported in Table I were calculated by analysis of the crude reaction product. The melting points refer to products purified by several recrystallizations.

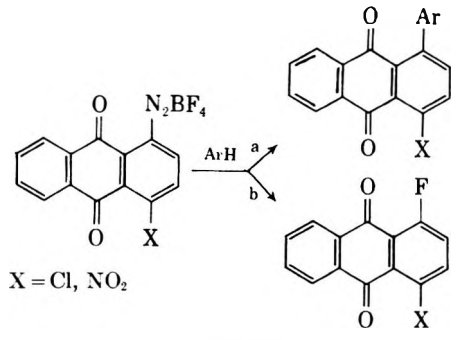
TABLE I

Anthraquinone-1-chloro-4-	Yield, %	M.p., °C.
o-Dichlorophenyl-	61	267–268
Nitrophenyl-	44	273–274
α-Chloronaphthyl-	48	274–275
α-Bromonaphthyl-	43	260–264
Anthraquinone-1-nitro-4-		
o-Dichlorophenyl-	43	261–264
Bromophenyl-	39	295–298

It has been suggested that arylations by thermal decomposition of diazonium fluoroborates involve cationoid radical intermediates. Phenyl diazonium fluoroborate decomposed in methyl benzoate gives *m*-phenyl benzoate but little of the *para* isomer.[5] In the Pschorr synthesis the operation of two distinct mechanisms, ionic and radical, has been suggested.[6] In the present work there is also evidence of a cationoid intermediate in that only with electron-attracting substituents can arylation (a) compete with the Schiemann reaction (b). (See p. 490 col. 1.)

The 1-aryl-4-chloroanthraquinones when treated with *p*-toluenesulfonamide[7] form 1-aryl-4-*p*-toluenesulphonamidoanthraquinones which on hydrolysis in sulfuric

(1) O. A. Reutow, *Angew. Chem.*, **72**, 198 (1960).
(2) L. G. Makarova and M. K. Matveeva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1974 (1960); *Chem. Abstr.*, **54**, 1403 (1960).
(3) R. Huisgen and W. D. Zahler, *Ber.*, **96**, 736 (1963).
(4) G. Valkanas and H. Hopff, *J. Org. Chem.*, **27**, 3680 (1962).
(5) L. G. Makarova and E. A. Gribtchenko, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 693 (1958); *Chem. Abstr.*, **52**, 20,002 (1958).
(6) R. Huisgen and W. D. Zahler, *Ber.*, **96**, 747 (1963).
(7) G. Valkanas and H. Hopff, *J. Chem. Soc.*, 1923 (1963).



acid yield 1-aryl-4-aminoanthraquinones. Identical amines are obtained by causing the chloro compound to react with ammonia in an autoclave.[8] The 1-aryl-4-nitroanthraquinones on heating with aqueous sodium sulfide[9] afford the corresponding amines in good yield. These appear to be the first arylated α-aminoanthraquinones prepared and could be valuable intermediates for new anthraquinoid dyes.

Experimental

Decomposition of 1-Chloro-4-diazonium Fluoroborate Anthraquinone in *o*-Dichlorobenzene to Yield 1-Chloro-4-(*o*-dichlorophenyl anthraquinone.—1-Chloro-4-amino-anthraquinone (50 g.) was dissolved in concentrated sulfuric acid (200 ml.) and diazotized with nitrosylsulfuric acid solution (200 ml., prepared from 20 g. of sodium nitrite and concentrated sulfuric acid) in 1 hr. at 0–10°. The resulting solution was stirred until on the addition of several drops to water a clear orange solution was formed. The product was poured onto ice (1 kg.). The **anthraquinone diazonium sulfate** was precipitated, removed by filtration, washed with a small amount of cold water, and dissolved in 5 l. of water, insoluble impurities being removed by filtration. Fluoroboric acid (40%, 50 ml.) was added with stirring and the precipitated **1-chloro-4-diazonium fluoroborate anthraquinone** (50 g., 82%) was removed by filtration, washed with methanol, and dried (decomposition temperature, 180–181°).

The diazonium salt (20 g.) was suspended in *o*-dichlorobenzene (150 ml.) and heated slowly to boiling while being stirred. During the decomposition the solution turned from red to brown and a heavy stream of boron trifluoride escaped. After 2 hr., the solution was decolorized with activated carbon and filtered while hot and the *o*-dichlorobenzene solution was reduced in volume to 30 ml. (Found: Cl, 19.2% or 61% of arylation.). The yellow product which separated on cooling was recrystallized from chlorobenzene to yield **1-chloro-4-(*o*-dichlorophenyl)anthraquinone**, 10.5 g., 49%, m.p. 267–268°.

Anal. Calcd. for $C_{20}H_9Cl_3O_2$: C, 61.9; H, 2.3; Cl, 27.5. Found: C, 61.85; H, 2.4; Cl, 27.4.

1-Chloro-4-(α-chloronaphthyl)anthraquinone.—1-Chloro-4-diazonium fluoroborate anthraquinone (15 g.) was suspended in α-chloronaphthalene (100 ml.) and slowly heated to 180–190° and kept at this temperature for 1 hr. with stirring. Decolorizing carbon was added, the solution was filtered, reduced in volume to 10 ml., and then boiled in chlorobenzene (100 ml.). On cooling the solution a yellow precipitate was obtained (Found: Cl, 15.5% or 48% of arylation.) which was recrystallized from chlorobenzene (6 g., 35%), m.p. 274–275°.

Anal. Calcd. for $C_{24}H_{12}Cl_2O_2$: C, 71.5; H, 3.0; Cl, 17.6. Found: C, 71.75; H, 3.0; Cl, 17.9.

1-Chloro-4-(nitrophenyl)anthraquinone.—1-Chloro-4-diazonium fluoroborate anthraquinone (20 g.) was thermally decomposed in nitrobenzene (150 ml.). Nitrogen analysis of the reaction product showed 44% of arylation had occurred. Two recrystallizations from chlorobenzene gave the yellow 1-chloro-4-(nitrophenyl)anthraquinone, m.p. 273–274°, 6.1 g., 30%.

Anal. Calcd. for $C_{20}H_{10}ClNO_4$: C, 66.1; H, 2.8; Cl, 9.8; N, 3.85. Found: C, 66.0; H, 3.0; Cl, 9.9; N, 3.8.

1-Chloro-4-(α-bromonaphthyl)anthraquinone.—Similarly, decomposition of 1-chloro-4-diazonium fluoroborate anthraquinone in α-bromonaphthalene gave 43% of arylation. Recrystallization from chlorobenzene afforded the red-brown 1-chloro-4-(α-bromonaphthyl)anthraquinone, m.p. 260–264°.

Anal. Calcd. for $C_{24}H_{12}BrClO_2$: C, 64.5; H, 2.7; Cl, 7.95. Found: C, 63.8; H, 2.8; Cl, 8.05.

Decomposition of 1-Nitro-4-diazonium Fluoroborate Anthraquinone in *o*-Dichlorobenzene to Yield 1-Nitro-4-(*o*-dichlorophenyl)anthraquinone.—1-Nitro-4-aminoanthraquinone (50 g.) was diazotized with nitrosylsulfuric acid solution and converted to 1-nitro-4-diazonium fluoroborate anthraquinone, 60 g., 89%, decomposition temperature of 171–172°, in the manner described.

The diazonium salt (20 g.) was suspended in o-dichlorobenzene (150 ml.), brought slowly to boiling, and further treated as in the above cases. The solution was reduced in volume to 30 ml. and filtered. The solid, 12.1 g. (Found: Cl, 7.7% or 43% of arylation), was recrystallized from chlorobenzene to yield 7.3 g., 37%, m.p. 241–244°.

Anal. Calcd. for $C_{20}H_9Cl_2NO_4$: C, 60.3; H, 2.25; Cl, 17.85; N, 3.5. Found: C, 60.8; H, 2.3; Cl, 17.3; N, 3.7.

1-Nitro-4-bromophenylanthraquinone.—1-Nitro-4-diazonium fluoroborate anthraquinone when decomposed in bromobenzene gave 39% of arylation (nitrogen analysis). The pure red-brown 1-nitro-4-bromophenylanthraquinone isolated after recrystallization from chlorobenzene had m.p. 295–298°.

Anal. Calcd. for $C_{20}H_{10}BrNO_4$: C, 58.8; H, 2.45; N, 3.45. Found: C, 59.3; H, 2.5; N, 3.4.

1-Amino-4-(*o*-dichlorophenyl)anthraquinone.—1-Chloro-4-(*o*-dichlorophenyl)anthraquinone (6 g.), toluene-*p*-sulfonamide (4 g.), copper acetate (2 g.), potassium carbonate (2 g.), and *o*-dichlorobenzene (100 ml.) were heated slowly to the boiling point and kept under reflux for 5 hr. After cooling the mixture was filtered, and the precipitate washed with boiling alcohol and water, and dried. The resulting **anthraquinonesulphonamide** was recrystallized from anisole to give 6.9 g., 85%, m.p. 268–269°.

The sulfonamide (4 g.) was dissolved in concentrated sulfuric acid (40 ml.) and heated for 1 hr. at 80–90°. It was poured on to ice to yield a red precipitate of 1-amino-4-(*o*-dichlorophenyl)-anthraquinone, which was recrystallized from anisole to yield 2.6 g., 93%, m.p. 283–284°.

Anal. Calcd. for $C_{20}H_{11}Cl_2NO_2$: C, 65.9; H, 3.35; Cl, 19.25; N, 3.8. Found: C, 66.0; H, 3.45; Cl, 19.95; N, 3.9.

Reduction of 1-Nitro-4-(*o*-dichlorophenyl)anthraquinone.—1-Nitro-4-(*o*-dichlorophenyl)anthraquinone (2.5 g.) was ground to a paste with sodium sulfide nonahydrate (5 g.), suspended in hot water, and maintained at 70–80° with stirring for 90 min. The 1-amino-4-(*o*-dichlorophenyl)anthraquinone was removed by filtration, washed with hot water, alcohol, and ether, and recrystallized from anisole to give brilliant red crystals, 2.1 g., 91%, m.p. 281–284°

Anal. Calcd. for $C_{20}H_{11}Cl_2NO_2$: Cl, 19.3; N, 3.8. Found: Cl, 19.4; N, 3.85

Similarly, 1-nitro-4-bromophenylanthraquinone (2 g.) was converted to 1-amino-4-bromophenylanthraquinone (1.8 g., 90%), m.p. 285–290°.

Anal. Calcd. for $C_{20}H_{12}BrNO_2$: C, 63.5; H, 3.2; N, 3.7 Found: C, 62.8; H, 3.1; N, 3.8.

(8) M. S. Whelen, U. S. Patent 2,100,527; *Chem. Abstr.*, **32**, 960 (1938).

(9) W. H. Beisler and L. W. Jones, *J. Am. Chem. Soc.*, **44**, 2304 (1922).

The Synthesis of 4′,5′-Diiodo-4-amino-fluorescein Iodine-131

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The method developed by Coons and colleagues[3] for labeling antibody proteins with fluorescein isocyanate has become a frequently used tool in immunology. Since Coons' original paper was published in 1942

(1) Regis Chemical Co., Chicago, Ill.

(2) Operated by the University of Chicago for the U. S. Atomic Energy Commission.

(3) A. H. Coons, H. J. Creech, R. N. Jones, and E. Berliner, *J. Immunol.*, **45**, 159 (1942).

several comprehensive reviews[4-6] and over 300 papers have appeared. It seemed desirable to extend the usefulness of the method by making a similar reagent which was adaptable to quantitative studies. The present work had been undertaken in order to prepare a fluorescein derivative that would couple with an antibody protein in the normal manner and be radioactive as well as fluorescent.

Nitro- and aminofluoresceins I and II were synthesized according to the standard method.[7-9] No attempt was made to determine the structure of these isomers until Borek[10a] carried out an infrared spectral study of the nitrofluoresceins and structurally related compounds. Borek concluded that the structure of nitrofluorescein I was 5-nitrofluorescein and that the II isomer was 4-nitrofluorescein. The ultraviolet spectra in this report (Table I) do not clearly differentiate between these designations. However, the nomenclature[11] used here is preferred over that used previously.[10]

TABLE I

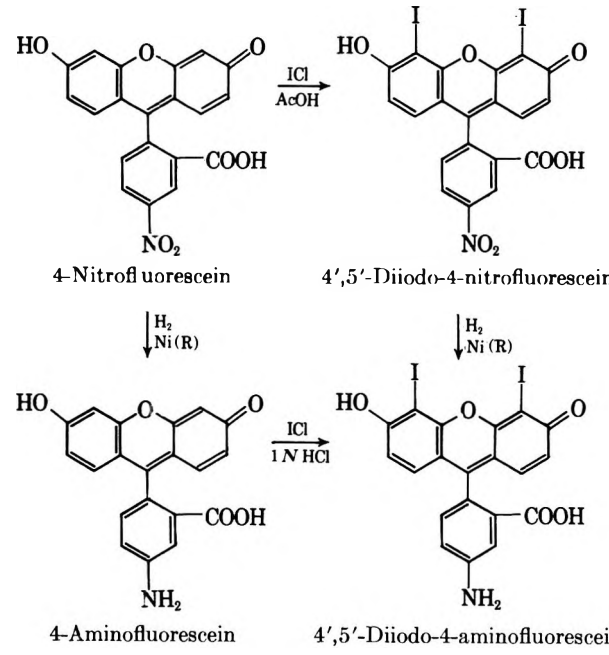
ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	λ, mμ	E_{max}
Fluorescein[b,c]	223	60,300
5-Nitrofluorescein (I)	222	68,200
4-Nitrofluorescein (II)	225	58,300
5-Aminofluorescein	222	60,000
4-Aminofluorescein	222	68,200
	285	20,600
5-Nitrofluorescein diacetate	219	70,000
4-Nitrofluorescein diacetate	218	65,500
4′,′5-Diiodo-4-aminofluorescein	205	42,800
	229	47,000
	290	22,300
4′,5′-Diiodo-4-nitrofluorescein diacetate	204	67,500
4′,5′-Diiodofluorescein[b]	204	52,000
	230	40,300

[a] Taken in ethyl alcohol from 200–400 mμ on a Beckman Model DK-1 recording spectrophotometer. [b] Eastman Kodak grade. [c] Previously reported by C. Hanna and W. T. Smith, *Proc. Iowa Acad. Sci.*, **58**, 251 (1951).

The unlabeled title compound was obtained quite readily by treating a solution of 4-aminofluorescein in 1 *N* hydrochloric acid with two equivalents of iodine monochloride. The immediate orange precipitate of 4′,5′-diiodo-4-aminofluorescein gave a reasonably acceptable elementary analysis and was used in subsequent iodide-131 exchange reactions. The radioactive 4′,5′-diiodo-4-aminofluorescein could then be converted to the corresponding isocyanate as needed and coupled with an antibody protein without isolation of the isocyanate.

A less satisfactory method was originally used in the preparation of this compound. In this series of reactions 4-nitrofluorescein was iodinated with iodine monochloride in acetic acid.[12,13] The crude 4′,5′-diiodo-4-nitrofluorescein was purified through the easily crystallized diacetate. Deacetylation followed by catalytic hydrogenation resulted in a 4′,5′-diiodo-4-aminofluorescein which was low in iodine. Under identical reduction conditions the iodines of 4′,5′-diiodofluorescein[14] were not affected.



The preference toward 4′,5′ substitution in fluorescein has been demonstrated effectively by previous workers.[15-18] In order to show that iodination with iodine monochloride in acidic media occurs in the 4′,5′-positions, fluorescein was treated with this reagent. Thin layer chromatography showed the main product to be identical with 4′,5′-diiodofluorescein obtained from a commercial source,[14] but several minor spots indicated impurities.[13]

The exchange reactions of sodium iodide-131 with 4′,5′-diiodo-4-aminofluorescein were accomplished in high radioactive yield by mixing the materials in acetic acid overnight (Table II). Warming was necessary to effect solution.

The mechanism of the exchange reaction with iodide-131 is uncertain. It has been reported[19] that iodine atoms and not iodide ions exchange into thyroxine and that only the iodides adjacent to the phenolic function exchange. It is possible that under our exchange conditions iodide ion was oxidized to iodine to catalyze the exchange with organic iodide adjacent to the

(4) A. H. Coons, "International Review of Cytology," Vol. 5, G. H. Bourne, Ed., Academic Press, Inc., New York, N. Y. 1955, pp. 1–23.

(5) E. H. Beutner, *Bacteriol. Rev.*, **25**, 49 (1961).

(6) A. H. Coons, *J. Immunol.*, **87**, 499 (1961).

(7) A. H. Coons and M. H. Kaplan, *J. Exptl. Med.*, **91**, 1 (1950).

(8) R. T. Bogert and R. G. Wright, *J. Am. Chem. Soc.*, **27**, 1310 (1905).

(9) It was found here that 4-nitrofluorescein diacetate exists in two crystalline forms. When crystallized from benzene the product had m.p. 194–196°, and from ethanol, m.p. 215–217°. Either form was readily converted to the other. The infrared spectra of these two forms were only slightly (in potassium bromide) different in the fingerprint region.

(10) (a) F. Borek, *J. Org. Chem.*, **26**, 1292 (1961); (b) R. M. McKinney, J. T. Spillane, and G. W. Pearle, *ibid.*, **27**, 3386 (1962).

(11) Nomenclature from "The Ring Index," RRI5935, Reinhold Publishing Co., New York, N. Y., 1961.

(12) G. Boyack, G. E. Moore, and D. F. Clausen [*Nucleonics*, **3**, 62 (1948)] treated fluorescein with iodine monochloride generated *in situ* from dichloramine T and potassium iodide-131 in acetic acid. No structural evidence was given for the positions of the iodines.

(13) A. Roe, R. L. Hayes, and H. D. Bruner [*J. Am. Chem. Soc.*, **73**, 4483 (1951)] repeated the work of Boyak, *et al.*,[12] but found that some chlorination as well as tri- and tetrahalogenation had occurred.

(14) The author would like to thank C. Kuimjiam of Distillation Products Industries for his comments on the iodination reactions and for a generous sample of 4′,5′-diiodofluorescein.

(15) R. B. Sandin and R. L. Orvis, *J. Org. Chem.*, **23**, 1235 (1958).

(16) W. R. Orndorf and A. J. Hemmer, *J. Am. Chem. Soc.*, **49**, 1272 (1927).

(17) M. A. Phillips, *J. Chem. Soc.*, 724 (1932).

(18) R. B. Sandin, A. Gillies, and S. C. Lynn, *J. Am. Chem. Soc.*, **61**, 2919 (1939).

(19) G. I. Gleason, *J. Biol. Chem.*, **213**, 837 (1955).

TABLE II

IODIDE-131 EXCHANGE REACTIONS

Reaction	1	2
4′,5′-Diiodo-4-amino-fluorescein	60 mg.	61 mg.
Acetic acid solvent	2.0 ml.	2.0 ml.
Sodium iodide-131 aqueous[a]	0.40 ml.	0.40 ml.
Initial activity[b]	4.36 mc.	6.02 mc.
Reaction conditions	8.5 hr. at 95–102°	19 hr. at 78–94°
Decay time[c]	46 hr.	29 hr.
Activity of product[d]	37 μc./mg.	88 μc./mg.
Per cent exchange	60%	99%

[a] Carrier free. [b] Activity at start of exchange reaction. [c] Time elapsed from start of exchange to time of counting. [d] Measured activity at time of counting.

phenolic function. However, it also is known[20–22] that halogenated quinones readily undergo nucleophilic displacement of their halogens. The organic iodide in our fluorescein has the character of an atom *ortho* to a quinoid as well as phenolic function, and the possibility of nucleophilic displacement by iodide-131 ion should not be dismissed.

Experimental[23]

4′,5′-Diiodo-4-nitrofluorescein.—A mixture of 1.00 g. of 4-nitrofluorescein, 894 mg. of iodine monochloride, and 25 ml. of glacial acetic acid was stirred for 5 hr. The original suspension of 4-nitrofluorescein gradually dissolved and a new orange solid precipitated. After standing overnight, 200 ml. of water was added and the precipitate became red. It was filtered, redissolved in cold 1 *N* sodium hydroxide, reprecipitated with acetic acid, collected, washed with water, and dried. The crude red 4′,5′-diiodo,4-nitrofluorescein, 1.56 g., had m.p. 228–240° dec. This crude product was purified somewhat through its diacetate.

Acetylation.—The crude 4′,5′-diiodo-4-nitrofluorescein was refluxed with sodium acetate in acetic anhydride for an hour. Working up the product with recrystallization from acetic anhydride gave 4′,5′-diiodo-4-nitrofluorescein diacetate as fine crystals with a slight yellow tinge, m.p. 296–298°.

Anal. Calcd. for $C_{24}H_{13}NO_9I_2$: C, 40.41; H, 1.84; I, 35.59. Found: C, 40.43; H, 1.96; I, 35.55.

Deacetylation.—A suspension of the above diacetate in a saturated solution of sodium hydroxide in 90% ethanol was stirred and warmed gently until all dissolved. Dilution with water and acidification with glacial acetic acid gave a purified 4′,5′-diiodo-4-nitrofluorescein monohydrate, m.p. 262–264° dec. On drying under vacuum at 110° this solid lost weight equivalent to an equimolar portion of water. On exposure to air the weight again gradually increased.

Anal. Calcd. for $C_{20}H_9NO_7I_2 \cdot H_2O$: C, 37.11; H, 1.71; I, 39.24. Found: C, 37.0; H, 1.38; I, 39.55.

4′,5′-Diiodo-4-aminofluorescein. A. Iodination of 4-Aminofluorescein in Hydrochloric Acid.—A warm solution of 470 mg. of iodine monochloride in 10 ml. of 1 *N* hydrochloric acid was added to a warm stirred solution of 501 mg. of 4-aminofluorescein in 60 ml. of 0.7 *N* hydrochloric acid. A solid precipitated immediately. The mixture was heated nearly to boiling and cooled, and the solid was collected, washed well with water, and dried. The bright orange 4′,5′-diiodo-4-aminofluorescein, 860 mg. (99%), m.p. 213–218° dec., gave a reasonable elemental analysis and was used in the exchange reactions.

Anal. Calcd. for $C_{20}H_{11}NO_5I_2$: C, 40.09; H, 1.85; I, 42.36. Found: C, 40.78; H, 2.03; I, 42.60.

B. Hydrogenation of 4′,5′-Diiodo-4-nitrofluorescein.—The hydrogenation of 286 mg. of purified 4′,5′-diiodo-4-nitrofluorescein was carried out in 10 ml. of ethanol at room temperature for 1 hr. using hydrogen at 53 p.s.i. and about 2 g. of Raney nickel catalyst. The catalyst was filtered, and the ethanol solution was reduced in volume by gentle heating in a stream of nitrogen. The addition of 100 ml. of water produced an unfilterable suspension which was extracted into ether. Evaporation gave 156 mg. of a crude bright orange 4′,5′-diiodo-4-aminofluorescein, m.p. 205–210° dec., which was low in iodine. Under identical conditions the iodines of 4′,5′-diiodofluorescein were not affected.

4′,5′-Diiodofluorescein.—A mixture of 3.32 g. of fluorescein and 3.24 g. of iodine monochloride in 25 ml. of glacial acetic acid was warmed to 115° for 1 min., cooled, and stirred for 8 hr. at room temperature. The solid was collected and washed successively with 10 ml. of acetic acid and 100 ml. of water. It was then suspended in acetone, collected, and dried giving 3.54 g. of crude orange 4′,5′-diiodofluorescein as a powder, m.p. 220–235°. An Eastman Kodak grade material had m.p. 247–250° dec. Thin layer chromatography on Merck silica gel G using methanol showed these compounds to be identical except for several minor spots in our product, which may be the chloride or other polyhalogenated material.[13] No purification of this product was attempted.

Exchange Reactions with Iodide-131.—The 4′,5′-diiodo-4-aminofluorescein was suspended in acetic acid in a centrifuge tube. Aqueous sodium iodide-131 was added and the mixture was stirred and heated to about 100° using a silicone bath. At this temperature nearly all of the solid dissolved. After the reaction time indicated in Table II, the mixture was cooled, diluted with water, and centrifuged. The solid was washed three times with water, then dried, and stored in a vacuum desiccator. There was no change in the melting point.

Acknowledgment.—The problem was suggested by Dr. Robert J. Hasterlik to whom the author is grateful for his encouragement. The author also would like to thank Mr. Robert Hart for doing the spectral studies, Mr. William Saschek of the University of Chicago Microanalytical Laboratory for the elemental analyses, and Mr. Leon Gortler for synthesizing the 4- and 5-nitrofluorescein diacetates. The generous and helpful comments, as well as the general assistance, of Dr. Weldon Brown of the Argonne National Laboratories also are appreciated.

(20) Ng. Ph. Buu-Hoi, R. Royer, and M. Hubert-Habart, *Rec. trav. chim.*, **73**, 188 (1954).

(21) A. Ya. Berlin and A. N. Makarova, *Zh. Obshch. Khim.*, **30**, 1380, 1582 (1960); *Chem. Abstr.*, **55**, 499, 1500 (1961).

(22) J. W. Hancock, C. E. Morrell, and D. Rhum, *Tetrahedron Letters*, 987 (1962).

(23) Melting points were taken on a calibrated Fischer-Johns hot-stage block.

The Reaction of Alkyl Borinates with α-Amino Acids

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Contribution No. 269 from the Central Research Laboratories, Minnesota Mining and Manufacturing Company, St. Paul 19, Minnesota

Received July 22, 1963

The stabilization of boron compounds through complex formation with amines is well-established. By this method the air-sensitive alkyl- or aryl-substituted boron derivatives can be transformed into stable solids. For instance, a diarylborinic acid readily condenses with ethanolamine or 8-hydroxyquinoline to form an internally stabilized compound.[1]

Formation of mixed anhydrides of borinic and amino acids also should result in stabilization. A recent British patent[2] disclosed that heating trialkylborines with amino acids produces this type of compound, but no examples were given for the triarylborines.

(1) (a) J. Douglass, *J. Org. Chem.*, **26**, 1312 (1961); (b) R. Letsinger and I. Skoog, *J. Am. Chem. Soc.*, **77**, 2491 (1955).

(2) K. Lang, F. Schubert, and K. Nutzel, British Patent 905,093 (September 5, 1962).

During the investigation of biologically active boron compounds in this laboratory, compounds such as 2-aminoacetic diphenylborinic anhydride were formed by heating butyl diphenylborinate with glycine.

$$(C_6H_5)_2BOC_4H_9 + H_2NCH_2COOH \longrightarrow (C_6H_5)_2BOC(=O)CH_2NH_2 + C_4H_9OH$$

The low-molecular weight amino acids, such as glycine, react well without a solvent. A solvent, such as toluene, is more convenient with the higher molecular weight, more soluble amino acids. The white solid products appear to be stable and have not undergone change on storage in air for 4 years. These anhydrides may be recrystallized from alcohol–water without change, but they react readily with ethanolamine to form 2-aminoethyl diphenylborinate.

Experimental

All melting points were obtained on a Fischer-Johns melting point apparatus and were corrected by comparison with standard compounds.

Reaction with Glycine.—A mixture of 0.50 g. (0.0067 mole) of glycine and 1.59 g. (0.0067 mole) of butyl diphenylborinate[3] was boiled and stirred for 5 min. The mixture became solid. Toluene (5 ml.) was added, and the mixture was boiled for a few minutes. After cooling, the solid was collected on a filter and was washed with ether. The anhydride was boiled with 25 ml. of distilled water and was collected on a filter after cooling, 0.82 g., m.p. 244–245°, 51% (based on butyl diphenylborinate). A 0.33-g. portion was dissolved in 5 ml. of 95% ethanol, filtered while hot, cooled, and recrystallized once more from ethanol to yield 0.13 g., m.p. 244–245°.

Anal. Calcd. for $C_{14}H_{14}O_2NB$: C, 70.4; H, 5.91; N, 5.86; mol. wt., 239. Found: C, 70.2; H, 6.0; N, 5.76; mol. wt., 241.

If the anhydride is heated with ethanolamine in alcohol–water solution, 2-aminoethyl diphenylborinate crystallizes upon cooling. The melting point and mixture melting point with 2-aminoethyl diphenylborinate were 187–189°.

If toluene is used as a solvent for this reaction, the insolubility of the glycine is a problem, and the yield is lowered.

Similar compounds were prepared from DL-alanine and L-leucine. These are summarized in Table I.

TABLE I

PREPARATION AND PROPERTIES OF $(C_6H_5)_2BOC(=O)CHR(NH_2)$

R	Solvent	Yield, %	M.p., °C.	—Analysis, % N— Calcd.	Found
—H	None	51	244–245	5.86	5.76
	Toluene	39			
—CH_3	None	57	231–232	5.54	5.52
—$CH_2CH(CH_3)_2$	Toluene	88	180–181	4.75	4.62

(3) Distilled from the ammonia complex, see ref. 1b.

Hydrolysis of Cysteamine S-Phosphate

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Received August 26, 1963

In a recent paper in this journal, Dittmer, Ramsay, and Spalding[1] reported on the hydrolysis of cysteamine S-phosphate [S-(2-aminoethyl)phosphorothioate] and they found two rate maxima of hydrolysis, at pH 2–3 and at pH 8–9. The rate of hydrolysis at pH 2–3 was found to be approximately four times as large as that at pH 8–9.

In an earlier paper by Åkerfeldt,[2] cysteamine S-phosphate was reported to have only one rate maximum, at pH 3. The rate profiles for fifteen other compounds containing the $-SPO_3^{-2}$ group also were investigated.[3,4] In all instances a single rate maximum was found and its position was in the pH range 2–4. It could be shown conclusively that the most easily hydrolyzable ionic species of all compounds studied was the mono-anion.[3,5]

In view of the finding by Dittmer, *et al.*,[1] of a second rate maximum at pH 8–9 in the case of cysteamine S-phosphate, a re-examination of the hydrolysis of this compound has been carried out. The investigation was performed (a) under experimental conditions practically identical with those used by Dittmer, *et al.*, and using the same analytical procedure as these authors, (b) using the same technique of hydrolysis as in a but using the analytical procedure of Gomori,[6] and (c) using a low ionic strength incubation medium combined with the analytical procedure of Gomori.[6]

The results obtained with a 99% pure preparation of cysteamine S-phosphate (4.0 mmolar) showed practically the same low rate of hydrolysis at pH 7.0, 8.0, and 9.0. The first-order rate of hydrolysis constants at 35.0° were $k_{obsb} = (2.0 \pm 0.2) \times 10^{-5}$ sec.$^{-1}$ at ionic strength of 0.1 *M*, and $k_{obsb} = (1.0 \pm 0.2) \times 10^{-5}$ sec.$^{-1}$ at ionic strength of 1 *M*. The existence of a rate maximum from pH 8–9 has thus not been confirmed.

Dittmer, *et al.*, found at 37° and 1 *M* ionic strength the following rate constants (sec.$^{-1}$): 3.8×10^{-5} (pH 7.02), 13.1×10^{-5} (pH 8.06), and 9.9×10^{-5} (pH 9.08).

The rate constants reported in the present communication are thus lower than those found by Dittmer, *et al.* This implies the presence of an impurity in their preparation of cysteamine S-phosphate, which is the likely explanation for the observed rate increase at pH 8–9.

(1) D. C. Dittmer, O. B. Ramsay, and R. E. Spalding, *J. Org. Chem.*, **28**, 1273 (1963).

(2) S. Åkerfeldt, *Acta Chem. Scand.*, **14**, 1980 (1960).
(3) S. Åkerfeldt, *ibid.*, **15**, 575 (1961).
(4) S. Åkerfeldt, *ibid.*, **17**, 319 (1963).
(5) S. Åkerfeldt, *Svensk Kem. Tidskr.*, **75**, 231 (1963).
(6) G. Gomori, *J. Lab. Clin. Med.*, **27**, 955 (1942).

The Influence of Dicyclohexylcarbodiimide Concentration on the Rate of Phospho Diester Bond Formation

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Received August 14, 1963

Dicyclohexylcarbodiimide (DCC) has proven to be an efficient condensing agent for the synthesis of phos-

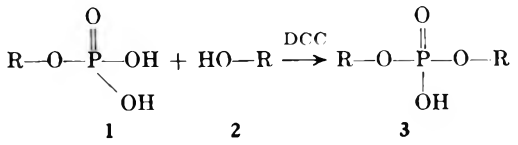
(1) Medical Research Associate, Medical Research Council of Canada. This work has been supported by the U. S. Public Health Grant C-5342.

TABLE I

THE PER CENT OF THE OPTICAL DENSITY[a]

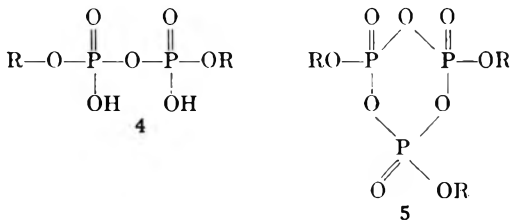
Molar ratio of pT–DDC	1:13 (146 mg. of DCC)			1:65 (731 mg. of DCC)			1:260 (2927 mg. of DCC)		
Reaction products	% pT	% $(pT)_2$	% CEpT	% pT	% $(pT)_2$	% CEpT	% pT	% $(pT)_2$	% CEpT
Time, hr.									
0.5	17	65	20	14	30	56	11	5	84
1	10	54	36	7	9	84	3	2	95
4	6	14	80	1	3	96		3	97
12	1	4	95		2	98		1	99
25	1	2	97		3	97		2	98

[a] At 267 mμ found in thymidylic acid (pT), dithymidine pyrophosphate $(pT)_2$, and the cyanoethyl ester of pT (CEpT) when 0.055 mmole of pT reacted with hydracrylonitrile (5.75 mmoles) in the presence of DCC.



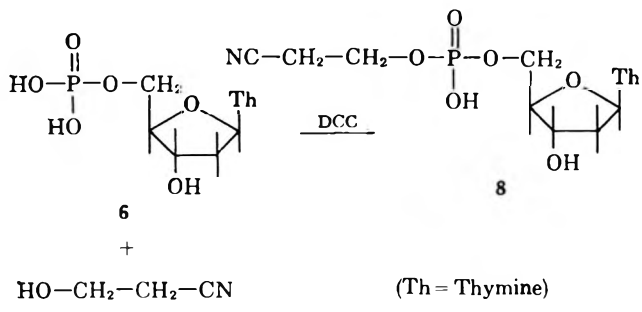
pho diesters (3) from a monoalkyl phosphate (1) and an alcohol (2).[2]

Recently, possible mechanisms for this reaction were suggested.[3,4] The work of Weimann and Khorana[3] showed that 1 reacts rapidly with DCC by way of the pyrophosphate (4) to form a trialkyl trimetaphosphate (5) which is apparently the initial phosphorylating species. Its formation is complete within a few minutes but formation of the phospho diester is a much slower process.



We now wish to report that the rate of phospho diester bond formation also depends on the concentration of DCC, a fact which would suggest that either a second mechanism must be involved or loss of the metaphosphate (5) by anhydride exchange reactions is prevented. The role played by the change in the dielectric constant of the solution in this process is not known. However, for synthetic purposes it is sufficient to note that a large excess of DCC completes the esterification reaction in a short time.

The reaction studied was the esterification of thymidine-5′ phosphate (6, pT) with hydracrylonitrile (7) to form the β-cyanoethyl ester (8, CEpT). The amount of this ester formed as a function of time and DCC concentration was followed chromatographically. The results shown in Table I demonstrate that the esterification was 95% complete after 1 hr. when thymidylic acid and DCC are present in a molar ratio of 1:280, whereas with a lesser ratio (1:13) it had gone only 36%.



In this reaction, the activated intermediates which undergo the nucleophilic attack by the alcohol cannot be only the DCC adduct[5] of pT but also must include poly- or metaphosphates as well. This statement is supported by the finding that dithymidine pyrophosphate $(pT)_2$ is not only isolated after hydrolysis of the reaction mixture at intermediate stages but also serves almost as well as a starting material. The results of these latter studies are shown in Table II. They are similar to those in Table I in that the reaction proceeds faster with higher concentrations of DCC and after an hour is almost complete. It should be noted, however, that the ratio of products, particularly at the short time intervals, is very different in the two cases.

TABLE II

THE PER CENT OF THE OPTICAL DENSITY[a]

Molar ratio of $(pT)_2$–DCC	1:55 (146 mg. of DCC)			1:550 (1460 mg. of DCC)		
Reaction products	% pT	% $(pT)_2$	% CEpT	% pT	% $(pT)_2$	% CEpT
Time, hr.						
0.5	8	73	19	11	18	71
1	6	47	47	4	4	92
4	1	18	81	.5	1.5	98
12		3	97		1	99
25		4	96		1	99

[a] At 267 mμ found in pT, $(pT)_2$, and CEpT when 0.013 mmole of $(pT)_2$ reacted with hydracrylonitrile (5.75 mmoles) in the presence of DCC.

Experimental

Synthesis of β-Cyanoethylthymidine-5′ Phosphate. A. From Thymidine-5′ Phosphate.—Three reactions mixtures were prepared by the following method. A solution containing 0.055 mmole of thymidylic acid in 1 ml. of water and 10 ml. of pyridine was concentrated to dryness. The residue was dissolved in 10 ml. of anhydrous pyridine and again concentrated to dryness. The residue was then dissolved in 5 ml. of anhydrous pyridine and 0.385 ml. (5.75 mmoles) of hydracrylonitrile. DCC was added to give the desired ratio of nucleotide to DCC (146 mg. of DCC for 1:13 ratio, 731 mg. of DCC for the 1:65 ratio, and 2927 mg. for the 1:260 ratio). The reaction was allowed to proceed at room temperature under anhydrous conditions. Aliquots of 0.5 ml. were removed from each reaction mixture at various time intervals and added to 0.5 ml. of water. After 1 hr., these solutions were extracted with three 5-ml. portions of ether and

(2) P. T. Gilham and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6212 (1958).
(3) G. Weimann and H. G. Khorana, *ibid.*, **84**, 4329 (1962).
(4) A. R. Todd, *Proc. Natl. Acad. Sci. U. S.*, **45**, 1389 (1959); *Proc. Chem. Soc.* (London), 187 (1961).
(5) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958).

the aqueous phase filtered to remove dicyclohexylurea. Samples were spotted onto Whatman No. 40 paper along with standards of thymidylic acid (R_f 0.12), dithymidine pyrophosphate (R_f 0.24), and β-cyanoethylthymidine-5′ phosphate (R_f 0.55) and chromatographed in isopropyl alcohol–water–concentrated ammonium hydroxide (7:2:1). The products were visualized under ultraviolet light and the areas containing the products cut out and eluted with 5 ml. of water. Not more than three components were found in each aliquot. Quantititive data (Table I) were obtained by comparing the ultraviolet absorption of each of these solutions at 267 mμ and the results expressed as the per cent of the component (in terms of its absorption) in the aliquot.

B. From Dithymidine Pyrophosphate.—Similar esterification reactions were carried out using 0.013 mmole of dithymidine pyrophosphate, 5.75 mmoles of hydracrylonitrile, 5 ml. of anhydrous pyridine, and either 146 mg. or 1460 mg. of DCC. The reaction was treated as in A with the results shown in Table II.

Condensation of Aromatic Aldehydes with Acetone-1,3-bis(triphenylphosphonium) Chloride in the Presence of Base[1]

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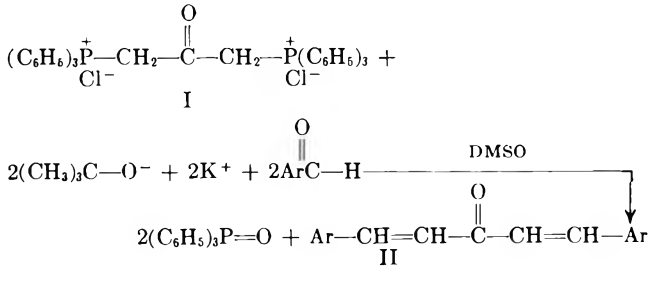
Received August 12, 1963

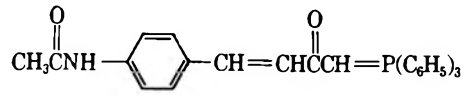
Recently Ford and Wilson[4] have reported that acetone-1,3-bis(triphenylphosphonium) chloride (I) does not give a stable mono- or diylide derived directly from I when treated with aqueous sodium carbonate, but rather undergoes hydrolysis to give triphenylphosphine oxide and acetylmethylenetriphenylphosphorane.

As part of other studies in this laboratory, I was prepared and allowed to react with butyllithium in ether. Reaction of the deeply colored solution with benzaldehyde gave dibenzalacetone.[5] These results indicated that ylide formation from I was possible and that a Wittig reaction could be effected.



It has now been found that I (1 mole) will react with aromatic aldehydes (2 moles) and 2 moles of potassium *t*-butoxide in dimethyl sulfoxide or 2 moles of sodium ethoxide in ethanol to give substituted dibenzalacetones (II). The potassium *t*-butoxide–dimethyl sulfoxide system was found to be the most synthetically useful. The yields of symmetrically substituted dibenzalacetones were di-*m*-nitro, 48%, di-*p*-chloro, 76%, and di-*p*-methoxy, 37%. It also was found that unsymmetrically substituted dibenzalacetones could be prepared if 1 mole of potassium *t*-butoxide and 1 mole of aldehyde were allowed to react with I followed by addition of another mole of base and a mole of another aldehyde. By this technique the mono-*m*-nitro compound was prepared in 57% yield and the *p*-chloro-*m*-nitro compound was prepared in 67% yield.

An attempt to condense I with 2 moles of *p*-acetamidobenzaldehyde and 2 moles of potassium *t*-butoxide gave no compound corresponding to II. There was isolated the phosphorane (III). Attempts to effect the reaction under more strenuous conditions were not undertaken.



III

Experimental[6]

Preparation of Acetone-1,3-bis(triphenylphosphonium) Chloride (I).—A mixture of 21.3 g. (0.168 mole) of 1,3-dichloroacetone, 112.5 g. (0.43 mole) of triphenylphosphine, and 225 ml. of chloroform was stirred under reflux for 20 hr. The cooled reaction mixture was treated with 150 ml. of dry ether. The precipitate was washed with 100 ml. of ether–chloroform (1:1.5) and dried *in vacuo* to give 103 g. of product. This material was further purified by dissolving it in 400 ml. of warm chloroform followed by precipitation with 300 ml. of dry ether. There was obtained 98 g. (86%) of I, m.p. 260–261, lit.[4] m.p. 266–267°.

Preparation of 1,5-Bis(*m*-nitrophenyl)penta-1,4-dien-3-one.—Sodium ethoxide solution (1.37 *N*, 14.5 ml., 0.02 mole) was added with stirring to a mixture of 5.98 g. (0.01 mole) of I and 3.02 g. (0.02 mole) of *m*-nitrobenzaldehyde. After stirring for 3 hr. at 30°, the precipitate was collected, washed with two 15-ml. portions of ethanol and water, and dried to give 1.4 g. (43%) of bis-*m*-nitrobenzalacetone, m.p. 238–241°, lit.[7] m.p. 238°. The infrared spectrum was commensurate with the assigned structure.

Preparation of 1,5-Bis(*p*-chlorophenyl)penta-1,4-dien-3-one.—A mixture of 2.24 g. (0.02 mole) of potassium *t*-butoxide, 5.98 g. (0.01 mole) of I, and 40 ml. of dimethyl sulfoxide was stirred under nitrogen at room temperature for 1 hr. The resulting solution was treated with 2.81 g. (0.02 mole) of *p*-chlorobenzaldehyde in 10 ml. of dimethyl sulfoxide. The mixture was warmed at 40° for 7 hr. The precipitate which formed after cooling was collected and washed with 5-ml. portions of ethanol and water. There was obtained 2.3 g. (76%) of material, m.p. 193–195°, lit.[8] m.p. 193–194°. The infrared spectrum was commensurate with the assigned structure.

Similarly 1,5-bis(*p*-methoxyphenyl)-1,4-dien-3-one was prepared in 37% yield, m.p. 123–125°, lit.[9] m.p. 125°. The infrared spectrum of this compound agreed with that predicted.

Preparation of 1-*m*-Nitrophenyl-5-phenylpenta-1,4-dien-3-one.—A mixture of 1.12 g. (0.01 mole) of potassium *t*-butoxide, 5.89 g. (0.01 mole) of I in 25 ml. of dimethyl sulfoxide was stirred for 1 hr. under nitrogen. There was added 1.06 g. (0.01 mole) of benzaldehyde and the mixture was warmed at 45° for 2 hr. This mixture was cooled and treated with 1.12 g. (0.01 mole) of potassium *t*-butoxide, and after stirring at 45° for 15 min. 1.51 g. (0.01 mole) of *m*-nitrobenzaldehyde in 15 ml. of dimethyl sulfoxide was added. The mixture was heated at 50° for 3 hr. and then cooled. The precipitate (inorganic salt) which formed on cooling was filtered and discarded. The filtrate was treated with 30 ml. of water and the crystals were collected to give 1.6 g. (57%) of material, m.p. 138–141°. A portion was recrystallized twice from ethanol, m.p. 142–143°, lit.[10] m.p. 140°.

Anal. Calcd. for $C_{17}H_{13}O_3N$: C, 73.20; H, 4.67. Found: C, 72.99; H, 4.89.

(1) Research supported by the National Science Foundation.

(2) Rutgers Research Council Faculty Fellow, 1963–1964.

(3) Recipient of an American Cyanamid Junior Educational Award, 1961–1963.

(4) J. A. Ford and C. V. Wilson, *J. Org. Chem.*, **26**, 1433 (1961)

(5) Unpublished results of C. Dennis Hall.

(6) All melting points are uncorrected. Analyses were by G. Robertson, Florham Park, N. J.

(7) P. Pfeiffer and B. Segal, *Ann.*, **460**, 131 (1928).

(8) R. E. Lutz and T. A. Martin, *J. Org. Chem.*, **14**, 286 (1949)

(9) G. V. Austerweil and R. Polland, *J. Appl. Chem.* (London), **5**, 213 (1955).

(10) H. Kauffmann and H. Burkhardt, *Ber.*, **46**, 3808 (1914).

Similarly 1-*p*-chlorophenyl-5-*m*-nitrophenylpenta-1,4-dien-3-one was prepared in 67% yield, m.p. 160°.

Anal. Calcd. for $C_{17}H_{12}NO_3Cl$: C, 65.00; H, 3.82. Found: C, 65.31; H, 4.05.

The infrared spectrum was in accord with the assigned structure.

Preparation of *p*-Acetamidocinnamoylmethylenetriphenylphosphorane (III).—A mixture of 2.24 g. (0.02 mole) of potassium *t*-butoxide, 5.89 g. (0.01 mole) of I, and 40 ml. of dimethyl sulfoxide was stirred under nitrogen at 40° for 2 hr. There was added 3.60 g. (0.022 mole) of *p*-acetamidehenzaldehyde in 13 ml. of dimethyl sulfoxide. The mixture was heated at *ca.* 46° for 8 hr. After cooling, the precipitate was collected to give 3.0 g. of material, m.p. 269–271. Titration with perchloric acid gave equiv. wt., 487; calculated for III, 476.[11] Two crystallizations from acetic acid gave material, m.p. 273–274°.

Anal. Calcd. for $C_{30}H_{26}O_2NP$: C, 77.75; H, 5.62; N, 3.10. Found: C, 77.32; H, 5.86; N, 2.98.

The infrared spectrum had N–H and amide carbonyl absorptions. The material gave a positive test for phosphorus.[12]

(11) S. T. Ross and D. B. Denney, *Anal. Chem.*, **32**, 1896 (1960).

(12) A. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Ed., Longmans Green and Co., London, 1957, p. 1043.

The Cyclization of N-Phenylcinnamamides to 3,4-Dihydro-4-phenylcarbostyrils with Polyphosphoric Acid[1]

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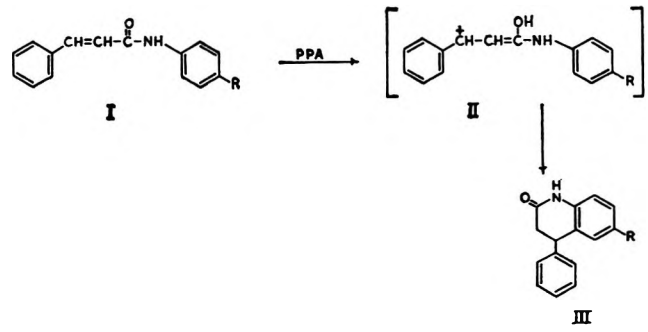
Received August 15, 1963

Recently, Koo[2] has reported the cyclization of 3-anilinopropionic acids to 4-keto-1,2,3,4-tetrahydroquinolines using polyphosphoric acid. A convenient preparation of 2-keto-1,2,3,4-tetrahydroquinolines (3,4-dihydrocarbostyrils) was observed by us sometime ago in the preparation of a series of substituted materials for pharmacological evaluation. The procedure reported here is analogous to the cyclization of 3-halopropionanilides[3] to 3,4-dihydrocarbostyrils in which typical Friedel–Crafts conditions using aluminum chloride were employed.



phenylcinnamamides were prepared. It was found that the amides could readily be cyclized with polyphosphoric acid to 3,4-dihydro-4-phenyl-6-substituted carbostyrils. N-(*p*-Nitrophenyl)cinnamamide could not be cyclized in polyphosphoric acid at reaction temperatures as high as 180°. In this case, the starting amide was recovered almost quantitatively. The parent amide and the *p*-substituted amides were prepared in benzene solution by reacting cinnamoyl chloride with the desired aniline derivative. The cyclization procedure described in the Experimental was typical and appears quite general for amides which do not have strong electron-deactivating groups on the aromatic ring. The structure of the lactams was confirmed in each case by examination of the infrared spectral characteristics, namely, by the absence of the α,β-unsaturated linkages in conjugation with the amide carbonyl and the amide II linkage of secondary amides which is generally absent in lactams. In the case of the known parent compound of the series, 3,4-dihydro-4-phenylcarbostyril, identity was established by both its characteristic spectrum and mixture melting point determination. The yields and physical properties of the substituted dihydrocarbostyrils are summarized in Table I.

It also should be noted that both N-phenylcrotonamide and N-(*p*-methoxyphenyl)crotonamide could not be cyclized to the 3,4-dihydro-4-methylcarbostyrils by this technique, thus presently limiting the synthetic applicability of this method to 4-phenyl-substituted carbostyrils. Apparently this failure is due to the instability of the intermediate alkyl carbonium ion.

TABLE I

SUMMARY OF N-PHENYL-α,β-UNSATURATED AMIDE CYCLIZATIONS

			Analysis, %					
			Calcd.			Found		
R	Yield, %	M.p., °C.	C	H	N	C	H	N
H	94	177–178[a]						
Br	83	188–190	59.62	4.00	4.63	59.40	3.79	4.50
CH_3	83	164–165	80.98	6.37	5.90	81.22	6.51	5.93
OCH_3	90	110–111	75.86	5.96	5.53	75.84	5.72	5.29

[a] Ref. 4 reports 177–178°.

It was reasoned that N-phenylcinnamamide (I) should readily protonate in hot polyphosphoric acid to give an intermediate (II) capable of undergoing a Friedel–Crafts cyclization to 3,4-dihydro-4-phenylcarbostyril (III). In an effort to confirm this proposal and to evaluate the synthetic value and general applicability of the reaction, a series of N-(4-substituted)

Experimental

All melting points are corrected. The infrared comparisons were determined on the solid samples in potassium bromide wafers using a Beckman IR-5A infrared spectrophotometer.

3,4-Dihydro-4-phenylcarbostyril.—A mixture of 1.00 g. of N-phenylcinnamamide and 20 g. of polyphosphoric acid was heated to 120°. After 10 min., the reaction mixture was cooled and hydrolyzed over crushed ice. The reaction products were ex-

(1) This work was supported by the Division of Neurological Disease and Blindness, National Institutes of Health under Grant No. NB-03628.

(2) J. Koo, *J. Org. Chem.*, **28**, 1134 (1963).

(3) F. Mayer, L. van Zutphen, and M. Philippa, *Ber.*, **60**, 858 (1927).

tracted with three 125-ml. portions of chloroform. The extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield, after two recrystallizations from ethanol–water, 0.94 g. (94%) of 3,4-dihydro-4-phenylcarbostyril, m.p. 177–178°, lit.[4] m.p. 177–178°.

(4) E. F. M. Stephenson, *J. Chem. Soc.*, 2557 (1956).

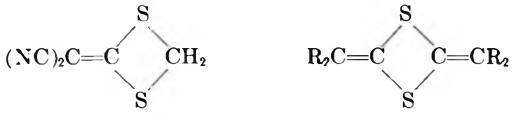
Dicyanomethylene-1,3-dithietane

D. C. DITTMER, H. E. SIMMONS, AND R. D. VEST

Contribution No. 880 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware

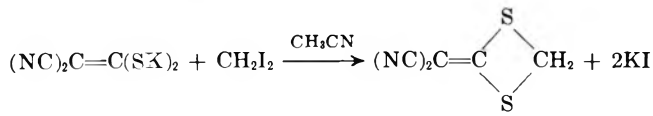
Received August 22, 1963

Dicyanomethylene-1,3-dithietane (I) is akin to the desaurins (II)[1] but differs from them in having only one exocyclic methylene group and in being much more reactive.



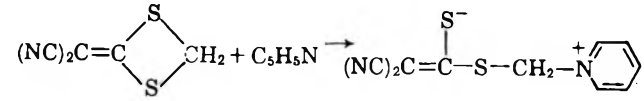
I II

This new dithietane is prepared in yields of 65% from dipotassio-1,1-dimercapto-2,2-dicyanoethylene and excess diiodomethane in refluxing acetonitrile. These conditions are similar to those used in the preparation of simple dialkyl derivatives.[2] The dithietane must be handled with great care because it causes severe itching and skin lesions.



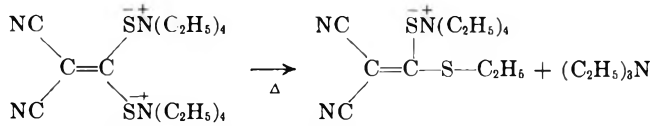
Conceivably, the methylene hydrogens of I might be acidic, especially since a 6-π-electron system could result on loss of a proton. In accordance with this hypothesis, a nearly quantitative yield of hydrogen is obtained when I reacts with sodium hydride in dimethoxyethane; however, dithietane was not recovered upon acidification. A stable sodium salt could not be isolated nor could any alkylation products be observed under these conditions. No deuterium exchange occurred when dithietane was heated in refluxing deuterium oxide. It appears that the anion of I forms only with strong base and, if it possesses unusual stability,[3] it is at the same time very reactive.

Ring-Opening with Pyridine.—The ring itself proved to be remarkably labile, being opened by nucleophilic reagents.[4] When the dithietane in hot benzene is treated with pyridine, the initially clear solution rapidly

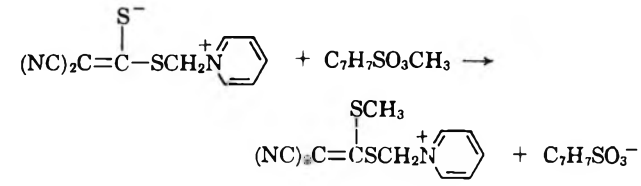


becomes turbid, and a pyridinium zwitterion is obtained in 80% yield.

Elemental analysis, molecular weight, proton magnetic resonance, and ultraviolet spectral data were in agreement with the zwitterion structure. The ultraviolet spectrum of the pyridinium zwitterion, λ_{max} 338 mμ (ϵ 19,300) and 263 (9860), compares favorably with that of tetraethylammonium 2,2-dicyano-1-ethylthioethylene-1-thiolate, λ_{max} 342 mμ (ϵ 21,800) and 285 (10,000), prepared by the pyrolysis of bis(tetraethylammonium) 2,2-dicyanoethylene-1,1-dithiolate.

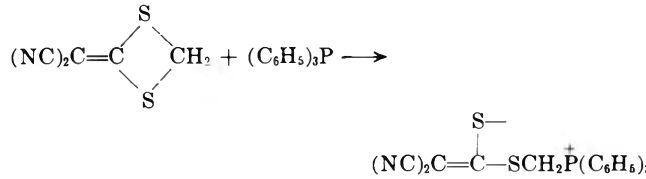


Treatment of the pyridinium zwitterion with methyl *p*-toluenesulfonate gave an S-methyl derivative whose ultraviolet spectrum is virtually identical with that of



1,1-dicyano-2,2-bis(methylthio)ethylene when allowance is made for the pyridinium and *p*-toluenesulfonate absorptions.

Ring-Opening with Triphenylphosphine.—Triphenylphosphine does not remove sulfur from the dithietane ring as it does readily with episulfides[5] and slowly with thietanes.[6] The reaction of I with triphenylphosphine opens the dithietane ring to give a phosphonium zwitterion. No reaction was observed with the weaker nucleophile triphenylarsine. Elemental analysis, molecular weight determination, and spectral data again supported the zwitterionic structure.



Experimental

Dipotassio-1,1-dimercapto-2,2-dicyanoethylene was prepared from carbon disulfide, malononitrile, and 2 moles of potassium hydroxide.[7] The salt was prepared earlier by Kendall and Edwards but was not isolated.[2]

Bis(tetraethylammonium) 2,2-Dicyanoethylene-1,1-dithiolate.—Dipotassio-1,1-dimercapto-2,2-dicyanoethylene (56 g., 0.26 mole) was dissolved in 290 ml. of methanol. Tetraethylammonium chloride (100 g., 0.6 mole) in 135 ml. of methanol was added. The reaction mixture was stirred for 15 min. and filtered to remove 31 g. of potassium chloride. The filtrate was evaporated on a rotary evaporator, and the yellow solid which remained was dried in a vacuum oven at 50° (18 mm.). The crude tetraethyl-

(1) P. Yates and D. R. Moore, *J. Am. Chem. Soc.*, **80**, 5577 (1958), references cited therein; A. Schönberg, L. Vargha, and H. Kaltschmitt, *Ber.*, **64**, 2581 (1931); A. Schönberg, A. Stephenson, H. Kaltschmitt, E. Petersen, and H. Schulten, *ibid.*, **66**, 243 (1933).

(2) H. D. Edwards and J. D. Kendall, U. S. Patents 2,533,233 and 2,493,071 (1953).

(3) The methylene protons in the diethylmercaptal of formaldehyde are acidic enough to give an anion which can be alkylated: J. F. Arens, M. Frohling, and A. Frohling, *Rec. trav. chim.*, **78**, 663 (1959).

(4) Cyclic acetals of dicyanoketene are attacked by nucleophilic reagents to give ring-opened products: W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2788 (1958).

(5) R. E. Davis, *J. Org. Chem.*, **23**, 1767 (1958); C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 282 (1949).

(6) S. M. Kotin, Ph.D. thesis, University of Pennsylvania, 1963.

(7) W. R. Hatchard, to be published.

ammonium salt (109 g.) recrystallized from ethanol–tetrahydrofuran as yellow crystals, m.p. 180° dec.

Anal. Calcd. for $C_{20}H_{40}N_4S_2$: C, 59.94; H, 10.06; N, 13.98; S, 16.01. Found: C, 60.47; H, 10.14; N, 14.12; S, 16.26.

The ultraviolet spectrum in ethanol had absorption at 340 mμ (ε 21,300) and 272 (14,500). The infrared spectrum had absorption at 2160, 2140, 2050, and 1440 cm.$^{-1}$.

Tetraethylammonium 2,2-Dicyano-1-ethylthioethylene-1-thiolate.—Bis(tetraethylammonium) 2,2-dicyanoethylene-1,1-dithiolate (20.0 g., 0.05 mole) was heated to 180° (20 mm.) in a flask connected to a trap cooled to −80°. The triethylamine evolved was collected and converted to its hydrochloride, m.p. 254–256°, in 95% yield (6.5 g.). The pyrolysis residue crystallized on cooling and was recrystallized from methanol as yellow crystals, m.p. 52–54°, in 85% yield (13.55 g.). The ultraviolet spectrum had absorption at 342 mμ (ε 21,800) and 285 (10,000).

Anal. Calcd. for $C_{14}H_{25}N_2S_2$: N, 15.38. Found: N, 15.43.

The salt was readily converted to known 1,1-dicyano-2,2-bis(ethylthio)ethylene,[2] with ethyl bromide in ethyl acetate.

Dicyanomethylene-1,3-dithietane.—Dipotassio-1,1-dimercapto-2,2-dicyanoethylene (109 g., 0.5 mole) was suspended in 1 l. of acetonitrile (Union Carbide commercial grade, not dried). Diiodomethane (267 g., 1.0 mole) was added, and the reaction mixture was stirred vigorously with a mechanical stirrer and was refluxed for 23 hr. A gray solid (136 g.), presumably potassium iodide, was separated by filtration from the dark brown solution. The acetonitrile filtrate was evaporated on a rotary evaporator. Then the residue was extracted with 500 ml. of water to remove any potassium iodide and was dissolved in about 1 l. of hot benzene. The brown benzene solution was partly decolorized with charcoal and a filter aid (Celite). Yellow-brown crystals, m.p. 145–149° (49.9 g., 65%), were obtained when the benzene solution was concentrated and cooled. Additional crystals, m.p. 146–150° (8.5 g.), were obtained by concentration of the mother liquors. The product can be purified further by sublimation, which is tedious, or by recrystallization from benzene or benzene–hexane. The infrared spectrum had absorptions at 3058, 2976, 1493, and 1425 cm.$^{-1}$, and the ultraviolet spectrum exhibited maxima at 303 mμ (ε 15,500) and 253 (5100).

Bis(tetraethylammonium) 2,2-dicyanoethylene-1,1-dithiolate could be used instead of the dipotassium salt, but the yields were not improved.

The dithietane is soluble at room temperature in glacial acetic acid, chloroform, dichloromethane, dimethyl sulfoxide, acetonitrile, dioxane, dimethylformamide, and acetone. It is somewhat less soluble in benzene, ethanol, methanol, water, and ethyl acetate and is insoluble in carbon tetrachloride, hexane, ether, and carbon disulfide.

Anal. Calcd. for $C_5H_2N_2S_2$: C, 38.93; H, 1.31; S, 41.58; mol. wt., 154. Found: C, 38.83; H, 1.55; S, 41.18; mol. wt., 166.

1,1-Dicyano-2-(S,N-methylpyridinium)mercaptoethylene-2-thiolate.—Pyridine (12 g., 0.15 mole) was added to a solution of dicyanomethylene-1,3-dithietane (7.7 g., 0.5 mole) in 150 ml. of hot benzene. The clear solution became turbid within 5 min. and was refluxed for 22 hr. At the end of this time there was considerable solid in the flask, and the solution was dark brown. The solid was removed by filtration and washed with benzene. The yield was 9.4 g. (81%). The tan solid was recrystallized three times from water–acetonitrile to give white to pale yellow crystals, m.p. 193–194° dec.

Anal. Calcd. for $C_{10}H_7N_3S_2$: C, 51.48; H, 3.03; N, 18.04; S, 27.49; mol. wt., 233. Found: C, 51.79; H, 3.06; N, 18.02; S, 27.86; mol. wt. (boiling point elevation of acetone), 235 and 250.

The infrared spectrum had absorption at 2260, 2240, 1650, and 1500 cm.$^{-1}$. The ultraviolet spectrum in acetonitrile showed absorption at 338 mμ (ε 19,300) and 263 (9860). The proton magnetic resonance spectrum in dimethyl sulfoxide (60 Mc., tetramethylsilane as internal reference) showed absorption at 455, 420, 395, and 294 c.p.s. The ratio of the total area of absorption at 455, 420, and 395 c.p.s. to the area of the absorption at 294 c.p.s. was 5:2.

The pyridinium zwitterion was soluble in dimethyl sulfoxide, acetonitrile, dimethylformamide, hot acetic acid, and hot methanol. It had low solubility in ethanol, benzene, chloroform, dioxane, tetrahydrofuran and carbon tetrachloride. A deep wine red color develops when the zwitterion in dimethyl sulfoxide is treated with basic reagents such as sodium carbonate, sodium methoxide, or sodium azide. It is not clear whether this color is due to the anion formed by removing a methylene proton or to a thiophene derivative formed by cyclization.[8]

1,1-Dicyano-2(S,N-methylpyridinium)mercapto-2-methylmercaptoethylene *p*-Toluenesulfonate.—The pyridinium zwitterion (6.9 g., 0.03 mole) was heated with 25 ml. of methyl *p*-toluenesulfonate. After about 12 hr. a buff solid (9.8 g.) was removed by filtration and washed with benzene. It was recrystallized three times from acetonitrile to yield white crystals, m.p. 175.6–176.0°.

Anal. Calcd. for $C_{18}H_{17}N_3O_3S_2$: C, 51.53; H, 4.09; N, 10.02; S, 22.93. Found: C, 51.79; H, 4.19; N, 10.18; S, 22.94.

The infrared spectrum had absorption at 2200, 1650, 1500 cm.$^{-1}$. The ultraviolet spectrum in acetonitrile had absorption at 332 mμ (ε 11,500), 263 (5770), and 219 (9860). The ultraviolet spectrum of 1,1-dicyano-2,2-bis(methylthio)ethylene had maxima at 330 mμ (ε 13,300), 290 (6850), and 220 (2995).

The proton magnetic resonance spectrum in deuterium oxide (60 Mc., tetramethylsilane as internal reference) showed a complex multiplet, poorly resolved, centered at 495, a singlet at 386, and two singlets at 183 and 172 c.p.s. The relative areas were, respectively, 9:2:3:3.

The compound was soluble in water and partially soluble in acetonitrile, ethanol, and chloroform. It was insoluble in methylene chloride and dioxane.

1,1-Dicyano-2-(S-methyltriphenylphosphonium)mercaptoethylene-2-thiolate.—Dicyanomethylene-1,3-dithietane (15.4 g., 0.10 mole) was dissolved in 350 ml. of hot benzene, and triphenylphosphine (34.3 g., 0.15 mole) in 150 ml. of benzene was added in one portion. Within 2 min. the clear solution became turbid and was refluxed for 20 min. The tan solid (27.4 g., 66%) was removed by filtration and washed three times with benzene. The filtrate was returned to the reaction flask and refluxed for 6 hr. more to give an additional 9.7 g. of tan solid. The over-all yield of crude material, m.p. 245–246° dec., was 89%.

The solid was recrystallized from acetonitrile as nearly white crystals, m.p. 245–246° dec. The crystals darkened above 230°.

Anal. Calcd. for $C_{23}H_{17}N_2PS_2$: C, 66.32; H, 4.12; N, 6.73; S, 15.40; P, 7.45; mol. wt., 417. Found: C, 66.62; H, 4.23; N, 6.59; S, 15.85; P, 7.60; mol. wt. (boiling point elevation of acetone), 465 and 483.

The infrared spectrum had absorption at 2200, 2180, 1575, and 1490 cm.$^{-1}$. The ultraviolet spectrum in acetonitrile had maxima at 342 mμ (ε 18,300) and 275 (9940). The proton magnetic resonance spectrum (60 Mc., tetramethylsilane as internal reference) in dimethyl sulfoxide showed absorption at 470, 443, and 347 c.p.s. The latter was a doublet (J = 8 c.p.s.). The ratio of the combined areas of the absorption at 470 and 443 c.p.s. to the absorption at 347 c.p.s. was 15:2.

The phosphonium zwitterion was soluble in dimethyl sulfoxide, acetone, acetonitrile, hot chloroform, and nitromethane. It was slightly soluble in ether, dioxane, and ethyl actetate, and it was insoluble in water, acetic acid, benzene, and ethanol.

Acknowledgment.—We wish to thank Dr. Owen Webster and Dr. B. C. McKusick for helpful discussions.

(8) R. Gompper and E. Kutter, *Angew. Chem. Intern. Ed. Engl.*, **1**, 216 (1962).

2,4-*p*-Menthadiene. A New Monoterpene from Valencia Orange Oil

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Received June 27, 1963

During an investigation of the constituents of cold-pressed orange oil, a new terpene hydrocarbon was isolated. Catalytic reduction yielded *cis*- and *trans*-

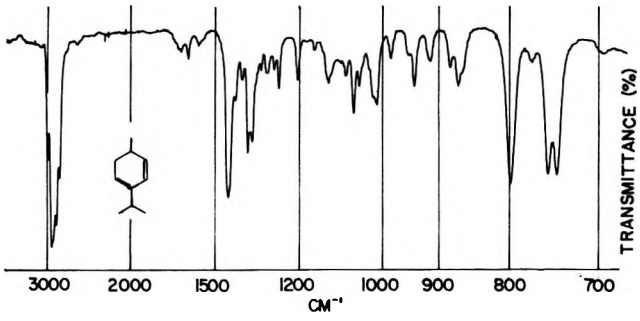

Fig. 1.—Infrared spectrum of 2,4-*p*-menthadiene.

p-menthane. Spectroscopic data indicated the presence of a triply substituted conjugated homoannular diene which was shown not to be 1,5-*p*-menthadiene (*p*-mentha-1,8-diene) by comparative infrared analysis. This previously uncharacterized terpene was identified as 2,4-*p*-menthadiene (*p*-mentha-2,4-diene).

The new terpene was synthetically obtained following dehydrohalogenation of 3,4-dibromo-*p*-menthane which resulted from the bromination of *p*-menth-3-ene. It was separated from both the orange oil and products of dehydrohalogenation by preparative gas chromatography.

Experimental

Isolation of 2,4-*p*-menthadiene.—Cold-pressed Valencia orange oil (300 ml.) was slowly added with stirring to 540 g. of silica gel in 500 ml. of hexane. The temperature was maintained at 5° throughout the addition. Upon complete addition the hexane solution was decanted and the silica gel washed three times with 300-ml. portions of hexane. The combined hexane solutions were distilled in a 5-ft. vacuum-jacketed packed column to give 30 ml. of material that boiled from 130–174°. Redistillation in a semimicro spinning-band column gave 10 ml. that boiled from 150–174°. The fourth peak of a gas chromatographic separation[1] of this fraction, having a retention time of 16 min. and following camphene, was collected to give the infrared spectrum shown in Fig. 1. Absorption at 795 cm.$^{-1}$ showed the presence of a triply substituted double bond and that at 750 cm.$^{-1}$ a *cis*-disubstituted double bond. The material was reduced with platinum black to yield *cis*- and *trans*-*p*-menthane. Its ultraviolet absorption at $\lambda_{max}^{ethanol}$ 260 mμ shows it to be a homoannular diene having at least two alkyl constituents by Woodward's rule.[3] Comparative infrared spectroscopy ruled out 1,5-*p*-menthadiene, the only *p*-menthadiene whose structural characteristics are similar. The parent mass spectral peak occurred at 136. 2,4-*p*-Menthadiene appears in the oil in trace amounts.

3,4-Dibromo-*p*-menthane.—*p*-Menth-3-ene was dissolved in ether and treated with equimolar amounts of bromine with stirring. The temperature was maintained at 25° by controlling the rate of bromine addition. The solution was washed with sodium bisulfite, extracted with ether, and distilled; b.p. 85–90° (0.025 mm.), n^{23}D 1.5276; lit.[4] n^{20}D 1.5260.

2,4-*p*-Menthadiene.—3,4-Dibromo-*p*-menthane was added to absolute ethanol containing an excess of potassium hydroxide and heated on a steam bath for 30 min. The mixture was filtered, neutralized with dilute hydrochloric acid, and then gas chromatogrammed to give a major peak having a retention time of 16 min.; n^{23}D 1.4660; ultraviolet, λ_{max} 260 mμ; the infrared spectra was identical with that shown in Fig. 1 (b.p. 56° at 25 mm. by the method of Garcia[5]). The compound gave *p*-menth-3-ene upon treatment with sodium and alcohol. Molecular weight by mass spectrometry was 136.

Anal. Calcd. for $C_{10}H_{16}$: C, 88.24; H, 11.76. Found: C, 88.20; H, 11.80.

Acknowledgment.—The authors thank G. S. Fisher, Naval Stores Laboratory, Olustee, Florida, for the 3-*p*-menthene.

(1) Column, 0.5 in. × 36 ft., containing 30% Carbowax 20M[2] on Chromosorb-W; flow rate, 200 ml./min.; temperature, 145°.

(2) Mention of brand names is for identification of type of material and does not constitute endorsement.

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p. 17.

(4) N. L. McNiven and J. Read, *J. Chem. Soc.*, 153 (1952).

(5) C. R. Garcia, *Ind. Eng. Chem., Anal. Ed.*, **15**, 648 (1943).

Synthesis and Spectra of Derivatives of α-Bromo-*p*-phenylisobutyrophenone. A Comment upon the Mechanism of Quasi-Favorskiĭ Rearrangement

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Received May 27, 1963

Silver nitrate in acetonitrile has for several years been recognized as a useful reagent for conversion of alkyl halides into alkyl nitrates.[2] It has been found that this reagent is very selective towards a direct replacement of halogen. Tertiary α-bromo ketones, very sensitive to rearrangement or dehydrobromination, will react with this reagent to give an excellent yield of the corresponding α-nitrato ketone.

Although reaction of tetraethylammonium nitrate with α-bromo-*p*-phenylisobutyrophenone (I) leads to a complex mixture of products, reaction of silver nitrate with an acetonitrile solution of I has been found to give an excellent yield of the direct replacement product, α-nitrato-*p*-phenylisobutyrophenone (II), with no evidence for any significant amount of rearrangement or elimination product. For instance, from reaction at 92° was isolated a 77% yield of II and about 8% of a high melting point material[3] with an infrared spectrum indicating the absence of nitrate groups. The structure of II was confirmed by conversion to the known[4] 1,2-epoxy-2-methyl-1-methoxy-1-(4-biphenylyl)-propane (III) and α-hydroxy-*p*-phenylisobutyrophenone (IV). Spectral characteristics of III, of IV, and of α-acetoxy-*p*-phenylisobutyrophenone (V) are reported for the first time.

In acetonitrile solution, under identical conditions, silver nitrate was found to react with α-bromo ketone I at 130 times the rate of silver perchlorate and at 13 times the rate of tetraethylammonium nitrate. These results represent over-all initial rates, and the kinetics were not further investigated, but it is possible that in the rate-determining stage of the silver nitrate reaction, both electrophilic assistance by silver ion and nucleophilic assistance by nitrate ion are operative.

Reaction of α-bromo ketone I with silver nitrate in aqueous ethanol previously has been shown to give a 69% yield of 2-(4-biphenylyl)-2-methylpropanoic acid (VI)[5] formed by a Favorskiĭ rearrangement. α-Bromoisobutyrophenone similarly has been shown[6]

(1) To whom communications concerning this paper should be addressed.

(2) L. F. Fieser and W. Von E. Doering, *J. Am. Chem. Soc.*, **68**, 2252 (1946).

(3) This product probably represents a small amount of reaction involving solvent participation; see, for example, J. Cast and T. S. Stevens, *J. Chem. Soc.*, 4180 (1953).

(4) C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **75**, 5975 (1953).

(5) N. H. Cromwell and P. H. Hess, *ibid.*, **83**, 1237 (1961).

(6) A. C. Cope and E. S. Graham, *ibid.*, **73**, 4702 (1951).

to give a 40% yield of rearranged acid. These Favorskiĭ rearrangements are of interest, since, α-hydrogens being absent, they cannot proceed through the usual cyclopropanone intermediate.[7] Mechanisms proposed for these silver ion-catalyzed rearrangements have been a push–pull type, involving nucleophilic assistance from water molecules either directly[7] or after prior hydration of the carbonyl group.[6]

Nucleophilic assistance in the rate-determining step of these electrophilically assisted rearrangements in aqueous ethanol has, however, never been established. The absence of any aryl migration during reaction in acetonitrile suggests that reactions proceeding to rearranged products may involve a rate-determining electrophilic removal of the halide ion with accompanying aryl migration. The rearranged carbonium ion intermediate subsequently can react with a water molecule with formation of the acid.

Two alternative explanations are possible for the observation that I undergoes displacement with silver nitrate in acetonitrile but rearrangement in aqueous ethanol; it is possible that these two effects may act in unison, both being partially responsible for the observation. In acetonitrile the silver ion is complexed by the solvent with a reduction in its electrophilicity and, under these conditions, aryl migration may be unable to provide sufficient driving force towards the silver ion-assisted rupture of the carbon–bromine bond such that intervention by the nucleophilic nitrate ions is required. It also has been established[8] that protic solvents inhibit the reactivity of anions in displacement reactions by hydrogen bonding to the anions. In aprotic solvents, such as acetonitrile, anions are much less solvated, and hence less energy must be supplied to overcome solvation of the anion in going to the transition state for the displacement. In the present case I may undergo silver ion-assisted rearrangement with aryl migration in aqueous ethanol, because the competing silver ion-assisted displacement reaction has been greatly slowed by hydrogen-bonding solvation of the nitrate ion.

The proton magnetic resonance spectrum of the reaction product formed from an acetonitrile solution 0.16 *M* in α-bromo ketone I and 0.32 *M* in tetraethylammonium bromide maintained at 92° for 23 hr. showed that I has been completely destroyed with formation of a 25% yield of the α,β-unsaturated ketone, α-methyl-*p*-phenylacrylophenone (VI), and a 64% yield of the β-bromo ketone, β-bromo-*p*-phenylisobutyrophenone (VII), formed through an elimination–addition reaction.[5] The conversion of VI to VII was completed by dissolving the product in an ether solution of hydrogen bromide.

Hydrogen Bonding in α-Hydroxy-*p*-phenylisobutyrophenone (IV).—The infrared spectrum of the α-hydroxy ketone (IV) shows a weak hydroxyl stretching absorption at 3608 cm.$^{-1}$ and a relatively strong absorption at 3477 cm.$^{-1}$, ascribed to nonhydrogen-bonded and hydrogen-bonded species, respectively. Dilution studies show that the hydrogen bonding is intramolecular in nature.

Reeves, Allan, and Strømme[9] have attempted, for intramolecularly hydrogen-bonded phenols and naphthols, to correlate the shift in the hydroxyl stretching frequency on formation of the hydrogen bond, $\Delta\nu$OH, with the proton magnetic resonance chemical shift of the hydroxyl proton at infinite dilution relative to the shift for the parent phenol or naphthol at infinite dilution, $\Delta\tau$OH. A rough correlation was found to exist; the best graphical correlation for twenty-four *ortho*-substituted phenols and naphthols was $\Delta\nu$OH (cm.$^{-1}$) = 67 $\Delta\tau$OH (p.p.m.). Differing classes of compounds differed in value since the treatment neglects the additional chemical shift caused by the diamagnetic anisotropy of the group introduced *ortho* to the hydroxyl group. For example, values (in cm.$^{-1}$/p.p.m.) of 50 for *o*-chlorophenol, 51 for *o*-methoxyphenol, 68 for *o*-bromophenol, and 79 for *o*-iodophenol were obtained.

The value for $\Delta\nu$OH in α-hydroxy-*p*-phenylisobutyrophenone (IV) is 131 cm.$^{-1}$, conveniently obtained (with use of lithium fluoride optics), since the infrared spectrum shows the stretching frequencies of both hydrogen-bonded and nonhydrogen-bonded hydroxylic groups. *t*-Butyl alcohol was chosen as the standard to which to refer the chemical shift in the p.m.r. spectrum, the required value at infinite dilution in carbon tetrachloride (τ 9.41) has been accurately obtained by Saunders and Hyne.[10] Dilution studies showed the chemical shift of the hydroxyl proton in IV to be τ 6.30 at infinite dilution, giving a value for $\Delta\tau$OH of 3.11 p.p.m. and a relationship $\Delta\nu$OH (cm.$^{-1}$) = 42 $\Delta\tau$OH (p.p.m.). It will be of interest to see whether the fairly good agreement between the value for the aryl α-hydroxyalkyl ketone (IV) and the previously determined values for *ortho*-substituted phenols and naphthols is fortuitous, or whether this criterion for intramolecular hydrogen bonding is of more general application than has been indicated previously.

Experimental[11]

The preparation of α-bromo-*p*-phenylisobutyrophenone (I) previously has been described.[5] The acetonitrile was Eastman Organic Chemicals Spectro Grade. Anhydrous silver perchlorate (G. F. Smith Chemical Co.) was recrystallized from aqueous dioxane and dried under vacuum at 80°. Tetraethylammonium nitrate and tetraethylammonium bromide were prepared by neutralization of an aqueous solution of the hydroxide, evaporation to dryness and recrystallization from acetonitrile.

The α-bromo ketone (I) was converted *via* the epoxy ether (III) to the α-hydroxy ketone (IV) and, hence, to the α-acetoxy ketone (V) by the methods of Stevens and Dykstra.[4]

1,2-Epoxy-2-methyl-1-methoxy-1-(4-biphenylyl)propane (III).—The melting point was 79–80°; ν 1240 (51), 1138 (85), 1118 (89), 1061 (59), 1031 (39), 940 (49), and 906 (34), cm.$^{-1}$. The p.m.r. spectrum shows nine aromatic protons and three peaks, each corresponding to three protons, at τ 6.82 (the methoxy group) and at τ 8.50 and 8.98 (the two methyl groups).

α-Hydroxy-*p*-phenylisobutyrophenone (IV).—The melting point was 94–95°; ν 3598 (12, free OH), 3472 (41, hydrogen-bonded OH), 1679 (86, sh, free C=O), 1672 (94, hydrogen-

(7) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

(8) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(9) L. W. Reeves, E. A. Allan, and K. O. Strømme, *Can. J. Chem.*, **38**, 1249 (1960).

(10) M. Saunders and J. B. Hyne, *J. Chem. Phys.*, **29**, 1319 (1958).

(11) 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 10 mg./ml. 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 carbon tetrachloride solutions with a trace of tetramethylsilane (τ 10.00) as internal reference.

TABLE I

POTENTIOMETRIC TITRATIONS

α-Bromo ketone I, 0.0800 *M*; [$AgNO_3$], 0.0160 *M*
(titers are in milliliters of 0.0100 *M* KCl; initial velocity is 3.4×10^{-7} moles $l.^{-1}$ $sec.^{-1}$)

Time (min.)	0	155	340	1220	1300	1790	2880
Titer	7.86	6.59	5.30	2.65	2.50	1.96	1.01
Time (min.)	4560	7380					
Titer	0.55	0.29					

α-Bromo ketone I, 0.0800 *M*; [$AgClO_4$], 0.0160 *M*
(titers are in milliliters of 0.0100 *M* KCl; initial velocity is 2.6×10^{-9} moles $l.^{-1}$ $sec.^{-1}$)

Time (min.)	0	1220	1300	1790	2880	4560	7380
Titer	7.96	7.86	7.86	7.83	7.80	7.60	7.40

α-Bromo ketone I, 0.0800 *M*; [NEt_4NO_3], 0.0160 *M*
(titers are in milliliters of 0.0100 *M* $AgNO_3$; initial velocity is 2.6×10^{-8} moles $l.^{-1}$ $sec.^{-1}$)

Time (min.)	0	30	60	90	120	190	270
Titer	0.06	0.10	0.11	0.14	0.16	0.20	0.26
Time (min.)	370	2950					
Titer	0.35	2.33					

bonded C=O), 1370 (72), 1179 (99), 966 (84); λ_{max} 283 mμ (ε 22,800).

Dilution studies with lithium fluoride optics show superimposed infrared spectra for solutions 10 mg./ml. in 1-mm. cell and 3.3 mg./ml. in 3-mm. cell; ν 3608 (16), 3477 (38), 1678 (72, sh), 1671 (76) $cm.^{-1}$.

The p.m.r. spectrum of α-hydroxy-*p*-phenylisobutyrophenone shows in addition to peaks corresponding to nine aromatic protons, a peak corresponding to six methyl protons, and a peak due to the hydroxyl proton. Due to hydrogen bonding, the positions of hydroxyl protons in p.m.r. spectra are, in general, concentration dependent even at low concentrations; this dependence is minimized when intramolecular hydrogen bonding is operative.[12] Dilution studies with IV (mg./ml.) showed little concentration dependence, consistent with the evidence for extensive intramolecular hydrogen bonding from infrared spectroscopy.

IV	67	43	25	17	10	6
τOH	6.22	6.25	6.28	6.30	6.30	6.30
τCH_3	8.43	8.42	8.42	8.40	8.40	8.40

α-Acetoxy-*p*-phenylisobutyrophenone (V).—The melting point was 125–127°; $\nu_{C=O}$ 1745 (93) and 1691 (93); λ_{max} 283 mμ (ε 23,000).

Preparation of α-Nitrato-*p*-phenylisobutyrophenone (II).—In a sealed tube, 20 ml. of acetonitrile, 0.95 g. of α-bromo ketone I, and 1.00 g. of silver nitrate were heated at 92° for 17 hr. The solvent was removed by evaporation, and the residue was ether extracted; evaporation yielded 0.76 g. of residue which gave a negative Beilstein test. The infrared spectrum was identical with that of pure II except for a slight shoulder around 1680 $cm.^{-1}$; in particular, no disturbance was observed at 1663 $cm.^{-1}$ where the α,β-unsaturated ketone shows carbonyl absorption.[5] A small amount (0.08 g.) of product was found to be insoluble in boiling benzene–petroleum ether (b.p. 60–70°), m.p. 224–227°, $\nu_{C=O}^{KBr}$ 1681 $cm.^{-1}$.

Reaction of an identical mixture for 9 days at room temperature led to 69% reaction as measured by silver bromide precipitation; recrystallization from petroleum ether–benzene gave pure II, m.p. 127–128°; λ_{max} 288 mμ (ε 23,800); $\nu_{C=O}$ 1692 (93), ν_{NO_2} 1647 (95) and 1306 (94).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.35; H, 5.30; N, 4.91. Found: C, 67.32; H, 5.32; N, 4.70.

Reaction of α-Nitrato-*p*-phenylisobutyrophenone (II).—Using a method identical with that which Stevens and Dykestra[4] employed for α-bromo ketone I, derivatives III and IV were prepared from II and were identified by melting points and infrared spectra.

Reaction of α-Bromo Ketone I with Silver Perchlorate.—A solution of 1.00 g. of I and 1.00 g. of silver perchlorate in 20 ml. of acetonitrile was maintained, in a sealed tube, at 91.9° for 48 hr. Silver bromide was removed by filtration, and the solution evaporated to dryness and extracted with ether and water. An insoluble, dark green fraction (0.52 g.), after recrystallization from acetone, charred on heating but did not melt below 250°. Evaporation of the ether solution yielded 0.35 g. of material, m.p. 73–95°. The infrared spectrum of the ether soluble portion included ν 1739 (30), 1691 (72, sh), 1680 (90), and 1666 (42, sh) $cm.^{-1}$. The shoulder at 1666 $cm.^{-1}$ may represent a small quantity of VI. It is possible that VI is initially formed in reasonable yield only for it to undergo further reactions.[13]

Reaction Velocities for Attack upon α-Bromo Ketone I.—Sealed ampoules, each containing 5.00 ml. of reaction mixture, were maintained at 74.0°. Ampoules were removed from time to time, and reaction was quenched by immersion in Dry Ice–alcohol slush until the extent of reaction was determined by potentiometric titration in a titration medium of 30 ml. of acetone containing 1 ml. of 1 *N* nitric acid using a silver wire electrode and a potassium nitrate–agar bridge to a calomel reference electrode. (See Table I.)

Preparation of β-Bromo-*p*-phenylisobutyrophenone (VII).—A sealed tube containing 20 ml. of an acetonitrile solution 0.165 *M* in α-bromo ketone I and 0.333 *M* in tetraethylammonium bromide was maintained at 92° for 23 hr. A 1.00-ml. aliquot was removed and titration in acetone, using Lacmoid as indicator, required 3.90 ml. of 0.0114 *M* methanolic morpholine for neutralization. This titer corresponds to 27% acid formation from the α-bromo ketone (I). The remaining solution was evaporated to dryness, extracted with ether, washed with water, and the ether solution was evaporated to dryness to give 0.80 g. of an orange oil (from 0.95 g. of I).

A portion of the oil was retained for p.m.r. investigation, and the remainder was dissolved in an ether solution of hydrogen bromide; evaporation to dryness gave a white solid whose p.m.r. spectrum indicated the absence of α-methyl-*p*-phenylacrylophenone (VI). Recrystallization from petroleum ether gave pure β-bromo-*p*-phenylisobutyrophenone (VII), m.p. 72.5–73.5°, λ_{max} 285 mμ (ε 23,600), $\nu_{C=O}$ 1683 (89). The p.m.r. spectrum shows two equivalent β′ aromatic protons at τ 2.07 and two equivalent γ′ protons at τ 2.41 ($J_{\beta'\gamma'}$ = 8 c.p.s.), other peaks to give a total of nine aromatic protons, several peaks corresponding in total to three protons in the region τ 6–7 and three methyl protons, as a doublet (J = 7 c.p.s.), at τ 8.71.

Anal. Calcd. for $C_{16}H_{15}OBr$: C, 63.38; H, 4.99; Br, 26.36. Found: C, 63.37; H, 4.88; Br, 26.19.

The p.m.r. spectrum of the 0.80 g. of oil formed by reaction in acetonitrile showed no disturbance around τ 1.82 where the signals from the β′ aromatic hydrogens of the α-bromo ketone (I) occur, consistent with I having been completely destroyed. The α-bromo ketone (I) also shows two γ′ hydrogens at τ 2.43 ($J_{\beta'\gamma'}$ = 8 c.p.s.) and six methyl hydrogens at τ 7.97.

The α,β-unsaturated ketone (VI), previously prepared in these laboratories,[5] was found to have doublets ($J_{\beta'\gamma'}$ = 8 c.p.s.) due to β′ and γ′ protons at τ 2.26 and 2.42 and to have two broad peaks, with fine structure, each corresponding to one ethylenic proton at τ 4.20 and 4.43. The peak corresponding to the three methyl protons, at τ 7.95 has a characteristic structure, identical

(12) T. M. Connor and C. Reid, *J. Mol. Spectry.*, **7**, 32 (1961).

(13) Olefins in the presence of acids are known to be somewhat reactive towards acetonitrile; see, for example, H. Plaut and J. J. Ritter, *J. Am. Chem. Soc.*, **73**, 4076 (1951).

with that for the similarly situated ethylenic methyl group in methacrylates.[14]

The p.m.r. spectrum of the reaction product showed protons from both α,β-unsaturated ketone VI and from β-bromo ketone VII, and the intensities of the signals indicated that the product contained 64% of 3-bromo ketone VII and 25% of α,β-unsaturated ketone VI. After treatment with hydrogen bromide in ether, all signals due to VI disappeared, and the p.m.r. spectrum was essentially identical with that for pure β-bromo ketone VII.

Reaction of α-Bromo Ketone I with Tetraethylammonium Nitrate.—Reaction, in a sealed tube, at 89.4° for 21 hr. of 1.00 g. of I and 2.60 g. of tetraethylammonium nitrate in 20 ml. of acetonitrile followed by evaporation to dryness, ether extraction, water washing, and ether evaporation gave 0.74 g. of solid product. A portion (10%) of the product was insoluble in carbon tetrachloride. The melting point of this portion, 222–228°, indicated identity with the small amount of material, m.p. 224–227°, obtained in reaction of an acetonitrile solution of I with silver nitrate. P.m.r. signals at τ 4.20 and 4.43 (olefinic protons) and at 7.95 (three methyl protons) all corresponded in intensity to a 0.26 mole fraction of α,β-unsaturated ketone VI. Other intense peaks occurred at τ 8.15 and 8.29, and less intense peaks occurred at τ 8.22 and 8.45. Infrared peaks at 1647 and 1300 cm.$^{-1}$ indicated some incorporation of nitrate groups. Further characterization of the apparently complex mixture of products was not attempted.

Acknowledgment.—The investigation was supported in part by Grants No. G-14469 and G-20149, from the National Science Foundation.

(14) See, for example, the spectrum of methyl methacrylate [N. S. Bhacca L. F. Johnson, and J. L. Shoolery, "N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, spectrum 113].

A New Synthesis of Naphtho[1,2-*b*]pyran-2-ones

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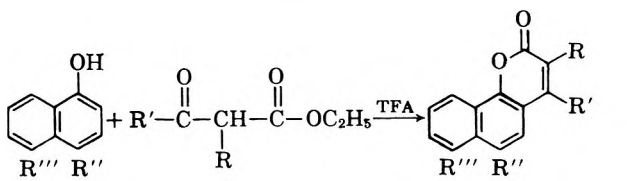
We recently reported a one-step method for preparing coumarins,[2] esters of coumarin acetic acids,[3] and coumarin carboxylic acids obtained from phenolic acids.[4] This contribution deals with the condensation of 1-naphthol and 1,4- and 1,5-naphthalenediols with β-keto esters in the presence of trifluoroacetic acid as shown in Chart I. The compounds synthesized are listed in Table I. 2-Naphthols fail to undergo the reaction.

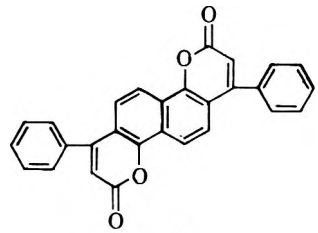
The reaction of 1,5-naphthalenediol and ethyl acetoacetate using the Von Pechmann conditions[5] has been reported[6] to give the naphthopyrone Ie, dec. pt. 299–302°. With trifluoroacetic acid, we obtained a product with dec. pt. 225°; under the previous conditions,[6] a product with dec. pt. above 360° was obtained. The *p*-nitrobenzoyl derivative was probably the 3-[4-nitrobenzoyl]-5-hydroxynaphtho[1,2-*b*]pyran-2-one from the recent observations of Kloss and Wiener[7] who prepared an acetyl coumarin in a similar manner. With trifluoroacetic acid as the catalyst and solvent we were

CHART I



	R	R'	R''	R'''
Ia	H	CH_3	H	H
b	$CH_2C_6H_5$	CH_3	H	H
c	CH_3	CH_3	H	H
d	H	C_3H_7	H	H
e	H	CH_3	H	OH
g	H	CH_3	OH	H

unable to condense 1-naphthol with ethyl benzoylacetate; however with 1,5-naphthalenediol two equivalents condensed smoothly and in high yield to form the interesting compound If whose proposed structure is shown.



If

Table II describes the ultraviolet, infrared, and fluorescence spectral characteristics of the series.

Efforts have been made to prepare suitable derivatives of the series; however, none of the usual derivatives of coumarins could be prepared from all the compounds. Therefore, we have adapted a C-acylation method developed previously[8] for the preparation of a uniform series of benzoylated compounds (see Table III).

The benzoyl group presumably enters the 3-position of these naphthopyran-2-ones except in compounds Ib and Ic in which substitution of the naphthalene 6-position would be expected.

Experimental[9]

Preparation of the Members of the Ia–g Series.—A mixture consisting of 0.1 mole of the naphthol, 0.1 mole of the β-keto ester, and 25 ml. of trifluoroacetic acid was refluxed for the period of time indicated in Table I. In the case of the compound If, 0.1 mole of the naphthol was used along with 0.2 mole of the β-keto ester and 50 ml. of trifluoroacetic acid. At the termination of the reflux period the solutions were diluted with 250 ml. of water (500 ml. in the case of If), chilled, filtered with suction, and dried in air. Purification of the crude naphtho[1,2-*b*]pyran-2-ones was effected by taking the dry compounds up in the smallest amount of ethyl acetate possible and then filtering the ethyl acetate solution into about ten volumes of heptane. Chilling the heptane–ethyl acetate mixtures produced a precipitate which was taken through this same procedure for a second and a third purification.

Determination of the Fluorescence of the Members of the Ia–g Series.—A small amount of the compound (about a milli-

(1) Submitted in partial fulfillment of the requirements for the Master of Science degree.

(2) L. L. Woods and J. Sapp, *J. Org. Chem.*, **27**, 3703 (1962).

(3) L. L. Woods and J. Sapp, *J. Chem. Eng. Data*, **8**, 235 (1963).

(4) L. L. Woods and J. Sterling, *Texas J. Sci.*, **15**, 200 (1963).

(5) H. Von Pechmann and C. Duisberg, *Ber.*, **16**, 2122 (1883).

(6) R. Robinson and F. Weygand, *J. Chem. Soc.*, **387** (1941).

(7) R. A. Kloss and C. Wiener, *J. Org. Chem.*, **28**, 1671 (1963).

(8) L. L. Woods and P. A. Dix, *ibid.*, **24**, 1126 (1959); L. L. Woods, *ibid.*, **24**, 1804 (1959).

(9) Analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J., and Galbraith Laboratories, Knoxville, Tenn. All melting points were determined on a Fisher-Johns melting point block.

TABLE I

COMPOUNDS OF Ia–g SERIES

No.	Phenol used	β-Keto ester used	Yield, %	M.p., °C.	Reaction time, hr.	Empirical formula	Analysis, % Calcd. (found) Carbon	Hydrogen
Ia[b]	1-Naphthol[a]	Ethyl acetoacetate	90	175	5	$C_{14}H_{10}O_2$	79.98	4.79
							(79.74)	(4.71)
Ib[c]	1-Naphthol	Ethyl α-benzylacetoacetate	93	199–200	24	$C_{21}H_{16}O_2$	83.97	5.36
							84.03	(5.32)
Ic[d]	1-Naphthol	Ethyl α-methylacetoacetate	91	208.5–209.5	24	$C_{15}H_{12}O_2$	80.33	5.39
							(80.46)	(5.26)
Id[e]	1-Naphthol	Ethyl butyroylacetate	37	104–104.5	24	$C_{16}H_{14}O_2$	80.64	5.92
							(80.87)	(5.91)
Ie[f]	1,5-Naphthalenediol	Ethyl acetoacetate	95	225–dec.	3	$C_{14}H_{10}O_3$	74.32	4.45
							(74.23)	(4.67)
If[g]	1,5-Naphthalenediol	Ethyl benzoylacetate	100	239–240	16	$C_{28}H_{16}O_4$	80.75	3.87
							(80.49)	(4.11)
Ig[h]	1,4-Naphthalenediol	Ethyl acetoacetate	98	Above 254 dec.	2.5	$C_{14}H_{10}O_3$	74.32	4.45
							(74.56)	(4.47)

[a] Prepared previously by Kurt Bartsch, *Ber.*, **36**, 167 (1903); m.p. 167°. [b] Ia, 4-methylnaphtho[1,2-*b*]pyran-2-one. [c] Ib, 3-benzyl-4-methylnaphtho[1,2-*b*]pyran-2-one. [d] Ic, 3,4-dimethylnaphtho[1,2-*b*]pyran-2-one. [e] Id, 4-propyl-naphtho[1,2-*b*]pyran-2-one. [f] Ie, 4-methyl-7-hydroxynaphtho[1,2-*b*]pyran-2-one. [g] If, 1,10-diphenyl[1]benzopyrano[8,7-*h*][1]benzopyran-3,8-dione. [h] Ig, 4-methyl-6-hydroxynaphtho[1,2-*b*]pyran-2-one.

TABLE II

SPECTRAL CHARACTERISTICS OF THE MEMBERS OF THE Ia–g SERIES

No.	Infrared absorptions in cm.$^{-1}$[a]	Ultraviolet absorption bands range of 200–350 mμ (log ε)[b]	Fluorescence measured in q.r.u.[c]
Ia	1717, 1582, 1374, 1083, 942, 810, 756	220.7 (4.40), 265.7 (4.51), 274 (4.40)	3.40
Ib	1695, 1597, 1488, 1093, 1019, 815, 759, 749, 699	225 (4.13), 268 (sh, 4.36), 277 (3.61)	1.90
Ic	1701, 1605, 1093, 804, 767	221 (4.45), 267 (4.42), 275.5 (4.49)	0.77
Id	1712, 1678, 1626 w, 1377, 841, 813, 796, 777, 760	221 (4.36), 265 (4.26), 274.5 (4.35)	0.04
Ie	3300, 1595, 1372, 1290, 1263, 925, 772	230 (4.15), 300 (3.71), 330 (3.15)	0.15
If	3300, 1658, 1595, 1372, 1261, 1203, 925, 772	230 (4.55), 292 (4.19), 330 (3.55)	0.01
Ig	3322, 1686, 1592, 1558, 1418, 1342, 1269, 1244, 1078	217 (4.23), 287 (4.24)	0.10

[a] Spectra run on Beckman IR-5 using potassium bromide pellets; w, weak. [b] Spectra run on Bausch and Lomb 505 spectrophotometer in Spectro Grade methanol; sh, shoulder. [c] See Experimental.

TABLE III

BENZOYL DERIVATIVES OF THE MEMBERS OF Ia–g SERIES

Compound used	Emperical formula of compound produced	M.p. °C.	Analysis, % Calcd. (found) Carbon	Hydrogen
Ia	$C_{21}H_{14}O_3$	177–178	80.24	4.48
			(80.20)	(4.68)
Ib	$C_{28}H_{20}O_3$	196–197	83.14	4.98
			(83.29)	(4.84)
Ic	$C_{22}H_{16}O_3$	203	80.47	4.91
			(80.60)	(5.01)
Id	$C_{23}H_{18}O_3$	121.5–122.5	80.68	5.29
			(80.84)	(5.14)
Ie	$C_{28}H_{18}O_4$	122.5–123	80.36	4.33
			(80.49)	(4.50)
If	$C_{42}H_{24}O_6$	120–124.5	80.75	3.87
			(80.97)	(3.99)
Ig	$C_{28}H_{18}O_4$	218	80.36	4.33
			(80.05)	(4.60)

gram) was weighed accurately, dissolved in 10 ml. of methanol, and then diluted to 50 ml. in distilled water. If the fluorescence of this solution was too concentrated, then subsequent dilutions were made on aliquots from this stock solution.

The fluorescence of the compound as measured on a Turner fluorophotometer Model 110 using a 365-mμ filter was compared with that of a quinine sulfate solution prepared the same way and the results given in Table IV as q.r.s. (quinine reference units). The formula for the calculation of the units is q.r.u. = concn. of quinine sulfate (g./ml.) × dial reading for substance/concn. of substance (g./ml.) × dial reading for quinine.

Preparation of the Benzoates of the Compounds of the Ia–g Series.—To 0.01 mole of the naphtho[1,2-*b*]pyran-2-one was added 10 ml. of trifluoroacetic acid and 0.01 mole of benzoyl chloride, except in the cases of Ie–g in which 0.02 mole of benzyl chloride was used. The mixtures were gently heated at reflux in the hood until hydrogen chloride vapors were no longer evolved—about 0.5 hr. The solutions were diluted with 100 ml. of water, chilled, and the precipitates filtered. The air-dried samples were recrystallized three times from boiling heptane to give the analyses and melting points indicated in Table III.

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Preparation of (S)-(−)-2,4-Dimethyl-4-isopropylcyclopent-2-enone

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2,3-Dimethyl-4-isopropylcyclopent-2-enone was required and, in repeating the work of Short and Read,[2]

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(2) A. G. Short and J. Read, *J. Chem. Soc.*, 1040 (1939).

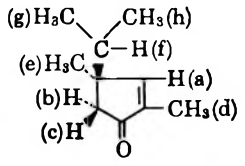
TABLE I

PROTON MAGNETIC RESONANCE SPECTRUM OF I

Hydrogen type	τ-Values	Multiplicity	No. of hydrogens: Found		No. of hydrogens: Theoretical		J[a]
a	3.0	Quartet	1.0		1		J_{ad} = 1.5
b or c	7.75	Doublet[b]	0.9		1		
c or b	8.15	Doublet[b]	1.0		1		J_{bc} = 18.0
d	8.33	Doublet	3.4		4		
f	8.5	Multiplet[c]					$J_{fg} = J_{fh}$ = 8.1
e	8.88	Singlet	3.0	13.1	3	13	
g or h	9.11	Doublet	6.7		6		
h or g	9.18	Doublet					
			16.0		16		

[a] Peak separation in cycles per second. [b] AB pair. [c] Obscured by overlapping bands.

the hydrogenolysis of (+)-sabinyl acetate[3] was found not to occur in the manner reported. Saponification and oxidation of the reduction product was shown to yield (S)-(−)-2,4-dimethyl-4-isopropylcyclopent-2-enone (I). Hydrogenolysis, therefore, resulted in cleavage at the least hindered bond in the cyclopropane ring as reported by Norin.[3]



I

racemic I recently has been shown to be one of the products from the thermal isomerization of thujone.[4] Structure I was established by comparison of the reported[4] ultraviolet, infrared, and n.m.r. spectra and by oxidation to (S)-(+)-α-methyl-α-isopropylsuccinic acid.[5] The n.m.r. chemical shifts, multiplicities, coupling constants, and the hydrogen distribution[6] are consistent with I. The proton magnetic resonance spectrum values for I are found in Table I.

Experimental[7]

General Procedure.—During the initial studies the procedures used were exactly as described.[2] Later it was found that the oxidation of the cyclopentenol fraction was best carried out by the procedure of Brown and Garge.[8] From 10 g. of the alcohol, 7.3 g. of the ketone fraction[2] was obtained. The infrared spectrum showed hydroxyl group absorption and a doublet in the carbonyl region, 1743 and 1700 cm.$^{-1}$. Analysis by g.l.p.c. on a Carbowax capillary column[9] indicated a mixture of four substances. To remove the small amount of unoxidized alcohol, the mixture was treated with semicarbazide, and the product was recrystallized from methanol. This material was added to 6 *N* sulfuric acid and steam distilled. Ether extraction of the distillate and vacuum distillation gave a material, b.p. 88–90 (15 mm.). G.l.p.c. showed[9] the presence of three substances. Separation was achieved by preparative gas chromatography[10] using a $^3/_8$ in. × 15 ft. 15% Versamid column at 180°. Best separation was realized with a sample volume of 0.2 ml. The retention times were 11 (component A), 14 (B), and 16 (C) min. Component A (25%) was shown by the melting points and mixture melting points of the 2,4-dinitrophenylhydrazones to be (−)-thujone.[11] Component B could not be completely separated from component C but had a strong infrared band at 1743 cm.$^{-1}$. Component C (70%) was shown to be 2,4-dimethyl-4-isopropylcyclopent-2-enone.

(S)-(−)-2,4-Dimethyl-4-isopropylcyclopent-2-enone (I).—This substance, (component C) separated in the above manner, distilled at 90–91° at 14 mm., n^{22}D 1.4694, $[\alpha]^{25}$D −24.6° (neat).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.90; H, 10.59; mol. wt., 152. Found: C, 78.67; H, 10.53; mol. wt., 160.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner[12] and was recrystallized from ethanol, m.p. 144–145°, $[\alpha]^{27}$D +52.0° (*c* 0.511, chloroform); for the (±) form, lit.[4] m.p. 120–21°.

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: C, 57.81; H, 6.06; N, 16.68. Found: C, 57.64; H, 6.17; N, 16.62.

The semicarbazone of I was prepared[13] and was recrystallized from methanol, m.p. 164°, $[\alpha]^{28}$D +54.0° (*c* 1.052, methanol).

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.24; H, 9.18; N, 19.86.

Ozonolysis of I to (S)-(+)-α-isopropylsuccinic Acid.—The ozonolysis[14] of I was carried out in the same way as described[4] for the racemate prepared from thujone. Three recrystallizations from benzene gave a single large crystal with a constant melting point of 136–137°, $[\alpha]^{30}$D +15.0° (*c* 1.050, ethanol); lit.[3,5,15] m.p. 127°, 132°, and 134°, $[\alpha]^{26}$D +19.1° (*c* 1.572) and $[\alpha]^{21}$D +16° (*c* 2.9).

The (±) form of this succinic acid was prepared by a general procedure,[16] m.p. 158°, from benzene (lit.[3–5,15,17] melting point range, 137–155°). The infrared spectra (potassium bromide) of the (+) and (±) forms were different.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10; neut. equiv., 87. Found: C, 55.27; H, 8.00; neut. equiv., 84.

Acknowledgment.—This work was supported by a grant from The Robert A. Welch Foundation and grateful acknowledgment is made.

(3) This study was initiated before the recent publication on the hydrogenolysis of (+)-sabinene, (+)-sabinol, and (+)-sabinyl acetate [T. Norin, *Acta Chem. Scand.*, **16**, 640 (1962)] and completed before it came to the authors' attention.

(4) W. von E. Doering, M. R. Willcott, III, and M. Jones, *J. Am. Chem. Soc.*, **84**, 1224 (1962).

(5) J. Porath, *Arkiv Kemi*, **1**, 385 (1949).

(6) N.m.r. studies by N.M.R. Specialties, Inc., New Kensington, Pa., and by Mr. N. F. Chamberlain and his group, Research Division, Humble Oil and Refining Co., Baytown, Tex. The authors are greatly indebted to Mr. Chamberlain for his assistance.

(7) All melting points were taken on a Fisher-Johns apparatus and are reported uncorrected. Microanalyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Colo.

(8) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(9) The authors gratefully acknowledge the assistance of Mr. W. A. Dark, Spencer Chemical Co., Orange, Tex., on this determination.

(10) The authors are indebted to Mr. Don Wreyford and Mr. Frank Owens, Wilkins Instrument and Research, Inc., Houston, Tex., for assistance and use of an Aerograph A-700.

(11) The authors are indebted to Professor Eastman, Stanford University, for a sample of (−)-thujone.

(12) 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. 219.

(13) Ref. 12, p. 218, procedure 16B.

(14) The authors are indebted to Dr. W. Hakki of Professor P. S. Bailey's laboratory, University of Tex., Austin, Tex., for performing this ozonolysis.

(15) H. E. Smith and A. W. Gordon, *J. Am. Chem. Soc.*, **84**, 2840 (1962).

(16) P. A. S. Smith and J. P. Horwitz, *ibid.*, **71**, 3418 (1949).

(17) R. H. Eastman and A. Oken, *ibid.*, **75**, 1029 (1953).

Thermal Cyclization of Certain Carbinol Quaternary Ammonium Ions to Form Phthalans[1]

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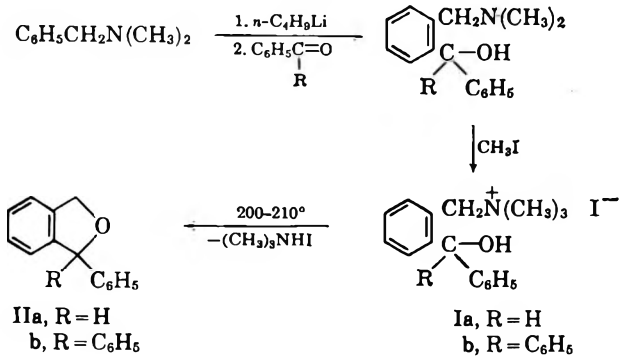
Benzyldimethylamine recently has been metalated with *n*-butyllithium in ether to form the *o*-lithioamine, which was condensed with benzaldehyde and benzophenone to give the corresponding carbinolamines.[2] The methiodides of these compounds (Ia and b)[3] have been cyclized thermally to produce phthalans IIa and b in yields of 76 and 56%, respectively; trimethylamine hydroiodide was eliminated.

SCHEME A



IIa, R = H
b, R = C_6H_5

Ia, R = H
b, R = C_6H_5

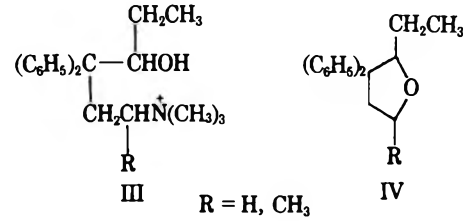
Structures IIa and b were supported by elemental analysis and by physical and chemical evidence. Their infrared spectra showed bands for a cyclic ether at 1036 and 1022 cm.$^{-1}$ for IIa and at 1022 and 1013 cm.$^{-1}$ for IIb.[4] Oxidations (alkaline permanganate) of IIa and IIb afforded *o*-benzoylbenzoic acid and 3,3-diphenylphthalide, respectively.

The n.m.r. spectrum[5] of phthalan IIa[6] showed the expected ABX system[7] which could be closely approximated by a first-order approach. The chemical shifts were, for the methylene hydrogens, $\omega_A = -242 \pm 1$, $\omega_B = -228 \pm 1$, and, for the benzhydryl hydrogen, $\omega_X = -287 \pm 1$ c.p.s.; the coupling constants were $J_{AB} \cong 12.3$ c.p.s. and $J_{BX} = J_{AX} \cong 2.1$ c.p.s. Phthalan IIb gave a quite simple n.m.r. spectrum[6] consisting of a singlet at -230 ± 1 c.p.s., assigned to the methylene hydrogens, with only an aromatic multiplet centered at approximately -356 c.p.s.

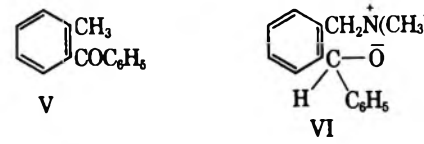
Phthalans IIa and b have been prepared earlier, but the reported boiling point of the former[8] and melting point of the latter[9] differ somewhat from our values. The purity of our IIa was indicated by a single peak in its vapor phase chromatogram, and that of our IIb by its sharp melting point.

One earlier method for the preparation of phthalan IIa involved an acid-catalyzed cyclization of 2-hydroxymethylbenzhydrol,[10] and another method a base-catalyzed cyclization of the carbinol quaternary ammonium ion represented in Ia.[8] In the latter method methiodide Ia was made by a process much less convenient than that shown in Scheme A and converted to the corresponding quaternary hydroxide, which was refluxed with 50% sodium hydroxide.[8] Phthalan IIb previously has been prepared by acid-catalyzed cyclization of 2-hydroxymethyltriphenylcarbinol, which was obtained from phthalide and phenylmagnesium bromide.[9]

It should be mentioned that the related thermal cyclization of carbinol quaternary ammonium ion III to form furan IV has been reported previously.[11]



In connection with the present work, the earlier[8] method for IIa involving the carbinol quaternary ammonium hydroxide corresponding to Ia was repeated. Interestingly the reaction afforded not only phthalan IIa but also the isomeric ketone V in the ratio of 7:3 as determined by v.p.c. Actually V was isolated as its 2,4-dinitrophenylhydrazone.



Since phthalan IIa would presumably arise through an intramolecular displacement of trimethylamine by the alkoxide ion in VI, the formation of ketone V might appear to involve a 1,4-hydride shift within VI. Another possible mechanism would involve ionization of the benzhydrylic hydrogen of phthalan IIa and isomerization of the resulting carbanion. Indirect support for the hydride shift is the observation that phthalan IIa failed to afford ketone V with refluxing 50% sodium hydroxide. However, this mechanism is not considered established.

Experimental[12]

Cyclizations of Methiodides Ia and b.—The appropriate methiodide[2,3] was placed in a round-bottomed flask fitted with a two-

(1) Supported by Army Research Office (Durham).

(2) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

(3) R. L. Vaulx, G. C. Jones, and C. R. Hauser, *J. Org. Chem.*, **27**, 4385 (1962).

(4) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 119.

(5) The authors are indebted to J. C. Randall for the determination and interpretation of these spectra.

(6) These spectra were taken using a 9% by weight solution of the phthalan in carbon tetrachloride with a cyclohexane external reference.

(7) See K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, p. 30.

(8) H. W. Bersch, R. Meyer, A. v. Mletzko, and K. H. Fischer, *Arch. Pharm.*, **291**, 82 (1958).

(9) F. Seidel, *Ber.*, **61**, 2267 (1928).

(10) A. Pernot and A. Willimart, *Bull. soc. chim. France*, **20**, 321 (1953).

(11) N. R. Easton and V. B. Fish, *J. Am. Chem. Soc.*, **77**, 2547 (1955).

(12) Melting points were taken using a Laboratory Devices Mel-Temp block and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Infracord 137. Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Boiling points are uncorrected and vapor phase chromatograms obtained on F & M Model 500 programmed temperature gas chromatograph using an Apiezon L–Chromasorb W column.

necked adaptor for gas inlet and condenser. The system was evacuated to 1 mm. and refilled with dry nitrogen three times. After flushing the system for 30 min. with a slow stream of nitrogen (which was continued during the reaction), the flask was immersed in a Woods' metal bath which was preheated to 200–210° After 0.5–1 hr. at this temperature, the red mixture was allowed to cool, then boiled with several portions of anhydrous ether to remove the phthalan from the solid residue. The combined etheral extracts were dried over anhydrous magnesium sulfate. Removal of the solvent afforded an oil which was treated as described below.

The oil obtained from 85.9 g. (0.224 mole) of methiodide Ia was distilled to give 33.3 g. (76%) of 1-phenylphthalan (IIa), b.p. 108–110° (0.05 mm.), lit.[6] b.p. 127–129° (0.03 mm.). This product was stored under nitrogen to prevent slow decomposition.

Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.44; H, 6.30.

The oil obtained from 13.8 g. (0.03 mole) of methiodide Ib crystallized when the last trace of solvent was removed *in vacuo*. The solid was recrystallized from acetone (cooled in Dry Ice) to give 4.6 g. (56%) of 1,1-diphenylphthalan (IIb), m.p. 99–100.5°, lit.[9] m.p. 95.

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.07; H, 5.88.

A sample of the solid residue left after the ethereal extractions of the reaction product was warmed with 6 *M* sodium hydroxide to evolve trimethylamine, which was bubbled through ethanolic picric acid to give the yellow picrate of this amine, m.p. 224–226°, after recrystallization from ethanol. This melting point was not depressed on admixture with an authentic sample of the picrate.

Oxidations of phthalans IIa and IIb were effected by treatment of refluxing mixtures of 0.5-g. samples of each in 25 ml. of 1 *M* sodium hydroxide with 1-g. portions of potassium permanganate until the purple persisted. After refluxing for 6 hr., ethanol was added, the suspension filtered, and the filtrate acidified. The mixture was extracted with ether, and the solvent removed from the dried ethereal extracts. The residue from the experiment with IIa was recrystallized from water–ethanol to give *o*-benzoylbenzoic acid, m.p. 128–130°, undepressed on admixture with an authentic sample. The residue from the experiment with IIb was recrystallized from hexane to give 3,3-diphenylphthalide, m.p. 116–117°, undepressed on admixture with an authentic sample.[13] The two products were further identified by comparison of their infrared spectra with the spectra of the authentic samples.

Reaction of Carbinol Quaternary Hydroxide with Alkali.—A solution of 9.16 g. (0.025 mole) of methiodide Ia in 250 ml. of hot water was treated with 11.2 g. (0.05 mole) of silver oxide, and the resulting carbinol quaternary hydroxide treated (after filtration) with 35 g. of sodium hydroxide essentially as described previously.[8] After refluxing until trimethylamine ceased to be evolved (3 hr.), the reaction mixture was cooled, diluted with water, and extracted with ether. The solvent was removed from the dried ethereal solution and the oily residue distilled *in vacuo* to give 2.4 g. (49%) of a mixture of phthalan IIa and ketone V, b.p. 108–110° (0.05 mm.). The infrared spectrum of the mixture showed peaks at 1031 and 1019 cm.$^{-1}$ for a cyclic ether and a strong peak at 1637 cm.$^{-1}$ for a carbonyl group.[14] A vapor phase chromatogram of the mixture showed two peaks (approximate ratio, 7:3), the retention times of which corresponded to those of IIa and V,[15] respectively. A solution of a sample of the mixture in 95% ethanol was treated with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of ketone V, m.p. 179–189°, undepressed on admixture with an authentic sample, m.p. 181–189°. The infrared spectra of the two samples were identical.

The stability of phthalan IIa in refluxing 50% sodium hydroxide was demonstrated by the observation that no ketone V was obtained after 4 hr. refluxing. Recovery IIa (90%) was identified by boiling point, v.p.c., and n.m.r. spectrum.

(13) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3364 (1962).

(14) See ref. 4, p. 132.

(15) Authentic ketone V, b.p. 110–113° (0.6 mm.), was prepared in 83% yield from *o*-tolyl chloride and benzene by means of aluminum chloride as described previously [H. Goldschmidt and H. Stoker, *Ber.*, **24**, 2805 (1891)].

Additional Rearrangements of 5-Phenyl-1,4-benzodiazepines

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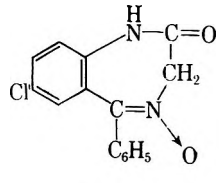
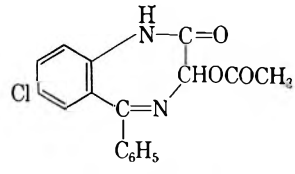
Received September 30, 1963

7-Chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one 4-oxide (I) has been shown to undergo a Polonovski-type rearrangement upon treatment with acetic anhydride to afford 3-acetoxy-7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (II).[1] The acetyl group of II has been removed, leaving an isomer of I (III).[2] In studying the scope of this rearrangement, I was treated with *p*-toluenesulfonyl chloride and with phosphorus oxychloride. The product (IV), obtained in either case, was isomeric with I but was not III; neither was it 7-chloro-5-phenyl-4,5-dihydro-2H-1,4-benzodiazepine-2,3(1H)-dione nor 6-chloro-4-phenyl-3,4-dihydroquinazoline-2-carboxylic acid, two other isomers of I that were prepared earlier.[1]

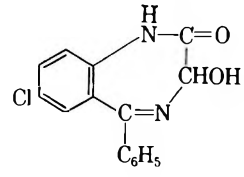
Compound IV, m.p. 255–257°, absorbed in the infrared at 3.15 and at 6.01 μ suggesting the persistence of NH and C=O in the product. The n.m.r. spectrum showed a singlet (2H) at δ 4.56.[3] The reaction conditions suggested the possibility of a Beckmann-type rearrangement. The expected product (*trans* shift) of such a rearrangement is 4-benzoyl-6-chloro-3,4-dihydroquinoxalin-2(1H)-one, a structure consistent with the physical data.



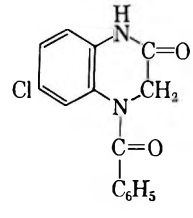
I



II



III



IV

Compound IV was hydrolyzed with hot sodium hydroxide removing the benzoyl group and affording the known 6-chloro-3,4-dihydroquinoxalin-2(1H)-one.[4] Catalytic dechlorination of IV resulted in 4-benzoyl-3,4-dihydroquinoxalin-2-(1H)-one, identical with an authentic sample made from 3,4-dihydroquinoxalin-2(1H)-one by benzoylation.[5] The structure of IV was thus established.

(1) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(2) Compound III has been assigned the generic name oxazepam.

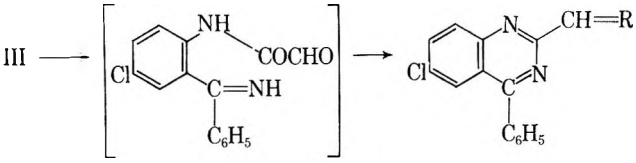
(3) N.m.r. measurements were made in deuteriochloroform (tetramethylsilane) with a Varian A-60 spectrometer.

(4) A. F. Crowther, F. H. S. Curd, D. G. Davey, and G. J. Stacy, *J. Chem. Soc.*, 1260 (1949).

(5) S. Motylewski, *Ber.*, **41**, 800 (1908).

Walker[6] recently has described a treatment of the oxime of 2-benzoyl-4-chlorooxaniloyl chloride with phosphorus oxychloride to afford 6-chloro-4-phenylquinazolin-2(1H)-one. Since the properties ascribed to this compound differed from those of a preparation made in this laboratory by two independent methods,[7] it seemed more likely to us that a Beckmann rearrangement had taken place, *followed* by cyclization and decarboxylation to give 6-chloro-3-phenylquinazolin-4(3H)-one (V). In order to test this hypothesis, 5-chloroanthranilic acid was fused with formanilide to yield V in an unambiguous way. Compound V melted at 182–184° and absorbed in the infrared at 5.97, 6.20, and 6.28 μ (Nujol). Walker gave m.p. 185° and infrared bands at 5.97, 6.20, and 6.26 μ.

In addition to those reported earlier,[1] still another rearrangement has been observed with III. Heating in acetic acid afforded 6-chloro-4-phenylquinazoline-2-carboxaldehyde (VI). Compound VI with hydrazine gave a hydrazone (VII) that was also obtainable directly from hydrazine and III. Methylamine was observed also to bring about this ring contraction leading to the methylimine (VIII) of the aldehyde. The structure of VI was proved easily by elemental analysis, positive Tollens test, and infrared and n.m.r. data (5.81 μ; δ = 10.1 p.p.m.), as well as its oxidation to the known 6-chloro-4-phenylquinazoline-2-carboxylic acid.[8]



VI, R = O
VII, R = NNH_2
VIII, R = NCH_3

Experimental[9]

4-Benzoyl-6-chloro-3,4-dihydroquinoxalin-2-(1H)-one (IV).—A mixture of 5.0 g. of I, 15 ml. of phosphorus oxychloride, and 50 ml. of chloroform was heated under reflux for 0.5 hr. until the solid had dissolved. The resultant dark reaction mixture was concentrated to dryness *in vacuo*. The residue was recrystallized from acetonitrile to afford 1.3 g. of IV, m.p. 255–257°; λ_{max}^{KBr} 3.15, 6.01 μ; δ = 4.56 p.p.m. (s, 2H).

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.81; H, 3.81; Cl, 12.37; N, 9.77. Found: C, 62.34; H, 3.85; Cl, 12.30; N, 9.87.

Hydrolysis of IV in refluxing 4 *N* sodium hydroxide for 10 min., followed by acidification, gave 6-chloro-3,4-dihydroquinoxalin-2(1H)-one, m.p. 180–182°. Crowther, *et al.*,[4] reported m.p. 184°.

Compound IV (0.3 g.) in 10 ml. of ethanol containing 0.5 ml. of 4 *N* sodium hydroxide was hydrogenated in the presence of palladium–charcoal (5%). After filtering from the catalyst, the solution was diluted to precipitate 4-benzoyl-3,4-dihydroquinoxalin-2(1H)-one, m.p. 204–206°. There was no depression upon mixing with a sample prepared according to the procedure of Motylewski.[5]

6-Chloro-3-phenylquinazolin-4(3H)-one (V).—A mixture of 17.5 g. of 5-chloroanthranilic acid and 12.1 g. of formanilide was fused at 130–150° for 15 min. The melt, which solidified on cooling, was dissolved in alcohol and the resultant solution was diluted with water. The precipitate so obtained was collected and recrystallized from ethanol to give 3 g. of V, m.p. 182–184°; λ_{max}^{Nujol} 5.97, 6.20, 6.28 μ.

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.50; H, 3.53; Cl, 13.82. Found: C, 65.58; H, 3.80; Cl, 14.00.

6-Chloro-4-phenylquinazoline-2-carboxaldehyde (VI).—A mixture of 10.0 g. of III and 100 ml. of acetic acid was heated under reflux for 10 min., then cooled, and diluted with water. The resultant precipitate was recrystallized from an alcohol–water mixture, then hexane, and finally acetonitrile. Compound VI (6 g.) was obtained as a light yellow solid, m.p. 176–178°; λ_{max}^{KBr} 5.81 μ; δ = 10.1 p.p.m. (s, 1H).

Anal. Calcd. for $C_{15}H_9ClN_2O$: C, 67.04; H, 3.38; Cl, 13.20; N, 10.43. Found: C, 67.01; H, 3.36; Cl, 13.12; N, 10.38.

Alkaline oxidation of VI with dilute potassium permanganate afforded 6-chloro-4-phenylquinazoline-2-carboxylic acid, m.p. 212–214°, identical with an authentic sample.[8]

6-Chloro-4-phenylquinazoline-2-carboxaldehyde Hydrazone (VII).—A solution of 1.5 g. of III, 50 ml. of ethanol, and 3.0 ml. of hydrazine hydrate (85%) was heated under reflux for 0.5 hr. Upon cooling 0.8 g. of product was collected. Recrystallization from isopropyl alcohol gave VII, m.p. 166–167°. An identical compound was prepared by treating VI with hydrazine.

Anal. Calcd. for $C_{15}H_{11}ClN_4$: C, 63.88; H, 3.93; Cl, 12.57; N, 19.86. Found: C, 63.72; H, 3.72; Cl, 13.00; N, 19.90.

6-Chloro-4-phenylquinazoline-2-carboxaldehyde Methylimine (VIII).—A mixture of 3.0 g. of III, 50 ml. of ethanol, and 15 ml. of 30% aqueous methylamine that had refluxed for 1 hr. was diluted with 100 ml. of water. The precipitate was collected and recrystallized from cyclohexane. There was obtained 1.7 g. of VIII, m.p. 153–154°.

Anal. Calcd. for $C_{16}H_{12}ClN_3$: C, 68.20; H, 4.29; Cl, 12.59; N, 14.91. Found: C, 68.27; H, 4.20; Cl, 12.60; N, 15.18.

Acknowledgment.—We are indebted to Dr. Gordon Ellis for the microanalyses, to Mr. Bruce Hofmann for the infrared data, and to Dr. C. A. Hetzel for the n.m.r. spectra.

(6) G. N. Walker, *J. Org. Chem.*, **27**, 1929 (1962).
(7) T. S. Sulkowski and S. J. Childress, *ibid.*, **27**, 4424 (1962).
(8) S. C. Bell, C. Gochman, and S. J. Childress, *ibid.*, **28**, 3010 (1963).
(9) The melting points are uncorrected.

Electron Spin Resonance Spectra of the Negative Ions of Phenothiazine and Some of Its Derivatives[1]

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Continuing earlier work on thiazine and oxazine dye radicals,[2] we have obtained well-resolved spectra of phenothiazine, 3,7-diaminophenothiazine (Lauth's violet), 3,7-bis(dimethylamino)phenothiazine (methylene blue), and 7-dimethylaminophenothiazin-3-one (methylene violet).

Previously[2] the radicals were produced in various alkaline and acid solutions. The four spectra discussed later were obtained from radicals produced in *p*-dioxane with the sodium mirror technique at room temperature The hyperfine structure lines observed had an average width of 0.07 gauss. A section of the spectrum of Lauth's violet between the central line and one outer component of the central nitrogen triplet is shown in Fig. 1. This section is typical for all spectra recorded.

(1) Work supported by the (U. S.) National Science Foundation, the Research Corporation, and by the Rockefeller Fund of the School of Arts and Sciences of the American University of Beirut.

(2) F. W. Heineken, M. Bruin, and F. Bruin, *J. Chem. Phys.*, **37**, 1497 (1962).

TABLE I

SPLITTING CONSTANTS IN GAUSS OF TRIPLETS DUE TO NUCLEAR SPINS OF NITROGEN (N) AND RING PROTONS (H)[a]

Free radical of	Position 1,9 (H)	2,8 (H)	3,7 (H)	4,6 (H)	5	10
Anthracene	2.74	1.57	1.57	2.74	5.56 (H)	5.56 (H)
Phenazine	1.93	1.61	1.61	1.93	5.14 (N)	5.14 (N)
Thianthrene	*b*	1.62	1.62	*b*	0 (S)	0 (S)
Phenothiazine	2.82	0.81	3.80	1.00	0 (S)	7.10 (N)
Lauth's violet	2.77	1.53	*c*	0.93	0 (S)	7.50 (N)
Methylene blue	2.66	1.36	*c*	0.88	0 (S)	7.08 (N)
Methylene violet	2.73	1.46	*c*	0.90	0 (S)	7.29 (N)

[a] For assignments see text. [b] Not observed. [c] Not completely resolved.

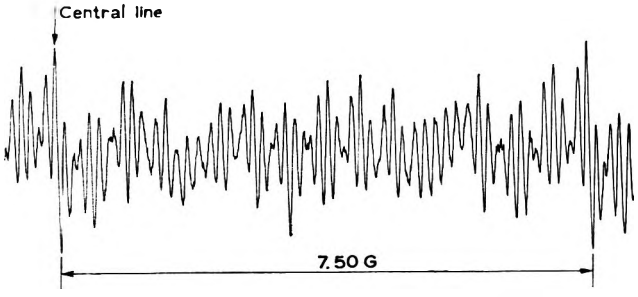
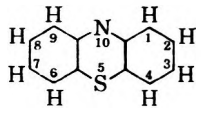


Fig. 1.—Section of the spectrum of Lauth's violet between the central line and one outer component of the central nitrogen triplet.

Recording and analyzing the spectra were hampered by (a) the instability of the free radicals, (b) the many hyperfine structure lines involved, and (c) the pronounced asymmetry of the spectra. This asymmetry, for which theoretical arguments have been given,[3] was most prominent for 7-hydroxyphenoxazine-3,10-dione (resazurin), and will not be discussed further here.

The splittings due to the central nitrogen atom could be determined with higher precision than previously[2]. In addition new splitting constants, due to various protons, were found and are collected in Table I. The inaccuracy in the values is $\leq 5\%$. Data on anthracene in tetrahydrofuran,[4] phenazine in either tetrahydrofuran or dimethoxyethane,[5] and thianthrene in sulfuric acid[6] are included for comparison. Our measurements on these radicals served as a check on the new results. The numbering used in Table I is as follows.



The assignment for the splitting due to the nitrogen atom in position 10 is unique. Comparison of phenothiazine with the phenazine data shows that replacement of nitrogen by sulfur in position 5 notably increases the spin density in position 10. Furthermore appreciable changes are introduced in various proton splittings. For thianthrene in sulfuric acid an incompletely resolved spectrum has been reported,[6] showing five lines at about 1.62 gauss spacing, attributed to the 2,3,7,8 protons. Since the largest proton triplet splitting occurring in phenothiazine is absent in the radicals substituted at the 3,7-positions, one may tentatively assign the largest splitting in phenothiazine to these positions. The other splittings are tentatively assigned by comparison with those of anthracene and phenazine. However, due to the addition of the auxochromic groups, the whole relative spin density pattern in the benzene rings may, of course, have changed, so that the proton splitting assignments are still ambiguous.

The last three substituted radicals of Table I show consistent splittings not only among themselves, but also when compared to a number of other radicals. These were 3-amino-7-dimethylaminophenothiazine (azure A), 3-dimethylamino-7-diethylamino-8-methylphenoxazine (capri blue GN), and 7-hydroxyphenoxazine-3,10-dione (resazurin). These are not included in the analysis, because of less detailed resolution of their spectra.

The splittings shown in Table I by themselves do not fully represent the observed details of the substituted phenazine spectra. To account for all lines observed, one has to assume additional splittings of about 0.5 gauss, which appear to be due to protons of the auxochromic groups. These splittings could not be fully analyzed.

(3) H. M. McConnell, *J. Chem. Phys.*, **25**, 709 (1956); D. Kivelson, *ibid.*, **33**, 1094 (1960); M. J. Stephen and G. K. Fraenkel, *ibid.*, **32**, 1435 (1960).

(4) A. Carrington, F. Dravnieks, and M. C. R. Symons, *J. Chem. Soc.*, 947 (1959).

(5) A. Carrington and J. dos Santos-Veiga, *Mol. Phys.*, **5**, 21 (1962).

(6) H. J. Shine, C. F. Dais, and R. J. Small, *J. Chem. Phys.*, **38**, 569 (1963).

Electron Density and Nucleophilic Substitution in the Purine Ring

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In a recent paper in this journal, Sutcliffe and Robins[1] draw attention to some discrepancies between electron density calculations and experimental observations relative to the nucleophilic substitution in the purine ring. Without questioning the results of these authors concerning the possible occurrence in the course of

(1) E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, **28**, 1662 (1963).

such substitutions of different reacting species, we should like to stress that the appearance of discrepancies may be due, wholly or at least partially, to the misuse of the results of quantum-mechanical calculations by the aforementioned authors.

In the first place, electronic charges calculated for the isolated, unreacting molecules should not be used without care for the interpretation of their chemical reactivity. This reactivity depends on the properties of the molecule in the activated complex. Information about these properties, although rarely complete, may be reached, *e.g.*, through calculations of localization energies. While, in some cases, predictions based on the results of charge distribution in the ground state correlate with those obtained from the localization energies, this is in no way a general rule. We have already discussed the significance of this situation for the particular case of purine.[2,3] It also may be useful to add that the same observation concerns properties other than chemical reactivity, in particular the basicity which Jones and Robins[4] have also proposed to correlate recently in the case of purines with the electron density on the nitrogen atoms. Fundamental studies of this problem[5,6] show that the basicity of the nitrogens, in particular in a polyazaheterocyclic compound like purine, depend on a more complex set of factors than the electronic charges of the nitrogen atoms.

In the second place, the calculations to which Sutcliffe and Robins refer are those concerning the purine molecule, while the experimental results with which they are correlated refer to 2,6,8-trichloropurine. Now, it cannot, of course, be assumed without proof or at least without caution that the distribution of the indices responsible for nucleophilic reactivity in a 2,6,8-trisubstituted purine parallels exactly the distribution of the same indices in purine itself. No calculations are available, unfortunately, for 2,6,8-trichloropurine, but an illustration of the fact that this may not be the case is offered by the calculations available for 2,6,8-trihydroxypurine (the enol form of uric acid).[7] The calculations of localization energies predict that the most reactive center towards nucleophilic substitution in this molecule should be carbon 6, while in purine itself equal reactivity was found from that point of view for carbons 6 and 8.

In conclusion, while it is, of course, true that a careful examination of the actual species undergoing the reaction is a most important factor to be considered, it is not less important that the correlation with quantum-mechanical calculations refer to the proper or at least very closely related structure and that the theoretical indices (taken into account) be appropriate for the phenomenon investigated.

Acknowledgment.—This work was sponsored by Grant CY-3073 of the U. S. Public Health Service (National Cancer Institute).

(2) B. Pullman, *J. Chem. Soc.*, 1621 (1959).
(3) B. Pullman, *Tetrahedron Letters*, **4**, 231 (1963).
(4) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963).
(5) T. Nakajima and A. Pullman, *J. chim. phys.*, 793 (1958).
(6) A. Pullman, "Electronic Aspects of Biochemistry," Proceedings of an International Symposium, Ravello, September, 1963, Academic Press, New York, N. Y.
(7) B. Pullman and A. Pullman, "Quantum Biochemistry," Wiley's Interscience Division, Inc., New York, N. Y., 1963, p. 227.

The Effect of an α-Bromine on the Dienone–Phenol Rearrangement

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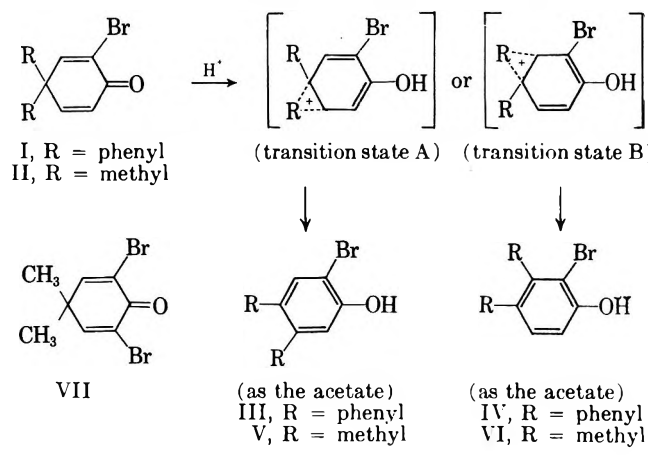
Kirk and Petrow have reported that substitution of a chlorine in the 2- and/or 4-position of $\Delta^{1,4}$-dien- and $\Delta^{1,4,6}$-trien-3-keto steroids results in a marked decrease in the facility with which they undergo the dienone–phenol rearrangement.[2] Likewise, Inhoffen and coworkers found that the rearrangement of the methyl ester of 2,4-dibromo-3-keto-12α-acetoxy-$\Delta^{1,4,6}$-cholatrienic acid was sluggish as compared to the unbrominated substance.[3] The availability of 2-bromo-4,4-diphenylcyclohexa-2,5-dienone (I) and 2-bromo-4,4-dimethylcyclohexa-2,5-dienone (II)[4] offered an opportunity to study the influence of an α-bromine atom on the dienone–phenol rearrangement unencumbered by subsequent reactions which often complicate such rearrangements in steroids.[5]

Acid-catalyzed rearrangements of either I or II in acetic anhydride led to two isomeric products. In both instances the major product was the 2-bromo-4,5-disubstituted phenyl acetate, the minor component being the 2-bromo-3,4-disubstituted phenyl acetate. The preference was about 2 to 1 in the dimethyl series but only about 1.2 to 1 in the diphenyl series.

The major product formed in a dienone–phenol rearrangement can generally be accounted for by considering the relative stabilities of the transition states for the possible modes of rearrangement. Of the two possible transition states A and B, A will be favored in that the positive charge is further removed from the electrophilic carbon atom bearing the bromine than is true for B. Steric factors also favor transition state A, but this effect cannot be a deciding factor, since a larger amount of the more sterically crowded product is



(1) Allied Chemical Corp. Fellow, 1960–1961; Eastman Kodak Co. Fellow, 1961–1962.
(2) D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 877 (1959).
(3) H. H. Inhoffen and W. Becker, *Ber.*, **86**, 116 (1953); see also H. H. Inhoffen, H. Jahnke, and P. Nehring, *ibid.*, **87**, 1154 (1954).
(4) F. G. Bordwell and K. M. Wellman *J. Org. Chem.*, **28**, 2544 (1963).
(5) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950); C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and St. Kaufmann, *ibid.*, 4540; E. J. Bailey, J. Elks, J. F. Oughton, and L. Stevenson, *J. Chem. Soc.*, 4535 (1961).

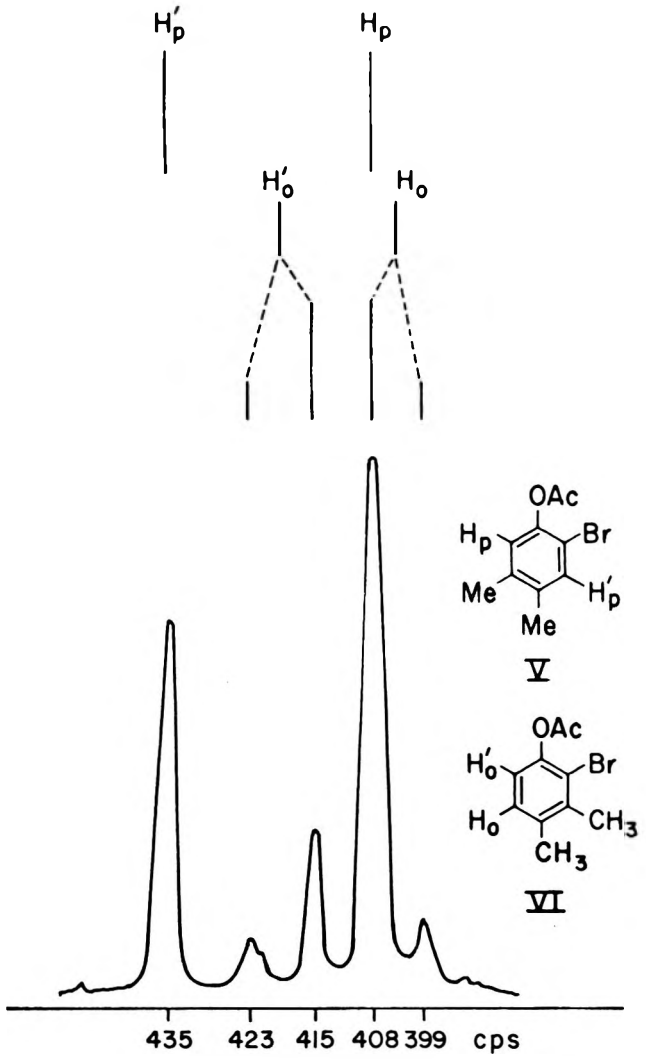


Fig. 1.—The partial 60-Mc. n.m.r. spectrum of the 2-bromo-4,4-dimethylcyclohexa-2,5-dienone rearrangement product.

formed in the diphenyl case than in the dimethyl case. Apparently, the ability of the phenyl group to delocalize the positive charge stabilizes both transition states A and B, thereby making the reaction less selective in the diphenyl series.

The capacity of an α-bromine to destabilize a transition state such as B is further indicated by the failure of 2,6-dibromo-4,4-dimethylcyclohexa-2,5-dienone (VII) to rearrange except under forcing conditions. Here methyl migration in either direction will require a transition state comparable to B. The expected product, 2,6-dibromo-3,4-dimethylphenyl acetate, is formed only on heating VII with *p*-toluenesulfonic acid in acetic anhydride for 37.5 hr.; even then, a small amount (11%) of starting dibromodienone remains. (Of course, the lower basicity of VII also causes a slower reaction.)

The structural assignments to 2-bromo-3,4-diphenyl- and 2-bromo-4,5-diphenyl acetates (III and IV) are based on their common conversion to 3,4-diphenyl acetate and on their proton magnetic resonance (p.m.r.) spectra. One of the two phenolic ring protons was masked in each spectrum by the phenyl protons at about 7.1 p.p.m. In III a singlet aromatic proton (relative area of one) was observed at 7.59 p.p.m. as would be expected for weakly coupled *para* protons,[6] whereas in IV an unsymmetrical doublet at 7.40 p.p.m. (relative area of one) with a first-order coupling constant of 8.5 c.p.s. was observed, as would be expected for one of two *ortho* protons in the phenolic ring.

It is of interest to note that IV was catalytically debrominated only very slowly and could be recovered essentially unchanged when treated under conditions where III was readily debrominated. It seems likely that the slower rate for IV is a consequence of greater hindrance to adsorption of the bromine atom on the palladium catalyst.

In the dimethyl series, gas–liquid chromatography (g.l.c.) of the rearrangement product showed only two components. 2-Bromo-4,5-dimethylphenyl acetate (V) was identified as the major product by introducing an authentic sample and noting which peak was enhanced. The presence of V was confirmed by isolation of the corresponding phenol from the hydrolysis mixture. A second phenol isolated from the hydrolysate afforded 2,6-dibromo-3,4-dimethylphenol on monobromination, thereby verifying the structure of the second monobromide as the phenol of VI. P.m.r. spectra were used to support the g.l.c. analyses and structural assignments (see Experimental).

Experimental[8]

Dienone–Phenol Rearrangement of 2-Bromo-4,4-diphenyl-cyclohexa-2,5-dienone (I).—A solution of 1.402 g. (0.00431 mole) of I,[4] 0.147 g. of *p*-toluenesulfonic acid monohydrate, and 30 ml. of acetic anhydride was heated at reflux for 1.75 hr. and then poured into water. Solid sodium bicarbonate was added to destroy the excess acetic anhydride, and the hydrolysis mixture was extracted with 600 ml. of ether. A solid suspended at the water–ether interface was separated and dissolved in 200 ml. of benzene. The combined benzene–ether fractions were dried and concentrated to an oily solid. The solid was washed thoroughly with about 20 ml. of ether to give 0.6003 g. (0.00166 mole, 38%) of **2-bromo-3,4-diphenylphenyl acetate (IV)**, m.p. 208–211°. One recrystallization from chloroform raised the melting point to 214°. An analytial sample melted at 214.5°; λ_{max}^{KBr} 5.68, 8.27, 10.7 μ.

Anal. Calcd. for $C_{20}H_{15}BrO_2$: C, 65.41; H, 4.18. Found: C, 65.22; H, 4.27.

The ethereal mother liquors were concentrated to an oil which was adsorbed onto a silica gel column (3 × 65 cm., eluted with 10% ether–hexane). The first fraction (250 ml.) was blank. The second fraction (1400 ml.) gave 0.7458 g. (0.00203 mole, 47%) of **2-bromo-4,5-diphenylphenyl acetate (III)** as thin plates, m.p. 102–103°, after one crystallization from hexane. Further recrystallization raised the melting point to 103–104°; λ_{max}^{KBr} 5.65–5.69 (limits of the broad carbonyl band at its peak), 6.78, 7.30, 8.30–8.40 (broad), 11.08 μ.

Anal. Calcd. for $C_{20}H_{15}BrO_2$: C, 65.41; H, 4.18. Found: C, 64.99; H, 4.22.

The third fraction (500 ml.) gave 0.0090 g. (1%) of IV, m.p. 208–210°, m.m.p. 208–211°.

Debromination of III and IV.—A 62.2-mg. (0.17 mmole) sample of III was stirred with 0.204 g. of 10% palladium–carbon in 5 ml. of acetic acid for 10 hr. under 45 lb. of hydrogen pressure. The mixture was diluted with 50 ml. of ether, filtered through diatomaceous earth, and the filtrate poured into about 100 ml. of water. Solid sodium bicarbonate was added, and the

(6) *para* protons are known to have small coupling constants of the order of 0–1 c.p.s., whereas, *ortho* protons have coupling constants of about 7–10 c.p.s.[7]

(7) See H. Conroy, "Advances in Organic Chemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960, p. 309; and L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 85.

(8) Microanalyses were by Miss Hilda Beck and Micro-tech Laboratories, Skokie, Ill. P.m.r. spectra were recorded by Mr. Larry Shadle on a Varian high resolution spectrometer operated at 60 Mc. using either carbon tetrachloride or chloroform as a solvent. Chemical shifts were measured relative to tetramethylsilane (δ 0); a positive value signifies a downfield shift from the reference.

ethereal layer was separated and dried. Concentration gave 47.5 mg. of material melting at 100–115°. Two recrystallizations from hexane gave 18.7 mg. (0.064 mmole) of 3,4-diphenylphenyl acetate, m.p. 126–128°, identified by mixture melting point and infrared spectral comparison with an authentic sample prepared in 86% yield (m.p. 129.5–130.5°, lit.[9] m.p. 130.0–131.5°) according to the method of Zimmerman and Schuster.[9]

In a similar manner, 91.7 mg. of IV in 5 ml. of acetic acid with 0.2 g. of 10% palladium–carbon was stirred for 1 week under 40–45-lb. of hydrogen pressure. The same processing gave 58.9 mg. of ether-insoluble starting material and 17.2 mg. (m.p. 105–115°) of ether-soluble material. Infrared analysis of the ether-soluble material indicated it was mainly 3,4-diphenylphenyl acetate. Crystallization from hexane gave 7.7 mg., m.p. 124–127°, m.m.p. 125–127°.

Dienone–Phenol Rearrangement of 2-Bromo-4,4-dimethylcyclohexa-2,5-dienone (II). A. Gas–Liquid Chromatography and Proton Magnetic Resonance Analyses.—A solution of 1.506 g. (0.00749 mole) of II[4] and 0.705 g. of *p*-toluenesulfonic acid monohydrate in 45 ml. of acetic anhydride was heated at reflux for 2.5 hr. Processing in the usual manner gave 1.719 g. (0.00707 mole) of a liquid. G.l.c. analysis[10] showed only two components (partially resolved) with areas in the ratio of 1.98:1.00. V was identified as the major component by introducing an authentic sample, prepared according to Wegand, *et al.*,[11] and noting which peak was enhanced.

The aromatic proton region in the p.m.r. spectrum (see Fig. 1) of the oil showed a singlet for each *para* proton in V and a partially hidden quartet corresponding to the AB system of *ortho* protons in VI with a first-order coupling constant of 8 c.p.s. Areas under proton signals H_p' and H_o', corresponding to one proton in each molecule, were in the ratio of 1.95:1.00, respectively, in excellent agreement with the ratio obtained by g.l.c. A pure sample of V had singlet aromatic proton signals at 6.80 and 7.25 p.p.m.

B. Hydrolysis and Isolation.—A solution of 1.010 g. (5.00 mmoles) of the bromodienone II and 0.507 g. of *p*-toluenesulfonic acid monohydrate dissolved in 30 ml. of acetic anhydride was refluxed for 10 hr. The dark reaction mixture was poured into 250 ml. of water and shaken for several minutes to hydrolyze most of the acetic anhydride. The aqueous mixture was extracted with two 250-ml. portions of ether, and the combined extracts were washed with dilute sodium bicarbonate, dried, and concentrated to give about 2 ml. of liquid. The liquid was dissolved in 30 ml. of 5% methanolic sodium hydroxide and refluxed for 1 hr. After neutralizing the excess base with acetic acid, the solution was concentrated almost to dryness. The residue was taken up in an ether–water mixture, the ethereal layer separated, and the water fraction washed with ether. The combined organic extracts were dried and concentrated to yield an oil (0.8267 g.) which solidified on standing. Attempts to obtain the pure phenol from this material by recrystallization or sublimation were unsuccessful. The material was chromatographed on a 2 × 45 cm. column packed with silica gel and eluted with 6% ether–hexane. Fractions 1 (250 ml.) and 7 (125 ml.) were blank. Fractions 2 (100 ml.) and 3 (40 ml.) were combined to yield 0.0742 g. (0.37 mmole) of an oil which appeared to be a phenol (presumably 2-bromo-3,4-dimethylphenol) from its infrared spectrum [$\lambda_{max}^{CS_2}$ 280 mμ (sharp), 6.20 μ] and monobromination product (following). The oily phenol could not be caused to solidify[12] and definitely was not V (by infrared analysis). Fraction 4 (125 ml., 0.1513 g., 0.75 mmole) appeared, by rough infrared analysis, to be a mixture of approximately equal amounts of the phenols of V and VI. Fraction 5 (250 ml.) yielded 0.2654 g. (1.26 mmole, m.p. 60–70°) of 2-bromo-4,5-dimethylphenol. One recrystallization gave pure phenol (m.p. 77°), identified by infrared comparison and mixture melting point with an authentic sample prepared according to Heiken[14]; λ_{max}^{KBr} 2.94, 6.19, 11.5, 12.8, 13.6 μ.

Twenty milligrams (0.1 mmole) of the oily phenol in 1 ml. of acetic acid was treated with 25 mg. (0.16 mmole) of bromine in 0.4 ml. acetic acid and the solution allowed to stand in the dark at 25° for 30 min. After pouring into water, neutralizing the acid with sodium bicarbonate, and extracting with ether, 22.8 mg. (0.082 mmole) of an oil was obtained, which solidified to oily needles when seeded with 2,6-dibromo-3,4-dimethylphenol (see below). Recrystallization afforded the dibromophenol as needles, m.p. 33–34°, further identified by infrared analysis.

Dienone–Phenol Rearrangement of 2,6-Dibromo-4,4-dimethylcyclohexa-2,5-dienone (VII).—A solution containing 0.9509 g. (0.0034 mole) of VII[4] and 0.4971 g. of *p*-toluenesulfonic acid monohydrate in 30 ml. of acetic anhydride was heated at reflux for 37.5 hr. Processing as above gave 0.5920 g. of a partially solid material. Fractional crystallization gave 0.1093 g. (0.38 mmole, 11%) of starting material (m.p. 142–144°), further identified by its infrared spectrum. The mother liquors from the crystallization were concentrated and adsorbed onto a chromatographic column (2 × 40 cm.) which had been packed with silica gel and eluted with 8% ether–hexane; 250-ml. fractions were collected. Fractions 1 and 2 gave 0.3417 g. of 2,6-dibromo-3,4-dimethylphenyl acetate containing a small amount of VII as an impurity. Several recrystallizations from petroleum ether (b.p. 40–50°) gave 0.2373 g. (0.74 mmole, 22%) of pure **2,6-dibromo-3,4-dimethylphenyl acetate**, m.p. 57–58°. It was identified by mixture melting point and infrared comparison with an authentic sample (m.p. 57–58°, λ_{max}^{KBr} 5.60, 8.35, 9.68 μ) prepared by acetylation of 2,6-dibromo-3,4-dimethylphenol.[15]

Anal. Calcd. for $C_{10}H_{10}Br_2O_2$: C, 37.30; H, 3.13. Found: C, 37.47; H, 3.06.

(9) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **84**, 4527 (1962).

(10) G.l.c. analyses were made on an F & M Model 300 chromatograph using a 15-ft. column packed with 8% 550 silicon oil on 60–80-mesh Chrom P, programmed over 140–190°.

(11) F. Wegand, K. Vogelback and K. Zimmerman, *Ber.*, **80**, 391 (1947).

(12) Hunsberger, *et al.*,[13] have reported that 2-bromo-3,4-dimethylphenol exists as an oil.

(13) I. M. Hunsberger, D. Lednicer, H. S. Gutowsky, D. L. Bunker, and P. Taussig, *J. Am. Chem. Soc.*, **77**, 2466 (1955).

(14) K. Heiken, *Angew. Chem.*, **52**, 236 (1939).

(15) E. von Auwers, *Ann.*, **344**, 171 (1906).

The Structure of Carolic Acid

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Carolic acid,[1] a metabolite of *Penicillium charlesii* G. Smith, possesses the molecular formula $C_9H_{10}O_4$. Consideration of the reactions of the acid in aqueous solution led Clutterbuck,[2] *et al.*, to suggest that the compound resembled the α-acyltetronic acids and could best be represented as a hydrated form (I). It was postulated that the crystalline compound was derived from the hydrated form by loss of water and might possess structure II. Clutterbuck, *et al.*,[2] found that in dry anisole, carolic acid contained no active hydrogen, whereas in pyridine one active hydrogen atom was shown to be present; in order to explain this observation they postulated that the —$COCH_2$— group of the seven-membered ring in II may undergo enolization to —C(OH)=CH— in pyridine. Duncanson[3] has commented that the infrared spectrum of carolic acid under anhydrous conditions suggests that the structure is more closely related to those of the alkyl ethers of the tetronic acids than to the tetronic acids themselves.

A study of the n.m.r. spectrum[4] of carolic acid now confirms its formulation as II. Unlike those of typical acyltetronic acids[5] the spectrum shows no absorption

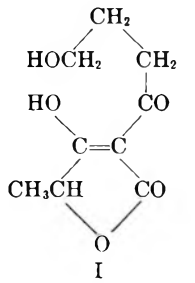
(1) P. W. Clutterbuck, W. N. Haworth, H. Raistrick, G. Smith, and M. Stacey, *Biochem. J.*, **28**, 94 (1934).

(2) P. W. Clutterbuck, H. Raistrick, and F. Reuter, *ibid.*, **29**, 300 (1935).

(3) L. A. Duncanson, *J. Chem. Soc.*, 1207 (1953).

(4) Measured on Varian A-60 spectrometer in deuteriochloroform solution with tetramethylsilane as internal standard (δ = 0.00 p.p.m.).

(5) L. J. Haynes and J. R. Plimmer, unpublished observations.



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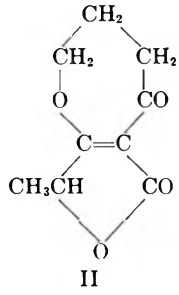

II

due to a proton in a hydrogen-bonded hydroxyl group ($\delta \sim 13$ p.p.m.). An integrated spectrum shows the presence of ten proton signals which occur in the following regions: (a) $\delta = 1.45$ p.p.m., a doublet (3 protons) due to the methyl group coupled with a single hydrogen atom $CH_3-\underset{|}{C}-H$; (b) $\delta = 2.35$ p.p.m., a multiplet (5 lines, 2 protons) due to the protons of the central methylene group of the seven-membered ring coupled with their neighbours; (c) $\delta = 3.45$ p.p.m., a triplet (2 protons) probably due to the hydrogen atoms of the $-CH_2CO$ group (this allocation is based on a study of other α-acyl tetronic acids[5]); (d) $\delta = 4.63$ p.p.m., a quartet ascribed to the single hydrogen atom of the $CH_3\underset{|}{C}-H$ group coupled with the protons of the methyl group; (e) $\delta = 4.82$ p.p.m., a triplet probably due to the two remaining methylene protons which are linked to oxygen in the group $-OCH_2CH_2-CH_2CO-$. Integration of signals d and e shows the presence of three protons.

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A New Method for Preparing Ethyl Peroxide ("Diethyl Peroxide")

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An important member of the dialkyl peroxide series, ethyl peroxide, has been difficult to prepare in good yield until rather recently. First synthesized by Baeyer and Villiger[2] in 1900, no yields greater than 5% were reported until 1944, when Du Pont[3] disclosed that improved yields could be obtained by the repetitive addition of hydrogen peroxide to a heated mixture of diethyl sulfate and aqueous potassium hydroxide, with the ethyl peroxide distilling as formed. However, the yield of purified peroxide is only moderate, and the operation is extremely hazardous. Recently, Nangia and Benson[4] described an improved yield of about 30% by the use of sodium stearate as dispersing agent. In all of these cases, ethyl sulfate was used as the reactant.

In the course of preparing ethyl peroxide for kinetic studies, we first tried the synthesis of Nangia and Benson, and a number of variations, but were unable to obtain yields greater than 5%. We have found, however, that by using ethyl methanesulfonate as starting material, using a dispersing agent, and by distilling the peroxide as formed, a 50% yield of triple-distilled material can readily be obtained in a rapid and simple synthesis. This material is identical with previously prepared ethyl peroxide, as shown by infrared and refractive index, but is of a higher degree of purity. We have studied the purity of ethyl peroxide by infrared and by n.m.r. spectra (following); the material prepared here is 98.5% pure.

Experimental

Ethyl methanesulfonate[5] (62.0 g.), 30% hydrogen peroxide (28.4 g.), and 25 mg. of stearic acid were placed in a three-neck, 300-cc. flask equipped with a mechanical stirrer and thermometer. A solution of 27.3 g. of potassium hydroxide in 30 ml. of water was added dropwise over a period of about 1 hr., keeping the contents of the flask at 0 to 15°. Upon completion of the addition, the ice bath was removed, a simple distillation head with condenser was attached, and the flask was allowed to warm up. After climbing slowly to 60° the flask temperature rose sharply to about 90°, during which time rapid evolution of ethyl peroxide occurred. Additional heating was applied to maintain the temperature at this level for 30 min. The material collected in the trap was transferred to a separatory funnel, neutralized with a few drops of 4 *N* sulfuric acid, and washed three times with distilled water. The crude peroxide was dried over anhydrous sodium sulfate for a day and distilled twice through a 25-cm. micro Vigreux column, yielding 11.1 g. (49.3%) of product, b.p. 62–63°. A comparison of the infrared spectrum of this material with that of standard solutions in carbon tetrachloride of several commonly reported impurities, using a cell of fixed thickness, showed there to be approximately 0.4% water and 1.2% acetaldehyde present. No ethanol or ethyl ether were detectable. All other peaks observed were identical with those reported by Minkoff.[6] The refractive index of the purified ethyl peroxide was $n^{14}D$ 1.3724, agreeing with literature values. Distillation of the peroxide using a more efficient, packed column was found to be less effective for the removal of water and only slightly more effective in reducing the amount of acetaldehyde than the Vigreux column.

The nuclear magnetic spectrum of this material compares favorably with that for propyl peroxide and isopropyl peroxide prepared in these laboratories. Ethyl peroxide had a quartet centered at δ 3.95 and a triplet at 1.18, with a relative intensity of 2:3. Acetaldehyde is detectable by its doublet at δ 2.20, and a comparison of the relative intensities of the β-hydrogens in the two compounds indicates that 1.1% acetaldehyde is present. Other peaks are detected, but in negligible intensity.

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(2) A. Baeyer and V. Villiger, *Ber.*, **33**, 3387 (1900).

(3) R. H. Wiley, U. S. Patent 2,357,298. Yields are given only for crude material boiling at 61–65°. Our experience indicates such material is extremely impure.

(4) P. Nangia and S. W. Benson, *J. Org. Chem.*, **27**, 1882 (1962).

(5) Prepared by the method of H. R. Williams and H. S. Mosher, *J. Am. Chem. Soc.*, **76**, 2987 (1954), in 61% yield. Ethyl methanesulfonate has b.p. 84–85° (9 mm.).

(6) G. J. Minkoff, *Proc. Roy. Soc.* (London), **224A**, 176 (1954).